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Editorial

VACCINATION AGAINST LEPROSY—THE VIEW FROM 1996

Results of the latest leprosy vaccine trial were reported in the 6 July 1996 *Lancet*[1]. This 'Karonga Prevention Trial' was unusual in several respects: because it combined two diseases (leprosy and tuberculosis), because it evaluated two vaccine comparisons (two versus one BCG, and BCG plus killed *Mycobacterium leprae* versus BCG alone), and because of its size (120,000 individuals randomized, making it the largest trial ever carried out in Africa). The results, based on 5–9 years of follow up, indicated the following:

Concerning leprosy

The BCG booster reduced the risk of leprosy by approximately 50%. Given that previous studies in this population had indicated that an initial BCG vaccination imparts at least 50% protection,[2,3] these new results indicate that a two-dose regimen imparts on the order of 75% protection in this environment.

The combined BCG plus killed *M. leprae* vaccine showed no convincing evidence of imparting more protection than did BCG alone (a slight excess of leprosy among those who were less than 15 years of age and received only BCG, compared to those who received the combined vaccine, was based upon small numbers, and failed to reach statistical significance.

Concerning tuberculosis

There was no evidence that either repeated BCG or combined BCG plus killed *M. leprae* imparted any protection against pulmonary tuberculosis. There was some evidence for protection against glandular tuberculosis, but this was based upon small numbers and failed to reach statistical significance.

We thus have yet another surprising result in the history of BCG trials. What do we make of it? First, we note that the results concerning leprosy are consistent with those of the trial carried out a few years earlier in Venezuela.[4,5] Though the Venezuela trial did not formally evaluate repeat BCG in a randomized fashion, it provided observational data which suggested that the practice of repeated BCG vaccination, as has been carried out routinely in Venezuela, was effective in enhancing protection with successive doses.

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The Venezuela trial also failed to show evidence that the addition of killed *M. leprae* to BCG enhanced protection against leprosy.

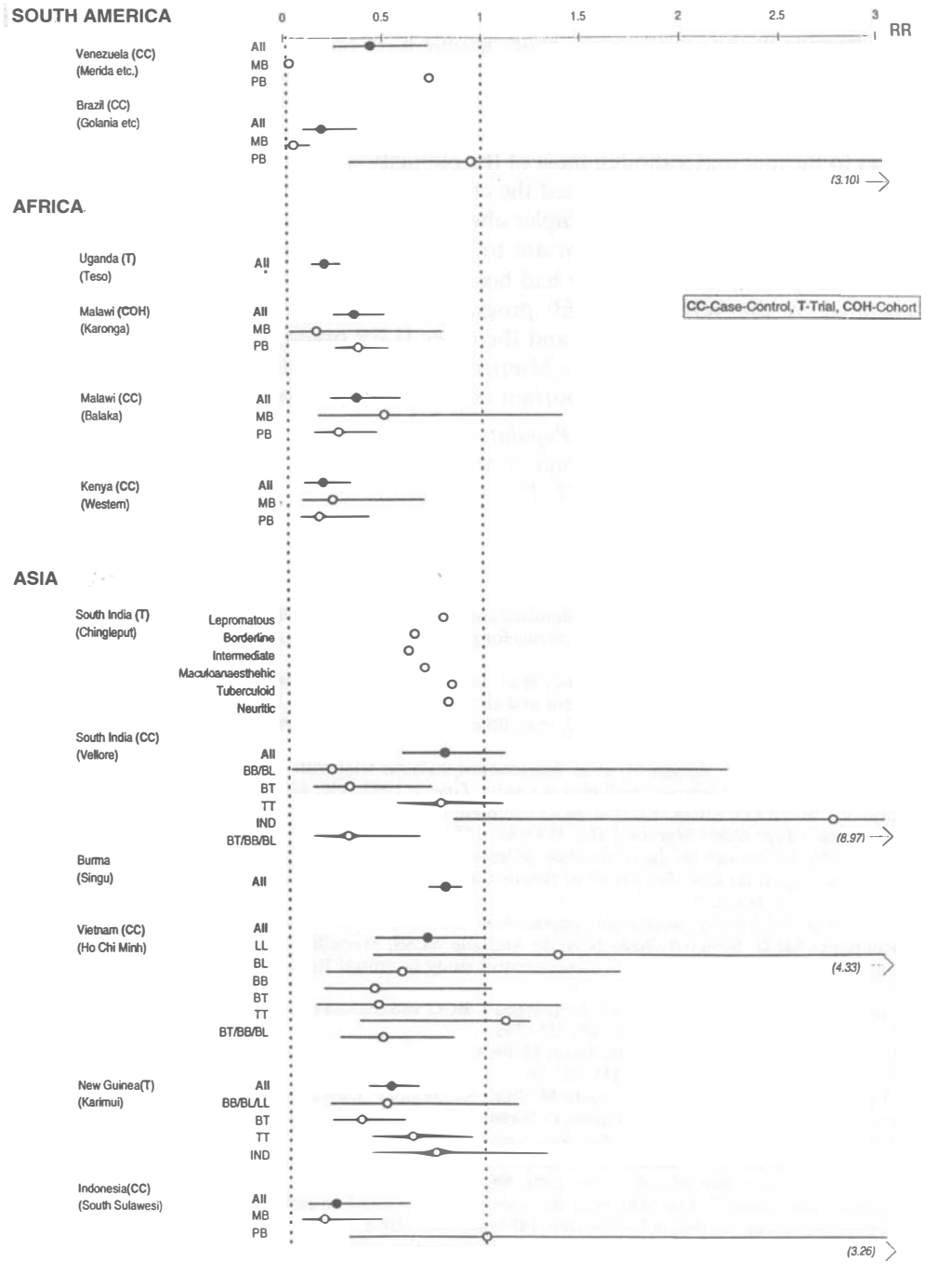
Taken together, these two trials, both originally fostered by the IMMLEP programme of WHO, provide very strong evidence that repeating a BCG vaccination adds protection against leprosy. They thus support the policy of repeat BCG vaccination of leprosy contacts, as has been routinely carried out in Cuba, Venezuela and Brazil.

The trials do not support the addition of *M. leprae* antigens to BGG, to enhance its protection against leprosy. It may even be fortunate that killed *M.leprae* did not prove a useful adjunct as a vaccine—because killed *M. leprae* material is expensive, and difficult to standardize. Instead, we are given assurance that BCG, which is both cheap and readily available everywhere, is increasingly effective in repeated doses against leprosy. This is an important contribution; for although many countries have employed repeated BCG vaccination, these studies provide the first evidence that such a policy is justified—though it must be said that the justification for the second and subsequent doses in most situations has been because of an assumed enhancement of protection against tuberculosis; an effect which has yet to be confirmed.

What do we do with this new evidence? First, we should recognize its implications for leprosy control. The evidence accumulated to date shows that BCG is protective to at least some degree against leprosy in all populations, and that it protects against multibacillary as well as paucibacillary disease (see Figure 1). The protection against multibacillary disease is particularly important, in that it multiples the impact of BCG on leprosy incidence, by reducing transmission as well as by reducing susceptibility. Given the wide use of BCG in the world, this is surely making an important contribution to the declines in leprosy incidence recorded in many countries[6]. Second, more leprosy programmes should seriously consider utilizing this new evidence on repeat BCG to their advantage. Given that BCG is readily available in almost all vaccination clinics in leprosy endemic countries, leprosy control programmes may wish to consider the possibility of using these routine vaccine services to enhance leprosy control. It may be feasible in some areas to encourage contacts of leprosy patients (who are known to be at highest risk of disease) to attend the local vaccination clinic for BCG vaccination. The only concern with such a policy would be the danger of giving BCG vaccination to individuals who are immunocompromised because of HIV. According to WHO recommendations, BCG is contraindicated for individuals who are immunocompromised with AIDS, but may be given to healthy HIV positives[7]. The HIV concern may raise a problem in some populations—in which case it would be appropriate to restrict the repeat BCG recommendation to leprosy contacts who are below 15 years of age or who are in otherwise low risk groups for HIV. Given the simplicity of implementing such a policy, it would be worth setting up a formal community randomized trial to evaluate its impact.

We close by noting three ironies. First, it has sometimes been said that there is no vaccine against leprosy[8]. Nothing could be farther from the truth! Not only is there a

Figure 1. BCG protection against leprosy. Summary of published estimates of BCG protection (one or more doses) against leprosy, by classification, location, and study design (trial, case control study or cohort study).[2,3,5,9–18] For each study, the solid circle represents the estimate for all leprosy and the open circles represent estimates by clinical classification. Protection is expressed as the relative risk (RR) of disease among vaccinees compared to that in nonvaccinees. A relative risk of less than one thus indicates protection (the conventional protective efficacy statistic is defined as $100(1 - RR)\%$. Horizontal lines are 95% confidence intervals.


SOUTH AMERICA
0
0.5
1
1.5
2
2.5
3
RR
Venezuela (CC)
(Merida etc.)
All
MB
PB
Brazil (CC)
(Golania etc)
All
MB
PB
(3.10)
AFRICA
Uganda (T)
(Teso)
All
Malawi (COH)
(Karonga)
All
MB
PB
CC-Case-Control, T-Trial, COH-Cohort
Malawi (CC)
(Balaka)
All
MB
PB
Kenya (CC)
(Western)
All
MB
PB
ASIA
South India (T)
(Chingleput)
Lepromatous
Borderline
Intermediate
Maculoanaesthehic
Tuberculoid
Neuritic
South India (CC)
(Vellore)
All
BB/BL
BT
TT
IND
BT/BB/BL
(8.97)
Burma
(Singu)
All
Vietnam (CC)
(Ho Chi Minh)
All
LL
BL
BB
BT
TT
BT/BB/BL
(4.33)
New Guinea(T)
(Karimui)
All
BB/BL/LL
BT
TT
IND
Indonesia(CC)
(South Sulawesi)
All
MB
PB
(3.26)

vaccine against leprosy, but it is actually being given to more individuals than is any other vaccine in the world today. More people have received BCG than have received any other vaccine. The second irony is the recognition that although BCG is generally considered a vaccine against tuberculosis, and its use is rationalized on that account, it has been shown to be more consistently protective against leprosy. And the third irony relates to the fact that although most of the publicity which surrounded the Malawi and Venezuela vaccine trials emphasized the combined BCG plus killed *M. leprae* product, both studies have found that a simpler alternative, merely repeating BCG, is of greater benefit against leprosy. It is important to recognize that neither trial would have been carried out if their only rationale had been to test repeat BCG. It was the enthusiasm generated by the WHO/IMMLEP programme which created these trials, and that programme (along with LEPRA and the other ILEP organizations which support the Malawi trial, and the Venezuelan Ministry of Health which supported the Venezuela trial) deserves credit for their important contributions to leprosy control.

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Editorial

THE MANAGEMENT OF ERYTHEMA NODOSUM LEPROSUM: CURRENT AND FUTURE OPTIONS

Erythema nodosum leprosum (ENL) is the most serious immunological complication affecting patients with multibacillary (MB) leprosy. Before the introduction of multidrug therapy (MDT) as many as 50% of lepromatous leprosy (LL) and 30% of borderline (BL) patients were affected.[1] The introduction of WHO–MB-MDT has reduced both the frequency and severity of ENL and this reduction is attributable to the clofazimine component of MDT since multibacillary patients treated with drug regimes without clofazimine continued to experience high levels of ENL.[2] There are few published data on the current frequency of ENL. In Ethiopia incidence rates of 2·7% and 11·1% were found in BL and LL patients respectively[3] but higher incidences have been reported in SE Asia and Brazil. For the individual patient ENL is serious and produces considerable morbidity particularly in the chronic recurrent form. This editorial reviews the evidence for the various treatments of ENL with particular emphasis on data derived from trials that used a randomized controlled design.

The pathology of ENL is now understood to involve both immune complex deposition and dysfunction of cell-mediated immunity. The principal event involves deposition of antigen–antibody complexes in tissue,[4] with activation of complement, development of local inflammation, neutrophil polymorph migration to the site[5] and local release of tissue damaging enzymes.[6] Macrophages and T cells are activated[7] and circulating TNF α levels are elevated during ENL episodes.[8]

ENL affects many organs and this should be remembered when assessing a patient with this complication. It is important to ask about symptoms indicating involvement of skin, nerves, eyes, joints, testes, kidneys and lymphatics and then to examine for evidence of on-going disease. In mild cases of ENL the skin lesions do not cause discomfort, but in more severe cases lesions are active with pain, pustule formation and ulceration.

The management of ENL is guided by the need to control the acute inflammation and neuritis, ease the pain, halt eye damage and prevent further attacks. In all cases of ENL, patients should rest and receive anti-inflammatory medication. If there is any evidence of nerve tenderness or active neuritis affected limbs should be rested, and splinted in severe cases. The eyes should be carefully monitored. If there is any evidence of irido-cyclitis treatment with steroid and atropine eye drops should be started.

Mild cases of ENL may be managed with anti-inflammatory medication and rest. There is no data showing an advantage for any particular anti-inflammatory. In a double-blind trial acetylsalicylic acid (Aspirin) 400 mg 6 hourly was shown to be helpful,

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producing improvement in 48% lesions at 48 hr.[9] A double-blind controlled trial comparing Aspirin (1 g 8 hourly), indomethacin (50 mg 8 hourly) and chloroquine (250 mg 8 hourly) in ENL showed no significant difference in the relief of symptoms obtained with any of these three drugs, although the time to relief of neuritis was significantly longer in the group treated with indomethacin (mode of 14 days for indomethacin, as compared with 7 days for the other two drugs). Patients treated with Aspirin had fewest side-effects (29%), versus 63·6% for indomethacin and 58·5% for chloroquine. Patients treated with indomethacin had the lowest incidence of visual disturbance which the author attributes to early absorption of the exudate associated with ENL.[10] Other nonsteroidal anti-inflammatory agents have not been evaluated in randomized controlled trials in mild ENL. In an open unblinded study, colchicine was used with some success, with relief of acute symptoms starting within 24 hours and a maintenance dose suppressing further attacks.[11] A double-blind controlled trial in India compared Aspirin and colchicine in both mild and moderate ENL. In mild disease both drugs were equally effective but in moderate disease colchicine was superior, being far more effective in the relief of nerve pain (50% relief with colchicine, 18·2% with Aspirin) and joint pain (81·8% relief with colchicine, 34·8% with Aspirin).[12] However in the subsequent internally controlled trial colchicine treatment had no effect on the steroid requirements of patients with chronic ENL and diarrhoea was a serious and limiting side-effect.[13] Other workers report that colchicine is not a useful alternative treatment in ENL.[14]

Prednisolone is the anti-inflammatory of choice in moderate and severe ENL. Most doctors recommend a starting dose of 60 mg[15,16] but doses up to 200 mg have been used.[14] However no comparisons of different starting regimes have been made. The response to high dose steroids is usually rapid and the steroid dose should be reduced to 30 mg daily as soon as possible and then tapered down over the next two months. Although steroid treatment is effective, ENL patients are at great risk of becoming steroid dependent, especially those with chronic ENL.

Thalidomide is a controversial yet highly effective drug in the management of acute severe and recurrent ENL. *In vitro* work has shown that it enhances degradation of TNFα mRNA.[17] In a Brazilian study reduction of serum TNFα levels in patients with ENL was accompanied by an improvement in clinical symptoms.[18] Thalidomide also acts on T cells reducing the number of circulating CD4 cells and increasing CD8 numbers.[19] The placebo controlled trial by Sheskin *et al.*,[20] showed a highly significant benefit from thalidomide in acute ENL with 86% of patients improving clinically. The response to thalidomide is rapid, usually within 8–48 hr.[21] A later uncontrolled study in acute ENL showed that thalidomide produced a significant decrease in both the dose and length of prednisolone requirements.[22] A WHO coordinated double-blind trial compared thalidomide with Aspirin; thalidomide was consistently superior to Aspirin producing faster resolution of fever, greater regression of skin lesions and a decreased chance of further reactions.[9] The value of thalidomide in chronic ENL was suggested in an uncontrolled study by Levy[23] who showed a significant decrease in the frequency of admissions for ENL after taking thalidomide. A double-blind cross-over study in Malaysian patients with severe ENL showed that 90% improved whilst taking the drug permitting a concomitant 60% decrease in steroid requirement.[24] Pearson & Vedagiri[25] compared thalidomide with placebo in mild ENL, finding clinical improvement, reduction in fever and anti-inflammatory requirements with thalidomide. They also commented that patients preferred thalidomide to other drugs. Thalidomide is

reported as having few minor side-effects, notably mucosal dryness, rashes and constipation but interestingly, in the blinded trials in leprosy patients, there were no differences in side-effects reported between the treated and control groups.[9,20,25] In a study of 94 Indian patients dose-related oedema was reported as the commonest side-effect.[22]

Although the clinical evidence demonstrating the usefulness of thalidomide in ENL is excellent, there are serious problems associated with its use. These include its teratogenicity, possible neurotoxicity and limited availability. The teratogenicity of thalidomide when given in early pregnancy has been well described. Physicians have a heavy burden of responsibility to ensure that firstly a woman is not newly pregnant and secondly can be adequately protected against pregnancy whilst taking thalidomide. WHO recommends that only males and postmenopausal women should be treated with thalidomide. When prescribing thalidomide to men it is also important to warn the patient against sharing the drug with friends or relatives whom he feels might benefit from treatment. Guidelines have been produced in the UK for the use of thalidomide and emphasize the importance of obtaining written consent from patients before prescribing this drug as well as ensuring that patients understand the potential risks and are able to comply with prescribing instructions.[26] The other serious side-effect of thalidomide is peripheral neuropathy. This has been well described in nonleprosy patients treated with thalidomide. In prurigo nodularis the risk of axonal induced neuropathy approaches 100%.[27] However peripheral neuropathy does not appear to be a major side-effect in leprosy patients and several workers have commented on its rarity.[28] There are several possible explanations: leprosy patients may already have neuropathy and so do not complain of paraesthesiae; iatrogenic neuropathy may not have been looked for in leprosy, or these patients may be relatively resistant to thalidomide-induced peripheral neuropathy.[29] The first two explanations seem unlikely. Leprosy patients do experience paraesthesiae and most main leprosy centres check voluntary muscle and sensory nerve function routinely. In a small electrophysiological study thalidomide treatment was associated with arrest of nerve damage as measured by motor conduction velocities.[30] However this is clearly an important issue and as Jakeman & Smith[31] have suggested, a study involving careful observation, nerve conduction studies and nerve biopsy of a series of thalidomide-treated patients is badly needed.

The role of clofazimine in the management of chronic ENL is well established. Its anti-inflammatory effect on ENL was initially noted as a beneficial side-effect when using clofazimine as an antibacterial agent.[32] Subsequent non randomized uncontrolled trials by Imkamp[33,34] and Hastings[35] showed that clofazimine treatment of patients with severe ENL lead to a significant reduction in steroid requirement. In Malaysia, a placebo-controlled cross-over trial of 300 mg clofazimine daily in 10 patients with moderate ENL showed a decrease in requirement for anti-inflammatory medication and a reduction in clinical activity whilst on clofazimine.[36] Clofazimine is not as effective or as rapidly acting as prednisolone or thalidomide[37] and its major role is in preventing further attacks and decreasing steroid dependence. Imkamp[34] reported that with long-term clofazimine therapy many of her patients were able to resume employment. Clofazimine accumulates in the skin and gastrointestinal tract so accounting for the major side-effects, skin pigmentation and abdominal symptoms, notably diarrhoea and abdominal pain. The skin pigmentation and dryness develop within a few weeks of starting treatment and may take two or more years to fade.[38]

So what can be offered to the patients with ENL? Mild attacks of ENL can be treated with analgesics. Steroids should be reserved for moderate and severe attacks or where there is evidence of neuritis. The recurrent nature of ENL means that patients started on steroids are at risk of becoming steroid dependent and every effort should be made to keep steroid courses as short as possible whilst relieving clinical symptoms. Thalidomide is probably the drug of choice for male patients with severe or recurrent ENL. In centres where thalidomide is available treatment with thalidomide should be instigated early. Several authors have reported that the response to thalidomide was blunted and slower in patients already receiving steroids, suggesting an adverse interaction between thalidomide and steroids.[22,39,40] For premenopausal women steroids and clofazimine should be used. It is important to use a large enough dose of clofazimine to prevent recurrence. Pettit[41] reported no significant benefit for clofazimine 100 mg daily in a controlled study in patients with severe ENL needing high doses of steroids. The apparent treatment failure was probably due to inadequate dosing with clofazimine. Doses of up to 300 mg can safely be used for several months.[42] Charting the frequency of attacks and episodes requiring prednisolone will help both physician and patient assess the effect of clofazimine.

It is surprising that no randomized controlled trials of new therapies for ENL have been published in the last twenty years. Even if only 10% of lepromatous patients are experiencing ENL this is still a large problem on a global scale and there is an urgent need for multicentre trials. The current available treatments all have drawbacks and are not always effective, in three thalidomide studies failure rates of 7·4%,[22] and 10%[24] patients and 8·2% episodes[20] were reported. Mishra & Girdhar reported 8 treatment failures in a series of 30 patients with chronic ENL managed with clofazimine 100–300 mg per day.[43] The underlying pathology of ENL has several components and no single immune defect is consistently present in patients with ENL. Immune complex deposition can only be demonstrated in 50% of patients, not all LL patients have raised TNFα levels during episodes of ENL and 36% of skin biopsies do not have a neutrophil infiltration.[44] Whilst timing of sampling accounts for some of these differences they may also reflect a balance of different humoral and cell-mediated dysfunction. This has implications for the development and testing of new treatments and a wide range of immunosuppressive drugs, acting on both the humoral and cell-mediated immune systems should be considered.

The tissue damaging neutrophil infiltration of blood vessels in the systemic vasculitides has some similarities with the skin biopsy of ENL. Intravenous methylprednisolone is now well established as an initial treatment in vasculitis and its anti-inflammatory action probably reduces vessel inflammation.[45] One might postulate that methylprednisolone could have a similar effect in ENL and perhaps early methylprednisolone treatment could ameliorate ENL. A controlled study would be required to test this hypothesis.

One might predict that plasma exchange would be useful in ENL, by binding and removing immune complexes from the circulation. It has been used successfully in four patients who had failed with conventional ENL treatment, and no relapses occurred in the four years following treatment.[46] However plasma exchange requires expensive technology and safe blood products, so making it unsuitable for most leprosy endemic countries. In a series of randomized trials neurologists have shown that plasma exchange and intravenous immunoglobulin (IgG) have similar efficacy in the treatment of Guillain-Barre Syndrome.[47] Intravenous immunoglobulin has anti-inflammatory and

immunoregulatory effects including interference with Fc receptor function, down-regulation of antibody production, alterations in T-cell function and cytokine inhibition.[48] These immunomodulatory actions and the experience in the treatment of Guillain-Barre Syndrome suggest that a trial of IgG in ENL would be useful.

Cyclosporin A was first proposed as a treatment for ENL by Mshana[49] in 1982, and has been shown *in vitro* to restore suppressor cell activity during ENL.[50] It is used extensively in transplant patients to prevent graft versus host disease. Three patients with chronic steroid dependent ENL have been treated with cyclosporin A and excellent results were obtained in two, both of whom had failed to respond to second courses of thalidomide.[51] A larger, randomized trial is needed to confirm these preliminary findings.

TNFα antibody treatment is another modality that should be tested. TNFα antibodies have been developed for human use and their human safety has now been established.[52] Randomized controlled trials have established the value of TNFα antibody treatment in patients with rheumatoid arthritis.[53,54] In a trial in Addis Ababa TNFα antibodies had a highly significant effect in ameliorating the Jarisch Herxheimer reaction, a TNFα dependent phenomenon.[55] The clear association between elevated serum TNFα levels and the development of ENL suggests that binding and removing TNFα from the circulation might improve ENL.

Tenidap is a new agent from a class of drugs that act both as anti-inflammatory agents and disease modifying drugs in rheumatoid disease. Tenidap inhibits neutrophil-mediated damage and the synthesis and release of cytokines including TNFα. In numerous double-blind studies in patients with rheumatoid arthritis it has been shown to be equivalent to treatment with second-line agents such as hydroxychloroquine.[56] Its immunological and disease modifying properties make it another agent appropriate for testing in ENL.

Trials are also needed to assess whether adjunct therapy can ease the symptoms of mild ENL. A nonplacebo controlled trial in India showed that oral zinc reduced the frequency, duration and severity of ENL episodes and this should be tested formally.[57]

The better understanding of the pathological processes underlying ENL and the development of new treatments for other immune-mediated conditions mean that there are now good prospects for testing new drugs in ENL and finding better and more effective treatments for patients. The challenge is to find people able to draft protocols and co-ordinate centres willing to participate in good trials.

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Response to treatment by multidrug regimens in the THELEP controlled clinical drug trials

Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

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Summary During the period 1977–1983, clinical trials of five multidrug regimens were conducted among 215 patients with previously untreated multibacillary leprosy at the Institut Marchoux, Bamako, Mali, and the Central Leprosy Teaching and Research Institute, Chingleput, South India. The trials were designed primarily to permit measurement of the proportions of persisting *Mycobacterium leprae* in the patients' skin lesions. In addition, the combination of the large number of patients studied, the large volume of carefully standardized data, and the employment of multidrug regimens provided a unique opportunity to measure the clinical response of patients to treatment by these regimens.

Persisting *M. leprae* were detected in 7·8% of all specimens; the frequency did not vary with centre, regimen, or duration of treatment. The bacterial index (BI) decreased by a mean annual rate of 75%, the logarithmic biopsy index by a mean annual rate of 87%, and the logarithm_{10} number of acid-fast bacilli per g tissue by a mean annual rate of 69%. The rate of decrease of these measures of the numbers of *M. leprae* was related to the 'strength' of the regimen.

Although no difference of clinical status as a function of regimen was demonstrated, a difference was observed between the two centres, probably the result of different clinical criteria employed by the responsible physicians. A change of histopathological classification in the course of the trials was recorded for 12% of the patients, most representing upgrading from LL_s to BL, without relation to regimen or treatment centre.

ENL was less severe for the patients treated by the maximal regimen in Chingleput, which included daily clofazimine; as expected, the majority of patients treated by this regimen were found to have maximal pigmentation. Prednisolone was evidently preferred for treatment of ENL in Chingleput, whereas thalidomide was preferred in Bamako.

Fourteen cases of jaundice were observed, primarily among the patients treated by the maximal regimens, that included daily administration of rifampicin for the entire two years of the trials. Measurements of weight and blood pressure, and studies of the blood and of hepatic and urinary tract function revealed only negligible differences among regimens and between centres. In many cases, those differences that were observed were associated with ENL.

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This report was prepared by L. Levy, M. Anker and Y. Fushimi.

Introduction

During the period between August 1977 and the end of 1983, 215 patients with previously untreated multibacillary leprosy—99 at the Institut Marchoux, Bamako, Mali, and 116 at the Central Leprosy Teaching and Research Institute, Chingleput, South India—were recruited into clinical trials of treatment by one of five

* Deceased.

regimens*. Treatment was continued for 2 years, in the course of which the patients were closely observed, and the results of numerous examinations recorded. The primary objective of the trials was the detection of persisting *Mycobacterium leprae* in the skin lesions of patients treated by different drug regimens. For this purpose, lesions were subjected to biopsy at intervals after the start of treatment, and *M. leprae* were recovered from the biopsy specimens and inoculated into the footpads of thymectomized-irradiated (TR) mice. In addition, the combination of the large number of patients studied, the large volume of carefully standardized data, and the employment of regimens of multidrug treatment (MDT) have provided a unique opportunity to measure the clinical response of patients to MDT.

Materials and methods

The patients recruited into the trials and many of the methods employed have already been described.[1–8] In brief, patients with previously untreated multibacillary leprosy were assigned by random allocation to a treatment regimen. Before treatment was begun, the patients were carefully examined. Skin lesions were biopsied, and specimens were submitted for inoculation of mice, histopathological examination[9] and measurement of the logarithmic biopsy index (LIB)[10]; smears for measurement of the bacteriological index (BI)[11] were made from both ear lobules and four other standard sites; a nose-blow was obtained; and specimens of urine, faeces and blood were obtained for a variety of laboratory studies.

At intervals of 3, 12 and 24 months after initiation of treatment by one of the trial regimens, skin-biopsy specimens were obtained and portions were air-shipped fresh on wet ice to the National Institute of Medical Research (NIMR), London. There, the largest possible number of *M. leprae*, but no more than 10^5, were inoculated into each hind footpad of TR mice, usually 8 mice per specimen. About one year after inoculation, long enough for a single viable organism to have multiplied to a readily countable number, *M. leprae* were harvested from the hind footpads of all surviving mice and counted. Persisters—drug-susceptible *M. leprae* that survived antimicrobial treatment[12]—were said to have been detected: if organisms had multiplied to at least 10^6 in at least one footpad; or, in the event that the inoculum included fewer than 10^5 organisms, if multiplication had occurred to a number at least 10-fold the number inoculated, and to at least 10^5 in at least one footpad; or if *M. leprae* multiplied in

* Patients were allocated among six treatment-groups, three in each centre; however, one of the five regimens (regimen C) was employed in both centres. The regimens were in Bamako:

A_2: rifampicin, prothionamide and dapsone, each in a daily dose of 600, 500, and 100 mg, respectively, for 2 years;

C_B: rifampicin, in a single initial dose of 1500 mg, and dapsone, 100 mg daily for 2 years;

E_2 : rifampicin, 900 mg once weekly, and prothionamide, 500 mg daily for the first 3 months, together with dapsone, 100 mg daily for 2 years;

and in Chingleput:

A_1: rifampicin, clofazimine and dapsone, each in a daily dose of 600, 100, and 100 mg, respectively, for two years;

C_C: as for Bamako; and

D_1: rifampicin, in a single initial dose of 1500 mg, clofazimine, in a daily dose of 100 mg for the first 3 months, and dapsone, 100 mg daily for 2 years[1].

passage. Portions of the biopsy specimens were also fixed and shipped to Oxford for histopathological examination and measurement of the LIB.

