Volume 64, Number 1, March 1993

LEPROSY REVIEW

Published Quarterly for the
British Leprosy Relief Association

ISSN 0305-7518

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Typeset and printed at Alden Press Limited, Oxford and Northampton, Great Britain

Lepr Rev (1993) **64,** 1–6

Editorial

IMMUNOPATHOLOGY OF NERVE INVOLVEMENT IN LEPROSY

Nerve granulomas may be found at all points across the leprosy spectrum. At the lepromatous end the granuloma is of the typical macrophage type, whereas at the tuberculoid end the granuloma is more like that associated with delayed hypersensitivity. In between one-third and one-half of the tuberculoid cases there may be discordance as to the type of granuloma seen in nerves and skin.[1]

The nature of the cellular infiltrate, particularly cells of the macrophage–monocyte system in neural granulomas in leprosy, has been studied using electron microscopy.[2] At the tuberculoid end of the spectrum, large mononuclear cells with abundant cytoplasm with vacuoles containing finely granular material and pale indented nuclei were seen and identified as epithelioid cells. At the lepromatous end of the spectrum the Schwann cells were often heavily bacillated, as were the macrophages and perineural cells. The end result of inflammatory changes caused by leprosy bacilli in the nerves is the total destruction of the nerve. At the tuberculoid end of the spectrum, and especially in reversal reactions (Type I), it is clear that the inflammatory reaction is related to hypersensitivity and is an immunological phenomenon. However, it is not clear what causes the inflammatory reaction in lepromatous cases. In erythema nodosum leprosum (Type II reaction), which occurs at the lepromatous end of the spectrum, the inflammation of nerves is probably immune complex mediated since it is associated with other aspects of immune complex disease in which there is evidence of circulating immune complexes.[3] Immune complexes in the nerve could be formed directly with mycobacterial antigen released locally, or may be the result of the deposition of circulating immune complexes. A further cause of granuloma formation in nerves in lepromatous leprosy in the absence of immune complexes is likely to be the direct activation of the alternative pathway of complement by *Mycobacterium leprae* or its breakdown products.[4] The activation of the complement cascade by the classical or alternative pathways will result in the local release of the inflammatory components C3a, C3b, C5a and C5b which could lead to macrophage accumulation at the site. Immunohistology revealed deposits of C3 and C9 on the Schwann cells of affected nerves in patients with lepromatous leprosy. There was also moderate staining for C9 in tuberculoid leprosy patients.[5] The role of the C9 in nerve damage is still open to interpretation.

Lymphocyte subtyping in leprosy neuritis has been studied in small numbers of patients across the leprosy spectrum, using monoclonal antibodies to identify T cells and anti-IgG antibodies to identify B cells.[5] Between 40% and 50% of the mononuclear cells were T cells and between 20% and 25% were B cells. The CD4/CD8 ratio in paucibacillary

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nerves was 1·8:1 while in multibacillary nerves it was 0·5:1. Narayanan *et al.*[6] found an average of 85% of lymphocytes in the nerve granulomas of patients at the tuberculoid pole to be CD3 positive, 80% CD4 positive and 30% CD8 positive. CD4+ cells were diffusely scattered within the epithelioid cell granulomas, while CD8+ cells were localized in the peripheral mantle of the granuloma. At the lepromatous end of the spectrum, very few T cells were found in nerve granulomas.

Thus, the cellular infiltration of granulomas within the peripheral nerve mirrored the type of cellular infiltration seen in granulomas of the skin. Where the lesion is paucibacillary, there is a typical epithelioid cell granuloma with the presence of a high proportion of CD4+ lymphocytes. Where the lesion is multibacillary, cells of the macrophage/monocyte series are phagocytosing cells and T cells are less evident, with a lower CD4/CD8 ratio. An interesting group of nerves was studied, in addition, by Nilsen *et al.*[5] This consisted of untreated patients with a histology of BT leprosy in the skin and multibacillary leprosy (BI > 3) of the nerve. These nerves contained similar proportions of T cells to those found in patients in both the tuberculoid and lepromatous groups (40–50%). However, the CD4/CD8 ratio (0·6:1) was similar to that found in the lepromatous group (0·5:1) and considerably lower than that found in the tuberculoid group (1·8:1). Thus, the granuloma of the nerve in all cases resembled that found in lepromatous leprosy rather than that found in the skin.

Nerve axons are enclosed by the cytoplasm of Schwann cells, which are actively phagocytic and can engulf mycobacteria. Dastur *et al.*[2] showed intact acid-fast bacilli within swollen Schwann cells of nerves from patients with lepromatous leprosy. Shetty *et al.*[7] found bacilli within the Schwann cells of unmyelinated fibres from lepromatous nerves. There has been much interest in recent years as to whether or not Schwann cells are capable of presenting *M. leprae* antigens to T lymphocytes in leprosy. Samuel *et al.*[8] cultured human foetal Schwann cells. These normally express Class I MHC antigens, but not Class II. Schwann cells in culture phagocytose *M. leprae*. Treatment of normal and *M. leprae* infected cultures with gamma-interferon induces Class II expression on Schwann cells, but not fibroblasts. This suggested that the Schwann cells might be able to present *M. leprae* antigens to T lymphocytes *in vivo*. Class II staining cells presumed by their morphology to be Schwann cells were found in leprosy nerves in frozen tissue sections by light microscopy.[5] However, resolution at the light microscopic level is not sufficient to distinguish Schwann cells from fibroblasts and infiltrating cells. Schwann cells can only be clearly identified and their intercellular relationships observed, at the electron microscopic (EM) level. Using immunoEM techniques it was possible to label cell surface proteins such as the MHC antigens whilst preserving the morphology of the cellular ultrastructure sufficiently well to distinguish Schwann cells from other cells in the granuloma.[9] Class II positive macrophages, lymphocytes and fibroblasts were found in paucibacillary and multibacillary leprosy nerves. However, Schwann cells were consistently negative. These observations indicate that it is unlikely that Schwann cells are involved in presenting *M. leprae* antigens to T cells *in vivo* in leprosy patients, despite the suggestion that they might be able to do so *in vitro*.[8]

Axonal changes in leprosy neuritis

The changes that occur in the axons in early leprosy neuritis have been studied.[7]

Quantitative measurement of the frequency distribution of myelinated fibres, comparing leprosy nerves (BT and BL) with controls, showed a shift to the left in the histogram with an increased proportion of small fibres. There was evidence of 'inappropriately' thin myelin sheaths and of some loss of unmyelinated axons. Oedema was the most consistent finding in these nerves. This included endoneurial oedema. There was some evidence of axonal atrophy in nearly all the nerves examined. These authors emphasize the increased numbers of macrophages and fibroblasts to be seen in the lesions.

Another way of looking at nerve function in leprosy is to study the change in neuropeptides in cutaneous nerves.[10] The peptides visualized by immunocytochemistry were substance P (SP), calcitonin gene-related protein (CGRP), vasoactive intestinal protein (VIP), neuropeptide tyrosine (NPY) and its C-terminal flanking peptide (CPON). Cutaneous nerves in all types of leprosy showed a reduction or complete absence of staining for these neuropeptides. Substance P and CGRP are found in unmyelinated sensory C fibres which are responsible for initiating pain and temperature reactions. These were completely absent from leprosy nerves. VIP and NPY are found in the nerves supplying sweat glands. The absence of these neuropeptides indicates the involvement of autonomic nerves and underlines the absence of sweating that occurs in areas of the skin supplied by leprosy nerves. This study demonstrates an almost total absence of sensory and autonomic neuropeptide immunoreactivity in nerve fibres across the leprosy spectrum.

Experimental models of leprosy granulomas in nerves

The intradermal injection of mycobacteria into the guinea-pig ear results in the development of mycobacterial granulomas in the draining post auricular, lymph node.[11] The injection of *Mycobacterium bovis* BCG induced the development of secretory epithelioid cell granulomas similar to those found in the skin at the tuberculoid pole of the leprosy spectrum. *M. leprae*, on the other hand, induced the development of a granuloma that consisted exclusively of phagocytosing macrophages as found at the lepromatous pole.

The establishment of similar mycobacterial granulomas in guinea-pig sciatic nerves[12] enabled a deeper study of the relationship between such granulomas and nerve damage. As with the lymph node granulomas the intraneural injection of BCG induced a mainly epithelioid cell granuloma maximal 2 weeks after injection, whilst the intraneural injection of *M. leprae* induced a granuloma consisting mainly of phagocytosing macrophages maximal 5 weeks after injection. Nerve damage correlated with the degree of endoneurial infiltration. Axonal degeneration was preceded by demyelination. Electrophysiological studies showed that both types of granulomas produced a functional impairment of the ability of nerve fibres to conduct action potentials. It was generally impossible to elicit a peak relating to the fastest conduction velocity. Intraneural *M. leprae* granulomas appeared to cause more chronic functional impairment, up to 150 days more, than intraneural BCG granulomas where the nerve had functionally recovered by 150 days.

Morphometric analysis of the myelinated fibres in the granuloma or distal to the granuloma showed a considerable decrease in fibre numbers 5 weeks after the intraneural injection of *M. leprae*. By 150 days, the number of fibres had recovered slightly, but was

still significantly different from normal values in the nerve distal to the granuloma. BCG injection leads to significantly reduced numbers of myelinated fibres after 2 weeks, again with fewer fibres in the distal part of the nerve. However, by 150 days the number of fibres had nearly regained normal levels.

In addition, there was a marked reduction in mean fibre diameter in *M. leprae* injected nerves at 5 weeks which persisted distal to the granuloma beyond 150 days. In BCG injected nerves mean fibre diameters were significantly lower than normal after 2 weeks, but recovered by 150 days. Overall, the morphometric findings indicated that *M. leprae* injected nerves were still chronically damaged at 150 days after injection, whereas BCG injected nerves had recovered by that time.[13]

The experimental model of mycobacterial induced nerve granulomas can also be studied by immunocytochemical techniques for MHC Class II and CD markers.[14] As in human leprosy nerves, by using electron microscopy it was shown that in *M. leprae* induced granulomas in guinea-pig nerves, macrophages and fibroblasts were Class II positive. However, no evidence of Class II expression could be detected on the cell membrane of Schwann cells. This again suggested that these cells played little role in antigen presentation *in vivo*.

Mechanism of axonal damage in leprosy neuritis

The functional deficit in leprosy neuritis is mainly due to axonal damage occurring as a result of granuloma formation within the nerve. There is no doubt that some damage is caused by pressure on the nerves resulting from perineurial oedema, as nerve decompression can have a certain beneficial effect.[15]

The mechanism of axonal damage at the tuberculoid end of the spectrum may differ from that at the lepromatous end. In lepromatous leprosy there is likely to be complement activation. This might be by the classical pathway in Type 2 reactions where there is evidence of immune complex formation. The alternative pathway can be activated by the high concentration of *M. leprae* antigens.[4] Activation of the terminal components of complement[5] can produce a membrane attack complex that is well known to be active in cell membrane damage.

At the tuberculoid end of the leprosy spectrum, the epithelioid cell granuloma that is formed has certain analogies with delayed type hypersensitivity reactions. It is, therefore, likely to be CD4 T lymphocyte mediated. CD4 cells produce cytokines that activate macrophages, such as interferon gamma. The macrophages will then produce other cytokines such as TNFα (tumour necrosis factor). TNFα may also be produced by macrophages in lepromatous leprosy. Lipoarabinomannan, a major component of mycobacterial cell walls, can induce macrophages to produce TNFα.[16] The role of TNFα in axonal damage is yet to be determined, although treatment with antibodies against TNFα can protect experimental animals from immune mediated demyelination.[17,18]

CD8 lymphocytes may also be involved. Murine Schwann cell lysis by CD8 cells occurs when they present *M. leprae* antigens in association with MHC Class I.[19] Murine CD8 lymphocytes against mycobacterial heat shock protein 65 recognize and lyse stressed Schwann cells even in the absence of *M. leprae*[20] and could explain nerve damage when there is a low bacterial load.

The role of lymphocyte factors in inducing axonal damage must also be considered.

The cytokine TNFβ (lymphotoxin) is produced by CD4 lymphocytes. However, it is proposed that T cells, both CD4 and CD8, might produce cytotoxicity more directly by secreting a 'killer' protein, perforin/cytolysin.[21] Perforins may exhibit considerable structural homology with complement components. It has been proposed that perforins, as well as complement, damage biological membranes through the formation of 10–20 nm transmembrane pores. Both perforins and complement seem to need Ca^{++} ions for their action *in vitro*.

In conclusion, *M. leprae* is the only bacterium that penetrates the epineurium. In leprosy, axonal damage occurs as a result of the release of pharmacological mediators produced by infiltrating inflammatory cells. These cells come in as a result of either an immunological reaction or a paraimmunological reaction such as the activation of the alternative pathway of complement.

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References

[1] Ridley DS, Ridley MJ. Classification of nerves is modified by the delayed recognition of *Mycobacterium leprae*. *Int J Lepr*, 1986; **54:** 596–606.
[2] Dastur DK, Porwal GL, Shah JS, Revankar CR. Immunological implications of necrotic, cellular and vascular changes in leprous neuritis: light and electronmicroscopy. *Lepr Rev*, 1982; **53:** 45–65.
[3] Ramanathan VD, Parkash O, Ramu G, Parker D, Curtis J, Sengupta V, Turk JL. Isolation and analysis of circulating immune complexes in leprosy. *Clin Immunol Immunopath*, 1984; **32:** 261–268.
[4] Ramanathan VD, Curtis J, Turk JL. Activation of the alternative pathway of complement by mycobacteria and cord factor. *Infection Immunity*, 1980; **29:** 30–35.
[5] Nilsen R, Mshana RN, Negesse Y, Mengistu G, Kana B. Immunohistochemical studies of leprous neuritis. *Lepr Rev*, 1986; **57** Suppl 2, 177–187.
[6] Narayanan RB, Girdhar A, Girdhar BK, Malaviya GN. Immunohistological analysis of nerve granulomas in neuritic leprosy. *Int Arch Allergy appl Immunol*, 1990; **92:** 50–55.
[7] Shetty VP, Antia NH, Jacobs JM. The pathology of early leprous neuropathy. *J Neurol Sci* 1988; **88:** 115–131.
[8] Samuel NM, Mirsky R, Grange JM, Jessen KR. Expression of major histocompatibility complex Class I and Class II antigens in human Schwann cell cultures and effects of infection with *Mycobacterium leprae*. *Clin exp Immunol*, 1987; **68:** 500–509.
[9] Cowley SA, Gschmeissner SE, Negesse Y, Curtis J, Turk JL. Major histocompatibility complex Class II antigen expression in nerves in leprosy: an immunoelectronmicroscopical study. *Int J Lepr*, 1990; **58:** 560–565.
[10] Karanth SS, Springall DR, Lucas S, Levy D, Ashby P, Levene MM, Polak JM. Changes in nerves and neuropeptides in skin from 100 leprosy patients investigated by immunocytochemistry. *J Path*, 1989; **157:** 15–26.
[11] Narayanan RB, Badenoch-Jones P, Turk JL. Experimental mycobacterial granulomas in guinea pig lymph nodes: ultrastructural observations. *J Path*, 1981; **134:** 253–265.
[12] Cowley SA, Butter C, Verghese S, Curtis J, Turk JL. Nerve damage induced by mycobacterial granulomas in guinea pig sciatic nerves. *Int J lepr*, 1988; **56:** 283–290.
[13] Cowley SA. A model of nerve damage in leprosy. PhD Thesis University of London, 1990.
[14] Cowley SA, Butter C, Gschmeissner SE, Curtis J, Turk JL. An immunoelectronmicroscopical study of the expression of major histocompatibility (MHC) Class II antigens in guinea pig sciatic nerves following induction of intraneural mycobacterial granulomas. *J Neuroimmunol* 1989; **23:** 223–231.
[15] Bourrel P. Surgical rehabilitation. *Lepr Rev*, 1991; **62:** 241–254.
[16] Moreno C, Taverne J, Mehlert A, Bate CAW, Brealey RJ, Meager A, Rook GAW, Playfair JHL. Lipoarabinomannan from *Mycobacterium tuberculosis* induces the production of tumour necrosis factor from human and murine macrophages. *Clin exp Immunol*, 1989; **76:** 240–245.

[17] Ruddle NH, Bergman CM, McGrath ML, Lingeheld EG, Grunnet ML, Padula SJ, Clark RB. An antibody to lymphotoxin and tumor necrosis factor presents transfer of experimental allergic encephalomyelitis. *J exp Med*, 1990; **172:** 1193–1200.
[18] Selmaj K, Raine CS, Cross AH. Anti tumor necrosis factor therapy abrogates autoimmune demyelination. *Ann Neurol*, 1991; **30:** 694–700.
[19] Steinhoff U, Kaufmann SH. *Eur J Immunol*, 1988; **18:** 969–972.
[20] Steinhoff U, Schoel B, Kaufmann SH. *Int Immunol*, 1990; **2:** 279–284.
[21] Berke G. T Cell-mediated cytotoxicity. *Current Opinions Immunology*, 1991; **3:** 320–325.

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Immunotherapy with *Mycobacterium w* vaccine decreases the incidence and severity of Type 2 (ENL) reactions

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Accepted 7 October 1992

Summary Immunotherapy with *Mycobacterium w* (*M.w*) vaccine was given to 45 patients with multibacillary (MB) leprosy; 41 similarly classified patients served as controls. All patients received standard multidrug therapy (MDT). Incidence, severity and frequency of type 2 (ENL) reactional episodes were monitored in both groups in a follow-up extending up to 4 years. Reactions were seen in fewer vaccinated (10/37) BL and LL patients than in the control group (12/34). A total of 20 episodes were recorded in the vaccine group as against 29 in the controls, 75% of reactions were mild in vaccinated and 51·72% were mild in the control group patients, and 3 patients in the control group had more than 3 reactional episodes. None of the vaccinated patients showed this. No additional incidence of neuritis were seen among vaccinated individuals during reactional episodes.

Introduction

Erythema nodosum leprosum (type 2 reaction) affects patients with multibacillary BL and LL types of leprosy. Over 50% of LL and 25% of BL patients experience type 2 reactions.[1] There is a sudden development of crops of small, tender, subcutaneous nodules which persist for a few days and then subside. Other clinical features include fever, neuritis and polyarthralgia.[2] Histological features consist of 3 distinct changes: 1, intense infiltration of neutrophilic granulocytes within the lepromatous macrophage granuloma; 2, abundant presence of fragmented and granular bacilli; and 3, oedema of endothelium of vessel walls with granulocyte infiltration and local vasculitis.[3] The aetiopathogenesis of this symptom complex is the formation of immune complexes which are deposited in selective tissue sites. These complexes consist of mycobacterial antigens,

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IgG or IgM antibodies and complement.[4] It has been postulated that in ENL, there is an imbalance of immunoregulatory T-cell subsets. This is manifested as an increased ratio of helper (CD4+) to suppressor/cytotoxic (CD8+) T cells in blood.[5] Decrease in CD8+ T-cells may favour formation and deposition of immune complexes.[6]

Mycobacterium w (*M.w*) was selected from a panel of 16 mycobacteria on the basis of its immunological potentials.[7] It is a nonpathogenic, atypical, rapid growing mycobacterium.[8] It has undergone Phase I trials in Calcutta[9] and is currently in Phase III trials in Delhi and large-scale field trials in District Kanpur Dehat of Uttar Pradesh, State of North India. Results on the 1st series of multibacillary patients have been reported and have evidenced some immunotherapeutic benefits of combining this vaccine with standard MDT. The vaccine effectively brought about: 1, rapid BI fall; 2, faster clinical improvement; 3, lepromin conversion; and 4, histological upgrading. Due to a rapid overall improvement, treatment duration in vaccinated patients was shorter and more patients could be released from treatment (RFT) within the stipulated 2 treatment years.[10–13]

This report gives the incidence, frequency and severity of ENL (type 2) reactions in 86 patients who have been followed up for up to 4 years—45 have received MDT + *M.w* vaccine (vaccine group) and 41 of them are included in a group receiving MDT + micronized starch as placebo.

Materials and Methods

Patients inducted in this study form part of the large-scale Phase III immunotherapeutic trials being conducted at the Urban Leprosy Centres (ULCs) of Safdarjung and Dr Ram Manohar Lohia Hospitals of New Delhi.

Patients falling in a, BB, BL and LL spectrum of disease (Ridley–Jopling Scale); b, showing evidence of bacilli in slit-skin smears; c, negative in their Mitsuda reaction to lepromin-A; and d, having histological features of BB, BL or LL type disease are enrolled. Standard MDT as recommended by NLEP of India was given to all those inducted.[14] Half the patients, in addition, received intradermally *M.w* vaccine (containing 1×10^9 killed bacilli per dose as the 1st dose and 5×10^8 killed bacilli as the 2nd and subsequent doses every 3 months up to a maximum of 8 doses). The other half of the patients received a placebo injection of micronized starch at the same time intervals. Allotment of patients into the vaccine and control groups was done in a randomized manner according to a code supplied to the clinician.

Evaluation of reactions

A detailed history of the patient experiencing any previous reactions (type, severity, frequency and duration) was taken at the time of enrollment. A reaction proforma was filled for each reactional episode during the 2 or more years of treatment and subsequent follow-up. This proforma included eliciting a history of fever, joint pains, epistaxis, conjunctivitis, pedal oedema, lymphadenopathy and epididymo-orchitis. Examination of skin for ENL lesions, ulceration or desquamation was looked for. Pain/tenderness of peripheral nerves, recent development of sensory and motor deformities were especially

Table 1. Patients under study

Type of leprosy (No. of patients)	Vaccine group (MDT + *M.w* vaccine)	Control group (MDT + placebo)	Total
BB	8	7	15
BL	14	14	28
LL	23	20	43
Total	45	41	86

elicited. Grading of reaction was as 'mild', 'moderate' or 'severe'.[15] Treatment details during reactional episode were recorded separately on the proforma. Mild reaction was managed with rest and nonsteroidal anti-inflammatory drugs (NSAID). Moderate cases were managed on an outdoor basis on oral steroids and NSAID. Severe cases were hospitalized and oral steroids were given.

Results

Of the 86 patients enrolled in the study, 45 were inducted in the vaccine group and 41 in the control group (Table 1).

A total of 11 patients in the vaccine group had a previous history of Type 2 reaction and 10 of these showed subsequent reactions during the 2 years or more of chemoimmunotherapy; 1 patient with a previous history of 2 reactional episodes before treatment had no ENL during treatment. In the control group, 8 patients had a previous history of ENL. During 2 or more years of treatment with MDT, 12 patients had reactions. Thus, 4 patients with no previous history of ENL had first-time reactions after treatment in this group.

During the course of 2 or more years of follow-up, 20 reactional episodes in 10 (out of 37) BL and LL patients were recorded in the vaccine group (Table 2). The number of episodes were higher in the control group where 29 were seen in 12 (out of 34) BL and LL patients.

With regard to the onset of Type 2 reactions (Table 3), in the vaccine group, reactions were seen throughout 2 or more years, although most occurred within the 1st year (13 out

Table 2. Incidence of reactional episodes during treatment

Group	BL	LL
Vaccine	4 (2/14)	16 (8/23)
Control	5 (2/14)	24 (10/20)

Figures in parentheses give the number of patients experiencing reactional episodes by total number of patients; 11 patients in the vaccine group and 8 patients in the control group had a history of reaction prior to initiation of therapy.

Table 3. Onset of reactional episodes (in months) and their severity

	Group							
	0–3	3–6	6–12	12–24	> 24	Mild	Moderate	Severe
Vaccine	3	4	6	4	3	15	4	1
Control	8	2	3	10	6	15	11	3

Table 4. Frequency of reactional episodes

	Group			
	Once	Twice	Thrice	> Thrice
Vaccine (No. of patients)	3	4	3	—
Control (No. of patients)	3	4	2	3

Table 5. Changes in BI values (mean ± SEM)

Type of disease	Group	No. of patients	Initial	Months			
				6	12	18	24
LL	Vaccine	23	3·90 ± 0·27	2·78 ± 0·25	2·21 ± 0·25	1·35 ± 0·28 ($p < 0·03$)	0·92 ± 0·28 ($p < 0·06$)
	Control	20	3·67 ± 0·25	3·02 ± 0·27	2·59 ± 0·24	2·34 ± 0·27	1·78 ± 0·29
BL	Vaccine	14	2·51 ± 0·29	1·22 ± 0·20	0·53 ± 0·15 ($p < 0·003$)	0·24 ± 0·07 ($p < 0·001$)	0·02 ± 0·01 ($p < 0·003$)
	Control	14	2·02 ± 0·30	1·66 ± 0·26	1·41 ± 0·26	1·06 ± 0·19	0·63 ± 0·20

All statistical analyses were done using analysis of variance. Significant decreases in BI in vaccinated patients were seen in BL and LL types of leprosy. The p values are indicated in parentheses.

of 20); 3 episodes occurred beyond 2 years. In the control group, 13 out of 29 reactional episodes occurred in the 1st year and 16 out of 29 beyond 1 year; 6 episodes were recorded after 2 years.

With reference to severity of reactional episodes, reactions were mild in 15 out of 20 episodes in the vaccine group and 15 out of 29 in the control group; 14 reactions were moderate to severe in the control group (Table 3).

Frequency of reactional episodes in vaccine and control groups were: vaccine, 3 patients (30%) once, 4 (40%) twice and 3 (30%) thrice; and control, 3 (25%) once, 4 (33%) twice, 2 (16·6%) thrice and 3 patients (25%) more than 3 episodes (Table 4).

In the vaccine group 5 patients (2-BL, 3-LL) had neuritis during episodes of ENL. This resulted in a left ulnar claw in a BL patient and a bilateral claw in an LL patient. In

Table 6. Analysis based on 95% Confidence interval

Group	Incidence (%)	Confidence interval (%)
Incidence of reactional episodes		
Vaccine	27	−13·2 to 29·8
Control	35	
Reactions occurring early (within 1st year)		
Vaccine	65	−7·5 to 47·8
Control	44·8	
Reactions being mild		
Vaccine	75	−3 to 49·57
Control	51·7	

the control group neuritis was seen in 6 patients (2-BL, 4-LL); 1 BL patient had a left ulnar claw and facial palsy.

BI CHANGES

Changes in the BI of patients in the study are given in Table 5. The fall in LL patients receiving the vaccine was from 3·90 (±0·27 SEM) to 0·92 (±0·28 SEM) after 2 years of immunochemotherapy, whereas in the control group corresponding values were 3·67 (±0·25 SEM) to 1·78 (±0·29 SEM). In BL type leprosy the fall over 2 years was 2·51 (±0·29 SEM) to 0·02 (±0·01 SEM) in the vaccine group and 2·02 (±0·30 SEM) to 0·63 (±0·20 SEM) in the control group.

Discussion

Erythema nodosum leprosum (ENL) is triggered when there is an abundance of fragmented or granular bacilli in tissues. These 'nonviable' bacillary forms act as antigens and in the presence of precipitating antibodies and complement factors result in formation of immune complexes.[4]

Data regarding the incidence of Type 2 (ENL) reactions with use of MDT is scarce. In 2 studies, MDT seems to have caused no worsening or development of fresh reactions over monotherapy (in a 2-year follow-up).[16,17] In another study in Madras, 62 out of 177 (35%) BL or LL patients showed evidence of Type 2 reactions.[18] Some of the patients in this study showed reactions even up to 60 months of follow-up. In our experience, the incidence of reactions in the control group (receiving MDT alone) BL and LL patients was 12/34 (35·29%), which is quite comparable with reports in the literature. After immunization with *M.w* vaccine, patients had accelerated bacteriological clearance. The fall at the end of 2 years of treatment was statistically significant in both LL ($p < 0{\cdot}06$) and BL ($p < 0{\cdot}003$) vaccine group patients. In fact, the BI after 12 months of treatment in vaccine group BL patients was lower than that achieved by control group patients at 24

months (Table 5). Several earlier reports have also documented a rapid clearance of bacilli from slit-skin smear sites[19,20] and from biopsy tissues[13] in *M.w* vaccinated patients. Some patients with high BI of 5–6 have shown clearance of AFB within 18–24 months.[20] BI fall per 12 treatment months in LL patients in the vaccine group was reported to be 1·84 (±0·18 SEM) compared to 0·98 (±0·11 SEM) in the control group. In BL patients, it was 1·64 (±0·20 SEM) (vaccine group) and 0·63 (±0·14 SEM) (control group).[19] This rapid clearance of AFB from the body may explain: 1, less incidence of reactions in the vaccine *vs* control group (10 patients/20 episodes *vs* 12 patients/29 episodes); and 2, most reactional episodes occurring early in the vaccine group (13 out of 20 in the 1st year (65%), 17 out of 20 by the 2nd year (85%) and only 3 episodes beyond 2 years (15%)). In the control group figures were 13/29 (44·82%) in the 1st year, 23/29 (79·31%) by the 2nd year and 6 episodes beyond 2 years (20·6%). The reactions were also less severe in the vaccine group; 15 of 20 reactions (75%) were mild, 4 (20%) were moderate and only 1 severe (5%). In contrast, patients in the control group had 15 (51·72%) mild, 11 (37%) moderate and 3 (10·3%) severe reactional episodes. Frequency of reactional episodes was quite comparable in the 2 groups. The difference was that in the control group 3 patients (25%) had more than 3 episodes, which was not seen among vaccinated patients. Statistical analysis of data using test of proportions showed insignificant differences between the vaccine and control groups for incidence of reactional episodes ($z = 0{\cdot}7525$), early occurrence of reactions (within the 1st year) ($z = 1{\cdot}39$) and being milder in the vaccinated patients ($z = 1{\cdot}6435$). As can be seen by the *'z'* values the differences were at the margin/border of being significant. One reason for this could be the small sample size.

