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Leprosy Review

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

LEPRA

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

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

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Lepr Rev (1997) **68,** 293

Editor's Choice

Leprosy chemotherapy is again a topical issue. Over the last 15 years multidrug therapy (MDT) has been widely and successfully implemented. Now important changes are occurring since the executive report of the 7th WHO Expert committee on Leprosy (Geneva, 1997) gave individual countries the option of implementing two major alterations to current treatments: first, treating monolesion cases with a single dose triple antibiotic combination, rifampicin, ofloxacin and minocycline (ROM), and second reducing the duration of multidrug treatment for multibacillary cases from twenty-four months to twelve months. In this issue we highlight these changes with an editorial by Colin McDougall reflecting on leprosy chemotherapy. This reminds one of the confusion of the pre-MDT days and the benefits of MDT for individuals and leprosy programmes although these benefits were not instantly recognized. It is very important to assess the newer drugs and shorter regimens carefully and be sure that they do represent both clinical and operational improvements. For this reason we have reprinted the ROM trial report from the *Indian Journal of Leprosy* together with an editorial appraisal of the trial. I hope these data will help readers to decide how best to use ROM.

Many aspects of the transmission of leprosy are still poorly understood and the paper by Ian Cree and colleagues in which they combined using a nasal PCR to detect *Mycobacterium leprae* DNA and mucosal challenge to assess mucosal immunity to *M. leprae* shows that both carriage of *M. leprae* DNA and local immunity can be transient events. However it does indicate that encountering and responding to *M. leprae* is not uncommon in the tropics.

This Issue has a very active letter section with continuing debate over the optimum monofilament to use for detecting nerve damage and an interesting contribution from Mumbai on drug treatment in India.

The Internet is fast becoming part of all our lives and I am grateful to John Gilbody for his useful article on how to access the Net and where to find leprosy-related articles. The contents page of *Leprosy Review* is now posted on the Lepra web site and we hope to be putting the full text of editorials up as well. Do visit the Lepra site (http://www.lepra.org.uk) and let us know how you would like to see the electronic version of the journal.

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Lepr Rev (1997) **68,** 294–298

Editorial

RECENT DEVELOPMENTS IN THE CHEMOTHERAPY OF LEPROSY

The use of chaulmoogra (hydnocarpus) oil may well be regarded as the first step towards effective chemotherapy for leprosy. Although an ancient remedy, it began to attract attention in medical circles in the second half of the nineteenth century, following the first comprehensive description of its use for leprosy by Mouat,[1] a surgeon in the Bengal Medical Service, in 1854. It was used fairly extensively in the first few decades of this century, but the pain caused by its administration, coupled with reports of relapse in many patients, were disconcerting and by 1941 its use had markedly diminished. In the late 1930s however, a number of chemical compounds were under development for streptococcal infections, including sulphonamides and chemically-related sulphones. Working in the National Leprosarium at Carville, Louisiana, USA, Faget first tried sulphanilamide in a group of patients, but without success. His later use of Promin (glucosulphone sodium) gave impressive results[2] and this led to the use of two other compounds, Diasone (sulphoxone sodium) by Edwin Muir and sulphetrone by Frank Davey (a former editor of this journal), both of whom reported good results. It was however dapsone, a compound synthesized by Fromm and Whittmann in 1908 and used for the treatment of streptococcal mastitis in veterinary medicine, which attracted the attention of Robert Cochrane in 1945 and very soon achieved widespread use, giving rise to the hope that it would not only cure or arrest the disease in individual patients, but also lead to the control of leprosy by mass use in endemic areas.

Dapsone achieved cure or arrest of the disease in hundreds of thousands of patients and probably helped to reduce the spread of bacilli in communities where it was used, but it failed in the above objectives for two main reasons. First, health services and leprosy control programmes as we understand them today were either poorly developed or nonexistent. Second, bacillary resistance to dapsone was revealed by WHO and other agencies from the 1960s onwards to be widespread and increasing in many parts of the world. Partly to offset this situation, other compounds were added to dapsone in the 1970s, including the pioneering combination of dapsone, isoniazid, prothionamide and rifampicin by Freerksen and colleagues in an eradication programme in Malta.[3] However, by the time of the *XI International Leprosy Congress in Mexico* in November 1978, the situation generally with regard to the chemotherapy of leprosy was almost chaotic and it was clear that radical changes were needed. Apart from the spectre of increasing dapsone resistance (coupled with fears about the longer-term significance of organisms persisting despite apparently adequate courses of treatment), the number of drugs in use and the bewildering range of combinations, was alarming. It included dapsone, acedapsone, rifampicin, clofazimine,

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prothionamide/ethionamide, isoniazid, thiacetazone, thiambutosine and long-acting sulphonamides. More than one experienced observer commented that current drug regimens were unduly complicated for field workers and patients.

In 1981, under the dynamic leadership of Dr H. Sansarricq, Chief Medical Officer, Leprosy, WHO convened a meeting of experts in Geneva with the following objectives: 1, to review the information collected since 1976 (the year when the *WHO Expert Committee on Leprosy* last met) on the problems related to chemotherapy and chemotherapeutic regimens of leprosy; 2, to recommend, for use in leprosy control programmes, appropriate multidrug regimens for multibacillary case, including new, treated and drug-resistant cases, whether clinically suspected or proved; 3, to recommend regimes for paucibacillary cases; and 4, to identify further research needs in the clinical and operational aspects of chemotherapy of leprosy.

The findings were published in a WHO Report of 1982,[4] which has now become part of the history of the control of this disease—'*Chemotherapy of leprosy for control programmes*', advising regimens of relatively short duration for all cases of leprosy, based on the use of two drugs (dapsone and rifampicin) for paucibacillary, and three drugs (dapsone, rifampicin and clofazimine) for multibacillary cases. 'MDT' had started. In the early years, largely due to fears that implementation might be difficult or even hazardous, many agencies considered that it was essential to devote much time and effort to orientation and training of staff and the provision of 'optimum' facilities in control programmes before implementation—and progress was therefore slow. However, as the years went by and more experience was gained, it became increasingly clear that the regimens were remarkably robust under a range of field conditions and that implementation could safely be achieved using general staff and referral centres, with extension to involve primary health care workers.

A series of reports and publications from WHO in the 1980's described the widening use of MDT in virtually all leprosy-endemic countries, accompanied by progressive reduction in prevalence rates and a steadily accumulating total of patients cured and released from treatment. In 1991, the World Health Assembly, obviously convinced of the momentous progress being made, adopted a resolution calling for the elimination of leprosy as a public health problem (less than 1 case per 10,000 of the population) by the year 2000. By 1993, WHO confirmed that, 'The elimination of leprosy is now under way', quoting a reduction of prevalence from 5·4 million in 1983 to 2·3 in that year.[5] At the beginning of this year (1997), WHO estimated 1·15 million cases worldwide and recorded a reduction in recorded cases to 888,340.[6]

In the September issue of the journal (page 285), there is a review of the *WHO Meeting on Chemotherapy Research in Leprosy, Madras, India*, January 1997, which includes reference to 'second generation MDT regimens' of significantly shorter duration than those currently advised by WHO. Dr Panniker (WHO) presented evidence from a multicentre trial that single-lesion paucibacillary leprosy could be treated with a single day's dose of three drugs—rifampicin, ofloxacin and minocycline ('ROM'). The full findings of this important study, which are to appear in the *Indian Journal of Leprosy* in the near future,[7] are reprinted on page 000 of this issue.

In May this year, the *Seventh WHO Expert Committee*, meeting in Geneva, endorsed these findings, together with important changes in the duration of treatment for multibacillary cases. The content and wording of these recommendations by the Committee, which appear in the latest *Status Report* from the *Action Programme for the Elimination of Leprosy, Updated 1997*,[8] clearly warrant careful study:

‘ FURTHER SHORTENING DURATION OF MB LEPROSY TREATMENT

Currently MB leprosy includes all smear-positive patients as well as patients with more than five lesions. Among the newly detected cases, the skin-smear positive patients represent only 13% of the total number of leprosy patients, and 48% of those classified as MB leprosy. Because rifampicin is by far the most powerful bactericidal drug against *M. leprae*, and more than 99·999% of viable organisms (which is the limit of detectability by current technology) are killed by the administration of three monthly doses of rifampicin, it can be assumed that the elimination of drug-susceptible organisms is almost entirely due to the bactericidal effect of the initial few doses of rifampicin. The major role of the dapsone-clofazimine component in MDT is to ensure the elimination of rifampicin-resistant mutants from the bacterial population.

However, the results from both nude mouse experiments and a clinical trial have demonstrated that the bactericidal effect of the dapsone-clofazimine component was significantly greater than expected; three months of treatment killed more than 99·999% of viable *M. leprae*, suggesting that the rifampicin-resistant mutants in an untreated lepromatous patient are likely to be eliminated by 3 to 6 months of treatment with the dapsone-clofazimine component in MDT regimen.

The Seventh WHO Expert Committee on Leprosy, which met in Geneva from 26 May to 3 June 1997, considered the possibility of further shortening the duration of MDT. This possibility is being evaluated in an ongoing rifampicin-ofloxacin field trial, which is a multicentre, double-blind trial organized by the Steering Committee on Chemotherapy of Mycobacterial Diseases (THEMYC), a component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Patients were randomized into four groups and treated, respectively, with 24 months of standard WHO-MDT (as positive control), 12 months of WHO-MDT, 12 months of WHO-MDT plus ofloxacin 400 mg daily during the initial four weeks, and rifampicin 600 mg plus ofloxacin 400 mg daily for four weeks. Each tested group had about 500 MB cases. After three to five years of follow-up from intake (or two to four years of follow-up after stopping treatment with any of the three shorter tested regimens), not a single relapse has been detected so far in the trial, suggesting that all three tested regimens are as effective as that of the 24-month standard WHO-MDT regimen. In other studies, including those on defaulted cases, patients who received 12 or fewer doses of MDT performed as well as others who took complete treatment.

Based on all the above information, the Expert Committee considered it possible that the duration of the current MDT regimen for MB leprosy could be further shortened to 12 months without increasing the risk of developing rifampicin-resistance.

FLEXIBLE DRUG DELIVERY

It was also agreed that, because of poor coverage of the health services in most of the leprosy-endemic countries, supervision of the monthly administered drugs by health workers may not always be possible. In that case, more than a month’s supply of MDT blister packs may be provided to the patient. But every effort should be made to educate the patient to take the monthly and daily components of MDT regularly, and to identify a family or community member who can supervise the monthly drug administration. In addition, patients who self-report for diagnosis and treatment may be considered as sufficiently motivated to take full responsibility for their own care, provided they are given appropriate information and

guidance regarding the dosage, rhythm and necessary duration of treatment, and are advised to report any untoward signs/symptoms promptly. This will help to make MDT easily accessible even to those who live in difficult-to-access areas, to the benefit of both the patients and the health service personnel.

TREATMENT OF SINGLE-LESION PB LEPROSY

There is some evidence to suggest that single skin-lesion leprosy is a clinical entity and may be cured by a limited amount of chemotherapy, so a separate regimen for these patients will be useful. The efficacy of a single dose of drug combination consisting of rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg (ROM) for the treatment of single-lesion PB leprosy has been proved in a multicentre, double-blind field trial in India. Although a single dose ROM proved marginally less effective, in terms of clinical improvement, than the six-month MDT, the operational advantages of a single dose treatment over the six-month treatment are enormous, especially when it is taken into account that, in some countries such as India, more than 50% of newly detected cases belong to this category. The Committee therefore considered that a single dose ROM is an acceptable and cost-effective alternative regimen for the treatment of single skin-lesion PB leprosy.''

A further development of potentially great importance is the acceptance (July 1997) by the *Government of India* (*Leprosy Division, Directorate General of Health Services*) of the above recommendations for both multibacillary and single-lesion paucibacillary leprosy. The '*Government of India Guidelines on Modified MDT*'[9] have already been drawn up for distribution; the necessary 'ROM' drugs will be in place by October this year and it is hoped to start the new programme in November. If only in consideration of the fact that India still accounts for 62% of all global cases and also has a high percentage of all newly-detected cases yearly, the impact of these changes may indeed prove to be enormous.

For many years—in fact for centuries—leprosy has been regarded as a slow-moving disease with limited resources for the treatment of those afflicted. That this has changed profoundly and almost beyond recognition must surely now be apparent to all concerned. It is of course true that programme performance has improved in many parts of the world; political commitment is now seen where it did not exist before; drugs are available, free of charge and in blister–calendar packs to all patients who need them and in many leprosy-endemic countries general health services, including BCG immunization, have improved considerably in recent years. Nevertheless, the main element in the success of leprosy control in recent decades undoubtedly centres on the use of multiple drug therapy, leading to the increasingly strong expectation of achieving elimination levels by the year 2000. We should congratulate those who, in 1981, had the vision to convene a meeting in Geneva and the experts who used their knowledge and experience to formulate regimens of such historic importance. However, this is not a time for complacency. Dr S. K. Noordeen, Director of the *Action Programme for the Elimination of Leprosy*, has recently stressed the need to reach the remaining 2 million patients by: 1, making MDT available to all health facilities in endemic countries; 2, using Leprosy Elimination Campaigns (LEC) and Special Action Projects for the Elimination of Leprosy (SAPEL); 3, encouraging high political commitment; and 4, generating community participation, involvement and action through mass communication and a 'trialogue' approach involving patients, people and providers.[10] If we combine these approaches with the careful implementation of the recent changes recommended by the *Expert Committee*, we

surely have an opportunity, absolutely beyond parallel in the history of this disease, to achieve elimination levels by the year 2000.

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Editorial

RIFAMPICIN/MINOCYCLINE AND OFLOXACIN (ROM) FOR SINGLE LESIONS—WHAT IS THE EVIDENCE?

Earlier this year the results of a double-blind randomized controlled trial comparing a potential new treatment (single dose rifampicin/ofloxacin and minocycline (ROM)) for monolesion paucibacillary leprosy with the current 6-month treatment with rifampicin and dapsone (WHO–PB–MDT) were published. The executive report of the 7th WHO Expert Committee on Leprosy (Geneva, 26 May–3 June 1997) noted that the Committee considered the single-dose ROM an acceptable and cost-effective regimen for the treatment of single skin lesion PB leprosy. The paper and report have been highly influential and already strategic planners in several countries, notably India and Brazil, have introduced ROM treatment for single-lesion disease into their national programmes. We are reprinting this important paper in this issue of *Leprosy Review* (p. 299–300) by kind permission of the Editor of the *Indian Journal of Leprosy* since we feel that readers may wish to study the original publication for themselves.

The introduction of single-dose treatment for a subset of leprosy patients is obviously attractive from an operational standpoint and will make a significant impact in reducing prevalence in some areas. However it is also fraught with dangers, and hence the evidence for its effectiveness should be considered in some depth.

The trial involved nine different centres, each recruiting between 103 and 400 patients over a 10-month period to give a total of 1483 patients. Follow-up over an 18-month period was good with a 93% completion rate.

There are a number of difficulties in interpreting the data. The first of these relates to the diagnosis of leprosy in these patients. It is not clear how lesions were tested for anaesthesia nor which modalities of sensation were examined. Much of the initial testing (skin biopsy, histamine testing, lepromin testing and even detailed neurological examination) was optional. Hence it is not possible to know how many patients in the trial had definite evidence of leprosy. The system used in the Karonga trial, of grading patients on a scale of diagnostic certainty for leprosy is a useful way of addressing the problem of diagnosis.[1] From an operational point of view it would be helpful to know how many patients were evaluated and prepared for entry to the trial but then proved to be slit-skin smear positive and so ineligible for treatment with ROM. There is no information on how many patients had skin biopsies with microscopic evidence of leprosy.

Children above the age of 5 were eligible for the trial but no details are given of numbers of children treated nor the drug doses used. The side-effects observed in the trial patients are briefly discussed. No mention is made of monitoring for specific side-effects and no details are given of potential side-effects such as tooth discoloration in children given minocycline.

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The major outcome measure was derived from a scoring system based on five different clinical observations of the lesions. No details of how this scale was constructed nor what weights were given to the five components nor how scoring was standardized between centres are provided. This makes interpretation of the results difficult. Of the 1381 patients who completed the trial only 12 patients failed to improve, and of these 2 deteriorated. The investigators set an improvement of 13 points in the clinical score as their definition of marked clinical improvement; their other outcome measure was complete cure. Patients treated with the conventional WHO–PB–MDT regimen showed statistically significantly *better* results on both these measures when compared with the patients treated with the ROM regimen. The significance level for the difference in complete cure rates is *incorrectly* given in Table V as $P = 0{\cdot}04$, the correct figure is actually even more significant at $P = 0{\cdot}004$ as given in the text. It is not possible from the data given to discern which modalities improved most. A more detailed analysis of the data such as an analysis of covariance would have allowed examination of the effect of age, sex or type of improvement on response to treatment. This would be valuable in determining which patients would benefit most from treatment with ROM. These details are important because this trial was designed to be a gold standard trial of ROM showing its medical effectiveness, not an operational trial showing that it is an easy treatment to administer.

The follow-up period of 18 months for ROM treated patients and 12 months for WHO–PB-MDT treated patients is too short to detect relapses with a relapse rate for paucibacillary disease of 1% per year. It is to be hoped that the patients will continue under active surveillance so that this important figure can be determined.

ROM is undoubtedly an attractive treatment. It is operationally easy to administer and is probably suitable for some patients. If it is to be incorporated into treatment schedules then it is important that workers follow good practice guidelines. It is vital that all patients should be examined carefully to ensure that there really is only a single lesion. Women may be reluctant to be examined fully and if so, should not be prescribed ROM. It is also vital that a careful neurological examination is done to ensure that no nerve thickening or impairment of motor or sensory function is present. There was no statistical difference in the number of reactions or neuritis in each of the treatment groups. This serves as a reminder that even patients with monolesions can suffer reactions and so need to be kept under follow-up even after single dose treatment when it will be very tempting to have less stringent follow-up.

In conclusion this trial as published leaves many doubts: how many of the patients treated in this trial actually had leprosy, which outcome measure improved, did sensation in the lesions improve, what side-effects were monitored? The analysis reveals few details but the two measures reported showed significant superiority for the existing WHO–PB–MDT regimen. Thus it is inaccurate to claim on the basis of the published data, as the authors did in their abstract that ROM is 'almost as effective as WHO–PB–MDT'. The implementation of single dose ROM should be undertaken with care; it is likely to be of value for some patients, but the attraction of operational expediency could easily result in misuse.

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Transmission and protection in leprosy: indications of the role of mucosal immunity

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Summary Recent advances in treatment have achieved a large drop in the prevalence of active leprosy cases, but the incidence is at best decreasing slowly. Most people within leprosy-endemic populations have been exposed to *Mycobacterium leprae*, but few develop disease and it seems likely that the majority of the population develops protective immunity. If the site of initial infection is in the nose, dissemination of bacilli around the body to skin and nerve implies that the initial infection is bacilliferous and it has been shown that nasal *M. leprae* are detectable by polymerase chain reaction (PCR) of nasal swabs. Since salivary anti-*M. leprae* IgA (sMLIgA) levels are correlated with protection,[5] we have surveyed groups of leprosy patients, contacts and the general population for both their sMLIgA and nasal PCR positivity. A total of 304 subjects were enrolled in the study: PCR and mucosal challenge tests were performed in 204 of these individuals. sMLIgA was present in 66% of treated patients, 76% of leprosy workers and 72% of healthy contacts. However, only 33% of indigenous subjects were sMLIgA+, in contrast to the earlier studies showing 74% positivity.[5] PCR for *M. leprae* was present in both household contacts (2%) and indigenous controls (5%). In a subsequent follow-up study, nasal swabs were taken from 97 of those studied in the first series: three PCR+ individuals followed up after one year became negative, while of the remaining 94 PCR− individuals retested, 2

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became positive. Of 112 subjects retested with the mucosal challenge test for sMLIgA: 22 converted from positive to negative and 12 from negative to positive. These results suggest that there is widespread subclinical transmission of *M. leprae* with transient infection of the nose resulting in the development of a mucosal immune response, despite the fact that few individuals will develop clinical disease. This may explain the current lack of effect of multidrug therapy (MDT) control programmes on incidence, although the reduction in general population immunity is consistent with some effect of MDT on transmission.

Introduction

Despite the recent success of multiple drug therapy (MDT) in reducing the number of active cases of leprosy in the world to an estimated 1·3 million[1] from 12 to 15 million only 10 years ago, there are still about 8 million bacteriologically cured cases, many of whom suffer from disability as a result of their leprosy. Although prevalence has fallen, there is little evidence of an effect on incidence in the main endemic countries, even in those with good MDT-based control programmes. Since MDT is only given to those with clinically apparent disease, this suggests that there may be substantial subclinical transmission of *Mycobacterium leprae* infection to individuals within the population, the majority of whom will not develop overt disease. The occurrence of subclinical transmission is also suggested by the poor correlation between lepromatous (multibacillary) rates and overall leprosy prevalence: good correlation would be expected if lepromatous patients were largely responsible for spread of infection. A significant level of subclinical infection has considerable implications for the future success of the WHO's stated aim of eliminating leprosy as a public health problem, since transmission would not be controlled by current MDT-based control programmes.

Studies of leprosy transmission are hindered by the need to follow up contacts of leprosy patients for up to 10–15 years before new infection becomes clinically apparent. However, the recent development of sensitive polymerase chain reaction (PCR) methods for the detection of small numbers of *M. leprae* should enable infection rates to be determined. The sensitivity of PCR is limited to approximately 5 bacteria on the end of a nasal swab.[2,3] PCR of nasal swabs cannot distinguish infection from nasal carriage, or live from dead bacteria. In the case of leprosy, infection is likely to mean penetration of the nasal mucosa—ENT examination of PCR positive cases is required to confirm this. Use of PCR technology by Klatser *et al.*[2,3] in Indonesia has indicated infection/nasal carriage of *M. leprae* in 5–8% of the general population. This is much higher that the prevalence rate of leprosy in the region, which is approximately 0·1%. While positive results due to environmental contamination of the nasal mucosa without active infection cannot be totally excluded, it is likely that a high proportion of these PCR+ individuals are infected, and that they will never develop clinical disease.

The high rate of nasal *M. leprae* PCR positivity adds weight to the hypothesis that initial infection by *M. leprae* occurs in the nose.[4] Previous work has shown that prevalence of a salivary IgA response to *M. leprae* (MLIgA) is inversely related to risk of disease development.[5] It seems likely that local mucosal immunity within the nose is the first line of defence against leprosy. We therefore developed a mucosal challenge test for nasal immunity to *M. leprae* and demonstrated anamnestic salivary IgA

responses in people previously exposed to leprosy.[6] This is in line with the hypothesis that widespread *M. leprae* infection within a population will result in protective immunity in most individuals, evidenced by a mucosal immune response.[5] We anticipated that few individuals would be PCR positive at any one time, and that this would be transient, while recurrent exposure would lead to high rates of mucosal immunity to *M. leprae*. To test this, we have related the mucosal immune response to infection by combining measurements of the salivary IgA response to *M. leprae* with detection of nasal *M. leprae* by PCR to characterize the immune status of putative at risk and protected individuals within a leprosy endemic population. In addition we have performed serological studies to provide corroborating information on recent and past exposure to *M. leprae*.

Materials and methods

Most of the field and laboratory work described as part of this international collaborative study was performed in Miraj by the staff of the Richardson Leprosy Hospital. Audit and training were provided from the European centres.