Every 4 weeks, patients were examined by the clinical investigator, who noted changes of the lesions, and questioned the patients with respect to symptoms suggesting adverse reactions to the drugs employed. In addition, specimens of urine and blood were obtained for laboratory study, and the occurrence of ENL and other leprosy reactions was recorded. In addition, at the first interval after the start of treatment, a nose-blow specimen was obtained.

Twelve weeks after the start of treatment, a formal clinical assessment was carried out, and a skin-lesion was biopsied, to provide specimens for both histopathological examination and inoculation of TR mice. Skin smears were made, and a nose-blow specimen was obtained. Beginning 24 weeks after the start of treatment, and every 24 weeks thereafter, skin smears were made, and specimens of urine and blood were obtained for laboratory study. Finally, after 12 and 24 months of treatment a formal clinical assessment was carried out.

The resulting data have been analysed by means of the 't'-test, and the techniques of χ^2, exact probability, analysis of variance (ANOVA), and analysis of covariance.[13]

Results

As shown in Table 1, 215 patients were recruited—99 in Bamako and 116 in Chingleput—and allocated in approximately equal numbers to the six regimens studied, with the exception of regimen A_2; the allocation of patients to regimen A_2 was stopped after only 12 patients had been assigned, because of a suspicion of hepatotoxicity, discussed below in detail. As shown in Table 1, 164 patients completed the trials, and an additional 16 patients were treated for at least one year but less than two years. There does not appear to be an association between regimen and failure to complete the trial. The results of the

Table 1. Numbers of patients and biopsy-specimens as a function of regimen

Numbers of specimens*	Regimen					
	A_2	C_B	E_2	A_1	C_C	D_1
	Numbers of patients					
4	7	37	32	34	31	33
3	3	3	2	2	3	3
2	1	3	2	3	4	0
1	1	1	7	0	1	2
Total	12	44	43	39	39	38

* Those patients who completed the trials are shown as having had four specimens examined for the presence of persisting *M. leprae*—a pretreatment specimen as well as specimens after 3, 12 and 24 months of treatment. In those cases in which only a single specimen was examined, the specimen was the pretreatment specimen; as a result, no specimens from these patients was examined for the presence of persisters.

Table 2. Detection of persisting *M. leprae* as a function of centre, regimen, and duration of treatment

	Patients			Specimens		
Variable	All	Persisters detected	% (95% CI)*	All	Persisters detected	% (95% CI)*
Centre and regimen						
Bamako	90	18	21·1 (13·2–31·0)	243	20	8·2 (5·1–12·4)
A_2	11	4	36·4 (10·9–69·2)	27	4	14·8 (4·2–33·7)
C_B	43	7	16·3 (6·8–30·7)	119	8	6·7 (3·0–12·8)
E_2	36	7	22·2 (10·1–39·2)	97	7	8·2 (3·6–15·6)
Chingleput	113	20	17·7 (11·2–26·0)	311	23	7·4 (4·8–10·9)
A_1	39	5	12·8 (4·3–27·4)	107	6	5·6 (2·1–11·6)
C_C	38	8	21·0 (9·6–37·3)	101	9	8·9 (4·2–16·2)
D_1	36	7	19·4 (8·2–36·0)	103	8	7·8 (3·4–14·7)
Duration of treatment†						
3 months	201	17	8·5 (5·0–13·2)			
12 months	185	18	9·7 (5·9–14·9)			
24 months	168	8	4·8 (2·1–9·2)			
3 + 12 + 24 months	564	43‡	7·8‡ (5·7–10·3)			

The proportion of specimens in which persisters were detected did not differ significantly as a function of centre, regimen or duration of treatment.

*95% confidence interval.

† Because only one specimen was obtained from a patient at each interval during the trial, the numbers of patients are identical to the numbers of specimens.

‡ Not significantly different from the corresponding values reported in the earlier paper,[5] nor from the corrected values shown here for specimens reported by 31 December 1984.

clinical trials are further considered under two headings: therapeutic effects, and adverse effects.

Therapeutic effects

Detection of persisting M. leprae. This analysis includes results from the study of 554 specimens, representing 203 patients. No specimens were obtained from the remaining 12 patients, once treatment had been initiated, and the results from the study of 10 specimens, which yielded too few organisms to be counted, are excluded.

As shown in Table 2, persisting *M. leprae* were detected in 43 specimens, representing 38 patients. These numbers are not different from those presented in the preliminary report,[5] which considered the 468 specimens, the study of which had been completed

Table 3. Change of bacterial indices during treatment by THELEP regimens

Regimen	Mean regression coefficient (regression of variable on time)				Mean regression coefficient (regression of first variable on second)		
	BI	LIB	LAFBPG	NB	BI/LIB	BI/LAFBPG	LIB/LAFBPG
Individual regimens							
Bamako							
A_2	−0·57*	−0·70	−0·59	−0·47	0·33	0·13	0·38
C_B	−0·50	−1·08	−0·56	−1·53	0·30	0·32	0·95
E_2	−0·64	−0·93	−0·79	−1·13	0·41	0·40	0·54
Chingleput							
A_1	−0·64	−1·35	−0·65	−0·88	0·42	0·61	1·08
C_C	−0·44	−0·75	−0·36	−1·10	0·38	0·34	0·64
D_1	−0·65	−0·98	−0·52	−1·12	0·43	0·46	0·85
Mean	−0·57	−0·89	−0·5	−1·10	0·37	0·43	0·84
$p_{individual}$	<0·006	0·001	0·026	0·180	0·037	0·020	0·520
Number of observations	989	865	713	577	693	653	688
Combined regimens							
$A_2 + A_1$	−0·61	−1·17	−0·64	−0·76	0·4	0·48	0·83
$C_B + C_C$	−0·47	−0·79	−0·46	−1·33	0·32	0·34	0·82
$E_2 + D_1$	−0·65	−0·94	−0·64	−1·12	0·45	0·45	0·71
$p_{combined}$	<0·0001	0·018	0·070	0·085	0·016	0·190	0·530

Abbreviations: BI, bacteriological index; NB, BI of nose-blows; LIB, logarithmic biopsy index; LAFBPG, logarithm_{10} of the number of AFB per g biopsy specimen; $p_{individual}$, probability that the differences among the individual regimens occurred by chance; $p_{combined}$, probability that the differences among the combined regimens occurred by chance.

* All the regression coefficients have been calculated on the basis of 365 days, except for those describing the changes of the BI of the nose-blows, which have been calculated on the basis of 90 days.

before 1 January 1985. In fact, among the 86 specimens, the study of which was completed after this date, persisting *M. leprae* were detected in only one—that obtained from patient 2059 after treatment for 12 months. This specimen is balanced by that obtained from patient 2051 after 3 months of treatment, which had been erroneously recorded as having yielded evidence of multiplication of *M. leprae*. Thus, persisting *M. leprae* were detected in 7·8% of all specimens; and the frequency with which persisting *M. leprae* were detected could not be shown to vary with centre, regimen, or duration of treatment.

Bacteriological status. Changes during treatment of the BI of smears of skin-scrapings and nose-blows, the logarithmic biopsy index (LIB), and the logarithm_{10} of the number of *M. leprae* per g tissue (LAFBPG)[3] are summarized in Table 3. For these analyses, analysis of covariance was employed to test for differences among regimens of the mean change of the BI per unit time.

The BI decreased at the average rate of 0·571 $\log_{10}$ units (73%) per year. The data of Table 3 suggest that the BI decreased more slowly among the patients treated by regimen C in both Bamako and Chingleput, than was the case for the other regimens. This suggestion is confirmed by combining the data from both centres for regimen C (the 'minimal' regimen[1]), for regimens A_1 in Chingleput and A_2 in Bamako (the 'maximal' regimens[1]), and for regimens D_1 in Chingleput and E_2 in Bamako (the 'intermediate'

regimens[1]). As shown in the lower half of the Table 3, the rate of fall of the BI was significantly slower among the patients treated by regimen C than among those treated by the other regimens. No relationship was found between primary resistance to dapsone[2] and the rate of fall of the BI. The LIB decreased with a mean annual rate of 0·894 $\log_{10}$ units (87%); as was the case for the BI, a relationship between the rate of decrease of the LIB and the 'strength' of the regimen is apparent. Finally, as is also shown in Table 3, the LAFBPG decreased during treatment, with a mean annual rate of 0·504 $\log_{10}$ units (69%), and the rate of decrease of the LAFBPG was slower for the patients treated by regimen C than for those treated by the remaining regimens. Thus, the numbers of organisms decreased more slowly during treatment by regimen C than during treatment by the other regimens; this was demonstrated more consistently in Chingleput than in Bamako.

The BI of nose-blows was initially higher among Bamako than among Chingleput patients. The median value for 72 Bamako patients was 3, whereas that for 111 Chingleput patients was 2 ($p < 0{\cdot}0001$); in addition, only one Bamako patient failed to exhibit AFB in the pretreatment nose-blow specimen, whereas this was the case for 24 Chingleput patients ($p < 0{\cdot}0001$) (the initial values had not been analysed in the paper[3] describing the pretreatment characteristics of the patients). Perhaps as the result of the initially higher values, the nose-blows of fewer Bamako (17) than Chingleput patients (53) achieved a BI of 0 by the end of three months of treatment ($p < 0{\cdot}001$). These initial differences between centres notwithstanding, the BI of nose-blows decreased at a mean rate of 1·10 $\log_{10}$ units (92%) during the first 90 days of treatment, with no significant variation among regimens.

The BI, LIB and LAFBPG were found to be well correlated; all of the three possible correlation coefficients were greater than 0·5, and the slopes of the regression of one variable on another were significantly greater than 0 in every case. The mean regression coefficients of LIB on LAFBPG did not differ significantly among regimens.

Clinical change. Clinical change during the course of the trials is considered in Table 4, in terms of clinical status, change of the proportion of skin visibly affected, change of the degree of skin-infiltration, and change of the size of the ulnar, median and lateral popliteal nerves. At the time of the formal clinical assessments, after treatment for three, 12 and 24 months, the patient's clinical status was assessed as 'definitely improved' (score = 1), 'slightly improved' (score = 2), 'unchanged' (score = 3), or 'deteriorated' (score = 4) since the last examination. The mean score was calculated for each patient, and the means were calculated for each regimen and centre. No difference of mean clinical status as a function of regimen was demonstrated by analysis of covariance. On the other hand, a significant difference was observed between the two centres; definite clinical improvement was recorded more frequently in Bamako than in Chingleput. Perhaps most important is that deterioration was reported in the case of only two patients, both of whom were treated by the minimal regimen in Bamako.

Also at the time of each formal clinical assessment, the proportion of skin visibly affected had been scored for each patient as >75% (score = 3), between 50 and 75% (score = 2), between 1 and 50% (score = 1), or <1% (score = 0); the head, trunk, arms and legs were assessed separately, and scores for each portion of the body were summed. The change of the proportion of skin visibly affected was calculated for each patient by subtracting the latest from the first (pretreatment) value, and the mean values were subjected to analysis of covariance. Analysis of covariance showed that the mean

Table 4. Clinical change during treatment by THELEP regimens

Centre and regimen	Mean scores of: Clinical status	ΔSkin	ΔInfiltration	ΔSize	Histopathological change (proportion of patients)
Bamako					
A_2	1·99	−6·5	−6·5	−2	1/11
C_B	1·78	−6	−6	−1	5/41
E_2	1·73	−6	−7	−2	6/34
Mean	1·79	−6	−6	−2	12/86
Number of patients	88	93	93	82	86
p_B	0·30	0·62	0·60	0·86	0·70
Chingleput					
A_1	2·31	0	−3	0	5/39
C_C	2·24	−2	−4	0	3/36
D_1	2·08	−3	−4	−1	3/35
Mean	2·21	−1	−4	0	11/110
Number of patients	113	116	116	113	110
p_C	0·12	0·0004	0·095	0·019	0·76
p	<0·0001	<0·0001	0·0036	0·0047	0·39

Abbreviations: ΔSkin, change of the proportion of skin involved; ΔInfiltration, change of the degree of infiltration of the skin; ΔSize, change of the sizes of the peripheral nerves; p_B, probability that the differences among the Bamako regimens occurred by chance; p_C probability that the differences among the Chingleput regimens occurred by chance; p, probability that the differences between treatment centres occurred by chance.

decrease of the proportion of affected skin varied according to regimen among Chingleput patients, being greater among those patients treated by regimens C_C and D_1 than among those treated by regimen A_1, as may be noted in Table 4. The mean decrease of the proportion of affected skin did not vary according to regimen among Bamako patients, and significantly more dramatic decreases of the proportion of affected skin were recorded in Bamako than in Chingleput.

In similar fashion, on the occasion of the formal clinical assessment, the degree of infiltration of the skin of the head, trunk, arms and legs had been assessed as 'marked' (score = 3), 'mild' (score = 2), 'macular' (score = 1), or 'none' (score = 0). The degree of infiltration was calculated for each patient, as was done for the proportion of skin visibly affected. Analysis of covariance indicated that the mean change of the degree of infiltration did not vary according to regimen. On the other hand, as may be noted in Table 4, significantly greater decreases of the degree of infiltration were recorded in Bamako than in Chingleput.

Also at the time of the formal clinical assessment, the sizes of both ulnar, median and lateral popliteal nerves were evaluated and recorded. Enlargement to greater than three times normal was given a score of 2, enlargement to a lesser degree a score of 1, and no enlargement a score of 0. For each patient, the scores of all six nerves were summed, and the total at the time of the last examination was subtracted from that at the time of the first examination, yielding an expression of the change of nerve-size. Analysis of covariance indicated that the mean size of the nerves decreased among the patients treated by all three regimens in Bamako, and among those treated by only one of the three regimens in Chingleput, as shown in Table 4; decreases of nerve-size were recorded

significantly more frequently among Bamako than among Chingleput patients. No significant variation according to regimen was shown for Bamako, whereas, in Chingleput, decreases of nerve-size was significantly greater among patients treated by regimen D_1 than among those treated by either of the two remaining regimens.

In addition to the proportion of skin involved, the degree of infiltration of the skin, and enlargement of the peripheral nerves, other assessments were made at the time of the periodic clinical examinations; these included erythema of the skin, nerve-pain and nerve-tenderness, disability of the hands and feet, and pathological changes of the eye. Because abnormalities had been noted initially in very small proportions of the patients in both treatment centres, improvement in the course of the trials could have occurred in the cases of only a very few of the patients; therefore, these data were not further analysed.

Histopathological change. As shown in Table 4, a change of histopathological classification in the course of the trials was recorded for 23 (12%) of the 196 patients, for whom more than one specimen had been received in Oxford. Of the 23 changes of histopathological classification, 15 represented upgrading—in most cases a change from LL_S to BL, whereas 8 represented downgrading—half of them a change from BL to LL_S. Analysis by means of the χ^2 statistic did not demonstrate a relationship of centre or regimen to these changes.

Adverse effects

ENL. In the course of the trials, the occurrence of ENL was recorded at monthly intervals; on these occasions, ENL was classified as absent (score = 0), mild (score = 1) or severe (score = 2), and the number of weeks during which the patient had demonstrated lesions of ENL was noted. In addition, the total quantities of prednisolone and thalidomide administered during the month were recorded. The data relating to ENL are summarized in Table 5. For the purpose of this analysis, an index of severity of ENL for each patient for the 2-year duration of the trials was constructed from three variables: SUMENL, the severity score × the number of weeks; SUMPRED, the total quantity of prednisone administered in the course of two years; and SUMTHAL, the total quantity of thalidomide administered. Analysis of these data suggests that ENL was less severe for the patients treated by regimen A_1, and that prednisolone was preferred for treatment of ENL in Chingleput, whereas thalidomide was preferred in Bamako.

Pigmentation. At the time of the monthly clinical examination, patients were observed for evidence of the skin-pigmentation that characteristically occurs in the course of the prolonged administration of clofazimine. At these intervals, pigmentation was noted to be 'present and probably caused by clofazimine' (score = 3), 'present but probably unrelated to clofazimine' (score = 2), or 'absent' (score = 1). The numbers of Chingleput patients whose total pigmentation scores lay in the range 0–3, 4–16 or 19–24 are shown in Table 6 (clofazimine was not a component of any of the regimens employed in Bamako). As expected, the majority of patients treated by regimen A_1 were found to have maximal scores, whereas all of the patients treated by regimen C_C, of which clofazimine was not a component, were observed to have no or minimal pigmentation; most of the patients treated by regimen D_1 demonstrated intermediate scores. Analysis of these data by the χ^2 statistic suggests that the likelihood that such a distribution could have resulted from chance was small indeed ($\chi^2 = 166_{df=4}$; $p < 0{\cdot}0001$).

Table 5. ENL during treatment by THELEP regimens

Centre and regimen	Numbers of patients		Mean SUMENL*	Mean SUMPRED	Mean SUMTHAL
	Total	With ENL			
Bamako					
A_2	12	9	6·1	119	6550
C_B	44	23	6·6	112	6595
E_2	43	26	7·1	272	7271
p_B		0·34	0·45	0·45	0·67
Chingleput					
A_1	39	8	3·2	735	1183
C_C	39	23	17·7	1703	1844
D_1	38	25	17·2	1744	3096
p_C		0·0001	0·0001	0·026	0·10
p		0·13	0·78	0·01	0.0001

Abbreviations: SUMENL, sum over the entire course of the trial of the monthly values of severity score × number of weeks during which ENL was present; SUMPRED, total quantity in mg of prednisolone administered; SUMTHAL, total quantity in mg of thalidomide administered; p_B, probability that the differences among Bamako regimens occurred by chance; p_C, probability that the differences among Chingleput regimens occurred by chance; p, probability that the differences between treatment centres occurred by chance.

* Numbers of patients demonstrating ENL of any degree of severity.

Changes of weight and blood-pressure. At the time of the monthly clinical examination, patients were weighed, and the arterial blood-pressure was measured by sphygmomanometry. As shown in Table 7, 31 (27%) of 116 Chingleput patients and 8 (8%) of 96 Bamako patients were found to have sustained weight-loss, defined as a loss of >5 kg from the maximal weight recorded on more than one occasion during the trial, at some time during the course of treatment. Analysis by the χ^2 statistic demonstrated no difference in terms of the frequency of weight-loss among regimens at each centre. Although fewer Bamako than Chingleput patients sustained weight-loss, many more measurements of weight were made in Chingleput (2444; 21·1 per patient) than in Bamako (633; 6·6 per patient); therefore, comparison of the frequency of weight-loss between centres may not be valid. It is also of interest that, according to the measurements of bodyweight made at the time patients were admitted to the trials, Bamako patients were considerably heavier than Chingleput patients (57·8 *vs* 44·8 kg; $p < 0·0001$) (this difference was not described in the earlier report[3]).

Table 6. Pigmentation of Chingleput patients as a function of regimen

Regimen	Pigmentation score		
	0–3	4–16	19–24
	Number of patients		
A_1	0	6	33
C_C	39	0	0
D_1	7	31	0

Table 7. Weight-loss and elevated blood-pressure as a function of treatment centre and regimen

Centre and regimen	Total	Weight-loss*	Increase of blood-pressure			
			$BP_S > 140$ once	$BP_D > 90$ once	$BP_S > 140 >$ once	$BP_D > 90 >$ once
			Number of patients			
Bamako						
A_2	12	0	1	0	1	0
C_B	42	5	10	2	6	1
E_2	42	3	7	0	6	0
All regimens	96	8	18	2	13	1
p_B		0·39	0·43	0·27	0·85	0·52
Chingleput						
A_1	39	8	3	4	2	0
C_C	39	11	3	5	1	1
D_1	38	12	3	4	1	0
All regimens	116	31	9	13	4	1
p_C		0·53	1·0	0·92	0·78	0·37
p		0·0008	0·029	0·016	0·014	1·0

Abbreviations: BP_S, systolic blood pressure; BP_D, diastolic blood pressure, p_B, probability that the differences among the Bamako regimens occurred by chance; p_C, probability that the differences among the Chingleput regimens occurred by chance; p, probability that the differences between treatment centres occurred by chance.

* Weight-loss is defined as a loss of >5 kg from the maximal weight recorded on more than one occasion during the trial.

Although no differences were demonstrated among the regimens at each centre, elevations of the blood-pressure, both systolic and diastolic, were recorded more frequently in Bamako than in Chingleput, as is also shown in Table 7. These differences between centres are consistent with the fact that the initial measurements of blood pressure were higher in Bamako (mean 127/71) than in Chingleput (mean 106/68) ($p = 0{\cdot}0001$) (this difference between centres was also not reported in the earlier paper[3]).

Adverse reactions and incidents. Evidence of adverse reactions was recorded at the time of the monthly clinical examination. In addition, adverse reactions and other incidents were recorded when they occurred. As shown in Table 8, with the exception of jaundice, few adverse reactions occurred; these were generally not serious, and were not thought to be related to the treatment. The cutaneous reactions, all of which were recorded in Chingleput, were two cases of erythema multiforme, one case of pruritus, and two rashes not otherwise described. Similarly, the abdominal reactions consisted, in Chingleput, of one case of nausea, and four of abdominal discomfort; in Bamako, six cases of nausea were recorded. The 'other' reactions, also all recorded in Chingleput, consisted of two cases of peripheral neuropathy, two of arthralgia, and one of fever.

The cases of jaundice, five in Bamako and nine in Chingleput, represent a potentially much more serious reaction; in fact, one of the two deaths recorded among patients treated by regimen A_2 represented the culmination of an episode of jaundice. That four cases of jaundice, one resulting in death, occurred among the first 12 patients admitted to treatment by regimen A_2 in Bamako stimulated the THELEP Steering Committee (SC) to suspect toxic hepatitis, and, until a review of the situation had been completed, to

Table 8. Adverse reactions and related incidents as a function of centre and regimen

Reaction or incident	Bamako			Chingleput			
	A_2	C_B	E_2	A_1	C_C	D_1	p*
	Number of patients						
Adverse reactions							
Skin	0	0	0	2	2	1	0·047
Abdominal	2	3	1	3	0	1	0·33
Jaundice	4	0	1	5	2	2	0·32
Other	0	0	0	2	0	3	0·047
All reactions	6	3	2	12	4	7	0·07
Incidents							
Removal	6	5	11	7	8	7	0·13
Death	2	0	1	0	1	1	0·50
Voluntary withdrawal	2	4	3	1	1	1	0·033
All incidents	10	9	15	8	10	9	0·052
All patients	12	42	42	39	39	38	

*p, probability that the differences between treatment centres occurred by chance.

suspend further recruitment into that regimen, and to stop the treatment by that regimen of patients who had already been recruited, but who had not completed 24 months' treatment. Although the review led to the conclusion that the jaundice had not resulted from toxic hepatitis, the SC decided not to resume admission of new patients to treatment by regimen A_2; the rate at which new patients presented for admission into the trial had decreased to such a degree that the SC feared that resuming admission to treatment by regimen A_2 would result in an insufficient number of patients having been treated by any regimen. The clinical investigators in Chingleput had concluded that the cases of jaundice did not represent toxic hepatitis. On the other hand, that jaundice occurred among nine of the 51 patients who had been treated by the maximal regimen in each centre and among only five of the 161 patients who had been treated by all of the other regimens suggests that those treated by the maximal regimens were at a significantly greater risk of jaundice ($p = 0{\cdot}0011$). That jaundice occurred primarily among patients treated by the maximal regimens accounts for the significant difference among regimens of the frequency with which adverse reactions were noted.

Because patients suffering from adverse reactions to the prescribed treatment may withdraw from treatment prematurely, incidents—especially deaths, removal of patients from the trials, and voluntary withdrawal of the patients from the trials—are considered together with adverse reactions. That six of the 12 patients treated by regimen A_2 were removed from the trial in Bamako, reflecting the decision of the SC, and that two of the three deaths among Bamako patients occurred among patients treated by this regimen account for the differences of frequency of incidents among regimens. The frequency of incidents was not found to differ between centres, except for that of voluntary withdrawal.

Haematologic changes. Specimens of blood for haematologic examination were obtained by venipuncture at intervals in the course of the trials in Bamako and

Table 9. Haematologic changes as a function of centre and regimen

Centre and regimen	Number of patients or observations	HCT		WBC		PMN		PLAT	
		High*	Low	High	Low	High	Low	High	Low
				Number of patients					
Bamako									
A_2	12	1	3	1	1	4	2	0	4
C_B	42	1	6	3	3	8	11	0	13
E_2	42	1	6	4	3	6	12	0	13
Total	96	3	15	8	7	18	25	0	30
p_B		0·54	0·63	0·92	0·99	0·33	0·71	1·0	0·99
Chingleput									
A_1	39	1	15	8	10	1	14	1	3
C_C	39	1	18	17	4	1	10	2	4
D_1	38	1	20	24	6	4	11	2	4
Total	116	3	53	49	20	6	35	5	11
p_C		1	0·46	0·00075	0·19	0·19	0·60	0·80	0·90
p		1	<0·0001	<0·0001	0·047	0·0036	0·61	0·094	0·0001
				Number of observations					
Bamako									
A_2	92	NA†	6	1	1	5	3	0	4
C_B	315	NA	19	4	6	9	11	0	15
E_2	278	NA	10	5	4	8	21	0	21
Total	685	NA	35	10	11	22	35	0	40
p_B			0·33	0·82	0·83	0·43	0·056	1·0	0·28
Chingleput									
A_1	830	NA	44	19	17	1	28	1	9
C_C	726	NA	32	36	4	2	26	11	4
D_1	793	NA	58	54	6	5	23	6	5
Total	2349	NA	134	109	27	8	77	18	18
p_C			0·042	<0·0001	0·0097	0·20	0·74	0·007	0·42
p			0·56	<0·0001	0·34	<0·0001	0·025	0·023	<0·0001

Abbreviations: HCT, hematocrit; WBC, number of white blood cells per mm^3 peripheral blood; PMN polymorphonuclear leucocytes as per cent of WBC; PLAT, number of platelets per mm^3 peripheral blood; p_B, probability that the differences among Bamako regimens occurred by chance; p_C, probability that the differences among Chingleput regimens occurred by chance; p, probability that the differences between treatment centres occurred by chance.

* High or low, with respect to the following criteria for each centre: HCT, Bamako and Chingleput: >50% and <30%; WBC, Bamako: ≥12,000 and <4000; Chingleput: ≥16,000 and <5000; PMN, Bamako: ≥70% and <20%; Chingleput: ≥90% and <40%; PLAT, Bamako: >400,000 and <200,000; Chingleput: >500,000 and <100,000.

† NA, not analysed, because the cases of elevated HCT were too few.

Chingleput, and determinations of haematocrit (HCT), numbers of white blood cells (WBC) and blood platelets (PLAT) per mm^3 of blood, and per cent of polymorphonuclear leukocytes (PMN) were performed at each centre. Because of the different frequencies with which these determinations were made in the two centres—approximately 20 per patient in Chingleput, and seven per patient in Bamako, these data have been analysed in terms of the numbers of both patients and observations, as summarized in Table 9. (The numbers of observations recorded per patient did not appear to be greater among those patients demonstrating abnormal values.) Three patients in each centre were each found on one occasion to have HCT > 50%; except in one case, in which the HCT was 55%, the values were 51 or 52%.

A large number of patients in both centres were found to have HCT < 30%, many of these on more than one occasion. The frequency of low values of the HCT was significantly greater in Chingleput than in Bamako; however, the frequency did not vary among regimens. On the other hand, considering numbers of observations, the frequency of HCT < 30% did not differ between centres; in fact, although almost twice as many Chingleput as Bamako patients demonstrated HCT < 30%, the proportion of observations demonstrating HCT < 30% was virtually identical in both centres. The frequency of HCT < 30% varied significantly among Chingleput regimens, but not among Bamako regimens, being greatest among the patients treated by regimen D_1, and least among those treated by regimen A_1.

Considering both numbers of patients and numbers of observations, the frequency of elevated WBC was greater among Chingleput than among Bamako patients, despite the apparently more stringent criterion employed in Chingleput (see footnote to Table 9), a difference not accounted for by different numbers of observations. In addition, the frequency of elevated WBC was smaller among patients treated in Chingleput by regimen A_1 than among those treated by the remaining two regimens. Low values of the WBC were equally infrequent among Bamako and Chingleput patients, but, considering the numbers of observations, significantly more frequent among Chingleput patients treated by regimen A_1 than among those treated by regimens C_C and D_1.

Considering numbers of both patients and observations, elevated values of PMN were more frequent among Bamako than among Chingleput patients. In fact, considering numbers of observations, the frequency of elevated values of PMN among Bamako patients was ten-fold that in Chingleput. The greater frequency of elevated values of PMN in Bamako appears to have resulted from the different criteria employed in the two centres (see footnote to Table 9); in fact, applying the less rigorous criterion (PMN $\geq$ 70%) to the measurements in both centres yields a greater frequency of elevated PMN in Chingleput (16% of observations) than in Bamako (3% of observations). Considering numbers of patients, the frequency of low values of PMN did not differ significantly between the two centres; on the other hand, considering numbers of observations, low values of PMN were significantly more frequent among Bamako (5% of observations) than among Chingleput (3% of observations) patients, this despite the difference of criteria.

Elevated values of PLAT were not reported in Bamako, and were infrequent in Chingleput. Considering numbers of observations, elevated values of PLAT were less frequent among Chingleput patients treated by regimen A_1 than among those treated by the other two regimens. Although low values of PLAT appear to have been more frequent among Bamako than among Chingleput patients, this appears to have resulted from the employment in Chingleput of a more rigorous criterion (see footnote to Table 9). In fact, fully 10% of the values of PLAT among Chingleput patients were lower than $1{\cdot}5 \times 10^5$ per ml, whereas fewer than 2% of values among Bamako patients were lower than this level. The frequency of low values of PLAT was not found to vary among regimens.