However, analysis based on a 95% confidence interval[21] brought out distinct differences between the 2 groups more evocatively (Table 6). Confidence intervals indicated that at best the vaccine was a great advantage (29·8; 47·8; 49·57%) and at worst a slight disadvantage (−13·2; −7·5; −3%) (see Table 6).

Immunotherapy with *M. vaccae* in patients with chronic repeated ENL has shown resolution of reaction some 2–3 months later in about half the cases in an on-going study.[22] Using immunotherapy with killed *M. leprae* and live BCG, Convit *et al.*[23] reported that vaccination coincided with the disappearance of ENL lesions in some patients.

When using ICRC vaccine, Deo *et al.*[24] reported that half the vaccinated LL patients, with BI 3–5, developed ENL reactions 2–6 weeks postvaccination. These patients had no previous history of ENL. ENL in these patients, according to the authors, was precipitated by either the presence of appropriate antigens of ICRC bacillus or large quantities of antigens released through breakdown of *M. leprae* upon vaccination.[24] Effects of immunotherapeutic cytokines gamma interferon and interleukin 2 on ENL reactions have not been reported in the literature.

An important observation was that the use of *M.w* vaccine did not precipitate any additional incidence of neuritis or deformity during the course of Type 2 reactions. This has also been evidenced histologically where vaccinated patients did not show evidence of an increase in dermal nerve twig inflammation.[13]

Experiences using immunotherapeutic candidate vaccines, 1, *M. leprae* and BCG, and 2, *M. vaccae* indicate that there is a decrease in incidence of type 2 reactions postvaccination. This is similar to our experience using *M.w* vaccine, where a decrease in incidence, frequency and severity of reactions have been recorded. Contrary to these findings are the results with ICRC vaccine (where half of LL patients with BI 3–5 had

ENL reactions postvaccination). Based on our experience and that of others, it appears that any immunotherapeutic agent capable of inducing rapid bacterial clearance should also secondarily decrease the incidence of Type 2 reactions.

References

[1] Pfaltzgraff RE, Bryceson A. Clinical leprosy. In: *Leprosy*, 1st Ed. Hastings RC (ed), Churchill Livingstone Publishers. 1985, 170–71.

[2] Jopling WH, McDougall AC. In: *Handbook of leprosy*, 4th Ed. Jopling WH, McDougall AC (eds), Oxford: Heinemann Medical Books, 1988.

[3] Ridley DS. Histological classification and the immunological spectrum of leprosy. *Clin Exp Immunol*, 1973; **14:** 541.

[4] Wemambu SN, Turk JL, Waters MFR, Rees RJW. Erythema nodosum leprosum, a clinical manifestation of the Arthus phenomenon. *Lancet*, 1969; **ii:** 933–35.

[5] Modlin RL, Gebhard JF, Trylor CR, Rea TH. In-situ characterisation of T-lymphocyte subsets in the reactional states of leprosy. *Clin Exp Immunol*, 1983; **53:** 17–24.

[6] Van Voorhis WC, Kaplan G, Sarno EN, Horwitz MA, Steinman RM, Levis WR, Nogueira N, Hair LS, Gutas CR, Arrick BA, Cohn Z. The cutaneous infiltrates of leprosy. Cellular characteristics and the predominant T cell phenotypes. *New Eng J Med*, 1982; **307:** 1593–97.

[7] Talwar GP. Towards development of a vaccine against leprosy. *Lepr India*, 1978; **50:** 492–97.

[8] Saxena VK, Singh US, Singh AK. Bacteriological study of a rapidly growing strain of mycobacterium. *Lepr India*, 1978; **50:** 588–96.

[9] Chaudhuri S, Fotedar A, Talwar GP. Lepromin conversion in repeatedly lepromin negative BL/LL patients after immunisation with autoclaved *Mycobacterium w*. *Int J Lepr*, 1983; **51:** 159–68.

[10] Talwar GP, Zaheer SA, Mukherjee R, Walia R, Misra RS, Sharma AK, Kar HK, Mukherjee A, Parida SK, Suresh NR, Nair SK, Pandey RM. Immunotherapeutic effects of a vaccine based on a saprophytic cultivable mycobacterium, *Mycobacterium w* in multibacillary leprosy patients. *Vaccine*, 1990; **8:** 121–29.

[11] Talwar GP, Mukherjee R, Zaheer SA, Sharma AK, Kar HK, Misra RS, Mukherjee A. Present approaches to immunotherapy and immunoprophylaxis in leprosy. In: *Progress in Vaccinology*, Vol. II. Talwar GP (ed), New York, Springer Verlag, 1989, 301–11.

[12] Talwar GP, Zaheer SA, Suresh NR, Parida SK, Mukherjee R, Singh IG, Sharma AK, Kar HK, Misra RS, Mukherjee A. Immunotherapeutic trials with a candidate anti-leprosy vaccine based on *Mycobacterium w*. *Trop Med Parasitol*, 1990; **41:** 369–70.

[13] Mukherjee A, Zaheer SA, Sharma AK, Misra RS, Kar HK, Mukherjee R, Talwar GP. Histopathological monitoring of immunotherapeutic trials with *Mycobacterium w*. *Int J Lepr*, 1992; **60:** 28–35.

[14] Indian Association of Leprologists (IAL). Consensus treatment regimens in leprosy and the problems of drug delivery. *Ind J Lepr*, 1984; **56:** 158–59.

[15] Waters MFR. Treatment of reactions in leprosy. *Lepr Rev*, 1974; **46:** 337.

[16] Katoch K, Ramu G, Ramanathan U, Sengupta U, Sreevatsa. Follow up of BL/LL patients on a slightly modified WHO regimen of multi drug therapy. *Ind J Lepr*, 1987; **59:** 36–43.

[17] Kaur S, Sharma VK, Kumar E, Singh M, Kaur I. Multidrug therapy in bacilliferous leprosy—two years experience. *Ind J Lepr*, 1985; **57:** 483–90.

[18] Thomas A, Balakrishnan A, Muthiyalusamy N, Prabhakar R, Tripathi SP, Christian M, Somasundaram PR. Controlled clinical trial of 2 multidrug regimens with and without rifampicin in highly bacilliferous BL/LL South Indian patients. A five year report. *Int J Lepr*, 1990; **58:** 273–80.

[19] Zaheer SA, Mukherjee R, Ramkumar B, Misra RS, Sharma AK, Kar HK, Kaur H, Nair SK, Mukherjee A, Talwar GP. Shortening of treatment period in patients with multibacillary leprosy by combining immunotherapy with chemotherapy. Combined multidrug and *Mycobacterium w* vaccine therapy in patients with multibacillary leprosy. *J. Infect. Dis.* in press.

[20] Zaheer SA, Suresh NR, Kar HK, Sharma AK, Mukherjee A, Mukherjee R, Talwar GP. Immunological upgrading with combined immunotherapy and chemotherapy in an LL patient. A case report. *Lepr Rev*, 1991; **61:** 297–302.

[21] Radhakrishna S, Murthy BN, Nair NGK, Jayabal P, Jayasri R. Confidence intervals in medical research. *Ind J Med Res*, 1992; **96:** 199–205.

[22] Stanford JL, Rook GAW, Bahr GM, Dowlati Y, Ganpati R, Ghazi Saidi K, Lucas S, Ramu G, Torres P, Ho Minh Ly, Austey N. *Mycobacterium vaccae* in immunoprophylaxis and immunotherapy of leprosy and tuberculosis. *Vaccine*, 1990; **8:** 525–30.

[23] Convit J, Aranzazu N, Ulrich M, Pinardi ME, Reyes O, Alvarado J. Immunotherapy with a mixture of *Mycobacterium leprae* and BCG in different forms of leprosy and in Mitsuda negative contacts. *Int J Lepr*, 1982; **50:** 415–24.

[24] Deo MG, Bapat CV, Chulawala RG, Bhatki WS. Potential anti-leprosy vaccine from killed ICRC bacilli—a clinico-pathological study. *Ind J Med Res*, 1981; **74:** 164–77.

L'immunothérapie par le vaccin *Mycobacterium w* réduit l'incidence et la sévérité des réactions de type 2 (ENL)

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Résumé L'immunothérapie par le vaccin *Mycobacterium w* (*M.w*) a été administrée à 45 patients atteints de lèpre multibacillaire; 41 patients classés de façon similaire ont servi de témoins. Tous les patients ont reçu la thérapeutique multidrogue standard (MDT). L'incidence, la sévérité et la fréquence des épisodes réactionnels de type 2 (ENL) ont été suivis dans ces 2 groupes pendant une période qui a duré jusqu'à 4 ans. On a observé des réactions chez un plus petit nombre de patients BL et LL vaccinés (10/37) que dans le groupe témoin (12/24). Au total, 20 épisodes ont été enregistrés dans le groupe des vaccinés contre 29 dans le groupe des témoins, 75% des réactions ont été faibles dans le groupe des vaccinés et 51,72% ont été faibles dans celui des témoins, et 3 patients du groupe des témoins ont eu plus de 3 épisodes réactionnels, ce que l'on n'a observé chez aucun des patients vaccinés. Aucune incidence supplémentaire de névrite n'a été observée parmi les individus vaccinés au cours des épisodes réactionnels.

La inmunoterapia con vacuna *Mycobacterium-w* reduce la incidencia y severidad de las reacciones (ENL) de tipo 2

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Resumen Se administró inmunoterapia con vacuna *Mycobacterium-w* (*M.w*) a 45 pacientes con lepra multibacilar (MB); 41 pacientes con clasificaciones similares actuaron de controles. Todos los pacientes recibieron la terapia multidroga (MDT) normal. Se controló la incidencia, severidad y frecuencia de episodios reaccionales (ENL) de tipo 2 en ambos grupos en un estudio posterior de hasta 4 años. Se observaron reacciones en menos pacientes vacunados BL y LL (10/37) que en el grupo de control (12/34). Se registraron un total de 20 episodios en el grupo vacunado comparado con 29 en el grupo de control. 75% de las reacciones eran leves en el grupo vacunado, y 51, 72% eran leves en el grupo de control, y 3 pacientes en el grupo de control tuvieron más de 3 episodios reaccionales. No se observó esto en ninguno de los pacientes vacunados. No se observó una incidencia adicional de neuritis entre los individuos vacunados durante los episodios reaccionales.

Lepr Rev (1993) **64,** 15–24

Serological response of leprosy patients to *Mycobacterium leprae* specific and mycobacteria specific antigens: possibility of using these assays in combinations

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Accepted for publication 23 October 1992

Summary The serological response of 147 leprosy patients to 3 mycobacterial antigens, PGL-I, 35 kDa (*Mycobacterium leprae*-specific) and LAM (which is a common mycobacterial antigen) were analysed. A stronger serological response was seen amongst the MB patients than the PB patients in all the assays. The 3 antibody levels correlated positively with each other in both MB and PB cases. An overlap of seropositivity was seen between anti-PGL-I and anti-LAM ($p > 0{\cdot}05$). A progressive increase in seropositivity and a significant difference of absorbance or titre in antibody levels in all 3 assays over increasing grades of BI were seen in the MB patients ($p < 0{\cdot}05$). A signficant difference in seropositivity between untreated and treated groups of patients was observed for anti PGL-I ($p < 0{\cdot}05$) and antiLAM ($p < 0{\cdot}01$) antibodies. The sensitivity, specificity and efficiency of antiPGL-I (50%; 99%; 70%), antiLAM (43%; 95%; 64%) and anti35 kDa (66%; 100%; 80%) assays taken individually were less than that of combinations of antiPGL-I/anti-35 kDa (74%; 99%; 84%) or antiPGL-I/anti-35 kDa/antiLAM (80%; 94%; 86%). The difference in the efficiency of both sets of combination of assays were not statistically significant ($p > 0{\cdot}05$).

Introduction

In recent years the serological response of leprosy patients to different mycobacterial antigens has been studied. Species-specific capsular phenolic glycolipid-I (PGL-I),[1,2] protein antigens like 35 kDa,[3] 36 kDa[4] and 18 kDa[5] of *Mycobacterium leprae* and common mycobacterial antigens like lipoarabinomannan (LAM),[6] a potent B cell stimulator, have been used in enzyme-immunoassays to study serological response

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amongst leprosy patients. Strong serological responses to these antigens have been shown in the lepromatous (LL) pole of the spectrum and a weaker response in the tuberculoid (TT) pole. These studies were carried out in a mixed group of treated and untreated[2,4,7–12] and also selectively in untreated patients[13] of multibacillary (MB) leprosy. Such studies have also been done in paucibacillary (PB) leprosy.[3,7,14–17] Here, a cross-sectional study involving both MB and PB leprosy patients has been carried out to analyse: (a) the serological response of both MB and PB patients to 2 *M. leprae* specific antigens (PGL-I and 35-kDa) and a common mycobacterial antigen (LAM); (b) the correlation of the antibody levels with the bacterial index (BI) in MB patients; (c) the association of the antibody levels with treatment status; (d) the efficiency of 3 assays individually and in combination.

Materials and methods

A total of 147 leprosy patients attending CLT & RI were included in this study, comprising of 91 lepromatous (LL), 10 borderline lepromatous (BL), 26 tuberculoid–borderline (TT–BT) and 20 indeterminate (IND) leprosy cases, all who had been clinically diagnosed. They consisted of both untreated and treated patients. In addition, 100 healthy subjects working in different departments of CLT & RI were included in the study as controls. Sera from all patients and controls were collected and stored at $-20°C$ until used.

A routine slit-skin smear was done for all leprosy patients and the average BI was calculated according to the Ridley's scale.

SEROLOGICAL ASSAYS

AntiPGL-I ELISA

IgM antiPGL-I antibodies were measured by using the procedure reported earlier.[18] Briefly D-BSA antigen and BSA supplied by IMMLEP/WHO, diluted in carbonate-bicarbonate buffer (CBCB) were coated in duplicate in a 96-well flat bottom microtitre plate (Dynatec Micro-ELISA system, Germany). Sera at 1 : 300 dilution were added to both antigen and BSA coated wells. After incubation, antihuman IgM peroxidase conjugate (DAKO, Denmark) was added at 1 : 2000 dilution. Colour was developed with *o*-phenylenediamine (SIGMA, USA) with H_2O_2 in citrate-phosphate buffer, pH 5·0. The reaction was stopped with 5 NH_2SO_4. The plates were read at 492 nm in an ELISA reader (MR 600 micro plate reader, Dynatec). Samples with a difference in the mean absorbance between the antigen and BSA coated wells equal to or more than 0·200 OD were considered positive.

Serum Antibody Competition Test—ELISA (SACT-E)

Antibodies to the *M. leprae* specific 35-kDa protein were detected by the protocol of J. Ivanyi, using peroxidase conjugated ML-04 monoclonal antibody (kindly supplied by J. Ivanyi, MRC, the Royal Postgraduate Medical School, London). Microtitre plates (Immulon, M129 B Dynatec) were coated with 10 μg/ml (50 μl/well) of *M. leprae* soluble

extract (kindly supplied by R. J. W. Rees, IMMLEP *M. leprae* bank) in phosphate-buffered saline (PBS), pH 7·2, and incubated overnight at 4°C. After washing once with Tris-buffered saline, pH 7·4, containing Tween 20 (TBST), blocking was done with 150 μl/well of 1% skimmed milk powder in TBST (TBSTM). Sera in 10-fold dilution of 1:10, 1:100 and 1:1000 in TBSTM (25 μl/well) were added in duplicate and incubated for 1 hr. After removing the sera, 25 μl/well of appropriately diluted peroxidase conjugated ML-04 was added and incubated for 2 hr. After washing with TBST, colour was developed with *o*-phenylenediamine substrate solution (50 μl/well for 20 min). The reaction was stopped with $5NH_2SO_4$ and reading was done at 492 nm in an ELISA reader. Positive control wells incubated with ML-04 conjugate without inhibiting sera were included in all the plates.

The dilution of the sera causing 50% inhibition of binding of ML-04 to the antigen (ID_{50}) was calculated. Samples with ID_{50} titres equal to or more than 10 were considered SACT-E positive. All the 100 control sera tested were SACT-E negative.

AntiLAM ELISA

IgG antiLAM antibodies were measured by coating with LAM from *M. tuberculosis* H37Ra (kindly supplied by D. Chatterjee, Colorado State University, Fort Collins, Colorado, USA) at a concentration of 1 μg/ml, diluted in CBCB, pH 9·6 in duplicate. Control wells were coated with buffer (CBCB) alone. Sera at a dilution of 1:1000 were added (50 μl/well) to both antigen and control wells. After incubation for 2 hr, antihuman IgG peroxidase conjugate (DAKO, Denmark) at 1:6000 dilution was added. *o*-phenylenediamine with H_2O_2 in phosphate citrate buffer, pH 5·0, was used as a substrate solution. The reaction was stopped with 5 NH_2SO_4 and plates were read at 492 nm in an ELISA reader. Samples with a difference in the mean absorbance between the antigen and control wells equal to or more than 0·500 OD (mean + 3 standard deviations of 100 controls) were considered positive.

STATISTICAL ANALYSIS

The Mantel–Haenzsel Chi-squared method (cases, control as strata) was used to study the significance of differences between the antibody assays. The coefficients of correlation among 3 assays and between each assay and BI in individual patients were determined by Pearson's correlation coefficient. The Mann–Whitney *U* test was done for the differences in the distribution of absorbances or titre between the different BI groups. The Krushkal–Wallis test was applied when more than 2 groups were compared. The significance of differences of seropositivity between MB and PB groups and between smear positive and smear negative MB cases were derived from 2×2 contingency tables by applying Yate's corrected Chi-squared test. Probability (p) values $< 0{\cdot}05$ were considered as significant.

All the statistical tests were carried out using SSPS/PC+ and EPI-INFO software packages.

Results

SEROLOGICAL RESPONSE

The serological response among the MB group of patients was found to be uniformly

Table 1. Serological response of both MB and PB leprosy patients to 3 mycobacterial antigens.

	Percentage of seropositive (absolute number in parentheses)			
	PGL	LAM	35 kDa	Any of 3 antibodies
Patients (N)				
MB (101)	58 (59)	44 (44)	90 (91)	93 (94)
LL (50) BI (+)	74 (37)	52 (26)	100 (50)	100 (50)
LL (41) BI (−)	34 (14)	24 (10)	76 (31)	83 (34)
BL (10) BI (+)	80 (08)	80 (08)	100 (10)	100 (10)
PB (46)	33 (15)	41 (19)	13 (06)	52 (24)
TT-BT (26)	27 (07)	35 (09)	12 (03)	46 (12)
IND (20)	40 (08)	50 (10)	15 (03)	60 (12)
Control (100)	1 (01)	5 (05)	0 (0)	6 (06)
Sensitivity	50	43	66	80
Specificity	99	95	100	94

Significant difference of seropositivity of IgM antiPGL-I and anti35 kDa antibodies between MB and PB patients ($p < 0{\cdot}01$).

Significant difference of seropositivity of IgM antiPGL-I and IgG antiLAM and anti35 kDa antibodies between smear positive and smear negative MB cases ($p < 0{\cdot}001$).

Significant difference of seropositivity between antiPGL-1 and 35 kDa in total ($p < 0{\cdot}05$).

No significant difference of seropositivity between antiPGL-1 and anti-LAM in total ($p > 0{\cdot}05$).

higher than on the PB group of patients (Table 1). In MB cases, 58% had IgM antiPGL antibodies, 44% antiLAM antibodies and 90% anti35 kDa antibodies; 93% of patients in the MB group had any of the 3 antibodies. In the PB cases, 33% had antiPGL antibodies, 41% antiLAM antibodies and 13% anti35 kDa antibodies; 52% of patients in the PB group had any of the 3 antibodies. In the MB group, smear positive patients had a higher percentage of seropositivity (antiPGL-I, 75%; antiLAM, 57%; anti35 kDa, 100%) compared with smear negative (antiPGL-I, 34%; antiLAM, 24%; anti35 kDa, 76%) patients. In general, the 35 kDa antigen was found to elicit a serological response in a higher proportion of different types of the MB patients compared to the other 2 antigens. Within the PB group, apparently a higher percentage (antiPGL-I, 40%; antiLAM, 50%; anti35 kDa, 15%) of IND type patients showed a serological response to all the 3 antigens compared to the TT–BT patients (antiPGL-I, 27%; antiLAM, 35%; anti35 kDa, 12%).

Out of 100 controls employed in the study 1% had antiPGL-I antibodies, 5% antiLAM antibodies and none had anti35 kDa antibodies.

ASSOCIATION WITH BI

Of the 101 MB cases studied, 60 were smear positive with a BI ranging from 0·16 to 3·67.

Table 2. Relationship between serological responses to 3 mycobacterial antigens and BI in MB leprosy patients (% seropositive (mean absorbance/titre)).

Bacterial index	No. patients	PGL	LAM	35 kDa
Negative	41	34% (0·462)	24% (0·855)	76% (174·5)
<1	20	65%* (0·622)	45%* (0·913)	100%* (223·9)
$>=1$ to <2	21	76%* (0·514)	52%* (0·946)	100%* (284·4)
$>=2$	19	84%* (0·579)	74%* (1·032)	100%* (673·6)

* Significant differences in the distribution of absorbance (or) titres of antibodies with BI positive group compared to BI negative group (Mann–Whitney, $p<0·05$).

The increase in the absorbances (or) titres over the range of BI was significant for all the 3 antibody assays ($p<0·001$) by Krushkal–Wallis analysis.

All the 3 assays showed progressive increase of seropositivity with an increase in BI. Such a trend was also observed in mean antibody titres (Table 2). All the 3 levels of the antibodies positively correlated with BI (anti35 kDa *vs* BI, $r=0·4638$, $p<0·001$; antiPGL-I *vs* BI, $r=0·3119$, $p<0·01$; and antiLAM *vs* BI, $r=0·3689$, $p<0·001$).

ASSOCIATION WITH THE TREATMENT STATUS

The multibacillary group consisted of 19 untreated and 82 treated cases. Amongst untreated cases, 84% had antiPGL-I antibodies, 88% antiLAM antibodies and 100% anti35 kDa antibodies. Amongst treated cases 52% had antiPGL-I antibodies, 38% antiLAM antibodies and 88% anti35 kDa antibodies (Table 3). The paucibacillary group consisted of 30 untreated and 16 treated cases. Amongst untreated cases 43% had antiPGL-I antibodies, 57% antiLAM antibodies and 13% anti35 kDa antibodies. Amongst treated cases 13% had antiPGL-I antibodies, and the same percentage of cases were also positive for the other 2 assays. Though the untreated cases had a higher percentage of seropositivity in all the 3 assays than did the treated, the differences were significant for antiPGL-I ($p<0·05$) and antiLAM ($p<0.01$) assays but not for the anti35kDa assay ($p>0·05$).

CORRELATION BETWEEN THE ANTIBODY ASSAYS

In the MB group, all the 3 assays positively correlated with each other. There was a strong correlation between antiPGL-I and antiLAM antibodies ($r=0·5048$, $p<0·001$) and also between antiPGL-I and anti35kDa antibodies ($r=0·3917$, $p<0·001$). A moderate correlation was seen between antiLAM and anti-35kDa antibodies ($r=0·3172$, $p<0·01$).

In the PB group, a moderate positive correlation between the assays was observed (antiPGL-I vs anti-35 kDa, $r=0·4385$, $p<0·01$; antiPGL-I *vs* antiLAM, $r=0·3495$, $p<0·05$ and antiLAM *vs* anti35 kDa, $r=0·4183$, $p<0·01$).

Multibacillary patients with antiPGL-I antibodies were also more likely to have antiLAM antibodies ($p>0·05$), but such an overlap was not seen between anti35 kDa and

Table 3. Serological responses to 3 mycobacterial antigens in untreated and treated groups of patients.

Patients	Treatment status	PGL	LAM	35 kDa
MB (101)	UNT (19)	84% (16)	88% (14)	100% (19)
	TRT (82)	52%* (43)	38%† (31)	88%‡ (72)
PB (46)	UNT (30)	43% (13)	57% (17)	13% (04)
	TRT (16)	13% (02)	13% (02)	13% (02)

* Differences in seropositivity of antiPGL between treated and untreated groups ($p < 0{\cdot}05$).

† Differences in seropositivity of antiLAM between treated and untreated groups ($p < 0{\cdot}01$).

‡ Differences in seropositivity of anti35 kDa between treated and untreated groups ($p > 0{\cdot}05$).

UNT, untreated; TRT, Treated.

the other 2 antibodies. In the PB group as well, an overlap of seropositivity was only seen between anti-PGL-I and anti-LAM antibodies ($p > 0{\cdot}05$). The seropositivity for any of the antibodies, when taken in combinations like antiPGL-I/antiLAM, antiPGL-I/anti35 kDa, or antiPGL-I/anti35 kDa/antiLAM, showed sensitivity and specificity higher than the corresponding assays taken individually (Figure 1). Thus, when the seropositivity for any of the 2 assays using the *M. leprae* specific antigens, namely, PGL-I and 35 kDa, were taken together, the combined sensitivity (74%) and specificity (99%), and thereby the

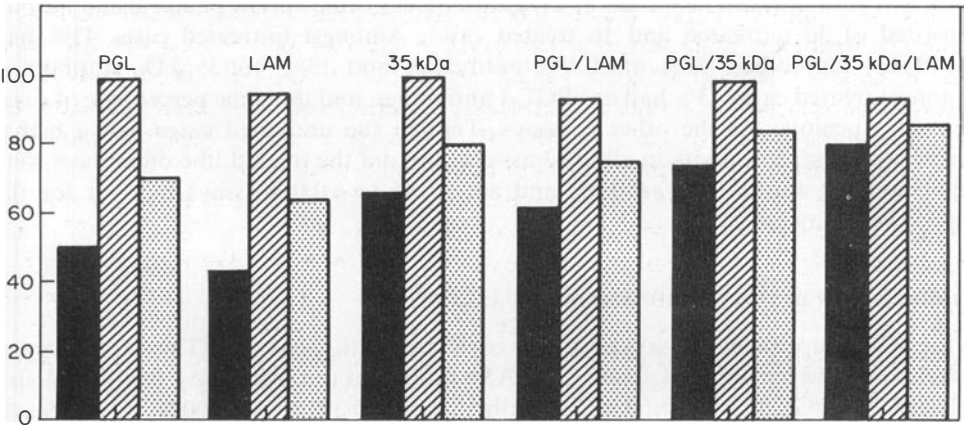

Figure 1. Sensitivity, specificity and efficiency of the assays, alone and in combinations. ■, sensitivity; ▨, specificity; ▩, efficiency.* Difference of seropositivity between combinations of antiPGL-I/anti-35 kDa and antiPGL-I/antiLAM ($p > 0{\cdot}05$); difference of seropositivity between combinations of antiPGL-I/anti-LAM and antiPGL-I/anti-LAM/anti35 kDa ($p < 0{\cdot}01$); difference of seropositivity between combinations of antiPGL-I/anti-35 kDa and antiPGL-I/antiLAM/anti35 kDa ($p > 0{\cdot}05$).

* Efficiency (index of usefulness) $= \dfrac{\text{No. of true positives} + \text{No. of true negatives}}{\text{Total no. of subjects studied}}$

efficiency (84%), was higher. Similarly, when the seropositivity for any of the 3 assays, using both the species specific (PGL-I and 35 kDa) and the genus specific (LAM) antigens was taken together, the combined sensitivity (80%) and efficiency (86%) was even higher, though there was a decline in specificity (94%). Yet the utility of both the sets of combination assays was comparable ($p > 0{\cdot}05$).

Discussion

Many mycobacteria-specific and *M. leprae*-specific antibodies have been demonstrated in the sera of leprosy patients. Though they are not known to be protective, their presence in the sera of leprosy patients may be used as markers of bacillary load, monitors of prognosis of the disease and predictors of occurrence of future relapse or reactions. Several studies have been done against this background.[7–14,16,17,19] In the present study, a cross-sectional analysis of 147 leprosy patients showed a stronger serological response in the MB group of patients than the PB group to all the 3 antibodies, but significantly to both *M. leprae*-specific antigens (PGL-I and 35-kDa). The response to 35 kDa antigen was higher in both smear-positive and smear-negative MB patients, with sensitivity being greater than in the other 2 assays. These findings are consistent with the observations of other researchers.[12,13,16,17,19] In the PB group the sensitivity of 35 kDa was less, though others have shown higher sensitivity.[16,17] However, all the 3 assays, when individually analysed, had a higher specificity with considerably lower sensitivity.