SUBJECTS

A total of 304 subjects from four groups (healthy household contacts, treated patients, leprosy workers and indigenous controls with no history of leprosy contact) were recruited to the first clinical study. Of these individuals, 243 completed mucosal challenge tests, and 227 nasal swabs were tested for *M. leprae* by PCR: 204 had both tests. Subsequently, 133 were traced for the second follow-up study one year later. PCR was performed in 97 of these individuals and a mucosal challenge test in 112 subjects. The remainder in the initial and follow-up studies declined part or all of the investigations required. A detailed breakdown of the subject groups by age, sex and group is shown in Table 1. Leprosy patients were all either inpatients or outpatients of the Richardson Leprosy Hospital, Miraj. They were classified on the Ridley–Jopling scale by clinical and smear results as BT (10 cases), BB (1), BL (15) and LL (15). Two

Table 1. Age, sex and subject category information, together with the number in the study and the number retested

Group	Age mean and range	Sex % male	Number in study	Number with both tests	Number retested
Indigenous subjects	22 (15–54)	97	89	41	35
Healthy contacts	28 (15–60)	39	134	95	73
Leprosy workers	40 (27–55)	88	33	25	11
Patients (treated)	43 (13–82)	81	48	43	14
.....Active*	44 (13–74)	91	32	31	13
.....Inactive*	49 (21–82)	58	12	12	1
All subjects	30 (13–82)	66	304	204	133

*Activity could not be determined in three patients due to insufficient information.

remaining cases were thought to have polyneuritic leprosy on clinical grounds. Biopsy results were available for 2 cases. For analysis, paucibacillary patients were classified as active if they had received less than 6 months MDT or their last smear was positive. Multibacillary patients were classified as active if their last smear was positive or they had received less than 24 months treatment. On this basis, 32/44 assessable treated patients were classified as active cases. Healthy household contacts were identified by reference to patients of the same hospital's outpatient clinics. They were individuals living in the same house as a known previously treated leprosy patient who was therefore unlikely to be excreting bacilli. An additional group from the indigenous population was drawn from people of similar socioeconomic status living close to leprosy clinics thoughout the study area and known socially to the paramedical workers. Ethical clearance for the study was obtained from the Richardson Leprosy Hospital Ethics Committee, the Leprosy Mission, and Tayside Ethics Committee. All studies were conducted in accordance with the Helsinki declaration and informed consent obtained from the patients.

Each subject was asked to attend two clinic appointments. At the first appointment the procedures explained, a history and examination were performed and samples were taken. Nasal swabs (Medical Wire and Equipment Co, Corsham, UK) dipped in sterile saline were passed pernasally along the base of the inferior turbinate until it encountered the posterior wall of the nasopharynx. Swabs were cooled and transported to the laboratory the same day. A 10 ml venous blood sample was taken and saliva obtained without stimulation by asking the subject to expel saliva over 5 min into a beaker. Finally, each subject was given an intranasal administration of 1 ml of 0·1 μg/ml leprosin A (Rees' skin test antigen, gift from Dr M. J. Colston, National Institute for Medical Research, London, UK) 0·5 ml to each nostril with the head tilted back.[6] Laboratory staff were present at each clinic appointment to collect the samples and complete records on each subject. At the second visit three days later, a history was taken to check that there were no side-effects of the leprosin A, and a further saliva sample was obtained.

ELISA PROTOCOL FOR ANTI-*M. LEPRAE* IGA

This was performed as previously described.[5] Flat bottom Immulon 2 polystyrene plates (Dynatech Ltd, Billingshurst, UK) were coated with 0·1% gelatin (Sigma Chemical Co Ltd, Poole, UK). For coating, 0·5 g gelatin was dissolved in 500 ml distilled water and placed in a waterbath at 60°C for 1 h. Plates were immersed in gelatin vertically twice and tapped on bench to remove bubbles, the solution was flicked off and the plates tapped on towels to remove excess. Following this, the plates were dried for 2 hr at 60°C in a dry oven. Whole *M. leprae* in volatile ammonium acetate/carbonate buffer pH 8·0 (50 μl of 1×10^7 bacilli/ml) was added to each well in alternate columns of 3 wells (*M. leprae* wells) across the plates, which were then dried overnight at 37°C in dry oven. The remaining wells acted as negative control (No *M. leprae*) wells.

The ELISA was performed by blocking with 200 μl per well 3% bovine serum albumin (BSA, Sigma) in phosphate-buffered saline (PBS) pH 7·4 for 2 hr at 37°C, washing with PBS containing 0·1% BSA 4 times over 15 min using a repeating pipette to remove any loosely adherent bacilli, and then adding 100 μl test saliva or standard (pooled saliva) diluted 1 in 2, 1 in 4, 1 in 16 and 1 in 32 with PBS + 0·1% BSA to test wells. Following saliva addition, the plates were incubated at 37°C for 120 min in

humidified chamber and then washed 4 times over 15 min with PBS containing 0·1% BSA using a repeating pipette. For detection of bound antibody, a volume of 100 μl per well of optimally-diluted polyclonal affinity purified anti-IgA antibody conjugated to alkaline phosphatase (Sigma: 1:1000 for A3400; 1:2000 for A3063) was added across the plate. The conjugate was diluted in 50 mM Tris buffer pH 8·0. The plates were then incubated at 37°C for 90 min and washed in 50 mM Tris buffer pH 8·0 containing 0·1% BSA over 15 min using a repeating pipette before addition of 100 μl substrate to each well (Sigma; pNPP 1 mg/ml in DEA diethanolamine pH 9·8). Plates were incubated in the dark at room temperature for 15–20 min until the lowest standard was visible. The reaction was terminated by adding 25 μl 2N NaOH and read using an automated Dynatech MR5000 ELISA reader (410 nm).

While we would have preferred to use a standard saliva to avoid the use of titres, the dilute nature of saliva made this impossible to construct. To obtain the true result for each test sample, the 'No *M. leprae*' control result was subtracted from the '*M. leprae*' result.

ELISA FOR TOTAL SALIVARY IGA

Flat bottom Dynatech Immulon 2 polystyrene plates were coated with 100 μl per well affinity purified anti-human IgA in carbonate buffer pH 9·0 and incubated overnight at 4°C. The plates were then blocked with 200 μl per well 2% milk protein in 50 mM carbonate buffer pH 9·0 for 2 hr at 37°C, washed with PBS containing 0·1% milk protein and 0·05% Tween (PBS/TM) 4 times using a wash bottle, and 100 μl test saliva diluted 1 in 1000 with PBS/TM, or standard IgA (Sigma) in PBS/TM added and the plate incubated at 37°C for 120 min in humidified chamber. Following this, the plate was washed with PBS containing 0·05% Tween (PBS/T) 4 times using a wash bottle. Captured IgA was detected by adding 100 μl per well of optimally diluted (Sigma: 1:1000 for A3400; 1:2000 for A3063) polyclonal affinity purified anti-IgA antibody conjugated to alkaline phosphatase in 50 mM Tris buffer pH 8·0 and incubating at 37°C for 90 min. The plates were then washed with 50 mM Tris buffer pH 8·0 4 times using a wash bottle and 100 μl substrate added to each well (pNPP 1 mg/ml in DEA diethanolamine pH 9·8). The plates were incubated in the dark at room temperature for 15–20 min until lowest standard was visible and the reaction terminated by adding 25 μl 2N sodium hydroxide (Sigma). Plates were read in an automated Dynatech MR5000 ELISA reader (410 nm).

ELISA FOR ANTI-PGL1 ANTIBODIES (BSA GLYCOCONJUGATE WITH PGL1 DISACCHARIDE)

A glycoconjugate with bovine serum albumin which mimics the immunodominant epitope of the phenolic glycolipid coat of *M. leprae* (BSAC) was obtained from Dr M. J. Colston and used as before.[7] BSAC was dissolved in PBS adjusted to pH 9·6 with 4N NaOH at 2 μg/ml and adsorbed onto Immulon II plates (Dynatech) overnight at 37°C (humidified) using 100 μl per well. Serum samples were thawed and prediluted 1:100 in sample dilution buffer (PBS + 0·5% Tween 20 + 5% Normal Goat Serum) and stored at 4°C overnight in plastic tubes. Standards were also made up in sample dilution buffer using pooled serum from 20 subjects with high absorbances in an initial screen at

1:25 to 1:800 with a buffer only control. Coated plates were washed four times over 15 min in wash buffer (PBS + 0·5% Tween 20 + 0·1% BSA) and then incubated with 100 μl/well of the prediluted test samples buffer for 90 min at 37°C. The plates were washed a further four times over 15 min in wash buffer and the second antibody added (100 μl/well anti-Ig peroxidase conjugate, 1:2000 in wash buffer, Sigma) and incubated at 37°C for 90 min. The plates were washed a further four times over 15 min in wash buffer and o-phenylenediamine (OPD, Sigma) substrate at 1 mg/ml with 1 μl/ml H_2O_2 in Citrate-Phosphate buffer, pH 5·0. The citrate-phosphate buffer was made up with citric acid (4·668 g) and dibasic sodium phosphate (Na_2HPO_4; 7·299 g) in distilled water (100 ml) and adjusted to pH 5·0 with sodium hydroxide or hydrochloric acid. The plates were incubated at 37°C for 30 min and the reaction stopped with 2 N sulphuric acid. The plates were read in an automated Dynatech MR5000 ELISA reader at 490 nm and the results analysed using the standards to produce a reference curve (linear fit–arbitrary units [AU]).

ELISA FOR ANTI-LIPOARABINOMANNAN ANTIBODIES

Serum ELISAs for anti-lipoarabinomannan antibodies (LAM) were performed using LAM as antigen, coated directly overnight at 50 μl/well 2 μg/ml LAM in 30% PBS, 70% Methanol onto Immulon II plates. LAM was obtained as a gift from Dr P. Brennan and Dr J. Bellisle, to whom we are most grateful. Following coating, the ELISA was performed in exactly the same way as the whole *M. leprae* ELISA, avoiding the use of Tween in washes.

PCR DETECTION OF *M. LEPRAE*

PCR detection of *M. leprae* was performed using the nested primer set S13/S62 resulting in amplification of a 531 base pair fragment of the *M. leprae* genome.[2,8] Nasal swabs were frozen at −30°C until extraction, which was performed by cutting the cotton end off the swab, placing it in lysis buffer and incubating at 60°C under paraffin oil for 18 hr in a 1·5 ml plastic tube (Nycomed), followed by 97°C for 15 min. Lysis buffer was prepared from two stock solutions: (A) proteinase K 10 mg/l in 1 M Tris-HCl, pH 8·5 and (B) 0·5% Tween 20 frozen in aliquots, and made up by adding 100 μl of A and B with 800-μl distilled water immediately before use.

The PCR reaction was performed using prepared vials containing 35 μl PCR-mix, made up as 5 μl 10 × PCR buffer, 2 μl dNTPs (1mM dATP, dCTP, dGTP, dUTP), 100 ng primer S13, 100 ng primer S62, 23 μl distilled water, 5 μl DMSO, 2·5 U Taq polymerase (Pharmacia) and 0·5 U Uracil-N-Glycosylase (UNG). Paraffin liquid (40 μl) was placed on top of the mix and the vials frozen at −20°C. In early trials, frozen PCR mix vials were sent out from Amsterdam to Miraj in dry ice. *M. leprae* DNA stock solution 25 ng/μl was diluted in distilled water to provide 8 positive controls (2·5 ng/μl to 8 fg/μl) and test samples diluted 1:12·5 before use. Negative controls included distilled water (Amsterdam and local), and lysis buffer alone from the batch used for extraction. The PCR-mix vials were thawed immediately before use and placed on ice. To each vial was added 15 μl of extracted test, positive control, or negative control samples. PCR was performed in a Hybaid Omnigene machine with up to 48 wells in one run. UNG incubation was performed for 10 min at 25°C, then UNG inactivation for 10 min at 95°C, following by 35 cycles, each consisting of denaturation (2 min at 94°C), annealing

(2 min at 60°C), and elongation (3 min at 72°C). Following PCR amplification, samples were either tested on a 2% agarose gel immediately or stored at −20°C pending analysis. Positive samples showed a band at 531 bp.

Confirmation of positive samples was performed by gel electrophoresis and hybridization of the amplified product with digoxigenin-NBT-BCIP detection.[2] Negative samples were checked for PCR inhibition activity by the addition of an artificial template. Positive samples were retested in Amsterdam and confirmed if found positive on retesting. To avoid laboratory contamination, sample preparation, mix preparation/storage, sample addition, and PCR/sample analysis were physically separated by performing each step in separate rooms with individually air conditioned and filtered air. Each room contained separate glove boxes and pipettes allowing complete separation of each stage.

ANALYSIS OF RESULTS

Clinical and laboratory data were collected and analysed in an Access (Microsoft) database. Criteria of positivity for the ELISA and PCR assays were as follows:

- Salivary anti-*M. leprae* IgA (sMLIgA): Positive = antibody titre of 2 or more over negative control wells.
- Salivary anti-LAM IgA (sIgALAM): Positive = antibody titre of 4 or more over negative control wells.
- Total salivary IgA: Measurements were related to standards of purified IgA (Sigma) allowing expression of the results as mg/ml.
- Serum anti-*M. leprae* IgA (MLIgA): Positive = antibody titre of 25 or more over negative control wells.
- Serum anti-*M. leprae* IgG (MLIgG): Positive = antibody titre of 50 or more over negative control wells.
- Serum anti-LAM IgG and IgM: Positive = antibody titre of 100 or more over negative control wells.
- Serum anti-BSAC (glycojugate ELISA) IgG, IgM and IgA: Positive = 100 or more arbitrary units (AU) defined by reference to a pooled serum standard constructed by pooling sera from 20 lepromatous patients. Results are given in arbitrary units and a figure of > 100AU was accepted as a positive result.

Statistical analysis was performed on grouped data by the χ-squared test and on normally distributed datasets by Student's *t*-test.

Results

The results of the ELISA and PCR measurements are shown in Table 2 for each group of subjects tested. Comparisons between salivary anti-*M. leprae* IgA and the two most robust markers of infection, PCR and serum IgM anti-BSAC are shown in Table 3. The results of retesting after an interval of one year are shown in Table 4.

RESULTS FOR ANTI-*M. LEPRAE* SALIVARY IGA (SMLIGA), TOTAL IGA, AND ANTI-LAM

There was an overall sMLIgA positivity rate of 62%, a figure which is similar to the 72%

Table 2. Results of salivary and serum ELISAs for antibodies against *M. leprae* and *M. leprae* antigens compared with PCR for *M. leprae* for each group tested

Group	sMLIgA+ (%) Mean range	sIgALAM+ (%) Mean range	MLIgA+ (%) Mean range	MLIgG+ (%) Mean range	IgG-LAM (%) Mean range	IgM-LAM (%) Mean range
Indigenous subjects	19/58 (33%) 2·4 (0–64)	7/40 (18%) 0·7 (0–8)	13/59 (22%) 31·0 (0–200)	35/62 (56%) 296·6 (0–600)	31/50 (62%) 133·0 (25–200)	17/51 (33%) 161·8 (25–800)
Healthy contacts	83/116 (72%) 4·4 (0–64)	46/118 (39%) 1·2 (0–8)	44/90 (49%) 42·7 (0–200)	26/111 (23%) 142·5 (0–1200)	42/100 (42%) 105·8 (25–200)	5/69 (7%) 65·9 (25–200)
Leprosy workers	19/25 (76%) 8·4 (0–64)	16/26 (62%) 3·4 (0–32)	16/29 (55%) 47·7 (0–250)	24/30 (80%) 462·9 (0–900)	12/24 (50%) 112·9 (25–200)	8/25 (32%) 129·8 (25–200)
Patients	29/44 (66%) 3·1 (0–16)	12/40 (30%) 1·5 (0–16)	23/35 (54%) 55·6 (0–250)	21/43 (49%) 248·9 (0–600)	13/44 (29%) 84·2 (25–200)	7/40 (18%) 102·1 (25–800)
...Active	24/32 (75%) 3·0 (0–32)	10/31 (32%) 1·8 (0–16)	18/27 (67%) 55·6 (0–200)	17/31 (55%) 261·3 (0–600)	10/32 (31%) 88·6 (25–200)	4/30 (13%) 113·0 (25–800)
...Inactive	5/12 (42%) 2·4 (0–16)	2/9 (22%) 1·0 (0–8)	5/8 (63%) 50·2 (0–200)	4/12 (33%) 200·0 (0–600)	3/12 (25%) 82·9 (25–200)	3/10 (30%) 79·2 (25–150)
All subjects	150/243 (62%) 4·1 (0–64)	81/224 (36%) 1·5 (0–32)	96/213 (45%) 45·5 (0–250)	106/226 (47%) 286·2 (0–1200)	98/218 (45%) 108·9 (25–200)	37/185 (20%) 103·9 (25–800)

sMLIgA = salivary IgA anti-whole *M. leprae*, sIgALAM = salivary IgA anti-lipoarabinomannan, MLIgA = serum IgA anti-whole *M. leprae*, MLIgG = serum IgG anti-whole *M. leprae*, IgG-LAM = serum IgG anti-lipoarabinomannan, IgM-LAM = serum IgM anti-lipoarabinomannan, BSAC-IgG = IgG anti BSA-C, BSAC-IgM = IgM anti BSA-C, BSAC-IgA = IgA anti BSA-C, PCR = polymerase chain reaction.

positivity found during previous studies in both Bangladesh and Fiji.[5] While most groups' sMLIgA rates are similar (healthy contacts 72%, leprosy workers 76%, patients 66%), the low level of sMLIgA positivity (33%) in the small group of subjects taken from the general population is striking (Table 2). As expected, sMLIgA rates were similarly high amongst healthy contacts, leprosy workers and treated patients (Table 2). There was considerable physiological variation in the concentration of IgA actually present in the saliva, ranging from 2 to 250 mg/ml with a mean of 49 mg/ml. While there was no significant difference in salivary IgA concentration between subject categories, those found to be negative for sMLIgA were more likely to have a low total salivary IgA (mean 42 mg/ml, sd 35 mg/ml) than those with sMLIgA titres > 2 (mean 59 mg/ml, sd 49 mg/ml) (*t*-test, $p < 0{\cdot}005$), consistent with reduced sensitivity of the sMLIgA ELISA due to low IgA secretion or dilution by increased salivary flow. Antibodies to LAM have

Table 2 *(Continued)*

Group	BSAC-IgG (%) Mean range	BSAC-IgM (%) Mean range	BSAC-IgA (%) Mean range	PCR+ (%) Mean range
Indigenous subjects	18/60 (30%) 96 (0–654)	4/55 (7%) 25 (0–130)	1/55 (2%) 21 (0–117)	2/43 (5%)
Healthy contacts	19/111 (17%) 62 (0–293)	9/118 (8%) 40 (0–198)	4/116 (3%) 29 (0–434)	2/106 (2%)
Leprosy workers	6/24 (25%) 64 (0–211)	0/24 (0%) 14 (0–82)	1/24 (4%) 25 (0–106)	5/31 (16%)
Patients (treated)	27/43 (63%) 213 (0–597)	16/44 (36%) 93 (0–309)	25/44 (57%) 224 (0–1074)	4/44 (9%)
...Active	20/31 (65%) 231 (0–597)	13/32 (41%) 95 (0–300)	18/32 (56%) 252 (0–1074)	2/32 (6%)
...Inactive	7/12 (58%) 164 (0–481)	3/12 (25%) 61 (0–151)	7/12 (58%) 148 (31–471)	2/12 (17%)
All subjects	70/238 (29%) 98 (0–654)	29/241 (12%) 44 (0–310)	31/239 (13%) 63 (0–1074)	13/227 (6%)

previously been found in saliva[9] and we have extended this work in the current study. The results show that 34% of all sMLIgA+ subjects were also sIgALAM positive while only 18% of the sMLIgA− subjects were positive for sIgALAM (χ^2 test, $p < 0{\cdot}0001$), showing that a salivary anti-LAM response occurs in many of those with salivary IgA responses to whole *M. leprae*. In the indigenous subject group, only 18% of the subjects showed an IgA anti-LAM response in contrast to 39% of healthy contacts, 62% of leprosy workers and 30% of patients.

PCR RESULTS

PCR positivity rates (Table 2) were also in keeping with previously reported data.[2,3] In contrast to the immunity rate, the PCR+ rate was not reduced in subjects drawn from the general population in comparison with previous studies. The high numbers of PCR+ results amongst leprosy workers probably reflects environmental contamination of nasal secretions rather than infection, as discussed below. Of the PCR+ patients, 2 were treated for < 1 year: all were multibacillary.

Table 3. Comparison of ELISA for IgA antibodies to whole *M. leprae* (sMLIgA) with (a) nasal PCR for *M. leprae*, and (b) IgM anti-BSAC antibody positivity. Subjects with incomplete PCR or ELISA and/or mucosal testing were excluded from analysis

(a)

Subject category	PCR− sMLIgA−	PCR+ sMLIgA−	PCR+ sMLIgA+	PCR− sMLIgA+	Total
Indigenous subjects	27	2	0	12	41
Healthy contacts	27	0	2	66	95
Leprosy workers	3	3	2	17	25
Patients (treated)	13	2	2	26	43
All subjects	70	7	6	121	204

(b)

Subject category	sMLIgA− BSAC−	sMLIgA− BSAC+	sMLIgA+ BSAC+	sMLIgA+ BSAC−	Total
Indigenous subjects	34	3	1	17	55
Healthy contacts	30	2	5	73	110
Leprosy workers	6	0	0	18	24
Patients (treated)	11	4	12	17	44
All subjects	81	9	18	125	233

RESULTS OF SERUM ELISAS FOR WHOLE *M. LEPRAE*, LAM AND PGL1 (BSAC)

ELISAs to whole *M. leprae* using whole serum are often unreliable, and it is also likely that there is cross-reaction between serum *M. leprae* antibodies and those directed against other mycobacteria.[7] Nevertheless, it is interesting to note that the differences between group positivity rates for serum anti-*M. leprae* IgA (MLIgA) are similar to those for IgA in saliva with few indigenous subjects (22%) showing positivity (Table 2). Sera were regarded as anti-LAM positive if the titre was $>1{:}100$. Since this test also lacks specificity and can be compromised by cross-reacting antibodies to other mycobacteria, it is probable that the levels of positivity are high in comparison with the true level of *M. leprae* exposure. BSAC represents a highly specific immunodominant epitope of PGL1, the outer cell wall lipid unique to *M. leprae*. IgM antibodies to PGL1 have previously been used as markers of recent infection[10,11] and to follow the outcome of treatment.[12–14] Small numbers of BSAC-IgM positive subjects (Table 2) were found in the indigenous subject and healthy contact groups, consistent with the PCR results suggesting small numbers of subclinically infected individuals in these groups. However, none of the leprosy workers were BSAC-IgM positive, suggesting that they were not infected and that the PCR positives in this group may be due to environmental nasal contamination of the subjects from hospital dust. Only two PCR positive individuals were IgM-BSAC+, the remainder being negative. This suggests that PCR positivity may precede PGL1/BSAC positivity, as might be expected from the pathogenesis of leprosy postulated at the start of this study. Since most of the patients tested were still under treatment (Table 1), their higher serological positivity than the other groups (Table 2) is expected.

Table 4. Results of (a) sMLIgA ($n = 126$) and PCR ($n = 100$) retesting one year following initial test, and (b) BSAC IgM ($n = 86$) and IgG ($n = 85$) antibody status one year later showing the number changing their status from positive to negative ($+ \gg -$) and negative to positive ($- \gg +$)

(a)	sMLIgA $+ \gg -$	sMLIgA $- \gg +$	PCR $+ \gg -$	PCR $- \gg +$
Indigenous subjects	7/13	7/17	0/0	3/19
Healthy contacts	19/52	13/19	1/1	3/55
Leprosy workers	0/10	0/1	0/0	0/10
Patients (treated)	1/10	2/4	2/2	1/13
All subjects	27/85	22/41	3/3	7/97

(b)	BSAC-IgM $+ \gg -$	BSAC-IgM $- \gg +$	BSAC-IgG $+ \gg -$	BSAC-IgG $- \gg +$
Indigenous subjects	0/1	0/21	2/3	0/6
Healthy contacts	2/2	1/42	8/12	3/43
Leprosy workers	0/0	0/8	3/4	0/4
Patients (treated)	0/5	0/7	4/7	0/6
All subjects	2/8	1/78	17/26	3/59

COMPARISON OF SERUM IGM ANTI-BSA-C AND PCR RESULTS WITH SALIVARY IGA ANTI-*M. LEPRAE*

Comparison of the PCR and sMLIgA ELISA results (Table 3) shows considerable differences between the subject groups (χ^2 test, all groups, $p < 0{\cdot}0001$). Low numbers of subjects showed both sMLIgA and PCR positivity (3%). Many subjects were negative for both sMLIgA and PCR (34%), with most occurring in the control subject group; 66% were negative for both tests. PCR-/sMLIgA+ individuals were common in the healthy contact, leprosy worker, and treated patient groups, and least frequent in the general population group. PCR+/sMLIgA− subjects were rare in all groups.