Changes of hepatic function. Specimens of blood for tests of hepatic function were also obtained at intervals during the clinical trials in Bamako and Chingleput, and measurements of serum bilirubin (SB), serum glutamic pyruvic transaminase activity (SGPT), and serum alkaline phosphatase activity (SAP) were performed. The results of these studies are summarized in Table 10. Elevations of SB were significantly more

Table 10. Abnormal hepatic function tests as a function of centre and regimen

Centre and regimen	Number of patients or observations	Elevations* of: SB	SGPT	SAP
		Number of patients		
Bamako				
A_2	12	7	3	1
C_B	42	6	3	7
E_2	42	6	8	6
Total	96	19	14	14
p_B		0·0016	0·17	0·77
Chingleput				
A_1	39	7	12	10
C_C	39	10	17	12
D_1	38	10	11	14
Total	116	27	40	36
p_C		0·62	0·33	0·57
p		0·020	0·0014	0·0074
		Number of observations		
Bamako				
A_2	92	8	4	1
C_B	299	11	3	8
E_2	271	6	15	6
Total	662	25	22	15
p_B		0·019	0·0089	0·67
Chingleput				
A_1	829	8	18	24
C_C	770	25	58	32
D_1	792	28	40	24
Total	2391	61	116	80
p_C		0·0015	<0·0001	0·31
p		0·092	0·099	0·16

Abbreviations: SB, serum bilirubin; SGPT, serum glutamic-pyruvic transaminase activity; SAP, serum alkaline phosphatase activity; p_B, probability that the differences among the Bamako regimens occurred by chance; p_C, probability that the differences among the Chingleput regimens occurred by chance; p, probability that the differences between treatment centres occurred by chance.

* Elevated with respect to the following criteria for each centre; SB, Bamako: ≥1·5 mg%; Chingleput: >1 mg%; SGPT, Bamako and Chingleput: >65 Karmen units; SAP, Bamako: >30 KA units; Chingleput: >20 KA units.

frequent among Bamako than among Chingleput patients; this is almost entirely the result of the greater frequency of elevations of SB among Bamako patients treated by regimen A_2 ($p = 0{\cdot}0003$). Among Chingleput patients, elevations of SB were significantly less frequent among patients treated by regimen A_1.

Elevations of SGPT were significantly less frequent among Bamako than among Chingleput patients in terms of numbers of patients, but not in terms of numbers of observations. Considering numbers of observations, elevations of SGPT were significantly more frequent among Chingleput patients treated by regimen C, but significantly less frequent among Bamako patients treated by this regimen. A larger proportion of Chingleput than of Bamako patients demonstrated elevated values of the SAP, probably reflecting the larger number of determinations performed in Chingleput.

Table 11. Abnormalities of the urinary tract as a function of centre and regimen

Centre and regimen	Number of patients or observations	Elevation of the BUN*	Number of patients or observations	Abnormal urinalysis	
				Once	>once
		Number of patients			
Bamako					
A_2	12	3	12	2	4
C_B	42	2	42	9	10
E_2	42	6	42	9	10
Total	96	11	96	20	24
p_B		0·11		0·93	0·77
Chingleput					
A_1	39	5	39	7	15
C_C	39	4	39	11	16
D_1	38	6	38	7	20
Total	116	15	116	25	51
p_C		0·77		0·46	0·41
p		0·74		0·88	0·004
		Number of observations			
Bamako					
A_2	91	3	91	–	13
C_B	299	2	295	–	32
E_2	270	7	275	–	35
Total	660	12	661	–	80
p_B		0.12		–	0·62
Chingleput					
A_1	830	6	845	–	82
C_C	792	4	799	–	81
D_1	794	11	812	–	98
Total	2416	21	2456	–	261
p_C		0·15		–	0·25
p		0·038		–	0·28

Abbreviations: BUN, blood urea nitrogen in mg%; p_B, probability that the differences among the Bamako regimens occurred by chance; p_C, probability that the differences among the Chingleput regimens occurred by chance; p, probability that the differences between the centres occurred by chance.

* Elevated with respect to the following criteria for each centre: SB, Bamako: ≥40 mg%; Chingleput: >20 mg%.

Changes of urinary tract function. The results of the measurements of blood urea nitrogen (BUN) and of the urinalyses are summarized in Table 11. As shown in Table 11, no differences among regimens were recognized. On the other hand, differences between the two treatment centres were evident. Although proportionately more measurements of the BUN were performed at Chingleput than at Bamako, and although the proportions of patients at each centre in whom elevations of the BUN were noted are similar, elevations of the BUN were recognized approximately twice as frequently at Bamako than at Chingleput. The situation with respect to abnormal urinalyses is the opposite. Approximately twice as many Chingleput patients as Bamako patients were noted to demonstrate abnormal urinalyses. However, this finding may be attributed to the greater number of urinalyses performed in Chingleput; approximately 10% of the urinalyses performed in Chingleput and 12% of those performed in Bamako were abnormal.

Table 12. Relationships between ENL and weight-loss, elevated BP, hameatologic abnormalities, abnormalities of hepatic function, and urinary-tract abnormalities

	ENL			
Variable	Presence	p*	Severity	p†
Weight-loss	25% *vs.* 10%	0·008	18·0 *vs.* 7·99	0·0003
Elevated BP	–	>0·05	–	>0·05
Reduced HCT	39% *vs.* 25%	0·047	18·5 *vs.* 6·00	0·0001
Elevated WBC	36% *vs.* 17%	0·002	21·0 *vs.* 6·00	0·0001
Elevated SB	–	>0·05	–	>0·05
Elevated SGPT	–	0·02	15·7 *vs.* 8·10	0·01
Elevated SAP	33% *vs.* 15%	0·002	14·1 *vs.* 8·70	0·04
Elevated BUN	–	>0·05	–	>0·05
Abnormal urinalysis	–	>0·05	12·8 *vs.* 6·40	0·003

* The statistical significance of these differences was examined by means of the χ^2 test.

† The statistical significance of these differences was examined by means of a 't' test.

Correlations among BP, weight-loss, voluntary withdrawal, and changes of haematologic status, hepatic function and urinary tract function with ENL. In the attempt to distinguish abnormalities resulting from adverse reactions to drugs from those resulting from other causes—especially ENL, relationships between ENL on the one hand and weight-loss, voluntary withdrawal, changes of haematologic status, and abnormalities of function of liver and urinary tract on the other, were sought. The results of this search are summarized in Table 12.

Weight-loss, defined as a loss of >5 kg from the maximal weight recorded on more than one occasion during the trial, occurred with a significantly greater frequency among those patients demonstrating ENL of any degree of severity than among those without ENL. In addition, the ENL was found to be significantly more severe (the severity score was taken as the product of the severity recorded on each occasion and the number of weeks during which ENL was recorded) among those patients demonstrating weight-loss than among those who did not. In addition, as is also shown in Table 12, ENL was found to be related to reduction of the HCT and to elevations of the WBC, SGPT and SAP. Severity of the ENL but not its mere presence was found to be related to an abnormal urinalysis.

On the other hand, although one might expect that those patients suffering from more severe ENL might be more likely to withdraw from the trial, no such relationship was found. Similarly, no relationship was demonstrated between elevation of the BP or an elevated SB and ENL.

Discussion

The primary objective of the analyses reported in this paper is the search for differences of therapeutic and adverse effects that might be attributed to the regimens employed in the trials. The therapeutic effects studied included the frequency with which persisting

M. leprae were detected, change of the various measures (BI, LIB and LAFBPG) of the numbers of AFB harboured by the patients, and change of the patients' leprosy in terms of both clinical changes (clinical status, ΔSkin, ΔInfilt and ΔSize) and histopathological changes.

Among 554 specimens, representing 203 patients, persisting *M. leprae* were detected in only 43 specimens (7·8% of all specimens), representing 38 patients. As was reported earlier,[5] the demonstration of persisting organisms appeared to be a random phenomenon, unrelated to regimen, centre or duration of treatment. It appears likely that, had a more sensitive means of detection been employed, such as, for example, the neonatally thymectomized rat,[14] persisting organisms would have been demonstrated in a larger proportion of patients than was actually the case. The BI was found to decrease at the average rate of 0·571 $\log_{10}$ units (73%) per year, a rate slower than one of 90% per year, which is often assumed, but much like that reported earlier by Ridley.[15] The LIB decreased with a mean annual rate of 0·894 $\log_{10}$ units (87%), and the LAFBPG with a mean annual rate of 0·504 $\log_{10}$ units (69%). The BI of nose-blows decreased by a mean of 1·10 $\log_{10}$ units (92%) during the first 90 days of treatment. As expected, the BI LIB and LAFBPG were found to be well correlated. The numbers of AFB were found to decrease more slowly among the patients treated in both centres by regimen C.

Clinical deterioration was reported in the case of only two patients, both of them treated in Bamako. The decrease of the proportion of skin involved was found to vary only in Chingleput; here, the decrease was least among the patients treated by the maximal regimen, regimen A_1. The decrease of mean nerve size also was found to vary only in Chingleput; the decrease was greater among the patients treated by regimen D_1 than among those treated by either regimen A_1 or regimen C_C.

Change of histopathological classification in the course of the trials was recorded for 23 (12%) of 196 patients, with no relationship to regimen or treatment centre. None of the remaining variables studied was found to differ among regimens. Thus, except for the slower rate of decrease of the number of AFB among the patients treated by regimen C, no difference of therapeutic effect among the regimens was demonstrated. Given that the proportion of viable organisms did not differ among regimens, the significance of the difference among regimens of the total number of organisms, both viable and dead, is not clear.

Analysis of the measures of therapeutic effects by treatment centre reveals a few apparent differences. Bamako patients differed from those in Chingleput in several respects. Although the rate of fall of the BI of nose-blows during treatment did not differ between centres, the values observed before the start of treatment were larger in Bamako than in Chingleput, consistent with the larger pretreatment values of the BI measured from six skin sites in the former centre.[3] Bamako patients weighed more on admission to the trial than did Chingleput patients, and elevated pretreatment values of the BP were recorded more frequently in Bamako. In addition to these differences among the patients of the two centres, differences of practice between the centres are apparent. Clinical improvement was recorded more frequently in Bamako than in Chingleput, and the decreases of ΔSkin, ΔInfilt and ΔSize were greater in Bamako.

Adverse effects were analysed in terms of ENL, pigmentation, changes of weight and BP, adverse reactions—especially jaundice—and incidents, haematologic changes (HCT, WBC, PMN and PLAT), changes of hepatic function (SB, SGPT and SAP), and changes of urinary tract function (BUN and urinalysis). In addition, correlations

with ENL were sought among BP, weight-loss, voluntary withdrawal, and changes of haematologic status, hepatic function and urinary tract function. In addition, other clinical assessments were made, including erythema of the skin, nerve-pain and nerve-tenderness, disability of the hands and feet, and pathological changes of the eye. Because abnormalities had been noted initially in very small proportions of the patients in both treatment centres, improvement in the course of the trials could have occurred in the cases of only a very few of the patients; therefore, these data were not further analysed.

A number of apparent differences among regimens were encountered. As might have been expected, ENL was less severe among those patients treated by regimen A_1 than among all of the remaining patients. Similarly, the degree of pigmentation was proportional to the dosage of clofazimine, being greatest among the patients treated by regimen A_1, and least among those treated by regimen C_C. Although the proportions of patients demonstrating low values of the HCT did not differ among regimens, analysis by number of observations shows a greater frequency among those patients treated by regimen D_1 than among all of the remaining patients. Compared to the patients treated by all of the remaining regimens, both high and low values of the WBC were observed more frequently among the patients treated by regimen A_1, whereas elevations of PLAT and of SB were less frequent among these patients. Finally, elevations of SGPT were found more frequently among the patients treated by regimen C in Chingleput than among the corresponding patients in Bamako. The explanations of these differences are not immediately evident. That some of these differences may represent effects of ENL rather than of the regimen is considered below.

Analysis of adverse effects by treatment centre demonstrates that prednisolone was preferred for treatment of ENL in Chingleput, whereas thalidomide was preferred in Bamako. Because none of the regimens employed in Bamako included clofazimine, pigmentation by the drug was observed only in Chingleput. Several differences between the two centres appeared because observations were performed much more frequently in Chingleput than in Bamako; this was the case for weight-loss, abnormal values of the SGPT and SAP, and abnormal urinalyses. Finally, certain differences appear to reflect differences of criteria between the centres; such was the case for elevated values of PMN and low values of PLAT.

Perhaps not unexpectedly, certain of the adverse effects were associated with ENL, and may even be considered components of the ENL syndrome. Thus, ENL was found to be associated with weight-loss, reduced HCT, elevated WBC, elevations of the SGPT and SAP, and abnormal urinalyses. On the other hand, elevations of the BP and of the SB were not so associated, nor was there evidence that patients with ENL were more likely than those without to withdraw voluntarily from the trials.

Potentially the most important of the adverse effects is jaundice. Although the responsible clinicians, an expert consultant, and the members of the THELEP SC all came to the conclusion that jaundice among the trial patients did not represent an adverse reaction to a drug or drug-combination, it is perhaps of great importance that nine of the 14 cases occurred among patients treated by the maximal regimens in both treatment centres. Presumably, all 212 patients treated in both centres were more-or-less equally at risk of viral hepatitis and jaundice of other causes unrelated to the treatment prescribed. One wonders if the preference for daily rifampicin, as opposed to monthly administration of the drug, that has been so frequently expressed in discussions of

multidrug regimens to be used in leprosy control, and currently the standard in the US[16] should not be reconsidered.

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Primary resistance to single and multiple drugs in leprosy—a mouse footpad study

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Summary Skin biopsy homogenates obtained from three cases of lepromatous leprosy with no prior history of antileprosy treatment were tested in the mouse footpad for the sensitivity of *Mycobacterium leprae* to multiple drugs.

One of the inocula was sensitive to all the three drugs tested using the highest concentration each of DDS 0·01 g%, RFP 0·03 g% and CLF 0·01 g%. The 2nd inocula showed growth in the presence of 0·01 g% DDS only. While the 3rd inocula (Pt. KU) tested resistant to all the three drugs in the first, i.e. man to mouse, as well as in the second passage, i.e. mouse to mouse.

Introduction

Since its introduction in 1982,[1] multidrug therapy (MDT) is heralded as one of the most important and stimulating contributions to leprosy control.[2] Data from field programmes also indicate a high degree of efficiency of WHO/MDT after about 10 years of follow up.[3] While it took over a decade to first suspect dapsone resistance, its prevalence has since increased at an alarmingly high rate.[4,5] In a much shorter period thereafter, secondary resistance has been reported with rifampicin, clofazimine, ethionamide and prothionamide.[6–10] To date, however, primary resistance to multiple drugs in leprosy has not been documented.

We report here a study on 3 cases of previously untreated lepromatous leprosy of which two exhibited primary resistance to single and multiple drugs of MDT respectively using the well established mouse footpad technique. Their significance is discussed.

Materials and methods

Skin biopsy homogenates obtained from three cases of lepromatous leprosy with no prior history of antileprosy treatment, were tested individually using mouse footpad for the growth of *M. leprae* and their sensitivity to multiple drugs. The patients in question, two males aged 40 and 29 years and a female aged 19 years were part of an ofloxacin trial

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Table 1. Inocula 1 - Patient KS. Bacterial count per footpad in normal and drug-treated mice at the 12th month (counts × 104).

No.	No Rx	DDS (1) 0·01 g%	RFP (2) 0·03 g%	CLF (3) 0·01 g%	Mixture (1 + 2 + 3)
M1	80·25	1·5	0	0	0
M2	81·75	5·25†	0	0·75	0
M3	48·00	15·06*	0	0	0
M4	186·00	48·00*	0	0·75	0
M5	-	4·5†	0	0	0
Take (%)	4/4 (100)	5/5 (100)	0/5 (0)	2/5 (40)	0/5 (0)

* ≥ ten-fold growth.
† ≥ five-fold growth.
0 No AFB seen in more than 200 fields.

Table 2. Inocula 2 - Patient SB. Bacterial count per footpad in normal and drug-treated mice at the 12th month (counts × 10^4).

No.	No RX	DDS (1) 0·01 g%	RFP (2) 0·03 g%	CLF (3) 0·01 g%	Mixture (1 + 2 + 3)
M1	51·75	0·75	0	0	0
M2	33·75	0	0	0	0
M3	30·03	0	0	0	0
M4	31·5	0	0	0	0
M5	-	0·75	0	0	0
M6	-	0·75	0	0	0
Take (%)	4/4 (100)	3/6 (50)	0/6 (0)	0/6 (0)	0/6 (0)

Table 3. Inocula 3 - Patient KU. Bacterial count per footpad in normal and drug-treated mice at the 12th month (counts × 10^4).

No.	No Rx	DDS (1) 0·01 g%	RFP (2) 0·03 g%	CLF (3) 0·01 g%	Mixture (1 + 2 + 3)
M1	97·5	9·00†	4·5†	0	0·75
M2	60·75	1·5	3·00	1·5	0·75
M3	178·00	3·00	0	1·5	0·75
M4	65·25	12·00*	0	3·75	0
M5	-	1·50	60·00*	1·5	0
M6	-	7·50†	0	6·00†	-
Take (%)	4/4 (100)	6/6 (100)	3/6 (50)	5/6 (83·3)	3/5 (60)

* ≥ 10-fold.
† ≥ 5-fold.
0 No AFB seen in more than 200 fields.

conducted in one of the leprosy centres in Bombay. All three patients presented with diffused nodular lesions. The bacteria were harvested from the skin biopsies using the standard protocol.[11] Their bacterial index (BI) were more than 5 + their and morphological index (MI) were over 4%. Ten thousand bacilli each were injected into both the hind footpads of 3-4 months-old nonimmunosuppressed Swiss white (S/W) female mice. A test for sensitivity to a single large dose each of diaminodiphenylsulphone (DDS 0·01 g%) rifampicin (RFP 0·03 g%) clofazimine (CLF 0·01 g%) and to a mixture of all three drugs in the same concentration were set, along with an untreated control group of mice. All the drugs were given to the test mice through the feed from day zero (continuous method).[12] Drugs were incorporated into the commercially available powdered mash feed, through wet mixing and blending.

The harvesting of footpads and recordings of *M. leprae* growth in the footpads of the control group of mice were carried out at monthly intervals beginning from the 6th month, while drug treated mice were harvested only at the 12th month following infection. A minimum of 5 to 6 counts each (left and right pooled harvest) were obtained at the 12th month.

Suspensions of *M. leprae* derived from two sources, i.e. one from the untreated lepromatous leprosy patient (KU) and the other from an armadillo biopsy (obtained from Ellenor Storrs) were heat killed and injected into the footpads of the normal mice with an inocula containing 10,000 bacilli in 0·03 ml. Harvestings were done at monthly intervals beginning from the 1st month and were followed up to the 12th month.

CONFIRMATION OF DRUG RESISTANCE IN SECOND PASSAGE

Only the drug-resistant organisms derived from mice treated with DDS (0·1 g%), RFP (0·3 g%), CLF (0·01 g%) and the mixture, in the primary passage for inocula No. 3 (Pt KU) were repassaged into groups of 10 mice each and were maintained in the absence and presence of respective drugs for which they were resistant. Footpad harvests were carried out at the 12th month.

Results

Normal growth curves were obtained in the footpads of control (untreated) S/W mice with all the three inocula. Results obtained in the drug-treated mice using these inocula were as follows:

Primary drug-screening test in normal Swiss white mice:

Inocula 1. (patient KS, aged 40, male) Harvests done at the 12th month showed no detectable count in the footpads of mice treated with 0·03 g% RFP and with the mixture of all three drugs. Two out of 5 CLF treated mice showed a very small count ($0{\cdot}75 \times 10^4$ not significant), while in DDS-treated mice there were counts in all the 5 mice (left and right pooled harvest). Two of the counts were more than 10-fold while in others it was less than 10-fold, nevertheless suggesting, primary resistance to 0·01 mg/% DDS which is equivalent to 100 mg human dose (See Table 1).

Inocula 2. (patient SB, aged 19, female) At the 12th month there were no detectable counts in any of the mice treated with RFP, CLF and the mixture. The DDS-treated group of mice showed a marginal count (less than 10-fold) in 3 out of 6 mice suggesting

that this inocula was fully sensitive to RFP and CLF and probably a low-grade resistance to DDS (See Table 2).

Inocula 3. (patient KU, aged 29, male) There was a good take in the footpads of mice treated using DDS, RFP and CLF tested individually, while mice treated with the combination of drugs showed a small count (not significant) in 3 out of 5 mice (see Table 3). The percentage of footpads showing counts as well as the per footpad counts were highest in the DDS treated mice followed by RFP, CLF and the mixture suggesting the presence of a subpopulation each of *M. leprae* that were resistant to all the three drugs tested individually.

CONFIRMATION OF DRUG RESISTANCE IN THE SECOND PASSAGE

As mentioned earlier only the drug-resistant strains of *M. leprae* obtained in the primary screening of inocula number 3 (patient KU) were reinoculated into the footpads of normal Swiss white mice (inocula size were approximately 1×10^3) and were further maintained both in the absence (5 mice) and presence (5 mice) of respective drugs for which they were resistant.

In the second passage, the respective drug-resistant strains again showed a good-fold increase and very good morphological index, i.e. 15–20%, in the footpads of both drug-treated and untreated mice at the 12th month, thus confirming their continued resistance to these drugs (Table 4). However, it was noted that the percentage take in the second passage ranged between 20 and 80%. Moreover inocula derived from DDS-treated mice (DDS resistant) showed a better take (60%) in the presence of 0·01 g% DDS than the control group of mice (take = 25%).

Two experiments using heat-killed *M. leprae* derived from two different sources, i.e. inocula 3 patient KU and armadillo-derived *M. leprae* (see Table 5) showed presence of acid-fast bacilli in the footpads of normal Swiss white mice till the end of the 6th month. There was a steady decline in the percentage take with time. Moreover the average per footpad count in these experiments 1 and 2 (namely, $0{\cdot}3 \pm 0{\cdot}21$ and $0{\cdot}4 \pm 0{\cdot}25$ respectively) were less than the original inocula at any point in time.

Table 4. Drug-resistant bacteria derived from inocula 3 (Pt-KU) in second passage (mouse to mouse). *M. leprae* count/footpad $\times 10^5$ at 12th month in the absence (C) and presence of respective drugs.

	1°DDS Res		1°RFP Res		1°CLF Res		1°Mix Res	
	C*	DDS† 0·019%	C*	RFP† 0·039%	C*	CLF† 0·019%	C*	Mix†
M1	20·3	20·3	6·8	6·8	3·4	3·4	0	ND
M2	0	13·6	6·8	0	8·5	0	6·8	ND
M3	0	0	1·4	0	0	5·1	0	ND
M4	0	6·8	0	0	6·8	1·7	0	ND
M5	-	0	-	-	1·7	-	0	ND
Take	1/4	3/5	3/4	1/4	4/5	3/4	1/5	
%	(25)	(60)	(75)	(25)	(85)	(75)	(20)	

C*, mice on normal diet.
†, not defined.
ND, not done.
0, no bacilli seen in > 100 fields.

Table 5. Profile of bacterial clearance. Heat killed *M. leprae* in the footpads of normal S/W mice.

Post	Expt. 1 armadillo *M. leprae*	Expt. 2 human *M. leprae* (KU)
1st	3/4 (75%)*	3/4
2nd	2/4 (50%)	-
3rd	2/4	2/4
4th	1/4	-
5th	3/4	-
6th	1/4	1/4
7th	0	0
8th	0	0
9th	0	0
10th	0	0
11th	0	0
12th	0/10	0/6

* *Number showing M. leprae count.*
Number of harvests.

Discussion

Drug susceptibility testing by the mouse footpad technique is considered the most reliable.[6] Primary dapsone-resistant patients verified by the mouse footpad technique were first reported in the year 1977.[5] Subsequently several surveys carried out worldwide to assess the prevalence of primary and secondary resistance to DDS showed an alarming increase in the annual incidence rate and prevalence of DDS-resistant leprosy.[1] In addition secondary resistance to other bactericidal drugs such as rifampicin, ethionamide and clofazimine also became apparent using the mouse footpad method.[6]

In the present study inocula derived from one of the untreated patients (KU) revealed subpopulations of *M. leprae* that were primarily resistant to DDS, RFP and CLF at the highest concentrations, in both primary and secondary screenings. While it was not very surprising to find primary resistance to DDS in two out of three patients considering the high incidence of DDS resistance that was prevailing since 1982,[1] primary resistance to multiple drugs has not been documented to date to the best of our knowledge. However there are recent reports indicating clinical evidence of non-responsiveness to MDT both in paucibacillary and multibacillary cases of leprosy.[13–15] In one of the multibacillary cases bacteria were subsequently shown to be resistant to all the three drugs using mouse footpads.[15]

One of the findings that we are unable to explain is the poor percentage take that was obtained in the second passage, particularly with DDS-resistant organisms that were maintained in the absence of DDS (see Table 4). This was unlike the earlier experience where isolates of dapsone-resistant *M. leprae* have shown a better take in the subsequent passage.[5]

The drugs given through feed prepared in the laboratory on a weekly basis were indeed effective was ascertained from the results obtained with three different inocula that were tested more or less simultaneously using identical protocol. In a study carried

out at Karigiri, rifampicin mixed with feed prepared in a similar manner was systematically tested and was found to be effective in controlling the growth of *M. leprae* in the footpads of mice.[16] To exclude technical error one of the controls used in the present study was to inject an equal number of heat-killed *M. leprae* into the footpads of normal mice and record the counts at regular intervals using different inocula. It was noteworthy that the number of acid-fast organisms recovered at any point were less than the inocula, and there was a steady decline in the number of positive harvests in the footpads of normal mice. Also no acid-fast organisms were recorded (in over 200 fields) beyond 6 months in any of these mice.

Indeed one of the criteria for multiplication of *M. leprae* in the footpads is 10^5 per footpad, i.e. at least a 10-fold increase.[17] Special mention must be made of the limitations of the technique as a whole and the possible underlying significance of some of the results obtained in the present study using mouse footpads. Unlike the standard protocol[17] only a single concentration of each drug were tested, thus limiting the extrapolation of the results. On the other hand, in the normal Swiss white strain of mice that are routinely in use in our laboratory, the platue phase counts recorded were often less than 10-fold,[18] which could either be a limitation of the technic or a mice strain related variance or both. Under the circumstances we are inclined to put forward an argument that some of the 'NOT significant counts' obtained at the 12th month in the present study that are recorded in Tables 1, 2 and 3 could well be an indication of presence of a 'smaller' subpopulation of *M. leprae* that were refractory to the respective drugs and to their mixture. Admittedly the inclusion of serial dilution of drugs and harvesting at more intervals might have yielded a more clearer picture. However significance of these findings cannot be underscored and demand a more broad-based large-scale study.

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Borderline–tuberculoid leprosy: clinical and immunological heterogeneity

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Summary The authors analysed some immunological criteria in leprosy patients diagnosed as borderline tuberculoid by the presentation of different grades of skin lesions as well as different grades of nerve involvement. Only 50% of the patients presented a single skin lesion and 58% had none or only one affected nerve. Nineteen patients (39·6%) showed a positive lepromin reaction (induration $\geq$ 5 mm).

Patients with a positive skin test had a greater number of skin lesions when compared with patients with a negative lepromin test. Fifty-seven percent of the patients were found to be positive using a lymphoproliferation test (LTT) in response to *Mycobacterium leprae* antigens. Positive LTT results did not correlate with the number of skin lesions, but patients unresponsive to LTT had a lesser extent of nerve involvement. Four out of 18 patients (22%) released high IFNγ levels in PBMC culture stimulated by *M. leprae*. (mean U/ml $\pm$ SD = 142 $\pm$ 72). All of these 4 patients presented only one skin lesion, although three of them had more than one affected nerve.

Nineteen out of 21 patients (90·5%) showed no anti-PGL-1 antibodies in their serum. The low levels of anti-PGL-1 antibodies among these patients confirmed their tuberculoid background even in those with multiple skin lesions.

These findings seem to attribute an important role to IFNγ in restraining the spreading of the infection in the skin, but IFNγ may have an opposite effect on the nerves. The potential pathological effects of IFNγ during the delayed type of hypersensitivity can be related to its ability to synergise with other inflammatory cytokines such as TNFα, IL-1β, and others.

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Introduction

Leprosy is a chronic infectious disease that affects skin and peripheral nerves. The clinical spectrum in leprosy seems to correlate with the host immune response.[1] T-cell-dependent immunity to *Mycobacterium leprae* is high in healthy-exposed individuals and in tuberculoid leprosy patients with localized disease, but is strikingly absent in lepromatous leprosy patients who have a high bacillary load and widely disseminated lesions. Thus, cell-mediated immunity (CMI) protects against dissemination of bacteria and disease. It has recently been hypothesized that the spectrum of leprosy reflects the balance between T-helper-cell populations (Th1 and Th2 CD4+ T cells).[10] Indeed, analysis of mRNA expression in tissue samples of leprosy patients through RT-PCR showed two distinct lymphokine patterns.[12] Tuberculoid lesions were characterized by prominent expression of IL-2 and IFNγ mRNA, a Th1 pattern associated with cell-mediated immunity. Moreover, lepromatous lesions primarily expressed IL-4, IL-5 and IL-10 mRNA, the Th2 pattern which favours humoral immunity and supression of DTH.

IFNγ, a product of activated T lymphocytes, has been considered the major mediator at the effector end of the immune response.[8] Its production correlates with the ability of mononuclear phagocytes to kill microorganisms. It was also demonstrated that household contacts of lepromatous patients who were unable to secrete IFNγ upon specific *in vitro* stimulation had a higher risk of developing leprosy as compared to high responders.[14] Tuberculoid leprosy patients (TT, BT) are known to respond *in vitro* to *M. leprae* antigens, although nonresponder BT patients have also been reported.[15] However, the *in vitro* immunological status of paucibacillary patients and its correlation to their clinical activity, lepromin response, and the occurrence of relapse has not yet been investigated. Nerve lesions and the extent of body area affected are important parameters in determining the treatment of leprosy patients.[3] The aim of this study was to correlate the *in vitro* and *in vivo* immunological responses of tuberculoid leprosy patients with the extension of skin lesions and the involvement of peripheral nerves.