All the 3 antibodies studied correlated positively with each other, both in the MB and the PB cases. Further, an overlapping of positivity was seen only between antiPGL-I and antiLAM antibodies, but not between anti35 kDa and other antibodies. Thus, this specific 35 kDa epitope of *M. leprae* was observed to pick up, at least in the MB group, those leprosy patients who were negative for antibodies against the other 2 antigens.

All the 3 antibody assays showed a progressive increase of seropositivity and mean antibody titres over the increasing grades of BI, all the 3 antibodies positively correlated with BI as well. This correlation was highly significant for anti-35 kDa antibody. Thus, this positive association of antibody titres with bacterial load can be used to monitor the prognosis of patients in conjunction with BI. Hence, these assays would be complementary to BI in detecting additional cases of multibacillary patients.[13]

Both in the MB and the PB groups, the seropositivity among untreated patients was higher than in the treated patients. This difference was significant for antiPGL-I and antiLAM antibodies only. But a relatively steep fall in the anti35 kDa antibody titre with least individual variability on treatment has been observed by others.[19] Thus the antibody assays would seem to supplement the clinical evaluation in assessing the prognosis of patients on chemotherapy. Further prospective studies may throw some more light on this observation.

Amongst the PB group, 'IND' type patients showed apparently high seropositivity for all the 3 antibodies in comparison to 'TT–BT' type. This might suggest that most 'IND' leprosy patients are likely to progress to the MB type of leprosy, as has been observed by other reporters.[21]

An assay using lipoarabinomannan of *M. tuberculosis* was used in this study because of its similarity with the LAM of *M. leprae*.[22] Despite not being species-specific this antigen appears to be useful in the serology of leprosy. The sensitivity of this assay is

comparable to that of antiPGL-I assay. Further, this assay could differentiate between smear positive and smear negative MB cases and also between treated and untreated cases like antiPGL-I assay. AntiLAM antibodies correlated positively with *M. leprae*-specific antibodies in MB and PB cases. AntiLAM assay, when combined with other assays, increased the efficiency in both antiPGL-I/antiLAM and antiPGL-I/antiLAM/anti35 kDa combinations. Hence the value of antiLAM assay in leprosy serology.

Thus this analysis on the serological responses of leprosy patients to *M. leprae*-specific (PGL-I and 35 kDa) and a genus specific antigen (LAM) revealed that these antibody assays are complementary to clinical evaluation of leprosy patients. This was evidenced by a strong immunological response amongst leprosy patients to the 3 antigens, significant correlation with BI and with the treatment status of the patients. The assays, though individually highly specific, were less sensitive. This could be compensated by analysing the seropositivity for any of 2 *M. leprae*-specific antibodies (antiPGL-I/anti35 kDa) or any of the 3 antibodies (antiPGL-I/anti35 kDa/antiLAM) in combinations. In this way we obtain an improved application of the serological assays in the management of leprosy patients, until an antigen which is highly sensitive in detecting both MB and PB cases equally is developed.

Acknowledgment

We thank IMMLEP/WHO for the supply of D-BSA antigen; Dr R. J. W. Rees for the provision of *M. leprae* soluble extract through IMMLEP/WHO/UNDP/World Bank Tropical Disease Research Programme; Professor J. Ivanyi for providing ML-04 conjugate; and Dr D. Chatterjee for supplying LAM antigen. We give sincere thanks to Mr L. Rathinavel and Mr K. Kuberan, Laboratory Division, CLT & RI, for their dedicated technical assistance, and we thank Dr P. Krishnamoorthy, Epidemiology and Statistics Division, CLT & RI for the assistance in statistical analysis and Dr N. Elangeswaran, Laboratory Division, Dr A. V. Paul, Clinical Division and Dr P. S. Rao, Director-In-Charge of CLT & RI for their encouragement.

References

[1] Young DB, Buchanan TM. A serological test for leprosy with a glycolipid specific for *Mycobacterium leprae*. *Science*, 1983; **221:** 1057.

[2] Brett SJ, Draper P, Payne SN, Rees RJW. Serological activity of a characteristic phenolic glycolipid from *M. leprae* in sera from patients with leprosy and tuberculosis. *Clin Exp Immunol*, 1983; **52:** 271–279.

[3] Sinha S, Sengupta U, Rumu G, Ivanyi J. Serological survey of leprosy and control subjects by a monoclonal antibody based immunoassay. *Int J Lepr*, 1985; **53:** 33–38.

[4] Klatser PR, de Wit MYL, Kolk AHJ. An ELISA-inhibition test using monoclonal antibody for serology of leprosy. *Clin Exp Immunol*, 1985; **58:** 468–473.

[5] Britton WJ, Hellqvist L, Basten A, Raison RL. *Mycobacterium-leprae* antigens involved in human immune responses. 1. Identification of four antigens by monoclonal antibodies. *J Immunol*, 1985; **135:** 4171–4177.

[6] Miller RA, Dissanayake S, Buchanan TM. Development of an enzyme-linked immunosorbent assay using arabinomannan from *Mycobacterium smegmatis*: A potentially useful screening test for the diagnosis of incubating leprosy. *Am J Trop Med*, 1983; **32:** 555–564.

[7] Bach MA, Wallach D, Flageul B, Hoffenbach A, Cottenot F. Antibodies to phenolic glycolipid-I and to whole *Mycobacterium leprae* in leprosy patients; evolution during therapy. *Int J Lepr*, 1986; **54:** 256–267.

[8] Cho SN, Yanagihara DL, Hunter SW, Gelber RH, Brennan PJ. Serological specificity of phenolic glycolipid-I from *Mycobacterium leprae* and use in serodiagnosis of leprosy. *Inf Immun*, 1983; **41:** 1077–1083.

[9] Levis WR, Meeker HC, Schuller-Levis GB, Sersen E, Brennan PJ, Fried P. Mycobacterial carbohydrate antigens for serological testing of patients with leprosy. *J. Infect Dis* 1987; **56:** 763–769.
[10] Lyons NF, Shannon EJ, Ellis BPB, Naffs B. Association of IgG and IgM antibodies to phenolic glycolipid antigen of *M. leprae* with disease parameters in multibacillary leprosy patients. *Lepr Rev*, 1988; **59:** 45–52.
[11] Meeker HC, Levis WR, Sersen E, Schuller-Levis G, Brennan PJ, Buchannan TM. ELISA detection of IgM antibodies against phenolic glycolipid-I in the management of leprosy, a comparison between laboratories. *Int J Lep* 1986; **54:** 530–539.
[12] Mwatha J, Moreno C, Sengupta U, Sinha S, Ivanyi J. A comparative evaluation of serological assay of lepromatous leprosy. *Lepr Rev*, 1988; **59:** 195–199.
[13] Roche PW, Britton WJ, Failbus SS, Williams D, Pradhan HM, Theuvenet WJ. Operational value of serological measurement in multibacillary patients. Clinical and bacteriological correlates of antibody responses. *Int J Lep,* 1990; **58:** 480–490.
[14] Touw JML, Diepen TW, Harboe M, Belehu A. Relationship between anti-*mycobacterium leprae* antibody activity and clinical features in borderline tuberculoid (BT) leprosy. *Int J Lep,* 1983; **51(3):** 305–311.
[15] Harboe M, Closs O, Reiton LJ, Draper P. Demonstration of antibodies reacting with different determinants on *Mycobacterium leprae* antigen 7. *Int J Lep,* 1981; **49:** 147–158.
[16] Roche PW, Britton WJ, Failbus SS, Theuvent WJ, Adiga RB. Heterogeneity of serological responses in paucibacillary leprosy–differential responses to protein and carbohydrate antigens and correlation with clinical parameters. *Int J Lep,* 1990; **58:** 319–327.
[17] Chaturvedi V, Sinha S, Giridhar BK, Katoch K, Bhatia AS, Sengupta U. Association of mycobacteria specific and *Mycobacterium leprae* specific antibody levels with clinical activity in tuberculoid leprosy; A comparative study of three serological enzyme immunoassays. *Lep Rev*, 1991; **62:** 122–133.
[18] Dhandayuthapani S, Anandan D, Vasanthi P, Bhatia VN. Use of eluates of filter paper blood spots in ELISA for the serodiagnosis of leprosy. *Ind J Med Res*, 1989; May: 150.
[19] Chaturvedi V, Sinha S, Giridhar BK, Sengupta U. On value of sequential serology with a mycobacterium leprae-specific antibody competition ELISA in monitoring leprosy chemotherapy. *Int J Lep,* 1991; **59:** 32–40.
[20] Klatser PR, de Wit MYL, Fajardo TT, Cellona RV, Abalos RM, de la Cruz EC, Madarang MG, Hirsch DS, Douglas JT. Evaluation of *Mycobacterium leprae* antigens in the monitoring of a dapsone-based chemotherapy of previously untreated lepromatous patients in Cebu, Philippines. *Lep Rev*, 1989; **60:** 178–186.
[21] Takhashi MD, Andrade Jr HF, Wakamatsu H, Siqueira S, de Britto T. Indeterminate leprosy; Histopathological and histochemical predictive parameters involved in its possible change to paucibacillary (or) multibacillary leprosy. *Int J Lep,* 1991; **59:** 12–19.
[22] Gaylord H, Brennan PJ, Leprosy and leprae bacillus; present development in characterisation of antigens and immunology of the disease. *Ann Rev Microbial*, 1987; **41:** 645–675.

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Réponse sérologique des patients lépreux aux antigènes spécifiques de *mycobacterium leprae* et spécifiques des mycobactéries: possibilité d'utiliser ces essais en association

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Résumé Nous avons analysé la réponse sérologique de 147 patients lépreux à 3 antigènes mycobactériens, PGL-I, 35 kDA (spécifique de *Mycobacterium leprae*) et LAM (qui est un antigène mycobactérien commun). Une réponse plus forte a été observée parmi les patients MB que parmi les patients PB dans tous les essais. Les taux des 3 anticorps étaient en corrélation positive entre eux à la fois dans les cas MB et PB. Une séropositivité croisée a été observée entre anti-PLG-I et anti-LAM [$p > 0{,}05$]. Une augmentation progressive de la séropositivité et une différence significative entre l'absorption ou le titre des taux d'anticorps dans les 3 essais sur des degrés croissants de BI ont été observés chez les patients MB ($p < 0{,}05$). Une différence significative de la séropositivité entre les groupes de patients non-traités et traités a été observée avec les anticorps anti-PLG-I ($p < 0{,}05$) et anti-LAM ($p < 0{,}01$). La sensibilité, spécificité et efficacité des essais avec anti-PGL-I (50%; 99%; 70%), anti-LAM (43%; 95%; 64%) et anti-35 kDA (66%; 100%; 80%) pris séparément étaient inférieures à celles des associations anti-PLG-I/anti-35 kDA (74%; 99%; 84%) ou anti-PLG-I/anti-35 kDa/anti-LAM (80%; 94%; 86%). La différence entre l'efficacité des deux séries d'associations d'essais n'était pas statistiquement significative ($p > 0{,}05$).

La respuesta serológica de los pacientes leprosos a antigenos específicos para *Mycobacterium leprae* y Micobacterias: la posibilidad de usar estos ensayos en combinaciones

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Resumen Se analizaron las respuestas serológicas de 147 pacientes leprosos a 3 antigenos micobacterianos, PGL-I, 35 kDa (específico a *Mycobacterium leprae*) y LAM, un antigeno micobacteriano común. Se observó una respuesta serológica más fuerte entre los pacientes MB que entre los PB, en todos los ensayos. Los tres niveles de anticuerpo correlacionaban positivamente entre sí, tanto en los casos MB como los PB. Se observó un traslapo en los resultados de seropositividad entre anti-GPL-I y anti-LAM ($p > 0{,}05$). Se observó un aumento progresivo de seropositividad y una diferencia significativa de absorbancia o titulación de los niveles de anticuerpo en todos los 3 ensayos con crecientes tipos de BI en los pacientes MB ($p < 0{,}05$). Se observó una diferencia significativa de seropositividad entre los grupos de pacientes sin tratar y tratados con anticuerpos anti-PGL-I ($p < 0{,}05$) y anti-LAM ($p < 0{,}01$). La sensibilidad, especificidad y eficiencia de los ensayos anti-PGL-I (50%; 99%; 70%), anti-LAM (43%; 95%; 64%) y anti-35 kDa (66%; 100%; 80%) tomados individualmente eran menos que las combinaciones de anti-GPL-I/anti-35 kDa (74%; 99%; 84%) o anti-GPL-I/anti-35 kDa/anti-LAM (80%; 94%; 86%). La diferencia de eficiencia entre ambos juegos de combinación de ensayos no era significativa ($p > 0{,}05$).

Lepr Rev (1993) **64,** 25–36

Long-term active surveillance of leprosy suspects —what are the likely returns?

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Accepted for publication 17 September 1992

Summary Data are presented from the Karonga District in Northern Malawi on the long-term follow up of 277 leprosy suspects who were not given antileprosy treatment or kept on active surveillance. Individuals who were started on antileprosy treatment within a year after leprosy was first suspected, usually on the basis of histopathology results, are excluded from this analysis, because their active surveillance would not usually cause an organizational or financial problem for leprosy control projects. After an average follow-up period of 4·5 years 35 of the 277 suspects included in the analysis (13%) were diagnosed with what we consider to be 'unequivocal' leprosy, and 3 of the 35 had developed disabilities. In 211/277 (76%) all signs of leprosy had disappeared completely.

Comparing clinical certainties at first and last examinations and comparing clinical with histopathological certainties at last examinations it is estimated that up to 50% of the 35 cases of unequivocal leprosy which 'arose' in this group were attributable to misdiagnosis at the 1st or 2nd examination rather than to genuine progression of the disease. This estimate is compatible with an overall sensitivity of 90% and an overall specificity of 95% at each examination. Leprosy suspects with 1 cardinal sign of leprosy, either a typical lesion without loss of sensation, or loss of sensation in an otherwise untypical lesion, should be considered a high-risk group in that approximately 25% of such suspects (19/78) were later found with unequivocal leprosy. Policies towards such suspects should be formulated by leprosy control projects.

Introduction

In any leprosy control or research project some individuals self-report or are found who have clinical signs (skin lesions, possibly enlarged nerves, or areas of sensory loss) which might be due to leprosy but in whom the diagnosis can neither be confirmed nor discarded

0305-7518/93/064025+12 $01.00

with the usual diagnostic procedures.[1,2] Policies towards such leprosy suspects vary. In some projects such individuals may not be treated but are encouraged to return if they notice any change in their lesions, or if additional lesions appear. Other projects may have a policy of active surveillance. Yet others may give antileprosy treatment to such suspects (in contrast to the WHO recommendation that 'if there is even the slightest doubt, the patient should be kept under observation until further evidence confirms the diagnosis'.[3]) This latter approach continues a tradition dating from medieval days, 'that doubtful cases be observed over time so that the disease could declare itself unequivocally.'[4] In general, policies towards suspects are not clearly defined and are rarely stated within evaluation reports or national manuals.[5,6]

In this paper we present long-term follow-up data, derived from total population surveys, for leprosy suspects who were not given any antileprosy treatment and who were not kept on active surveillance. Several questions are at issue.

First, what percentage of leprosy suspects are likely to develop 'unequivocal' leprosy years after the disease was first suspected? We use the term unequivocal to imply that definite histopathological and/or clear clinical evidence of leprosy was found, at which point it would appear to be unethical not to give antileprosy treatment.

Second, can high risk suspects be identified, whom it would be particularly rewarding to follow-up? In contrast to short-term surveillance, long-term surveillance is expensive, and organizationally difficult. Thus, a policy of active long-term surveillance needs to be focused and well justified.

Third, to what extent can the finding of unequivocal leprosy at repeat examinations be attributed to genuine progression from early disease and to what extent might it be attributable to imperfect sensitivity and specificity at the successive examinations, which in theory may be improved.

We anticipate that information on these questions will be of use to control projects when formulating policies towards leprosy suspects.

Comparable data have not been published before. Several researchers have discussed the follow-up of untreated patients and have described self-healing rates among them.[7–9] Browne reported that lesions in 2749 patients with untreated indeterminate or tuberculoid leprosy resolved spontaneously.[7] Noordeen described an inactivation rate of 10·9% per year for tuberculoid leprosy patients—a large proportion were said to have minimal lesions.[8] Sirumban *et al.* found a cumulative healing rate of 38·8% (92/237) within 2 years.[9] Interpretation of and comparison between these investigations is difficult on account of the vagueness of the case definitions in the published reports. It may be that at least some of the 'patients' followed up did not have leprosy at all and would better have been described as 'suspects' in the first place.[10]

Methods

Between 1979 and 1990 two total population house-to-house surveys were carried out in Karonga District (Northern Malawi) as part of a longitudinal epidemiological study and leprosy vaccine trial.[11,12]

The paramedical workers (Leprosy Control Assistants, LCAs) engaged in the surveys were trained to suspect paucibacillary leprosy if they found any of the following: a hypopigmented lesion with a healing centre, a hypopigmented macule with a 'different'

Table 1. Clinical certainty grades of suspected leprosy lesions (in the absence of a positive slit skin smear result)

Grade	Definition	Cardinal signs	Lesion	Anaesthesia
0	Not leprosy	0	0	0
1	Possible leprosy	0	Untypical lesion for which no other explanation can be found	No anaesthesia to light touch
2–	Leprosy to be considered seriously	0	Lesion of less than typical appearance	No anaesthesia
2+		1	Untypical lesion	Definite anaesthesia to light touch
3	Leprosy most likely	1	Lesion of typical appearance	No anaesthesia
3–		1	Definitely enlarged nerve, no skin lesion	No anaesthesia
3+		1	Lesion of less than typical appearance	Definite anaesthesia to light touch
4	Leprosy extremely likely	2	Lesion of typical appearance	Definite anaesthesia to light touch or definitely enlarged nerve
5	Leprosy certain	3	Lesion of typical appearance	Definite anaesthesia to light touch and definitely enlarged nerve

skin texture, a more or less infiltrated hypopigmented plaque, any other unexplained skin lesion, a nerve which appeared to be larger than normal, or any unexplained ulcer or wasting of muscles. They were trained to suspect multibacillary leprosy if they found multiple macules, plaques or papules. Anaesthesia to light touch, diminished pain sensation and loss of thermosensation were sought, but the suspicion of leprosy did not require such additional evidence. All individuals found with any signs suggestive of leprosy were reviewed by a project medical officer (generally J.M.P.). If the Medical Officer (MO) agreed that leprosy was a possible explanation for the signs, he assigned a clinical certainty grade to the findings, unless he was already aware of a positive slit-skin smear.[13] At the same time, provided the suspect agreed, a biopsy was obtained from the lesion(s). Usually one or several 4 mm punch biopsies were taken from skin lesion(s), and occasionally a split nerve biopsy was obtained from a nerve thought to be enlarged. When carrying out repeat examinations the LCAs or the MO were never aware of clinical certainty grades given at previous examinations.

The clinical certainty scale evolved gradually during the 10 years of the project (Table 1). Inevitably results of more than 2000 biopsies taken and reported during the decade influenced the MO's opinion of what constitutes a typical lesion. Despite such experience, the scale remains subjective, and the precise boundaries between 'untypical', 'less than typical' and 'typical' (= textbook-like) lesions will always remain a matter of personal judgement. It will be noted that only anaesthesia to light touch is formally taken into account in this certainty scale, as this test alone is carried out at every examination. Tests

Table 2. Clinical and histopathological certainty grades in 1313 previously untreated leprosy suspects at first examination, Karonga District 1979–1990.* Row percentages in parentheses. Numbers of suspects who were started on antileprosy treatment within a year after leprosy was first suspected are given in ***bold italics***.

Clinical certainty grade		Definite anaesthetic to light touch	Histopathological certainty grade: Definite evidence	Probable evidence > October 1985	Some evidence < October 1985	Possible evidence > October 1985	No evidence	Total
1	Possible leprosy	No	40 (10·2)* ***36***	11 (2·8) ***1***	35 (8·9) ***3***	68 (17·4) ***0***	238 (60·7) ***3***	392 ***43***
2	Consider seriously	No	115 (30·4) ***114***	13 (3·4) ***2***	27 (7·1) ***0***	65 (17·2) ***1***	158 (41·8) ***0***	378 ***117***
2+		Yes	24 (39·3) ***24***	6 (9·8) ***2***	0	7 (11·5) ***0***	24 (39·3) ***1***	61 ***27***
3−	Most likely	No	166 (49·7) ***163***	4 (1·2) ***2***	61 (18·3) ***28***	18 (5·4) ***5***	85 (25·5) ***13***	334 ***211***
3+		Yes	79 (53·4) ***77***	10 (6·8) ***6***	3 (2·0) ***3***	28 (18·9) ***7***	28 (18·9) ***3***	148 ***96***
Total			424 ***414***	44 ***13***	126 ***34***	186 ***13***	533 ***20***	1313 ***494***

for diminished pain sensation are frequently impracticable due to lack of understanding on the part of the patient or suspect, and the test for loss of thermosensation has only recently become a matter of routine. A comparison of results between these 3 sensory loss tests has been published.[14]

For the purpose of this paper we define leprosy suspects as individuals with clinical certainty grades 1–3 at the first examination. Depending on whether definite anaesthesia to light touch was recorded as absent or present in the field, we have split certainty grades 2 and 3 into 2− and 2+, and 3− and 3+, respectively (Table 2). The first examination is the one at which leprosy was first suspected. Unequivocal leprosy is defined as definite histopathological evidence of leprosy and/or a clinical certainty grade of 4 or 5. We use the phrase last examination to refer to the examination at which unequivocal leprosy was diagnosed or else the examination when the suspect was last seen without unequivocal leprosy. As the purpose of this paper is to investigate the usefulness of long-term surveillance of leprosy suspects, we have restricted the analysis to suspects whose last examination was more than 1 year after leprosy was first suspected. So, suspects are excluded from this analysis if they were started on antileprosy treatment within a year of the 1st examination either because of a histopathology result or at a further review examination prompted, e.g. by a histopathology result. This criterion implies a large increase in the sensitivity of the initial diagnostic evaluation (494/1313 suspects were registered within a year after leprosy was first suspected, as shown in Table 2) but

probably only a marginal decrease in specificity. Histopathology results were examined critically by the project MOs, which explains why 10/424 with definite histopathological evidence of leprosy were not started on antileprosy treatment. In most of them the true diagnosis was secondary (granulomatous) syphilis, which may resemble very closely tuberculoid leprosy histologically.

Nearly all suspects discussed here (87/102 for whom the mode of case finding has been coded) were found during the house-to-house surveys.

All leprosy suspects included in this analysis agreed to have biopsies taken. Until late 1985 the histopathologist (A.C.M.) was provided with basic information about the biopsied lesion; after that date all biopsies were examined 'blind' (by A.C.M. or S.L.), with no clinical information except the part of the body from which the biopsy was taken. The histopathologist always provided an indication of his confidence that the lesion was attributable to leprosy, using a certainty scale which we have described elsewhere.[15,16] In short, criteria for definite leprosy in a skin biopsy are: a, endoneurial granuloma(s) disrupting nerve; and/or b, one or more genuine (noncontaminant) AFB in a nerve or granuloma in association with perineural inflammation. Initially, until October 1985, there was only one grade if histopathological findings were consistent with but not pathognomonic of leprosy, called: 'some evidence'. Later, after October 1985, two grades were used for this situation: 'suggestive of but not diagnostic of leprosy = probably leprosy' and 'possibly leprosy'.

A major problem in the interpretation of follow-up data such as those presented here is the distinction between true changes over time and apparent changes which are in fact attributable to misdiagnosis at initial or subsequent examination. In order to quantify this misdiagnosis effect, we explored the implications of different levels of sensitivity and specificity on expected results of follow-up examinations of individuals not considerred to have unequivocal leprosy at the first examination. Using the following symbols:

TP, true prevalence rate of leprosy in the population;
SN1, SN2, sensitivity of diagnosis at the 1st and subsequent examinations, respectively;
SP1, SP2, specificity of diagnosis at the 1st and subsequent examinations, respectively;
OP1, OP2, 'observed unequivocal' leprosy rates at the 1st and subsequent examinations, respectively;
RP1, remaining true prevalence in those not considered positive at the 1st examination.

The following relationships hold:

$$OP1 = TP \times SN1 + (1\text{-}TP) \times (1\text{-}SP1)$$
$$RP1 = TP \times (1\text{-}SN1)/(1\text{-}OP1)$$
$$OP2 = RP1 \times SN2 - (1\text{-}RP1) \times (1\text{-}SP2).$$

The proportion observed with unequivocal leprosy at a 2nd examination (OP2) is thus equal to the remaining true prevalence of unequivocal leprosy among initially negative suspects (RP1) times the sensitivity at the repeat examination (SN2), corrected for the effects of imperfect specificity of the repeat examination.

Results

During the total population surveys a total of 1313 previously untreated leprosy suspects were found and biopsied. An additional 13 suspects refused to be biopsied. Table 2 gives a

Table 3. Clinical certainty grades at the 1st examination (rows) versus clinical certainty grades at the last examination (columns) of 277 suspects. Individuals with 'unequivocal leprosy' on clinical and/or histopathological grounds at last examination are shown in ***bold italics***.

Clinical certainty grade	Last examination								Total
	0	1	2−	2+	3−	3+	4	5	
1	95	2	4	4	3	1	4	2	115
	0	***1***	***1***	***1***	***1***	***0***	***4***	***2***	***10***
2−	66	2	5	1	5	2	3	0	84
	0	***0***	***0***	***0***	***3***	***0***	***3***	***0***	***6***
2+	2	0	0	0	0	0	1	0	3
	0	***0***	***0***	***0***	***0***	***0***	***1***	***0***	***1***
3−	41	0	8	1	6	1	6	0	63
	0	***0***	***5***	***1***	***2***	***1***	***6***	***0***	***15***
3+	7	0	1	0	0	2	1	1	12
	0	***0***	***0***	***0***	***0***	***1***	***1***	***1***	***3***
Total	211	4	18	6	14	6	15	3	277
	0	***1***	***6***	***2***	***6***	***2***	***15***	***3***	***35***

+, with definite anaesthesia to light touch.
−, without definite anaesthesia to light touch.

cross-tabulation of the clinical and histopathological certainty grades at the 1st examination of these 1313 individuals. Table 2 shows that 494 of the 1313 were started on antileprosy treatment because of definite histopathological evidence (414) or because further clinical evidence came to light at a review examination within a year after leprosy was first suspected (80). Of the remaining suspects, 277 have so far been re-examined in the course of the house-to-house surveys more than a year after leprosy was first suspected, and are the subject of this paper.

A strong correlation between clinical and histopathological certainty gradings is evident in Table 2. Among suspects with one cardinal sign of leprosy (clinical certainty grades 2+, 3−, 3+) definite histopathological evidence of leprosy was found in $(24+166+79)/(61+334+148)=49{\cdot}5\%$ of the biopsy specimens taken. This may be compared to those in whom leprosy was considered to be only a 'possibility', in whom only 40/392 (10·2%) of biopsy specimens offered definite evidence of leprosy. In 115/378 (30·4%) of those with a clinical certainty grade 2− (lesions of less than typical appearance and without anaesthesia to light touch) the histopathologist found definite evidence of leprosy.

Table 3 provides a cross-tabulation of clinical certainties at the 1st and the last examinations. All signs of leprosy had disappeared (=clinical certainty zero at last examination) in $211/277=76{\cdot}2\%$. The average follow-up period was 4·8 years for those in whom no signs of leprosy were found any more, 4·0 years for 31 individuals whose lesions, still unconfirmed as leprosy, persisted at the last examination and 4·1 years for the remaining 35 individuals whose lesions persisted and who were ultimately confirmed as having unequivocal leprosy. A comparison of the 1st and the last examinations of these 35

Table 4. Clinical and histopathological certainty grades in 80 individuals who were considered still to have signs of leprosy and who were biopsied more than a year after an initial examination at which leprosy had first been suspected. Individuals considered to have unequivocal leprosy on either histopathological or clinical grounds are shown in ***bold italics***.

Clinical certainty grade	Histopathological certainty grade					
	Definite evidence	Probably leprosy	Some evidence	Possibly leprosy	No evidence	Total
1	***1***	1	0	3	1	6
2	***8***	1	0	3	13	25
3	***8***	1	0	9	13	31
4	***10***	0	0	0	***5***	15
5	***3***	0	0	0	0	3
Total	***30***	3	0	15	32	80

Table 5. Eventual outcome for 277 leprosy suspects who were reviewed more than a year after leprosy was first suspected, in relation to initial clinical certainty, Karonga District 1979–1990.

Original clinical certainty	Definite anesthesia to light touch	Number of suspects who were subsequently found with unequivocal leprosy	Total
1 'Possible leprosy'	No	10* (8·7)‡	115
2− 'Leprosy to be considered seriously'	No	6 (7·1)	84
2+	Yes	1 (33·3)	3
3− 'Leprosy most likely'	No	15 (23·8)	63
3+	Yes	3† (25·0)	12
Total		35 (12·6)	277

* Two individuals or † one individual in each of these groups developed disabilities during the interval between two examinations.

‡ Numbers on parentheses are percentages.

individuals (numbers in ***bold italics*** in Table 3), shows that clinical certainties had increased by at least 2 grades in 12/35 (34·3%), increased by 1 grade in 12/35 (34·3%), stayed the same in 5/35 (14·29%), and decreased by 1 grade in 6/35 (17·14%).