Comparison of the IgM-BSAC results with the salivary IgA results yields a similar pattern to that seen with PCR, with marked differences between groups (χ^2 test, $p < 0{\cdot}0001$). Relatively few subjects are IgM-BSAC+/sMLIgA− or IgM-BSAC+/sMLIgA+ (putative active infection). The highest proportion of IgM-BSAC−/sMLIgA− (putative non-immune and non-exposed) individuals is in the indigenous subject group (62%), just as found using PCR, whereas only 25–27% of those in the other groups fall into this category.

RESULTS OF RETESTING

Retesting was performed one year after the initial screen. A number of subjects declined part of the test (usually the blood sample) or failed to return on day 3 as asked. However, it was possible to determine the change in status of approximately half of the subjects in each group (sMLIgA 51%, PCR 44%), as shown in Table 4. sMLIgA status changed from positive to negative in 32% of subjects and from negative to positive in 54% of subjects. Considerable variation in sMLIgA positivity is expected given the variable concentration of IgA in saliva and the relatively low sensitivity of the whole *M. leprae*

ELISA method. However, the number changing from sMLIgA− to sMLIgA+ is clearly greater than the reverse, suggesting that there is conversion in at least 20% of non-immune subjects over the year (χ^2 test, all subjects, $p < 0{\cdot}001$). Some of those changing from sMLIgA+ to sMLIgA− may represent loss of immunity. This could be transient as the result of intercurrent infection and further follow-up studies would be useful. Of those who converted from PCR− to PCR+, 3 were sMLIgA+ and 4 sMLIgA−. The numbers are too small for statistical analysis. However, the PCR results confirm that PCR positivity is transient and can change within a year. Fewer subjects showed BSAC-IgM or BSAC-IgG conversion, but again this supports the presence of continuing transmission particularly within the healthy contact group.

Discussion

The numbers of PCR+ and sMLIgA+ individuals in each group are within expected limits based on previous PCR and IgA surveys, with exception of the indigenous control group which shows a strikingly low level of IgA positivity in comparison with the other groups, despite showing a similar PCR positivity rate to that found in Indonesia.[3] Although in this study the indigenous control group had a preponderance of males, there was no evidence in any of the other groups of a sex or age-related difference in immunological parameters. The explanation for the low sMLIgA positivity in the indigenous population may lie in the rapidly increasing prosperity of this part of Maharashtra, but could also be due to the impact of some 14 years of aggressive case-finding and MDT treatment on transmission of the disease and hence on immunity rates. Further studies of the general population are needed to confirm this finding, since the sMLIgA results suggest that MDT programmes may reduce transmission sufficiently to reduce population immunity, but not to the point where subclinical infection (PCR positivity) disappears.

The sMLIgA response figures are low for a protective immune response which is apparently effective in most ($> 90\%$) of the population. This may be explained by poor sensitivity of the ELISA and the prevalence of individuals with low salivary IgA secretion. However, it may also represent the limited utility of the salivary anti-*M. leprae* IgA response as a marker for protection, which may be due mainly to local cell-mediated responses within the nose.[5] Such responses are difficult to study adequately: lymphocytes were not found in nasal washings with sufficient frequency to permit immunophenotyping (data not shown). We were unable to produce any better results that the previous Western blotting approach to analysis of salivary IgA responses.[9] As before, there was no demonstrable salivary response to PGL1. As predicted from previous work,[9] many of those found to be sMLIgA+ also had salivary IgA responses to LAM. There were relatively few salivary IgA anti-LAM responses amongst indigenous control subjects in comparison with the other groups tested. This provides further support for the observation that relatively few of the indigenous subject group showed salivary IgA responses to *M. leprae* antigens in comparison with the other groups tested.

PCR+ individuals were found in both household contacts and indigenous controls, suggesting that bacilliferous nasal lesions occur without clinical disease. In follow-up studies, all those PCR+ individuals who were re-examined were negative. This corroborates evidence from Indonesia[3] showing transient subclinical nasal infection. As

expected, some patients under treatment were positive. The leprosy workers' PCR results were not a great surprise considering the ability of leprosy patients to secrete large amounts of bacilli from the nose.[15] Dead bacteria still contain DNA and it is likely that, dead or alive, *M. leprae* in hospital dust was responsible for this finding. However, a formal study of *M. leprae* in the environment is required and PCR is likely to prove a useful method for this purpose. Our contention that the PCR positive results amongst leprosy workers represent nasal contamination rather than infection is strengthened by the finding of low serum IgM antibody levels to PGL1 in these individuals since this is associated with active infection.[10–14] Leprosy workers are at low risk of disease despite virtually continuous exposure to leprosy bacilli, which may be responsible for the 25% prevalence of serum IgG to BSA-C found in this study. In contrast to IgM responses, IgG responses to PGL1 (BSA-C) appear to be much more long-lasting.[12] Nasal examination of those with PCR positivity is required to establish whether they have nasal lesions, and we hope to undertake this shortly. We agree with Hatta *et al.*[3] that there may be subclinical transmission from those with transient bacilliferous nasal lesions to non-protected individuals.

Serum serology for whole *M. leprae* is unreliable for diagnosis,[7,17,18] although it is notable that in this study the serum IgA data are generally similar to the salivary IgA data. The LAM used was derived from a fast-growing mycobacterial species and our results probably suffer from cross-reaction with serum antibodies to other mycobacteria.[16] However, IgM antibodies to the immunodominant epitope of PGL1 (BSAC, a glycoconjugate of BSA) show results remarkably similar to the PCR results. There were too few PCR+ individuals retested to be sure of the relationship between PCR and PGL1 serology, but in other work it has been shown that there is no direct correlation.[3,17] There may of course be a temporal relationship, and it would be worth looking to see if IgM anti-PGL1 antibodies appear after PCR positivity has resolved as part of a larger study. These results raise the possibility that PGL1 serology may prove useful for the detection of sub-clinical clusters of infection, as suggested by Baumgart *et al.*[19] Since ELISA technology is much more easily applicable than PCR in the field, this finding is of considerable importance.

It appears that sMLIgA positivity and PCR positivity (presumed infection) are *not* mutually exclusive. Since first infection is likely to be followed by immunity in most individuals, it seems likely that those not yet infected (PCR−/sMLIgA−) will become transiently PCR+/sMLIgA− during primary infection and then develop immunity while infection resolves (PCR+/sMLIgA+). The results are broadly in line with this hypothesis. PCR+/sMLIgA+ individuals may be engaged in a successful defence against recent infection, and we have pursued this by retesting them one year after their previous test results when they would be expected to be PCR−/sMLIgA+ (putative protected). It is also possible that some of those thought to be immune (PCR−/sMLIgA+) could revert to the non-immune, non-infected state. Unfortunately, the numbers of individuals retested in these groups was too small in this study to be sure and larger studies are required. Our results indicate that more individuals convert from sMLIgA− to sMLIgA+ than vice versa, consistent with a general gain in salivary mucosal immunity within the population reflecting continuing exposure of naive individuals to *M. leprae*. In populations with high exposure to *M. leprae*, most individuals would be expected to be those who are immune, with a proportion of non-immune individuals. Those with putative infection and either no immunity or developing immunity would be expected to

be smaller groups, as indeed they are. However there were very few PCR+/sMLIgA− individuals, suggesting that the sMLIgA response develops relatively soon after infection in most individuals.

In conclusion, this study corroborates previous work from Indonesia[2,3] which is consistent with widespread subclinical transmission of *M. leprae* producing transient nasal infection and the development of a mucosal immune response which may be protective. Subclinical transmission may explain the current lack of effect of MDT control programmes on incidence, although if confirmed in larger studies, the reduction in general population immunity is consistent with some effect of MDT on transmission.

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Field treatment of acute nerve function impairment in leprosy using a standardized corticosteroid regimen—first year's experience with 100 patients

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Summary In this study, a fixed regimen of prednisolone for the treatment of acute nerve function impairment (NFI) in leprosy patients was developed and introduced at field level in one area (Thakurgaon) of the Danish–Bangladesh Leprosy Mission's field in NW Bangladesh. The assessment, management and follow-up of patients was undertaken by leprosy control supervisors and physiotechnicians.

One hundred patients were treated and followed up 6–8 months after completion of a 4-month course of prednisolone. At a level of change of 2 points (where a change of at least 2 points in the motor/sensory score was taken to indicate a change of status, i.e. full or partial recovery, or deterioration), 42/65 (64·6%) patients with sensory loss experienced some sensory recovery at completion of prednisolone treatment, and 40/65 (61·5%) at 6–8 months' follow-up. 41/85 (48·3%) of patients with motor loss experienced improvement, and 42/85 (49·4%) at follow-up. Analysis of the mean scores at start of prednisolone treatment, completion and at follow-up using Student's *t*-test showed highly significant ($p < 0{\cdot}001$) differences between scores before and after treatment. The benefit is maintained as seen after a period of 6–8 months follow-up.

It was concluded that treatment of acute nerve function impairment at field level by paramedical workers, using a standardized regimen of prednisolone is feasible, practical and effective.

Introduction

In many leprosy control programmes, treatment of leprosy reactions using corticosteroids

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is confined to a hospital setting. Unfortunately, a proportion of patients who would benefit from corticosteroid administration are for various reasons unable or unwilling to be admitted to hospital. As a result they go on to develop nerve function impairment (NFI) with resulting disability and handicap. This problem was phrased by Becx-Bleumink *et al.* as follows: *'When the management of patients on corticosteroids is the responsibility of medical officers only, we will deprive many patients of adequate treatment for their reactions.'* [1] A recent study of a cohort of new patients in Bangladesh that started MDT in 1990 shows that over a third of cases with recent NFI were not treated with corticosteroids for the above reason.[2] Introduction of treatment in the field of recent NFI using standardized corticosteroid regimens has been hesitant. Organizational and logistic problems are one reason, reservations concerning side-effects of corticosteroids, and placing the responsibility of their management into the hands of paramedical workers, another.

It is well known that corticosteroids are effective in the treatment of leprosy reactions and acute NFI in leprosy.[1,3–7] It is generally agreed that in order to be effective, corticosteroids must be administered within 6 months of an episode of NFI.[1,8] As stated above, attention has been drawn to the need for such treatment to be given by suitably trained field workers in order for the maximum number of patients to receive benefit.[1,9]

Several standardized or semi-standardized regimens for the treatment of NFI have been proposed using prednisolone. For example, 40 mg/day tapering over 12 weeks for paucibacillary (PB) patients and 20 weeks for multibacillary (MB) patients.[9] Another regimen recommended is 25 mg prednisolone daily, reducing by 5 mg per month.[6] For the latter regimen it was recommended that the starting dose should be higher for 'severe reactions'.

All of the studies referred to above comment on the absence of serious side-effects of prednisolone in relatively long courses. A recent meta-analysis reviewing 93 articles and 6602 patients found that peptic ulceration was not significantly associated with prolonged steroid use.[10] In the meta-analysis, a mean daily dose of 35-mg prednisolone for a mean duration of 64 days was given—comparable to the courses used for the treatment of leprosy reactions.[11] Other side-effects including diabetes, hypertension, psychosis and dermatological side-effects were found to be significantly associated, but bacterial sepsis, osteoporosis and tuberculosis while occurring more frequently in the treatment group, did not achieve statistical significance. Overall, a picture of relative *safety* emerged from this meta-analysis.

In 1994 the Danish–Bangladesh Leprosy Mission (DBLM) began with the implementation of a fully field-based programme of the treatment of leprosy reactions and acute NFI. The decision to give corticosteroids to individual patients was delegated to the lowest appropriate level, that of leprosy control supervisor (LCS) and physiotechnician (PT). A protocol for management of reactions was developed by a committee, training provided, and a 7-month pilot programme initiated. This study reports on the outcome of this initial programme after the first year's experience.

Methods

LOCATION

The study was conducted at the Danish–Bangladesh Leprosy Mission (DBLM) in

Nilphamari, in NW Bangladesh. DBLM is a private organization involved in a vertical leprosy programme situated in a highly endemic area (prevalence: 5/1000).[12] The field programme is geographically divided into three 'fields', each with separate reporting. One area, the Thakargaon field, was selected for this study. It covers the two districts of Thakargaon and Panchagar with a total area of 3,214 km^2 and 1,7 million population (1991 census).

ORGANIZATIONAL STRUCTURE

The DBLM Thakargaon field is divided into 6 'blocks', each with its own staffing of leprosy control assistants (LCA) who work under the direction of a leprosy control supervisor (LCS), responsible for that block. In turn, the LCS relates to the leprosy control officer (LCO) who is responsible for the entire field. The LCO relates directly to the field director, who is a medical officer. In addition, there are physiotechnicians (PT) assigned to the field who visit on every clinic day and who are involved in nerve function testing, the teaching of special exercises and health education. New leprosy cases are charted by LCAs who also take skin smears. The cases are then confirmed by the LCS, and MDT is given at his direction. All cases at every clinic visit (during multidrug therapy (MDT) and surveillance) have sensory testing and quick muscle testing carried out by the LCA. If any abnormality is found, the case is referred to the PT and LCS for confirmation. Equivocal results were not accepted for corticosteroid treatment and in such cases were reassessed the following month.

NERVE FUNCTION TESTING

Sensory testing was carried out using a ball-point pen as described by Watson.[13] Testing took place at 12 standard points on each hand palm and 11 standard points on each foot sole. Either partial or complete anaesthesia was taken as a positive finding. The sensory score is calculated by counting the number of sensory points which were abnormal. **Motor function testing** of the facial, radial, ulnar, median and lateral popliteal nerves was carried out by means of 'quick muscle testing' (QMT) and graded according to a revised MRC scale[14] (Table 1). The regular MRC score was *reversed* so that zero always indicated normality for both motor or sensory testing. The reversed score is referred to as the *DBLM score*. Details of muscles tested are also given in Table 1. Each muscle or muscle group tested is assigned a DBLM score up to a maximum of 5.

Corneal sensation testing was performed in those patients who were observed to blink infrequently (less than 5 times per minute), but the evaluation of this parameter is not included in this study.

ACUTE NFI TREATMENT PROTOCOL

The complete guidelines as used for this study are reproduced in the Appendix. According to these guidelines leprosy reactions and NFI are graded according to severity and treatment assigned accordingly. Patients with signs of acute NFI were given 40-mg prednisolone daily and tapered off over 4 months in the field. This was

Table 1. Muscle strength scoring (MRC scale[14])

Muscle strength finding	MRC score	DBLM score
Full ROM[1], full resistance	5	0
Full ROM, reduced resistance	4	1
Full ROM, no resistance	3	2
Reduced ROM, some joint movement	2	3
Flicker only	1	4
Full paralysis	0	5

[1]ROM = range of movement.
Details of muscles tested in quick muscle test:

Facial nerve:	Tight eye closure (orbicularis oculi)—MRC scale
	Lid gap on light eye closure (mm)
Ulnar nerve:	Abduction of little finger
Median nerve:	Abduction of thumb
Radial nerve:	Wrist extension
Lateral popliteal nerve:	Dorsiflexion of foot; Eversion of foot

defined as the reduction by 1 point in the MRC muscle strength grade of any of the movements routinely tested in the QMT; the loss of 1 standard sensory point on the hands or feet; or the development of corneal anaesthesia. Acute was taken to mean occurring within the previous 6 months. Other signs of leprosy reaction or NFI may or may not have been present, e.g. inflamed skin patches, painful nerves.

Patients with acute NFI according to the criteria of DBLM grade 2 (see Appendix) seen between July 1994 and January 1995 were included in this study. There were no patients with impairments according to DBLM grade 3, although patients whose nerve function deteriorated after starting field prednisolone were admitted during treatment. Patients with signs of Type I reaction or neuritis without signs of NFI (DBLM grades 1a and 1b) were excluded, even if they were treated with prednisolone. Out of the initial group of 103, one died and two were lost to follow-up. A total of 100 patients were included in the study group.

Table 2. General data of 100 patients who received a standardized regimen of prednisolone in the field

Age in years at diagnosis acute NFI	Male		Female		Both sexes			Status		
	PB	MB	PB	MB	PB	MB	Tot	New pt	On MDT	RFT pt
0–9	0	0	0	1	0	1	1	1	0	0
10–19	3	5	1	4	4	9	13	3	8	2
20–29	3	10	3	2	6	12	18	4	8	6
30–39	4	16	4	7	8	23	31	9	15	7
40–49	1	8	1	7	2	15	17	2	11	4
50–59	2	6	2	4	4	10	14	8	3	3
>60	2	3	0	1	2	4	6	2	3	1
Total	15	48	11	26	26	74	100	29	48	23

FOLLOW-UP

Data relating to NFI was collected at the followings times:

0 Before the start of the acute NFI episode (usually at registration).
I At the start of field prednisolone treatment.
II At completion of field prednisolone treatment.
III 6 to 8 months after completion of field prednisolone treatment.

(The measurement of NFI scores before starting field prednisolone treatment was not possible in new patients presenting in reaction or with acute NFI.)

DEFINITIONS OF OUTCOME

Full recovery — Restoration of sensory or motor score to zero (normality).
Partial recovery — Partial improvement in sensory or motor score.
Same — No overall change in sensory or motor score.
Deterioration — Deterioration in sensory or motor score.

Results

Table 2 shows the general data of the 100 patients who received a standardized regimen of prednisolone in the field. The mean age of patients was 35·3 years (median: 34·5 years, range: 8–70 years). The distribution of study patients according to the Ridley–Jopling classification was as follows: BT: 64; BB: 12; BL: 13; LL: 7; PN: 4.

The outcome of sensory function amongst the study group is shown in Table 3, the outcome of motor function is shown in Table 4. Outcome has been expressed at different 'sensitivity levels'. Where a change of ≥ 1 point in the sensory score was taken as

Table 3. Outcome of sensory function amongst study group patients with acute sensory loss expressed at three levels of sensitivity ($n = 65$)

	At end of prednisolone therapy						6–8 months after completion of prednisolone therapy					
	Outcome at 3 sensitivity levels* (absolute)			Outcome at 3 sensitivity levels* (%)			Outcome at 3 sensitivity levels* (absolute)			Outcome at 3 sensitivity levels* (%)		
Outcome	≥1	≥2	≥3	≥1	≥2	≥3	≥1	≥2	≥3	*≥1*	*≥2*	*≥3*
Full	25	19	16	*38·5*	*29·2*	*24·6*	25	19	15	*38·5*	*29·2*	*23·1*
Partial	28	23	16	*43·1*	*35·4*	*24·6*	25	21	18	*38·5*	*32·3*	*27·7*
Same	6	21	31	*9·2*	*32·3*	*47·7*	4	18	27	*6·1*	*27·7*	*41·5*
Deteriorated	6	2	2	*9·2*	*3·1*	*3·1*	11	7	5	*16·9*	*10·8*	*7·7*
Total	65	65	65	*100*	*100*	*100*	65	65	65	*100*	*100*	*100*

***Sensitivity levels** Outcome is expressed at 3 sensitivity levels. These indicate numbers of patients whose sensory scores changed either ≥1, ≥2 or ≥3 points relative to the score at start of prednisolone therapy.

Table 4. Outcome of motor function amongst study group patients with acute motor loss expressed at three levels of sensitivity ($n = 85$)

	At end of prednisolone therapy						6-8 months after completion of prednisolone therapy					
	Outcome at 3 sensitivity levels* (absolute)			Outcome at 3 sensitivity levels* (%)			Outcome at 3 sensitivity levels* (absolute)			Outcome at 3 sensitivity levels* (%)		
Outcome	≥1	≥2	≥3	*≥1*	*≥2*	*≥3*	≥1	≥2	≥3	*≥1*	*≥2*	*≥3*
Full	52	27	14	*61·2*	*31·8*	*16·5*	60	34	18	*70·6*	*40·0*	*21·2*
Partial	27	14	8	*31·8*	*16·5*	*9·4*	17	8	6	*20·0*	*9·4*	*7·1*
Same	4	42	63	*4·7*	*49·4*	*74·1*	3	39	58	*3·5*	*45·9*	*68·2*
Deteriorated	2	2	0	*2·4*	*2·4*	*0*	5	4	3	*5·9*	*4·7*	*3·5*
Total	85	85	85	*100*	*100*	*100*	85	85	85	*100*	*100*	*100*

***Sensitivity levels** Outcome is expressed at 3 sensitivity levels. These indicate numbers of patients whose motor scores changed either ≥1, ≥2 or ≥3 points relative to the score at start of prednisolone therapy.

significant, a total of 81·6% of patients showed sensory improvement after completion of prednisolone therapy (38·5% with full recovery), a percentage maintained with 77% improved (38·5% full) after 6–8 months of follow-up. With a change of ≥ 2 points in the sensory score, this was 64·6 % (29·2% full) at completion of therapy and 61·5% (29·2% full) at 6–8 months; at the ≥ 3-point change in sensory score there was 49·2% (24·6% full) at end of therapy and 50·8% (23·1% full) at follow-up. Thus, the level of improvement in sensory function was of the order of 50–60% at more conservative levels of sensitivity, a level which was maintained 6–8 months after the end of

Table 5. Total sensory scores and mean sensory scores at diagnosis of NFI (I), completion of prednisolone therapy (II), and at follow-up (III), with significance of mean differences calculated using *t*-test. Complete anaesthesia of hands and feet in one patient would score 46, with a best possible total score of 0

		Total sensory scores			Mean sensory scores			*p*-value of mean differences		
Category	*n*	I	II	III	I	II	III	I–II	I–III	II–III
Male	37	401	187	227	10·84	5·05	6·14	<·001	<·001	·347
Female	28	228	122	133	8·14	4·36	4·75	·001	·042	·778
PB	14	149	81	71	10·64	5·79	5·07	·024	·016	·325
MB	51	480	228	289	9·41	4·47	5·67	<·001	·002	·278
<1 month*	28	300	180	133	10·71	6·43	4·75	<·001	<·001	·109
1–3 months*	26	267	77	164	10·27	2·96	7·31	<·001	·024	·058
4–6 months*	11	62	52	63	5·64	4·73	5·73	·453	·957	·484
All	65	629	309	360	9·68	4·75	5·54	<·001	<·001	·372

*Duration of NFI.

prednisolone treatment. Comparison of mean differences in sensory scores calculated before and after prednisolone therapy (Table 5) shows highly significant differences for mean scores both immediately after prednisolone and at 6–8 months' follow-up using the Student *t*-test ($p < 0{\cdot}001$). The only exception was for the small group of patients with NFI of 4–6 months' duration ($n = 11$) where there was no significant differences between the mean scores before treatment and at either time after treatment. Although this number is too small to draw statistical conclusions from, it suggests that there may be less recovery in patients with more established NFI. There was no significant difference between mean sensory scores immediately after prednisolone treatment and at 6–8 months' follow-up ($p = 0{\cdot}372$), indicating that sensory recovery is maintained.