Material and methods

PATIENT POPULATION

Leprosy patients from the Leprosy Out-Patient Unit, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, were diagnosed according to the Ridley–Jopling classification.[11] A total of 48 borderline–tuberculoid (BT) leprosy patients (18 male and 30 females), 15 to 78 years of age (mean $\pm$ sd $= 41 \pm 12$), were studied. Patients were included in the World Health Organization (WHO) multidrug therapy (MDT) regime for paucibacillary patients. None of them had been previously treated. All of them received 6-monthly supervised doses of 600 mg rifampin and daily self-administered doses of dapsone 100 mg/day. At diagnosis, dermatological and neurological examination was performed on all patients. Number and characteristics of cutaneous lesions were noted. Peripheral nerves were assessed through palpation of the main nerve trunks and corresponding pain and/or thickness, when found, was noted. Sensory and voluntary muscle evaluation was done in all patients using simple techniques and Semmes–Weinstein monofilaments, by trained personnel. Patients were assessed monthly during treatment by way of

dermatoneurological examinations. The immunological tests were performed following patients' consent for blood collection at diagnosis. Six patients (12·5%) presented reactional episodes (either reversal reaction (RR) or neuritis), 3 during multidrug treatment, and 3 during the surveillance period. Reactional lesions were biopsied to confirm clinical diagnosis of a reactional state.

ENUMERATION OF BACILLI

Slit smears for bacterial index (BI) determination taken from three sites (both earlobes and a cutaneous lesion) were performed at the time of diagnosis, as a routine procedure. All 48 patients were BI negative.

ANTIGEN

Skin tests were done with lepromin A, Carville, USA (provided by WHO). For *in vitro* tests, armadillo-derived sonicated *M. leprae* antigen was provided by Dr R. J. W. Rees (IMMLEP Bank, The National Institute of Medical Research, Mill Hill, England). Optimal antigen stimulating concentration was found to be 20 μg/ml.

LYMPHOCYTE TRANSFORMATION TEST (LTT)

Heparinized venous blood was collected for *in vitro* tests and peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-hypaque (Pharmacia Fine Chemicals, Piscataway, NJ, USA) density centrifugation. PBMC were incubated in triplicate at 2×10^5 cells/well at 37°C in 96-well U-bottom plates (Costar Corporation, Cambridge, MA, USA) in 200 μl RPMI 1640 medium (Gibco Laboratories, Grand Island, NY, USA), supplemented with 10% pooled AB serum, 100 U/ml penicillin, 100 μg/ml streptomycin and 2 mM L-glutamine (Gibco Laboratories). Cells were cultured for 5 days in the presence or absence of antigen, when supernatant was collected for determination of cytokine production. The remaining cells were pulsed with 1 μCi of ^{3}H-thymidine for another 18 hr. Results obtained as counts per minute (cpm) are expressed as stimulation index (SI, cpm obtained from stimulated cultures/cpm obtained in control cultures).

INTERFERON-GAMMA (IFNγ) PRODUCTION

The amount of IFNγ on a 5-day culture supernatant was assayed using a commercial RIA kit (IMRX Corp., Centocor Malvern, PA), specific for the active human IFNγ as described.[15] Levels of IFNγ are expressed as Units/ml (U/ml) in stimulated cultures minus U/ml obtained in control cultures. The cut-off point for positive response was 40 U/ml, which is 4 sd above mean values obtained in unstimulated cultures.

ELISA TEST FOR PGL-1

Serum samples from all tuberculoid patients were collected aseptically, processed under sterile conditions, and kept frozen (−20°C) until use. The presence of specific IgM antibodies anti-ND-BSA (natural disaccharide conjugated to bovine serum albumin,

which represents an immunodominant part of the phenolicglycolipid 1, PGL-1) in the serum was assayed in 21 patients as described.[9] Plates were read in a Titertek Multiscan (Flow Laboratories), at 492 nm, and the results expressed as optical density variation (Δ OD = OD obtained in the antigen coated wells minus the OD obtained in the control wells). A sample was considered positive when its OD exceeded by 2 sd the mean results obtained in the healthy control population. Cut-off OD value for positive response was 0·27.

SKIN TEST

Lepromin skin tests were performed by intradermal injection of 0·1 ml of the standardized crude antigen preparation (lepromin A, $1{\cdot}6 \times 10^8$ bacilli/ml, National Hansen's Disease Center, Carville, LA, USA) in the volar surface of the left forearm. Readings were performed after 21–28 days and reactions $\geq$5 mm were considered positive (National Guide – Leprosy Control Program). All patients were lepromin tested before initiating specific leprosy treatment. All the injections and readings were done by the same trained person.

SKIN BIOPSIES

All patients underwent biopsies at the periphery of skin lesions before starting treatment. Biopsy specimens were processed and stained by hematoxilin and eosin, and by Wade method for acid-fast bacteria. Typical infiltrates of BT leprosy, as stated by Ridley & Jopling classification system,[11] were found in all 48 patients, as a prerequisite for inclusion in the study. None of the patients had acid-fast bacilli identifiable in biopsy specimens.

STATISTICAL ANALYSIS

Tests were used for statistical evaluation of significance. Chi-squared test, Correlation, Regression and Somer's Deviance were used when appropriate. Immunological tests were related to each other, and to skin lesions and nerve involvement. Standard deviation (sd) was used to express variance. Probability (P) less than 0·05 in the statistical tests was considered statistically significant.

Results

CLINICAL EVALUATION

BT patients included in the study presented characteristics clinical lesions and typical epithelioid granulomas in skin lesions, but had no detectable acid-fast bacilli in skin smears. All patients were treated with the paucibacillary WHO regime, and none of them has presented clinical diagnosis of relapse (mean of 6 years of follow-up). Among the 48 BT patients studied, 24 (50%) presented a single cutaneous lesion with well-defined borders, which were infiltrated in some patients, either anaesthetic or hypoaesthetic. The other patients presented $\geq$2 cutaneous lesions and at least 5 patients (10·4%) presented 10 or more lesions. Concerning the number of affected nerves at the diagnosis, 28

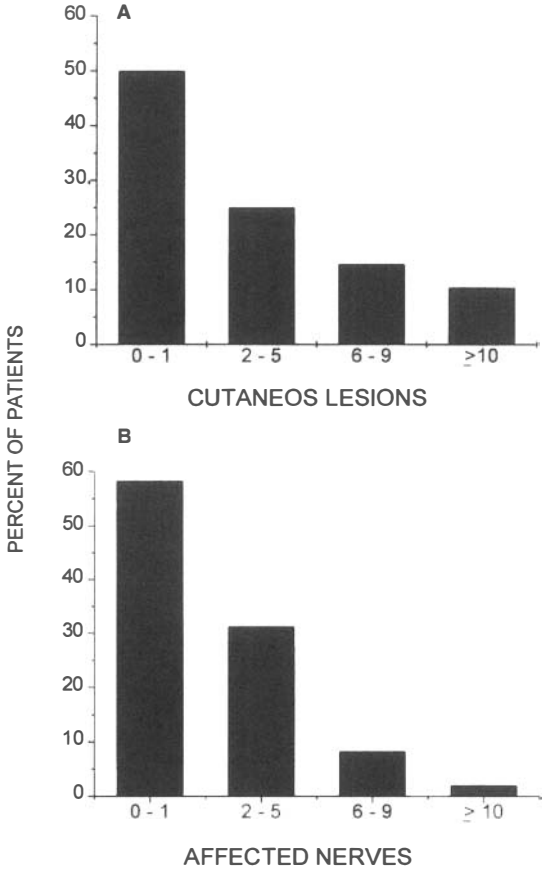

Figure 1. Distribution of the 48 BT patients according to the number of (A) cutaneous lesions, and the number of (B) affected nerves.

patients (58·3%) showed only one affected peripheral nerve or none at all. Of the other 20 patients, 19 had from 2 to 9 nerves that were damaged and only one patient (2·1%) had 10 affected nerves (Figure 1). Fifteen patients (53·6%) among those with no affected nerves or only one showed a single cutaneous lesion, and 11 patients (55%) with more than one affected nerve had also more than one lesion. However, no significative correlation was observed between the number of cutaneous lesions and the number of affected nerves.

IMMUNOLOGICAL TESTS

Lepromin test

Nineteen out of 48 patients tested (39·6%) showed a positive lepromin reaction. Patients with positive lepromin tests had more skin lesions when compared to patients with negative lepromin tests (Figure 2). Although not statistically significant, it was noted that among the 19 patients positive for lepromin, 7 (36·8%) presented a single skin lesion

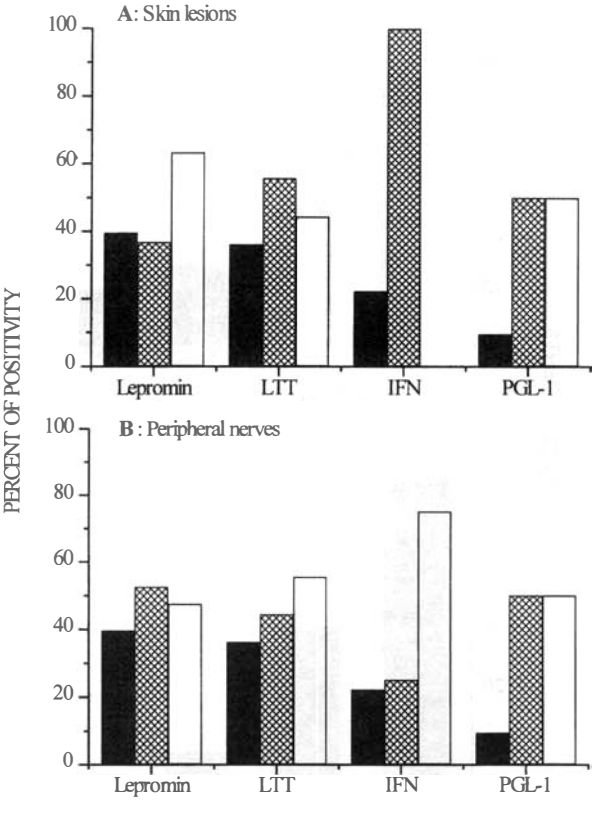

Figure 2. Relationship between the positivity of BT patients in the immunological tests and the extent of skin involvement, or the amount of affected peripheral nerves. Bars represent numbers of patients above cut-off in each immunological test. ■, total positive cases; ▤, single; or □ multiple involvement. Cut-off values are: lepromin tests (≥5 mm); LTT (SI ≥ 3); IFNγ (≥ 40 U/ml); IgM anti-PGL-1 (OD ≥ 0·27).

and 12 (63·2%) had multiple lesions. When results are expressed as the percentage of patients that responded to the lepromin test with an induration ≥ 3 mm, 91·7% of the patients showed a positive reaction. Again, no significative relationship was noted between the positivity in the lepromin test and the number of skin lesions (Table 1).

Lymphoproliferation test (LTT)

Among the 47 patients whose lymphocytes were submitted to LTT, 27 (57·4%) showed positive results (SI ≥ 3·0). As shown in Figure 2, no significative correlation was observed between the positive lymphoproliferative test and the number of skin lesions, but a significative relationship was shown between LTT and the extent of nerve involvement ($P < 0{\cdot}05$). Actually, 75% of the patients unresponsive to *M. leprae* in the LTT presented only one affected peripheral nerve or none at all (Table 1). Patients with positive LTT were equally distributed in relation to the number of skin lesions and/or to the number of affected nerves. Among the 27 patients with positive LTT, 13 patients (48·1%) also had positive lepromin skin tests. In addition, 15 of the 20 patients with negative LTT were negative in the lepromin test as well. There was 59·6% agreement between these two immunological tests.

Table 1. Relationship among immunological tests and the number of cutaneous lesions, and among immunological tests and the number of affected nerves, in BT patients. Number of tested patients was 48 for lepromin tests; 47 for LTT; 18 for IFNγ and 21 for PGL-I

Immunological tests	Number of skin lesions				Number of affected nerves			
		1		+ than 1		0–1		+ than 1
Lepromin (≥5 mm)	7	(36·8%)	12	(63·2%)	10	(52·6%)	9	(47·4%)
Lepromin (<5 mm)	17	(58·6%)	12	(41·4%)	18	(62·1%)	11	(37·9%)
Lepromin (≥3 mm)	22	(50%)	22	(50%)	25	(56·8%)	19	(43·2%)
Lepromin (<3 mm)	2	(50%)	2	(50%)	3	(75%)	1	(25%)
LTT (+)	15	(55·6%)	12	(44·4%)	12	(44·4%)	15	(55·6%)
LTT (−)	8	(40%)	12	(60%)	15	(75%)	5	(25%)
IFNγ (+)	4	(100%)	0		1	(25%)	3	(75%)
IFNγ (−)	6	(42·9%)	8	(57·1%)	7	(50%)	7	(50%)
PGL-I (+)	1	(50%)	1	(50%)	1	(50%)	1	(50%)
PGL-I (−)	10	(52·6%)	9	(47·4%)	14	(73·7%)	5	(26·3%)

Inteferon-gamma (IFNγ) assay

When patients' blood ($n = 18$) was tested for the release of IFNγ into culture supernatants, only four individuals (22·2%) were found to be positive. These four patients had only one skin lesion ($P < 0{\cdot}05$) (Figure 2(A)), but three of them had more than one affected nerve (Figure 2(B)). On the other hand, only 6 IFNγ negative patients (42·8%) presented a single skin leprosy lesion. Two out of the four IFNγ positive patients (50%) showed a positive lepromin reaction. In addition, eight out of 14 individuals (57·1%) with negative IFNγ were also negative in the lepromin test. There was an agreement of 55·5% between these two tests. All four patients with positive IFNγ were positive in the LTT. Of the 14 patients found to be negative in the IFNγ assay, six (42·9%) were also negative in the LTT (55·5% concordance).

PGL-1 Elisa test

Twenty-one patients had their sera submitted to Elisa for detection of anti-PGL-1 IgM antibodies. Nineteen were negative (90·5%). No correlation was noted when compared to skin and nerve involvement. The two patients (9·5%) who showed positive results were lepromin negative, and only one had positive LTT. The low levels of anti-PGL-1 antibodies observed among these patients confirmed their tuberculoid background including those with multiple lesions.

REACTIONAL EPISODES

A total of 6 patients (12·5%) developed reaction. Of the four patients who developed reversal reaction (RR), two showed no nerve involvement, and two had multiple nerves affected. All patients presented more than one leprosy lesion. Two patients developed isolated neuritic episodes. Both had more than one affected nerve, but only one presented multiple cutaneous lesions. The fact that blood samples were collected from these patients during the initial examination and not during the reactional episode made the correlation between reaction and immunological tests unreliable.

HISTOPATHOLOGY

Histological analysis confirmed the diagnosis of borderline–tuberculoid leprosy in all cases.

Discussion

Forty-eight borderline–tuberculoid patients were included in this study. Besides all clinical characteristics of the resistant form of the disease delineated in this study, only 50% of the patients presented single skin lesion and 58% had none or only one affected nerve. Interestingly, we have observed that patients with positive lepromin skin tests had more skin lesions, when compared to patients with negative lepromin tests. Although not statistically significant, these data emphasize the current interpretation that the lepromin test is evidence of delayed type hypersensitivity (DTH) and does not necessarily reflect protection in leprosy. On the other hand, no significative correlation was observed between the lymphoproliferative response and the number of skin lesions, but patients unresponsive to LTT had less nerve involvement, which may reflect a hypersensitivity effect. IFNγ is perhaps the key cytokine responsible for the activation of the oxidative and anti-microbial activity of human macrophages.[9] The finding that all responder BT patients who released high IFNγ levels in PBMC culture supernatant had only one skin lesion ($P < 0{\cdot}05$), attributes an important role to IFNγ in restraining the spread of infection. IFNγ is a key component in determining the type of effector function that eventually develops during the course of an immune response. There is considerable evidence that the presence of IFNγ in the milieu induces inhibition of the expansion of Th2-like cells. In addition, during *M. leprae* infection, a protective response is sometimes observed in the absence of granuloma formation, such as in the indeterminate form of the disease, which in some patients is supposed to be self-healing. All these data suggest that protective immune response and DTH are not the same phenomenon, in spite of being frequently simultaneous.[7] However, 75% of the high responder patients in the IFNγ assay had more nerves damaged when compared to the nonresponder ones. These results have very important implications and strongly suggest that nerve damage may represent a hypersensitivity phenomenon following cell-mediated immunity against the pathogen. The potential pathological effects of IFNγ can be related to its ability to synergize with inflammatory cytokines, such as TNFα, IL-1β and others. Previous studies[2] have demonstrated that IFNγ acting synergistically with inflammatory cytokines is able to induce or to increase the expression of adhesion molecules on endothelial cells and keratinocytes that affects directly the type and the amount of leukocytes attracted to the site of inflammation. Recently, a higher expression of TNFα mRNA as well as TNFα protein was demonstrated in the nerves and skin of borderline patients with RR.[6] Although in some patients, absence of or low IFNγ production was detected *in vitro*, the immunohistochemical findings suggest that, at least *in situ*, levels of IFNγ are sufficient to maintain the activation state (data not shown).

Six patients presented reactional episodes (12·5%). All but one (83·3%) had more than one skin lesion. Correlation between the reactional features and the *in vivo* and *in vitro* immunological tests was not reliable. This may in part be explained by the fact

that tests were performed at the diagnosis, which, for the most part, was quite distant from the reactional episode. Neuritis following multidrug therapy seems to occur infrequently in bacteriologically negative BT patients. Only two patients (4%) presented neuritis after MDT.

In a previous report,[12] it was found that seropositivity to anti-PGL-1 antibodies was associated with subsequent manifestation of RR. This association was strongest in patients who were both anti-PGL-1 antibody and lepromin positive. However, to our way of thinking, no correlation was noted between levels of anti-PGL-1 antibodies and development of reaction. The two patients who were anti-PGL-1 antibody seropositive were lepromin negative and were not included among the six individuals who developed reaction during the study.

The present study confirms previous reports indicating the role of IFNγ in mediating resistance to mycobacterial infection.[4,5] However, other mechanisms might be involved in restricting bacterial growth in borderline–tuberculoid patients.

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Nerve function impairment in leprosy at diagnosis and at completion of MDT: a retrospective cohort study of 786 patients in Bangladesh

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Summary This retrospective cohort study includes all new leprosy patients registered for multidrug therapy (MDT) in 1990 at the Danish–Bangladesh Leprosy Mission project in Bangladesh. The main objective was to determine the extent of nerve function impairment (NFI) at diagnosis and at completion of MDT, and to identify opportunities for intervention and their relative impact on the prevention of disabilities (POD).

A total of 786 patients were included; 486 males and 300 females. There were 315 PB, and 471 MB patients. In terms of the WHO leprosy disability grading system, at the time of diagnosis 31/315 (9·8%) had grade 1 or grade 2 disability in the PB group, and 177/471 (37·6%) in the MB group. The incidence rate of NFI during MDT was 3·5 per 100 person years at risk (PYR) in the PB group, and 7·5 per 100 PYR in the MB group. In the MB group 37 (7·9%) previously normal patients sustained NFI during MDT, whilst 19 (4·0%) with NFI at diagnosis showed complete recovery at completion of MDT. The most commonly involved nerves were the ulnar (motor function) and the posterior tibial nerves (sensibility). Reversal reactions were observed in 0·6% of the PB patients during MDT, giving an incidence rate of 1 per 100 PYR. The percentage of MB patients diagnosed with reversal during MDT was 14·2%, giving an incidence rate of 6 per 100 PYR. The percentage of MB patients diagnosed with ENL during MDT was 2·1%, with an incidence rate of 1 per 100 PYR.

It was concluded that early detection of new cases of leprosy would prevent disabilities in more than 30% of all patients, thus having the highest impact in the quest for the prevention of disabilities. POD activities during and after MDT will prevent disabilities in approximately 10% of all cases. This study also indicates that treatment with prednisolone is effective and should be available at field level for all patients with recent NFI.

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Introduction

Leprosy can lead to disability and handicap through peripheral neuropathy. The importance of prevention of disability (POD) activities as integral part of leprosy control programmes is being increasingly recognized.[1] Despite the success of MDT in curing patients from leprosy infection, if the occurrence of disability and handicap cannot be prevented, treatment remains a failure as far as the patient is concerned. Gradually more information concerning the aetiology, incidence, risk factors and treatment of peripheral neuropathy in leprosy patients is becoming available, although there are still many gaps.[2,3] New techniques for early detection of nerve function impairment (NFI), imperative for successful therapeutical intervention, have been developed and tested.[3] The challenge at present is to translate new knowledge and techniques into simple and practical methods for implementation in field programmes so that the majority of leprosy patients may benefit. This requires further insight into the epidemiology of NFI, and more extensive field trials of simple and standardized methods of detection and treatment.

This study is primarily concerned with the incidence of NFI at the time of diagnosis (registration) and at completion of MDT, within the context of a well established (vertical) leprosy control programme covering three highly leprosy endemic districts of north-west Bangladesh. The main objective is to determine retrospectively the extent of the problem of NFI at diagnosis and at completion of MDT, and to identify opportunities of intervention and their relative impact on prevention of disabilities.

Methods

The study was conducted at the Danish–Bangladesh Leprosy Mission (DBLM) in Nilphamari, in the north-west of Bangladesh. DBLM is a private organization involved in a vertical leprosy programme situated in a highly endemic area.[4] At the time of recruitment of patients to this study (1990) the programme covered three districts with a total population of approximately 4 million.

This study is a retrospective cohort study. The data was generated within a busy (routine) field programme, primarily by paramedical staff. The project has maintained good quality charts on all patients over a long period of time. MDT coverage was virtually 100% and over 95% of patients completed MDT within the required time frame. In spite of this it had to be accepted that data might not be completely accurate and consistent, and only basic descriptive statistics are applied as appropriate.

Included in this analysis were all new, previously untreated, leprosy patients first registered in 1990 for treatment with multidrug therapy (MDT). All patient charts were reviewed and the following data compiled: age, sex and leprosy classification (MB, multibacillary; PB, paucibacillary). In addition the results of body charting, voluntary muscle testing (VMT), and sensory testing (ST) at the time of registration and completion of MDT were reviewed. ST was carried out using a ball-point pen as described by Jean Watson;[5] 12 standard points were allotted to each hand, 11 to each foot. VMT was carried out using the revised MRC scale (Table 1).[2] Special note was taken of the duration of nerve function impairment at the time of registration, which

Table 1. MRC score and muscles tested.

Muscle strength finding	MRC score
Full ROM*, full resistance	5
Full ROM, reduced resistance	4
Full ROM, no resistance	3
Reduced ROM, some joint movement	2
Flicker only	1
Full paralysis	0
Nerve	Muscle and movement
(Common) Peroneal/Lateral popliteal	Dorsiflexion of foot
Radial	Extension of wrist
Median	Abduction of thumb (*abductor pollicis brevis*)
Ulnar	Abduction of little finger (*abductor digiti minimi*)
Lagophthalmos (Facial nerve)	Tight closure of eye (*orbicularis oculi*)

*ROM, range of movement

nerves were involved, the occurrence of reactions (type I and II), and whether the patients had received prednisolone during their time on MDT.

Nerve function impairment (NFI) is defined as a clinically detectable impairment of motor, sensory or autonomic nerve function.[6] If NFI has existed 6 months or less, it is considered to be 'recent' (RNFI). Treatment of the underlying neuritis with corticosteroids is usually considered indicated within this time span. It is practice at DBLM to register NFI according to the WHO recommended disability grading scale of impairments in leprosy.[7] The term 'normal' is used when there is no NFI as detectable with the applied sensory and voluntary muscle tests. 'Abnormal' includes WHO disability grading 1 and 2.

Results

A total of 786 patients are included in this study; 486 males and 300 females (male : female ratio is 1·6 : 1). The total number of MB patients is 471 and the total number of PB patients is 315 (MB : PB ratio is 1·5 : 1). The distribution according to age is given in Table 2.

Tables 3 and 4 show the disability status at registration and at release from treatment (RFT) of PB and MB patients respectively. Also included in the tables is information about the occurrence of recent nerve function impairment (RNFI) at the time of registration and during treatment with MDT, and if prednisolone was provided.

Of the PB patients, 284 (90·2%) had no NFI at registration and of these, 279 (88·6%) had no NFI at RFT. A total of 6 patients were diagnosed with RNFI during MDT. One was treated with prednisolone and recovered completely. The other 5 patients did not receive prednisolone and remained with NFI at RFT. In 25 of the 31 patients who had NFI at registration, the impairments had existed longer than 6 months. Of the 6 remaining patients, none received prednisolone (although this would probably have

Table 2. General data of all new leprosy patients who started MDT in 1990.

Age in years	PB		MB		Total PB	Total MB
	Male	Female	Male	Female		
0 to 9	26	14	21	12	40	33
10 to 14	23	25	23	12	48	35
15 to 19	24	12	21	16	36	37
20 to 29	38	29	59	28	67	87
30 to 39	26	25	87	40	51	127
40 to 49	15	22	45	24	37	69
50 to 59	9	12	28	24	21	52
≥ 60	14	1	27	4	15	31
Total	175	140	311	160	315	471

been indicated). However, 4 of these patients apparently recovered spontaneously and were registered with no NFI at the time of completion of MDT.

Table 4 shows similar data for the MB group of patients. Only 294 (62·4%) of this group had no NFI at the time of registration. A total of 53 developed RNFI during MDT of which 40 received prednisolone. Recovery was complete in 16 of these patients. The remaining 13 did not receive prednisolone and were all left with NFI at RFT. One hundred and sixteen (24·6%) had NFI of longer than 6 months, and no recovery was found in this group. The remaining 61 (13·0%) were observed with NFI at registration, but of short duration. Of this group 50 received prednisolone and 11 had recovered completely at the time of RFT. Again there are 8 patients who had NFI at registration and did not receive any prednisolone during MDT, who showed recovery at the time of RFT. The percentages of patients at registration and RFT with NFI in the PB and MB

Table 3. Disability status at registration and release from treatment (RFT) of MDT of PB leprosy patients.

Status at registration	RNFI* +/−	Pred† +/−	Status at RFT	No of patients Male	Female	Total
Normal	−	na‡	Normal	154	124	278
	+	+	Normal	1	0	1
	+	+	Abnormal	0	0	0
	+	−	Normal	0	0	0
	+	−	Abnormal	2	3	5
Abnormal	−	na‡	Abnormal§	13	12	25
	+	+	Normal	0	0	0
	+	+	Abnormal	0	0	0
	+	−	Normal	3	1	4
	+	−	Abnormal	2	0	2
Total				175	140	315

*RNFI, recent nerve function impairment;
†Pred, prednisolone treatment received during treatment with MDT;
‡na, not applicable;
§This group had nerve damage of more than 6 months duration.

Table 4. Disability status at registration and release from treatment (RFT) of MDT of MB leprosy patients.

Status at registration	RNFI* +/−	Pred† +/−	Status at RFT	No of patients Male	Female	Total
Normal	−	na‡	Normal	142	98	241
	+	+	Normal	11	5	16
	+	+	Abnormal	20	4	24
	+	−	Normal	0	0	0
	+	−	Abnormal	8	5	13
Abnormal	−	na‡	Abnormal§	86	30	116
	+	+	Normal	7	4	11
	+	+	Abnormal	27	12	39
	+	−	Normal	7	1	8
	+	−	Abnormal	3	0	3
Total				311	160	471

See Table 3 for notation.

groups are summarized in Tables 5 and 6. PB and MB patients with no NFI at detection had a 1·8% and 14·4% risk of having NFI at RFT. The proportion of PB patients with NFI at diagnosis is 9·8% compared to 10·2% at RFT, the corresponding figures for MB were 37·6% and 41·4%.

Table 7 gives a breakdown of the nerves showing NFI at the time of registration, and the initially normal nerves at registration that sustained NFI during treatment and were still abnormal at the time of RFT. The percentages represent the number of patients with the particular nerves involved. This means that if there is bilateral nerve involvement, it is only counted once. Finally, Table 8 shows the number of patients with observed leprosy reactions in both the PB group (reversal, or Type I, reaction only) and the MB group (both reversal and ENL (Type II) reactions).

Discussion

In terms of the WHO leprosy disability grading system, it was found that at the time of registration a total of 31/315 (9·8%) had grade 1 or grade 2 disability in the PB group, and 177/471 (37·6%) in the MB group (Tables 5 and 6). The figures in the PB group for

Table 5. Summary of disability status of PB patients at registration and RFT.

	At RFT		
At registration	Normal	Abnormal	Total
Normal	279 (88·6%)	5 (1·6%)	284 (90·2%)
Abnormal	4 (1·3%)	27 (8·6%)	31 (9·8%)
Total	283 (89·8%)	32 (10·2%)	315 (100%)

Table 6. Summary of disability status of MB patients at registration and RFT.

	At RFT		
At registration	Normal	Abnormal	Total
Normal	257 (54·6%)	37 (7·9%)	294 (62·4%)
Abnormal	19 (4·0%)	158 (33·5%)	177 (37·6%)
Total	276 (58·6%)	195 (41·4%)	471 (100%)

males was 18/175 (10·3%) and for females 13/140 (9·3%). In the MB group more males had disability; 130/311 (41·8%) against females 47/160 (20·4%). The incidence rate of NFI during MDT was approximately 3·5 per 100 person years at risk (PYR) in the PB group, and approximately 7·5 per 100 PYR in the MB group. The incidence rate of disability (or crude disability attack rate) in patients treated with MDT has recently been estimated to be between 1 to 5 per 100 PYR.[8] The findings of this paper seem to be higher, but this is caused by the fact that the figures in this paper include both WHO grade 1 and 2 disability, whilst in the referred article only grade 2 is taken into consideration. This is the case in most studies, since grade 2 (visible deformity) is a more objective parameter, but it does make comparison difficult at times.