Repeat biopsies were obtained from 80 of the 277 leprosy suspects at one or another repeat examination (Table 4). Of these 80 individuals, 35 were considered to have unequivocal leprosy. As can be seen in Table 4, the strong evidence for unequivocal leprosy was both clinical (certainty grades 4 and 5) and histopathological (certainty grade 1) in $10+3=13$ (37·1%); histopathological alone in $1+8+8=17$ (48·6%); and clinical alone in 5 (14·3%). A total of 6 of the 35 with unequivocal leprosy is known to have self-

Table 6. Eventual outcome for 277 leprosy suspects who were reviewed more than a year after leprosy was first suspected in relation to initial histopathological certainty, Karonga District 1979–1990.

Original histopathological certainty	Number of suspects who were later found with unequivocal leprosy	Total
Probable leprosy > October 1985	0	1
Some evidence < October 1985	17 (22·7)†	75
possible leprosy > October 1985	6 (27·3)	22
no evidence	12* (6·7)	179
Total	35 (12·6)	277

* In this group 3 individuals developed disabilities during the interval between 2 examinations.

† Numbers in parentheses are percentages.

Table 7. Expected observed proportion positive at a 2nd screening procedure as a function of true original prevalence rates and different sensitivities and specificities of the screening procedures. In this context we consider the combined clinical and histopathological examinations to be the screening procedure.

Sensitivity of 1st and 2nd screen	Specificity of 1st and 2nd screen	True original prevalence rate		
		0·1	0·3	0·5
		Proportion positive expected at 2nd screening (in the absence of self-healing and progression)		
0·9	0·98	0·030	0·057	0·101
0·95	0·98	0·025	0·040	0·065
0·9	0·95	0·060	0·087	0·131
0·95	0·95	0·055	0·070	0·095

reported to LCAs while 28 were found during the house-to-house surveys. For 1 patient the mode of detection was not recorded.

Table 5 shows the numbers and percentages of suspects later found with unequivocal leprosy by clinical certainty at the 1st examination—3 of the suspects had developed disabilities by the time they were seen again, 2 of whom had a clinical certainty of only 1 ('possibly leprosy') when leprosy was first suspected. Nearly a quarter (19/78) of those originally found with 1 cardinal sign of leprosy have developed unequivocal leprosy so far. The percentages of suspects who developed unequivocal leprosy were similar for males and females and did not vary significantly by age (not shown).

Table 6 provides a breakdown of numbers and percentages which developed unequivocal leprosy by original histopathological certainty. Only 6·7% (12/179) of those in whom the histopathologist did not find any evidence of leprosy in the first specimen(s)

were later found with unequivocal leprosy, compared to 23·5% (17+6/1+75+22) for those in whom some histopathological evidence was found in the initial biopsy. However, 3 of the 12 with no initial histopathological evidence of leprosy developed disabilities during the interval between 2 examinations.

Table 7 shows the implications of various levels of sensitivity and specificity on the percentage expected to be found with unequivocal leprosy at a repeat examination (='2nd screening'). If we assume that the original true prevalence rates among those with clinical certainty grades 1 ('possibly leprosy'), 2 ('leprosy to be considered seriously') and 3 ('leprosy most likely') were 0·1, 0·3 and 0·5, respectively, and that the sensitivity and specificity were 0·9 and 0·95, respectively, we would expect to observe between 6 and 13% of individuals as having 'unequivocal leprosy' on the 2nd examination as an effect of misdiagnosis at the 1st and 2nd examinations. If the sensitivity and specificity were higher, 95% and 98% respectively, we would expect to find 'unequivocal leprosy' at the 2nd examination attributable to misdiagnosis in only 2·5%, 4·0% and 6·5% of suspects, with original clinical certainty grades of 1, 2 and 3, respectively.

Discussion

This paper reports the follow-up results of 277 individuals who were identified initially as leprosy suspects, but to whom no antileprosy treatment was given on account of insufficient evidence to support the diagnosis. After an average of 4·5 years, 35 (12·6%) were considered to have unequivocal leprosy, whereas 211 (76·2%) had lost all signs of the disease. The probability of unequivocal leprosy eventually emerging was a function of the clinical and histopathological certainty at the 1st examination. Nearly a quarter of those with 1 cardinal sign of leprosy (clinical certainty of 2+, 3− or 3+) or some histopathological evidence of leprosy at the 1st examination were later thought to have unequivocal leprosy. These findings identify such suspects as a high-risk group which a control project may consider worthy of active long-term surveillance. On the other hand, only 1 of the 3 suspects who developed disabilities during the interval between 2 examinations was in the clinical high-risk group. The risk factor 'some histopathological evidence of leprosy' is of course less useful for most control projects which do not have histopathology services.

It should be recognized that the figures concerning the development of unequivocal leprosy are a function of our definition of a suspect. If a wider definition of leprosy had been used such as that 'eliciting impairment in sensibility in a suggestive skin lesion . . . clinches the diagnosis leprosy',[17] up to (3+63+12)/277=28% (see Table 3) of the suspects in this investigation would have been considered to have leprosy at the 1st examination, and the percentage of suspects found eventually with unequivocal leprosy would probably have been lower than reported here (given that lesions disappeared completely from more than three-quarters of the suspects).

Given that there is no 'gold standard' for the diagnosis of clinical leprosy, in particular of 'early' leprosy, no self-healing rates of early leprosy can confidently be derived from this series of suspects. If it were assumed that all the suspects had early leprosy the percentage which had self-healed by the time they were last seen would be 76·2% (211/277). However, such an assumption is extreme and we would not like to make it.

For the purposes of control projects the issue of whether a later finding of unequivocal leprosy is due to progression of disease or to misdiagnosis at one examination or other is important. Sensitivity and specificity may in theory be improved, whereas progression rates are presumably inherent in the disease process.

We have therefore investigated to what extent the finding of unequivocal leprosy at later examinations might be due to the effects of misdiagnosis, that is, imperfect sensitivity and specificity, at the examinations. It may be argued that at least in those (5+6)/35 (31·4%) in whom the clinical certainty had stayed the same or decreased (see Table 3), the finding of definite histopathological evidence at the last examination was a result of misdiagnosis—of either a false-negative misdiagnosis at the 1st or a false-positive misdiagnosis at the 2nd examination. In addition it can be suspected that in some of those 5/35 (14·3%) in whom the clinical certainty of 4 (extremely likely) at the last examination was not supported by histopathological findings the diagnosis of unequivocal leprosy was due to false-positive clinical misdiagnosis at the last examination. So, if up to half of all 'unequivocal leprosy' identified at the last examination were the result of such sensitivity and specificity problems this would be about 6% of the suspects, i.e. half of the 12·6% found with unequivocal leprosy at the last examination. It is interesting to note that a sensitivity of 90% combined with a specificity of 95% would be compatible with this figure (see Table 7) if the overall true prevalence rate among suspects were around 10%. In the absence of additional data we do not wish to speculate further on the most likely sensitivity and specificity values in this investigation. There have been very few attempts to estimate these parameters in leprosy studies, though Gupte *et al.* estimated sensitivity rates of 74–91% and a specificity of 98% in a study carried out in South India.[18]

It is beyond the scope of this paper to discuss in detail the practicalities of following suspects over long periods of time rather than giving them antileprosy treatment. However, we would emphasize our principal finding that suspects with 1 cardinal sign of leprosy form a group of people which should receive considerable thought and attention in any project. A quarter of them are likely to manifest unequivocal leprosy as the years pass. Maybe, as a first step, the sensitivity and specificity of their examinations can be improved using histopathology and serology if practicable?

Few field workers will consider long-term active surveillance of leprosy suspects a feasible policy, as it is not only very difficult and time consuming but might, in some communities, cause unacceptable stigma. Intensive health education towards subsequent self-reporting directed at particular groups of suspects found to be at a high risk could be another possible approach.

Acknowledgments

The Lepra Evaluation Project—Karonga Prevention Trial is funded by LEPRA (The British Leprosy Relief Association), ILEP (The International Federation of Anti-Leprosy Organizations) and IMMLEP (The Immunology of Leprosy component of the WHO/TDR). We express our sincere thanks to the leprosy control assistants engaged in the total population surveys, in particular Messrs B. Mwamondwe, E. Msosa, P. Mwafulirwa, D. Chavula, H. Phiri, A. Kasunga, M. Munthali, J. Nyierenda and Ms M. Nafukwe.

References

[1] Jacob M, Mathai R. Diagnostic efficacy of cutaneous nerve biopsy in primary neuritic leprosy. *Int J Lep*, 1988; **56:** 56–60.

[2] Neelan PN, Noordeen SK, Ramu G, Desikan KV, Prabhu KPM, Christian M. Inter-observer variations in diagnosis and classification of early lesions of leprosy. *Leprosy in India*, 1982; **54:** 485–488.

[3] World Health Organization. A guide to leprosy control (2nd edition). WHO, Geneva, 1988.

[4] Ell SR. Leprosy and social class in the middle ages. *Int J Lepr*, 1986; **54:** 301–305.

[5] Rangaraj M. Leprosy Control Programme Sierra Leone Evaluation Report 1973–1987.

[6] Tuberculosis/Leprosy Control Unit. Manual of the National Tuberculosis/Leprosy Programme in Tanzania of the district tuberculosis/Leprosy Coordinators (2nd edition, 1987). Ministry of Health, P.O. Box 9083, Dar-es-Salaam.

[7] Browne SG. Self-healing Leprosy: Report on 2749 patients. *Lepr Rev*, 1974; **45:** 104–111.

[8] Noordeen SK. Evolution of tuberculoid leprosy in a community. *Leprosy in India*, 1975; **47:** 85–93.

[9] Sirumban A, Kumar Ashok, Neelan PN. Healing time in untreated paucillary leprosy. A cross-sectional study. *Int J Lep*, 1988; **56:** 223–227.

[10] Pettit JHS. Should indeterminate leprosy ever be diaagnosed? (letter to the editor). *Int J Lep*, 1981; **49:** 95–96.

[11] Pönnighaus JM, Fine PEM, Bliss L, Sliney IJ, Bradley DJ, Rees RJW. The Lepra Evaluation Project, an epidemiological study of leprosy in northern Malaŵi. I—Methods. *Lepr Rev*, 1987; **58:** 359–375.

[12] Fine PEM, Pönnighaus JM. Leprosy in Malaŵi 2. Background, design and prospects of the Karonga Prevention Trial, a leprosy vaccine trial in Northern Malaŵi. *Trans Royal Soc Trop Med Hygiene*, 1988; **82:** 810–817.

[13] Pönnighaus JM, Fine PEM, Bliss L. Certainty levels in the diagnosis of leprosy. *Int J Lepr*, 1987; **55:** 454–462.

[14] Pönnighaus JM, Fine PEM. A comparison of sensory loss tests and histopathology in the diagnosis of leprosy. *Lepr Rev*, 1989; **60:** 20–27.

[15] Fine PEM, Job CK, McDougall AC, Meyers WM, Pönnighaus JM. Comparability among histopathologists in the diagnosis and classification of lesions suspected of leprosy in Malaŵi. *Int J Lepr*, 1986; **54:** 614–625.

[16] McDougall AC, Pönnighaus JM, Fine PEM. Histopathological examination of skin biopsies from an epidemiological study of leprosy in Northern Malaŵi. *Int J Lepr*, 1987; **55:** 88–98.

[17] Srinivasan H, Stumpe B. Value of thermal sensibility testing in leprosy diagnosis in the field—field trial of a pocket device. *Lepr Rev*, 1989; **60:** 317–326.

[18] Gupte MD, Valli Shayee RS, Nagaraju B, Ramalingam A, Lourdusamy G, Kannan. Inter-observer agreement and clinical diagnosis of leprosy for prophylaxis studies. *Ind J Lepr*, 1990; **62:** 281–295.

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Surveillance active à long terme de suspects lépreux—que faut-il en attendre?

J. M. Pönnighaus, P. E. M. Fine, J. A. Sterne, S. B. Lucas et A. C. McDougall

Résumé Nous présentons les résultats de la suivie à long terme de 277 suspects lépreux du District de Karonga en Malawi du Nord qui ne recevaient pas de traitement contre la lèpre ou n'étaient pas sous surveillance active. Sont exclues de cette étude les personnes qui ont été mises sous traitement anti-lèpre moins d'un an après avoir été déclarées pour la première fois suspects de lèpre, habituellement sur la base d'examens histopathologiques; en effet, leur surveillance active ne devrait pas poser de problèmes d'organisation ou de financement dans les projets de contrôle de la lèpre. Après une période de suivie de 4,5 années en moyenne, nous avons diagnostiqué ce que nous considérons comme lèpre sans équivoque chez 35 des 277 suspects compris dans notre étude (13%) et 3 de ces 35 suspects présentaient des infirmités. Chez 211 des 277 (76%) tout signe de lèpre avait complètement disparu.

En comparant les certitudes cliniques au premier et dernier examen et en comparant les certitudes cliniques aux certitudes histopathologiques au dernier examen on estime que jusqu'à 50% des 35 cas de lèpre sans équivoque qui sont survenus dans ce groupe pouvaient être atribués à une erreur de diagnostic au 1er ou 2ème examen plutôt qu'à une progression réelle de la maladie. Cette estimation est compatible avec une sensibilité globale de 90% et une spécificité globale de 95% à chaque examen. Les suspects de lèpre qui présentent 1 signe cardinal de lèpre, soit une lésion typique sans perte de sensation, soit une perte de sensation sur une lésion par ailleurs non typique, devraient être classés dans un groupe à haut risque, car, par la suite, nous avons observé 25% environ de cas de lèpre sans équivoque dans cette catégorie de suspects (19/78). Il faudrait formuler la conduite à tenir vis-à-vis de ces suspects dans les projets de contrôle de la lèpre.

Vigilancia activa a largo plazo de posibles leprosos—¿Qué posibilidad hay de que tenga éxito?

J. M. Pönnighaus, P. E. M. Fine, J. A. Sterne, S. B. Lucas y A. C. McDougall

Resumen El Distrito de Karonga en el Norte de Malaui presenta datos sobre el estudio posterior a largo plazo de 277 posibles leprosos que no recibieron tratamiento contra la lepra ni fueron activamente vigilados. Los individuos que comenzaron el tratamiento antilepra dentro de un año después de que se sospechase lepra, generalmente basado en los resultados histopatológicos, fueron excluidos de este análisis, porque una vigilancia activa normalmente no causaría un problema organizacional o financiero para los proyectos de control de la lepra. Después de un período de estudio posterior con un promedio de 4, 5 años, 35 de los 277 posibles leprosos incluidos en el análisis (13%) fueron diagnosticados de leprosos inequívocos, y 3 de los 35 habián desarrollado incapacidades. En 211/277 (76%), todas las indicaciones habían desaparecido totalmente.

Comparando las certezas clínicas en los primeros y últimos examenes, y comparando certezas clínicas con las histopatológicas, se calcula que hasta 50% de los 35 casos de lepra inequívoca que apareció en este grupo se debía a un diagnóstico equivocado en el 1er. o 2o. examen, más bien que a un progreso verdadero de la enfermedad. Este cálculo es compatible con una sensibilidad global del 90% y una especificidad global de 95% en cada examen. Los posibles leprosos con 1 indicación cardenal de la lepra, sea una lesión típica sin pérdida de sensación, sea con pérdida de sensación en el caso de una lesión que en otro caso sería atípica, deben ser considerados un grupo de riesgo elevado ya que aproximadamente un 25% de tales posibilidades (19/78) posteriormente presentaron lepra inequívoca. Los proyectos para el control de la lepra deberán formular políticas para el trato de tales posibles leprosos.

Lepr Rev (1993) **64,** 37–43

Oral manifestations of leprosy

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Accepted for publication 9 October 1992

Summary A total of 37 out of 187 patients with leprosy had oral lesions. All were biopsied. Oral lesions were found most frequently in patients with lepromatous leprosy. Prevalence of oral lesions was higher in males than in females (73%:27%). Oral lesions were recorded on the WHO topographical map, and in most cases (92%) several topographical locations were affected, including hard palate in all cases. Topographical locations affected increase with age; males are more extensively affected than females ($p=0{\cdot}001$); and patients with oral lesions who reported affected family members (11 out of 37) had more extensive oral lesions than those who did not. In 27 cases with oral lesions histopathological diagnosis was possible.

Introduction

The current estimated prevalence of leprosy in Africa as a whole is about 3·14/1000 of the population. This is more than double the figure of 1·56/1000 for Asia, and far greater than the figures of 0·46/1000 for the Americas combined and 0·02/1000 for Europe.[1,2]

In the Republic of South Africa there are no accurate prevalence figures available; but incidence figures have declined strikingly in the last 55 years from 8/100,000 in 1935 to about 0·2/100,000 in 1990, [3, Mars PW personal communication] and it may be said with confidence that the prevalence is very much lower than for Africa as a whole.

Materials and methods

Over a 2-year period, 187 patients newly admitted or readmitted for treatment of leprosy at Westfort Hospital, near Pretoria, South Africa, were examined—110 were male and 77 were female (Table 1).

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0305-7518/93/064037+07 $01.00

Table 1. Number of patients with the various subtypes of leprosy

Type of leprosy*	Male	Female	Total
TT	0	0	0
BT	45	23	68
BB	18	13	31
BL	19	18	37
LL	28	23	51
Total	110	77	187

* TT, 'True' tuberculoid leprosy; BT, borderline tuberculoid leprosy; BB, 'true' borderline leprosy; and BL, borderline lepromatous leprosy.

In every case in which oral lesions were found, biopsies were done with the consent of the patients. Information about the patients and the locations of the oral lesions were recorded on a form which incorporated the WHO topographical map for oral lesions (Figure 1).

Results

Out of 187 patients, 37 had oral lesions. According to the diagnoses at admission, oral lesions were strikingly more prevalent in patients with lepromatous leprosy (Table 2), and in males (27 males, 10 females).

The ages of patients with oral lesions ranged from 14 to 59 with a peak of distribution in the 30–39 age group.

In objectively evaluating the oral lesions, the number of WHO topographical locations (Figure 1) affected was used as the criterion for the extent of the lesions; and the presence or absence of ulceration as the criterion for the severity of the lesions.

The number of affected locations recorded on the WHO topographical map increases with age; but the oral ulceration occurred most often in the 30–39 age group.

Judged by the number of WHO topographical locations affected, males had significantly more extensive oral involvement ($p = 0{\cdot}001$); but there was not a statistically-significant difference in oral ulceration between males and females ($p = 0{\cdot}056$).

Compared to those who did not have a family member with leprosy, those patients who did were significantly more extensively affected (number of WHO topographical sites affected) ($p = 0{\cdot}001$) although the difference in severity of the oral lesions (ulceration) was not statistically significant. Figure 1 is the composite picture which emerged when 37 WHO topographical maps for the 37 patients with oral lesions were combined. Locations within the oral cavity affected in order of frequency are illustrated in Figure 1.

Clinical photographs of representative oral lesions are shown in Figures 2 and 3. Aspects of the histology of the oral lesions are summarized in Table 3.

Epithelial atrophy was noted only in patients with lepromatous leprosy. Hyperkerato-

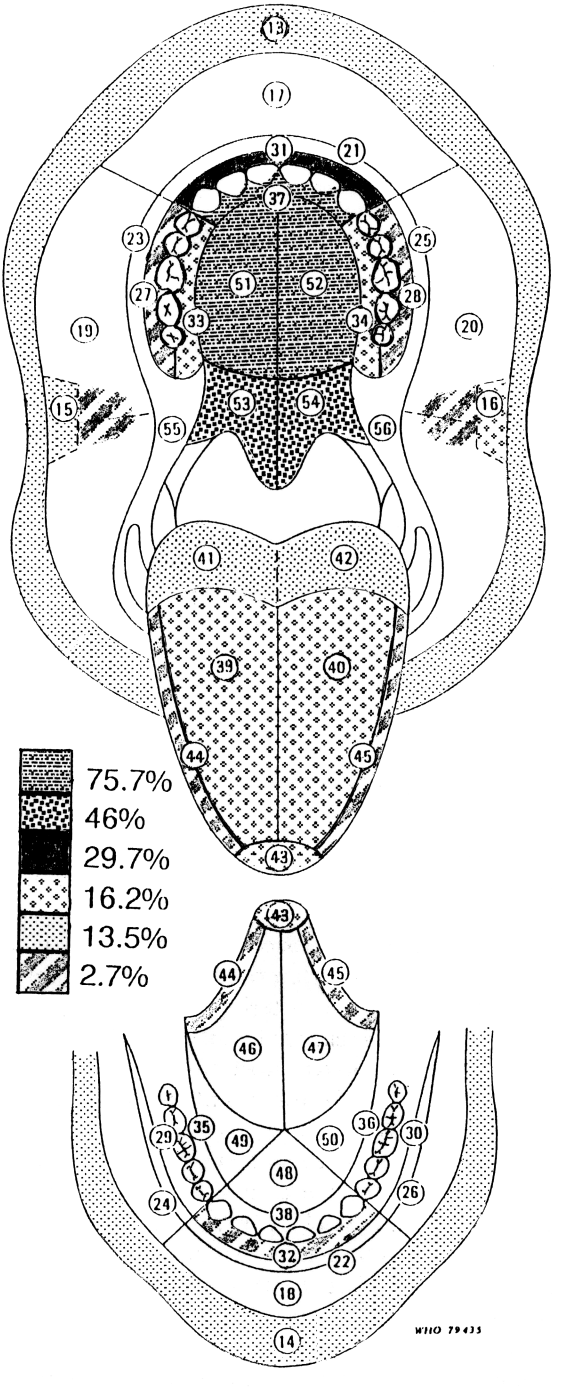

Figure 1. Frequency of involvement of each WHO topographical location as a percentage of the number of patients with oral lesions.

Table 2. Prevalence of oral lesions

Type of leprosy	Patients examined	Patients with oral lesions	% with
TT	0	0	0
BT	68	3	4·4
BB	31	2	6·5
BL	37	3	8·1
LL	51	29	56·9
Total	187	37	19·8

* See Table 1 for key.

sis was observed in 5 of the 8 cases in the borderline subgroups, but in only 5 of 29 cases in the lepromatous leprosy subgroup.

Only 1 oral lesion showed an infiltrate-free subepithelial zone, in contrast to skin lesions where this is the rule. Heavy infiltrations of macrophages, lymphocytes and plasma cells were a constant observation in the oral lesions of lepromatous leprosy, and numerous acid-fast bacilli were usually seen.

In 27 of the 37 oral biopsy specimens, *Mycobacterium leprae* bacilli were seen, permitting a definite histopathological diagnosis. All but 2 of the remaining cases showed varied histological features consistent with the clinical diagnosis, but not in themselves diagnostic. Oral lesions were classified on clinicohistopathological evidence as lepromatous response (30 cases), Type 1 lepra reaction (5 cases), Type 2 lepra reaction (2 cases).

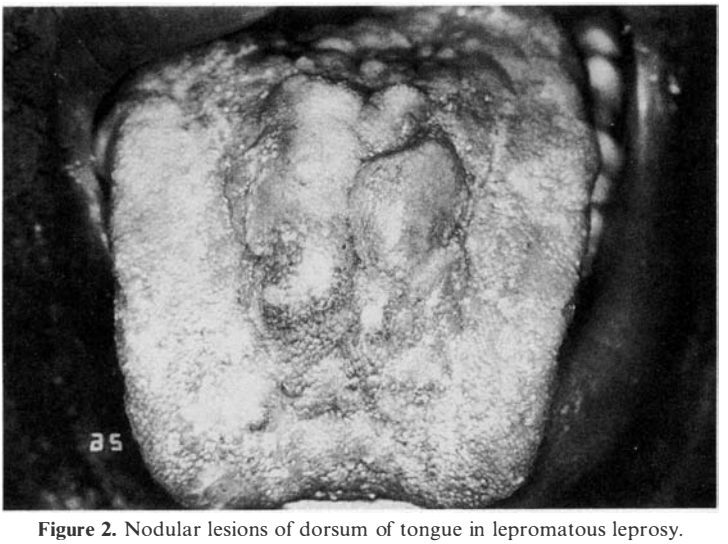

Figure 2. Nodular lesions of dorsum of tongue in lepromatous leprosy.

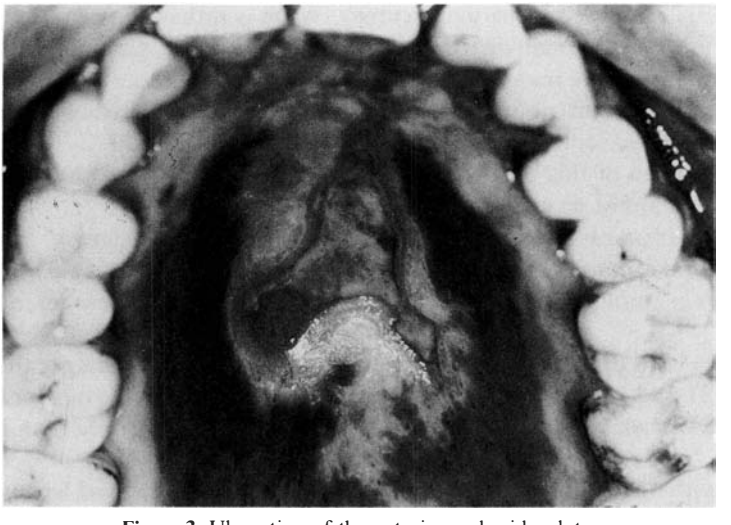

Figure 3. Ulceration of the anterior and mid-palate.

Table 3. Histological features of the oral lesions

Aspect of histology (Diagnosis* and number of cases)	Number of cases				
	BT (3)	BB(2)	BL (3)	LL (29)	Total
Epithelium					
Normal	2	0	3	10	15
Atrophy	0	0	0	9	9
Hyperplasia	1	2	0	9	12
Hyperkeratosis	2	1	2	5	10
Connective tissue					
Normal	1	1	0	2	4
Infiltrate-free	0	0	0	1	1
Subepithelial zone					
Macrophages	1	1	2	27	31
Lymphocytes/Plasma cells	2	1	3	21	27
Bacilli					
None	3	2	1	4	10
Few	0	0	0	2	2
Moderate	0	0	0	1	4
Numerous	0	0	2	19	21

* See Table 1 for key.

Discussion

None of the oral lesions may be said to be clinically entirely characteristic or pathognomonic of leprosy; but advanced lesions like those shown in Figures 2 and 3

should certainly raise the suspicion of leprosy. What is rather constant, as borne out by the topographical locational distribution (Figure 1), is the palatal position and the bilateral symmetry of the majority of the lesions.[4]

This rather specific distribution of the oral lesions has speculatively been attributed to the preference of the leprosy bacillus for temperatures below 37°C.[5,6] The apparently simple confirmation of this postulation has to date been frustrated by the fact that the leprosy bacillus cannot be cultured *in vitro*.[7]

Oral lesions are considered to be a manifestation of advanced leprosy[8–10] and as female patients with oral lesions constituted only 5·4%, while male patients constituted 14·4% of all the patients examined, it may be that the females seek treatment earlier in the course of the disease.

In patients with oral lesions, the females were also slightly younger than the males (averages of 31 and 34·7 years, respectively). The presentation by younger females with less-advanced disease may reflect a greater concern with appearance than is the case in males.

Patients with oral lesions and with family members who also had leprosy, in general were more severely affected than those whose family members were free of the disease. This favours the possibility of an hereditary predisposition to leprosy, although the published evidence for this is inconclusive.[1]

Mukherjee, Girdhar & Desikan[11] described the histopathology of lesions of the tongue in a small series of 8 patients with leprosy. They reported none with the bacilli-free subepithelial zone typically reported in skin lesions.[1] The same was true of the present study with the exception of a single case. The proximity to the epithelium of innumerable micro-organisms in the lamina propria as well as their presence in the epithelium itself supports the contention that bacilli may enter the oral fluids, with obvious epidemiological implications in ethnic cultures where spitting is a common habit.[11,12]

Of Mukherjee's cases,[11] 4 had epithelial hyperplasia, which is also in contrast to skin lesions where atrophy and flattening of the epithelium-corium interface are observed. In the present series, epithelial hyperplasia was a common finding with 12 cases noted either as the primary histological feature or as an associated feature (Table 3).

In general, the oral lepromatous granulomata in the present series show the same histopathological features of inflammatory infiltrate and striking bacillary population as described in the literature.[9,11]

Lesions related to the Type 1 lepra reaction in the skin are known to desquamate after some time. The hyperkeratosis noted in 3 of the oral lesions in patients with Type 1 lepra reactions in this series may be analogous to desquamation of the skin.

Where leprosy is endemic, the increasing prevalence of AIDS, which is expected to be associated with progressive, fulminating leprosy,[13] may also bring about a pattern of oral lesions different to that which we have described.

References

[1] Jopling WH. *Handbook of Leprosy*, 3rd Ed. London: Heinemann, 1986; **5:** 16.
[2] World Health Organization. *A Guide to Leprosy Control*. 3rd Ed. Geneva: WHO Publications; 1988: 3.
[3] Schulz EJ, Pentz HHL. Leprosy control in South Africa. *Lepr Rev*, 1970; **41:** 15–19.
[4] Girdhar BK, Desikan KV. A clinical study of the mouth in untreated lepromatous patients. *Lepr Rev*, 1979; **50:** 25–35.