Turning to motor recovery, there is also a good level of response, but less marked than for sensory outcome. At the $\geq$1 point change of motor function score there is a 93% (61·2% full) overall improvement at the end of prednisolone therapy and 90·6% (70·6% full) at end of follow-up. However, at the $\geq$ 2-point level it is 48·3% (31·8% full) and 49·4% (40% full) respectively. At the $\geq$ 3 level it is 25·9% (16·5% full) and 28·3% (7·1% full) respectively. Thus the level of motor recovery was in the range 25–50% at the $\geq$2 or $\geq$3 point levels in change of motor function score. Again, analysis of mean differences using the Student *t*-test between mean motor scores before and after prednisolone treatment showed a highly significant difference with $p < {\cdot}001$. Interestingly, the longer duration NFI group (4–6 months' duration) did show a significant difference in mean scores before and after treatment ($p = 0{\cdot}001$), unlike the parallel sensory group. Again, there was no significant difference between mean motor scores immediately after prednisolone treatment and at 6–8 months' follow-up ($p = 0{\cdot}361$), indicating that motor recovery, like sensory recovery, is maintained.

Discussion

This study is primarily concerned with the feasibility and effectiveness of treating acute NFI with a standardized regimen of prednisolone in the field. A single standardized regimen for the treatment of NFI was developed based on the recommendations made by Rose & Waters[9] as well as Becx-Bleumink.[1] This was taught to field staff in the DBLM Thakurgaon field and implemented, using experienced leprosy control supervisors and physiotechnicians as the key persons at field level to assess patients and give treatment.

Results of the field treatment of NFI with prednisolone were analysed in two separate ways: the first method described change in nerve function in terms of full and partial recovery, same (no change) and deterioration, using three different levels of sensitivity in defining a relevant change in sensory or motor function score. In the second method mean differences of total sensory and motor function scores at the time of diagnosis, completion of prednisolone therapy and after follow-up were compared and statistically analysed. Both approaches demonstrate marked improvement in both sensory and motor function, even when applying the very strict criteria of a change of $\geq$3 points in the sensory and motor function scores. This conclusion applies to the overall study group. Only in patients with NFI of 4 to 6 months duration, improvement in the sensory scores in marginal, if at all (Table 5). There does seem to be

Table 6. Total motor scores and mean motor scores at diagnosis of NFI (I), completion of prednisolone therapy (II), and at follow-up (III), with significance of mean differences calculated using *t*-test. Complete motor paralysis of hands and feet in one patient would score 25, with a best possible total score of 0

		Total motor scores			Mean motor scores			*p*-value of mean differences		
Category	*n*	I	II	III	I	II	III	I–II	I–III	II–III
Male	56	171	64	72	3·05	1·14	1·29	<·001	<·001	·453
Female	29	71	22	28	2·45	0·76	0·97	<·001	·001	·607
PB	20	48	12	13	2·40	0·60	0·65	<·001	<·001	·834
MB	65	194	74	87	2·98	1·14	1·34	<·001	<·001	·375
<1 month*	34	94	36	48	2·76	1·06	1·41	<·001	·002	·321
1–3 months*	37	107	36	34	2·89	0·97	0·92	<·001	<·001	·827
4–6 months*	14	41	14	18	2·93	1·00	1·29	<·001	<·001	·218
All	85	242	86	100	2·85	1·01	1·18	<·001	<·001	·361

*Duration of NFI.

improvement in the motor scores in this group (Table 6). The size of the study was too small to identify risk factors for nerve damage and to look at the response of subsets of patients to treatment. However, that is the subject of a large prospective cohort study into acute nerve damage now running in DBLM (Bangladesh acute nerve damage study).

The results of this study compare well with those of Van Brakel & Khawas.[7] In that study touch sensibility testing was performed using a nylon monofilaments giving a force of 10 g for the hands, and a thicker one giving a force of 75 g for the sole of the foot, whereas DBLM uses the ball-point pen in the field. The criteria they used for change in sensory and motor function are a difference of more than 1 point (or ≥ 2) on the touch sensibility test (TST) or voluntary muscle test (VMT). Van Brakel & Khawas analyse in depth changes seen in individual nerves and also describe time trends and prognostic factors, elements outside the scope of the study presented in this paper. Nevertheless, the overall picture of improvement in sensory scores (app. 65%), and motor function scores (app. 50%) at a change of ≥ 2 point in score, is similar. The improvement was maintained over a follow-up period of more than 6 months.

A number of patients experienced deterioration in nerve function during the period, including a few patients who initially fully recovered. All of these patients required a second course of prednisolone or a hospital admission. However, given that a fixed regimen was used (the field staff were not given freedom to alter it at will) the results can still be considered as very satisfactory.

In this study, no cases of peptic ulcer, TB, sepsis or psychosis occurred. Blood pressure was not routinely measured by field staff and urine glucose was also not tested. Dermatological side-effects including acne, tinea corporis and cushingoid fat redistribution occurred only in a small number of patients. The overall experience has been very positive with the field staff enthusiastic towards the programme despite the increased workload for them. They reported good compliance from patients once they understood that they were avoiding a hospital admission; positive feedback from patients recovering lost nerve

function; and the staff themselves felt happy about their increased responsibility. Since the field treatment of reactions has been extended to the whole of DBLM there has been a marked drop in hospital admissions, freeing beds which are now being used for an increasingly busy reconstructive surgery programme.

We share the conclusion of Van Brakel & Khawas[7] that further research is needed to optimize the results of treatment of acute NFI. There are still too many patients for whom the present detection and treatment options are not sufficient, and who remain with impairments after successful treatment of their leprosy infection with MDT. On the other hand we are strongly convinced that as a first step, and pending further improvements in detection and therapy, the present knowledge and possibilities of early detection and treatment of NFI should be made available for *all* leprosy patients. This study shows that field treatment of NFI with a standardized regimen of prednisolone, administered by paramedical staff is feasible, practical and effective.

Acknowledgments

The authors wish to acknowledge the help and cooperation given by all the field staff working from DBLM Thakurgaon. In particular, Mr Kiron Chakrabarty and Mr Yakub Ali, physiotechnicians, gave long hours of overtime to complete the domiciliary follow-up required for this study.

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Appendix

Table showing treatment regimens for Type I reactions/neuritis

Grade/symptoms	Action
DBLM Grade 1a • Reacting skin patch not overlying truncal nerve • Mild nerve pain only • No sensory or motor loss	• **Aspirin** for up to 3 weeks (or PARACETAMOL if problems) • ST/QMT by LCA • Weekly follow-up and medicine supply • *If no improvement, grade as DBLM 1b*
DBLM Grade 1b • Reacting skin patch not responding to Aspirin • Reacting skin patch overlying truncal nerve or any big facial patch • Cutaneous neuritis • No sensory or motor loss	• **Low dose prednisolone** (not reproduced here) • ST/QMT by LCA • Body chart if RFT • Skin smear if RFT • Weekly follow-up 1 month, then 2 weekly • *If no improvement, grade as DBLM grade 2*
DBLM Grade 2 • Grade 1b pt not responding to low-dose Prednisolone • New sensory loss • New motor loss to not less than MRC grade 3 • Moderate/severe painful nerve trunk • Ulcerating/extensive skin reaction • Not pregnant/no ulcer present • Eye not in danger[1] • *Sensory/motor score must have newly decreased by at least 1 point*	• **Full-dose type 1 prednisolone** (see dose regimen) • ST/VMT by physiotechnician • Body chart if skin reaction present • Skin smear if RFT • Record level of pain[2] • Fill up reaction treatment record sheet • Rest, splinting, warmth, exercises as appropriate by PT/LCS • Weekly review at home 1 month, then 2 weekly • ST/VMT by PT at clinic on visits 1,2,last (at least) • *If patient worsens, grade as DBLM grade 3*
DBLM Grade 3 • Grade 2 patient not responding to full-dose prednisolone • New motor loss to less than MRC grade 3 • Eye in danger[1] • Pregnant patient/patient with ulcer with reaction needing steroids • Any seriously ill patient • Patient with compelling social reasons	• **Admit to hospital** • Patients refusing to go to hospital can be treated in the field using full-dose prednisolone except if pregnant

[1]**Eye in danger:** New development of lid gap, loss of blinking reflex or corneal anaesthesia.
[2]**Pain level:** Severe—disturbs sleep; Moderate—sleep OK, painful at work; Mild—slight problem; Tender - painful on pressure only.

Dosage of prednisolone used in treatment of acute nerve damage ('Full dose prednisolone')

Adult > 35 kg		Small adult child 10–14 y 20–35 kg		Child 6–9 y 15–19 kg		Child < 6 y < 15 kg	
40 mg/d	4 wks	30 mg/d	4 wks	20 mg/d	4 wks	10 mg/d	4 wks
30 mg/d	2 wks	25 mg/d	2 wks	15 mg/d	2 wks	5 mg/d	4 wks
25 mg/d	2 wks	20 mg/d	2 wks	10 mg/d	2 wks	2·5 mg/d	2 wks
20 mg/d	2 wks	15 mg/d	2 wks	5 mg/d	2 wks		
15 mg/d	2 wks	10 mg/d	2 wks				
10 mg/d	2 wks	5 mg/d	2 wks				
5 mg/d	2 wks						
Total	**16 wks**	**Total**	**14 wks**	**Total**	**10 wks**	**Total**	**10 wks**

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Excess mortality associated with blindness in leprosy patients in Korea

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Summary Vision loss and blindness are potential complications of leprosy. There is little data available to indicate the impact of eye complications on life expectancy and quality of life. We sought to determine the relative risk of death in blind leprosy patients compared to nonblind leprosy patients.

A population-based ocular survey of 510 mycobacteriologically negative leprosy patients in rural South Korea, conducted in 1988, formed the study population. After a 7-year period patients were traced to determine their status (alive, dead, lost to follow up).

Blind patients showed a 4·8-fold risk of death, even after adjusting for other factors, compared to nonblind patients. Young blind leprosy patients had the highest relative risk of death. Excess mortality was not associated with any specific cause of blindness, ocular pathology, or type of disease.

Findings from our study suggest that all leprosy patients with ocular disabilities (including those released from antileprosy treatment) should be targeted to receive eye care to prevent vision loss. Particular emphasis should be placed on young patients.

Background

Evidence was accumulated over 40 years ago demonstrating that leprosy patients, particularly lepromatous patients, have higher age-standardized mortality rates compared to the general, non-leprosy population.[1] Long-term effects of some of the complications of leprosy, e.g. tropic ulcers, can reduce life span through repeated infection and exposure to economic hardship and malnutrition. Since then, a number of studies have demonstrated 1·5 to 2 fold higher mortality rates among multibacillary patients compared to paucibacillary patients[2,3] suggesting that leprosy-related reactions and increased frequency of intercurrent diseases, such as tuberculosis predict a higher mortality rate. This may be particularly true where

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medical care is limited. Researchers from the Philippines have also suggested that leprosy patients with an early age at onset of disease (less than 18 years of age) have a higher mortality rate than patients whose onset was when they were older.[4]

Recent evidence in the ophthalmologic literature has suggested that in the general population in developing countries blind people have standardized mortality rates three to four times higher than in the non-blind population.[5–7] The mechanism by which mortality is increased in blind people has not been adequately explored although it is likely that blindness leads to decreased socioeconomic status, malnutrition, and infections secondary to injury.

Finally, more recently, three population-based surveys have shown that people with cataract (controlling for vision loss) have standardized mortality rates 1·5 to 2 times higher than patients without cataract.[8–10] Changes in the lens protein are hypothesized to reflect similar system changes that lead to more rapid aging and early mortality.

There is no published information on the relative contribution of disease type, age at leprosy onset, blindness or cataract to mortality in leprosy patients. Thus, our study goal was to determine if the age standardized mortality rate among blind leprosy patients was significantly higher than among nonblind leprosy patients. We also sought to assess the contribution of gender, cataract, type of leprosy, and age at onset of leprosy to increased mortality.

Methods

In 1988, 593 leprosy patients, resident in 7 resettlement villages in South Korea were encouraged to receive an eye examination. Our study methods have been described previously.[11] Briefly, in each village best corrected vision was measured followed by a slit lamp examination. A standardized examination form was used to record information on cause of vision loss or blindness and the presence of lid, conjunctival, corneal, uveal, or lens abnormalities. Although all of these patients were mycobacteriologically negative it has been a common practice in Korea to maintain antileprosy therapy and up-to-date records are kept on all patients. Five hundred and ten patients underwent an ophthalmologic examination.

In October 1995, all patient records were reviewed to determine current status (alive and living in the village, died, or moved from the village), regardless of whether they received an eye exam in 1988 or not. Patients no longer living in the village were traced by phone to their new residence. Death certificates are not routinely kept in the leprosy record files and were not available for review.

Age was stratified into three groups and age-adjusted relative risk and confidence limits were calculated. Age at onset of leprosy was divided into those with an onset age of <18 and those 18 and over. Stepwise logistic regression modelling was used to determine the risk of death while controlling for the possible confounding effects of other variables. Survival curves based on Kaplan-Meier cumulative probabilities were also calculated; these provide a graphic illustration of the mortality experiences of the two groups.

Results

At the 7-year follow-up 49 (9·6%) of the 510 patients had died. We were unable to locate nine patients. Baseline information on this population in 1988 is given in Table 1. Although only

Table 1. Study population ($n = 510$) in 1988

Median age	53 years
Gender	49·0% male 51·0% female
Median age at onset of leprosy	19 years
Median duration of leprosy	34 years
Disease type	77·4% multibacillary 22·6% paucibacillary
Clinical information	
Best corrected vision	
Blind (<3/60)	21 (4·2%)
Visually disabled (6/18–3/60)	23 (4·6%)
Not visually disabled (>6/18)	454 (91·2%)
Ocular conditions	
Lagophthalmos	144 (28·9%)
Corneal disease	67 (13·6%)
Corneal disease and/or decreased corneal sensation	102 (20·7%)
Chronic uveitis	141 (30·3%)
Leprosy-related eye disease†	240 (51·6%)
Cataract or aphakia	76 (15·6%)
Any eye disease‡	270 (53·0%)

*The numbers do not always total to 510; clinical information could not be recorded for patients with phthisis bulbi. Also excluded were cases where corneal disease did not permit examination of the iris and lens.

†Leprosy related eye disease is defined as presence of lagophthalmos, lagophthalmos-related corneal disease, decreased corneal sensation, or chronic uveitis.

‡Any eye disease is defined as leprosy-related eye disease or cataract.

4·2% of the study population were blind (< 3/60 in the better eye), 52% of those examined had leprosy-related potentially blinding ocular pathology.

Blind patients had an unadjusted risk of death 4·53 times higher (95% CI 2·72–7·54) than nonblind patients. The relative risk of death in multibacillary and paucibacillary patients was the same. As expected, increasing age and gender (= males) were both associated with higher mortality. The risk of death of patients with a young age at onset of leprosy was 1·29 times (95% CI 0·91, 1·81) the risk of death of patients with an older age at onset.

Stepwise logistic regression analysis revealed that only age (odds ratio = 1·10, 95% CI 1·08, 1·12, $p < 0·001$) and blindness (odds ratio = 4·78, 95% CI 2·87, 7·96, $p = 0·002$) were independently associated with mortality. The graphical association between blindness and mortality, controlling for age, is shown in Figure 1.

Age-stratified analysis revealed that young blind leprosy patients had a mortality ratio 5·7 times higher than among the nonblind cohort (Table 2). There were only 35 patients under 40 years of age, none of whom were blind. Of those patients under 50 years of age ($n = 180$) only one patient was blind in 1988; he died 6 years after the baseline examination.

Excess mortality was not associated with cataract, lagophthalmos, chronic uveitis or any of the other specific ocular pathology findings. The risk of death of patients with visual impairment (6/24–3/60) was not different than those patients with adequate vision (≥ 6/18).

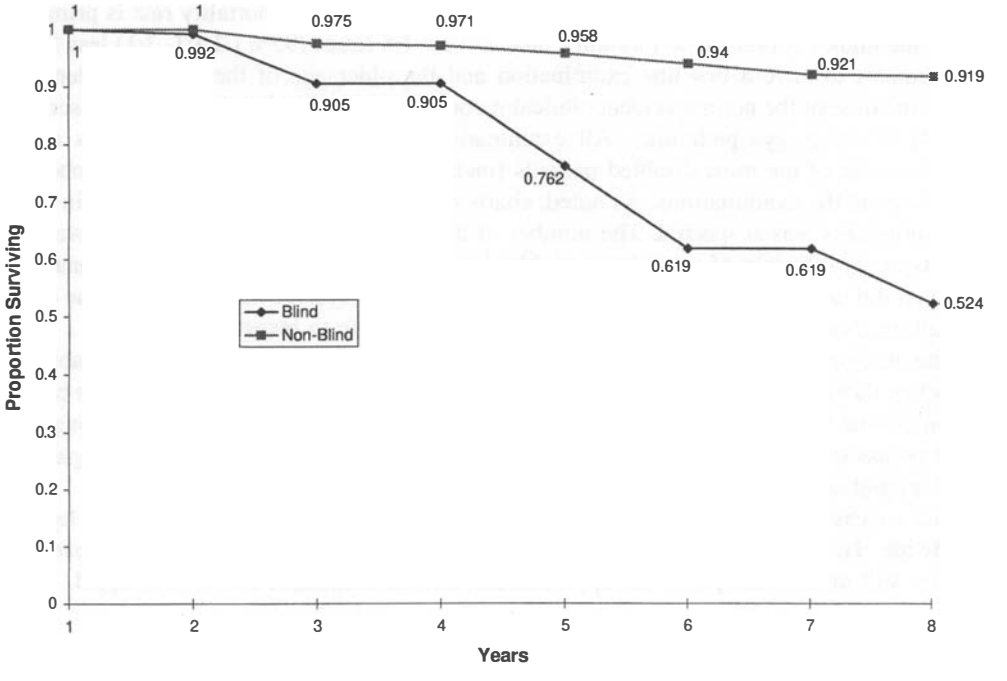

Figure 1. Cumulative survival of blind (<3/60 in better eye) and nonblind leprosy patients in Korea.

Discussion

Our study has shown that leprosy patients who are blind have a significantly higher age adjusted risk of death compared to normally-sighted patients. Young blind people have the highest mortality rates. This study has several limitations. Among the 1988 baseline study population, nonrespondents were more likely to be male (17·0%) than female (10·1%) ($p = 0{\cdot}01$). They were also slightly older (mean age = 54 years) compared to respondents (51 years). Mortality among respondents was 97·8/1000, significantly lower than the

Table 2. Age-stratified risk of death among the blind and non-blind

Age group	No.	Died	Death rate	Relative risk of death (95% Confidence interval)
<60 years				
Blind	7	2	28·7	5·6 (1·6, 19·5)
Not blind	350	18	5·1	
60–69 years				
Blind	9	4	44·4	3·3 (1·4, 8·1)
Not blind	97	13	13·4	
70+ years				
Blind	5	3	60·0	1·9 (0·8, 4·6)
Not blind	28	9	32·1	

192·3/1000 mortality rate among the nonrespondents. The higher mortality rate is primarily due to the higher overall male mortality; males were 1·8 times (95% CI 1·1, 3·1) less likely than females to have a baseline examination and the older age of the nonrespondents. A review of some of the nonrespondent clinical records in 1995 revealed that some had serious, possibly blinding, eye pathology. All examinations were done at centralized sites in the villages; some of the most disabled patients (including those with vision related problems) did not attend the examinations. As noted, charts of nonrespondents were reviewed; in some cases, blindness was suspected. The number of blind were relatively small. There were no patients under 40 years of age who were blind. Excluding these patients from the analysis, however, did not significantly change our findings. We do not have information on the cause of death in these patients and this would be a valuable topic to investigate.

The findings from this study suggest that all leprosy patients with ocular disabilities (including those released from antileprosy treatment) should be targeted to receive eye care to prevent vision loss. Particular emphasis should be placed on young patients. Although we found no association between specific ocular diseases and mortality it is likely that patients with lagophthalmos, chronic uveitis, and cataract have a reduced quality of life.

The success of antileprosy therapy has led to a reduction in the incidence of leprosy worldwide. However, it is important to ensure that the visual needs of leprosy patients, whether still under antileprosy therapy or released from treatment, are not neglected.

Acknowledgments

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CASE REPORT

Rifampicin-induced urticaria in leprosy

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A 28-year-old housewife from Uttar Pradesh, India had suffered from lepromatous leprosy with necrotic erythema nodosum leprosum (ENL) for the last 2 years. Her bacteriological and morphological indices were 4+ and 1%, respectively and a skin biopsy confirmed the diagnosis of lepromatous leprosy with ENL. Her renal, hepatic and haematologic parameters were within normal limits except for haemoglobin of 8 g%. She was started on WHO–MBR (rifampicin, dapsone and clofazimine) and prednisolone 40 mg daily. Within half an hour of the first loading dose the patient developed severe itching over the trunk and extremities followed by urticaria. There was no rhinorrhoea, fever, bronchospasm or hypotension. Urticaria subsided within 4–6 h after administration of an antihistaminic and there was no recurrence of symptom during daily intake of dapsone and clofazimine. Urticaria recurred within 30 min of the 2nd and 3rd loading doses and increased in severity. Urticaria did not recur when rifampicin was omitted from the 4th loading dose onwards. Patient was treated with oflaxacin 400 mg daily for 8 weeks and continued on dapsone and clofazimine. There was no recurrence of urticaria during 2 years follow up.

An open patch test and prick test with rifampicin dissolved in acetone was negative but administration of 300 mg rifampicin under observation lead to the development of itching and urticaria within 30 min.

Discussion

Side-effects of rifampicin are well documented and occur more frequently with intermittent administration especially flu syndrome, shock, shortness of breath, haemolytic anemia and renal failure.[1–3] Daily and intermittent administration also gives rise to cutaneous and gastrointestinal syndrome, hepatitis and purpura.[4] Cutaneous syndrome includes itching and flushing of face and it may be associated with rash. Patients may develop hypersensitivity syndrome, Steven's Johnson Syndrome, pemphigus, porphyria cutanea tarda and acneform eruption. Rarely it can induce neutropenia, agranulocytosis; thrombocytopenia, eosinophilia,

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psychosis, osteomalacia and adrenal crisis.[3,5] Recently one patient with impaired blood clotting associated with fever, chills and hypotension has been described with intermittent rifampicin therapy.[6] There are isolated reports of urticaria and anaphylaxis due to rifampicin in the literature.[7,8] Type I hypersensitivity especially anaphylaxis is rare with rifampicin therapy and accounted for only 6 out of 30,000 possible allergic reactions to rifampicin. It is more common with intermittent therapy and associated HIV infection.[9] In a recent study of adverse effects of WHO multidrug therapy for leprosy, hypotension was recorded in 3 and urticaria in 6 cases in a study of 20,667 patients in Sao Paulo, Brazil.[10] It was, however, not clear whether all these were attributable to rifampicin. We have observed only one patient with Type I hypersensitivity after treatment of more than 2500 patients with WHO–MDT over the last 14 years. Cases of shortness of breath described in literature probably are not Type I hypersensitivity as the majority of them occur in association with flu syndrome and may not be associated with wheezing. We believe that this is the first case report of rifampicin-induced urticaria from India. It is possible our patient could have developed more serious symptoms like anaphylaxis but for concurrent administration of 30–40 mg prednisolone throughout the course of illness because of necrotic erythema nodosum leprosum. Prednisolone may have also interfered with results of prick test, provocation was however, positive with rifampicin. The aim of present communication is to re-emphasize to all the clinicans and paramedical workers in remote areas to watch out for rare occurrence of rifampicin-induced urticaria and anaphylaxis.

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CASE REPORT

Ulnar nerve abscess in a multibacillary patient during post-multidrug therapy surveillance

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Summary An old borderline–lepromatous leprosy patient, treated initially with DDS monotherapy followed by MDT, 11 years later during surveillance presented with 3-month-old asymptomatic cystic swelling, arising from the right ulnar nerve without exhibiting any evidence to document relapse of the disease. It responded promptly to corticosteroid therapy.

This unusual clinical presentations of ulnar nerve abscess has not been reported elsewhere.