The overall disability status before and after MDT in the PB group hardly changed; 9·8% at registration and 10·2% at RFT. Although 5 (1·6%), previously normal patients developed NFI during the 6- to 9-months period of MDT, 4 (1·3%) other patients who had NFI at registration had apparently recovered at RFT, interestingly enough without the benefit of treatment with corticosteroids. In the MB group, this picture is more dramatic: 37 (7·9%) previously normal patients sustained nerve damage during the 2 to 3 year period of MDT with NFI recorded at RFT. At the same time 19 (4·0%) patients with NFI at registration showed complete recovery at RFT.

In the early 1990s, it was still practice within the project to provide treatment with corticosteroids to hospitalized patients only. Patients with a clear indication because of leprosy reactions and/or signs of RNFI were advised to be admitted, but unfortunately this advice could not be followed by all patients for various reasons. The treatment

Table 7. Incidence of nerve involvement.

	Abnormal at registration ($n = 208$) (%)	Normal at registration, abnormal at RFT ($n = 42$) (%)
Peroneal nerve (strength)	14	4
Radial nerve (strength)	3	3
Median nerve (strength)	22	6
Ulnar nerve (strength)	47	39
Lagophthalmus	3	1
Sole sensory loss	73	31
Palm sensory loss	55	16

Table 8. Incidence of reversal (type 1) reaction and erythema nodosum leprosum (ENL or type 2 reaction) in PB and MB patients, with age–gender specific rates (%).

PB ($N = 315$)	Reversal reaction					
Age in years	Male	(%)	Female	(%)	Total	(%)
0 to 9	1	(3·8)	0		1	(2·5)
10 to 14	0		1	(4·0)	1	(2·1)
15 to 19	0		0		0	
20 to 29	0		0		0	
30 to 39	0		0		0	
40 to 49	0		0		0	
50 to 59	0		0		0	
≥ 60	0		0		0	
Total	1	(0·6)	1	(0·7)	2	(0·6)

MB ($N = 471$)	Reversal reaction						ENL reaction				
Age in years	Male	(%)	Female	(%)	Total	(%)	Male	(%)	Female	Total	(%)
0 to 9	2	(9·5)	1	(8·3)	3	(9·1)	0		0	0	
10 to 14	4	(17·4)	3	(25·0)	7	(20·0)	1	(4·3)	0	1	
15 to 19	3	(14·3)	4	(25·0)	7	(18·9)	1	(4·8)	0	1	
20 to 29	11	(18·6)	4	(14·3)	15	(17·2)	1	(1·7)	0	1	
30 to 39	11	(12·6)	7	(17·5)	18	(14·2)	5	(5·7)	0	5	
40 to 49	6	(13·3)	6	(25·0)	12	(17·4)	1	(2·2)	0	1	
50 to 59	2	(7·1)	2	(8·3)	4	(7·7)	0		0	0	
≥ 60	2	(7·4)	0		2	(6·5)	1	(3·7)	0	1	
Total	41	(13·2)	26	(16·3)	67	(14·2)	10	(3·2)	0	10	(2·1)

regimens with prednisolone in hospital were individualized, and varied considerably per patient. An evaluation of the impact of corticosteroids is therefore not possible. In this paper it is just simply recorded if a patient at any time during MDT received prednisolone. Nevertheless, it is interesting to see what happened to patients who had RNFI, especially in the MB group. A total of 40 patients with RNFI received prednisolone (any regimen). Of these 16 (40%) recovered completely. Also in the group of 50 patients who had RNFI at registration and received prednisolone during MDT, there was complete recovery in 11 (22%) patients. It should be noted that complete recovery was also seen in 8 patients who had RNFI at registration, but for various reasons did not receive prednisolone. It is unclear whether this finding represents a natural tendency to spontaneous recovery in some cases of RNFI, or if it is a consequence of lack of accuracy in examining the patient either at registration or RFT. The distribution of nerves involved is comparable with what is described in other studies.[9] The most commonly involved were the ulnar (motor function) and the posterior tibial nerves (sensibility).

Although the occurrence of NFI, and not of leprosy reactions is the focus of this paper, some general figures concerning reactions are presented. Reversal reactions were observed in 0·6% of the PB patients during MDT (a 6- to 9-month period only), giving an incidence rate of approximately 1 per 100 PYR. The percentage of MB patients

diagnosed with reversal during MDT (a period ranging from 2 to 3 years) was 14%, giving an incidence rate of approximately 6 per 100 PYR. The percentage of MB patients diagnosed with ENL during MDT was 2·1%, with an incidence rate of approximately 1 per 100 PYR. These figures appear lower than found by Van Brakel *et al.*,[9] and nearer to figures found in other studies.[10,11] The lower figures are due to the fact that the cohort in this paper primarily consisted of outpatients, in which reversal reactions were probably underdiagnosed by the attending paramedical staff, causing only the more severe reactions to be registered, referred and treated in hospital. Also the observation period (during MDT only) was shorter than in the studies mentioned. Finally, it must be pointed out that the incidence rate figures for leprosy reactions during MDT are essentially different from those of RNFI during MDT. Leprosy reactions can occur in all patients, regardless the presence of pre-existing NFI. The calculation of incidence rates for leprosy reactions is based on the complete cohorts PB or MB patients. Incidence rate figures for NFI include only those patients who had no NFI at registration.

In terms of opportunities for intervention and their relative impact on POD, there are some important conclusions to draw. This study clearly shows (again) that most cases with NFI at the completion of MDT treatment already had impairment at the time of registration (9·8% in the PB, and 37·6% in the MB group). During the time of MDT, another 1·6% in the PB, and 7·9% in the MB group are added to those with NFI. Early detection of new leprosy cases obviously will have the largest impact in the prevention of disability; by itself it could prevent disabilities in more than 30% of all patients. A comprehensive field programme with active case finding should therefore be the main thrust in any leprosy programme. The impact of POD activities during the time that patients receive MDT, i.e. regular examinations, VMT's ST's, and treatment in the field with prednisolone will prevent disabilities in less than 10% of the cases, according to this study. NFI impairment is also known to occur after completion of MDT. POD activities should also extend into this phase, with sufficient health education to all patients on the signs of early nerve damage and with regular follow-up of patients at risk. The impact of POD after completion of MDT will be another 5 to 10%.

Finally, the figures in this paper suggest that the provision of prednisolone is definitely effective when given appropriately in all indicated cases. Much more effort should be made to determine clear indications for the provision of prednisolone, appropriate techniques for use in the field by paramedical workers to determine early NFI, and effective steroid regimens that can be administered efficiently under field conditions.

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Vasomotor reflex testing in leprosy patients, healthy contacts and controls: a cross-sectional study in Western Nepal

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Summary Objective: To examine test characteristics of laser Doppler vasomotor reflex testing for leprosy and to determine the prevalence of abnormal responses in leprosy patients, healthy contacts and controls.

Design and participants: Cross-sectional study including 89 leprosy patients (mean age 35 years, 74% male), 36 healthy contacts (29 years, 64% male) and 47 controls (30 years, 68% male), for a total of 172 participants.

Setting: Leprosy hospital in an endemic region 200 km west of Kathmandu, Nepal.

Outcome measure: Finger-tip and toe-tip vasomotor reflexes elicited by inspiratory gasp were measured using a laser-doppler flow temperature technique. Results were expressed in per cent as the maximal reduction in bloodflow from baseline.

Results: For all 12 measurement sites there were highly significant ($p > 0{\cdot}0001$ to $< 0{\cdot}004$) differences between the three groups tested. Leprosy patients consistently had the lowest responses and controls the highest, with healthy contacts showing intermediate values. Thresholds defined as mean bloodflow reductions among controls minus 1·64 or minus 1·96 standard deviations provided optimal combinations of sensitivity and specificity. Using these cut-off values around 80% of leprosy patients, 50% of healthy contacts and 20% of controls had two or more abnormal reflexes ($p < 0{\cdot}0001$ for differences between groups).

Conclusions: In endemic regions, subclinical autonomic neuropathy may be an early but detectable marker for the risk of subsequent leprosy, making early treatment and prevention of transmission possible. Prospective studies are needed to establish the predictive value of abnormal vasomotor reflexes.

Introduction

The prevention of disability in leprosy depends on the early detection and treatment of neural impairment.[1] Treatment if implemented early prevents development of deformity,

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disability, results in a cure and eliminates transmission of further infection. However the early detection of leprous involvement of the peripheral nervous system is difficult, as even before clinical signs of leprosy are evident, there is evidence that extensive nerve damage has already taken place.[2,3] As early detection of leprosy neuropathy is based on clinical sensory and motor testing,[4,5] a considerable amount of underlying neural damage is present at the time of diagnosis. Much of the nerve damage will be irreversible. This and the recently proposed WHO goal of World-wide elimination of leprosy by the year 2000[6] has fuelled the research for detecting the earliest possible paraclinical changes in leprosy neuropathy.

As there is good evidence that the focus of early infection is directed against[2,7] autonomic nerve fibres, testing of autonomic nerve parameters is one possibility for early detection of leprosy. This is supported by the fact that several researchers have found impaired autonomic nerve reflexes in apparently healthy contacts of leprosy patients—possibly earliest form of leprosy neuropathy.[8–10] The vasomotor reflex is an autonomic nerve reflex with an efferent pathway carried by small non-myelinated or poorly myelinated nerves thought to be particularly vulnerable to damage from the inflammatory infiltrate of leprosy neuropathy. Testing of the reflex was developed by Low *et al.*[11] using laser Doppler velocimetry, to enable detection of neuropathic autonomic abnormalities. The transient fall in fingertip blood flow following inspiratory gasp is measured. The test has been studied extensively in clinical and experimental context and shown to be reproducible and reliable in the detection of abnormal autonomic reflexes.[8,11]

In light of the above arguments in favour of early autonomic nerve fibre involvement in leprosy we have investigated the frequency and magnitude of vasomotor disturbances across the clinical and chronological spectrum of leprosy ranging from early untreated to patients released from therapy. As clinically healthy contacts of leprosy patients are likely to include the earliest stages (subclinical) of leprosy we compared the leprosy and control groups with a group of healthy contacts.

The study was conducted in an area endemic for leprosy in Pokhara, Western Nepal.

Patients and methods

PATIENTS

The study was conducted at the Green Pastures Hospital, Pokhara, which is an International Nepal Fellowship (INF) hospital run in collaboration with the leprosy programme of His Majesty's Government of Nepal. Pokhara is located 200 km west of Kathmandu, and lies at the foot of the Annapurna mountain range.

Three groups of patients were recruited: 1, leprosy patients aged 10–55 years; 2, healthy contacts aged 10–55 years; and 3, controls aged 10–55 years. Only patients with a diagnosis confirmed by standard clinical criteria[12] were included. Patients were further classified with respect to bacillary load into multibacillary (MB) and paucibacillary (PB). The Ridley–Jopling classification was also used (TT, tuberculoid leprosy; BT, borderline tuberculoid; BB, borderline borderline; BL, borderline lepromatous, and LL, lepromatous leprosy). Healthy contacts were recruited among relatives and friends of patients living in the same house as untreated leprosy patients for at least 1 year before treatment commenced (intense contact group) and among health care professionals (physiotherapists, nurses and occupational therapists) working in close contact with leprosy patients

for at least 5 years (less intense contact group). Control participants were recruited among acquaintances of hospital personnel who did not work at the hospital or have friends or relatives with leprosy. Subjects with a history of diabetes, alcohol abuse or a diagnosis of polyneuropathy attributable to other causes were excluded from any of the three groups. The study protocol planned for frequency matching of healthy contacts and controls to leprosy cases for sex, and for age within 10-year-age bands.

All study participants were clinically examined for evidence of motor, sensory and autonomic impairment. This included a motor strength assessment of lower and upper extremities, and touch sensory testing with monofilaments as described previously[13] as well as clinical testing for evidence of impaired sweating by looking for loss of suppleness and cracking of skin. Hand and foot callouses were registered in all subjects as either extensive or nonextensive. In leprosy patients the number of skin lesions, the number of enlarged or tender nerves and the number of body areas affected was assessed, and a complete treatment history was taken.

The project was accepted by both the ethical committee of the Leprosy Control Project, Nepal and the University of Bern, Switzerland.

MEASUREMENT OF VASOMOTOR REFLEXES

The vasomotor reflex is defined as the vasoconstrictor response to an autonomic stimulus[14] and is usually measured with laser Doppler velocimetry of microvascular bloodflow. The pulp near the tip of the digit is the best site for measurement[11] as this area possesses a wealth of arteriovenous anastomosis under strict autonomic control, containing only vasoconstrictor fibres,[15] thereby allowing measurement of unmodified vasoconstrictor responses. Different stimuli can be used to elicit the skin vasomotor reflexes, (VMR) and responses are fairly uniform.[12] We chose the inspiratory gasp since in a small pilot study it gave the largest and most consistent relex response and was easiest of all the stimuli to conduct. Further details on the principles of laser Doppler velocimetry flux recordings are in the literature.[11,16–20]

We measured vasomotor reflexes of all 10 fingers and the big toes in order to obtain a complete as possible assessment of autonomic disturbances. Low et al,'s guidelines to measurement[11] were used. We summarize the procedure. As vasomotor reflexes are best measured at maximal vasodilation of the digit pulp microvasculature, all subjects were encouraged to relax whilst seated. Finger vasomotor reflexes were examined with the forearm and hand at heart level. The vasomotor reflexes were measured with the leg and foot in a horizontal position. Ambient temperatures above 26.5°C (mean, 30.5°C; maximum, 34.5°C) made heating of the extremeties unnecessary.

Bloodflow was measured using a laser Doppler flow-temperature monitor (Moor Instruments, Model DRT4, Axminster, England) with machine settings of: bandwidth 10 KHz; time constant 1 s. Gain control and zeroing were automatic. Double-sided adhesive disk secured attachment of the combined laser Doppler and temperature sensor probe to the skin, so ensuring optimal alignment of probe and skin surface. The procedure was explained in the patient's mother tongue. Persons were asked to practise to take the quickest and deepest breath you can and hold it for 10 s.

Vasomotor reflex testing was not begun until the inspiratory gasp was satisfactorily mastered and a stable baseline bloodflow was recorded for each subject. Subsequently the inspiratory gasp was performed. The onset of each inspiratory gasp was marked with

an event marker and the resultant maximal reduction in skin bloodflow recorded and expressed as a percentage of the resting skin bloodflow. Microvascular bloodflow (in flux) and skin temperature (in °C) was recorded simultaneously and continuously and each examination printed on paper. In each subject the inspiratory gasp was repeated three times and the maximal response taken for recording.

In order to assess the repeatability of test results a subgroup of control participants was re-examined on a different occasion.

The test has previously been shown to be reproducible.[11]

SAMPLE SIZE AND STATISTICAL ANALYSIS.

The minimal sample size was calculated to detect a difference in the prevalence of abnormal vasomotor response between leprosy patients and contacts or controls of 30% at a significance level of 0·05 and with a power of 90% for a range of contact or control prevalences from 5% to 30%. Results indicated that around 50 participants in each group were needed for this purpose.

Vasomotor reflex responses were analysed by calculating the maximum percent reduction in bloodflow for each of the 12 measurement sites. Mean reduction and standard deviation (sd) were calculated for each measurement site and participant group. In the case of absent responses, reductions were set to zero. For each finger and toe different threshold values separating abnormal from normal responses were calculated by subtracting 2·58, 1·96, 1·64, 1·28, 1·04 and 0·25 sd from the corresponding mean value obtained in controls. An overall abnormal test was defined as two or more measurements with reductions below this threshold value, as recommended by Low *et al.*[11] A receiver operating characteristic (ROC) curve was constructed to illustrate the influence of different threshold values on test sensitivity and specificity. Different threshold values were used in analyses comparing the prevalence of abnormal tests between groups.

Statistical evaluation of differences in responses between groups used generalized linear models for analysis of variance of unbalanced data. Linear regression models were computed to identify factors associated with lower responses in multivariate analysis. χ-square tests were used for the univariate comparison of categorical variables. Repeatability of test results in controls was assessed by comparing values in paired *t*-tests, by plotting the differences between the two measurements against the mean of the two measurements and by calculating the repeatability coefficient described by Bland & Altman.[21] This coefficient is defined as 1·96 sd of the differences between measurements. Therefore, 95% of differences will be included in the value given by the repeatability coefficient.

Probability values were not adjusted for multiple comparisons. The statistical packages EPI-INFO Version 6 (Centers for Disease Control and Prevention, Atlanta, USA) and SAS Version 6·08 (SAS Inc., Cary, NC, USA) were used for data entry and statistical analysis.

Results

PATIENT CHARACTERISTICS

A greater number of leprosy patients but less healthy contacts and controls than

anticipated were recruited. In the final analysis there were 89 leprosy patients, 36 contacts (24 intensive and 12 less intensive) and 47 controls, for a total of 172 participants. Frequency matching of contact and control groups for age and sex proved difficult and was only partly achieved. Mean age was 35·0 years (range 11–55) among patients, 29·4 years (11–54) among contacts and 30·2 years, (10–55) among controls ($p = 0{\cdot}013$ by analysis of variance). Male participants dominated all groups (74% male participants among leprosy patients, 64% among contacts and 68% among controls; $p = 0{\cdot}5$ by χ-square test). Because of the age difference between the three groups, an association between age and VMR was statistically tested for and not found.

Prevalences of extensive callouses was similar in all three groups (18% among leprosy patients, 11% among contacts, 15% among controls, $p = 0{\cdot}6$ by χ-square test).

The characteristics of leprosy patients are shown in Table 1. Most patients with leprosy were diagnosed less than one year ago (47%), mean interval to time of diagnosis being 46 months. BT was the most common type of leprosy (42%).

VASOMOTOR REFLEXES

A complete set of 12 measurements could be performed in all except 4 participants (one patients who had undergone amputations of fingers and three controls because of technical reasons). Ten or 11 measurements were performed in these cases.

Levels of resting bloodflow were generally similar among controls and healthy contacts but lower among leprosy patients. Among controls and contacts mean values fluctuated around 250 flux for thumbs. 300 flux for all other fingers and 125 flux for toes. The corresponding figures for leprosy patients were 210, 250 and 105 flux respectively.

Table 1. Characteristics of leprosy patients

Time since diagnosis (mean in months)	Percentage Patients
New	10%
1–6	26%
7–12	11%
13–24	16%
25–72	15%
73–396	21%
Leprosy classification	
MB (multibacillary)	50%
PB (paucibacillary)	50%
Ridley–Jopling	
TT	2%
BT	42%
BB	3%
BL	29%
LL	18%
PN	6%
Release from therapy	32%

Table 2. Vasomotor reflex in leprosy, controls and contacts

	Leprosy	Contacts	Controls	p*
Right hand				
Thumb	42·8 (22·9)	53·3 (22·0)	62·1 (14·1)	0·0001
R2	51·2 (20·2)	59·6 (20·3)	66·8 (15·4)	0·0001
R3	55·3 (21·5)	60·3 (24·0)	66·9 (15·4)	0·009
R4	51·8 (20·6)	58·8 (22·1)	70·8 (12·3)	0·0001
R5	50·2 (23·7)	66·6 (18·8)	72·3 (17·7)	0·0001
Left Hand				
Thumb	44·6 (22·5)	55·9 (21·2)	63·6 (16·3)	0·0001
L2	47·5 (23·1)	56·2 (19·7)	68·1 (16·6)	0·0001
L3	51·8 (23·0)	58·9 (23·9)	69·9 (14·0)	0·0001
L4	53·8 (22·8)	63·7 (17·3)	72·1 (10·5)	0·0001
L5	50·7 (24·1)	66·7 (20·8)	72·1 (15·3)	0·0001
Feet				
Left big toe	41·4 (21·6)	56·3 (21·7)	60·9 (16·4)	0·0001
R. big toe	41·2 (20·9)	55·6 (19·8)	56·6 (17·4)	0·0001
Combined	48·9 (15·0)	60·1 (14·7)	67·0 (7·6)	0·0001

*p is calculated by analysis of variance

The mean reduction of bloodflow with inspiratory gasp is expressed in percentage. Standard deviation is given in brackets.

R 1–5, right-handed digits 1–5; L 1–5, left-handed digits 1–5;

R6, right big toe; L6, left big toe.

Mean percent reduction of bloodflow for the different measurement sites and groups are shown in Table 2. Leprosy patients consistently had the lowest responses and controls the highest with healthy contacts showing intermediate values. The differences between the three groups were statistically highly significant ($p = 0{\cdot}0001$ in most instances). Significance levels were little affected when adjusted for age and sex. There were 12 patients (13·5%), one contact (2·7%) and three controls (6·4%) with one or more absent responses. In all groups responses were lower in big toes and thumbs than in the fingers. In controls, responses tended to increase from finger II to finger IV. No differences were noted between right and left sides.

Multivariate linear regression models showed that in leprosy patients lower responses were generally associated with positivity in skin smears and with a long history of disease. A detailed analysis of associations between reflexes and clinical characteristics will be presented elsewhere. In some regression models older age was weakly associated with decreased responses. In contacts and controls there was no association with age. Generally lower responses were recorded in the intensive contact group as compared to the less intensive group, although this did reach conventional levels of significance ($p = 0{\cdot}03$) only for one measurement site. The results of the contact group will be presented in detail elsewhere.

The ROC curve (Figure 1) shows the relationship between different threshold values and test sensitivity and specificity. Table 3 gives test sensitivity, specificity and prevalence of test positivity for a range of threshold values. High specificity (but low sensitivity) is obtained with high threshold values defined as control mean minus 2·58 sd while a low threshold of control mean minus 1·28 sd optimized sensitivity at the cost of specificity. For all thresholds pronounced and statistically highly significant ($p < 0{\cdot}0001$) differences

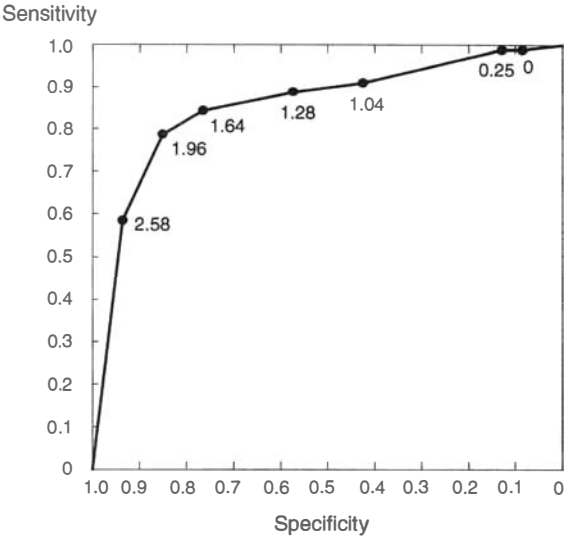

Figure 1. Receiver operating characteristic (ROC) curve for laser doppler vasomotor reflex testing in leprosy. The figures define cut-off points as the number of standard deviations subtracted from mean reductions in bloodflow.

in the prevalence of test positivity were evident between the three groups with the highest prevalence being evident among leprosy patients and the lowest among controls.

Comparing intense contact with less intense contact groups, generally higher prevelances were found among intense contacts, however these differences did not reach statistical significance ($p > 0{\cdot}03$). The prevalence of test positivity among intense and less intense contacts was 25% and 25% (2·58 sd threshold), 54% and 42% (1·96 sd threshold), 58% and 50% (1·64 sd threshold), and 67% and 50% (1·28 sd threshold).

REPEATABILITY

Seventeen controls could be re-examined 3–21 days (mean 10 days) after the initial

Table 3. Test sensitivity, specificity and prevalence of abnormal test results according to the definition of threshold values

Threshold (No of sd minus mean)	Sensitivity/ Specificity %	Prevalence of Test Positivity %			P*
		Patients	Contacts	Controls	
2·58	58·4 / 93·6	58·4	25·0	6·4	< 0·0001
1·96	78·7 / 85·1	78·7	50·0	14·9	< 0·0001
1·64	84·3 / 76·6	84·3	55·6	23·4	< 0·0001
1·28	88·8 / 57·5	88·8	61·1	42·6	< 0·0001

*from χ-square tests with continuity correction.
sd, standard deviation.

examination. Mean absolute differences between the two measurements were between -7% and 4% bloodflow reduction and probability values calculated from paired *t*-tests were between 0·14 and 0·8. There was thus no evidence of systematic error. However, plots of differences against the mean of the two measurements show considerable within person variability, with repeatability coefficients ranging from 23% to 47%. A number of participants would have been classified differently after the second measurement. Taking the most stringent threshold (2·58 sd) two out of three test positives were negative in repeat testing. Similarly, with the lowest threshold (1·28 sd) one out of three positives

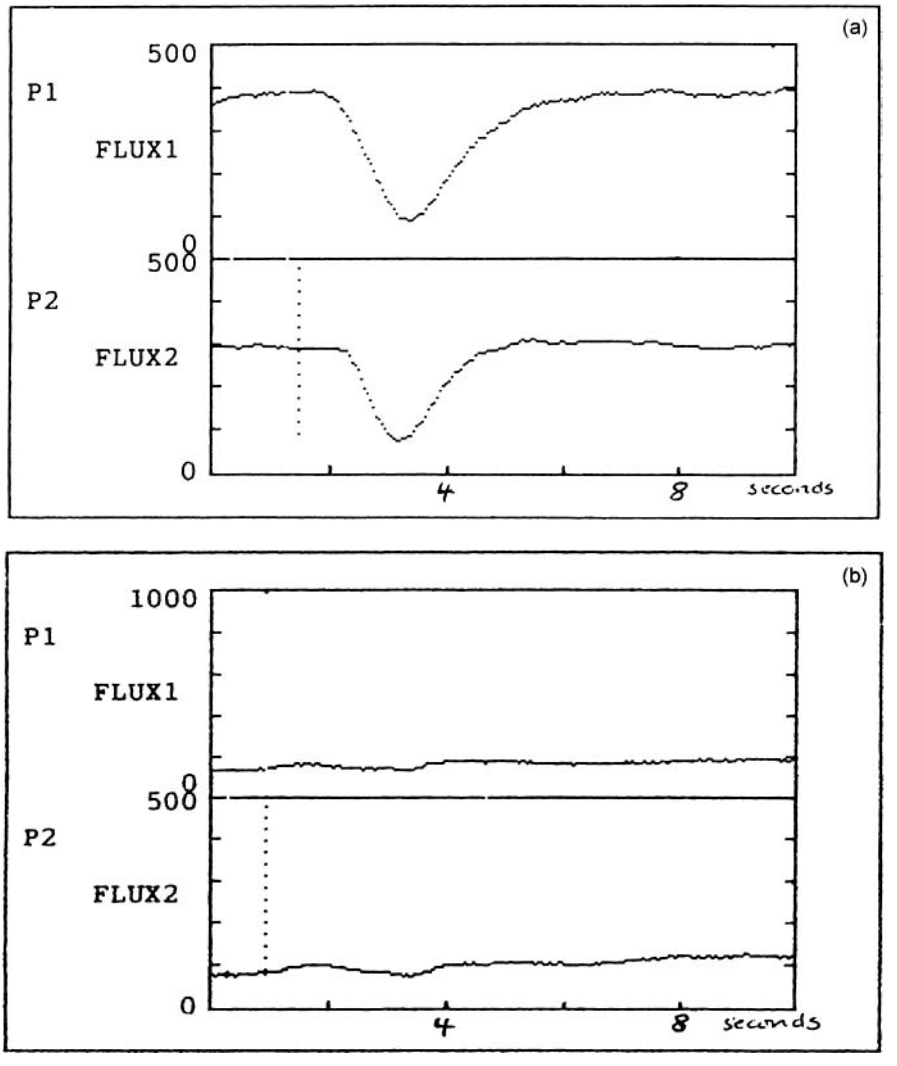

Figure 2. Examples of vasomotor reflexes. (a) Normal vasomotor reflexes in a Nepali control. P1, right third digit, P2, left third digit. The dotted line marks the inspiratory gasp. (b) Pathological vasomotor reflex in a leprosy patient. P1, right big toe, P2, left big toe. The dotted line marks the inspiratory gasp.

were negative in the second test. No initially test negative participant was later found to be positive.

Figure 2(a) illustrates the normal vasomotor reflex of both third digits in a healthy Nepali control subject. The sharp and steep fall in fingertip blood flow by 75% can be seen to occur 2 s after inspiratory gasp. Five seconds later the bloodflow has returned to its previous level. Figure 2(b) shows the pathologically reduced vasomotor reflex of both big toes in a leprosy patients.

Discussion

Leprosy is endemic in subtropical and tropical regions with an estimated 11–15 million people suffering active disease worldwide[22] with many more being infected. In approximately 5% of infections the disease leads to impairment due to blindness or deformities of the feet and hands. There is evidence that autonomic nerve damage in leprosy occurs before clinical manifestations become apparent.[2,23] By the time clinical signs are present, extensive and often permanent nerve damage has taken place. A method able to detect asymptomatic neuropathy could be of value to identify patients at high risk for symptomatic leprosy. One possibility is the measurement of damage to autonomic nerves using vasomotor reflex testing. The aim of the present study was to examine characteristics of a laser Doppler vasomotor reflex test system and to investigate differences in test outcomes between leprosy patients, healthy contacts and controls.

Results indicate important differences between the three groups, however, groups could only incompletely be matched for age and sex. It proved particularly difficult to recruit healthy contacts, perhaps because of the social stigma associated with leprosy in Nepal. The male preponderance in the leprosy group may be explained by the higher incidence in males and possibly by better access of males to specialized care in a leprosy hospital. The age and sex differences between the three groups were taken into account in multivariate analyses with little effect on results. Prevalences of extensive callouses of the extremities was similar across the groups.

Among controls resting bloodflow was higher and reflexes were more pronounced than reported previously.[11] This may be explained by the constant high ambient temperatures and high levels of humidity favouring maximal skin vasodilation and thus creating optimal testing conditions. For all 12 measurement sites there were pronounced and statistically highly significant differences in responses between the three groups. The strongest responses were consistently recorded in control participants and the least among leprosy patients, with healthy contacts in an intermediate position. Test characteristics and the prevelance of overall abnormal tests depend on the definition of normality. This is illustrated by the ROC curve which indicates that a cut-off value defined as the mean reduction in bloodflow among controls minus 1·64 to 1·96 sd provides optimal combination of sensitivity and specificity. Using these cut-off values around 80% of leprosy patients, 50%–55% of healthy contacts and 15%–23% of controls have abnormal results.