[5] Brand PW. Temperature variation and leprosy deformity. *Int J Lepr*, 1959; **27:** 1–7.
[6] Reichart P, Ananatasan T, Reznik G. Gingiva and periodontium in lepromatous leprosy. *J Periodontol* 1976; **47:** 455–460.
[7] Hutchinson J. Cultivation of the leprosy organism. *Int J Dermatol*, 1990; **29:** 189.
[8] Lighterman I, Watanabe Y, Hidaka T. Leprosy of the oral cavity and adnexa. *Oral Surg Oral Med Oral Pathol*, 1962; **15:** 1178–1194.
[9] Reichart P. Facial and oral manifestations of leprosy. *Oral Surg Oral Med Oral Pathol*, 1976; **41:** 385–399.
[10] Prabhu SR, Daftary DK. Clinical evaluation of oro-facial lesions of leprosy. *Odontostomatol Trop*, 1981; **4:** 83–95.
[11] Mukherjee A, Girdhar BK, Desikan KV. Histopathology of tongue lesions in leprosy. *Lepr Rev*, 1979; **50:** 37–43.
[12] Alfieri N, Fleury RN, Opromolla DVA, Ura S, de Campos I. Oral lesions in borderline and reactional tuberculoid leprosy. *Oral Surg Oral Med Oral Pathol*, 1983; **55:** 52–57.
[13] Schulz EJ. Congress report: 13th International Leprosy Congress, The Netherlands. *S Afr Med J*, 1989; **76:** 233–234.

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Manifestations buccales de la lèpre

A. SCHEEPERS, J. LEMMER ET J. F. LOWNIE

Résumé Un total de 37 sur 187 patients atteints de lèpre a présenté des lésions buccales. Une biopsie a été effectuée sur toutes ces lésions. Les lésions buccales étaient le plus souvent observées chez les patients atteints de lèpre lépromateuse. La fréquence des lésions buccales étaient plus élevées chez les hommes que chez les femmes (73% contre 23%). Les lésions buccales ont été marquées sur la carte topographique de l'OMS, et dans la plupart des cas (92%) plusieurs localisations étaient affectées, y compris le palais dans tous les cas. Les localisations topographiques affectées augmentent avec l'âge; les hommes sont plus affectés que les femmes ($p = 0{,}001$); et les patients qui ont signalé que d'autres membres de leur famille étaient affectés (11 sur 37) avaient des lésions plus étendues que ceux qui n'ont rien signalé. Dans 27 cas présentant des lésions buccales le diagnostic histopathologique a été possible.

Manifestaciones orales de la lepra

A. SCHEEPERS, J. LEMMER Y J. F. LOWNIE

Resumen Un total de 37 de 187 pacientes con lepra sufría de lesiones orales. Se hizo una biopsia en todos. Se encontraron las lesiones orales con más frecuencia en los pacientes con lepra lepromatosa. La frecuencia de lesiones orales era más en hombres que en mujeres (73% : 27%). Se registró la frecuencia de las lesiones orales en el plano topográfico de la OMS y, en la mayoría de casos (92%), varías situaciones topográficas fueron afectadas, paladar duro en la mayoría de los casos. Las situaciones topográficas afectadas aumentan con la edad; los hombres están más extensamente afectados que las mujeres ($p = 0{,}001$); y los pacientes con lesiones orales que informaron de parientes afectados (11 de los 37) tuvieron lesiones orales más extensas que los que no lo hicieron. En 27 casos de lesiones orales, fue posible un diagnóstico histopatológico.

Lepr Rev (1993) **64,** 44–52

A histological study of the eye lesions in 12 leprosy patients with tuberculoid lesion in 4 eyes

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Accepted for publication 9 October 1992

Summary The histological reactions in 12 eyes of 12 leprosy patients were studied (5 BT, 1 BB, 1 BL and 5 LL). Granuloma lesions composed of epithelioid cells, Langerhans giant cells, macrophages and lymphocytes were found in various intraocular tissues, e.g. cornea, sclera, iris, ciliary body or retina in 4 patients (1 BT and 3 LL). Of the 3 LL patients, according to the records, 2 were cured and in the other patient the outcome of the treatment was not mentioned. In view of the finding of the granulomatous lesions in the clinically cured patients and tuberculoid granuloma in the intraocular tissues in the LL patients, could there be some peculiarities in the intraocular sites? Or perhaps the tuberculoid reaction is just a manifestation of an upgrading reaction? More examinations on human leprosy eye specimens will be needed to answer these questions.

Introduction

Leprosy patients frequently suffer eye damage—about a million leprosy patients are blind.[1] The lesions of the eyes are either caused directly by the *Mycobacterium leprae* or its derivatives, or indirectly by the dysfunction of the sensory and motor nerves as a result of the disease. These lesions may finally lead to corneal opacity, changing of the intraocular pressure, cataract and then blindness.

The clinical aspects of the effects of leprosy on the human eye have often been described in detail,[3] but the pathohistological aspect of this has only rarely been documented and the cases investigated have been limited,[2,4,5,7–9] probably because it is hard to get eye specimens.

Over a period of many years we gathered eye specimens from 12 leprosy patients. Their pathological histology was studied and the results are presented.

‖ Correspondence.

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Table 1. The clinical aspect of the patients studied

Patient No.	Sex	Age	Type	Duration (year)	Therapy and outcome	Clinical manifestations
1	f	40	BT	14	7 yr, DDS	Left eye, no lagophthalmos, phthiasis bulbi, blind
2	m	70	BL	32	25 yr	Right eye, lagophthalmos III, opacity and vascularization of cornea, blind
3	m	40	BT	30+	12 yr, DDS	Left eye, no lagophthalmos, blind
4	m	56	BT	36	20 yr, DDS	*
5	m	28	BT	*	*	Right eye, corneal ulcer and perforation, panophthalmitis
6	m	42	LL	*	*	Right eye, pain and blind for 10 years, atrophy of the eyeball
7	m	48	LL	*	*	Right eye, blind and atrophy for 10 years
8	m	50	BT	24	12 yr, DDS	Right eye, lagophthalmos III, blind
9	m	45	BB	40±	35 yr, DDS	Left eye, lagophthalmos II, blind and atrophy
10	f	71	LL	45	cured	Right eye, lagophthalmos for 20 years, frequent redness, pain, sight lost for 6 years, eyeball atrophic
11	m	64	LL	45	cured	Right eye, lagophthalmos for 20 years, frequent redness, pain, lacrimation, photophobia, and eyeball atrophic
12	f	65	LL	32	cured	Right eye, frequent redness, pain, lacrimation, photophobia, sight loss for 30 years; lagophthalmos for 20+ years; corneal leucoma for 10+ years; eyeball atrophic

* Not known.

Materials and methods

We obtained eyes from 12 leprosy patients from leprosy clinics in China and Nepal, after enucleation. The operations were performed to stop pain in sightless eyes. The main clinical points of these patients are shown in Table 1.

The eyes were fixed in 10% formalin, dehydrated with graded alcohol and embedded in celloidin or paraffin. The sections were stained with H&E. Some of the sections were stained by the Fite–Faraco method.

Results

Atrophy of ocular tissues in various degrees was observed in all 12 eyes.

CORNEA

Focal or diffuse, mild or moderate infiltrations of lymphocytes, plasma cells, and some macrophages and neutrophils, as well as scar tissues were observed in the stroma of the cornea in all 12 cases. In 7 cases (Patients 1, 2, 3, 4, 8, 10 and 11) scar tissue was present in the whole thickness of the stroma with adhesion of the iris (corneal perforation and adhesive corneal leucoma) and there was focal thinning of the cornea in some of the cases. In 2 cases (Patients 5 and 12) small nodules composed of some epithelioid cells,

Figure 1. Granulomatous lesions in the stroma of the cornea (Patient 12) H&E ×100.

macrophages and Langerhans giant cells were seen (Figures 1 and 2) among the chronic inflammatory cell infiltrations.

SCLERA

Nonspecific chronic inflammatory cell infiltration in the anterior part of the sclera was the predominant lesion seen. In Patient 12 this cell infiltration was more significant around the nerves traversing the sclera. In Patient 6 epithelioid cells with Langerhans giant cells, mixed with some macrophages and lymphocytes, were gathered around nerves traversing the sclera. In some places thickening of the neurilemma was noted. In another eye (Patient

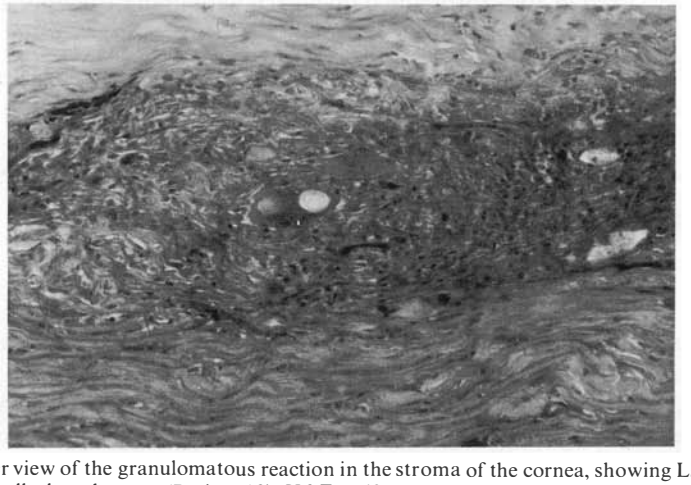

Figure 2. A higher view of the granulomatous reaction in the stroma of the cornea, showing Langerhans giant cells, epithelioid cells, lymphocytes (Patient 12). H&E ×400.

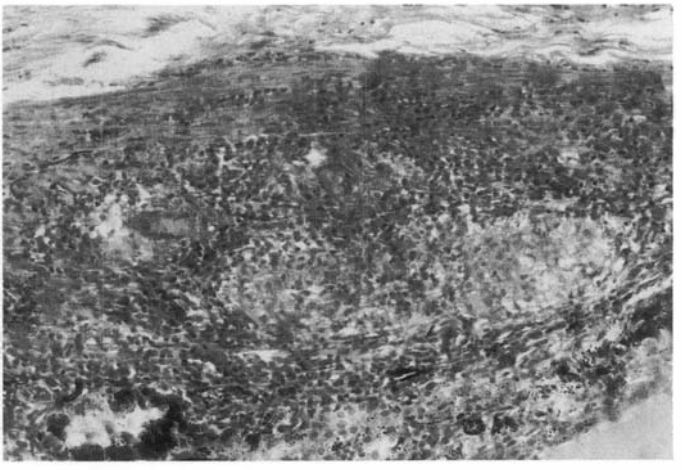

Figure 3. Granulomas in the ciliary body, showing the tuberculoid structure and many lymphocytes (Patient 6). H&E ×400.

2), a cyst, with pigment epithelia lining, was formed at the anterior part of the sclera and local thinning and ectasia was seen in the pre-equatorial region.

IRIS AND CILIARY BODY

Atrophy in various degrees occurred in 11 of the 12 specimens. Focal infiltrations of inflammatory cells were also found in 11 eyes. In 3 eyes small nodules composed of epithelioid cells, macrophages and Langerhans giant cells were seen among the other small round cells ((Patient 6 in the iris and in the ciliary body (Figure 3), Patient 11 (Figure 4) and Patient 12 in the ciliary body, and also in the anterior part of the choroid)). Fibrous membranes were formed at the anterior surface of the iris in 3 cases; in 3 cases there was occlusion of the pupil; and in another case oedema of the ciliary body was found.

CHOROID

In 3 cases, at the anterior part of the choroid, nonspecific chronic inflammatory cell infiltration was seen. In Patient 12 a small nodule composed of macrophages and a giant cell was seen at the anterior end of the choroid (Figure 5). Other changes seen in the choroid included congestion, oedema, fluid retention in the suprachoroid space, and scar tissue formation. In Patient 2, who showed a local thinning of sclera, the choroid adjacent to the thinned sclera showed atrophy, scar formation and adhesion to the atrophied retina. In 2 cases focal bone formation was noted under the degenerated or fibrosed retinal pigment epithelium layer.

RETINA

In all eyes, there was atrophy of the retina in various degrees. Mild perivascular small round cell infiltration was noted in some eyes. In Patient 6 small granulomas composed of macrophages, epithelioid cells, lymphocytes, and Langerhans giant cells, with some neutrophils were seen in 1 eye (Figure 6). Retinal detachment was seen in 5 cases and

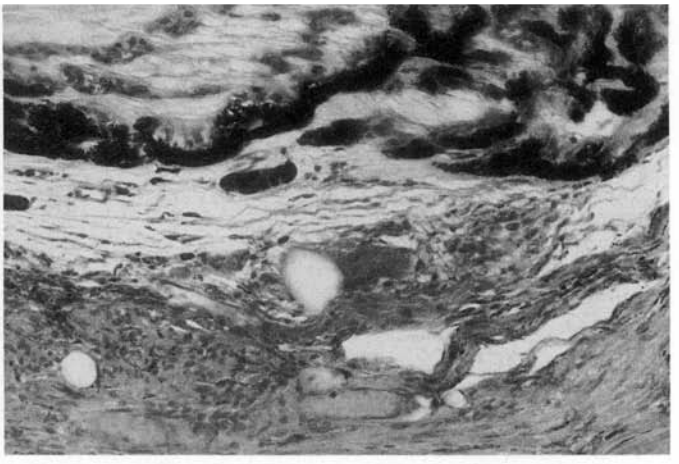

Figure 4. Giant cell and epithelioid cell reactions in the ciliary body (Patient 11). H&E ×400.

proliferated fibrous tissue protruding from the surface of the retina to the vitreous (retinitis proliferans) was seen in 2 cases, cystic degeneration in 4 eyes and haemorrhage in 1 eye. Destruction and proliferation of the retinal pigment epithelium were noted in many of these eyes.

OPTIC NERVE

Atrophic changes in various degrees was noted in all the 11 eyes in which optic nerve was found in the slides. Cavernous atrophy (in 1 eye) and cupping of the optic disc (in 3 eyes) were also found.

ANTERIOR CHAMBER

The anterior chamber angle was obliterated in 11 eyes. The changes in the trabeculae seen

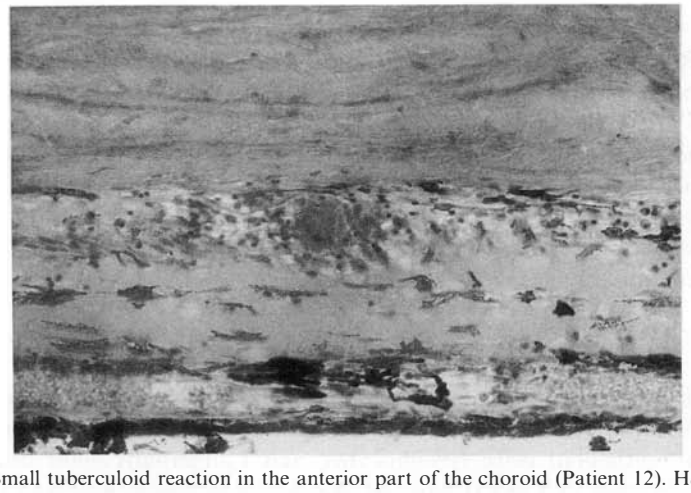

Figure 5. Small tuberculoid reaction in the anterior part of the choroid (Patient 12). H&E ×400.

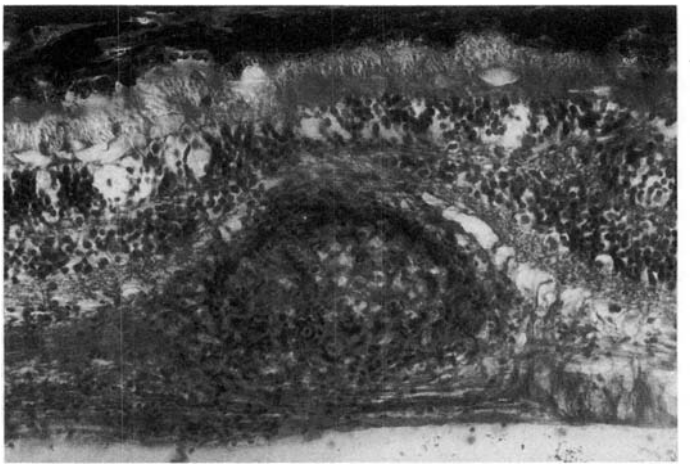

Figure 6. A small granuloma in the inner part of the retina (Patient 6). H&E ×400.

included homogenization, and fibrosis. In 5 eyes melanin granules were deposited in the trabecular tissue.

LENS

Cataractous changes were seen in all 10 eyes in which lens could be found in the sections. In Patient 7, the lens capsule was broken and the escaped lens material evoked a reaction with the appearance of foreign body giant cells, macrophages, eosinophils, lymphocytes and plasma cells. Fibrotic tissues were formed around the reacting cells. The proliferated fibrous tissue was stretching and adhering to the iris, ciliary body and the detached retina. In Patient 8, the lens capsule was broken, but no reaction was provoked.

VITREOUS BODY

In Patients 8 and 9, in the anterior part a cyclitic membrane was formed and in another case blood was dispersed in the vitreous.

In all the slides stained with the Fite–Faraco method, no acid-fast bacilli was found.

The various tissues of 4 cases in which nodules of granuloma were found are summarized in Table 2.

Table 2. The tissues harbor (+) the granulomas in 4 eyes

Patient		Disease		Tissues					
Number	Type	Duration (year)	Outcome of therapy	Cornea	Sclera	Iris	Ciliary body	Choroid	Retina
5	BT	*	*	+	–	–	–	–	–
6	LL	*	*	–	+	+	+	–	+
11	LL	45	cured	–	–	–	+	–	–
12	LL	32	cured	+	–	–	+	+	–

Discussion

The lesions in these 12 eyes involved all the intraocular structures showing degeneration and atrophy to various degrees.

Among the lesions seen, the most important were those in the cornea, iris and ciliary body, i.e. in the anterior segment of the eyes.

Nonspecific chronic inflammatory reaction and scar tissue formation were found in the corneas of all the 12 eyes and perforation of the cornea with adhesive leucoma was found in 7. The direct leprosy reactions usually would not cause a corneal perforation. Due to lack of detailed medical histories, we could only suspect that the perforation may be the result of a secondary infection caused by the insensitivity of the cornea and/or the lagophthalmos. The nonspecific inflammatory reaction in the cornea could be a secondary reaction, but the scar formation in the cornea might be the outcome of both a leprosy inflammation and a secondary manifestation.

Chronic nonspecific inflammatory reaction and atrophy in various degrees were found in the iris and ciliary bodies in 11 eyes. This kind of reaction could be the result of leprosy infection and also of intraocular infection secondary to the perforation of the cornea.

Anterior synechia of iris, anterior chamber angle closure secondary to iridocyclitis, scar formation in the trabeculae and pigment deposition in the trabecular region, could all raise the intraocular pressure and be the cause of the atrophy of retina and optic nerve. All the 11 eyes in which optic nerve was seen on their slides showed atrophy of the optic nerve in various degrees. In 3 of them cupping of the disc was noted, and in 1 cavernous degeneration.

The other alterations seen in these eyes, e.g. the nonspecific chronic inflammatory cell infiltration in the choroid and retina, retinitis proliferans, cystic degeneration, oedema, detachment and bone formation in and of the retina, could all be manifestations secondary to iridocyclitis, intraocular hypertension and perforation of the cornea.

The perilenticular ophthalmitis found in 1 eye showing phthisis bulbi was a reaction to the leaked lens material and not related directly to the leprosy infection.

In addition to the nonspecific inflammatory reactions, granulomas composed of macrophages, epithelioid cells, Langerhans giant cells, and lymphocytes, were found in various tissues in 4 eyes. There was no caseating necrosis noted. This kind of tuberculoid granuloma is a lesion found in the segment of the leprosy spectrum higher than the borderline type. The disease in Patient 5 was diagnosed as BT leprosy (without a record of the outcome of this therapy), but those of the other 3 were diagnosed as LL and the outcome of the therapy in 2 of the 3 was noted as cured and that of Patient 6 was not mentioned. Formerly, we had considered that this case might be a borderline leprosy patient,[11] but the encounter of tuberculoid granulomas in the eyes of 3 of the 5 LL patients made us wonder if there are possible explanations other than to recategorize the patients with this kind of leprosy lesion.

Discrepancy in the histopathological features of lesions in different tissues had been reported. In one report, the authors found in 36 patients the histopathology of their own skin and nerve biopsies differed in 21, the differences ranging from TT to BL.[10] Recently, a case with both lepromatous and tuberculoid histology in 1 skin lesion was reported.[6] There was a report of an autopsy case in which active lesions were found in the eyes while

the lesions in other tissues showed quiescence or the eye lesions were more active than the others.[8]

In view of these findings, we should consider the possibilities that the clinically 'cured' patients could still harbour tuberculoid inflammatory reactions, and that the manifestation of the tuberculoid granuloma in the eyes of LL patients (even after treatment) might not be rare, and whether an upgrading reaction had occurred in some of the patients. Such tuberculoid relapse as been observed in some patients with lepromatous leprosy, after many years of chemotherapy and bacteriological negativity.[12]

Tuberculosis infection in leprosy patients is not rare. But of eye tuberculosis almost all are haematogenous infections. The distribution of the granulomas in our cases does not seem to agree with that of an infection by this route, and ocular tuberculosis found in 4 cases in 12 randomly-gathered eyes of leprosy patients seems to be too improbable.

No acid-fast bacilli were found in the sections examined. That may effect the true nature but also might be due to the long storage of our specimens (and some were embedded in celloidin). If more sensitive methods to identify the *M. leprae* could be applied to the old slides, we would be glad to search and research them again.

Call for eye specimens

The findings of this study are clear and have been documented in the figures; however, the interpretation could vary—has to vary, in fact, especially until more material is available for histological examination. Therefore we are searching for eye specimens—either fixed in formalin or already bedded in a paraffin-block or kept in slides—in order to continue the studies. Naturally co-operation of any kind will result in co-authorship, should anything be published in future.

References

[1] Courtright P, Johnson GJ (eds). *Prevention of Blindness in Leprosy*. London: The International Centre for Eye Health, pp. 25–28, 1988.

[2] Bernard JC, Vazquez CAJ. Visceral lesion in lepromatous leprosy, study of 60 necropsies. *Int J Lepr*, 1973; **41:** 94.

[3] Brand ME, ffytche TF. Eye complications of leprosy, in Hastings RC (ed): *Leprosy*, pp. 223–242, Churchill Livingstone, New York, 1985.

[4] Desikan KV, Job CK. A review of postmortem findings in 37 cases of leprosy. *Int J Lepr*, 1968; **36:** 32.

[5] Desikan KV, Job CK. Report on the study of eye lesions in three autopsied cases of leprosy. *Ind J Lepr*, 1970; **42:** 1–4.

[6] Job CK, Jacobson RR, Hastings RC. Intralesional variations from lepromatous to tuberculoid histology—a case report. *Int J Lepr*, 1991; **59:** 116–119.

[7] Liu TC, Qiu JS. Histopathological study on peripheral nerves, lymph nodes and visceral organs in various types of leprosy. *Ind J Lepr*, 1984; **56** (No. 1) Suppl XI/447.

[8] Powell C, Swan L. Pathological changes observed in 50 consecutive necropsies. *Am J Path*, 1955; **31:** 1131–1147.

[9] Sakurai H *et al*. Histopathological findings on 115 corpses of leprosy. *Nagashima Arch Lepr*, 1964; **6:** 17–22. Abs in *Int J Lep* 1964; **32:** 349.

[10] Srinivasan H, Rao KS, Iyer CGS. Discrepancy in the histopathological features of leprosy lesions in the skin and peripheral nerve; report of a preliminary study. *Lepr India*, 1982; **54:** 275–282.

[11] Zhou HM, Shi ZR, Job CK. Unusual histological lesions in the eye of a leprosy patient. *Int J Lepr*, 1987; **55:** 507–509.

[12] Waters MFR, Ridley DS. Tuberculoid relapse in lepromatous leprosy. Lepr Rev, 1990; **61:** 353–365.

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Une étude histologique des lésions oculaires chez 12 patients lépreux avec lésion tuberculoïde dans 4 yeux

F. Brandt, Z. R. Shi, H. M. Zhou, B. Lu, H. Wu et N. Rai

Résumé Nous avons étudié les réactions histologiques dans 12 yeux de 12 lépreux (5 BT, 1 BB, 1 BL et 5 LL). Des lésions granulomateuses composées de cellules épitheliales, cellules géantes de Langerhans, macrophages et lymphocytes ont été observées dans divers tissus intra-oculaires, tels que cornée, scléreuse, iris, corps ciliaire ou rétine chez 4 patients (1 BT et 3 LL). Selon les dossiers, sur les 3 patients LL, 2 ont été guéris, et le résultat du traitement n'a pas été mentionné pour l'autre patient. Étant donné la présence de lésions granulomateuses chez les patients cliniquement guéris, et de granulome tuberculoïde dans les tissus intra-oculaires chez les patients LL, existerait-il quelques particularités dans les sites intra-oculaires? ou, peut-être, la réaction tuberculoïde est-elle seulement la manifestation d'une réactivité croissante? Pour répondre à cette question il faudra pratiquer d'autres examens d'yeux dans des cas de lèpre humaine.

Un estudio histológico de las lesiones oculares de 12 pacientes leprosos, con lesiones tuberculoides en 4 ojos

F. Brandt, Z. R. Shi, H. M. Zhou, B. Lu, H. Wu y N. Rai

Resumen Se estudiaron las reacciones histológicas en 12 ojos de 12 pacientes leprosos (5 BT, 1 BB, 1 BL y 5 LL). Se encontraron lesiones granulomatosas compuestas de células epitelioides, células gigantes Langerhans, macrofagos y linfocitos en varios tejidos intraoculares, p.e. la córnea, esclerótica, iris, cuerpo ciliar o retina en 4 pacientes (1 BT y 3 LL). De los 3 pacientes LL, según los registros, 2 fueron curados y no se mencionó el resultado del tercero. En vista del descubrimiento de las lesiones granulomatosas en los pacientes clínicamente curados, y el granuloma tuberculoide en los tejidos intraoculares de los pacientes LL, ¿es posible que hay algo extraño en los sitios intraoculares? ¿O quizás la reacción tuberculoide es solamente una manifestación de una reacción de mejora? Hace falta estudiar más ejemplos de casos oculares en leprosos humanos para poder contestar estas preguntas.

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Distinguishing post-kala-azar dermal leishmaniasis from leprosy: experience in the Sudan

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Accepted for publication 11 September 1992

Summary In this study 4 patients were post-kala-azar dermal leishmaniasis (PKDL), whose lesions were similar to those of lepromatous and borderline leprosy, are described. In 2 patients there was no previous history of kala-azar but they were residents of an area of known endemic kala-azar. Lack of proper clinical and laboratory assessment was behind the failure to diagnose PKDL. Consequently the patients were treated with antileprosy drugs without proof of leprosy. The 3rd and 4th patients, though suspected clinically of leprosy, were correctly diagnosed as PKDL with adequate history, clinical assessment and appropriate laboratory investigations.

The salient points in distinguishing PKDL from leprosy are described and discussed.

Introduction

Post-kala-azar dermal leishmaniasis (PKDL) is characterized by the development of macules, papules, nodules or infiltrative plaques in the skin, usually following treated kala-azar. In some patients there is no past history of kala-azar.[1,2] The condition is most frequent in India where it develops 1–5 years after the apparent cure of kala-azar.[3,4] PKDL also occurs in the Sudan[2,5] and Kenya.[6] Unlike the Indian form, African PKDL is less frequent and develops during or shortly after treatment of Kala-azar.[6]

Clinically the nodules and hypopigmented macules may be confused with leprosy, as may the pathology, particularly when the recently-described neuritis of the cutaneous nerves is present in the PKDL lesion[7] or when there is an epithelioid granuloma in which the parasites cannot be found.

In this paper we describe patients with PKDL who were misdiagnosed or who could have been misdiagnosed as leprosy sufferers because their symptoms strikingly resembled

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various forms of leprosy. Distinguishing features between PKDL and leprosy are described.

Case reports

The first patient was an Ethiopian refugee who reported with 2-year-old skin lesions on the face. At the onset of his illness, 5 years before, he had been diagnosed elsewhere as having leprosy on clinical grounds and was treated for 1 year with dapsone and rifampicin without improvement.

A skin biopsy was then performed. It showed a mononuclear cell infiltrate consisting of lymphocytes, plasma cells and macrophages. No leishmania parasites were found but the pathology was considered to be suggestive of leishmaniasis.

The patient was consequently treated with sodium stibogluconate (Pentostam, Wellcome Laboratories, U.K.) for 2 months. The lesions disappeared but recurred 1 year later and have persisted ever since. On physical examination the only abnormality was found in facial skin. This showed nodules and infiltrative plaques over the chin, the left cheek, the nose and the eyebrows.