Introduction

Abscesses in the peripheral nerves are not infrequent in patients with leprosy invariably, they occur in the active phase of the disease. We report here an ulnar abscess which developed under rather unusual circumstances.

Case report

In January 1964, a 26-year-old woman presented with clawing of the fingers of both hands. There were symmetrical, hypopigmented patches over both forearms, back, trunk and buttocks, with fine infiltration over the chin and ears. The ulnar and lateral popliteal nerves were enlarged. Her hands showed flexion and contractures, more pronounced on the right. She also had right foot drop with ulcers on the hands and foot.

She was diagnosed as having indeterminate leprosy. Treatment with thiambutosine was started and the ulcers grafted.

In August 1966 she began treatment with DDS 50 mg/day. Despite intensive re-education on the care of her hands and feet, she developed ulcers of her right hand on several occasions.

In December 1968, she was reclassified as borderline lepromatous leprosy.

Two months later, the patches on her face and body were exacerbated. Her ears were reddish and nodular. Satellite lesions were seen over the patches on her back. There was no neuritis.

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The diagnosis was: relapse and exacerbated BL. Her BI was 1·87+ at that time.

By May 1982, she had developed ulcers on 10 separate occasions and was left with the following deformities: complete resorption of four fingers of the right hand to the level of the metacarpophalangeal joints and of the thumb to the distal interphalangeal joint. All fingers were resorbed to the level of the distal interphalangeal joint on her left hand. She had complete loss of sensation in both feet. The third and fourth toes of the right foot were resorbed.

In June 1982, she was treated with WHO MB–MDT for 24 months. Her skin smears remained negative throughout.

On release from treatment her deformities had increased the right and little fingers of the left hand had resorbed to the proximal interphalangeal joints.

The third, fourth and fifth toes of her right foot were completely lost and the second toe resorbed to the distal interphalangeal joint.

She was assessed annually and had progressive deformities.

In September 1995, she noticed a small swelling above her right elbow. It was painless and she sought advice in December 1995.

Examination showed a 2-cm by 2-cm cystic mass about 10 cm above her medial epicondyle. The mass moved slightly, perpendicular to the course of the ulnar nerve. There was no inflammation. She had no constitutional signs or symptoms, nor was there any deterioration of sensory function. With her severe deformities, motor assessment was not possible.

Skin smears for acid-fast bacilli from routine sites and over the swelling were negative.

A tentative diagnosis of nerve abscess was made. The patient was started on 40 mg/day of methyl prednisolone. One week later, the swelling was half its original size, and by the thirty-fourth day of treatment it had almost disappeared, leaving a slight elevation on the ulnar nerve trunk. The steroids were tapered after 2 months.

The patient has shown no sign of relapse up to now.

Discussion

A nerve biopsy would certainly have clinched the diagnosis in the patient reported here, but was considered unwarranted as the response to treatment was excellent.

Nerve abscesses occur when the disease is active, but this patient had no physical signs to suggest a relapse.

The persistence of a granulomata long after 'cure' has been demonstrated in patients more than three years after cessation of treatment in Hansen's disease.[1] However it is difficult to assume that this had occurred in our patient 11 years after the completion of treatment. She developed a solitary nerve swelling without regional or constitutional signs and symptoms after 25 years of smear negativity and 11 years after completion of multidrug therapy.

Acknowledgment

The authors thank Mr Y. Nallathambi, Physiotherapist, Mr S. Vincent, Laboratory Technician, Mr C. Lewis Kumar and Ms J. Helen Jothi for the secretarial assistance and are grateful to the patient for her immense co-operation.

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Lepr Rev (1997) **68,** 336–340

CASE REPORT

Diffuse alopecia of the scalp in borderline–lepromatous leprosy in an Indian patient

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Summary A case of borderline–lepromatous leprosy exhibiting alopecia of the scalp along with lepromatous lymphadenitis of suboccipital lymphnode is reported. To our knowledge generalized leprous alopecia of the scalp with lepromatous lymphadenitis of the suboccipital node is a rare occurrence in female Indian patients.

Introduction

Alopecia is a common manifestation of leprosy especially in a few specific areas such as eyebrows, eyelashes and skin lesions. The scalp is usually spared. Cochrane in 1964[1] stated that in certain races, particularly the Mongolian, leprous alopecia of the scalp is fairly common. It is rare in Africans, and has never been reported in Indians.

In this paper an Indian borderline–lepromatous leprosy patient with generalized alopecia of the scalp is reported.

Case report

A 64-year-old female reported to one of the village clinics of the Schieffelin Leprosy Research and Training Centre (SLR & TC), Karigiri in November 1974, and on examination was diagnosed as having borderline–lepromatous leprosy. Dapsone, 5-mg daily, was prescribed and she was advised to take the drug regularly. But she never turned up for treatment and was next seen in the outpatient department of SLR & TC, Karigiri in May 1990 after a period of 16 years with an acute infection of the right ring finger. She was treated with antibiotics and the abscess was incised and drained. She had never had regular antileprosy therapy, and therefore her disease had progressed. She was again prescribed dapsone, 50-mg daily for one month and advised to attend the leprosy clinic near her home and to receive antileprosy treatment regularly. She was never seen again until November 1995 when she reported to the skin clinic, Gudiyatham, with complaints of stuffiness and a blood-stained discharge from the nose of one-year's duration.

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On examination there was diffuse infiltration of the skin over almost the entire trunk and extremities and the skin was dry and scaly. Scratch marks with multiple abrasions and post-inflammatory depigmented scars were found over the upper extremities. Bilateral madarosis and marked generalized alopecia of the scalp was present (Figure 1(a)). There was also loss of sensation in all four extremities and a trophic ulcer in the left foot, along with left foot drop and lagophthalmos on the right side. The suboccipital lymphnode on the left side was enlarged and measured 1·2 cm × 0·8 cm. It was discrete, freely mobile and rubbery in consistency. A clinical diagnosis of lepromatous leprosy with generalized alopecia of the scalp and suboccipital lymphadenitis was made.

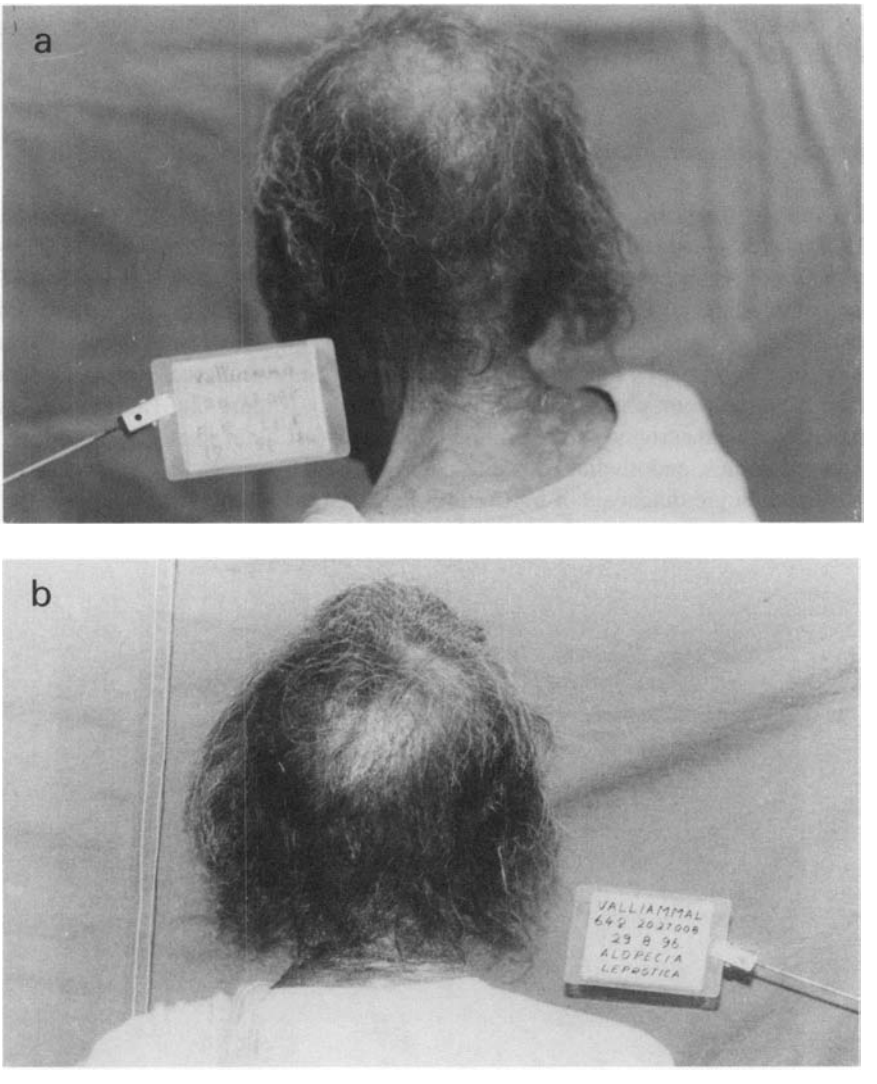

Figure 1. (a) Clinical photograph showing significant loss of hair throughout the scalp. (b) Clinical photograph of the same patient showing appreciable growth of scalp hair after 6 pulses of MDT–MBR.

Routine laboratory investigations, including a chest X-ray were normal. Special investigations like renal and liver function tests were within normal limits. Hormonal assays which included serum testosterone, serum thyroxin (T^4), thyroid stimulating hormone (TSH) and free thyroxin concentration did not show any abnormal levels. HIV and VDRL were negative. Abdominal ultrasonogram was normal.

Dermatological conditions like scabies, pediculosis, tinea, pyogenic infections, telogen effluvium, lichen planus, lupus erythematosus, sarcoidosis and scleroderma were ruled out. The patient was also not on any drugs that have been known to cause alopecia.

Skin smears showed a bacterial index (BI) of 3·80+. A biopsy of the lesion on the right buttock was done. Since she was found to have alopecia, biopsy of the scalp was also done. The lymph node from the suboccipital region was excised. She was started on multidrug therapy—multibacillary regimen (MDT–MBR). Six months later there was an appreciable growth of scalp hair (Figure 1(b)).

Histopathological examination

The skin biopsy, the scalp biopsy and the lymph node were fixed in 10% buffered neutral formalin for over 48 hr; processed for paraffin sections; 5-μm sections were cut and stained both with hematoxylin eosin stain and modified Fite's stain for acid-fast bacilli (AFB).

Histopathological examination of the skin showed epidermis with minimal epithelial hyperplasia and obliteration of rete ridges. There were discrete granulomas in the dermis composed of macrophages mixed with numerous diffusely scattered lymphocytes, dilated lymphatic vessels were present throughout the lesion (Figure 2). Dermal nerves were surrounded by the macrophage granuloma. The acid-fast stain showed clumps of bacilli inside nerve bundles, endothelial cells and macrophages.

A histopathologic diagnosis of borderline–lepromatous leprosy was made.

The scalp lesion showed epidermis with some epithelial hyperplasia. There was marked

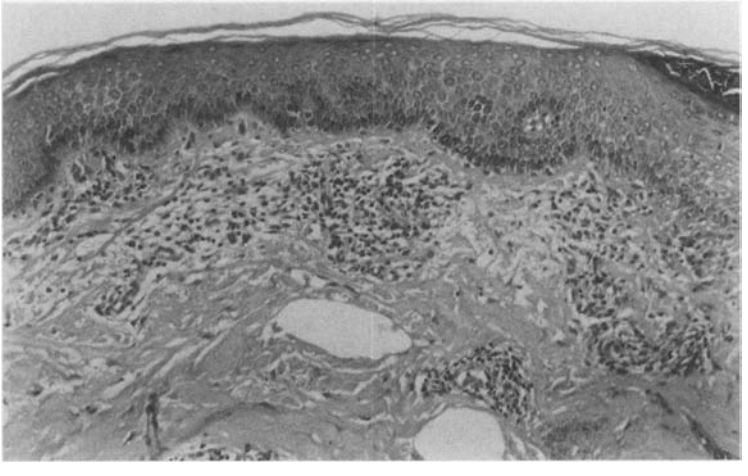

Figure 2. Photomicrograph of the skin lesion to show minimal epithelial hyperplasia and subepithelial granuloma composed of macrophages and lymphocytes. Two dilated lymphatics are also seen (H & E ×300).

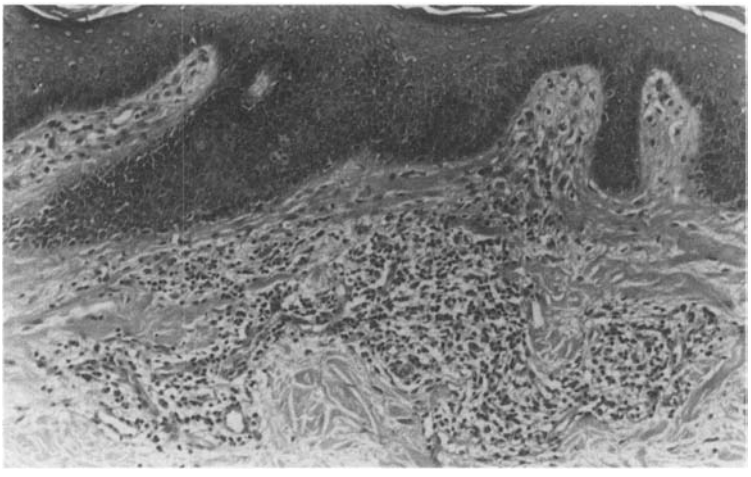

Figure 3. Photomicrograph of the scalp lesion to show hyperplasia of the epithelium and marked subepithelial infiltration with an admixture of lymphocytes and macrophages. An abortive hair follicle is also present (H & E ×300).

reduction in the number of hair follicles. Discrete granulomas composed of macrophages and lymphocytes unevenly mixed together were seen in the subepithelial tissue (Figure 3). Mononuclear cell infiltration was seen around several atrophic hair follicles. Acid-fast stain showed clumps of bacilli inside macrophages and nerve bundles. Borderline–lepromatous leprosy of scalp was diagnosed.

Histopathological examination of lymph node showed normal architecture. Both the cortical and paracortical regions were infiltrated by small focal collections of foamy macrophages (Figure 4). Some of the macrophages had melanin pigment. Acid-fast stain showed bacilli in clumps inside the macrophages. The histopathologic appearance was consistent with lepromatous lymphadenitis.

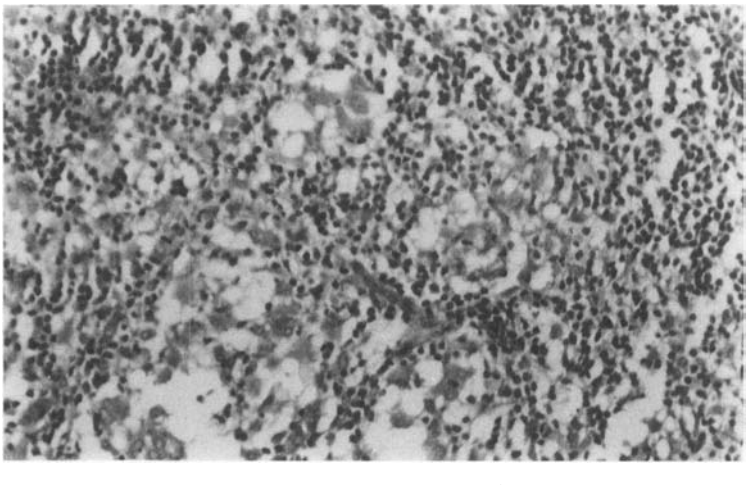

Figure 4. Photomicrograph to show lepromatous granuloma composed of foamy macrophages infiltrating lymph node tissue (H & E ×600).

Discussion

This patient, when she was first seen had a localized borderline–lepromatous disease which clinically degenerated into generalized subpolar lepromatous leprosy over a period of 21 years because she, inspite of all reminders, neglected to have adequate antileprosy therapy. She had generalized dry and scaly lesions almost all over the body and complete loss of hair over the eyebrows, and eyelashes. Histopathologic examination of the lesion over the buttock showed features diagnostic of borderline lepromatous disease.

In earlier reports patchy loss of hair had been recorded in tuberculoid,[2] borderline[3] and lepromatous leprosy patients.[4,5] Generalized loss of hair in the scalp (Figure 1(a)) of this Indian female patient is a rare finding. Histopathologic examination of the scalp clearly showed infiltration of skin over the scalp by lepromatous granuloma and destruction of hair follicles, thus confirming that alopecia is produced by lepromatous disease. *M. leprae* grows in areas of the body where temperature is less than normal body temperature. Therefore lesions of lepromatous leprosy are abundantly seen in the cooler parts of the body such as the earlobes, eyebrows and nasal mucosa. Scalp has a higher temperature[6,7] and therefore lepromatous leprosy lesions of the scalp are uncommon.

The suboccipital lymph node which drains the scalp, showed collections of foamy macrophages containing *M. leprae* (Fig. 4). Lepromatous lymphadenitis of the suboccipital lymph node is also a very rare finding as rare as the lepromatous involvement of the scalp.

Acknowledgment

The authors are thankful to Professor Charles K. Job, Consultant Pathologist, St Thomas Hospital and Leprosy Centre, Chettupattu for his encouragement and guidance. We also acknowledge Mr R. Soundararajan, Laboratory Technician, Mr M. Philip Benis, Social Worker, Mrs Rachel Charles, Librarian, and Ms Helen Jothi, Secretary for their assistance in the study.

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SPECIAL ARTICLE

Efficacy of single-dose multidrug therapy for the treatment of single-lesion paucibacillary leprosy*

SINGLE-LESION MULTICENTRE TRIAL GROUP†

Summary A multicentre double-blind controlled clinical trial was carried out to compare the efficacy of a combination of rifampicin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg (ROM) administered as single dose with that of the standard six-month WHO/MDT/PB regimen. The subjects included 1483 cases with one skin lesion who were previously untreated, were smear-negative, and had no evidence of peripheral nerve trunk involvement and they were randomly divided into study and control groups. The total duration of the study from the day of intake was 18 months, and 1381 patients completed study. Only 12 patients were categorized as treatment failure and no difference was observed between the two regimens. Occurrence of mild side-effects and leprosy reactions were minimal (less than 1%) in both groups. This study showed that ROM is almost as effective as the standard WHO/MDT/PB in the treatment of single lesion PB leprosy.

Introduction

As leprosy control services are expanding in endemic countries, particularly through the implementation of WHO-recommended multidrug therapy (MDT), the number of new cases being detected has been steadily increasing and had reached a peak of about 650,000 new cases in 1992. Since then, the number of newly detected cases every year in the world is relatively constant, between 550,000 and 600,000. About 85% of these are in Asia and it is found that the majority (50% or more) of these cases are being detected at the stage when the only visible sign of the disease is a single lesion (Gupte 1996, Peat *et al.* 1995, WHO 1996). Although it is well known that most of the single-lesion paucibacillary (PB) cases may heal spontaneously without any specific treatment (Ekambaram & Sithambaram 1977), a significant proportion of such cases may develop more severe disease and be at risk of developing nerve damage. Taking into consideration the facts that the number of single-lesion cases form a large proportion of registered and new cases in countries undertaking active case finding, that a significant proportion of these cases are children, that compliance with the standard six-month MDT regimen difficult to maintain and that the six-month regimen may really be over-treatment for this group of patients, it was possible to consider these cases as a special group requiring a substantially reduced period of treatment. Therefore, the possibility of treating such single-lesion PB cases with three highly bactericidal drugs administered in a single dose was explored through a multicentre study.

* Reprinted, with permission, from *Indian Journal of Leprosy*, 1997; **69**: 121–129.
† See p. 349 for individual members of the group.

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It had earlier been established that a single dose of rifampicin 600 mg exerts a very strong bactericidal effect on *Mycobacterium lepra* (Ji *et al.* 1992, Levy *et al.* 1976). Addition of ofloxacin 400 mg and minocycline 100 mg has the potential to prevent the selection of rifampicin-resistant mutants, if any, in early single-lesion PB leprosy where the bacterial population is expected to be well below one million.

Rifampicin is by far the most effective bactericidal drug against *M. leprae*. Its activity is greater than that of any single or combination of the other antileprosy drugs. Rifampicin given as a monthly dose of 600 mg is highly bactericidal against *M. leprae* and is almost as effective as daily rifampicin (Ji *et al.* 1996). The toxicity of the drug is related to the dosage and the interval between doses. The standard dose of 600 mg monthly in MDT regimens has proved to be relatively non-toxic, although occasional cases of renal failure, thrombocytopenia, influenza-like syndrome and hepatitis have been reported.

During the last decade, a large number of fluoroquinolones have been developed, and some, such as ciprofloxacin, are inactive against *M. lepra*; among those which are of most interest is ofloxacin. The results of clinical trials have indicated that its optimal dosage for the treatment of leprosy is 400 mg daily. A single dose of ofloxacin displayed a modest bactericidal effect against *M. leprae*, and 22 doses killed 99·99% of the viable *M. leprae* (Grosset *et al.* 1990). Side-effects include nausea, diarrhoea and other gastrointestinal complaints, as well as a variety of central nervous system complaints including insomnia, headache, dizziness, nervousness and hallucinations. Most of these symptoms do not usually necessitate discontinuing ofloxacin treatment and serious problems are rare (Ji *et al.* 1994).

Minocycline is the only member of the tetracycline group of antibiotics that has significant bactericidal activity against *M. leprae*. Its bactericidal activity against *M. leprae* is greater than that of clarithromycin, but much less than that of rifampicin. The standard dose is 100 mg daily, which gives a peak serum level that exceeds the minimum inhibitory concentration of minocycline against *M. leprae* by a factor of 10–20 and has shown promising bactericidal activity in lepromatous patients (Gelber *et al.* 1992). Side-effects include discolouration of teeth in infants and children, occasional pigmentation of the skin and mucous membrane, various gastrointestinal symptoms and central nervous system complaints, including dizziness and unsteadiness (Ji *et al.* 1993).

A multicentre double-blind controlled clinical trial was undertaken to compare the efficacy of a combination of rifampicin plus ofloxacin plus minocycline (ROM) administered as a single dose with that of the standard six-month WHO-PB regimen.

Material and method

PATIENTS

Based on a thorough clinical and bacteriological examination, all PB patients fulfilling the following criteria were included in the trial:

- having only one skin lesion (irrespective of size or location);
- previously untreated;
- skin-smear negative; and
- having no evidence of peripheral nerve trunk involvement.

The exclusion criteria were limited to the following:

- children below five years of age;

Table 1. Distribution of patients included in the trial, by regimen, mean age, sex and mean clinical score at intake

	Regimen					
	ROM		WHO-PB		Total	
No. of patients	739	(49·8%)	744	(50·2%)	1483	
Mean age	23·6	(SD 15·7)	23·4	(SD 15·6)	23·51	(SD 15·6)
Females	376	(50·9%)	353	(47·4%)	729	(49·2%)
Males	363	(49·1%)	391	(52·6%)	754	(50·8%)
Mean clinical score	14·3	(SD 0·7)	14·3	(SD 0·7)	14·31	(SD 0·7)

— patients who were pregnant at the time of intake;
— patients known to be allergic to any of the proposed drugs or their derivatives, and
— those who were HIV positive, if tested, at the time of intake.

A total of 1483 patients were included in the trial, involving 754 males and 729 females. The mean age of the patients was 23·5 of years (SD 15·6). Characteristics of the patients by type of treatments are shown in Table I. No difference was observed at the intake between the two groups, indicating that the selection and randomization were acceptable.

Nine centres participated in the study, the number of patients per centre ranging from 103 to 400. The intake of patients started in September 1994 and ended by July 1995. The total duration of the study was 18 months (six months of treatment phase and 12 months of follow-up). Patients were examined every month for the first six months, then at the end of 12 and 18 months. Any patient not showing improvement at 18 months was put on the standard WHO/MDT for PB.