The high rate of abnormal tests among controls is unexpected. There are two factors that may contribute to this. First, in the area of recruitment there is a concentration of leprosy patients from the hospital (100 inpatients, 4000 outpatients visits per year). A number of control participants could in fact have been exposed and should correctly be

classified as healthy contacts. They may have been reluctant to acknowledge contact to leprosy patients or may not have been aware of such contact. Other causes of abnormal VMR such as other polyneuropathies are unlikely since diabetes and a history of alcohol abuse were excluded.

Second, when re-examining a subgroup of controls a proportion of control participants with abnormal tests were normal on repeat testing, perhaps because of lack of compliance of the examinee during the first round of testing. Based on the literature,[11] we assumed adequate reliability of the method and therefore did not perform a prior reliability investigation. However, the current results indicate that reliability may have been less good than expected. We believe that this does not invalidate the main results, but further confirmation of this will be necessary. In particular, a thorough reliability study of laser Doppler flowmetry will need to be done.

We do not think it likely that subjects with previously successfully treated leprosy were included since distribution of antilepromatous therapy is government controlled and all cases of leprosy are registered and controlled. In addition the leprosy hospital has excellent treatment records of all leprosy patients treated over the past 40 years and documentation of contact examination. Contacts were all well known to the hospital staff. In the setting of this selected community, hidden leprosy treatment would have been evident.

The most important finding of our study is the high prevalence of subclinical neuropathy among healthy contacts. Within this group the prevalence tended to be higher among participants with intense contact and lower among those with less intense exposure. These findings confirm those from an earlier study conducted in India and Scotland.[9] The data strongly support the notion that autonomic nerve damage represents an early manifestation of the disease process. Indeed histopathological and immunocytochemical studies have demonstrated that nerve damage progresses from small unmyelinated to small myelinated and finally to large myelinated fibres.[23,24]

Early treatment of leprosy prevents progression to deformity and disability and eliminates transmission of the disease. Treatment is well tolerated, cheap and available worldwide.[25] Early detection of leprosy may thus be an important strategy which could substantially contribute to achieving the declared goal of worldwide elimination of leprosy.[6]

Screening for asymptomatic disease using vasomotor reflex testing could play an important role in this effort. A number of obstacles, however, need to be overcome before such screening could sensibly be implemented. First and an important principle of early disease detection, the progression from asymptomatic early stages to clinical disease needs to be understood more completely.[26] In leprosy, it is not clear at present if neuropathy detected among healthy contacts does in fact always represent an early stage of an active disease process. Alternatively, it could correspond to an 'immunopathological scar' associated with an earlier infection which was successfully overcome by the immune system. A parallel may be drawn to another mycobacterial infection, tuberculosis. After exposure to *Mycobacterium tuberculosis* the immune response results in the formation of a Ghon complex. In many cases the disease will not progress further as there is adequate immunity. Activation may nevertheless occur at a later time. Similarly, after exposure to *M. leprae*, the immune response may result in a 'Ghon-complex-type' damage to the peripheral autonomic nerves. Progression to symptomatic disease may or may not occur depending on the course of the interaction between host and bacteria. The

risk of progression to clinical disease among different groups of people with abnormal vasomotor responses clearly needs to be established in prospective studies before recommendations can be made regarding screening for and treatment of asymptomatic disease. Sampatavanich *et al.*[27] performed an immunoepidemiological study on subclinical infection among leprosy household contacts in Thailand and found that 33·5% of contacts were infected and probably at risk to develop leprosy as they had no evidence of cell-mediated immunity against *M. leprae*. A study using lymphocyte transformation tests found that people in contact with leprosy patients for more than one year had evidence of subclinical infection in more than 50%.[28] Unfortunately the risk for developing symptomatic disease was not prospectively assessed in these studies.

Second, a rapid and simple test appropriate for mass screening and acceptable to the target population would have to be developed. The system used in this study is expensive and testing is still time consuming. This system could prove useful in tertiary centres to monitor selected patients for early progression of neuropathy. For example, titration of anti-inflammatory treatment during acute reactions would thus become possible. Finally, any screening programme would have to be evaluated in carefully designed studies, and, once implemented on a large scale, would have to continue for a sufficiently long period of time.

In conclusion, we have shown a strong association between autonomic neuropathy as assessed by vasomotor reflex testing and leprosy, both among those with manifest disease and among healthy contacts at high risk of infection. Carefully planned prospective studies are now needed to better define the significance of these findings for early treatment and prevention of transmission.

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The pattern of cataract and the postoperative outcome of cataract extraction in Ethiopian leprosy patients as compared to nonleprosy patients

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Summary Cataract is a blinding disease occuring all over the world. One of the causes of cataract is leprosy.

Sixty leprosy and 100 nonleprosy patients were assessed and underwent intracapsular cataract extraction.

Leprosy patients with cataract were much younger than nonleprosy patients. The leprosy group had a significantly higher rate of complications and this was seen more in paucibacillary cases. There was a higher rate of visual disability in the leprosy group than in the nonleprosy group.

Cataract was seen in younger patients in the leprosy group. This raised the possibility of leprosy being the cause of the cataract. The leprosy group consisted mostly of multibacillary cases, however unlike in other studies the rate of complications tended to be higher in the paucibacillary group. There were no preoperative findings that correlated with a low postoperative intraocular pressure.

Introduction

Around 250,000 people in the world are blind from leprosy. One of the causes of blindness in leprosy is cataract.[1] Cataract is the leading cause of blindness in the developing world,[2] and has several causes in leprosy. It can be due to repeated inflammations, age[3] or steroid treatment, which is frequently used in the treatment of reactions in leprosy. Leprosy has also been incriminated as the cause of cataract.[4]

Cataract extraction in leprosy patients is said to be associated with a higher risk of complications. The anatomical changes due to repeated inflammations or infiltrations are said to be associated with intraoperative and postoperative complications.[5] Leprosy patients have a lower intraocular pressure when compared to nonleprosy patients. This is said to be due to atrophy of the ciliary body as a result of repeated inflammation,

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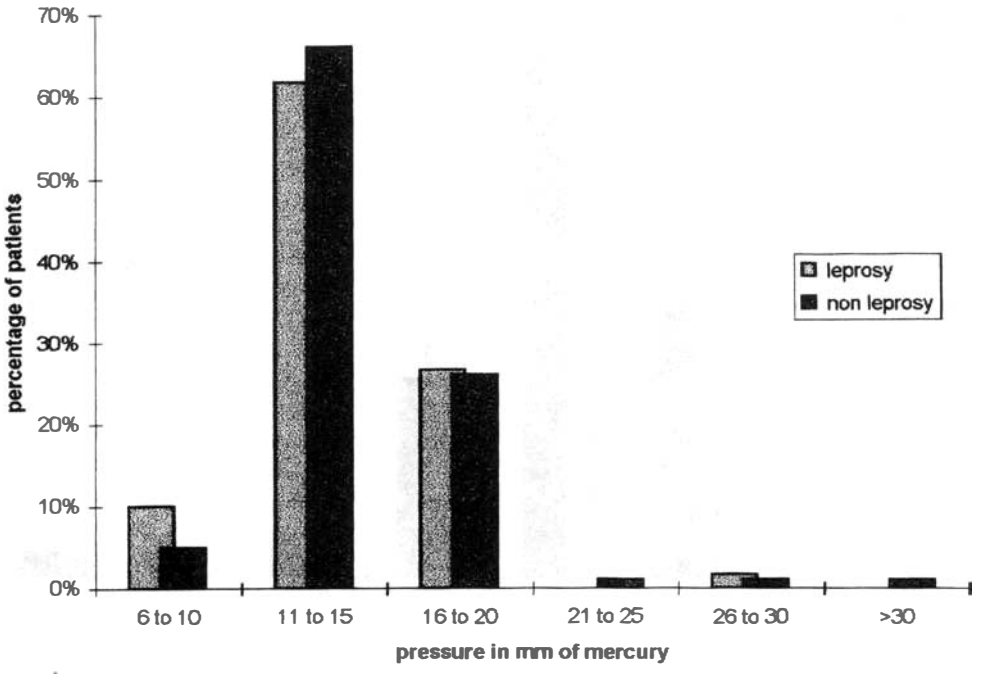

Figure 1. Pre-operative intraocular pressures of leprosy and nonleprosy patients.

resulting in a decreased production of aqueous humour.[5] The other speculation is that leprosy patients tend to have damage to the autonomic nerves that supply the eye. Changes in intraocular pressure associated with postural changes are regulated by these nerves. As a result of damage to these nerves, leprosy patients lose this equilibrium in intraocular pressure and tend to have lower intraocular pressure than normal.[6]

So far none of these parameters have been assessed in Ethiopian patients. The purpose of this paper is:

to compare the intraoperative and postoperative complications of intracapsular cataract extraction in leprosy and nonleprosy patients;

to compare the visual outcome of intracapsular cataract extraction of leprosy and nonleprosy patients; and

to find any preoperative findings that may correlate with a poor operative outcome.

Materials and methods

All leprosy and nonleprosy patients coming for cataract extraction in the Eye Department of the All Africa Leprosy and Rehabilitation Training Centre in Addis Ababa from September 1992 to June 1993 were examined. All patients with bilateral mature cataracts and no corneal opacities in their visual axes were selected. Those with bilateral cataracts were selected because the majority of the nonleprosy patients had bilateral mature

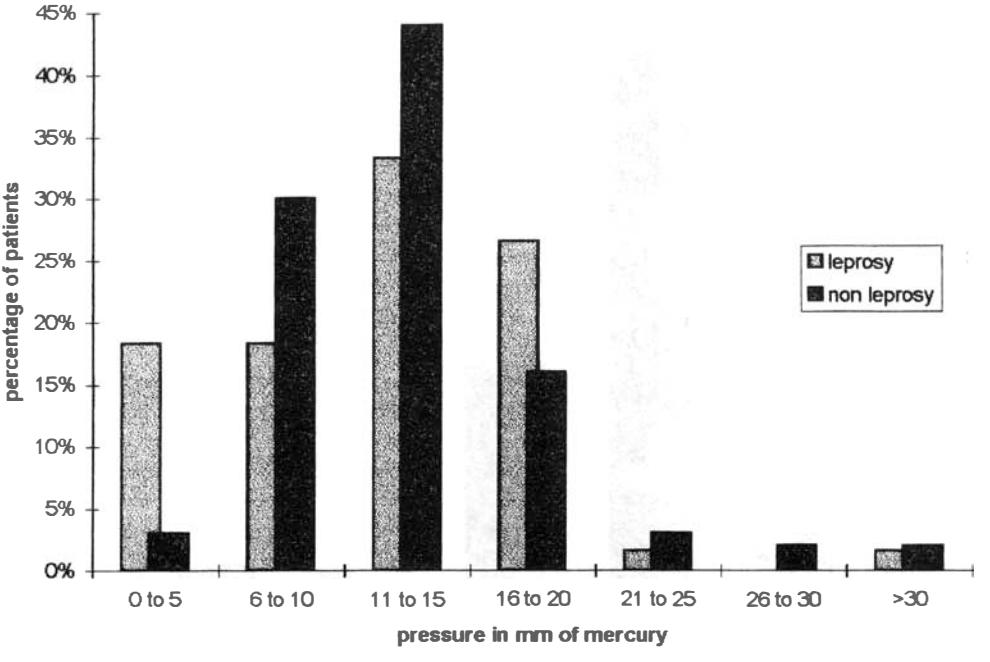

Figure 2. Post-operative intraocular pressures of leprosy and nonleprosy patients 4 weeks after operation.

cataracts (these were given priority for surgery) and we had to take leprosy patients with bilateral mature cataracts to make the groups comparable. There were 100 nonleprosy and 60 leprosy patients who fulfilled these criteria. All patients gave a history of their eye illness and underwent a general medical check-up to rule out other systemic illnesses. A thorough examination of the anterior segment and its adnexae was done using a biomicroscope. The status of the lids, the conjunctivae, the corneae, the anterior chambers, the irides, the pupils and the lenses were assessed. Intraocular pressure was measured using an applanation tonometer. The previous medical records of the leprosy patients were reviewed and duration of illness, history of recent reaction, steroid therapy, stage of treatment and leprosy classification were recorded.

Cataract extraction was done under retrobulbar anaesthesia using 2% lidocaine. A total of 160 eyes (one eye in each patient) were operated on under the microscope by three surgeons. The operations were randomly distributed amongst these three surgeons. The eyes were massaged before the operation to soften them. A fornix based conjunctival flap was made and after making a limbal groove the anterior chamber was entered, a peripheral iridectomy was done and the lens was extracted using a cryoprobe. In those with extensive posterior synechiae release was done using an iris repositor where possible and a sector iridectomy done where this was not possible. Occasionally a sphincterectomy was done in those with constricted pupils. The wound was closed with 4 to 5 9/0 nylon sutures. Topical and subconjunctival injection of antibiotic and steroid was given intraoperatively. Topical mydriatics were applied for 2 to 3 days and stopped but steroid antibiotics were applied from the first 24 hours to when the eye irritation ceased.

Ocular assessments were made 1 week and 1 month after operation. Visual acuity was tested using a Snellen's chart (both literate and illiterate charts were used as necessary) after giving the appropriate plus spheres by subjective refraction. Intraocular pressure measurement was done using an applanation tonometer. A thorough examination of the anterior segment was done with a biomicroscope. The anterior chamber was concentrated on and the presence of flare and keratic precipitates was observed. Subjective gradings of 1–4 were made both for flare and cells. The posterior segment was examined using a direct ophthalmoscope. All examinations were done by one individual. Masking was not possible due to the obvious physical changes in the leprosy patients.

Results

The leprosy group was mainly composed of multibacillary patients (41 (68%)). All patients were released from treatment. Seven patients had undergone steroid therapy lasting no more than 8 weeks, 6 months before study. The male to female ratio in the leprosy group was 2·3 : 1 while in the nonleprosy group it was 1·5 : 1. There was a statistically significant difference between the two mean ages ($p < 0{\cdot}001$) using the *t*-test).

Eight patients in the leprosy group had signs of previous uveitis. Synechiae were taken to be the only signs of a previous uveitis as the other findings could have been due to infiltration (Table 1).

In assessing the postoperative visual acuity of both groups it was found that blindness in the leprosy patients was significantly higher (relative risk 1·71 95% confidence interval 1·07–2·73) than in the nonleprosy patients.

There was a high rate of visual disability among leprosy patients than nonleprosy patients (Table 2) but this was not statistically significant.

The mean preoperative intraocular pressure of the leprosy group was 14·8 mmHg and for the nonleprosy group, it was 13·8 mmHg. There were no patients with intraocular pressures of 0–5 mmHg in either group preoperatively. The mean postoperative intraocular pressure of the leprosy group was 12·2 mmHg and 13·2 mmHg in the nonleprosy group. Eleven (18%) leprosy patients had a postoperative intraocular pressure of 0–5 mmHg, while only 3 (3%) of the nonleprosy group had a postoperative intraocular pressure of 0–5 mmHg. There were no specific findings in the leprosy group with low intraocular pressure.

Eighteen patients of the leprosy group had intra and postoperative complications

Table 1. Preoperative anatomical status of the anterior segment in the leprosy group

	PB	%	MB	%	Total	%
Iris atrophy			4	9·8	4	6·7
Anterior and posterior synechiae			8	19·6	8	13·3
Lagophthalmos with exposure keratitis	1	5·3	1	2·4	2	3·3
Constricted pupil			2	4·9	2	3·3
Iris holes			1	2·4	1	1·7
No major abnormalities	18	94·7	25	60·9	43	71·7
Total	19	100	41	100	60	100

Table 2. Postoperative visual acuity with +10 sphere correction 1 month after operation

Post-operative visual acuity	Leprosy	%	Nonleprosy	%
Blind (light perception—<3/60)	9	15	6	6
Visually disabled (3/60–6/60)	22	36·7	36	36
Not visually disabled (6/36–6/9)	29	48·3	58	58
Total	60	100	100	100

while only 6 patients of the nonleprosy group had complications. This was statistically significant (relative risk, 1·8 for 95% confidence interval 1·06–4·37 $p = 0·0409$). Out of the 18 leprosy patients, 7 were paucibacillary and 11 were multibacillary. Out of 11 multibacillary cases 5 had iris changes. The rate of complications was much higher in the paucibacillary group (Table 3).

Anterior chamber reaction was also assessed and it was found that the difference in anterior chamber reaction between the two groups was not statistically significant.

Discussion

The leprosy group had a higher rate of intra and postoperative complications. Out of these leprosy patients, the paucibacillary group had a higher rate of complications. This is different from similar studies done in India and Korea.[4,7,9,10] The small sample group may have contributed to this proportion of complications and things may be different if the sample was much larger. If we look into the complications that the paucibacillary group underwent they were: vitreous loss, capsular rupture and secondary glaucoma. These complications may not be necessarily due to uveal infiltration. Thus one may need to define complications as those with a possible association with ocular infiltration and inflammation and those without, and it may turn out that the multibacillary may have higher rates of infiltration-associated complications.

The blindness rate and the overall visual disability was much higher in leprosy patients. This is not similar to other studies done in India and Liberia.[8,9,11] This may have been due to corneal decompensation following an operation incision as this reduces the corneal

Table 3. Intra and postoperative complications in leprosy and nonleprosy patients

	Leprosy				Nonleprosy	
Complications	PB	%	MB	%		%
Vitreous loss	3	15·8	4	9·7	6	6
Secondary glaucoma	1	5·2	2	4·9	1	1
Retinal detachment					1	1
Vitreous haemorrhage			2	4·9	2	2
Capsular rupture	3	15·8	3	7·3	6	6
Total	7	36·8	11	26·8	16	16

sensation markedly exposing the cornea to microtrauma and cell death due to the lack of innervation. This can result in corneal damage and astigmatism leading to impaired vision.

All patients had a comparable density of cataract before operation, all the layers of the lens were opaque. However the patients in the leprosy group were younger than those in the nonleprosy group. One can make several speculations on the earlier occurrence of cataract in leprosy patients. According to Prabhakaran *Mycobacterium leprae* produce tyrosinase which oxidizes DOPA to quinones and these attach to proteins in the lens and cause opacification.[13] As most of our leprosy patients were multibacillary cases this increases the chance of *M. leprae* being in the ocular tissues. Thus one can speculate that leprosy could have been the cause of early cataract formation.[4] Repeated inflammation in leprosy can also cause early development of cataract.[4,12]

Seventy percent of the nonleprosy patients were paying for their treatment while all the leprosy patients were non-paying. Thus the nonleprosy patients could have remained longer with their cataracts before coming for treatment due to economic reasons. The majority of the leprosy patients were beggars thus the chances of these patients being well nourished are quite low, and their exposure to the sun is quite high. Thus malnutrition and sun exposure could have contributed to the early development of cataract.[14]

Steroids are the other factor that can contribute to cataract formation but only very few patients had had a course of steroid during their treatment and the courses were quite short.

Similar to other studies, there were a significant number of leprosy patients who had a low intraocular pressure.[5] This may have been due to the already compromised state of the ciliary body plus the operative trauma resulting in decreased aqueous production.[5] Autonomic nerve damage may have also contributed to the instability of the intraocular pressure.[6] The low intraocular pressure could not be correlated to any preoperative findings.

Cataract occurred early in the leprosy group in our study and larger studies must be done on a larger number of patients to confirm this observation. Intracapsular cataract extraction was associated with a higher rate of visual disability and care must be taken when doing this procedure. Unlike previous beliefs, intra- and postoperative complications in leprosy patients should not be associated with uveal changes only.

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Squamous cell carcinoma of the foot arising in chronic ulcers in leprosy patients

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Summary Squamous cell carcinoma (SCC) of the foot is a rare sequelae of chronic ulceration secondary to leprosy neuropathy. Most of the tumours are relatively slow growing and tend to metastasize late. Survival after local excision is generally good. In this series of 17 patients so far there have been 3 deaths attributable to SCC, all of whom presented with locally advanced tumours and lymph node metastasis.

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* which predominantly affects skin and peripheral nerves. Damage to peripheral nerves occurs as a result of host immunity (reversal reaction, i.e. delayed-type hypersensitivity) to the presence of bacteria in nerves or as a result of fibrosis due to chronic inflammation in peripheral nerves.

This results in sensory, motor and autonomic loss in the affected limbs. As a result of paralysis of the dorsiflexors (damage to the common peroneal nerve) of the foot the forefoot is subjected to more pressure than usual with each step. Damage to the posterior tibial nerve results in anaesthesia of the plantar surface and some loss of cushioning in the foot due to wasting of the foot intrinsic muscles. Patients with insensitive feet are prone to recurrent wounds which often become secondarily infected. Secondary infection can lead to the absorption of digits. A proportion of patients with chronic ulcers (usually those present for more than 10 years[3–5]) develop SCC[1] which is usually of low grade malignancy.

Materials

All patients with SCC who presented between January 1991 and June 1995 were included

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in this series. There were 17 patients with SCC (15 male and 2 female). The normal male to female ratio for admitted patients is 4 : 1 at our hospital. The average age was 52 years (30–74 years). Some had clinically obvious SCC, while others had a chronic nonhealing ulcer with some suspicious features which led to a biopsy being done. Information on the duration of the ulcer was retrospectively extracted from case notes.

Results

There were 7 cancers on the left and 10 on the right foot. The average duration of an ulcer prior to clinically malignant transformation was 9·4 years (range 1–15 years). The earliest clinical sign of malignancy is a white pasty discharge from the central area of the ulcer when the edges are squeezed. It is believed that these are squamous cells produced by the cancer. Six patients had palpable inguinal lymph nodes on initial presentation. In 3 of these the nodes had settled within 6 weeks of surgery indicating infection as the most likely cause. In 3 patients the nodes persisted and were biopsied (all 3 were positive for cancer).

All patients underwent surgery. Nine patients had a Pirigoff amputation[2] (amputation of the foot with talocalcaneal arthrodesis) while 2 patients had a forefoot amputation. Four patients had a below knee amputation (BKA) and 2 underwent an above knee amputation (AKA).

There was one death within 4 weeks of surgery from widespread metastasis. One death occurred 14 months after a Pirigoff amputation (no local recurrence) presumably from metastatic disease. Another patient died of an intercurrent illness (undiagnosed hypothyroidism with severe depression). The other death was in the patient described in the following case study and illustrates the outcome if adequate primary treatment cannot be provided.

Case study

A female patient aged 74 initially presented with a hyperkeratotic lesion on the dorsum of her ankle. This was fully excised and skin grafted. Three months later she developed a recurrence of two nodules which when biopsied were positive for early SCC. She refused further surgery at that time. She returned 6 months later with a large fungating tumour on the anterior aspect of her ankle and again refused surgery. She was given oral Methotrexate, 20 mg weekly, and her tumour shrank over 3 months and finally completely disappeared. She was kept on oral Methotrexate, 20 mg every alternate week for a year, with no recurrence. As she seemed well her Methotrexate was stopped. Within 3 months her tumour recurred and this time did not respond to oral Methotrexate. She then developed a severe infection in the tumour and consented to BKA. However two days after BKA she developed gas gangrene which was treated by AKA with the skin flaps left open. She recovered from her surgery and returned home in the care of her son. Some 5 months after discharge she died at home of unknown cause—presumably metastatic carcinoma.

Table 1. Detailed profile of patients

Pt	Year	Sex Age	Side/Site	Duration of ulcer (years)	Lymph nodes	Pathology	Surgery	Outcome
BBT	9/91	M/40	R forefoot	4	Yes	Poorly diff.	AKA	Died 4/52
SMT	1/94	M/45	R forefoot	10	Yes	Benign epith. SSC in LN	Pirigoff	No local recurrence. Died at 14/12
BK	1/92	F/74	R ank dor.	13	No	SCC	AKA	Died 1994
HB	9/93	M/64	R forefoot	1	No	Cornu cutaneum	Forefoot Amput.	Died Hypothyroid
SD	9/93	M/30	R heel	4	No	SSC	BKA	Not seen since
SR	9/93	M/50	L forefoot	14	Yes		Pirigoff	Well since 1993
GP	4/93	M/58	L short ft	35	No		Pirigoff	Well since 1993
TK	3/93	F/54	L midfoot	5	No	Well diff SCC	Pirigoff	Well since 1993
EKN	4/94	M/63	L forefoot	8	No	SCC—early invasiveness	Forefoot Amputation	Well
KB	3/94	M/43	L lat bord.	7	Yes	Cornu cutaneum	Pirigoff	Well since 1994
GR	4/94	M/60	R heel	5	Yes	SCC well diff	BKA	Well since
SMG	6/94	M/65	L heel	3	No	SCC well diff	BKA	Well since
DBT	7/94	M/55	L forefoot	9	Yes	SCC well diff	Pirigoff	Well since
KBM	3/93	M/40	R forefoot	15	No	SCC early invasiveness	BKA	No recurrence But BK stump wounds
KBB	3/95	M/35	R lat bord.	15	Yes	SCC well diff	Pirigoff	Well since
BRS	3/95	M/45	R instep	8	No	SCC well diff	Pirigoff	Well since
DL*	9/94	M/62	R lat bord	3	No	SCC	Pirigoff	Well since

Discussion

These patients were all treated at Anandaban Leprosy Hospital which is the referral hospital for reconstructive surgery for leprosy patients from the Central and Eastern regions in Nepal. Nepal is a developing country with very basic health services and has a largely rural population of 20 million living in villages among the foothills of the Himalayas. Patients with malignancy often present late with fungating tumours, as health is a lower priority than ensuring a food supply for the following year and other obligations to family.

Most day-to-day transport is on foot and patients often have to walk for days to the nearest basic health facility. Most of these patients had a local amputation, usually a Pirigoff amputation (as compared with a BKA). In Nepal, where the terrain is hilly, this amputation is far superior to a below knee amputation, after which the patient is constantly dependent on scarce prosthetic services. The patient is also able to walk within their home without any form of footwear and to squat when going to the toilet (a cultural prerequisite). Thus preservation of leg length and the use of simple footwear rather than complicated prosthetic devices are vital components in the rehabilitation of patients requiring amputation.

The duration of ulcers prior to malignant change was 9·4 years (range 1–15 years). It is likely that this duration is inaccurate for some of these patients. In general, rural villagers in Nepal have very loose concepts of time and this information was extracted retrospectively from case notes.

The high male to female ratio (7 : 1) may reflect a true greater risk as men in Nepal

walk much greater distances, and carry heavier loads than women. This would predispose those with insensitive feet to a much greater risk of chronic wounds and hence SCC. However women in Nepal are much less likely to present for hospital care (the ratio of men to women affected by leprosy is 2 : 1 but the ratio of admitted patients 4 : 1). One risk is the small margin of clearance available (often 1–2 cm of macroscopically normal tissue) but SCC in leprosy is usually a low grade malignancy[4,5] with moderately well-differentiated tissue. None of the patients who had a Pirigoff amputation have had any local recurrence.

Often the pathologist finds it difficult to differentiate the lesion from a benign basal cell epithelioma. In one patient (SMT) initially reported as a benign basal cell epithelioma, keratotic type, persistent inguinal lymp nodes were biopsied 6 weeks after the initial amputation, because they had not reduced in size despite an absence of infection. These lymph nodes showed well-differentiated SCC. On review of the initial specimen a small focus of invasive SCC was found. The difficulty in diagnosing these lesions has been documented, with some patients requiring up to 6 pre-operative biopsies for a definitive diagnosis in one series.[5]

The histological features include hyperplasia of epidermis showing hyperkeratosis, parakeratosis, and papillomatosis associated with lymphocytes and plasma cell infiltration in upper dermis and some cells with a large nucleus and disappearance of basement membrane suggesting well-differentiated squamous cell carcinoma.

It is essential that patients are taught self-care routines[6] in order to prevent chronic wounds and thus the development of SCC. Patients need to be instructed in a daily routine of skin care (inspection, soaking, scraping, oiling and exercise) as well as methods of wound avoidance to prevent wounds and wound care to help heal the wounds quickly. In addition to teaching patients these principles we provide them with leaflets in Nepali to help them remember what they have been taught.

Conclusion

SCC in chronic plantar ulcers in leprosy are usually well differentiated and only metastasize late. There can often be difficulty in making a firm diagnosis from the histology. Pirigoff's amputation is a valuable procedure in the preservation of leg length in patients requiring amputation for SCC in leprosy.

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Practical problems in the management of leprosy

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Summary The categorization of leprosy into paucibacillary or multibacillary depends on the report of slit-skin smears. Unfortunately, in many control programmes the quality of slit smears is below par. Taking the example of India, the main reasons were that the work of laboratory technicians was unrewarding as compared to serving in a general health care system. There was lack of equipment and an unrealistic patient to technician ratio. Future attempts were made by experienced workers to devise a clinical system for classifying leprosy as paucibacillary or multibacillary based on counting the number of lesions. However this method did not prove cost-effective because more paucibacillary patients were classified in the multibacillary group increasing the burden of treatment. A renewed attempt to improve slit-smear performance should be made by modifying the existing methods. This can definitely improve the situation. Patients with multiple macular lesions and those with neuritic leprosy are best treated with the MB–MDT regimen. The treatment for PB leprosy is to continue up to 6 months but in MB leprosy with a high bacterial index a longer duration of MDT may be required. Following completion of MDT many cases with deformity are accumulating and their care forms are a neglected part of many control programmes. In addition to strengthening the infrastructure, simple techniques must be imparted to those with deformities and disabilities. This involves the artful and innovative cooperation of the health worker, patient and the community. The leprosy worker should be motivated to promote such activities.