Peripheral nerves were normal and sensations were intact. A slit smear was negative for leishmania and acid-fast bacilli. A biopsy showed a chronic inflammatory reaction

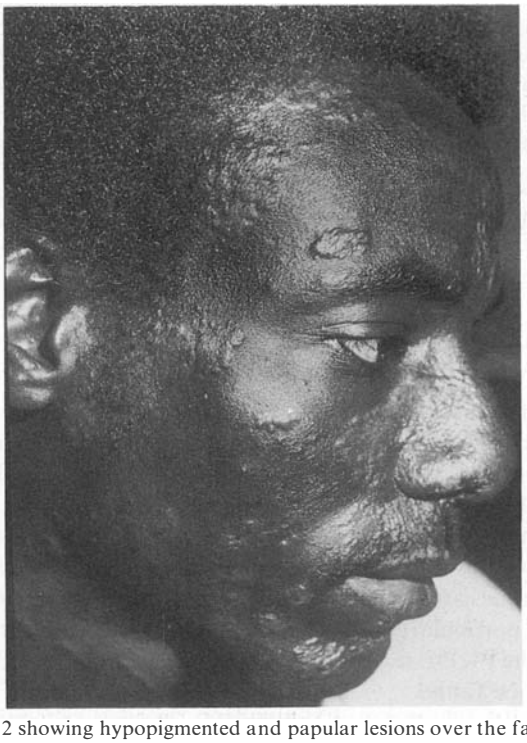

Figure 1. Patient number 2 showing hypopigmented and papular lesions over the face and neck. Some of the lesions are annular, have a hypopigmented centre, and raised papular margin.

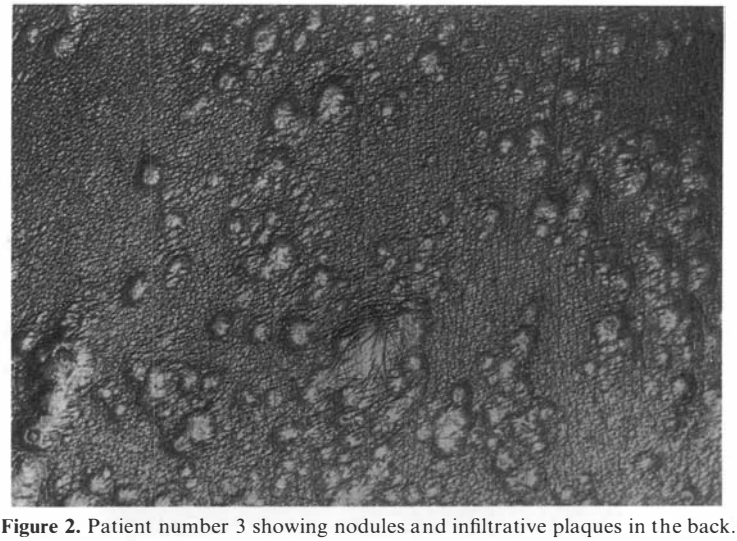

Figure 2. Patient number 3 showing nodules and infiltrative plaques in the back.

consisting of lymphocytes, plasma cells and macrophages. No leishmania parasites were detected. The patient was treated with Pentostam at a dose of 20 mg/kg daily for 3 months. Allopurinol at a dose of 20 mg/kg per day was also given at the same time. The lesions completely subsided and the patient remained well at 3 months follow up.

The second patient was a 24-year-old male from a known area of endemic kala-azar in the Sudan. He reported with a 10-year history of a skin rash involving the face, trunk, neck and limbs. He had no history of kala-azar. The patient had been on antileprosy treatment in another hospital for the previous 5 years without improvement.

The lesions were maculopapular and symmetrical. In some areas, particularly over the face, some of the lesions were annular with a coppery depigmented macule in the centre and papules at the margins (Figure 1). Peripheral nerves were normal and skin sensations were intact. A slit smear showed leishmania parasites and there were no acid-fast bacilli. A direct agglutination test for serum antibodies against leishmania (DAT) was positive.[8] The patient was treated with IV Pentostam at a dose of 20 mg/kg daily for 30 days. The lesions healed completely and he remained well for 1 year, when he reported with a recurrence.

He was then treated with Pentostam and Allopurinol at the same dosage and for the same duration as the 1st patient. His lesions cleared and he remained well at the 14-month follow-up.

The 3rd patient was a 20-year-old male who had kala-azar 5 years before reporting to us. He developed skin lesions on the face, ears, neck, upper limbs and trunk 1 month after treatment of the kala-azar. He was seen by a dermatologist, who made a provisional diagnosis of lepromatous leprosy. A biopsy, however, was diagnosed as tuberculoid leprosy by a pathologist.

Because of the discrepancy between the clinical and the pathological diagnosis the patient was referred for evaluation. Examination revealed symmetrical nodular lesions and plaques involving the skin of the extremities, face, neck and trunk (Figure 2).

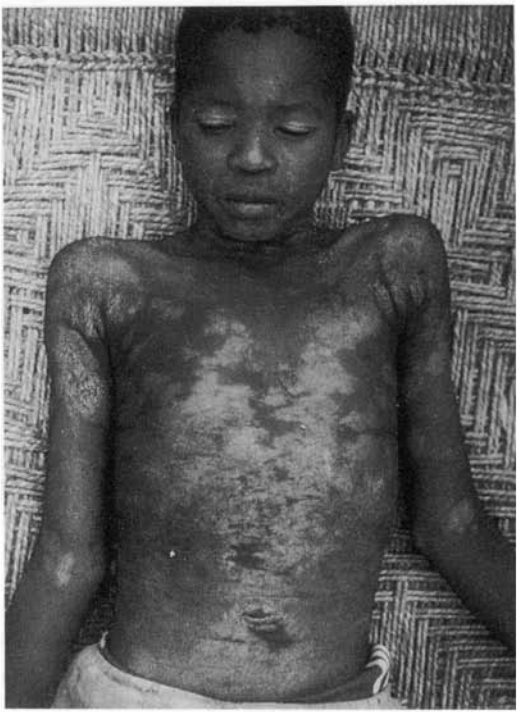

Figure 3. Patient number 4 before treatment with Pentostam showing extensive depigmented macules. Lesions in the face and limbs are symmetrical. Those over the trunk are confluent.

There was a marked lobulation of the ears. Peripheral nerves, motor power and reflexes were normal. Skin sensations were intact. A slit smear showed leishmania parasites. No acid-fast bacilli were found. A skin biopsy showed discrete epithelioid granulomas, lymphocytes and plasma cells. DAT was positive. The patient was treated with IV Pentostam at 20 mg/kg daily for 30 days. His lesions regressed markedly. After 6 months he was readmitted with a recurrence of lesions. He was treated with Pentostam and allopurinol, as described above. His lesions regressed but he was left with scars on the neck.

The 4th patient was discovered during a survey for kala-azar in a small village in the Eastern Sudan, near the border with Ethiopia. He was a 12-year-old male who had been treated for kala-azar when 8 years old. He developed a skin rash 10 days after the kala-azar treatment. He received no further treatment and the lesions gradually became worse. Examination showed macular and papular lesions on the face, upper limbs, neck and trunk. The lesions on the face and back were macules with a coppery appearance, and were symmetrical.

Over the chest and abdomen the depigmented areas were large and confluent (Figure 3). Over the shoulders and neck the lesions were maculopapular. Peripheral nerves and skin sensations were normal. DAT was positive. A slit smear showed leishmania parasites and there were no acid-fast bacilli. The patient was treated by a medical assistant in the village with Pentostam at a dose of 10 mg/kg daily for 15 days.

At follow-up 1 year later the lesions had improved markedly but the hypopigmentation did not disappear completely. Because the treatment given was considered inadequate the patient was given another course of Pentostam of 10 mg/kg/day for 30 days but was not seen again.

Discussion

The first 2 patients were misdiagnosed as having leprosy and received antileprosy treatment, without benefit. A possible reason why PKDL was not initially considered in the differential diagnosis was because the patients did not give a previous history of kala-azar. In the Sudan most cases of PKDL follow an attack of kala-azar but it may occasionally occur in the absence of a history of a clinically manifest kala-azar.[1]

The 1st patient was clinically diagnosed as lepromatous leprosy. Apart from the nodular lesions there were no other features of leprosy. A properly performed skin smear, which is always positive in lepromatous leprosy, would have been negative in this patient and therefore would have excluded that diagnosis. The original diagnosis was made in a refugee camp by an expatriate physician who perhaps had little experience of the endemic diseases of the area.

It was only after the patient failed to respond to antileprosy treatment that the possibility of leishmaniasis was entertained. Leishmania parasites were neither found in the 1st biopsy nor in the one performed in our hospital. This is not surprising since parasites are sometimes few in number and cannot be identified in the section.[9] In such cases culture, animal inoculation, or a polymerase chain reaction with appropriate primers may be helpful.

Clinically in this patient, diffuse cutaneous leishmaniasis, which occurs in Ethiopia, is an important differential diagnosis. Pathologically, however, this can be ruled out as leishmania parasites are numerous in diffuse cutaneous leishmansis and lymphocytes are scanty.[10] These features were absent in the present case.

The second patient simulated borderline leprosy. In the latter condition there may be a few or several asymmetrical hypopigmented erythematous or coppery, partly well-defined patches.[11] Annular and punched out lesions are characteristic. Our patient had annular lesions, papules and coppery macules. The lesions were possibly too symmetrical for borderline leprosy. A slit smear, which is usually positive for *Mycobacterium leprae* in borderline leprosy, was not done when the initial diagnosis was made, and biopsy was not performed. The patient was referred for evaluation only when the antileprosy treatment had failed to improve or clear the lesions. Eventually a slit smear and biopsy showed leishmania parasites and the patient responded to antileishmanial therapy.

The clinical appearance of the 3rd patient was remarkably similar to lepromatous leprosy. The lesions were symmetrical nodules and plaques. However, other features of long-standing lepromatous leprosy, such as madarosis, nasal involvement, thickened nerves, trophic ulcers and impairment of sweating were lacking. The diagnosis of lepromatous leprosy was dismissed when the pathology showed epithelioid granulomas and no mycobacteria. The diagnosis of PKDL was made on the demonstration of leishmania parasites in smears and the past history of kala-azar.

The 4th patient could easily have been mistaken for borderline leprosy. Indeed, when his photographs were shown to a group of dermatologists with experience in leprosy,

most favoured a clinical diagnosis of borderline leprosy. The demonstration of leishmania parasites, the previous history of kala-azar, the positive serology and the marked improvement following antileishmanial therapy proved the leishmanial aetiology of the disease.

In 3 of the patients in whom serology was done, antibodies against leishmania were found—El Hassan *et al.* have already demonstrated that such antibodies are not found in the various forms of leprosy.[1]

Acknowledgment

We thank the Medical Illustrations Unit, the Faculty of Medicine, University of Khartoum for the photographs and Miss Nashwa El Hassan for typing the manuscript.

References

[1] El Hassan AM, Ghalib HW, Zijlstra E, El Toum IA, Ali MS, Ahmed HMA. Post-kala-azar dermal leishmaniasis in the absence of visceral leishmaniasis. *Lancet*, 1990; **336:** 750.

[2] El Hassan AM, Ghalib HW, Zijlstra E, El Toum IA, Satti M, Ali MS, Ali HMA. Post-kala-azar dermal leishmaniasis in the Sudan: clinical features, pathology and treatment. *Trans Roy Soc Trop Med Hyg*, 1992; **86:** 245–248.

[3] Napier LE, Das Gupta CR. A clinical study of post-kala-azar dermal Leishmaniasis. *Ind Med Gaz*, 1930; **65:** 249–257.

[4] Thakur CP. Epidemiological, clinical and therapeutic features of Bihar Kala-azar (including post-kala-azar dermal leishmaniasis) *Trans Roy Soc Trop Med Hyg* 1984; **78:** 391–398.

[5] Kirk R, Satti MH. Studies in Leishmaniasis in the Anglo-Egyptian Sudan. IV. A punctate rash in treated cases. *Trans Roy Soc Trop Med Hyg*, 1940; **34:** 213–6.

[6] Rees PH, Kager PA. Visceral Leishmaniasis and Post-kala-azar dermal leishmaniasis. In: *The Leishmaniasis in Biology and Medicine*, vol 2. Peters, W., Killick-Kendrik, R. (Eds). London: Academic Press, 1987, pp. 583–615.

[7] El Hassan AM, Ali MS, Zijlstra E, El Toum IA, Ghalib HW, Ahmed HMA. Post-kala-azar dermal leishmaniasis in the Sudan: peripheral neural involvement. *Int J Dermatol*, 1992; **31:** 400–403.

[8] El Harith AE, Kolk AHJ, Kager PA *et al.* A simple and economic direct agglutinination test for sero-diagnosis and sero-epidemiological studies of visceral leishmaniasis. *Trans Roy Soc Trop Med Hyg*, 1986; **80:** 583–587.

[9] Ramesh V, Saxena Uma, Misra RS, Mukherjee A. Post-kala-azar dermal leishmaniasis: a case report strikingly resembling lepromatous leprosy. *Lepr Rev*, 1991; **62:** 217–221.

[10] Bryceson ADM. Diffuse cutaneous leishmaniasis in Ethiopia. The clinical and histological features of the disease. *Trans Roy Soc Trop Med Hyg*, 1969; **63:** 708–737.

[11] Thangaraj RH, Yawalker SJ. Clinical features. In: *Leprosy for Medical Practitioners and Paramedical Workers*. Basle, Switzerland: Ciba Geigy Limited, 1988, pp 27–41.

Comment distinguer entre la leishmaniose cutanée post-kala-azar et la lèpre: expérience au Soudan

A. M. El Hassan, F. A. Hashim, M. Abdullah, E. E. Zijlstra et H. W. Ghalib

Résumé Dans cette étude, nous décrivons 4 patients atteints de leishmaniose cutanée post-kala-azar (PKDL) dont les lésions étaient similaires à celles de cas de lèpre lépromateuse et borderline. Chez 2 patients il n'y avait pas d'histoire antérieure de kala-azar, mais ils habitaient une région où le kala-azar est reconnu comme endémique. Le manque d'un propre bilan clinique et de laboratoire est à la base de l'échec de diagnostic du PKDL. Les patients ont donc été traités avec des médicaments anti-lèpre sans preuve de lèpre. Chez les 3ème et 4ème patients, bien que le tableau clinique fasse suspecter la lèpre, un diagnostic correct de PKDL a été porté, appuyé sur l'histoire, le bilan clinique et les examens de laboratoires appropriés.

Les points qui ressortent dans le diagnostic différentiel entre PKDL et la lèpre sont décrits et discutés

Distinguiendo entre leishmaniasis dérmica post-kala-azar y la lepra: la experiencia en el Sudán

A. M. El Hassan, F. A. Hashim, M. Abdullah, E. E. Zijlstra y H. W. Ghalib

Resumen En este estudio, se describen 4 pacientes con leishmaniasis dérmica post-kala-azar (PKDL) con lesiones similares a la lepra lepromatosa y a la lepra incierta. En 2 pacientes, no habían antecedentes de kala-azar, pero residían en una zona conocida por ser endémica al kala-azar. El fracaso del diagnóstico para PKDL se debió a una falta de una evaluación clínica y de laboratorio apropiada. Por consecuencia, los pacientes fueron tratados con drogas contra la lepra sin prueba de la presencia de la lepra. El 3er y 4o pacientes, aunque sospechados clínicamente de ser leprosos, fueron correctamente diagnosticados para PKDL mediante una evaluación adecuada histórica y clínica, e investigaciones adecuadas de laboratorio.

Se describen y discuten los puntos sobresalientes cuando se distingue el PKDL y la lepra.

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Paralysis of occipitofrontalis in a borderline case of leprosy

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Accepted for publication 23 October 1992

Summary A patient with neuritic leprosy developed borderline skin lesions. Later, another skin lesion developed on the left side of the forehead with clinical involvement of the supraorbital branch of the ophthalmic division of the trigeminal nerve. Simultaneously, paralysis of the occipitofrontalis and mild paresis of orbicularis oculi occurred.

Introduction

Leprosy is treated as a disease that affects peripheral nerves, the skin and the mucous membrane of the nose, mouth and eyes. The most common cranial nerve involvement leads to paralysis of orbicularis oculi and lagophthalmos. Diwan[1] reported that there was an incidence of about 3% of this problem. Ishihara[2] reported 4 cases of bulbar palsy. Loss of taste sensation due to involvement of the chorda tympani fibres of the facial nerve was reported by Sheskin[3] and by Dharmendra & Ramu.[4] Later Malaviya & Ramu[5] reported a loss of taste sensation due to a combined involvement of facial, lingual and glossopharyngeal nerves.

Case report

RJ, a 37-year-old Hindu male, came to the Central Jalma Institute of Leprosy, Agra, complaining of a loss of sensation of the anterolateral aspect of the lower left leg of 6 weeks' duration. He had not received any treatment and was not aware of any relatives and friends suffering with similar problems.

* Correspondence: c/o Dr G. N. Mishra

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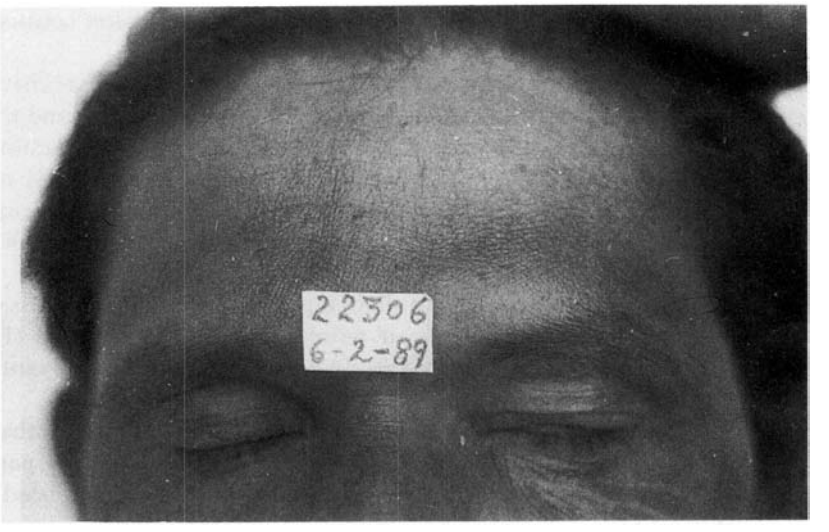

Figure 1. Hypopigmented lesion on the left side of the forehead and incomplete closure of the left eyelid due to lagophthalmos.

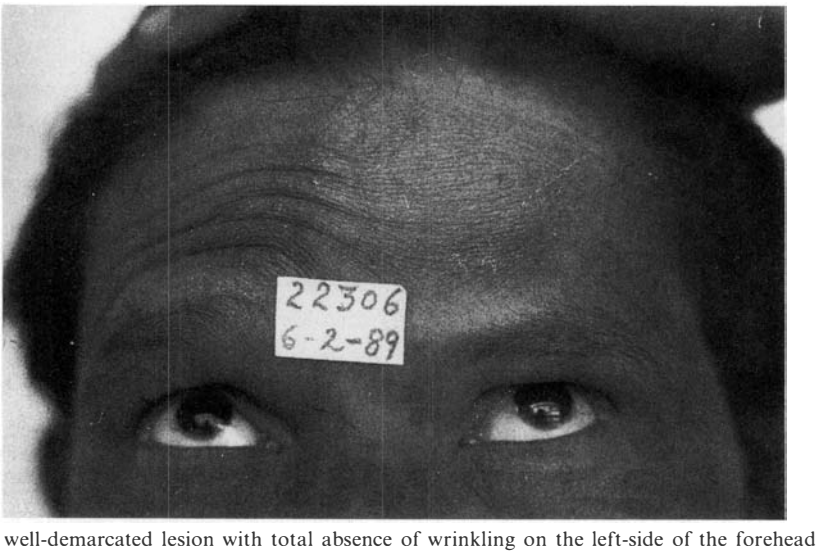

Figure 2. A well-demarcated lesion with total absence of wrinkling on the left-side of the forehead due to paralysis of the frontal belly of the occipitofrontalis.

On examination, there was anaesthesia on the anterolateral aspect of the lower two-thirds of the left leg. The left superficial peroneal nerve was thickened. The slit-skin smear on examination was negative but the Dharmendra Lepromin test was weakly positive for early reaction. A diagnosis of neuritic leprosy was made.

The patient received standard antileprosy therapy consisting of rifampicin 600 mg once a month and dapsone 100 mg daily for a month.

After treatment for 10 months, he noticed a hypopigmented erythematous patch where he first had anaesthesia. This was diagnosed as a BT lesion. As there was no change

in the bacteriological status the treatment was continued and the lesion became inactive after 1 year.

After the disease had been considered inactive at a subsequent visit a slight hypopigmentation was found on the left side of the forehead (Figure 1) and the patient complained of a tingling sensation whenever he pressed this area. On examination the supraorbital branch of the left ophthalmic division of the left trigeminal nerve was palpable and firm pressure evoked tingling. Within 1 month this skin lesion became more demarcated. At this stage steroids were added for symptomatic relief and 450 mg of rifampicin were given daily for a fortnight.

After 6 months, the patient developed a slight lagophthalmos and paralysis of the left occipitofrontalis muscle resulting in loss of wrinkling over the forehead (Figure 2). Steroids and Berin were presented in full doses. In addition to this, the relevant exercises were explained and he was asked to wear protective glasses.

Antileprosy therapy was continued as before. The disease became inactive after 12 months of therapy, but the anesthesia and lagophthalmos along with paralysis of occipitofrontalis and resultant loss of wrinkling on the forehead still persisted.

Discussion

In the last few years workers have reported a change from neuritic to borderline leprosy.[6–9] In this patient both types occurred together. Damage to the zygomatic branch of the facial nerve in the region of the zygomatic osseofibrous tunnel results in lagophthalmos. The temporal branches supplying to the frontal belly of the occipitofrontalis are also parallel to the zygomatic branch. The damage mechanism is probably similar.

The combination of paralysis of the occipitofrontalis and neuritis in the supraorbital branch of the trigeminal nerve is an unusual feature.

References

[1] Diwan VS. A survey of deformities in leprosy (with special reference to face). *Lepr Rev*, 1962; **33:** 255–264.
[2] Ishihara S. Bulbar palsy appearing in leprosy patients. *La Lepro*, 1967; **36:** 199 (Japanese: English summary).
[3] Sheskin J, Even Tov Y. *El Sentido del gusto en el mal de Hansen Lepro gia* 1974; **19:** 3 (Spanish: English summary).
[4] Dharmendra, Ramu. *Leprosy*, vol. 1, p. 311. Kothari Medical Publishing-House, Bombay, p. 311, 1979.
[5] Malaviya GN, Ramu G. Loss of taste sensation over the tongue in leprous facial palsy—A case report. *Lepr India*, 1981; **53(4):** 656–659.
[6] Noordeen SK. Epidemiology of polyneuritic type of leprosy. *Lepr India*, 1972; Vol. XLIV. No. 2, pp. 90–96.
[7] Chacko GJG. Evolution of pathological lesions in leprosy patients and their immunological significance. Proceedings of Indo-U.K. Symposium on leprosy (1986), pp. 82–89, published at the Central Jalma Institute for Leprosy.
[8] Shenoi, SD, Padhee A. Poly-neuritic leprosy changing in borderline tuberculoid (BT). *Ind Jr Lepr*, 1990; **62:** 363–364.
[9] Talwar S, Jha PK, Tiwari VD. Neuritic leprosy epidemiology and therapeutic responsiveness. (Abstract) XVII Biennial Conference and the Workshop of Indian Association of leprologists. 1992. Abstract of Scientific Papers (F.C.38), p. 36.

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Paralysie de l'occipito-frontal dans un cas de l'epre borderline

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Résumé Un patient atteint de lèpre névrotique a présenté des lésions cutanées borderline. Plus tard, une autre lésion cutanée s'est developpée sur le côté gauche du front avec atteinte de la branche supra-orbitale de la division ophtamique du nerf trijumeau. Simultanément, la paralysie de l'occipito frontalis et une faible parésie de l'orbicularis oculi ont été observées.

Parálisis del occipucio frontal en un caso de lepra incierta

B. MISHRA, G. N. MALAVIYA, A. GIRDHAR, S. HUSSAIN Y B. K. GIRDHAR

Resumen Un paciente con lepra neurítica desarrolló lesiones inciertas de la piel. Más tarde, otra lesión de la piel desarrolló en el lado izquierdo de la frente con implicaciones clínicas de la rama supraorbital de la división oftálmica del nervio trigeminal. Simultáneamente, occurrió una parálisis del occipucio frontal y una paresia del orbicular ocular.

Lepr Rev (1993) **64,** 64–72

SPECIAL ARTICLE

Leprosy—the challenge*

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It is a privilege to pay tribute to the Reverend Philip Thomas Byard Clayton, CH, MC, DD. Tubby Clayton was a supremely happy man, untidy, absent minded about meetings and agenda, but never about people. He believed that everyone was capable of contributing something towards the welfare of the world. An unmilitary figure, he is one of the most famous Army padres. During the First World War he created peace and beauty close behind the trenches in Belgium. He had a genius for making and encouraging lasting friendships irrespective of rank, race or creed. The lamp he lit at the original Toc H has never been extinguished. In 1932 he sailed to West Africa. Understandably, he was profoundly shocked by the degradation and squalour endured by people with leprosy who were driven outside the walls of Kano. He was as deeply impressed by the different conditions in the well run leprosarium in Zaria. As a result, he played a significant role in the foundation of BELRA which evolved into LEPRA, a many faceted registered charity.

Relief of suffering and cure of the disease are priorities for LEPRA and all other like-minded organizations but the ultimate aim is to eradicate the disease. It took 200 years for vaccination to abolish smallpox. Fears of diphtheria and poliomyelitis, nightmares of my distant schooldays, have been banished in the United Kingdom by immunization, but they exist elsewhere. The search for a specific leprosy vaccine has been only partially successful. Clinical trials demonstrated that the more easily obtained BCG gives a similar degree of protection. Therefore, it is suggested that newborn children of leprous parents should be given a protective dose of BCG.[1]

A senior and respected American physician told me that there was no urgency to raise funds for leprosy, 'the disease is declining and in any case all the patients are cared for by the State.' In some ways he is correct. In 1990 WHO published figures for the global prevalence of *reported* cases of leprosy, coverage by multidrug therapy and the numbers completing this treatment. There were 3·7 million registered cases and an estimated twice that number of unregistered ones. This suggests an incidence of about 11–15 million.[2,3] This number seems trivial when compared with the huge combined total of 560 million suffering from malaria, schistosomiasis or lymphatic filaria. Although not a killer, leprosy has a disproportionately severe effect upon the social, economic and psychological status

* This paper was presented as the Clayton Memorial Lecture, London, on 30 September 1992. The text has been modified where it dealt with information given in a recent publication.[5]

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of the patients. The geographical distribution is widespread and unfortunately the use of multidrug therapy is low in the worst affected areas.[3]

Multidrug therapy reduces infectivity in a matter of days, early lesions usually resolve within months or a year or two of beginning treatment. The duration of therapy is finite, the majority of paucibacillary and multibacillary cases are discharged within 9 months and 3 years, respectively, after initiating the therapy. The global relapse rates for

Figure 1. An unveiled Moslem woman and child were checked in the leprosy control programme in the N-W Frontier Province. Her child was astonished to see a white face for the first time.

paucibacillary and multibacillary cases are 0·1% and 0·06% per annum, respectively, as against 1–2% a year for necessarily prolonged dapsone monotherapy which carries the risk of inducing drug resistance. MDT has fewer erythema nodosum leprosum reactions than any other treatment regime. For these reasons the compliance rate of patients ranges from 80 to 90% in most areas as against a maximum of 50% for dapsone monotherapy.

I am not competent to discuss the detailed pros and cons of this treatment, but from data presented by WHO, provided it is given sufficiently early, it offers most hope for combating the disease, its disabilities and stigmata. Therefore, WHO now considers it reasonable to aim at eliminating the disease as a public health problem by the year 2000. Nevertheless, much work needs to be done to reach this more limited target.

Early detection may be difficult for many reasons, including attitudes, local cultures and geography, as exemplified by the vacation experiences of 2 English medical students working with the Marie Adelaide Leprosy Control Team in the North West Frontier Province of Pakistan (Figure 1). Although Moslem, the women are unveiled but no female over 10 years may be examined by a male. This is borne out by the figures for 1989 when only 59 of the 215 new cases were female.[4] Whilst both extrapriot women were treated with the greatest kindess and courtesy, it is not seemly for local women to do such work.