OUTCOME MEASURE

The efficacy was measured in terms of clinical improvement, which was based on a scoring system involving five measurements:

— disappearance of the lesion;
— reduction in hypopigmentation/erythema;
— reduction in the degree of infiltration;
— reduction in the size of the lesion (using maximum/mean diameter, and/or actual mapping of the lesion); and
— improvement in sensation in the lesion (using some or all modalities, such as touch/pain/thermal).

The maximal possible score at the intake was 15. During follow-up, the minimum possible score was zero.

TREATMENT

The study regimen (ROM): A single dose of rifampicin 600 mg + ofloxacin 400 mg + minocycline 100 mg.

(Children were given appropriately lower doses).

The control regimen (WHO): WHO/MDT/PB (i.e. rifampicin 600 mg monthly plus dapsone 100 mg daily) for six months.

(Children were given appropriately lower doses).

All patients were treated for the full period of six months with appropriate drugs and placebo preparations, and followed up for 12 months thereafter. Patients were randomly allocated to the study or control regimens. This was done through a system of pre-coded treatment packs (incorporating identical-looking placebo preparations, as appropriate).

The administration of drugs was fully supervised (including placebos) in both regimens during monthly contacts. The six-month treatment was expected to be completed within nine months.

EXAMINATION PROCEDURES

At intake: Collection of information on patient identification, medical history and obtained informed consent; initial clinical examination and recording of the findings on standard forms (the characteristics of skin lesion, including the size, marked on the body outline chart); result of the initial skin-smear examination. Skin biopsy, histamine test, lepromin test, tests for HIV and detailed neurological examination was undertaken on an optional basis by centres which were capable of carrying them out in a satisfactory manner.

During treatment: Patients were seen and interviewed every month, either by the investigator or by an experienced paramedical worker, for symptoms and signs suggesting adverse reactions to drugs and reversal reaction, especially neuritis. Any suggestion of an unfavourable development found was reported to the Principal Investigator who examined the patient and took appropriate action. Drug intake was monitored through questionning of the patients and tablet counts during house calls.

At the end of treatment: At the end of six months' treatment, a formal clinical and skin-smear examination was performed. The degree of clinical improvement was assessed and recorded on standard forms.

After treatment: At the end of 12 and 18 months after the intake (or six months and 12 months after completion of treatment), a formal clinical and skin-smear examination was performed. The degree of clinical improvement was assessed and recorded on standard forms.

Statistical analysis: The multicentre trial had an overall trial coordinator to ensure that the trial protocol was followed uniformly in all the centres. Reporting forms were centralized, monitored and compiled at WHO, Geneva. Results were analyzed by Fisher's exact test. Differences were considered significant at the 95% confidence level. Progress with the trial was reviewed periodically by the Steering Committee on chemotherapy of mycobacterial diseases (THEMYC), a component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

Results

Out of the 1483 patients included in the trail, 1381 (93%) were able to complete treatment and 18 months of follow-up after starting treatment. Information on the status at the end of 18 months was missing for eight patients and therefore they were not included in the analysis and 94 patients were removed from the trial for various reasons.

Table 2. Response to treatment by regimen

Response	Regimen				Total	
	ROM		WHO			
No improvement or deterioration	6	(0·9%)	6	(0·9%)	12	(0·9%)
Clinical improvement	691	(99·1%)	678	(99·1%)	1369	(99·1%)
Total	697		684		1381	

P = 1.

PATIENTS DROPPED OUT FROM THE TRIAL

Out of 1483 patients, 94 (6·3%) dropped out of the trial (49 ROM and 54 WHO) for the following reasons: eight died (0·5%), 10 were due to adverse drug reactions, 56 due to migration, 19 due to refusal to continue treatment or follow-up, and one due to a mistake in drug administratiion. No difference was observed between the two regimens regarding drop outs or their causes (P = 0·16).

RESPONSE TO TREATMENT

Treatment failure: Treatment failure was defined as no change or increase of the clinical score at the end of the trial as compared to the score at the intake. As shown in Table II, 12 out of 1381 patients (0·9%) fell in this category, i.e. they either did not improve (10 patients) or showed deterioration (two patients) at the 18-month examination. Comparison between the trial and control group showed no difference (P = 1) with regard to treatment failure between the two regimens.

Analysis of the characteristics of the patients who failed to respond to treatment showed that six of them were males and six were females, and their mean age was 22 years. None of the patients had experienced drug side-effects, reversal reaction or neuritis. None of them had to be given steroids during the course of the treatment or the follow-up.

Marked improvement: Table III indicates that 753 out of 1381 patients (54·5% of the patients or 36·3% of person-years) had shown a marked improvement at the end of the study. Marked improvement was defined as a difference of 13 between the initial score and the score at the end of 18 months. The cut-off point of 13 was selected on the basis of the distribution of the differences as shown in Table IV.

Table 3. Marked clinical improvement by regimen

Clinical improvement	Regimen		Total
	ROM	WHO	
No marked improvement	336 (48·2%)	292 (42·7%)	628 (45·5%)
Marked improvement	361 (51·8%)	392 (57·3%)	753 (54·5%)
Total	697	684	1381

Difference between two regimens statistically significant; P = 0·04.

Table III also shows that 51·8% of patients (or 34·5% of person years) treated with ROM and 57·3% of patients (or 38·2% of person-years) treated with the standard six-month WHO/PB regimen showed marked improvement. The small difference of 5·5% (0·1%–10·9%) between the two regimens, however is statistically significant (P = 0.04).

Complete cure: As seen in Table V, 701 out of 1381 patients (50·8% of patients or 33·8% of person-years) were completely cured at the end of the study. Complete cure is defined as the total disappearance of the lesion and of the signs associated with it (clinical score of 0). Of those among the two regimens 46·9% of patients (or 31·2% of person-years) treated with ROM and 54·7% of patients (or 36·3% of person-years) treated with the standard six-month WHO/PB regimen were cured. The difference of 7·8% (2·4%–13·2%) between the two regimens is statistically significant (P = 0·004).

SIDE-EFFECTS

During the course of treatment, 12 out of 1483 patients (0·8%) had symptoms which were related to possible adverse reaction to drugs. Ten of these were adverse reactions, leading to the exclusion of the patients from the trial, and for two patients the treatment was continued. Five out of the 12 patients had shown gastrointestinal problems (three ROM and two WHO regimen) and the other seven had allergies (one ROM and six WHO regimen). All these patients recovered fully after appropriate treatment. The occurrence of adverse reactions was not significantly different between the two groups (P = 0·10).

Table 4. Evolution of the clinical score between intake and 18 months by regimen

Clinical score difference* (Score at intake—score at 18 months	ROM regimen		WHO regimen		Total	
	Number of patients	Cumulative %	Number of patients	Cumulative %	Number of patients	Cumulative %
−2	0·1	0·1	0	0	1	0·1
−1	1	0·3	0	0	1	0·1
0	4	0·9	6	0·9	10	0·9
1	7	1·9	3	1·3	10	1·6
2	4	2·4	3	1·8	7	2·1
3	11	4·0	8	2·9	19	3·5
4	26	7·7	13	4·8	39	6·3
5	19	10·5	16	7·2	35	8·8
6	35	15·5	38	12·7	73	14·1
7	41	21·4	33	17·5	74	19·5
8	43	27·5	36	22·8	79	25·2
9	48	34·4	32	27·5	80	31·0
10	38	39·9	42	33·6	80	36·8
11	38	45·3	26	37·4	64	41·4
12	20	48·2	36	42·7	56	45·5
13	72	58·5	68	52·6	140	55·6
14	150	80·1	174	78·1	324	79·1
15	139	100·0	150	100·0	289	100·0
Total	697	100·0	684	100·0	1384	100·0

* A negative difference indicates deterioration, a positive one improvement.

Table 5. Number of patients completely cured by regimen

	Regimen		
Response	ROM	WHO	Total
Not completely cured	370 (53·1%)	310 (45·3%)	680 (49·2%)
Completely cured	327 (46·9%)	374 (54·7%)	701 (50·8%)
Total	697	684	1381

Difference between regimens statistically significant; P = 0·04.

LEPROSY REACTIONS DURING THE STUDY

Ten cases developed mild reversal reactions during or after treatment. On average, reactions had occurred within 42 weeks of starting the treatment. Seven cases belonged to ROM and three to WHO regimen (P = 0·22). None of these reactions required hospitalization and all recovered fully after appropriate treatment. Among the 10 reactions, four patients had developed neuritis (three with ROM regimen, and with WHO regimen, P = 0·37).

Discussion

The results of this trial indicate that a single dose of rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg is almost as effective as the standard WHO/PB/MDT in the treatment of single lesion PB leprosy. Less than 1% of the patients did not improve at the end of 18 months in both groups. Occurrence of mild side-effects and leprosy reactions were minimal (less than 1%), indicating that the ROM regimen can be as safely administered under field conditions as WHO/MDT.

Even if it was not possible to establish the bacterial cure of the patients, there is enough direct evidence from the trial to show that the ROM regimen is able to perform as well as the WHO/PB/MDT regimen in killing the relatively small population of *M. leprae* that single-lesion PB patients harbour.

Total disappearance of the lesion in 50% of the patients within 18 months of starting treatment can generally be considered as satisfactory. The marginal but statistically significant difference observed between the two regimens indicates that standard WHO/MDT is slightly more effective in the complete healing of skin lesion. This is possibly related more to non-antibacterial effects than to antibacterial effects of the drugs used. Assuming that the annual cure rates remain constant, it is expected that nearly all patients will be cured, although the standard WHO/PB/MDT is likely to do it slightly faster than ROM.

While the selection of patients and the multicentre randomized nature of the study helped in minimizing the biases, it was not possible to objectively confirm the specificity of all the diagnoses. In addition, the fact that a significant proportion of single-lesion patients have a tendency for self-healing could have had a confounding effect with regard to results obtained. For evident ethical reasons, it was not possible to have a control group without treatment and therefore the self-healing rate for this group of patients will not be known. It is believed that all the factors which could have introduced some bias were equally distributed and that the sample size was large enough to incorporate a significant proportion of patients who would

not have been cured without treatment. It should be recognized, however, that a significant number of single-lesion PB patients are being diagnosed in leprosy programmes of endemic countries and that they cannot be left without treatment irrespective of their tendency for self-healing. A single dose of ROM seems to be an acceptable and cost-effective alternative having many operational advantages. From the patient's point of view, a single-dose treatment would probably be the treatment of choice as it would definitely help in completing treatment quickly and in suppressing the stigma attached to leprosy. However, there may be several potential operational disadvantages, such as possible overdiagnosis, difficulties in handling powerful antibiotics under field conditions, difficulties in monitoring drug utilization and patients' registration, and these should not be overlooked.

Conclusion

This double-blind clinical trial has demonstrated that a single dose of rifampicin, ofloxacin and minocycline (ROM) is almost as effective as the standard six-months WHO/PB/MDT regimen in the treatment of single-lesion PB leprosy.

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SPECIAL ARTICLE

The impact of multiple drug therapy on leprosy disabilities*

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Summary In an overview of controlled trials, it is shown that bactericidal drugs increase the short–term risk of Type I reactions, but prevent the long–term development of new impairments caused by bacterial proliferation. Clinical experience suggests that the clofazimine component of multiple drug therapy (MDT) has reduced the incidence of Type II reactions or erythema nodosum leprosum (ENL). The principal impact of MDT, compared with monotherapy, has been to reduce the duration of active disease, thus preventing the deterioration of disability scores. Reduction of population disability rates is mainly achieved by earlier detection and treatment. MDT has a number of indirect benefits such as improved compliance, decreased cost, and increased motivation and availability of leprosy workers. However, MDT must be supplemented by other measures to prevent and treat disabilities.

Introduction

In 1994, there were an estimated 2·4 million active cases of leprosy in the world[1] and 2–3 million people had deformities (that is, visible physical changes) caused by this disease. Unlike the closely-related disease of tuberculosis, leprosy is rarely fatal and not highly infectious. Yet the disabilities it causes can ruin lives—not only because they may prevent patients from doing their normal jobs, but also because of the social stigma attached to them.[2,3] A recent survey in India[3] found that up to 46% of deformed patients may be rejected by their families.

Disabilities are part of a continuum of the effects of leprosy, which can be divided into three tiers:[4] impairment, disability and handicap. The disease damages nerves, producing impairments in sensory and motor function. These may cause disability directly—by making certain actions more difficult—or indirectly, by allowing injuries to occur unnoticed. Affected individuals may become handicapped in society when they can no longer fulfil their normal roles.

Combinations of antibiotics were first used to treat leprosy in 1971,[5] but did not become widespread until after 1982, when the World Health Organization introduced standardized regimes: 6 months for paucibacillary patients, and 24 months for multibacillary cases.

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This article will review the impact of multiple drug therapy (MDT) on leprosy disabilities at two different levels: therapeutic (the impact on different types of impairment, which cause disabilities), and preventive (the impact on individuals with different types of leprosy at risk of becoming disabled). The search for relevant papers was conducted systematically using the MEDLINE database, and the references of these papers were also searched for other relevant publications.

The therapeutic impact of multidrug therapy on different types of impairment

Leprosy disabilities result from impairments produced by disease. The pattern of disease determines which impairments develop and what treatment is required. In lepromatous leprosy, impairments result from bacterial proliferation, whilst in tuberculoid disease, the immune response damages nerves.

To review the impact of MDT, it is most useful to consider its effect on the two main processes causing impairments: neuritis and local proliferation. Neuritis may produce permanent motor impairments (often at a site remote from the actual lesion), and sensory impairments, which allow secondary damage of tissues to occur unnoticed. Local bacterial proliferation causes specific deformities in particular anatomical sites.

NEURITIS

Neuritis is usually asymptomatic and nerve function may gradually deteriorate without the patient noticing.[6–8] This may occur in spite of chemotherapy, perhaps due to gradually increasing pressure on the nerve.[9] Paradoxically, because it goes unnoticed, silent neuritis may cause at least as many impairments as the more severe (acute) neuritis, which presents with nerve pain and/or sudden loss of function.

While antileprosy therapy is required to kill the causative organisms, it may increase the risk of neuritis,[10] for which additional treatment is needed. If treated promptly with steroids, many patients recover, or at least their nerve damage is limited.[8,10] This has prompted leprosy workers to advocate regular screening of nerve function in their patients.[6,8] The fact that nerve damage can be reversed or limited is not appreciated by all field staff; when it is, treatment and screening are much improved.[6,8]

Type I Reactions (TIRs), episodes of increased inflammatory activity in skin lesions and/or nerves,[11] are one cause of neuritis. They may result from an increase in the cell-mediated immune response and the formation of granulomata.[12] Inflammation in the nerves causes pain, but the most important consequence are motor impairments and disability. TIRs also increase the risk of arthritis.[13]

The reported incidence of TIR varies widely from study to study. The comprehensive review by Lienhardt and Fine[11] found that TIRs occur commonly during and after chemotherapy. Indeed, for patients not in TIR at the time of diagnosis, the greatest risk of TIR is in the first 6–12 months of treatment. The lack of clinical trials with long-term follow-up before the introduction of MDT makes it difficult to compare the risk of TIR under monotherapy and MDT. A retrospective study is quoted from Malaŵi which found a lower risk of TIR with MDT than with DDS monotherapy.

Table 1 summarizes the randomized controlled trials which quote incidence of TIR. In paucibacillary patients, Orege *et al.*[14] found no difference between WHO and modified regimens. Groenen *et al.*[15] found a much higher incidence of TIR in rifampicin monotherapy (B)

than in a modified MDT regimen (A) or a single dose of rifampicin (U). The allocation of patients was not entirely random—those not prepared to come to the centre weekly were automatically given MDT (A)—but this is unlikely to account for the very large difference observed.

All the other studies refer to multibacillary patients. Groenen *et al.*[15] found a significantly lower incidence of TIR with the WHO regimen than with alternative high dose rifampicin regimens. Singh *et al.*[22] also found a greater incidence of TIR and neuritis in a modified WHO regimen with high dose rifampicin, but the difference was not statistically significant due to the small numbers studied. Thomas *et al.*[21] found no difference between a regimen containing high dose rifampicin and another containing no rifampicin. Interactions with other drugs make these results hard to interpret; it seems that rifampicin may increase the risk of TIR in certain drug combinations but not in others.

Groenen *et al.*[15] found that clofazimine seemed to reduce the frequency, duration and severity of TIR as compared to dapsone. However, their groups were not randomised: patients who had taken DDS monotherapy for more than 5 years received clofazimine, and those who had not continued with DDS. The authors also found that previously untreated patients were more at risk of TIRs, so this could explain the differences between their groups. Jamet *et al.*[16] found that clofazimine monotherapy did not suppress TIRs, and that high doses could increase their incidence.

The role of dapsone is unclear. Dietrich *et al.*[17] found no difference in the incidence of TIRs between dapsone monotherapy and two MDT regimens. Barnetson *et al.*[25] found that patients receiving low dose DDS monotherapy (5 mg od) were more at risk of TIR than those receiving higher doses (50 mg od). They observe that DDS must have an anti-inflammatory effect at higher doses since 1 mg daily is the minimal dose for antibacterial activity.

Any antibacterial chemotherapy could release antigens which could stimulate the cell-mediated immune response (CMI). A histological study of patients undergoing MDT found evidence of immune activation even in patients without a TIR.[26] More potent chemotherapy such as rifampicin may carry a greater risk, but other drugs such as DDS and clofazimine may help to diminish this risk. In summary, MDT probably increases the incidence of TIR in comparison to no treatment, but may or may not do so in comparison to dapsone monotherapy.

Type II reactions (erythema nodosum leprosum (ENL)) following MDT have been studied by several researchers. ENL is thought to be an immune-complex reaction; it causes not only neuritis but also systemic effects, such as widespread subcutaneous erythematous nodules, fever and iritis.[12] It rarely results in permanent loss of nerve function, but repeated attacks occasionally cause deformities in the hands such as 'swan-neck', 'twisted fingers' or 'nonparalytic clawing'.[10] ENL may also cause acute-onset arthritis, distinct from that mentioned see p. 356. This variety usually only causes temporary disability; nevertheless, extended episodes have been reported.[27,28] Atkin's survey[28] found 22% of patients had ENL-related arthritis, of whom only one (8%) had bone erosions.

Table 2 summarizes the randomized controlled trials (RCTs) of different chemotherapy regimes for MB leprosy, together with the percentage of patients reported to have suffered at least one ENL reaction during the follow-up. Cellona *et al.*[29] quoted a percentage for each year rather than an overall figure; the maximum for each year is reported in the table. Unfortunately percentages are not comparable between studies because of the varying follow-up periods, and because there is no indication of the severity of reactions. However, comparisons between groups within any study should be valid.

Starting any chemotherapy increases the risk of ENL, compared to no treatment.

Table 1. Randomised–Controlled Trials of MDT for PB and MB leprosy and incidence of Type I reactions

Ref	T	N		Treatment regimen	TIR (% of patients)	Acute Neuritis (%)
14 PB	1½ yr	64	A:	WHO–PB–MDT	23·3	
			B:	RMP 1500 mg 1/3 m, DDS 100 mg od, 6 m	20·3	
15 PB	>1 yr	184	A:	RMP 1500 mg 1 x DDS 100 mg od, 1 yr	2·2	
		59	B:	RMP 900 mg 1/wk, 10 wk	18·6	
		92	U:	RMP 40 mg/kg 1x	5·4	
15 MB		129	C:	RMP 600 mg od, 6 m ETH 500 mg od, 6 m either DDS or CLO, 100 mg od, 1 yr.	55	
		128	D:	RMP 600mg od, 6m ETH 500mg od, 1y either DDS or CLO, 100mg od, 1y.	45	
		23	W:	WHO–MB–MDT	17	
16 MB	6 m	16	A:	CLO 50 mg od, CLO 300 mg 1/m, 6 m	13	
		13	B:	CLO 600 mg 1/m, 6 m	8	
		16	C:	CLO 1200 mg 1/m, 6 m	44	
17 MB	8–11 yr	64	A:	DDS 100 mg od, ≥3 yr	(over the entire follow–up)	
		83	B:	DDS 100 mg od	18 (LL)	
				RMP 600 mg od, ≥3 yr	38 (BL)	
		81	C:	DDS 50 mg bd RMP 600 mg od PTH 175 mg bd INH 175 mg bd, ≥3 yr	No differences according to treatment	
18 MB	2 m	8	A:	OFL 400 mg od, 2 m	0	
		8	B:	OFL 800 mg od, 2 m	0	
		8	C:	OFL 400 mg od DDS 100 mg od CLO 300 mg 1/m CLO 50 mg od, 2 m	0	
19 MB	6 m	4	A:	MIN 200 mg od, 1 m, then 100 mg od, 6 m	0	
		8	B:	MIN 100 mg od, 6 m	0	
		2	C:	MIN 100 mg 6/m, 1 m, then 100 mg od, 5 m	0	
20 MB	2 m	11	A:	MIN 100 mg od, 2 m	0	
		12	B:	CLT 500 mg od, 2 m	0	
		12	C:	MIN 100 mg od, CLT 500 mg od, 2 m	0	
21 MB	5yr	88	A:	RMP 600 mg od, 3 m INH 300 mg od, 3 m DDS 100 mg od, 5 yr CLO 100 mg od, 5 yr	9·1	14·8
		89	B:	DDS 100 mg od, 5 yr CLO 100 mg od, 5 yr	7·9	10·1
22 MB	6m	15	L1:	WHO–MB–MDT, 6m	13	0
		15	L2:	RMP 600 mg od, 21d, DDS 100 mg od, 21d, CLO 100 mg od, 21d, then WHO–MB–MDT, to 6 m	20	7

Table 1. *(Continued)*

Ref	T	N	Treatment regimen	TIR (% of patients)	Acute Neuritis (%)
23	3 yr	157	M18: WHO–MB–MDT, 18 m	38·9	
MB	(mean)	148	M30: WHO–MB–MDT, 30 m	32·4	
24	2+	31	V: RMP 600 mg od, 2 wk,	27	26
MB	yr		DDS 100 mg od, 2 wk,	(12 LL,	
			CLO 50 mg od, 2 wk,	36 BL,	
			then WHO–MB–MDT, 2 yr	36 BB)	
			Vaccine:		
			1×10^9 bacilli, 1 x,		
			then 5×10^8 bacilli, 1/3 m, 2 yr		
		25	C: Drugs as above,	14	22
			Placebo 'vaccine',	(0 LL,	
			1/3 m, 2 yr	40 BL,	
				9 BB)	

Abbreviations:

T, length of follow–up period; N, number of subjects.

CLO, clofazimine; CLT, clarithromycin; DDS, dapsone; ETH, ethionamide; INH, isoniazid; MIN, minocycline; OFL, ofloxacin; PTH, prothionamide; RMP, rifampicin; THI, thiacetazone.

WHO–PB–MDT, WHO regimen for PB leprosy (RMP 600 mg 1/m, DDS 100 mg od, 6 m).

WHO–MB–MDT, WHO regimen for MB leprosy (RMP 600 mg 1/m, CLO 300 mg 1/m, CLO 50 mg od, DDS 100 mg od, 2 yr).

od, once daily; bd, twice daily; 1 x, single dose; 1/m, once a month; 1/3m, once every three months.

d, day(s); wk, week(s); m, month(s); yr, year(s).

Becx-Bleumink[32] reports a substantial rise in the number of ENL reactions during the first year of MDT, as compared to the time of diagnosis. Bwire & Kawuma,[33] in a 5-year study of 2317 leprosy patients in Uganda, found that 17 of 18 patients with ENL were on MDT. However, the incidence of ENL has decreased since MDT replaced monotherapy. ENL used to occur in 50% of LL patients and 30% of BL patients.[34] Since the introduction of MDT, ENL has become less common,[35,36] occurring in only about 20% and 10% of LL and BL patients respectively (Lockwood D.N.J., personal communication).