The introduction of multidrug therapy (MDT) in leprosy was recommended in 1982.[1] This has paid rich dividends to a disease where many aspects of therapy were unclear. It was a turning point in the strategy of leprosy control and it brought a uniform approach in the treatment of the disease. Within a few years the standard regimens were accepted and many of the control programmes were streamlined. The most visible achievement following the implementation of MDT was the drop in prevalence rate of the disease. India, the biggest country in South-East Asia shared this achievement and the effective

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caseload came down from 4 million leprosy cases in the year 1981 to 0·94 million by the end of March 1994.[2] These developments generated optimism among all personnel actively involved in the eradication of leprosy. At the same time it also brought to the fore some practical problems which need to be discussed on the basis of the accumulated experience and newer findings. These issues are:

Classification

The categorization of leprosy into paucibacillary (PB) and multibacillary (MB) for the purpose of MDT is based on a mathematical estimation of the bacterial population in the tissue[1] and depends on the report of slit-skin smears. In the widely used Ridley–Jopling classification, PB leprosy includes indeterminate (I), tuberculoid (TT) and borderline–tuberculoid (BT) with a bacterial index (BI) <2 (Ridley scale) at any site; MB leprosy includes midborderline (BB), borderline–lepromatous (BL) and lepromatous (LL) with a BI of 2 or more at any site. The distinction between PB and MB required the services of an equipped skin-smear laboratory. Contrary to this expectation, the performance of skin-smear laboratories has not been satisfactory except for those in selected institutions managed by government and nongovernment organizations catering to a limited population.[1,3–6] Attention to the low standard of performance of slit-skin smear laboratories had also been drawn by the WHO Expert Committee as early as 1977.[7] Following the recommendation of MDT in 1982[1] many countries attempted to organize their skin-smear services in their control programmes. Some of the centres also tried to evolve a system of quality control and cross-checking,[5,8,9] but inspite of these efforts the laboratory services did not improve to a satisfactory level. India runs one of the largest organized control programmes with an inbuilt evaluation system. It has been seen in independent evaluations that a significant number of the posts for laboratory technicians remained vacant and only 40% of the registered cases had skin-smear examination,[10] a situation that continued to prevail.[11] While commenting on the poor standard of laboratory services, some of the causative factors were also enumerated by the evaluating teams. These indicated that working in skin-smear laboratories has been less attractive for the technicians. They preferred to work in a general health care system as it was more rewarding than the monotonous and wearisome reporting of skin-smears.[3,5] Unrealistic patient to technician ratio and paucity of reagents and equipments had also added to their disinterest. Since most of the supervisory staff were not confident in skin-smear techniques, they failed to impart the necessary guidance. To address these shortcomings in the system the leprosy control programme in India,[12] from the very beginning of implementation of MDT, had advocated that all skin-smear positive patients be treated as MB leprosy irrespective of their classification. This compromise was later recommended by the WHO.[13]

At the end of almost a decade, the cumulative reports left an impression that the bacteriological services relating to slit-skin smears were less likely to improve. So in order to facilitate wider and speedy implementation of MDT, many in the Indian programme felt it necessary to categorize leprosy as PB or MB based on only clinical features, where both skin and nerve involvement were counted as separate lesions. This approach of bypassing smear examination is not exclusive to the Indian programme. Studies from Ethiopia[14], Nepal[15] and Bangladesh[16] showed that using only clinical

criteria more patients were classified as MB leprosy thus increasing the cost of treatment. This was similar to the Indian system[17] which advocated 10 or >10 lesions to be MB leprosy irrespective of the smear report. Improving the quality of skin-smear examination significantly reduced this overclassification.[18] We endorse the view that to make the programme cost-effective it is unwise to completely dispense with slit-smear examination. Fresh attempts should be made to improve the laboratory functioning by a more realistic and liberal approach to the problem. The decision to treat all skin-smear positive patients with MB–MDT is a welcome step in this regard.[12,13] Inadequately equipped peripheral laboratories can be closed and a district laboratory should be maintained to provide reliable service in doubtful situations.[3] Other suggestions[13,16] for maintaining a laboratory with reduced workload include taking smears from only three sites in MB leprosy, one earlobe and two active skin lesions, and in PB leprosy with a solitary skin lesion from its active edges at sites diametrically opposite to each other. Follow-up slit smears should be made from the site showing highest density of bacilli on initial examination.[19] Repeat skin smears from PB cases should be dispensed with. The morale of the technicians can be maintained by improving the system and making them feel an integral part of it.

The classification of macular lesions has also remained tenuous. Special mention has been made for careful consideration of these patients.[12,13] The fact that all determinate cases have a macular and an infiltrative stage is well known. The indeterminate cases by their early nature and the macular tuberculoid (or maculoanaesthetic) by virtue of better resistance have good prognosis. They are therefore to be considered as PB leprosy. The others with multiple macular lesions show the clinical features of borderline leprosy but biopsy and slit-skin smears are often not helpful. Histopathology shows either nonspecific lymphocytic infiltration[20] or a branching granuloma too small to produce induration. In the natural course these lesions eventually progress to the indurated forms of borderline leprosy.[21,22] Hence such patients should be taken as MB leprosy and given the appropriate MDT regimen. However it should also be borne in mind that the macular stage may represent the subsided or healed plaque forms of leprosy where the disease is inactive. A proper history and examination of previous records would bear this out.

The grouping of primary or pure neuritic leprosy is also not clear. With a high incidence of 17·7% of all leprosy cases in India[23] it accorded a separate category in the Indian system of classification and has been placed in the PB group.[12] However, it is really a grouping of all types of leprosy where due to lack of reliable indicators,[13] no distinction between PB and MB is made. So far as deformity is concerned it is more likely to occur in neuritic leprosy and a wrong decision in treatment can add to the risk.[24] Neuritic leprosy is perceived clinically as an insensitive area over the skin, muscle weakness, or tingling sensation, with or without nerve thickening and tenderness. Skin smears are of no use in neuritic leprosy and performing nerve biopsies are impractical. In some, neural signs may be an early manifestation and skin lesions can appear after a prolonged period,[25] sometimes even during therapy.[26] Though pure neuritic leprosy with a strong lepromin reaction similar to tuberculoid disease has been observed, the majority show borderline features in the nerve on histopathology.[27,28] Studies on patients with both skin and nerve lesions have often reported a higher bacillary load in the nerves as compared to the skin,[15,29,30] indicating that in clinical classification systems the definition of nerve involvement needs more elucidation.[13] The nerve lesions can neither be visualized nor expressed numerically except by naming the affected nerve(s) individually.

In our experience when skin lesions developed in some neuritic patients during therapy, they usually conformed to the borderline macular group. Hence, for the benefit of the patients and the ease of field staff it is reasonable to treat patients of neuritic leprosy with the MB-MDT regimen.

Length of treatment

The recommendation of the WHO Study Group[1] is to treat PB leprosy with MDT regimen using 2 drugs—rifampicin and dapsone for 6 months, and MB leprosy with three drugs comprising rifampicin, clofazimine and dapsone for 2 years or whenever possible upto smear negativity. Adequate therapy implied that a patient of PB leprosy has received 6 monthly doses of combined therapy within 9 months, and in the case of MB leprosy 24 monthly doses of combined therapy within 36 months.[31] Using a fixed duration of MDT for 6 months in histopathologically proven PB cases it was found that 40% still showed clinical signs of activity.[32] An additional 6 months' treatment with dapsone in PB patients with 4 to 9 lesions enhanced the disappearance of clinical signs of activity[33] and reduced the risk of relapse.[34] Nevertheless, the recent WHO Expert Committee[35] on the basis of available data pooled from other areas reiterated that the 6-month WHO-MDT regimen is adequate and should continue. In their opinion clearance of the lesions was related more to the individual's immune response and would gradually follow.

The treatment of MB leprosy has been reviewed in detail and it appears that the 2-year MDT regimen using three antileprosy drugs is effective but in patients with a higher initial BI a longer duration of treatment up to 4 years may be required[36] to diminish the chance of relapse. Such patients had registered a better fall in BI when immunotherapy with a vaccine was added to the WHO-MDT regimen[37] indicating a longer duration of therapy to achieve the same result when only MDT was administered. This approach has to be further evaluated in large scale field trials to assess its efficacy on other important issues like relapse.

Deformity and disability

Deformities and disabilities are the sequelae that persist even if the patient ceases to be a case of leprosy as defined by the WHO.[13] Though MDT implementation in India cured a large number of cases, a considerable number with leprosy-related impairments are accumulating. The extent of overall grade 2 deformity amounts to 15% of the total active and discharged cases.[38] An approximately equal percentage of leprosy affected persons also have grade 1 deformity. An independent survey in 19 SIDA supported districts revealed an increase in the deformity rate when both the old and new cases were included though there was a fall of 62·5% in the new cases.[39] In one district in South India in which the MDT programme was in operation for a period of 7 years, 98% of 2500 persons with leprosy-related disability have been declared cured.[40] They outnumber those under treatment. These observations indicate the formidable post-MDT residual problem in India. The infrastructure of the eradication programme in India has the provision of one physiotherapy technician for each control unit catering to a

population of about 4 lakhs. Different independent evaluation reports expressed poor deformity care in the control units.[10,11] Many physiotherapy technicians' posts remained vacant and out of these available only 50% of their time was utilized in disability care.[41] Undoubtedly, commendable support is being rendered by a limited number of voluntary and government organizations in the following areas. Reconstructive surgery facility with a fulltime surgeon is available in as many as 10 institutions. Visiting surgeons periodically operate in another 20 centres. Microcellular footwear is prepared and distributed in 11 centres and half a dozen centres are providing vocational rehabilitation.[38] But all facilities taken together are inadequate to meet the requirement, and there is need for a newer approach.

The last WHO expert committee on leprosy has for the first time acknowledged in its report that the leprosy programme is as much a patient care programme as it is a public health programme. Accordingly the government of India is in the process of launching measures to contain deformities and disabilities and to rehabilitate dehabilitated patients. In addition it is also being realized now that disability prevention rests primarily on the efforts of affected persons themselves and they need to be told simple techniques by which they can protect their anaesthetic parts and prevent worsening of impairments.[40] Due to the decrease of active cases in districts where the vertical programme is in operation for more than 5 years attempts are being made to deploy the leprosy workers as trainers for the patients. A workshop sponsored by the DANLEP recommended a composite approach involving the health workers, patients and the community.[42] This can be achieved by social action having complementary roles for these three groups. The leprosy staff will be acting as the trainers and motivators for such activities and continue their support as consultant when the affected persons approach them with special problems. This approach is already being practised in some of the centres in DANLEP-assisted MDT districts. In these centres one often witnesses camps where a large number of persons with leprosy-related impairments are engaged in oil massages, active and passive exercises, and hydro-oleotherapy. The community members support these camps with food, shelter, medicines and other utility items. Side by side a diagnostic camp also operates to detect new cases. All these constitute a package of treatment, deformity care and health education services. Spread of such movements will be of much help in preventing disabilities.

Conclusion

Classifying leprosy on the basis of clinical criteria will help in brining more cases under MDT. However the clinical picture can vary from place to place. For instance LL with few skin lesions were common in Bangladesh.[18] In such situations grouping on clinical findings alone can be deceptive. A reorganized supporting skin-smear laboratory as proposed must continue to assist the programme. Regarding length of treatment, 6 doses of MDT for PB is to continue with the hope that the residual granuloma will clear in the course of time. The MB cases with high BI need a longer duration of MDT. Services rendered for the prevention of deformity are inadequate. New strategies in which the patients will be taught the skill of taking care of their impairments with the leprosy worker acting as a trainer are being developed and practised in limited centres of the country. These practices need to be expanded.

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Obituary

J. A. CAP 1924–1996

Dr Jozef Arthur CAP, 72, died in Belgium on 22 April 1996. He was born in Nieuwkerken, a village near the town of St Niklaas, Belgium.

After obtaining his MD and DPH degrees from the State University of Ghent in 1948, and his DTM from the Institute of Tropical Medicine in Antwerp in 1949, he left with his wife to the then Belgian Congo, where he became a public health officer in the Kwango District, a highly prevalent area for leprosy. In 1952, he was made in charge of leprosy control in the Equator Province, and from 1955 to 1960, he was Director of the National Leprosy Control Programme in the Belgian Congo. From 1960 to 1971 he was associated with WHO. He worked successively in Pakistan, Bangladesh, Thailand; then, as leader of the well-known Leprosy Assessment Team, he carried out major epidemiological surveys in Burma (Myanmar), the Philippines, Colombia and Argentina; in 1967–1971 he was senior WHO leprosy advisor in India. In 1971, he became Director of the Leprosy Control Department at ALERT, Addis Ababa, Ethiopia, and from 1978 to 1986 while being at the Institut de Léprologie Appliquée in Dakar, he served as technical adviser to the Minister of Public Health of Senegal.

Dr Cap was the author of a considerable number of reports and state of the art presentations regarding the diagnosis of leprosy, control issues and epidemiological studies. He collaborated with a number of nongovernmental organizations, where he was most appreciated for his large experience of leprosy acquired over forty years in various continents. From 1982 to 1988, he was chairman of the Medical Commission of the International Federation of Anti-Leprosy Associations (ILEP). He was also a member of the Belgian Royal Academy of Overseas Sciences.

J. A. Cap was fine clinician. He was approaching the patient with great respect and human feelings. He was very able at motivating collaborators in most diverse contexts. It was an enlightening experience to discuss control issues with him, since his ideas were always marked by a great deal of common sense.

After his retirement, Dr Cap settled with his wife Julie in his native village. He remained interested in what was happening in the field of leprosy to which he had devoted his entire career.

He will be remembered as a man of wisdom by his friends and collaborators.

M. F. LECHAT & S. PATTYN

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Lepr Rev (1996) **67,** 338–344

Letters to the Editor

SUPPRESSION OF LYMPH NODE LYMPHOPROLIFERATION TO VIABLE *MYCOBACTERIUM LEPRAE* BY PERIPHERAL BLOOD-DERIVED MONOCYTES

Sir,

The presence of *Micobacterium leprae* reactive lymphocytes within the lymph node (LN) of lepromatous patients was convincingly demonstrated in our earlier study[1] without the use of any exogenous addition of lymphokines[2,3] or resorting to any *in vitro* manipulations, such as the depletion of suppressor cell populations[4] and/or using modified antigenic preparations of *Micobacterium leprae*.[5,6] It appears, therefore, that although antigen-specific cells are generated in the lymph node the inability to detect them in circulation[7] may either be due to a selective sequestration within the lymph node or due to differential handling of *M. leprae* within the two tissue compartments, namely peripheral blood (PB) and the lymph node.

The experiments designed to probe this aspect are comprised of the following: (a) depletion of monocytes by carbonyl iron (cFe) from blood and LN mononuclear cells (MNC); (b) determining the ability of LN lymphocytes to be suppressed by lepromatous PB-derived macrophage lysate; and (c) lymphoproliferation to viable *M. leprae* in a co-culture of PB monocytes with autologous LN lymphocytes.

The present communication demonstrates through co-culture experiments the exclusive suppressive function of PB monocytes as compared to lymph node (LN) adherent cells when presenting viable *M. leprae* to lymphocytes.

Twenty millilitres of heparinized PB and one inguinal LN (removed under local anaesthesia) were collected from each patient. Five lepromatous patients were included in the study. The LN of two of these patients were bacteriologicially positive (3+ and 5+) which the remaining 3 were negative.

The inguinal LN was divided into two, one part was fixed for histopathology while the other piece was dissected free of fat and gently rubbed on a fine wire mesh to obtain a single-cell suspension. The cells thus obtained were used in a lymphoproliferation assay.

Depletion of monoctyes by cFe (5 mg/ml) treatment was achieved by adding sterilized cFe to the mononuclear cell population and incubating the cells at 37°C for 1 hr with intermittent agitation. After incubation, they were again layered on lymphoprep. The cells which had ingested cFe settled to the bottom and were discarded, while those at the interphase were collected and used in the lymphoproliferation assay. Co-culture of PB-derived monocytes with autologous lymph node lymphocytes was undertaken as follows:

1×10^4 monocytes enriched on a Nycodenz–Monocyte gradient (Nyegaard & Co., Norway) were added per well of a flat-bottomed 96-well microtitre plate. Viable *M. leprae* (3×10^6 organisms/ml) or PPD (4 μg/ml) was added to the monocyte cultures. After 24 hr the cultures were washed and the nonadherent lymphocyte population was added at a concentration of 1×10^6 cells/100 μl. Cultures were maintained in 5% CO_2 atmosphere are 37°C for 5 days and assayed for lymphocyte proliferation.

Table 1. Effect of carbonyl iron (cFe) treatment on *M. leprae*/PPD stimulation of LN mononuclear cells from lepromatous patients

	CPM ± SE		LN	
Stimulation of cells	P2(BI-ve)	P3 (BI 5+)	P4 (BI-ve)	P5 (BI-ve)
Control	1331 ± 292	1565 ± 135	1522 ± 240	1305 ± 95
a. *M. leprae*	2784 ± 658	2968 ± 1258	3778 ± 141	3624 ± 282
b. PPD	44230 ± 3270	9773 ± 3935	31616 ± 975	—
After cFe treatment				
Control	1258 ± 180	1179 ± 85	969 ± 249	803 ± 57
c. *M. leprae*	2956 ± 136	4258 ± 411	3148 ± 430	2071 ± 144
d. PPD	3992 ± 456	4213 ± 555	8730 ± 65	—
a : c	N.S.	$P < \cdot 05$	N.S.	N.S.
b : d	$P < \cdot 01$	$P < \cdot 05$	$P < \cdot 02$	—

Lymphoproliferative response to M. leprae *in lepromatous leprosy patients*: An absence of a response to *M. leprae* was noted in the mononuclear cells derived from PB of lepromatous patients confirming earlier reports.[7] In contrast, mononuclear cells from LNs or these patients showed a significant response to viable *M. leprae* as reported earlier.[1] The stimulation index ranged from 2 to 4. No difference was observed in the extent of *M. leprae* reactivity in bacteriologically negative (BI-ve) patients (P_2, P_4, P_5) as compared to the bacteriologically positive (BI + ve) lepromatous cases (P_1, P_3).

Effect of cFe treatment on M. leprae/*PPD induced stimulation of LN mononuclear cells* (Table 1): To compare the role of macrophages versus other APC's in the LN, mononuclear cultures from LN were depleted of phagocytic cells by treatment with cFe and subsequently stimulated with *M. leprae*/PPD.

On cFe treatment the response to PPD was significantly reduced. However the response to *M. leprae* remained unaffected in 3 of the 4 patients studied.

Effect of L + -lysate on M. leprae *induced stimulation of lepromatous LN mononuclear cells* (Table 2): Earlier studies by Salgame *et al.*[9] had reported the presence of suppressor factors

Table 2. Effect of L + -lysate on *M. leprae* stimulation of LN mononuclear cells from lepromatous patient

	Mean cpm ± SE		
Stimulation of cells	P3 (BI 5+)	P4	P5
a. Control	1565 ± 135	1522 ± 240	1305 ± 94
b. *M. leprae*	2968 ± 1258	3778 ± 141	3642 ± 282
c. *M. leprae* + L + -lysate	1100 ± 157	2256 ± 683	1185 ± 377
P value b : c	N.S.	$P < 0{\cdot}05$	$P < 0{\cdot}001$
% suppression	63	41	68
After cFe treatment			
d. Control	1179 ± 85	969 ± 249	803 ± 57
e. *M. leprae*	4258 ± 411	3148 ± 430	2071 ± 144
f. *M. leprae* + L + -lysate	N.D.	637 ± 38	807 ± 74
p = value e : f		$P < 0{\cdot}05$	$P < 0{\cdot}001$
% suppresion		80	62

Table 3. Co-culture in lepromatous patients of peripheral blood-raleted monocytes (PB-Mo) with autologous LN lymphocytes in the presence of *M. leprae* / PPD.

	cpm + SE											
	PB-lymphocytes + PB-Mo			LN Lymphocytes + LN-Mo			LN lymphocytes			Ln lymphocytes + PB-Mo		
Patients	C	+ ML	PPD	C	+ ML	PPD	C	+ ML	PPD	C	+ ML	PPD
P1 (BI 3+)	1203 ±174	1419 ±216	N.D.	1182 ±282	4140 ±166	N.D.	1422 ±81	489 ±113	N.D.	849 ±179	800 ±85	N.D.
P2 (BI-ve)	1835 ±223	1459 ±202	16300 ±1300	1331 ±292	2784 ±658	44230 ±3270	626 ±125	1478 ±68	1646 ±228	1430 ±170	1612 ±171	4880 ±839
P4 (BI-ve)	1699 ±184	2182 ±512	89878 ±10466	1522 ±240	3778 ±141	31616 ±975	969 ±249	3148 ±438	8703 ±65	780 ±40	644 ±60	2474 ±164

(L + -lysate) from macrophages of lepromatous patients which significantly inhibited lymphoproliferative responses to *M. leprae*. To determine whether LN cells were sensitive to modulation by the suppressor factor, 200 μl L + -lysate (protein concentration: 200 μg/ml) was added to LN mononuclear cells stimulated with *M. leprae*. Substantial suppression of lymphoproliferation was observed to the antigenic stimulus. This indicates that the LN cell population is sensitive to suppression mediated by PB-derived macrophages.

Co-culture of (PB-Mo) with autologous LN lymphocytes in the presence of M. leprae/*PPD in lepromatous patients* (Table 3): Though substantial lymphoproliferation was seen when the total LN mononuclear cells were used, in co-culture with PB monocytes an absence of lymphoproliferative response was noted with viable *M. leprae* in spite of antigen reactive T cells being present within the lymph node. In contrast, significant lymphoproliferation was observed with PPD using a similar protocol. This suggests that PB monocytes but not LN macrophages are suppressive in the overt presence of viable *M. leprae* though they may be capable of normal functions with related antigens such as PPD.

Substantial early evidence of the suppressive function of PB macrophages with respect to viable *M. leprae* has been documented.[8,9] What is not known is whether tissue macrophages as reflected in this study by LN adherent cells also share similar suppressive function. When the entire cell population from the LN was used in the lymphoproliferative assay in this study, one would expect the *M. leprae*-laden macrophages to suppress the proliferative response. Despite that, we have observed significant stimulation with exogenously added viable *M. leprae*. In addition, even after depletion of the LN macrophages by cFe treatment the response to viable *M. leprae* was unaffected. Though this may imply non-participation of LN-derived adherent cells in the LN lymphoproliferative response, it also demonstrates that unlike the PB macrophages, they do not exert a suppressive function in the presence of viable *M. leprae*. The fact that the PB-derived macrophage lysate was suppressive indicates the sensitivity of the lymphoproliferation induced by cells of the B cell and dendritic lineage to suppression by peripheral blood-derived monocytes.

The central concept of immunosuppression in lepromatous leprosy therefore appears to involve the PB monocyte; since the tissue macrophages do not appear to be suppressive in the overt presence of viable *M. leprae*. Any attempt to restore immune function must take this fact into cognizance.

Acknowledgment

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THE EFFECTIVENESS OF CORTICOSTEROIDS IN THE TREATMENT OF LONG-TERM NERVE FUNCTION IMPAIRMENT

Sir,

There is indication that treatment with corticosteroids of patients with nerve function impairment (NFI) of long term duration (> 6 months) results in improved nerve function in a number of patients.[1] This finding in itself is important enough to warrant further well-controlled investigation. The potential for preventing (further) disability is significant while the risks of treatment are limited. In preparation of a possible randomized controlled trial we performed a pilot study, basically repeating the original study done by Moet & Rongong.

A total of 14 leprosy patients were selected with NFI of between 7 and 24 months duration from among patients in two leprosy clinics of the Danish-Bangladesh Leprosy Mission (DBLM) in NW Bangladesh. All patients except one were receiving MDT; the remaining patient was released from treatment. Each patient had a full nerve function assessment by a physiotechnician and was then given the standard dose of prednisolone used in the field (starting dose 40 mg/day, tapered off over 4 months). An assessment was made at the end of prednisolone treatment and results compared.

Sensory and motor loss was recorded on a special form which records each anaesthetic point on soles or palms as 1 point (max. 11 for soles, 12 for palms); corneal anaesthesia as 2 points; and 1 point for every step reduction in modified MRC grades for motor function in eye closure, little finger abduction, thumb abduction, wrist extension and foot dorsiflexion. In addition, eyelid gap on gentle closure was scored 1 point per 1-mm gap. Anaesthesia was tested using a ball-point pen. Zero indicates normality; increasing scores indicates increasing levels of nerve damage.

There were 13 males and 1 female with a mean age of 34·6 years (range: 20–60 years); 8 were MB and 6 PB. The mean duration of NFI was 16 months (range: 8–24 months). Seven patients had sensory and motor NFI; 6 patients sensory, and 1 patient motor NFI only.

Table 1 shows the results of nerve function testing before and after treatment with corticosteroids. 'Full' indicates return of nerve damage score to 0, i.e. no nerve function impairment; recovery was by at least 2 points in the nerve function score. 'Partial' indicates any recovery of

Table 1. Level of recovery of sensory and motor function

Level of recovery	Sensory No.	(%)	Motor No.	(%)
Full	3	(23)	3	(37·5)
Partial	4	(31)	1	(12·5)
Same	6	(46)	3	(37·5)
Deteriorated	0		1	(12·5)
Total	13		8	

function (2 points or more in nerve damage score); 'Same' indicates no significant change; and 'Deterioration' indicates further loss of nerve function (2 points or less in nerve function score). Table 2 shows the mean differences in nerve function scores before and after prednisolone treatment.

This pilot study was carried out with the aim of testing the hypothesis that prednisolone is effective in restoring nerve function in leprosy patients where the period of nerve damage exceeds 6 months. The results indicate that there is benefit, confirming the previous study undertaken in Bhutan.[1] A randomized controlled trial will be conducted to substantiate these results.

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COMMENT: DIVORCE AMONG SAUDI FEMALE LEPROTIC PATIENTS: AN EXPERIENCE AT IBN SINA HOSPITAL

Sir,

With reference to the Letter to the Editor published in *Lepr. Rev.* (1993) **64,** 163–73. It is appreciated that the authors have analysed the factors leading to divorces. They have rightly enumerated the factors that would decrease the length of hospitalization. It is also appreciated that they are concerned to decrease the number of divorces, this is shown in their efforts to arrange marriages in the hospital. However, I would like to mention the following points.

Observations made and conclusions drawn are that the single most important cause of divorce in those patients was a prolonged period of hospitalization, which leads me to presume that the actual or real cause of divorce is not the social stigma or hatred attached to the disease as in other parts of the world; but that the leprosy patients are well accepted by the family members and society at large.

What causes such long periods of hospitalization (from 0·5 to 4·5 years, Table 5) of leprosy patients when they are being cared for in the best possible place? The administering of supervised pulses without hospitalization is agreed and practised the world over. None of the indications for hospitalization causes a patient to be in hospital for 4·5 years. The only possibility that comes to my mind is that the same patient has been admitted and discharged several times for various indications over a period of many years (if it is, it is not mentioned by the authors), but that period too is quite long.

Another reason for hospitalization in Saudi could be to isolate the patients for better

compliance and management of the patient, but that too should not exceed 6–9 months for paucibacillary (PB) cases or 2–3 years for multibacillary (MB) cases. Also isolation is unreasonable in PB cases, so why hospitalization?

It would seem that the earlier detection of cases would help. The early detection, and prompt and regular treatment are the factors that can arrest leprosy, cure the patient, and prevent the complications that can make hospitalization necessary.

The authors have rightly enumerated the factors that will help them to not only decrease the duration of hospitalization but also avoid it. They must add to the list, the encouragement of the early detection of cases, and the training in leprosy of general duty doctors.

Of course, the role of social workers cannot be denied as it is they who can impart the health education for the removal of stigma and the importance of early and regular treatment.

Early detection, prompt and regular treatment should be given priority over other factors to decrease the length of hospitalization.

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Lepr Rev (1996) **67,** 345

Book Review

Biopsy of skin lesions in leprosy. Stains, Pathogenesis and Classification. **K. Harada**

This is a funny thing indeed. The title and appearance (A5 white booklet) looks similar to the publication of Dennis Ridley 'Skin biopsy in leprosy'. That went through 3 editions (the last in 1990), published by Ciba-Geigy, and covered synoptically the immunopathological spectrum of leprosy which Ridley (and Jopling) had so brilliantly conceptualized; the various patterns of dermatopathology of leprosy were discussed systematically and well illustrated; the standard staining methods and useful immunocytochemistry were covered, as was differential diagnosis.

Frankly, it would have better if the present production had been smothered before birth. The author is notable for contributing a useful additional staining method for leprosy bacilli—the periodic acid carbol pararosanilin stain—which helps detect degenerate bacilli that have lost acid fast-ness. Nearly one third of the booklet concerns the staining of acid-fast bacilli (historical, comparative, and illustrated in colour); but this is quite out of proportion, and most of the illustrations are of obviously multibacillary leprosy cases. No help with sorting out a problematic non-bacillated granulomatous dermatitis will be found here. The booklet cannot have been proof-read by a fluent English speaker, and the syntactic and spelling mistakes are innumerable. And does the phrase 'The indeterminate patients appear ''versine'' [sic] in the immune response for *M. leprae*...' (p. 51) mean anything, or is it another misprint?

The first section describing the range of histopathology of determined and early leprosy is jumbled without subheadings, includes ENL but not delayed hypersensitivity reactions, and confusingly introduces a novel subclassification of BB leprosy. Two tables (slightly different) are printed listing the histological features as they reflect the Madrid, Ridley–Jopling, and Harada's own, classifications. Under pathogenesis, the author holds the view that nerve Schwann cells evolve into epithelioid cells when infected by *M. leprae*—quite why is unclear. Tuberculosis is compared with leprosy histopathogenetically, but absent features include a proper account of differential diagnosis, the role of immunocytochemistry, DHRs and the bacterial index.

In summary, pathologists seeking assistance in their diagnostic work, whether they see frequent or only occasional specimens, will not find this booklet useful. Leprosy workers seeking a scientific background in their activities will be confused.