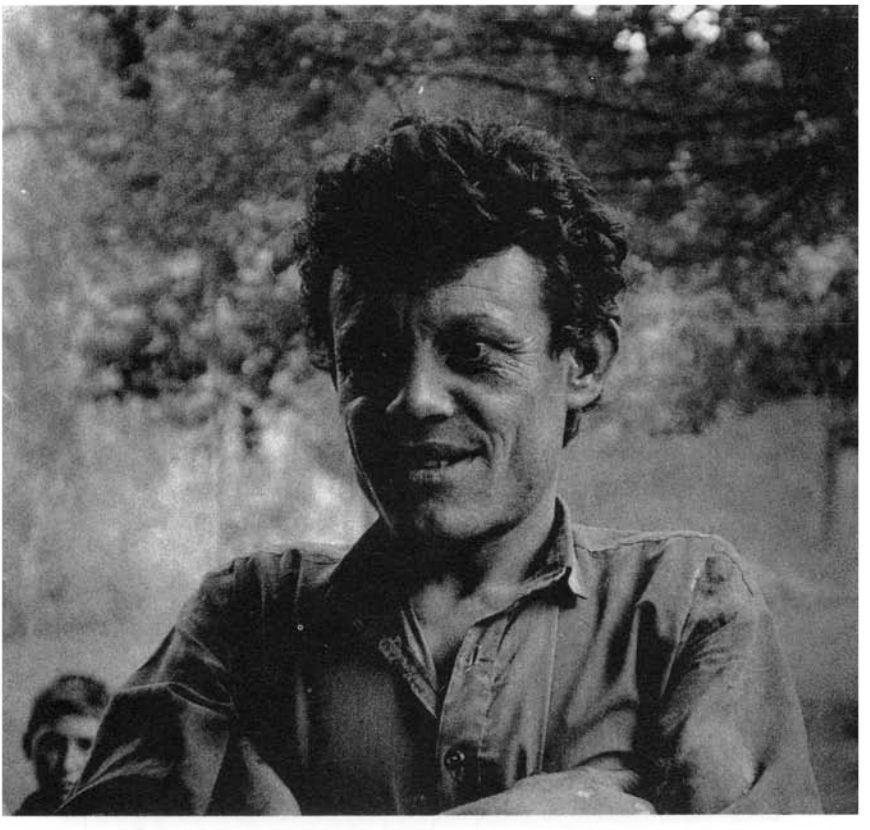

Figure 2. This farm labourer had been forced to leave his home and family when the disease of leprosy was diagnosed.

The scenery is as magnificent as travel is difficult. The main road from the south to Chitral is 10,000 ft above sea level and impassable for 9 months a year. The most reliable form of transport in some other regions is by donkey or by foot.

Miss Lawman examined hundreds of girls and women and found 3 early cases who had over 60 contacts between them. On a farm the source of infection was a labourer, who had lost his eyebrows and the bridge of his nose. Both hands and feet were ulcerated (Figure 2). He had 48 contacts, of whom 15 were women and 20 children. The farmer's wife had a single scaly patch on the left upper arm, swelling of the radial and ulnar nerves and no feeling in either hand. Extracts from the annual report of this control team for

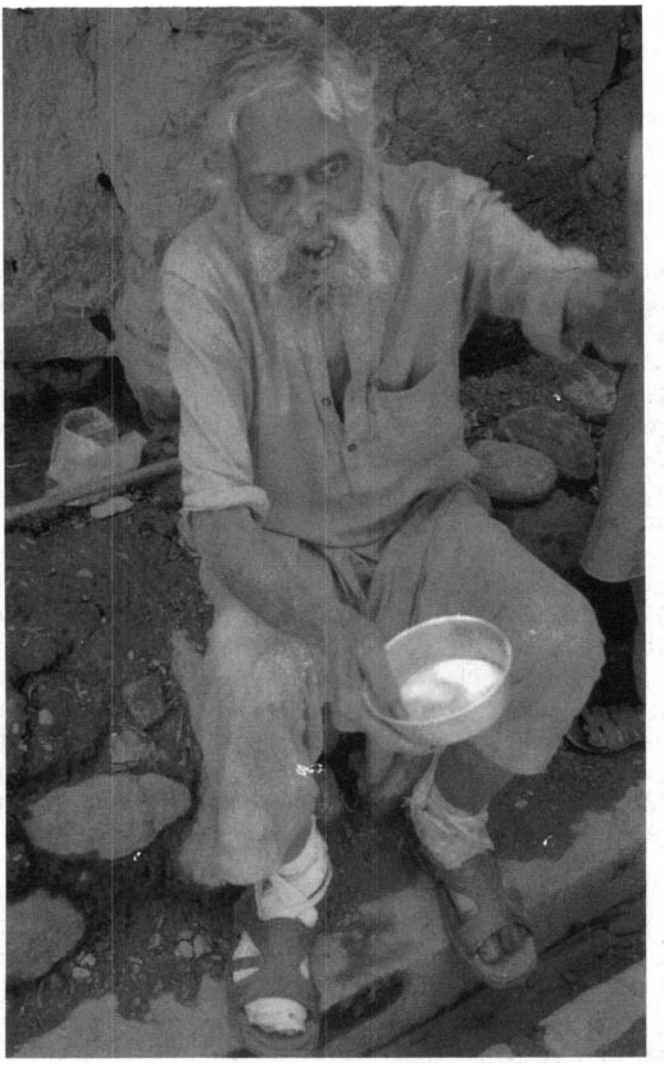

Figure 3. This destitute beggar was homeless, without family, blind and kept alive by the generosity of others. Arrangements were made with his consent for him to have a bed in a mission hospital.

1989 indicate the scale of arduous and patient work required to find and treat early cases and monitor the contacts.

The WHO data from India for 1980–90 are encouraging. The number of new cases is falling and the discharge rate is increasing. However, the state of some who are discharged from treatment for leprosy is distressing, e.g. a frontiersman was cured, but had lost the tips of all his digits through painless ulceration and destruction of bone from secondary infection and probably ischaemia of bone due to changes in nutrient arteries and deposits of granulomas. Every Sunday in Khartoum two rows of 'burnt out' cases lined the route from the cathedral door, none had any fingers, thumbs or toes. Alms were dropped on to their palms. After making his donations a 5-year-old boy marched back up the line and shook every man by the hand. The delighted smiles and roars of laughter indicated the depth of isolation to which these men were usually subjected. Figure 3 shows an elderly Pakistani who is homeless, destitute, without family and kept alive by the kindness of fellow villagers. He is completely blind with damaged hands and feet, and his leprosy is cured. With his consent, the Marie Adelaide Leprosy Control Group is making arrangements for him to have a bed in the mission hospital in Peshawar as he has neither a bed nor any possessions. If disfigurement and complications are to be avoided, early detection, prompt treatment and supervision are imperative. Delay may lead to disfigurement. Infiltration of the coatings of the eye may be complicated by glaucoma and blindness. When the facial nerve is involved, failure to provide eye drops, protective glasses or perhaps to narrow the palpabral fissure by tarsorrhaphy can result in avoidable blindness due to trauma and infection.

Other disabilities follow paralysis of peripheral nerves. Early signs may be subjective reports of tingling, numbness, 'a feeling of ants crawling on the skin' and even pain, both locally and in the cutaneous distribution of the nerve. Weakness or paralysis in the upper limb lead to characteristic paralytic deformities and to disturbances of skilled and unskilled prehensile movements. The loss of sensation can lead to severe damage from painless cuts and burns. Clawing of the hand means that only the tips of atrophied fingers take all the pressure of gripping a glass, and even holding tools with large handles is insecure. Skilful tasks such as sewing or writing are difficult without a pinch grip and sensitive fingers and thumb. Preserving mobility is vitally important to maintain independence and to prevent psychological amputation and stiffness, which make it impossible to restore movement by tendon transplants. Injury and paralytic deformity are 100% avoidable by explaining the risks to patients, enlisting their cooperation in regularly carrying out frequent daily passive movements, and wearing lively splints that allow movement and restore normal posture and function. Immobilizing splints are only indicated for short periods after surgery for relief of severe pain or ulceration. Protective gloves may be provided for certain types of work and simple modifications can assist weak hands.[5]

Damage to the common peroneal and posterior tibial nerves results in disturbances of gait and weight bearing with risks of forming callosities and trophic ulcers, risks which are increased in bare foot people. In normal walking the heel strikes in inversion because of the shape of the talus. The heel slides and weight is transmitted through the lateral border of the foot. The toes grip the ground prior to toeing off, which finally involves eversion of the foot and a grinding movement under the head of the first metatarsal, as demonstrated by Paul Brand.

In leprosy the common peroneal is involved at the head of the fibula. This results in

foot drop, and a high-stepping slapping gait. The foot strikes the ground in marked inversion and under the head of the fifth metatarsal. Gait can be corrected by a lively splint. This has a lateral leg iron with a spring at the level of the ankle joint and a square spur slotted into the heel of the shoe,[5] and whether wearing long trousers, shorts, a dhoti or a skirt, it is not only less conspicuous than the conventional toe-raising spring which has the spring attached at the level of the toe crease of the shoe, but also it is more efficient and less likely to be associated with a contracture of the calf muscle.

Lesions of the posterior tibial nerve commonly occur at the ankle, producing complete anaesthesia of the sole of heel and foot. Paralysis of the intrinsic muscles produces clawing of the toes. If shoes are worn callosities form on the dorsum of the proximal interphalangeal joints. Wasting of soft tissue, including muscles, reduces the surface area for weight bearing. The risk of ulceration is grave. The clawed toes can be corrected by an insole. This must go the whole length of the foot. Plasterzote has been advocated as insoles can be tailor made for each individual. Well fitting leather shoes are ideal but these are costly and conspicuous in bare foot communities, making patients unwilling to wear them despite the necessity for doing so.

Detecting early signs of disturbances of cutaneous functions requires a carefully taken history, avoidance of leading questions, visual inspection for signs of sweating, patterns of papillary ridges, atrophy of the pulps of fingers and toes, and signs of callosities, fissures or ulceration. Tests need to be conducted in a quiet room. They are time consuming and each one should be demonstrated and explained to a patient who is at ease and neither hungry nor needing to go to the lavatory. As both patient and examiner have to concentrate, frequent pauses are desirable. Calibrated equipment and accurate recording of progress are necessary. This does not entail sophisticated electronic equipment which has no place in routine clinical and field work. However, reliable, repeatable objective results are feasible. Measurement of nerve conduction rates and electrical reactions are only essential in research and in specialized base hospitals.

Equipment, which can be made by any hospital technician or handyman, has been described in detail in a previous publication, together with a few items that are obtainable commercially.[5]

Simple mapping of areas of loss or disturbance of sensibility can be recorded photographically or on standard diagrams. More elaborate recording has been advocated, but one suspects that this will be more time consuming but no more accurate than simple mapping. Practical experience will tell.

Disturbances of gait are revealed by examining soles and uppers of footwear. With an uncorrected foot drop heels are lightly worn, the outer border of fore foot and toe of the sole are heavily scuffed. Intrinsic palsy makes a deep toe crease on the upper part of the shoe whilst the toe of the sole is unworn.

Footprints in wet sand, or more conveniently made on paper by standing on a large ink pad, are instructive. More costly equipment such as Harris' mats,[6] can give calibrated estimates of pressure. The presence and location of callosities are danger signals and indicate urgent readjustment of lively splints or insoles.

The role of reconstructive surgery cannot be discussed fully, but 2 points are worth noting. The isolated lesions of the ulnar nerve at the elbow, the median at the wrist, the common peroneal at the knee and posterior tibial at the ankle joint are subcutaneous and at relatively low temperatures. However, each of these locations is proximal to a restrictive fibro-osseus tunnel. Carpal and tarsal tunnel syndromes are well recognized

and early, rather than late, release of pressure is necessary if serious structural nerve damage is to be avoided. Could the severity of these leprous lesions be lessened by early operation combined with steroids which are known to relieve pain?[7] The second point relates to the recent publication of results of resection and repair of localized lesions by autogenous muscle grafts in carefully selected cases.[8] Tendon transplants can alleviate mechanical defects, but regeneration of nerves is the only method of restoring sensation. Results of the pilot study of this operation are encouraging. There is no problem of rejection of the graft, no donor nerves are sacrificed. The criteria for selection of patients and the results are shown in Tables 1–5. These patients and those in the extended trials in Ethiopia and Brazil have to be followed up carefully for several years to avoid raising false hopes.

If the limited objective set by the WHO, the final goal of eradication of leprosy, is to be achieved, the public and the medical and paramedical professions need to be aware of problems, alert to possibilities of cure and rehabilitation, and active in instituting early

Table 1. Criteria of selection for repair by muscle graft*

Informed consent
At least 18 months stable complete motor and sensory paralysis
Completion of 6 months drug treatment
No active ulceration
Not receiving steroids

*All tables are based on the data of Pereira, Curtis & Turk.[7]

Table 2. Pilot study of muscle graft repair of nerves

Number of patients	10 (7M, 3F)
Age range (years)	17–37
Type of disease	
Borderline tuberculoid	7
Borderline lepromatous	1
Lepromatous	2

Table 3. Nerves repaired by muscle graft in the pilot study

Number of nerves grafted	12
Median nerves	3
Posterior tibial nerves	9
Duration of disease (years)	4·5–12
Duration of paralysis (years)	1·5–7
Length of grafts (cms)	2·5–6

Table 4. Information of progress given by patients

No recovery of movements
(Irreversible structural changes occur in muscles after prolonged denervation)
7/12 reported improved sensory function
5/9 reported ability to distinguish between walking on stones and treading on thorns*
0/12 had no signs of recovery
2/9 had reduction of ulcers and fissures on feet

* At the time of publication of this paper 14/20 reported this finding.

Table 5. (Pre) and postoperative clinical findings for 12 nerves (Duration of follow-up 8–18 months)

Tinel's sign distal to lesion (cms)	(0/12)	0 in 4* 1–16
Sweating	(3/12)	9
Joint position sense	(0/12)	11
Response to 10 gm PIN	(0/12)	5
Response to 20 gm HAIR	(0/12)	4

*Progressed to but not beyond distal suture line.

Vibration sense was present in 9 preoperative cases lost immediately after operation, recovered in 11/12.

and appropriate treatment. Therapy includes the psychological, social and economic rehabilitation of patients which begins *pari passu* with medication. A change in the attitude of the public to the sufferers and to the disease forms an essential part of the process of social reintegration of patients. Figures 4 and 5 summarize the plan of action and characteristics of therapy.

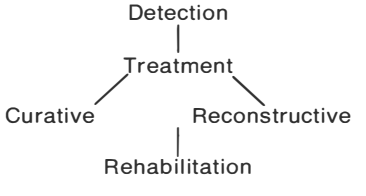

Figure 4. The plan of action in treating leprosy.

Appropriate
Educational
Intensive
Overseen
Understanding

Figure 5. The characteristics of sound therapy.

Acknowledgment

Figures 1–3 are published by kind permission of Miss Sarah Lawman, many of whose photographs were shown as slides in the lecture.

References

[1] World Health Organization. *Immunological problems in leprosy research: 2* (1973). Reproduced in *Lepr Rev*, 1974; **45**: 275.
[2] World Health Organization. *Multidrug therapy for leprosy: an end in sight*. Geneva (1988). 1–32.
[3] World Health Organization. *Towards elimination of leprosy: Leprosy Control Programme* (1992). 1–12.
[4] Marie Adelaide Leprosy Centre. Annual Report 1989, and Silver Jubilee of leprosy control measures in N.W.F.P. and celebrations marking the establishment of leprosy control in District Swat (1990).
[5] Palande D, Bowden REM. The early diagnosis of damage to nerves in leprosy. *Lepr Rev*, 1992; **63:** 60–72.
[6] Duckworth T. Pedobarography, in *The Foot* ed. Helal. B and Wilson. D. Churchill Livingston, Edinburgh, 1988, 108–130.
[7] Personal communication.
[8] Pereira JH, Palande DD, Subramanian A, Narayanakumar TS, Curtis J & Turk JL. Denatured autologous muscle graft in leprosy. *Lancet* 1991; **338:** 1239–40.

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Letters to the Editor

A CASE REPORT: DUAL MYCOBACTERIAL INFECTIONS IN A PARAGUAYAN PATIENT DUE TO *MYCOBACTERIUM LEPRAE* AND *MYCOBACTERIUM FORTUITUM*

Sir,

A 32-year-old Paraguayan male patient presented himself at the governmental dermatology clinic in Asunción, Paraguay with typical, sharply demarcated tuberculoid leprosy lesions. They were distributed over the dorsum, the left upper and right lower extremities. The lesions showed loss of tactile and thermal sensations. In addition, there were several elevated ulcerations on the dorsum of the right foot. A lesion located on the left shoulder was histopathologically classified as borderline–tuberculoid leprosy (BT). The patient was started on multidrug therapy (MDT) with the daily dosage of brodimoprim 200 mg, of rifampicin 600 mg and of dapsone 100 mg.[1,2] He was enrolled on this therapy trial on a voluntary basis, and 1 month later showed a distinct worsening of the infiltrated ulcerated skin lesions on the dorsum of the right foot. They fluctuated on touch. It was decided to aspirate them. The drained material had a viscous, cheesy consistency, was green in colour and mixed with blood. Direct microscopical examinations of the aspirate—stained with gram and methylene blue—revealed no bacteria. The Ziehl–Neelsen staining on the other hand showed numerous rods (4+). The cultures for bacteria other than acid-fast bacilli were negative. In the aspirate numerous leucocytes were to be seen, unexpected findings in a cold abscess found in BT.[3–5] Therefore, additional investigations were undertaken and MDT was stopped. The infiltrated ulcers on the dorsum of the right foot were re-aspirated and the material sent to the Research Institute for Experimental Biology and Medicine Borstel (Borstel, Germany). The results of the bacteriological cultures were positive for *Mycobacterium fortuitum*, i.e. an environmental bacterium. The organism was resistant to rifampicin, isoniazid, streptomycin and ethambutol. A blood sample was also drawn. No HIV antibodies were detected in ELISA. The treatment of the patient with ofloxacin was recommended. The drug, however, was not available locally. In the mean time the patient's condition deteriorated rapidly. The lesions on the dorsum of the right foot became worse. The recommended ofloxacin was replaced by norfloxacin (800 mg daily). After 2 days of therapy he showed some signs of improvement. The treatment was continued for a period of 8 weeks. At the time of this report, the lesions caused by *M. fortuitum* have completely subsided and the BT lesions have also disappeared.

It is known that environmental mycobacteria may be found on the skin of healthy individuals and in lesions of leprosy patients without causing disease.[6] We point out in this report the problems which may arise in such infections. We also want to emphasize that appropriate bacteriological diagnosis and treatment recommendations in infections due to environmental mycobacteria may be life-saving for leprosy patients.

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References

[1] Seydel JK, *et al. In vitro* and *in vivo* experiments with the new inhibitor of *Mycobacterium leprae* Brodimoprim alone and in combination with Dapsone. *Drug Res* 1990; 44(1): 69–75.
[2] Grosset JH, JI B, Guelpa-Lauras CC, Perani EG, N'Deli LN. Trail of perfloxacin and ofloxazin in the treatment of lepromatous leprosy. *Int J Lepr*, 1990; **58(2):** 281–295.
[3] Thangaraj RH, Yawalkar SJ. *Leprosy for medical practitioners and paramedical workers.* 1986. Ciba Geigy Ltd., Basel, Switzerland, 4th edition.
[4] Hastings RC. *Leprosy 1985*, Churchill Livingstone.
[5] Gatti JG, *et al. Manual de Dermatologia*, Editorial 'El Ateneo' Bs. As. 1986. 10th edition.
[6] Fandiho FCO, Salem JI, Gontijo-Filhop PF, Marója MF, David HL. Mycobacterial flora of the skin in leprosy. *Int J Lepr*, 1991, **54(4):** 569–575.

OPERATIONAL RESEARCH AND ITS AIMS

Sir,

In an effort to encourage more submissions on this topic we would like to express how useful the exchange of ideas in the field would be and that *Leprosy Review* would be well placed for doing this.

The basic aim of operational research is to carry out work to improve the operational efficiency as well as the effectiveness of leprosy work. This could be issues such as the packaging of drugs and their distribution; major reviews of the operation of a leprosy programme. Many simple studies are done looking at the compliance rates which involved interviewing field staff and patients, reviewing reports on the programme and then making simple changes which are effective in improving treatment and compliance. Other projects include looking at trials of health education materials, and validation of diagnostic criteria.

These projects are worth reporting for the benefit of others working in the field because they could have important effects on other programmes if this kind of information were shared.

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CONSIDERATIONS IN THE INTEGRATION OF EYE CARE INTO LEPROSY CARE SERVICES

Sir,

Courtright & Lewallen[1] rightly draw attention to the often neglected subject of the integration of eye care into leprosy services. I would like to comment on their selection criteria for the need of an eye-care programme within a leprosy-control programme.

A common and easy to recognize eye complication in leprosy, with good prospects for treatment, is lagophthalmos due to facial nerve damage. Most lagophthalmos is the result of reversal reaction in borderline patients (BT, BB, BL) and occurs either before registration or shortly (within 6–12 months) after the start of antileprosy therapy,[2] that is early in the disease and among young patients. At least half of such patients belong to the paucibacillary BT group. Overall, facial nerve damage, will exist or develop in 2–3% of all newly registered leprosy patients, in spite of multidrug therapy (MDT).

Elderly patients with a long history of disease will often show multiple and chronic eye complications due to leprosy, but alas it is true, that apart from possible cataract extraction or lid surgery for lagophthalmos, usually not much can be done. In general no new eye complications due to leprosy will appear in this group of patients, but it is certainly useful to screen them for treatable conditions.

A long delay between disease onset and commencing antileprosy treatment may result in more eye complications, but any MB patient may develop ENL with associated acute iridocyclitis or sclerouveitis, which, although rare, is a potentially blinding complication.

General eye diseases, such as senile cataract or trachoma, may well be responsible for half of the visual impairment and blindness in leprosy patients of all classifications. National and regional data on blindness will also give an indication of the existence of such eye diseases among leprosy patients.

The criteria, as mentioned in the article,[1] could therefore give the false reassurance to programme managers that there is no need for an eye care programme, because the majority of their patients are paucibacillary (as in most of Africa for example), or because they have rarely 'cured' patients over 50 years old, or with a disease history of more than 25 years while they are under their care, or because patients usually present with only a short delay between symptom onset and treatment commencement.

Any leprosy control programme should devise a step-by-step system for the treatment of eye complications taking into account the local situation, and starting with the peripheral leprosy fieldworker, via the paramedical leprosy supervisor to either the referral leprosy hospital or directly into the eye care services via the eye nurses and ophthalmic assistants towards the ophthalmologist. It should be kept in mind that the patient should be treated as near home as possible.

The leprosy fieldworker and the leprosy supervisor should be the frontline workers in this system and be trained in the recognition, treatment, follow-up, or referral of patients with lagophthalmos, 'the red eye', blindness due to cataract and the other most common eye diseases. These workers should, among others, have access to antibiotic eye ointment, for immediate treatment of conjunctivitis and early corneal ulcer. Eye-lid surgery should be made possible in the referral leprosy hospital and cataract and other surgery in the nearest hospital that has the necessary facilities.

It is true that some workers in the ophthalmic community may have to be motivated, involved and additionally trained in order to care for leprosy patients. To create good relationships, and to break any prejudice against leprosy that may still exist, it may be of help if leprosy programmes welcome eye workers in training for some studies or practical work in the relevant setting.

The Netherlands Leprosy Relief Association has been working along these lines for many years in the programmes it supports.

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References

[1] Courtright P, Lewallen S. Considerations in the integration of eye care into leprosy services. *Lepr Rev*, 1992; **63:** 73–77.
[2] Naafs W, Wheate HW. The time interval between the start of anti-leprosy treatment and the development of reactions in borderline patients. *Lepr Rev* 1978; **49:** 153–157.

REPLY: CONSIDERATIONS IN THE INTEGRATION OF EYE CARE INTO LEPROSY CARE SERVICES

Sir,

We are grateful for the comments and discussion by Dr M. Hogeweg regarding integration of eye care and leprosy care services. Our suggestions for defining the minimum criteria for the establishment of an eye-care programme are based on 2 assumptions: (1) in most leprosy-control settings access to eye-care services will be limited and we must try to formulate criteria which will apply to the bulk of patients with potentially blinding eye disease; and (2) programme managers need a rapid and relatively accurate method for assessing the needs for the development of a specific programme to address the eye-care needs of patients.

As Dr Hogeweg points out, in India only 2–3% of newly registered paucibacillary patients have or develop nerve damage resulting in lagophthalmos and/or ectropion.[1] She further points out that most lagophthalmos develops during reversal reactions occurring within 6–12 months of the initiation of MDT. Proper treatment of reversal reactions by systemic steroids, intended to reduce all nerve damage and deformities, has been shown to reduce the development of lagophthalmos by 75%.[2] We assume (*hope*) that this treatment will be part of any good leprosy-control programme even if special attention is not given to eye care. Lagophthalmos is not uncommon in multibacillary patients although the lack of proper population-based studies limits our ability to generate estimates. Steroids will not help these patients but surgical intervention will. They are likely to be neglected if considered 'cured' by the leprosy control programme.

The majority of blindness in leprosy patients, as in all blind patients, is caused by a cataract. There is strong evidence that multibacillary patients with chronic uveitis develop cataracts both at a younger age and more frequently than the general population.[3–5] Therefore, we have emphasized the importance of eye care in the group of patients > 50 years of age, with multibacillary disease, and with a history of leprosy > 25 years. Although, as Dr Hogeweg points out, there is currently little we can do to avoid chronic uveitis and cataract in these groups, the cataracts can be removed and blindness cured.

We would regret it if programme managers decided there was no potentially blinding ocular pathology in their leprosy patients based on the minimum criteria we presented; a proportion of patients will always require ophthalmologic intervention.

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References

[1] Hogeweg M, Kiran KU, Suneetha S. The significance of facial patches and type 1 reaction for the development of facial nerve damage in leprosy. A retrospective study among 1226 paucibacillary leprosy patients. *Lepr Rev*, 1991; **62:** 143–149.

[2] Kiran KU, Hogeweg M, Suneetha S. Treatment of recent facial nerve damage with lagophthalmos, using a semistandard steroid regimen. *Lepr Rev*, 1991; **62:** 150–154.

[3] Brandt F, Kampik A, Malla OK, Pokharel RP, Wos J. Blindness from cataract formation in leprosy. *Dev Ophthal*, 1983; **7:** 1–12.

[4] Malla OK, Brandt F, Anten JGF. Ocular findings in leprosy patients in an institution in Nepal (Khokana). *Br J Ophthalmol* 1981; **65:** 226–230.

[5] Kagame GK. Ocular leprosy in Africa. *Soc Sci Med*, 1983; **17:** 1737–1742.

COR PULMONALE SUBACUTE AND RECURRENT ERYTHEMA NODOSUM LEPROSUM

We would like to report an unusual case of a lepromatous leprosy patient, with recurrent ENL in the lower limbs, who presented with deep thrombophlebitis with subsequent multiple pulmonary embolism.

In 1989, this patient was submitted to the leprosy treatment scheme recommended by the WHO for a consecutive 2-year period,[1] during which time reccurring Type II reaction or erytherma nodosum leprosum (ENL) took place both isolatedly and in conjunction with systemic alterations, namely fever, arthralgia, anorexia, and other signs and symptoms typical of the toxemic state. In addition, neurological alterations also occurred, in the form of spontaneous pain and swelling of the posterior tibial and ulnar right nerves. During the reactional states, 300 mg/day of thalidomide and 50 mg/day of prednisone were administered with gradual dose reduction upon observation of clinical improvement. The patient was discharged at the end of the treatment and on our recommendation he continued taking the prescibed medication and returned to the Leprosy Care Centre within a year.

Approximately 10 months after discharge, he came to the Centre Unit with signs of ENL together with acute cor pulmonale as a result of repetitive pulmonary embolism (Figure 1), in connection with thrombophlebitis and panniculitis in the lower right limb. He informed the staff that the current episode had actually begun around 45 days before and that the symptoms at the tme had been fever, arthralgia of the right ankle and knee, oedema in the right foot, and pleuritic-type pain in the thorax. In addition, the staff was also informed that during that same period he had been admitted to a private hospital which was unaware of his leprosy condition and had been diagnosed as having pneumonia. He was released 15 days later without improvement, then readmitted to another hospital with fever, arthralgia, and repetitive abrupt dyspnoea together with fainting spells. He was diagnosed as having congestive cardiac insufficiency and diuretics were prescribed. He was discharged again with a slight improvement of his clinical symptoms.

Once at the Centre, the patient was immediately examined and found to have a fever,

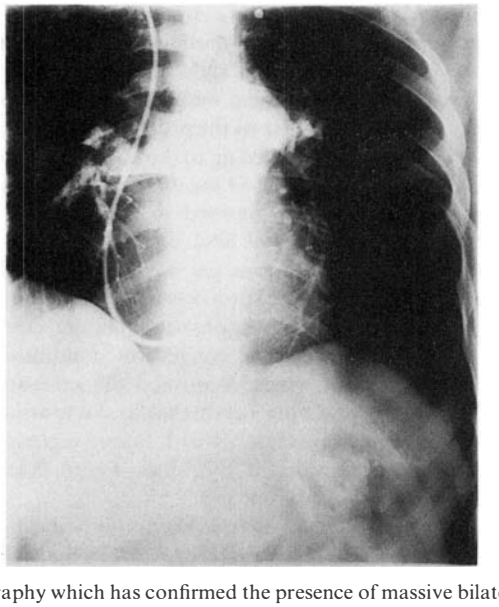

Figure 1. Pulmonary angiography which has confirmed the presence of massive bilateral pulmonary embolism.