It is a pity that the only trial comparing monotherapy with MDT[17] did not use WHO MDT; the MDT regimen used contained larger doses of rifampicin and did not include clofazimine. Not surprisingly, there was no significant difference in the incidence of ENL between groups. Large doses of rifampicin may increase the risk of ENL, while clofazimine may decrease it.

Clofazimine is known to be anti-inflammatory as well as bactericidal.[6,37,37a] Treatment of ENL by clofazimine has been reported by Burte *et al.*[37] All the symptoms of neuritis, with the notable exception of anaesthesia, showed complete recovery in 15 of their 20 patients treated for ENL with clofazimine, and the severity of the reaction was reduced in the five others. Helmy *et al.*[37a] found that clofazimine was significantly better than placebo for the treatment of ENL in a small double-blind randomized crossover trial.

Clofazimine is believed to be responsible for the decreased risk of ENL observed since the introduction of WHO–MDT (Lockwood D.N.J., personal communication). Unfortunately, no trials of sufficient quality have been conducted to prove this. Cellona *et al.*[29] found that clofazimine suppresses ENL: patients on their regimens IIA, IIB and IIC, which included

Table 2. Randomized–controlled Trials of MDT for MB leprosy and incidence of ENL reactions [for key to abbreviations, see Table 1]

Ref	T	N	Treatment regimen	ENL (% of patients)
15		129	C: RMP 600 mg od, 6 m ETH 500 mg od, 6 m either DDS or CLO, 100 mg od, 1 yr.	11
		128	D: RMP 600 mg od, 6 m ETH 500 mg od, 1y either DDS or CLO, 100 mg od, 1 yr.	16
		23	W: WHO–MB–MDT	0
17	8–11 yr	64	A: DDS 100 mg od, ≥3 yr	(over the entire follow–up)
		83	B: DDS 100 mg od RMP 600 mg od, ≥3 yr	49 (LL) 35 (BL)
		81	C: DDS 50 mg bd RMP 600 mg od PTH 175 mg bd INH 175 mg bd, ≥3 yr	No differences according to treatment
29	5 yr	97	IA: DDS 100 mg od, 5 yr RMP 1200 mg 1x	(maximum in any year) 45
		32	IB: DDS 100 mg od, 5 yr RMP 600 mg od, 4 wk	45
		39	IC: DDS 100 mg od, 5 yr RMP 1200 mg, 1x CLO 100 mg 3/wk, 24 wk	42
		34	ID: DDS 100 mg od, 5 yr RMP 1200 mg, 1x PTH 375 mg od, 8 wk	45
		83	IIA: CLO 100 mg 3/wk, 5 yr RMP 600 mg od, 4 wk	22
		16	IIB: CLO 100 mg 3/wk, 5 yr RMP 600 mg od, 2 wk	21
		28	IIC: CLO 100 mg 3/wk, 5 yr RMP 1200 mg 1/m, 6 m	32
		29	IID: RMP 600 mg od, 4 wk, then 600 mg 2/m, 5 yr PTH 375 mg od, 8wk, then THI 150 mg od, 5 yr	37
18	2 m	8	A: OFL 400 mg od, 2 m	0
		8	B: OFL 800 mg od, 2 m	0
		8	C: OFL 400 mg od DDS 100 mg od CLO 300 mg 1/m CLO 50 mg od, 2 m	25
19	6 m	4	A: MIN 200 mg od, 1 m, then 100 mg od, 6 m	0
		8	B: MIN 100 mg od, 6 m	0
		2	C: MIN 100 mg 6/m, 1 m, then 100 mg od, 5 m	0
20	2 m	11	A: MIN 100 mg od, 2 m	9
		12	B: CLT 500 mg od, 2 m	8
		12	C: MIN 100 mg od, CLT 500 mg od, 2 m	25
21	5y	88	A: RMP 600 mg od, 3 m INH 300 mg od, 3 m DDS 100 mg od, 5 yr CLO 100 mg od, 5 yr	31·8

Table 2. *(Continued)*

Ref	T	N	Treatment regimen	ENL (% of patients)
		89	B: DDS 100 mg od, 5 yr CLO 100mg od, 5yrs	38·2
30	2 y	47	I: RMP 600 mg od, 9 m, then 600 mg 1/m, 9 m DDS 100 mg od, 2 y CLO 50 mg od, 2 y	25·5
		41	II: WHO–MB–MDT, 2 y	7·3
22	6 m	15	L1: WHO–MB–MDT, 6 m	0
			L2: RMP 600 mg od, 21 d, DDS 100 mg od, 21 d, CLO 100 mg od, 21 d, then WHO–MB–MDT, to 6 m	0
23	3 yr (mean)	157 148	M18: WHO–MB–MDT, 18 m M30: WHO–MB–MDT, 30 m	3·2 2·7 (NB: severe ENL only)
24	≥2 yr	31	V: RMP 600 mg od, 2 wk, DDS 100 mg od, 2 wk, CLO 50 mg od, 2 wk, then WHO–MB–MDT, 2 yr Vaccine: 1×10^9 bacilli, 1x, then 5×10^8 bacilli, 1/3m, 2 yr	29 (35·2 LL, 21·4 BL)
		25	C: Drugs as above, Placebo 'vaccine', 1/3m, 2 yr	28 (40 LL, 10 BL)
31	≥2 yr	37	V: as above	27 (35 LL, 14 BL)
		34	C: as above	35 (50 LL, 14 BL)

regular clofazimine for 5 years, had a much lower incidence of ENL than those on other regimens. However, this trial was not truly randomized: subjects in group I were all newly-diagnosed patients whereas those in group II were all relapsed patients previously treated with dapsone monotherapy. Groenen *et al.*[15] found no difference in incidence of ENL, whether clofazimine or DDS was used as the third drug; but as discussed above, this trial was not randomized either. Furthermore, the effect of clofazimine could have been masked by large daily doses of rifampicin and/or ethionamide. Regimens containing these had a higher incidence of ENL than the WHO regimen, although a much smaller number of patients took the WHO regimen. Ji *et al.*[18] found more ENL in the regimen containing clofazimine and dapsone than in the regimens containing ofloxacin alone, but the number of subjects in their trial was too small for chance differences to be ruled out.

Rifampicin, known to be potently bactericidal, could increase the risk of ENL because of the rapid breakdown of bacilli and release of antigens into the circulation, which could then form the immune complexes believed to be involved in ENL.[12] This hypothesis is supported by Jadhav *et al.*,[30] but not by Thomas *et al.*[21] or Singh *et al.*[22] The trial by Jadhav *et al.*[30] seems to be the best test of high dose rifampicin: it found a much higher rate of ENL in the

regimen containing daily rifampicin for 9 months than in the standard WHO regimen. Thomas *et al.* gave rifampicin for three months only; Singh *et al.* gave it for 21 days, before reverting to WHO–MDT.

Motor and sensory impairments themselves have not been widely studied in relation to the impact of MDT. However, several researchers have investigated lagophthalmos. This motor impairment prevents normal eye closing and predisposes to corneal damage and loss of visual acuity, and may account for a large proportion of leprosy-related potentially blinding disease (35% in one study[38]).

Lagophthalmos occurred in 3·7% of the 678 patients surveyed by Waddell & Saunderson;[39] no link was found with type of treatment (monotherapy or MDT). In some cases, the lagophthalmos improved during chemotherapy. In a survey of 640 MB patients, Courtright *et al.*[38] found lagophthalmos in 3.8% of newly-diagnosed cases and in 10.2% of patients previously on DDS monotherapy. Good compliance with MDT diminished the risk (to 3%) and poor compliance increased the risk (to 50%). However, others[40] claim that the risk of lagophthalmos is raised in the first 6 months of MDT (presumably due to TIRs).

Plantar ulcers, the result of sensory impairment, were studied by Mane *et al.*[41] Ulcers were prevented by MDT, but not in patients who already had a sensory impairment at the start of therapy. For these, disability is best prevented by basic preventive measures such as protective shoes which are attractive enough for patients to wear.[6,42] MDT usually limits the further development of anaesthesia; but it does not always restore sensation which has already been lost.

SPECIFIC DEFORMITIES

Specific deformities occur in patients with lepromatous (LL and BL) leprosy. Some specific impairments are caused simply by local proliferation of bacteria, while others are caused by Type 2 or ENL reactions.

Iritis is an example of a localised infection which may result in a specific impairment, and eventually blindness. The best data on MDT and iritis comes from a prolonged follow-up study of 678 patients in Kasese District, Uganda.[39] Twelve per cent of patients surveyed had iritis, of whom 33% had visual loss in one or both eyes. Iritis was the primary leprosy-related cause of visual loss. The risk of iritis was not significantly greater in patients who received rifampicin late or not at all, compared to those who received it within a year after diagnosis (adjusted odds ratio = 1·8, 95% confidence intervals 0·88–3·9). MDT was not always immediately successful—four patients still suffered from iritis after 2–11 years of rifampicin. Iritis need not cause damage if treated early; the improved prognosis in recent years may result from improved overall management and earlier presentation, rather than MDT alone.

Nasal deformities are prevented by prompt chemotherapy, according to Srinivasan.[10] Within a few months of starting treatment, bacilli are cleared, mucosal ulcers heal and granulomas resolve. Some disfigurement may persist and require plastic surgery. Unfortunately, there is little published work comparing the effect of MDT with that of monotherapy on the incidence of nasal damage. Since it is caused by bacterial proliferation, any antileprosy chemotherapy would be expected to help.

Arthritis may be caused by localized proliferation of bacteria in the joints, or an immune mediated reaction against synovium. In a survey of 66 patients in an Egyptian leprosy colony, Atkin *et al.*[28] found 20 (30%) had an inflammatory symmetrical peripheral polyarthritis. 11 of these patients (55%) showed presence of bone erosion on radiography. All of the patients had

pain on active and passive movements of the joints, which may have been disabling. Treatment with MDT led to slow resolution of the arthritis and associated morning stiffness and joint pains. In some patients, the onset of arthritis coincided with noncompliance. Unfortunately the arthritis never resolved completely, although acute exacerbations became less frequent and less severe on MDT. Some patients had permanent structural deformities. However Singh and Kaur, in a study of 60 patients in India, found no evidence of bone erosion, and joint symptoms resolved completely in most patients after one year of MDT.[13]

In summary, MDT largely prevents the development of new impairments caused by bacterial proliferation. Rifampicin is very effective at killing bacteria. But it may precipitate damaging immune reactions, probably due to the release of bacterial antigens. Clofazimine, through its anti-inflammatory effect, may help to prevent Type II reactions.

The preventive impact of multidrug therapy on leprosy disabilities

Apart from neuritis, the most important drug-related risk factor for the development of impairments and disabilities is the duration of active disease. The impact of MDT on this will be reviewed, firstly for paucibacillary, then for multibacillary patients. Then it will be considered whether MDT can improve the 'disability scores' of patients.

PAUCIBACILLARY PATIENTS

In paucibacillary leprosy, dapsone monotherapy was prescribed for 3–5 years and the average time to reach inactivity was $15 \pm 8{\cdot}6$ months.[44] Table 3 shows the percentage of patients whose lesions become inactive after 6, 12 and 24 months, under different PB drug regimens. While definitions of inactivity vary from study to study, large differences between studies probably indicate true differences, and comparisons within studies are valid.

Husser *et al.*,[43] comparing DDS monotherapy with two short regimens of rifampicin monotherapy, showed clearly that it takes two years before most cases become inactive. At one year, fewer DDS cases have reached inactivity than rifampicin cases. In comparison, Bhate *et al.*[44] found that the majority of cases treated with two different MDT regimens became inactive within one year (average time to reach inactivity is $6{\cdot}95 \pm 2{\cdot}13$ months for I and $8{\cdot}21 \pm 2{\cdot}84$ months in group II). Orege *et al.*[14] also found that most patients on the WHO regimen reached inactivity by 8 months. The modified MDT regimen—two large doses of rifampicin at an interval of three months—produced inactivity within six months. Becx-Bleumink[32] found that after 6 months on WHO–MDT, 114 (30·3%) of 963 patients still had active skin lesions. Treatment was stopped according to the protocol and the skin lesions became inactive within two years in all except one of the 114 patients. The single-dose MDT regimens studied by Pattyn *et al.*,[45,46] potentially convenient and inexpensive, show a much slower progression to inactivity. The MDT regimen recommended by WHO dramatically reduced the duration of active disease in most paucibacillary patients; some other regimens may have an even greater impact. Thus MDT has prevented the development of impairments and disability in many PB patients.

MULTIBACILLARY PATIENTS

Curtailing the duration of active disease is especially important in MB leprosy, as nerve

Table 3. Randomized-controlled trials of MDT for PB leprosy; % of patients with all lesions inactive at 6 months, 1 year and 2 years

Ref	N	Treatment regimen	6 m	1 yr	2 yr
43	24	A: DDS 100 mg od, 3 yr	N/A	0–33	66–91*
	29	B: RMP 900 mg 1/w, 8 wk	N/A	28–57	51–86*
	22	C: RMP 900 mg 1/w, 12 wk	N/A	37–62	77–95*
44	40	A: RMP 600 mg 1/m, 6 m DDS 100 mg od, 1½ yr	50·0	92·5	N/A
	40	B: RMP 600 mg 1/m, 6 m CLO 100 mg 1/2d, 6 m DDS 100 mg od, 1½ yr	40·0	85·0	N/A
14	64	A: WHO–PB–MDT	63·3	83·0	N/A
	63	B: RMP 1500 mg 1/3 m, DDS 100 mg od, 6 m	82·3	88·1 (at 8 m)	N/A
45	247	A: RMP 1500 mg, 1x, DDS 100 mg od, 1 yr	N/A	12–22	56–67†
	240	U: RMP 40 mg/kg, 1x	N/A	8–24	53–54†
46	223	C2: RMP 40 mg/kg, 1x CLO 1200 mg, 1x	N/A	N/A	66·8–73·5‡
	212	C4: RMP 40 mg/kg, 1x CLO 100 mg, 1x DDS 100 mg, 1x ETH 500 mg, 1x	N/A	N/A	71·6–77·6‡

Abbreviations: see Table 1. 1/2d, once every two days.

N/A, not available, i.e. not quoted in the paper.

* Range from worst hypothesis (regressive lesions counted as uncured) to best hypothesis (regressive lesions counted as cured).

† Range across different patient groups, according to number of skin lesions and bacteriological index (0 or 1).

‡ 95% confidence intervals.

damage and paralysis occur only late in the course of the disease,[12] and the risk is much greater than in PB leprosy.[39] Yet duration of active disease is much more difficult to assess in MB than in PB patients.

The mouse footpad test involves inoculating mice with 10^4 *Mycobacterium leprae* from the patient, and checking for replication. If the test is negative, it simply implies that there are fewer than one viable organism per 10^4 inoculated.[47] There may still be some undetected 'persisters' in the patient, which could cause a relapse. Nevertheless, this test is useful in the initial stages of therapy to determine the speed of killing. An untreated MB patient may harbour 10^{11} *M. leprae*, of which 10^{10} may be viable. This technique has shown that *M. leprae* from the lesions of MB patients no longer infect mice after different periods according to the drug regimen (Table 4). Single-dose rifampicin (600–1500 mg) is clearly the best bactericidal treatment; there is no evidence in these studies to suggest that other drugs potentiate its effect in killing *M. leprae*.

Clinical evaluation of the duration of active disease is also important. The single randomized-controlled trial comparing DDS monotherapy with MDT[17] found that 20% of patients treated by monotherapy (group A) still had clinically 'progressive' disease at 6 months, compared to 0% of those on MDT (Figure 1). The three groups were broadly comparable, but more of group A had nerve motor function impairment (26% compared to

Table 4. Period after which *M. leprae* from MB patients are no longer infective to normal mice[47,48]

Regimen	Period	Ref
DDS 50–100 mg od	100d	47
CLO 100–200 mg od, or 100 mg 3/wk	150d	16, 47
RMP 600–1500 mg 1x	7d	47, 48
CLT, 500 mg od	28 d	20
MIN, 100–200 mg od	56d	19, 20
OFL 400–800 mg od	28d	18, 49
PEF 800 mg od	56 d	49

Abbreviations: see Table 1.

18% in B and 16% in C) and thickening of nerves (31%, compared to 21% in B and 19% in C). These may indicate an advantage of MDT, or more active disease at the outset of treatment in those given the DDS monotherapy. However, given the above data for the bactericidal impact of rifampicin, the first explanation is the most likely.

DISABILITY SCORES

The ideal test of the impact of MDT on disabilities in different individuals would be to monitor their 'disability scores' before and after treatment. Unfortunately the few studies that have done this do not use a common scoring system. WHO scales do not differentiate between deformity and disability, and significant changes can occur in the extent of disability without a change in the disability grades.[11]

Smith[50] notes that those with impairment naturally tend to deteriorate. Chemotherapy may help to prevent this deterioration. Smith & Parkhe[51] failed to find a change in the mean disability index of 153 patients after four years of DDS monotherapy. Pönnighaus & Boerrigter[23] found that MB patients receiving only 18 doses of WHO–MDT had a higher risk of developing disabilities than those receiving 30 doses. Groenen *et al.*,[15] in a prospective study of 335 PB and 280 MB patients taking various regimens (MDT, RMP monotherapy) found that deformity scores remained unchanged in 95% of patients, deteriorated in 3% and improved in 2%. Richardus *et al.*[52] obtained similar results: 1·6% of previously normal patients developed nerve function impairment and 1·3% with impairment recovered by the end of treatment; corresponding figures for MB patients were 7·9% and 4·0% respectively.

DISABILITY RATES

It is notoriously difficult to measure the level of disabilities in different populations if one adheres to the strict definition of disability as 'any restriction or lack of ability to perform an activity in the manner as within the range considered normal for a human being'.[50] It has been argued that any impairments should be taken into account because 'Grade I disabilities' may deteriorate into 'Grade II disabilities' unless preventive action is taken.[53] Nevertheless most studies take account only of 'Grade II' disabilities.

The prevalence, or proportion of *all* leprosy patients with disabilities (grade II) at a single point in time, is given by several surveys. It varies from 60% in Nigeria in 1988[54] to 12% in

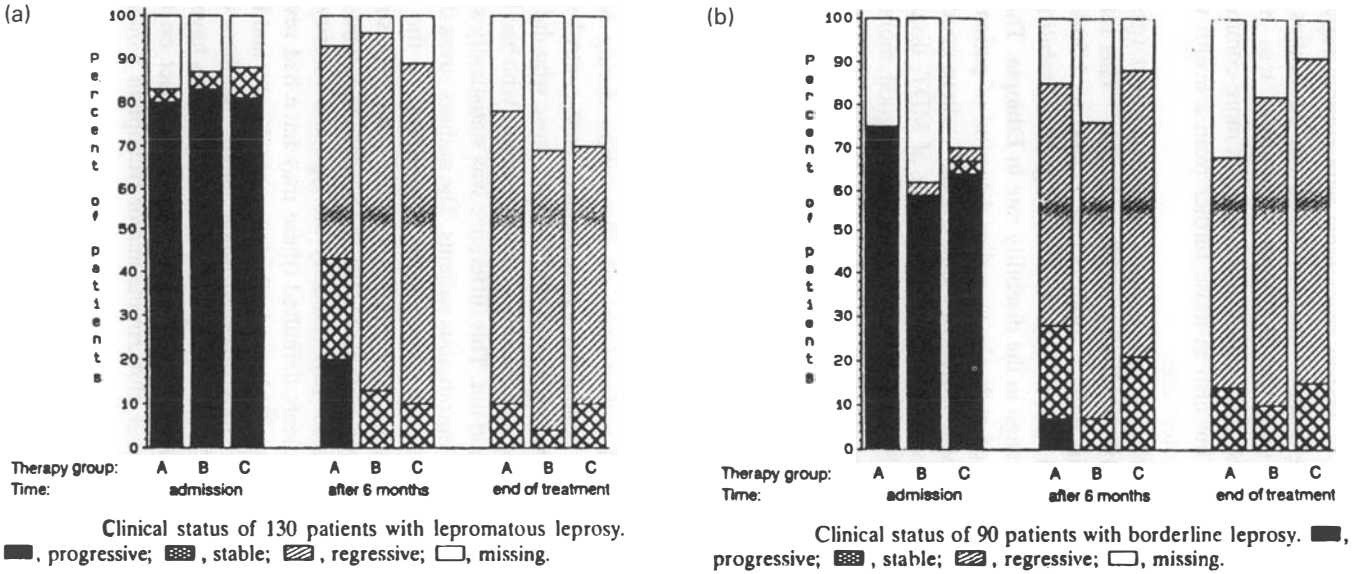

Figure 1. Clinical status of patients with MB leprosy: Group A: (N = 68) DDS 100 mg od; Group B: (N = 77) DDS 100 mg od, RMP 10 mg/kg od; and Group C: (N = 75) DDS 100 mg od, INH 350 mg od, PTH 350 mg od, RMP 10 mg/kg od. (Reproduced with permission from Dietrich *et al.*[17])

India in 1989.[53] Smith & Parkhe[51] demonstrated a decline in the proportion of patients with disabilities in spite of an increase in the number of cases of leprosy from 1979 to 1983 in India. They claimed that the leprosy control programme with monotherapy had slowed the deterioration in those with existing disability and prevented new disabilities. However, early detection of new cases before they had developed disabilities was probably equally important. Courtright *et al.*[55] found that ocular morbidity was more common in those who did not comply with their MDT, but also in those further from a health worker or health centre, who would have been detected later.

The disability rate, or proportion of *new* patients with disabilities (grade II) has been measured as 10·9% in China in 1982–3[56] and 12·7% in Nepal.[57] This rate has decreased following introduction of MDT in India,[58] from 6·15% (1984) to 1·50% (1987), and in Ethiopia,[32] from 20·6% (1984) to 13·9% (1989). However if grade I disabilities are also taken into account, there has been no change in the disability rate in Ethiopia. That the proportion with severe disabilities has declined is thanks to earlier detection of patients rather than an effect of MDT *per se*.[32] In Thailand,[59] Malawi[60] and China,[61] where good leprosy control programmes were already in place before the introduction of MDT, disability rates have remained stable. Yet in French Polynesia, which also had a good monotherapy control programme, the disability rate was stable at an average of 31·5% until the introduction of MDT when it dropped to an average of 11·7%.[62] This may have been thanks to household contact training, leading to better detection in children below the age of 15. The risk of disability is lower for younger patients.[63] Conversely, disability rates have increased in Bhutan despite the introduction of MDT, because fewer mass surveys are being done to detect patients early; these have become uneconomical as the prevalence of leprosy has fallen.[64]

The incidence of impairment during treatment is fairly low: 11·1% of patients receiving DDS for 5 years in India;[65] 2% of patients after 2–7 years of DDS chemotherapy in Trinidad and Tobago;[66] and 0·7 per 1000 patient-years of observation during MDT in India.[67] However, Radhakrishna & Nair[65] conducted a retrospective case-control study of patients on DDS monotherapy who developed leprosy disabilities and those who did not. They found that the incidence of disabilities was significantly higher in patients who had been taking their drugs regularly than in those who had not. This difference was statistically significant for PB and borderline patients, but not for lepromatous patients. The authors stress that they assessed regularity of drug-taking *before* the development of deformities; so the result is not an artefact due to deformed patients being more motivated to take drugs. The study suggests that regular DDS increases the risk of impairments for PB and borderline patients, possibly due to the increased risk of Type I reactions. Unfortunately the type and severity of impairments were not recorded, and 30% of patients defaulted (these may have had severe disabilities). This finding was replicated by Gupte,[68] also in India, but not by Keeler and Ryan in Trinidad and Tobago.[66] However the latter study involved much smaller numbers of patients (529, compared to 5746 in study 65 and 2608 in study 68). No similar studies have been conducted for MDT, so it is not clear whether it would have the same impact on the incidence of disabilities as DDS alone, or whether clofazimine and/or rifampicin would protect against development of deformities.