S. B. Luas

NEC Documents, Tokyo, Japan, 1995. 72pp

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Teaching Materials and Services

ALERT (All Africa Leprosy and Rehabilitation Training Centre: Courses in 1997)

Jan 13–Feb 21 Prevention and Management of Disabilities
Course aimed at qualified physiotherapists and occupational therapists as well as experienced leprosy workers involved in the prevention and care of disability. Emphasis on POD programme management and disability problem solving.
March 3–March 14 Introduction to Leprosy for Physicians
Although this course can be taken on its own, it is specifically aimed at the participants in the following 'Management of Combined Programmes' course who want to refresh their knowledge of clinical leprosy and the management of individual leprosy patients.
March 10–March 14 Introduction to Tuberculosis for Physicians
Although this course can be taken on its own, it is specifically aimed at the participants in the following 'Management of Combined Programmes' course who want to refresh their knowledge of clinical tuberculosis and the management of individual tuberculosis patients.
March 17–April 11 Management of Combined Leprosy and Tuberculosis Control Programmes for Physicians
Course aimed at experienced physicians responsible for managing a leprosy and tuberculosis control programme, preferably at the regional level or above. Participants are urged to enrol in one of the preceding introduction courses (either leprosy or tuberculosis according to their need), in order to be properly prepared for the management course.
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Course aimed at senior staff involved in human resource development. Emphasis on curriculum planning, learner centred teaching methods, appropriate teaching tools and course assessment.
May 5–May 16 Essentials of Leprosy and Tuberculosis for Administrative and Programme Support Staff
Course aimed at non-medical managers and administrative staff working in leprosy and TB programmes or donor agencies. Objectives: to gain a better understanding of the two diseases, to communicate more efficiently with the medical staff and to contribute more effectively in decision making and priority setting.
June 2–June 20 Tropical Dermatology for Physicians
Course aimed at physicians with experience and/or special interest in the diagnosis and management of skin diseases in Africa. Leprosy and its differential diagnosis will receive due attention.
June 23–July 11 Dermatology for Nurses and Other Paramedical Staff
Course aimed at clinical staff other than physicians, responsible for diagnosing and treating dermatological conditions. Leprosy and its differential diagnosis will receive due attention.
Sept 1–Oct 10 Essentials of Leprosy and Tuberculosis for Physicians
Introductory course aimed at physicians with limited experience in either leprosy or TB. Emphasis on clinical aspects and programme management.
Oct 20–Oct 31 Introduction to Leprosy for Senior Field Staff
Although this course can be taken on its own, it is specifically aimed at the participants in the following

'Management of Combined Programmes' course who want to refresh their knowledge of clinical leprosy and the management of individual leprosy patients.

Oct 27–Oct 31 Introduction to Tuberculosis for Senior Field Staff

Although this course can be taken on its own, it is specifically aimed at the participants in the following 'Management of Combined Programmes' course who want to refresh their knowledge of clinical tuberculosis and the management of individual tuberculosis patients.

Nov 3–Nov 28 Management of Leprosy and Tuberculosis Control Programmes for Senior Field Staff

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- consultation and technical support
- publication of learning resources and materials and maintenance of a resource library.

The School obtains funds through tuition fees, consultants' fees and contractual arrangements with WHO and other organizations. The WHO Regional Training Centre receives an annual grant from the Commonwealth Department of Human Services and Health (International Health).

Further information: School of Medical Education, The University of New South Wales, Sydney 2052, NSW, Australia. Fax: 61 2 385 1526.

Tropical Health Technology

Tropical Health Technology is a nonprofit organization formed to assist developing countries in the field of tropical medicine by providing low priced up-to-date publications, learning aids and microscopes.

For further details please write to: Tropical Health Technology, 14 Bevills Close, Doddington, March, Cambs PE15 0TT, UK. Fax: 44 1354 740 013; Tel: 44 1354 740 825.

Free books from: Italian NGO Amici de Raoul Follereau (AIFO)

AIFO has the following publications available free of cost:
Community-based rehabilitation: country experiences, Human mycosis in tropical countries, VI symposium on leprosy research, Disability & Developing countries: which rehabilitation, Health laboratories in developing countries, Leprosy control in developed countries, Innovations in developing countries for persons with disabilities.

Anyone wishing to receive any of these should write to: AIFO, Via Borselli No. 4, Bologna 40135, Italy. Fax: 39 51 43 40 46; email: aifo@iperbole.bologna.it.

Leprosy; basic information and management (Ciba-Geigy) now in Chinese

Dr Hsu-Mei Hsu, Deputy Director, *Bureau of Communicable Disease Control, Department of Health,* The Executive Yuan, 100, Al Kuo Road, Taipei, Taiwan, ROC, has recently sent copies of the above Ciba-Geigy booklet, translated into Chinese. The original aim of this booklet (43 pages) was to provide basic information in relatively simple terms for nonmedical readers, including community readers, social workers, teachers, students and journalists. It has also been found acceptable to some grades of paramedical workers and nurses. Since the first edition in 1987, many thousands of copies have been distributed worldwide and translations made in French, Spanish, Indonesian, Bengali and Urdu. The new translation in Chinese has already been distributed to 5000 workers in Taiwan in health bureaux, leprosy institutes, dermatologists and hospitals. Copies are available from Dr Hsu-Mei Hsu at the above address.

Geographic Information Systems

Geographic Information Systems (GIS) based on mapping from space satellites are being increasingly used in international public health to define the spatial relationships between disease distribution, health care systems and environmental factors. They enable information from one sector (such as safe water

supply, or education) to be combined with information from other sectors (such as health) to provide a comprehensive picture of the situation in a given community, district or country. This makes it easier to set priorities for control and surveillance activities, to plan effective control strategies and to conserve scarce resources.

Of particular interest to LEP is computerized mapping, whereby the distribution of 'pockets' of leprosy prevalence not yet fully covered by MDT can be instantly visualized and monitored. Inventories of comparable geographical data such as administrative boundaries and the location of villages can be made available for each selected country, with related databases comprising health infrastructure, disease indicators and so forth.

To take one example of its use: suppose we need to know the density of patients and the coverage with MDT in a given country. The data sent in by each leprosy unit concerned will be stored and updated at least once a month. In India alone, there are 64,000 leprosy points, so not all of them will have sent data. But those which have will suffice to give an immediate picture of the current situation throughout that country. The network will in effect provide a map of the epidemiology of leprosy, essential for accurate monitoring of the progress towards elimination.

Source: *LEPNews*, Vol. 5, No. 1, 1996, WHO, Geneva.

CMB/LEPRA Ophthalmic Course, Karigiri, India, 1996

The eleventh annual five-day ophthalmic teaching module was held at the Schieffelin Leprosy Research and Training Centre, Karigiri from 4 to 9 March 1996. The course, which was again sponsored jointly by the Christoffel Blindenmission and LEPRA, was designed to give instruction to leprologists on the detection, prevention and management of the ocular complications of leprosy by means of a series of lectures and videos, clinical and surgical demonstrations and a field trip.

Teaching included presentations on basic anatomy, physiology and pathology of the eye with special emphasis on leprosy: in addition there were lectures on the clinical signs and management of lagophthalmos, corneal ulcers, intraocular inflammation and infiltrative lesions, together with discussions on 'high risk eyes', ocular manifestations of relapsed disease, rehabilitation and the global aspects of blindness in leprosy.

The course, which was attended by fifteen participants working in India, Bangladesh and Thailand, was organised and run by Dr Margaret Brand of The Leprosy Mission, Dr Ebenezer Daniel of Karigiri and Mr Timothy ffytche from St Thomas's Hospital, London together with the assistance of several members of the staff of the Centre.

The Director of Karigiri, Dr P. S. S. Sundar Rao, is to be thanked for his continued support for this important and popular contribution to teaching.

Lepr Rev (1996) **67,** 350–356

News and Notes

TDR: Four TDR diseases, including leprosy, can be 'eliminated'

The following is extracted from the March issue of *TDR News*, 1996:

The means are now available to 'eliminate' four of TDR's original eight target diseases as public health problems (meaning reducing the cases of the diseases to a small and routinely manageable number), a TDR expert meeting has concluded.

This is a wonderful success for the Programme—and the world—but, interestingly, in no case did the tools arise out of TDR-sponsored basic research. Rather, they arose from TDR's judicious and timely use of large-scale, multicountry field trials of largely pre-existing drugs and simple control tools, combined with cost-effective epidemiology. The trials sharpened evidence of the tools' effectiveness and impact, identified or confirmed the best combinations of different tools, improved means of delivery and implementation, and, not least, generated an international consensus on intervention.

Basic research is likely to bring still greater benefits—such as anti-parasite vaccines or genetically disabled vectors—but only in the longer term, even in the case of the most advanced candidates. Meanwhile, however, basic science is making 'spin-off' contributions towards elimination in providing cheap and simple diagnostics, such as dip-sticks for detecting Chagas infection in blood banks, and a recently-developed day-time fingerprick test for lymphatic filariasis (where night-time blood samples were once required).

The diseases slated for elimination with existing tools are leprosy (using multidrug therapy), onchocerciasis (ivermectin), lymphatic filariasis (DEC and ivermectin) and Chagas disease (rational use of insecticides and control of blood banks), leaving malaria, schistosomiasis, leishmaniasis and African trypanosomiasis awaiting better tools.

TDR's contributions to leprosy included mapping and quantifying growing dapsone resistance (the lifelong monotherapy of the 1970s), developing clinical protocols for dapsone's great successor—miltidrug therapy (MDT)—and establishing large-scale 'post-marketing surveillance' of MDT. Now, WHO and partner organizations are well on their way to their target of reducing leprosy to one case per ten thousand population in each affected country by the year 2000.

From the same issue we reproduce:

Leprosy: from elimination to eradication?

Through the increasingly widespread distribution of multidrug therapy (MDT), and its effectiveness, the prevalence of leprosy (measured by numbers of registered cases) has been reduced from 5·4 million cases in 1985 to 1·3 million in 1995.

But there is much work still to do to reach the target of the 1994 'Hanoi Declaration'—the reduction in prevalence (registered cases) to one in 10,000 people in each endemic country by the year 2000. Countries numerically furthest from this ratio in 1995 were Brazil (10 per 10,000), Chad (10), India (9), Mozambique (9) and Nepal (8). Moreover in 1995, only 75% of those registered were receiving therapy, with treatment ratios worst in Africa. The largest total numbers of untreated registered cases are to be found in India (around 200,000) and Brazil (60,000).

And there is a further gap between the numbers registered and the estimated actual number of cases; this number of undetected cases is believed highest (in total) in India (150,000) and Bangladesh (120,000), with the proportion worst in Bangladesh, Indonesia, Vet Nam, Mali, Niger and Sudan. Globally, it is estimated that some 600,000 to 1 million cases escape detection.

The number of cases actually detected and registered per year has remained roughly constant for ten years, and stood at around 530,000 in 1995; it reflects a difficult-to-estimate combination of true incidence rates, delays in diagnosis, specificity and sensitivity of diagnosis, self-healing rates—and of the efficiency of control programmes.

However, recent studies suggest that only 10% of these newly detected cases are true incidence cases (new infections of that year); 75% started 3–5 years earlier and 15% as much as 5–10 years before.

Moreover, Special Action Projects for the Elimination of Leprosy (SAPEL) have been launched to accelerate MDT coverage in hard-to-reach areas (such as among forest workers and fishermen in Amazonas in Brazil, and nomads in eastern Chad). Other campaigns are being conducted to detect 'hidden leprosy cases of consequence' (hidden highly infectious cases); and officers of the WHO Action Programme for the Elimination of Leprosy (APEL) believe that, with the current determination being demonstrated among countries and NGOs, the goal of the Hanoi Declaration is achievable.

The success of this elimination strategy may then lead to a desire—in some areas of the world—to totally eradicate the disease from these areas. This would require epidemiological surveillance and treatment of the small numbers of cases that may continue to occur, and, most importantly, surveillance of sub-clinical infection, and effective interventions to abort those infections.

This work would require new tools and new research, including a diagnostic test for sub-clinical infection. The most important consideration in the development of such tools, according to APEL, will be cost-effectiveness—which implies simplicity, affordability and acceptability to the whole community. Research is also needed on the rehabilitation and re-assimilation into the community of nerve-damaged and disabled patients.

Source: *TDR News*. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, WHO, 1211 Geneva 27, Switzerland.

Yemen makes progress in reducing the transmission of leprosy, WHO

The following is extracted from *LEPNews*, December 1995:

As in most countries, leprosy in Yemen has a long and unhappy past history. It is even recorded that, many centuries ago, one ruler collected large quantities of wood with every intention of solving the leprosy problem by burning the patients on a funeral pyre. Fortunately he died before carrying out this drastic 'cure'.

Even today, it is common for victims of leprosy to be obliged to get a divorce and be isolated from their own families; the moment the disease is diagnosed, they are considered socially dead. As recently as 1964, they were forced to live in unsanitary leprosaria.

Now a more enlightened attitude is spreading as the word gets about that leprosy is indeed curable by MDT. The country's case-load of leprosy has declined from a peak of 2314 registered cases in 1989 to 828 at the end of September 1995; 84% of these cases were multibacillary. Between January and September this year, 291 new cases were detected.

In 1992, an NGO called the Yemen Leprosy Elimination Society (YELEP) was formed to further the activities of the National Leprosy Control Programme (NLCP) and to provide material, financial and technical support to patients, including rehabilitation for former sufferers. Both the national programme and the NGO still face constraints; the stigma of leprosy continues even among health workers, control activities are not yet integrated in the health care infrastructure, and poor communications and difficult terrain impede the activities of field supervisors.

Nevertheless, the attitude of the community towards leprosy is gradually changing, thanks to intensive health education activities (including regular newspaper features and the screening of a special

TV programme on the disease each year since 1990). National health planners are confident that transmission of leprosy in Yemen will have been effectively halted within the WHO time-frame by the year 2000.

Source: *LEPNews*, WHO Action Programme for the Elimination of Leprosy, 1211 Geneva 27, Switzerland.

Mexico intensifies its strategy for the elimination of leprosy at sub-national level

Having already achieved the elimination of leprosy (less than 1 case per 10,000 of the population) at national level, Mexico has now developed plans for the intensification of activities at state, health department and municipal levels. The State of Sinaloa in the western Pacific coastal area is due to start such activities in June 1996 and to pursue them intensively for 6 months, with the following main objectives: 1, discovery and treatment, to the maximum extent possible, of all hidden or occult cases; 2, examination of contacts of all registered cases; 3, identification of areas of high incidence and prevalence, with intensification of case-finding activities, including school children above the age of 9 years; and 4, orientation and basic training of health staff in peripheral health units in the recognition and referral of possible cases of leprosy, management of multiple drug therapy, and disability prevention.

It is anticipated that this intensive 6 months' project will reveal several hundred new cases (never treated before) and plans are already being made for similar activities in three other states in Mexico with relatively high prevalence. Sinaloa, for reasons which are far from clear, is currently the only state in the country with a prevalence of more than 1 case per 10,000; the figure is 4·9. It may be relevant that its population (2·5 million) has a high proportion of people of Chinese, Japanese, Philippine and European (mainly Spanish) origin, with a high degree of racial mixing, and from an epidemiological point of view the finding of numerous cases of Lucio leprosy ('smooth leprosy'; 'lepra bonita') could be of considerable importance; many of these cases are asymptomatic for long periods before diagnosis; do not develop nodules and frequently have little to show clinically except madarosis, despite positive smears at all sites.

Having done all possible, using an intensified, short-period approach, at health department and municipal levels in the above 4 states, attention will be given to any remaining areas or pockets with significant numbers of cases in other parts of the country. Rehabilitation centres with orthopaedic workshop facilities have been established in 18 endemic areas, with considerable help from Ciba-Mexicana and the Ciba-Geigy Leprosy Fund in Switzerland and these agencies have recently supported the printing and distribution of a revised edition of the *Manual of Procedures for Leprosy Control*, written by the Health Secretariat. In 1986, Mexico had 16,687 registered cases with a prevalence rate of 2·1/10,000. By March 1996 this had fallen to 5005 with a prevalence rate of 0·5/10,000. The control programme has exceptionally strong medical and political support and the prospects for still further reduction in prevalence, at sub-national level, are apparently excellent.

TB deaths reach historic levels, WHO

The following is taken from WHO Press Release, March 1996, WHO/22:

More people died from tuberculosis in 1995 than in any other year in history, according to a report released today by the World Health Organization. According to WHO, nearly three million people died from TB in 1995, surpassing the worst years of the epidemic around 1900, when an estimated 2·1 million people died annually (see Figure 1 below).

The WHO warned that the TB crisis will continue to grow unless immediate action is taken. At current rates, up to a half-billion people could become sick with TB in the next 50 years. Increasingly, these people may become sick with often-incurable miltidrug-resistant TB.

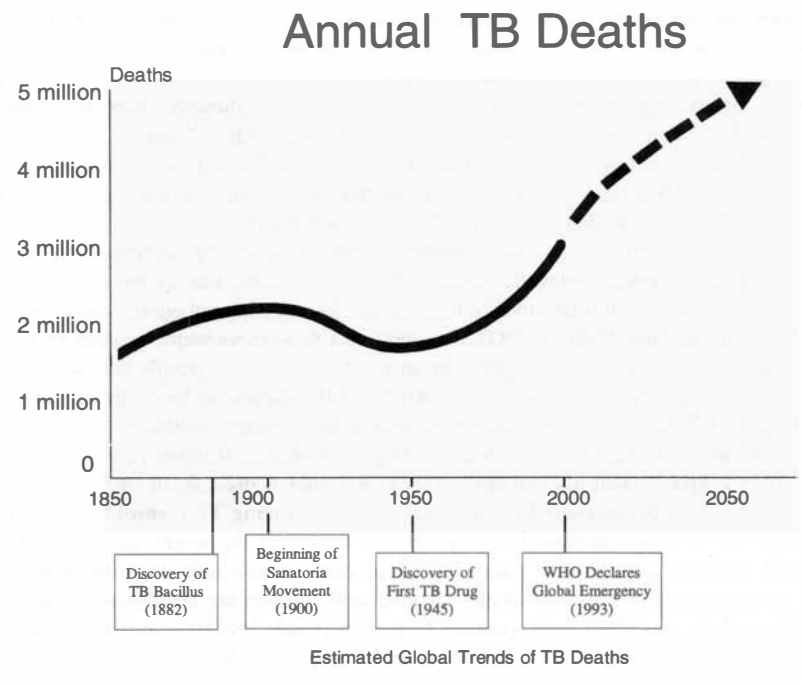

Figure 1.

'Not only has TB returned, it has upstaged its own horrible legacy,' said Dr Hiroshi Nakajima, Director-General of the World Health Organization.

According to the WHO report, entitled 'Groups at Risk', TB has increasingly assailed all segments of society. TB is now the leading infectious killer of youth and adults. It has become the principal killer of HIV-positive people and kills more women than all causes of maternal mortality combined. Nearly half of the world's refugees may be infected with TB. It is likely that no other infectious disease is creating as many orphans and devastating as many families.

'There is nowhere to hid from tuberculosis bacteria,' warned Dr Arata Kochi, director of the WHO Global TB Programme, 'Anyone can catch TB simply by inhaling a TB germ that has been coughed or sneezed into the air. These germs can remain suspended in the air for hours; even years. We are all at risk.'

TB has returned with a vengeance to wealthy countries, as increased air travel and migration have helped transport the disease throughout the world. Miltidrug-resistant TB, which has cost New York City hundreds of millions of dollars to fight, has now been reported in London, Milan, Paris, Atlanta, Chicago and cities throughout the developing world. In particular, the number of multidrug-resistant cases in Asia are expected to increase rapidly, unless TB control efforts are strengthened.

'The world is becoming smaller and the TB bugs are becoming stronger,' said Kochi, 'While international travel has increased dramatically, the world has been slow to realize the implications for public health. Only recently have wealthy governments begun to recognize that poor TB treatment practices of other countries are a threat to their own citizens.'

According to the WHO report, unprecedented levels of neglect during the 1970s and '80s helped to create this situation. In 1993, WHO declared a global TB emergency, prompting some governments to increase their response to TB. However, the TB epidemic continues to outpace these modest efforts.

'The scientists have done their part to help rid the world of TB' said Dr Kochi. 'But the politicians have yet to put these tools to use. The TB bacillus was discovered over a hundred years ago, and

medicines that can cure nearly every TB patient have been available for the past fifty years. But these tools are not being widely or correctly used. Many TB treatment programmes are so poorly supported that they are producing stronger bacteria and weaker patients.'

The World Health Organization endorses a strategy known as directly observed treatment, short-course, or 'DOTS', which has proven successful in fighting TB. Countries that follow WHO's recommended DOTS strategy, such as Tanzania, China, and Peru, have discovered that they can double the number of TB patients cured. The DOTS strategy can cure nearly 95 percent of TB patients, using medicines that cost less than $11 in some parts of the world.

The secret to the success of the DOTS strategy is that it places the responsibility for curing TB patients on the health workers—not the patients. The TB epidemic has spread rapidly over the past decades because patients often forget to take their medicines, remain contagious, and continue to infect others in their communities. With the DOTS strategy, health workers watch as patients swallow their medicines and tracks each patient's progress, ensuring that contagious people are cured.

According to WHO, only 10 percent of the world's TB patients are being treated with the DOTS strategy. If the DOTS strategy were used throughout a dozen large countries—such as Bangladesh, Brazil, China, Ethiopia, India, Indonesia, Mexico, Nigeria, Pakistan, Russian Federation, South Africa, and Zaire—nearly three-fourths of the world's TB cases could be cured. As of 1995, only a few of these countries had aggressively committed to establishing and expanding TB control based on DOTS.

'The longer we wait to establish DOTS programmes around the world, the more expensive TB treatment will become, and the less likely it will be that we will ever stop this disease,' said Dr Nakajima. 'In the meantime, millions of men, women and children are needlessly dying.'

'The TB epidemic must be fought globally to protect people locally,' said Dr Kochi. 'It is in the interest of wealthy countries to help less-developed countries fight tuberculosis, before their own countries become the battleground.'

The World Health Organization is releasing this report prior to World TB Day, 24 March. World TB Day commemorates the day in 1882 when Dr Robert Koch officially informed the scientific community that he had discovered the TB bacillus. Yet Koch's discovery and the effective drugs that were later developed have seen limited use. As a result, TB has sent at least 200 million people to their graves since 1882.

For more information, contact Kraig Klaudt or Colin Martin in London (21 March only) at (44) 171-798-4217 or Courtenay Singer or Richard Bumgarner in Geneva at (41) 22-791-2189 or (41) 22-791-4641.

Hepatitis A, B, C, D and E

In view of the fact that several of the drugs used for the treatment of both leprosy and tuberculosis may be hepatotoxic, the following information on the terminology and clinical effects of the various forms of viral hepatitis may be of interest. It is extracted from a '*Workshop on Hepatitis C Virus*', an account of which was published in the *Proceedings of the Royal College of Physicians of Edinburgh*, October 1995, Volume 25, Number 4, pages 583–622.

From the *Introduction* by the Editors:

'Older readers will remember that their textbooks in the 1930s contained a section on catarrhal jaundice which was distinguished from obstructive and haemolytic jaundice. The cause of the catarrh was unknown. The single diagnostic label was soon replaced by two, infectious hepatitis and serum jaundice, the latter being a common condition in patients being treated for syphilis with intravenous injections. When means were discovered for isolating and identifying viruses, these conditions were found to be due to separate viruses, hepatitis A and B (HAV and HBV). A third distinct virus with an affinity for the liver was yellow fever virus. Other identified viruses are hepatitis C virus (HCV), hepatitis D (HDV) and hepatitis E virus (HEV).

Yellow fever virus is spread by an arthropod vector from a pool of infection which still persists in

some jungle primates. HAV and HEV infection is spread from case to case by the faecal-oral route. Infection by HBV is transmitted via intimate (usually sexual) contact or parenteral injection through a contaminated needle or transfusion fluid. HCV is rarely transmitted by sexual contact, occasionally by needle stick injury but usually by infusion fluid.

There is extreme variation in the clinical manifestations of infection with hepatic viruses. A self limiting attack of fever with jaundice is the common presentation with yellow fever and with HAV and HEV infections, but is often absent with HBV and HCV infection. A fulminating, usually fatal, hepatitis is common in yellow fever, very rare with HAV, HCV and HEV, a well known tragedy with HBV infection. A persistent inflammatory response, with or without the continuing presence of virus, leading to cirrhosis and carcinoma is the main clinical feature of HCV infection and common in HBV infection. It is rare, if it ever occurs, in yellow fever or in HAV infection. Hepatitis D virus is strongly related to intravenous drug use but has similar epidemiological and clinical features to HBV with which it is often associated in time. In the immunocompromised patient, as with AIDS, the liver may be affected by other viruses, in particular cytomegalovirus, herpes simplex virus, measles virus in adults and Coxsackie virus B, all of which may give rise to hepatitis in occasional individuals.'

From a section entitled '*Historical Perspective*' under the heading '*Epidemiology of Hepatitis C*': 'In the 1960s, in Washington in the USA, a recipient of a blood transfusion had a 1 in 3 chance of developing post-transfusion hepatitis. In 1970 two things changed. Firstly, testing for hepatitis B became available, which reduced post-transfusion hepatitis by about 50%. Secondly, the blood donor service moved to an all-volunteer programme with a further significant reduction in hepatitis amongst recipients. In the 1980s, donors with raised ALT levels were excluded, but a rump of post-transfusion hepatitis cases remained. When testing for hepatitis C became available it became clear that 95% of non-A, non-B hepatitis was due to hepatitis C.

In 1982, the Centre for Disease Control, Atlanta, set up a 'Sentinel Counties Study', looking into the risk factors for non-A, non-B hepatitis in sporadically occurring cases in the community. It soon became apparent that transfusion only accounted for 3% of such cases and in approximately 50% no risk factors could be identified. In the first year of this study, 13% of cases were associated with intravenous drug abuse, but by 1988 this figure had risen to over 40%. When second generation assays for HCV antibody became available, retrospective testing confirmed that HCV was responsible for 100% of cases acquired through intravenous drug abuse. In 1988, no source of infection could be identified for approximately one third of cases, and HCV was only identified in 52% of these. It should be noted that when testing for anti-HCV in patients with acute non-A, non-B Hepatitis, sufficient time must be allowed to elapse for seroconversion to take place. For example in one study only 10 of 20 (50%) patients who developed non-A, non-B hepatitis following blood transfusion and were tested within 6 weeks of the onset of illness, were found to be anti-HCV positive, compared to 19 of 25 (76%) who were tested 6 months after the onset of illness.'

Chemotherapy of leprosy. Report of a WHO Study Group

The above booklet of 24 pp. is from the WHO Technical Report Series, No. 847 and was published in 1994:

Since the introduction of standardized multidrug therapy (MDT) for leprosy in 1981, over 5·6 million patients have been cured and the number of cases has been reduced by two-thirds. Although most countries are now aware of the critical role of MDT in leprosy control, there is still some uncertainty about the efficacy and optimum duration of such regimens.

The report contains the recommendations of a WHO Study Group on Chemotherapy of Leprosy, convened to review the performance of WHO's multidrug therapy regimens for paucibacillary and multibacillary leprosy. Intended for managers of leprosy control programmes, the report has five sections. The first reviews findings from several studies of leprosy chemotherapy involving large numbers of patients. The second section summarises accumulated data on the safety, efficacy, optimum

doses and costs of available antileprosy drugs. Recommended chemotherapeutic regimens are presented in the third section. The report concludes with practical advice on operational issues relevant to the quality of control programmes and reviews prospects for the development of new drugs.

Available in English, French and Spanish from: World Health Organization, Distribution and Sales, 1211 Geneva 27, Switzerland. Price: Sw.fr.6/US$5.40, and in developing countries Sw.fr.4.20.

Leprosy data on-line through the Internet

Essential information about leprosy and the efforts around the world to eliminate it are already available to everyone whose computers are plugged in to the Internet. WHO's Action Programme for the Elimination of Leprosy ensures that regularly updated statistics on the global burden of the disease can be brought on screen, as well as a brief summary of the situation in the major endemic countries.

LEPNews itself will be available on the net as soon as it is published. Other specific pages include: the disease and its treatment, the WHO Programme and its strategy for elimination, the most endemic countries, the Leprosy Information system, MDT drug supply monitoring and relevant publications.

Users need only to connect to the INET link http://www./who.ch/programmes/lep/lep_home.htm.

Source: *LEPNews*, Vol. 5, No. 1, 1996, WHO, Geneva, Switzerland.

IV Congress of the College of Hansenology of the Endemic Countries/IX Congress of the Brazilian Association of Hansenology, 4–8 June 1997, Foz do Iguaçu, Brazil

Topics to be covered: Elimination day: Diagnosis and treatment, Research methodology, and Social and educational aspects.

Conferences: Therapeutics, Immunology, Genetics, Rehabilitation, Elimination, and Neural lesions.

Seminars: Treatment, Reactions, Immunology, Epidemiology, Social Aspects, and Elimination.

For further details write to: Secretaria Executiva, IN TIME Promoções e Eventos Ltda, Av. Paulista, 2073 Horsa I cj 501 - CEP 01311–300 São Paulo, SP, Brazil. Tel: 55 11 285 5549; Fax: 55 11 283 5409.

Leprosy Review posters: ENL

The A3 poster enclosed with this issue of *Leprosy Review* is the second in a series of four covering important areas of management and research in leprosy and is distributed free to subscribers to the Journal.

We hope subscribers will find these posters informative and useful. Displayed prominently in clinics, they should serve as a useful teaching resource and aide memoire for all those involved in the treatment of leprosy and its reactions and in prevention of disability work.

We would welcome feedback and comments (to the Editor please) on this series and suggestions for future topics. Additional copies of the poster in this issue and those in future issues will be available from LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England.

Erratum

Development of life-threatening thrombocytopaenia in a patient on MDT and prednisolone. R. CROFT, Letter to the Editor, *Lepr Rev* (1996) **67**, 229. Please note that the author of the above Letter to the Editor is R. CROFT and not as printed.

paragraph 3, line 3 for 'crushingoid' read 'cushingoid'

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Instructions to Authors

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

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

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

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