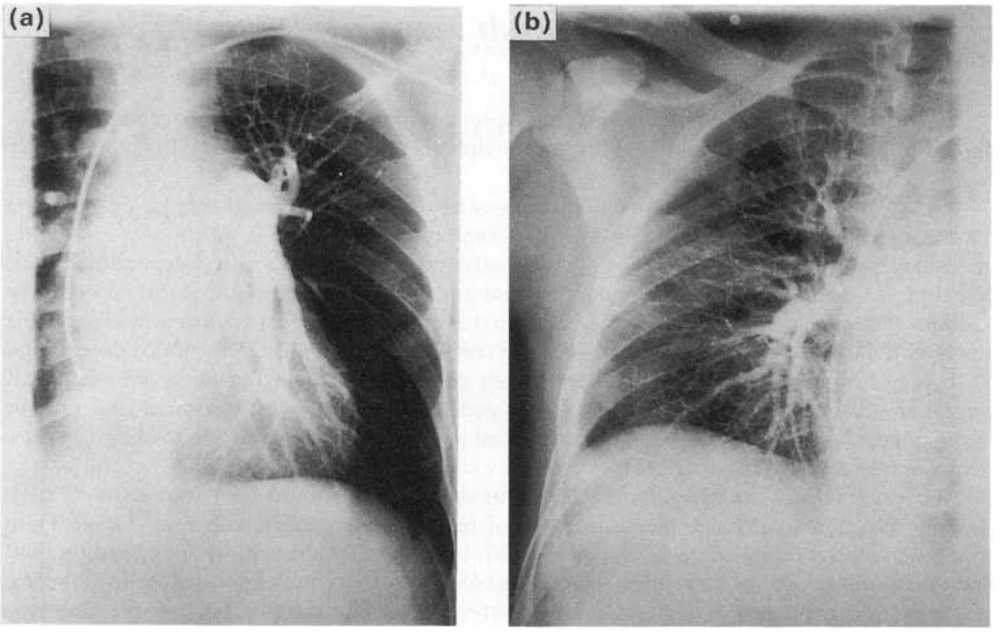

Figure 2 (a) and (b). Pulmonary angiography after anticoagulant therapy. Lysis of the clots and improvement of pulmonary perfusion was observed.

tachycardia, tachypinea, an arterial pressure of 120/80 mmHg, and a venous pressure of 15 cm H_2O. The precordial examination revealed propulsive and sustained ictus of the right ventricle, palpable pulmonic valve closure (P_2), regular cardiac rhythim, presence of the 4th heart sound of the right ventricle, fixed splitting of the 2nd heart sound, and p_2 hyperphonetical systolic murmur of tricuspid regurgitation. On listening to the pulmonic midsystolic murmur, the lungs showed a diminished vesicular whisper in the lower 3rd part of the right thorax, without adventitious noise The abdominal examination showed a liver of 18 cm with a congestive positive abdominal-jugular reflux, while the dermatology examination showed the presence of ENL, both isolated and in crops, situated on the lower limbs. Oedema was observed up to the knee on the lower right limb, along with hardening of the thigh and calf with the increased local temperature diagnosed as panniculitis.

After the examinations, the patient was interned in the Evandro Chagas Hospital of the Oswaldo Cruz Foundation with the diagnosis of ENL and subacute cor pulmonale. He had been taking 100 mg thalidomide and 20 mg prednisone per day on a regular basis up to that time and upon hospitalization an anticoagulation medication was prescribed and prednisone was increased to 60 mg. But even though a positive treatment response could be detected after 8 days of treatment, recurrences of dyspnoea and systemic venous congestion continued to persist. Whereupon pulmonary angiography was performed which confirmed the presence of bilateral pulmonary embolism, so it was decided to implant a filter (umbrella) in the lower cava vein below the renal veins. The patient thereafter progressed satisfactorily with a rapid regression of the signs of systemic venous congestion and absence of reccurrences of dyspnoea (Figure 2(a) and (b)). After 20 days he was discharged from the hospital without symptoms.

To date, there has been no written evidence of deep venous involvement having a significant an effect as it had in this particular case.[2-5] There also seems to be no previous knowledge of a leprosy patient showing such exaggerated local signs associated with the development of massive repetitive

pulmonary embolism, while lacking any other of the preconditions for venous thrombus. Thus, the purpose of this report is to alert leprosy health care personnel to the possibility of the occurrence of strong venous involvement in leprosy patients and development of acute pulmonary embolism.

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References

[1] World Health Organization. Report of a meeting on action plans for Leprosy control. New Delhi, 1982 (WHO/Lep/83.1).
[2] Mukherjee A, Girdhar BK, Desikan KV. Leprous Phlebitis. *Int J Lepr*, 1980; **48:** 48–50.
[3] Ashok M, Bhaneshwar K, Goyind N, Gopal R, Kottapalli V. Involvement of subcutaneous veins in lepromatous leprosy. *Int J Lepr*, 1983; **51:** 1–6.
[4] Basu SP, Ghosh S, Mukerj N, Roy KP. Angiography in leprosy. *India J Radiol*, 1960; **14:** 180–87.
[5] Guttierez F. Flebite Leprosa. *Rev Bras Leprol*, 1961; **29:** 123.

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Teaching Materials and Services

Centre for African Language Learning, London

Centre for African Language Learning (CALL), London, UK, provides a wide range of African languages taught by mother-tongue speakers through individual or group tuition. A variety of teaching and learning resources cover issues including development and Primary Health Care. Translating and interpreting services are also available. Contact: Saidi El Gheithy, CALL, Africa Centre, 38 King Street, London WC2E 8JT. Tel: 071 240 0199.

Health Policy and Planning

This Journal on health development published by Oxford University Press in association with the London School of Hygiene and Tropical Medicine, and edited by Patrick Vaughan and Gill Walt in the LSHTM, Keppel Street, London W1CE 7HT. A recent editorial note follows:

'The first issue of this volume (Number 7) of *Health Policy and Planning* was unusual—a special issue on rapid assessment methods in tropical disease research—and we are keen to elicit responses from readers about its impact. The papers took a critical look at a variety of purposes—rapid evaluation of disease prevalence, mortality estimates due to specific causes, assessment of community problems and priorities and rapid data analysis—and their potential for application to tropical settings. While the articles focused on tropical diseases the methodological issues raised by the authors are equally relevant to most other health problems.

What do readers think of the issue? Should *Health Policy and Planning* produce more special issues? Are there other topics suitable for this sort of presentation? Readers' comments and views, as always, are encouraged. Enquiries to the journal from other symposium and conference organizers would also be welcomed.

We are still keen to receive papers from the developing world and, while happy with the increase in numbers of papers from industrialized world writers, we would particularly welcome contributions from people living in the less developed world. We welcome articles and reports:

- reviewing major topics
- reporting original research
- short articles covering health policy issues
- short reports of research studies and evaluations of general interest.

A 1-year free subscription for the best articles from authors in developing countries is one way we try to encourage writers. The winners of a free subscription for 1992 are: Bong-min Yang in Korea, R. C. Sharma in India and R. Soebekti in Indonesia.

Volume, No. 3, September 1992 carries 2 articles on leprosy: 'Where are we now? Leprosy' by S. K. Noordeen and 'Ten best readings in leprosy' by A. C. McDougall.

Epidemiology Programme; Liverpool School of Tropical Medicine, UK

The Liverpool Epidemiology Programme (LEP) was set up in response to the World Health Assembly's call for greater use of epidemiology in monitoring strategies for health for all and for improved training in epidemiology, particularly to meet the needs of developing countries. The aim

of the programme is to promote the methods of epidemiology towards the improvement of health in developing countries.

LEP is based in the Unit for Statistics and Epidemiology (USE) in the Liverpool School of Tropical Medicine (LSTM) and receives financial support from the Overseas Development Administration. Our team of experienced epidemiologists and statisticians work alongside health professionals to define the role of epidemiology in their work and to identify training needs. Activities include the provision of short courses in Liverpool, assistance in running courses overseas and the development of training material.

We are inviting colleagues with similar interests to join the programme as visiting fellows for periods of between 3 and 6 months. The most suitable people will be health professionals involved in training programmes in their own countries who would like to develop and share their ideas with us in Liverpool. Their activities might include the development of:

Methodologies, for example, methods of needs assessment, alternative training strategies, techniques of evaluation.
Training material using various media, for example, case studies, computer based learning, reference material.
Syllabuses for short courses for groups of health staff, for example, working in maternal and child health, disease surveillance, district health management, refugee health care.

We are looking for people with innovative ideas for promoting epidemiology in health care.

Visiting fellows will have had some years' experience in senior government or university posts and it is essential that they receive in-country support to implement the projects which they develop in Liverpool.

Research fellows will each receive:

—a return fare to Liverpool;
—subsistence and accommodation in Liverpool;
—administrative support in Liverpool;
—access to the computing and library facilities in LSTM;
—academic and technical support from LEP staff during and after their stay in Liverpool.

Applicants should send:

—a detailed curriculum vitae;
—a 2-page summary of the work they would like to undertake in Liverpool indicating how long it will take (3–6 months);
—a statement from their employer indicating the support which will be given to implement the ideas after returning from Liverpool.

Applications will be assessed in terms of quality and of their likely contribution to the overall aims of LEP. Up to 6 fellowships will be awarded between September 1992 and December 1994. There are no closing dates for receipt of applications but applicants are encouraged to apply immediately.

Applications or requests for more information should be sent to:

Liverpool Epidemiology Programme, Unit for Statistics and Epidemiology, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK Fax 051-708 8733.

Action in International Medicine: AIM, London, UK

AIM wishes to promote improvements in health care to needy populations by helping to strengthen continuing education and postgraduate training for health professionals, and by assisting in the development of the infrastructure of health care. AIM works through interprofessional collaboration by responding to initiatives and requests from within countries of 'the South'.

More than 80 organizations have pledged their support in principle. What is needed now is to expand a programme of action which can be carried out in full participation with institutions and individuals.

AIM intends to proceed by enhancing skills and improving the working conditions of health professionals on the front line, and by focusing more public and political support on the health care of deprived communities.

Further information is available from: AIM, Windeyer Building, 46 Cleveland Street, London W1P 6DB, UK.

International Health Exchange (IHE)

Formerly called the Bureau of Overseas Medical Service, IHE has now expanded considerably. It aims to:

- facilitate the provision of health workers to developing countries;
- promote appropriate training for those preparing to work overseas;
- raise awareness among health workers of the health and human resource needs of the developing countries.

Short training courses include the following:

Introducing Primary Health Care in Developing Countries
Refugee Community Health Care
Surgery for Non-Surgeons
and an evening course on PHC, Branching Out

IHE publishes the annual *Short Courses Calendar* and provides information on training courses and resources in the UK.

Its bi-monthly magazine, *The Health Exchange*, explores issues and practical approaches to health care in developing countries. It provides an opportunity for health workers and non-governmental organizations to share experiences and viewpoints. The additional job and course listings make this magazine unique in the development field.

Amongst many valuable items of information available from IHE, the following is a list of Health Resource Centres in the UK:

AHRTAG (Appropriate Health Resources and Technologies Action Group), 1 London Bridge Street, London SE1 9SG, Tel: 071 378 1403. Provides an information and enquiry service for health workers going to work or working in developing countries; runs a resource centre comprising a comprehensive range of PHC information and materials; offers contacts with a network of health programmes and individuals; publishes practical manuals and free international newsletters: Dialogue on Diarrhoea; Acute Respiratory Infection; Community Rehabilitation News (CBR News) AIDS Action.

TALC (Teaching Aids at Low Cost), Barbara Harvey, PO Box 49, St Albans AL1 4AX, Tel: 0727 53869. Sends out 60,000 excellent, low cost health books and numerous teaching materials each year. Send off for a books/materials price list.

CENTRE FOR INTERNATIONAL CHILD HEALTH, Institute of Child Health, 30 Guilford Street, London WC1, Tel: 071 242 9789. All TALC books and materials on display and available; audio visual centre; Community Based Rehabilitation (CBR) resource centre; library on all aspects of child health and resource centre including country specific material. The Department runs short and long courses on the priority issues in PHC and Maternal and Child Health and Rehabilitation.

INTERNATIONAL PLANNED PARENTHOOD FEDERATION (IPPF), Regent College, Regents Park, Inner Circle, London NW1, Tel: 071 486 0741. Promotes family planning and mother and child health as part of the development process. Library and reading room; teaching materials, much material free and in a variety of languages; produces useful material on AIDS and a

newsletter. If visiting, see the Centre for World Development Education in the same building. Tel: 071 487 5438.

CHILD-TO-CHILD PROGRAMME, Institute of Education, 20 Bedford Way, London WC1H OAP, Tel 071 612 6650. This is a programme promoting an approach to health education and primary health care spread by a network of health and education workers in the developing world. It focuses on the role children play in caring for younger children, and how they can improve their community's health. Free materials available.

NATIONAL COMMUNITY HEALTH RESOURCE, 57 Chalton Street, London NW1 1HU, Tel: 071 383 3841. This is a UK-orientated organization working to promote and develop national and regional networks of community health initiatives and health workers, to discuss issues of common interest and to work towards influencing national health policy.

IDEA (International Disability Education and Awareness), William House, 101 Eden Vale Road, Westbury, Wiltshire BA13 3QF, Tel: 0373 827635. IDEA offers training courses and advisory services to health workers, organizations and individuals concerned with disability overseas and in Britain. Resource library and wide network of contacts available.

LIVERPOOL SCHOOL OF TROPICAL MEDICINE, Pembroke Place, Liverpool L3 5QA, Tel: 051 708 9393. Library, audiovisual department. Education Resource Group for Health Systems (ERGHS): support of training systems through planning, curriculum development, evaluation, support for health education and promotion, human resource management; resource centre (visitors welcome, postal loans available—phone extension 2256); international newsletter; also courses in training and health education/promotion for primary health care. ERGHS also runs CHESS, an information and advice service for field workers in health education/promotion, training and human resource management.

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, Keppel Street, London WC1, Tel: 071 636 8636. Comprehensive library and some excellent publications from the Ross Institute and Evaluation and Planning Centre. See also the Department of Tropical Hygiene and the Centre for Human Nutrition.

CENTRE FOR WORLD DEVELOPMENT EDUCATION (CWDE), 1 Catton Street, London WC1R 4AB, Tel: 071 831 3844. An independent education organization working to increase knowledge of development and less developed countries in Britain. The Centre provides an information service to teachers, students, and the public. Has produced a range of publications and slide sets; its resource centre includes material from international and voluntary organizations.

OXFAM RESOURCE CENTRE, Oxfam House, 274 Banbury Road, Summertown, Oxford OX2 7DZ, Tel: 0865 56777. Stocks materials and information on some of the countries in which Oxfam works and on key development issues, e.g. health, aid, debt, the environment and women's issues.

AFRICA CENTRE, 38 King Street, London WC2E 8JT, Tel: 071 836 1973. Small library, bookshop, exhibitions, evening lectures, courses on African culture, current affairs, etc. African languages school (CALL).

WOMEN'S INTERNATIONAL RESOURCE CENTRE, 173 Archway Road, London N6 5BL, Tel: 081 341 4403. Library and resources on women's issues including material on health. Runs seminars, network and produces a journal: 'Wiser Links'.

WHO Publications available from (in the UK): HMSO, 49 High Holborn, London WC1V 6HB; or 13a Castle Street, Edinburgh EH2 3AR; or 80 Chichester Street, Belfast BT1 4JY. All mail orders should be sent to: HMSO Publications Centre, 51 Nine Elms Lane, London SW8 5DR.

CONCORD FILM COUNCIL, 201 Felixstowe Road, Ipswich, Suffolk. Sells and hires out a wide range of films and videos on development issues including health.

INTERMEDIATE TECHNOLOGY DEVELOPMENT GROUP (ITDG), 103–105 Southampton Row, London WC1B 4HH. ITDG gathers and disseminates information, and advises on the

choice of technologies appropriate for developing countries. In Southampton Row is the bookshop, including a mail order service, producing and distributing a wide range of books including those on health development issues.

INSTITUTE OF DEVELOPMENT STUDIES (PUBLICATIONS UNIT), University of Sussex, Brighton BN1 9RE. Publishes and distributes a wide range of publications on development issues including health.

PROBSTHAIN (BOOKSHOP OF THE SCHOOL OF ORIENTAL AND AFRICAN STUDIES AT UNIVERSITY OF LONDON), Malet Street, London WC1, Tel: 071 637 2388 × 2295.

CIIR, 22 Coleman Fields, London N1 7AF, Tel: 071 354 0883. A cross-skill sending agency which produces useful publications including health issues.

Teaching and learning materials for tuberculosis

A selection of books on tuberculosis is now available from The Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex TW8 0QH, England.

Books have been selected for various categories of health worker. Because of demand, we may restrict the number of free items to any one individual. Students should order through their college principal. Training institutions with currency-exchange problems should order through their ILEP Co-ordinator.

Books for Programme Managers

T101	*Technical guide for sputum examination for tuberculosis by direct microscopy*. Bulletin of the International Union against Tuberculosis and Lung Disease, Supplement No. 2. 1978. This 16-page booklet is for field laboratories and presents general principles for collection, transportation and examination for tuberculosis by direct microscopy.	Free
T102	*Tuberculosis: Case-finding and chemotherapy. Questions and answers*, by K. Toman, 1979. Published by World Health Organization.	£7.75
T103	*Tuberculosis guide (for high prevalence countries)*. 1986. IUTALD.	Free
T104	*Tuberculosis and AIDS*, by G. Slutkin, J. Leowski and J. Mann. A 4-page article from the Bulletin of the International Union against Tuberculosis and Lung Disease (IUATLD), Vol 63: 2, June 1988.	Free
T105	*Tuberculosis*, by C. Murray, K. Styblo and Annik Rouillon. A Health Sector Priorities Review, undertaken by The World Bank is reported in this document.	Free

Books for Supervisors

T201	*Tuberculosis control programmes in developing countries*, by Paul Shears, Oxfam Practical Health Guide, No. 4. 1988. This booklet combines the most recent development in the scientific understanding of tuberculosis with the realities of working at a primary health care centre.	£2.95
T202	*Tuberculosis control as an integral part of primary health care*. WHO Geneva, 1988. The aim of this booklet is to help the managers of PHC programmes and of Tuberculosis control programmes achieve step by step integration, giving priority to case-finding and treatment.	£3.60

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News and Notes

Statement on the Chemotherapy of Leprosy, Greenville, USA, April, 1992

This is the report of a conference recently held in Greenville, South Carolina, USA, which '. . . brought together clinical leprologists, pharmacologists, epidemiologists, leprosy control programme managers, sociologists, health educators, therapists and patient representatives . . .' in order to address the following questions:

1. Are current WHO/MDT regimens working satisfactorily in the field?
2. Based on results to date, can application of the WHO/MDT regimens be improved, particularly in relation to duration of therapy, the classification of cases, drug delivery, and/or the use of a single regimen for all cases?
3. Can the duration of chemotherapy be shortened significantly through the use of alternative regimens and what would be the practical impact of this on leprosy control, on patients and on programme managers?
4. Are new strategies indicated for the delivery of chemotherapy and other aspects of leprosy in the light of contemporary health, cultural, psychological, and economic factors?
5. What should be the focus of leprosy therapy research during the next decade?

The Conference included presentations and discussions by a wide range of experts over a period of 3 days. The conclusions were as follows:

1. Experience to date with the WHO/MDT regimen is very satisfactory. Toxicity appears to be minimal, patient acceptance is excellent and the relapse rate thus far is very low. Prevalence rates have fallen radically, but incidence rates have not yet shown a consistent fall attributable to MDT. The currently recommended durations of 6 and 24 months for PB and MB disease, respectively, appear to provide sufficient therapy. Follow-up is no longer required for uncomplicated cases where resources are limited provided the patients understand they must return at once if complications or signs of relapse develop.
2. A better understanding is required of the economic, social and cultural factors which influence MDT coverage, case finding, compliance, and other aspects which may promote or impede leprosy programmes.
3. Application of MDT is not as widespread as desirable in many countries. Mobilization of additional resources and stimulation of political support are required to extend it to the whole population of leprosy patients in all countries.
6. New drugs may allow significant further shortening of therapy. The current trial of rifampin with ofloxacin should provide significant data in this regard. In evaluating any new treatment regimen, the incidence of disabilities during and after chemotherapy is as important a measure of the value of a new regimen as the relapse rate. Development of designer drugs specific for *Mycobacterium leprae* is possible but may be prohibitively expensive.
7. Development of an anti-leprosy vaccine continues to be a priority. Methods utilizing recombinant technology hold some promise here. BCG offers considerable protection against the development of both multibacillary and paucibacillary disease. Until a more effective anti-leprosy vaccine is developed, use of BCG should be encouraged in endemic countries. Although

effective immunotherapy would be useful, there is no data to support any of the current approaches to such treatment.

8. In view of the declining case loads, vertical leprosy control programmes will have to consider integration into basic health services or a combination with another vertical programme (e.g., tuberculosis or dermatology). The minimal requirements should be that MDT be maintained and that treatment of reactions be continued. In some countries basic health services may initially not be able to cope with the treatment of disabilities. An integrated programme should maintain specialized leprosy expertise for training, supervision and management of complications.

Copies of the report are available from ALM International, 1 ALM Way, Greenville, SC 29601, USA.

International low-price Sources for Essential Drugs, price indicator, 4th edition, 1991

Medico International has revised and updated this highly useful booklet, which gives current prices for generic drugs on the international market. Medico International is a non-profit medical relief organization with over 20 years' experience working with organizations in Africa, Asia and Latin America in the field of primary health care. This booklet was developed as a contribution toward making essential drugs available to all people, but particularly those of the developing world.

The list of drugs is based on the most recent WHO Model List of Essential Drugs, with a few additional products that are in widespread use. Lists of drugs are in English only, but the booklet's introductory and explanatory notes are in English, French and Spanish.

Prices are given in US dollars, based on the most recent price information available from a selected group of 8 suppliers of generic drugs. Additional information from the suppliers, such as terms of payment, minimum order, transport and packing costs in relation to price quoted, extra costs, and special product information, is also included.

Available at DM10 plus mailing costs (up to three copies free to non-profit organizations in developing countries) from:

Medico International, Obermainanlage 7, D-W-6000 Frankfurt/M, Germany.

International Health Exchange (IHE), London, UK

A British register has been launched, listing health professionals available at short notice for emergency relief work. The charity International Health Exchange (IHE) has set up the Emergency Disaster Relief Register in consultation with the UK government and such agencies as Oxfam and Médecins sans Frontières. To be included on the register, health workers must have had experience in a developing country and/or a disaster situation. *Details:* IHE, 38 King Street, London WC2E 8JT, London, UK.

Fractals, medicine and the epidemiology of leprosy

In *Leprosy Review*, 1992, **63,** Supplement 1, 31s–39s, Professor M. F. Lechat drew attention, in the final paragraph of his contribution entitled, 'Epidemiometric modelling in leprosy based on Indian data' to the potential value of fractals in the future study of the epidemiology of leprosy: 'Due to the present success of MDT-based control, this modelling approach in leprosy is no longer part of basic research. The future belongs to microscale modelling for disappearing diseases. What can be expected in terms of limited foci, clusters and erratic time fluctuations? This could be called, to use a fashionable new avenue of research, fractal epidemiology.'

To those not yet familiar with this term, the following information, extracted from an editorial in the *Lancet*, 338, 7 December 1991, may be helpful:

'Much medical investigation is concerned with the quantification of events. Since most of the existing methods of quantification rely on the principles of regular Euclidean geometry, the complex

patterns of many medical observations have to be considerably distorted or 'smoothed' to be described within this analytical framework. Fractal geometry may provide another way to fashion the answers.

The term fractal was introduced by the mathematician Benoit Mandelbrot to describe a type of distribution of points in space or time. The word is derived from the Latin *fractus*, meaning irregular or fragmented, and this reflects one of the fundamental properties of a fractal structure: self-scaling similarity over a wide range of scales. Consider, as Mandelbrot did, the outline of the coast of Britain at different map scales. A road atlas map with the whole of Britain on 1 page will show the major irregularities of the coast; on the pages with larger scale maps, one can identify smaller bays that are not apparent on the initial map; and a 1 : 50 000 Ordnance Survey map will show still smaller bays. Nevertheless, all the bays visible at the different scales have the same general shape. This self-similarity occurs over an infinite range of scales in abstract mathematical fractal structures, but over a limited range in natural objects.

An important feature of fractal objects is that the measurements used in regular Euclidean geometry are often inapplicable. If the length of the British coastline is measured by taking callipers of a fixed width and 'walking' them around the boundary of water and land, the total length of the coastline will depend on the size of the steps. With small step sizes, more of the tiny irregularities are included and the total length becomes greater, tending towards infinity if the steps are very small. Since the British coastline has a fractal structure, its absolute length cannot be measured but the complexity of its boundary can be expressed in terms of a fractal dimension. A fractal dimension differs from the Euclidean topological dimension in that it is not an integer: the outlines of coasts have fractal dimensions between 1 and 2, the more complex outlines having a fractal dimension closer to 2 than to 1. The limitation of topology is that it cannot tell one island from another except by measurement of area.'

The Editorial gives examples of the application of fractals in cardiology, respiratory medicine, ophthalmology, dentistry and the diagnosis of breast cancer. The final paragraph reads:

'What are the limitations of fractal geometry? Since fractal analysis is essentially mathematical, as with all mathematical models there must be a close link with the biological event if the model is to be useful. Relating the fractal dimension of an arterial tree to a diffusion-limited aggregation process may be a useful analogy, but it does not imply complete understanding of the process of angiogenesis. Natural objects are often self-similar over no more than 3 or 4 levels of recursion, so the scales at which the fractal dimension is calculated must be selected accordingly; many of the methods of fractal analysis require confirmation by further research. Nevertheless, the concept of fractal geometry is likely to prove very productive in areas of medicine where Euclidean geometry fails. With the availability of high-speed computers and high-resolution graphical displays we can now see that the iteration of very simple formulae can produce infinitely complex structures—perhaps the infinitely complex forms of nature will be revealed as repetitions of simple formulae after all.'

Health education materials needed

TDR's communications unit is about to start a pilot project in communications for development. The project will concentrate on health education for the TDR target diseases (malaria, schistosomiasis, lymphatic filariasis, onchocerciasis, African trypanosomiasis, Chagas disease, leishmaniasis and leprosy) and will be carried out in consultation with TDR's social and economic research steering committee and WHO's Divisions of Control of Tropical Diseases (CTD) and Health Education (HED).

As part of this project, TDR has hired a consultant to collect health education materials on the TDR diseases, as well as reports of studies relating to health education in these diseases.

TDR would greatly appreciate readers' help in putting this collection together.

If you have copies of such materials or can indicate where they can be obtained or can give

references to or send copies of relevant study results, please address your materials and information to: Ms Ane Haaland, TDR Communications Consultant, Skogbrynet 9, 1458 Fjellstrand, Norway [tel: (47-9) 918419; fax: (47-9) 918713].

Health Images

Health Images is a UK-based charity devoted to helping small groups in developing countries to produce their own, locally relevant, visual materials, usually in the form of posters. Founded several years ago by Bob Linney, the office is based at Holly Tree Farm, Walpole, Halesworth, Suffolk IP19 9AB, UK, but the work is mainly carried out by visits abroad to countries which in recent years have included Laos, Mexico, Brazil, Kenya, Zimbabwe, Sudan, India and Nepal. The subject matter has covered family planning, breast feeding, clean water supplies, diet and immunization, whilst at the same time encouraging local artists and health workers to explore various aspects of visual communication and possible misunderstandings in a poster's message.

International Leprosy Congress, Orlando, Florida, 29 August–4 September 1993

Message from the ILA President

Nearly 5 years ago, field workers, laboratory scientists, and others from around the world met to share their experiences and their goals to control and ultimately eradicate leprosy. The 14th International Leprosy Congress will take us a step closer to achieving those goals.

The number of registered patients has fallen dramatically in recent years, and in 1991 the World Health Organization resolved to eliminate leprosy as a public health problem by the year 2000. There is great hope, but questions remain: Is present technology sufficient? Are social, economic, and political conditions of endemic countries adequate? What will happen to patients with social and physical disabilities? The 14th Congress will address these issues and formulate plans of action.

The ILA is grateful to ILEP and WHO, Congress co-sponsors, and to the Gillis W. Long Hansen's Disease Center and ALM International for helping to organize the Congress.

We look forward to seeing you at the 1993 Congress and to renewing our efforts to help patients and to conquer leprosy.

WAYNE M. MEYERS
President, ILA Congress

Congress Subjects

Presentations at the Congress will cover all aspects of leprosy and its control including experimental and laboratory science, clinical science, programme planning and management, training, education, and the psychosocial sciences. Each day a State-of-the-Art lecture will be presented on one of the key Congress issues.

Poster Sessions

Special attention will be given to poster presentations in order to maximize the personal discussions and explanations of participants' research and work. The Organizing Committee will provide a well-planned schedule of poster presentations during the Congress in connection with, and completing, the Congress themes.

Teaching and Training Sessions

Teaching and training sessions will be held each day during the Congress. Videos, continuous slide presentations, and films will cover a variety of subjects.

Secretary for administration: ILA Congress, c/o ALM International, Greenville, South Carolina 29601, USA. Telephone 803-271-7040; Fax 803 271-7062.