MDT itself cannot affect the disability rate, which declines in response to earlier case detection. The incidence of impairments during treatment may be lower with MDT than with monotherapy, but this has yet to be proven definitively. It would be especially interesting to know whether those who take their MDT regularly are more or less likely to develop deformities than those who take it less regularly.

Discussion

MDT has a number of advantages over DDS monotherapy, which it has superceded. As well as its preventive and epidemiological impacts described above, MDT may have a number of important indirect effects. Compliance is improved,[69,70] partly because the regimens are shorter. Cost is also reduced.[69] Self-reporting may increase when patients know there is an effective treatment;[71] this has been observed in Bhutan,[64] although not in Malawi[60] or in all areas of China.[61] The caseload of leprosy workers decreases dramatically as patients are released from control much faster;[72–75] this releases time for surveillance work, prevention and treatment of disabilities.[53] The more frequent (monthly) contact between health workers and patients, for supervised administration of rifampicin, provides more opportunities for health education and disability prevention.[74] The greater efficacy of MDT may have motivated health workers to improve drug coverage and routine assistance to patients with leprosy,[76] stimulating better compliance, and setting in motion a virtuous circle.

Yet MDT also has its disadvantages. It does not eliminate microbial antigens from nerves, which may perpetuate neuritis and cause further impairments long after the patient is 'cured'.[77] For example, corneal sensation sometimes continues to decrease long after the completion of MDT,[78] and this leads to loss of vision. Second, allocation of patients to the PBor MB regimen is not always easy.[32,76] The higher cost of MDT in the short term[79] may be prohibitive in impoverished areas where leprosy is commonest. It would be tragic if statistics of declining global prevalence were misinterpreted to justify reduced funding for the treatment of leprosy.[80]

The problem of leprosy disabilities cannot be solved by MDT alone. Other approaches are also necessary, both to prevent disabilities and to help those already afflicted. These have often been neglected while the WHO has vigorously promoted MDT. Most important for prevention are early case-finding and adequate treatment of reactions, and also improvements in infrastructure and socioeconomic conditions. Good housing and schooling both decrease the risk of leprosy.[81]

Those who are already disabled need re-ablement, disability prevention and rehabilitation.[4] Programmes to prevent and treat disabilities have the added bonus of improving compliance with MDT.[74] Although MDT improves the recovery of lost function (50%, compared to 20% with monotherapy in Malawi[82]), it cannot cure many deformities. 8·3% of leprosy disabilities could be reversed by surgery, health education and physiotherapy.[63] Health education is important to prevent new disabilities from developing when the patient has lost sensation and/or movement in a part of their body. New habits for living and working must be learnt and harmful old habits discarded. This involves behaving differently from others, possibly provoking ridicule, so the support of family and neighbours must be enlisted.[4] Last but not least, rehabilitation is necessary to re-integrate disabled patients into society and to help them lead as normal a life as possible. Although some aid agencies are doing rehabilitation work it is relatively expensive: it costs £44 to establish a vegetable business, and £141 to train a tailor.[83] Therefore it has been argued that the money would be better spent on improving MDT coverage to prevent new disabilities from occurring.[84]

Conclusion

MDT has had an impact on leprosy disabilities, especially by stopping active disease and so

preventing the development of disabilities in the long term. This benefit outweighs the short-term cost of increased risk of immune reactions which may result in impairment and disability. Not surprisingly, MDT has had no impact on already existent disabilities, nor on the incidence of disabilities in untreated patients. These last two problems must be tackled by other means. Although the number of registered cases of leprosy has declined dramatically, many 'cured' people still suffer from disabilities and need re-ablement, health education and rehabilitation. These must be promoted in conjunction with MDT to tackle effectively the age-old problem of leprosy disabilities.

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Lepr Rev (1997) **68,** 367–370

SPECIAL ARTICLE

Leprosy and the Internet

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Few things have been hyped in the media as much as the Internet, and yet its practical value remains unappreciated by most people. I therefore thought it would be useful to list some practical ways in which the Net might benefit the leprosy worker or unit.

Background

When people talk about the Internet, they usually mean the World Wide Web (the *Web*), a relatively recent development, but undoubtedly the most user-friendly and useful part of the Internet. The Web is basically a global, open network of many computers, any of which can be easily and quickly accessed by users anywhere in the world. The beauty of the Web is that it is based on easy-to-use 'point and click' Windows-type Web *browsing* software, and it is flexible, allowing text, pictures and sound to be accessed and downloaded from Web *sites*. As technology improves (particularly data transfer speeds), the Internet should become a fully-fledged communications network, e.g. for telephones, videophones/videoconferencing, movies, and shopping and banking transactions.

To access a given Web site, the user need only type in the site's *address*, which usually has the format http://www.NAME OF WEB SITE. So, for example, the US Food and Drug Administration's Web address is http://www.fda.gov. The number of Web sites worldwide is growing rapidly (in fact exponentially), and currently stands at around one million. A huge amount of information is available on any subject, limited only by the imagination (and persistence!) of the user.

Equipment and cost

To access the Internet, you will need a PC (personal computer), modem and telephone line, by which means you dial up a *server*. The costs incurred by you therefore comprise a telephone call (usually local rate) plus on-line time paid to your server. To reduce cost, many servers now offer a fixed monthly charge, e.g. £10, which gives unlimited access to the Internet, i.e. no on-line charges apart from that of the telephone call. Beyond these costs, there are no other charges; most Web sites are free to access, and there are no extra costs for accessing overseas Web sites. A Web site on the other side of the world is as quick and easy to access as one 10 miles away. Geography ceases to be a limiting factor, which would be of great value to leprosy workers, particularly those in isolated rural areas. Within the next 1–2 years, low-cost, high-speed global satellite links and phones should become available,

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e.g. based on the satellites of the Iridium Network, which are currently being launched, so that even a telephone 'land line' won't be needed.

How to find relevant Web sites

How can information and relevant Web sites be found quickly, without spending hours *surfing the Net*? Web sites are 'indexed' by *search engines*, which are basically Web sites devoted to exploring and indexing other Web sites. As the number of Web sites and their contained text is so huge, powerful workstation computers are often used for this purpose. There are many dozens of different search engines, and some Web sites specialize in allowing multiple search engines to be utilized simultaneously (such as SavvySearch). One good search engine is Yahoo (http://www.yahoo.com), which rigorously classifies all of its data, and is a good place to start, e.g. for medical dictionaries and journals, regional newspapers etc. However, it is not as thorough as other search engines, the best of which are HotBot (www.hotbot.com) and AltaVista (www.altavista.digital.com).

Whichever search engine you use, searches can typically be performed in a few seconds, and may result in many thousands of *hits* (Web sites containing the word(s) you are interested in). Clearly, some Web sites will be more relevant to your search from others, ranging from sites mentioning your key word(s) just once, to sites devoted solely to your subject of interest. Thankfully, good search engines will indicate the best Web sites, by such means as a star system or percentage rating. When I did such a search for leprosy on HotBot, for example, I had 7,404 hits—although not all of these sites were useful, of course! Some good leprosy Web sites are as follows:

1 *The British Leprosy Relief Association* (LEPRA; http://www.lepra.org.uk): 'A medical charity with the single aim of the eradication of leprosy'. Includes the contents and editorial pages of *Leprosy Review*.
2 *World Health Organization Action Programme for the Elimination of Leprosy* (http://www.who.ch/programmes/lep/lep_home.htm): 'A world without leprosy is no longer a dream'.
3 *International Federation of Anti-leprosy Associations* (hhtp://www.oneworld.org/ilep/ilep_x.htm): 'ILEP is a federation of all the main donor non-governmental agencies supporting anti-leprosy work worldwide'.
4 *INFOLEP* (http://infolep.twinfo.nl/infolep): 'The leprosy information services of the Netherlands Leprosy Relief Association (NSL). … An information and documentation centre offering its services to all those who need information on leprosy in all its various aspects'.
5 *The ILEP Action Group on Teaching and Learning Materials* (TALMilep; http://www.oneworld.org/ilep/talmilep.htm): 'Undertakes to stimulate, facilitate and co-ordinate efforts to provide and distribute teaching materials in leprosy worldwide. Since its conception in 1983, TALMilep has produced and distributed a wide range of publications, many in multiple language editions'.
6 *American Leprosy Missions* (http://www.leprosy.org/): 'Celebrating 90 years of ministry to people with leprosy'.
7 *International Journal of Leprosy* (http://www.allenpress.com/catalogue/index/lepr/index.html).

8 *CIOMAL International Committee of the Order of Malta for Leprosy Relief* (http://www.oneworld.org/ilep/ilep_x.htm).
9 *Urban Leprosy Control Programme* (http://www.pcsadvt.com/glra-india/urban.htm): 'The Greater Madras Leprosy Treatment and Health Education Scheme (GERMALTES) was launched by GLRA in 1971, with the objective of controlling the spread of the disease in Madras'.
10 *Novartis Foundation* (http://www.foundation.novartis.com/leproj.htm): 'Leprosy projects: numerous countries and projects, including active case finding, comprehensive care (MDT and deformity care), mobile clinic and social marketing, and Mother Teresa's Leprosy Centre'.
11 *Leprosy Discussion List* (http://www.who.ch/programmes/lep/15.htm): 'An experimental discussion list for scientists, programme managers, agencies and individuals involved and interested in the elimination of leprosy as a public health problem ... set up by the WHO Action Programme for the Elimination of Leprosy'. This list started on 26 February 1996.
12 *American Leprosy Foundation* (http://www.charity.org/alf.html): 'Offers training courses, workshops and seminars to scientists, leprologists, and students of infectious diseases on an international scale. The Foundation establishes and maintains clinics and hospitals for diagnosis and treatment. Because of widespread misunderstanding of leprosy, the Foundation strives to educate the public that leprosy still exists and that its victims must be helped'.
13 *Flight Aid Trust* (http://www.mersinet.co.uk/flight-aid/.) A group of aviation enthusiasts and pilots that helps to fund the long-term treatment and rehabilitation of victims of leprosy in Zambia.
14 *Support Groups for Leprosy* (http://www.jaring.my/winweb/medical/category/med51.htm).

Other potential benefits of the Internet

E-mail: Apart from on-line charges, e-mail is free, instantaneous to anywhere in the world, and is not subject to local postal difficulties. Moreover, an e-mail sent to 100 recipients can be sent as quickly as one for a single recipient, in contrast to a fax, which would need to be sent 100 times.

'Free' telephone calls: Many computer programs now exist which allow your computer to be used like a speakerphone (provided you have a full-duplex soundcard, speakers and a microphone). It is then possible to communicate by telephone or fax with anyone else in the world having similar software and an e-mail address, all for the cost of on-line time only. This may have major cost-saving implications, particularly for international phone calls. The US company Intel (which manufactures about three-quarters of the world's computer chips) markets state-of-the-art Internet phone programs (audio and video), which can be downloaded free from its Web site (http://www.intel.com). Current developments in this area include telephones which can be plugged directly into the Internet, without the need for expensive software or computers, and programs which allow you to contact any telephone number, i.e. normal phones, from your computer.

Access to databases and medical journals: Many databases such as Medline, e.g. http://www.medscape.com, and journals such as the *Lancet* (www.thelancet.com), *British Medical Journal* (www.bmj.com) and *New England Journal of Medicine* (www.nejm.org) can be

accessed via the Internet, usually for free. In this way, the world's resources, greater than any single library, can be available to a leprosy worker or unit anywhere in the world, however remote. The other implication is that the time wastage and costs associated with travelling to libraries, subscribing to journals, or using expensive non-Internet databases can be avoided. Articles can be ordered on-line if desired, and *full-text* articles are increasingly put on Web sites, allowing the user to read the full article (rather than just an abstract) without even needing to order it.

Co-operation: Forums of like-minded people on any subject can easily be set up, e.g. Usenet newsgroups, if they don't already exist, which could enable leprosy workers anywhere in the world, for example, to share information and solve problems more easily. Problems posted on Web sites can also be answered by any interested 'visitors'. Recently, there was a case of a Chinese patient with a puzzling medical condition who was diagnosed by doctors browsing a Web site—the first such case of its kind. Even X-rays and CT scans can be viewed on Web sites, the only limitation being the user's imagination (together with the available technology and cost, of course!).

I hope that this article has given a hint as to how the Internet may be useful for leprosy workers and others, even if I have only scratched the surface of what is possible. Fundamentally, the Internet is as broad as the people who use it, and as the number of users inevitably grows, and technology advances, it will become increasingly heterogeneous and mainstream, e.g. incorporated within television sets and telephones; home shopping. The bottomline is that if you cannot see a current use of the Internet for you, invent one, share the information, and watch your ideas grow!

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Obituaries

WILLIAM H. JOPLING, 1911–1997

Dr William Jopling, well known to nearly all leprologists of his generation through his writings, research and friendship, died on 21 August 1997 at the age of 86. He was a specialist in leprosy, a humane physician and a family man who enjoyed life.

Born of British parents in Italy, he went to school in England and then studied medicine at St Bartholomew's Hospital, London. Later he gained the FRCP at both the London and Edinburgh Colleges. After undertaking a variety of junior hospital posts, he travelled as ship's surgeon on a six months voyage to the Far East. This was followed by appointment as Government Medical Officer in the Southern Rhodesia (now Zimbabwe) Medical Service, where at one time he was the only doctor for some 70,000 patients scattered over a huge area, about the size of Yorkshire. This proved to be an impossible assignment, and he was obliged to spend the war in Africa. He decided to learn more about leprosy after learning that a leprosy patient of his could only travel by rail if ankle deep in lime! He also took the patient to hospital by car. Subsequently, he paid visits to a leprosarium and spent one of his leaves there. After the war he returned to London, and took a post at the Hospital for Tropical Diseases where he was later appointed Consultant Leprologist. He also became Consultant in Tropical Dermatology at St John's Hospital for Diseases of the Skin, and he retained both these posts until his retirement. Other appointments included membership of the Editorial Board of *Leprosy Review* over a number of years. His contributions were always valuable.

William Jopling's eminence was as a clinician. He was an astute observer, with shrewd judgement with an understanding of his patients that owed much to the time he devoted to them; there was nothing he would not do for a patient in need, and many became devoted to him.

He seldom initiated research, but the dependability of his clinical judgement made him an invaluable and much sought after research partner, and for many years he was a central figure in the Hospital for Tropical Disease's leprosy research programme. When in 1950 the Jordan Hospital was established to cater for 24 leprosy inpatients at Earlswood in Surrey, the Jopling family were put in residence. (A situation that initially caused embarrassment among the local community.) Although there were only a small number of patients the proximity to London offered an outstanding opportunity for clinical research. These patients, perhaps the most intensively investigated leprosy patients anywhere at any time, became a model for what could be achieved in pilot trials. This hospital closed in 1967 when it became possible to treat the patients on an outpatient basis in London, but the programme continued. Jopling's first researches were therapeutic evaluations, old drugs versus new. This was a field that he never gave up, and later he conducted an early trial of multidrug therapy in Malta. He had a

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matter-of-fact turn of mind, and a preference when permissible to simplify. These qualities were much needed at a time when orthodox leprology was weighed down with niceties as the distinction between reactional tuberculoid and tuberculoid in reaction, borderline and dimorphous, and this was true particularly in relation to the classification with which his name is linked. His work in this field, which did so much to clarify the understanding of leprosy, was recognized by the award of the Sir Rickard Christophers medal of the Royal Society of Tropical Medicine and Hygiene in 1994.

His good humour and commonsense endeared him to students; teaching was one of his more important contributions to leprosy, and beyond that to tropical dermatology and medical practice in the tropics. In addition to lectures and articles Jopling was the author of a range of books that were all well received. His main work, *Handbook of Leprosy*, has just reached its fifth edition. Other titles were *Treatment of Tropical Diseases*, *Differential Diagnosis for Practitioners in the Tropics*, and *Travellers Guide to Health Protection Abroad*.

William Jopling was a generous friend, and long after retirement he remained in touch with old colleagues from around the tropics. In his younger days he was an athlete and rugby player, and he enjoyed fishing. Among his other interests he composed music, setting poems to song. He was a man of political conviction, and in a tolerant sort of way a supporter of left-wing causes. During the last three years he suffered progressive illness and failing eyesight, remaining always outwardly cheerful and grateful for his good fortune. He was twice married, and is survived by his first wife, their three sons, a daughter and eleven grand children.

D. S. RIDLEY

Obituary W. H. Jopling

Teaching Materials and Services

Schieffelin Courses, 1998 • ALERT Courses, 1998 • Health information for the developing world • Action Programme for the Elimination of Leprosy, LEC–SAPEL. Nongovernmental organizations: WHO Liaison • *The World Guide*, 1997–98. • The Cochrane Library • *Leprosy control in Myanmar*, 1948–1973 • *Treatment of neuritis in leprosy*.

News and Notes

'Indian research doesn't reflect country's needs' • Gender and leishmaniasis in Colombia: inequality in access to health services for women • Genetic engineering reverses antibiotic resistance • Human Development Report, OUP, 1997 • Why does HIV infection progress to AIDS? • Tuberculosis infection process pinpointed • Thalidomide ban to be lifted in the USA • Reaching undetected leprosy patients in endemic countries, ILEP-WHO Workshop, July 1997 • Independent evaluation of leprosy elimination activities in Bangladesh, September 1997 • Report of Strategies for elimination of leprosy from Maharashtra Workshop • Princess Diana Fund to raise millions • 'Leprosy of consequence' • Major breakthrough in leprosy using single-dose treatment inaugurated: treatment span slashed to half for multibacilliary cases • *Handbook of leprosy*, Fifth Edition • *Leprosy Review* Poster: Staining slit-skin smears.

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Letters to the Editor

ERYTHEMA NODOSUM LEPROSUM IN SUBGROUPS OF LEPROMATOUS LEPROSY

Editor,

Lepromatous leprosy has two subgroups, subpolar lepromatous leprosy (LLs) and immunologically stable and anergic polar lepromatous leprosy (LLp).[1–3] This subgrouping is based on genesis of lesions, clinical and histological examination[2] (Table 1). LLs patients acquire lepromatous status by gradual downgrading whereas LLp is de novo lepromatous.

Erythema nodosum leprosum (ENL) is an acute immune complex mediated reactional episode, occurring in patients at or close to the lepromatous end of leprosy spectrum and characterized by widespread crops of evanescent, erythematous and indurated subcutaneous nodules mainly on face and limbs, usually accompanied by fever and other constitutional symptoms.[4,5] Classical histological features of active ENL lesions include increased vascularity with many dilated capillaries in the upper dermis and neutrophilic infiltration, oedema and vasculitis in lower dermis.[4,5] We have retrospectively studied 659 lepromatous leprosy (LLs-552, LLp-107) patients out of 3500 leprosy patients registered in our leprosy clinic, over a 19-year period for the development of ENL with or

Table 1. Clinical profile of LLs and LLp

Observations	LLs	LLp
Genesis of lesions	Lesions arise by gradual down grading from higher spectrum	Lesions arise de novo
Clinical features		
– infiltration	Patchy	Diffuse
– peripheral neuropathy	+	++
– oedema hands & feet	+	++
– neuritis	++	–
– deformitis	++	+ (Late)
– trophic ulcers	++	+ (Late)
– nodules	+	+
Histopathology		
– compact macrophage granuloma	++	++
– lymphocytes	Moderate number	Scanty
– foamy change	+	++
– nerves	Onion skin appearance	Normal/Hyalinised
Bacteriological Index	Significant variation from site to site	Uniformly high at all sites (4^+-6^+)
Upgrading reactions	+	–
Lepromin conversion with immunotherapy	+	–

Table 2. ENL in patients of LLs & LLp

		Patients	ENL
LLs	M	432	110 (25·4%)
	F	120	35 (29·0%)
	Total	552	145 (26·2%)
LLp	M	82	9 (10·9%)
	F	25	3 (12·0%)
	Total	107	12 (11·2%)

(p. value < ·001).

without antileprosy drugs. ENL was diagnosed by clinical and histopathological findings. We have been giving rifampin daily for at least 1 year in all lepromatous leprosy patients along with dapsone and clofazimine as per WHO–MDT since 1984. Prior to this period some patients also received dapsone monotherapy. It may be mentioned here that about 31% of LL patients dropped out before completing two years treatment.

ENL was observed in 26·2% (M, 25·4%, F, 29·01%) patients of LLs while only 11·2% (M, 10·9%, F, 12%) patients of LLp showed ENL reaction ($p < 0{\cdot}001$) (Table 2). Interestingly, in our study, all patients of LLp who developed ENL, developed so on antileprosy drugs, while about 25% of LLs patients developed ENL before starting treatment. It is possible that in immunologically unstable LLs other factors such as intercurrent infections, stress, vaccination, etc., may precipitate ENL. Antileprosy drugs can precipitate ENL by disintegration of *M. leprae* and release of antigenic material.[6] Presence of raised levels of C3 break down product C_3d in ENL episodes is compatible with presence of extravascular complement fixing complexes at the sites of antigen release,[4,5] while circulating immune complexes, are not likely to cause ENL, because they occur equally commonly in patients of LL with or without ENL.[5]

Modlin *et al.*[7] showed that ENL tissue had more numerous cells of the helper–inducer phenotype and less suppressor/cytotoxic phenotypes as compared to nonreactional lepromatous tissues suggesting role of cell-mediated immune response in the pathogenesis of ENL.[7] Laal *et al.* also demonstrated a transient increase in cell-mediated immunity in ENL.[8] Transient changes in cell-mediated immune response may act directly, leading to the release of mycobacterial antigens in situ or permit production of an antibody critical to formation of the immune complex.[7,8] These changes in cell-mediated immunity are, however, expected to be less common in anergic and immunologically stable LLp. These immunological observations may explain our observations of an increased frequency of ENL in LLs and that none of our LLp patients developed ENL before antileprosy drug treatment.

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PERSONALISED THERAPY VS. FIXED DURATION THERAPY

Editor,

The therapeutic aspect of medical sciences cannot be equated to mathematics and cannot be standardized. The phrase itself 'Fix Duration Therapy' sounds unscientific and naïve. The 'ars therapeutica' is a complex art which needs time to be mastered and has to take into account many factors:

1 the objective therapeutic value of a given drug;
2 the absorption, metabolism, pharmacokinetics of the drug;
3 the personality and general conditions of the patients; and
4 the personality of the attending medical officer.

Too many variables for any standardization to be significant and practical.

As a matter of fact every physician has his/her own therapeutic regimen for any given disease. In the management of common ailments a physician will take the textbook's prescriptions as a broad guideline, filter them through his/her experience and finally adapt them to the patient's need, age, personality and general conditions.

Where communicable diseases are concerned—which pose a public health problem–the possibility of a conflict between the public health authorities and the physicians is not a remote hypothesis. Let us consider the case of leprosy.

The public health officer is, usually, a non-practising physician, therefore he/she thinks and behaves like a bureaucrat, whose main concern are statistics and the cost of therapeutics, that is the lowest cost! On the other hand a practising physician does resent the fact that somebody, with limited or no clinical knowledge at all, should dictate him.

The WHO guidelines of MDT are, I believe, just guidelines, i.e. that paucibacillary (PB) patients should be treated with *at least 2 drugs for at least 6 months and a multibacillary (MB) with three drugs for at least 2 years*. Unfortunately the bureaucrats read the guidelines with a different mind-frame: 6 months therapy is the *maximum* allowed for a PB patients and if the medical officer, in his judgement, feels that a particular patient requires 3 drugs for a longer period, he is labelled spendthrift or ignorant or both.

On the issue of fixed duration therapy (FDT) the Workshop on Chemotherapy held at Orlando in 1993 stressed two important points:

1, 'Fixed duration regimen may prove to be inadequate in previously untreated LL patients with a high bacterial load... caution (*should be used*) in the widespread adoption of 2-year fixed duration treatment, and 2, '... many relapses are occurring late and, therefore, five years' post-treatment follow-up appears to be inadequate, 8–10 years being the minimum required.'[1] Yet the Indian Government has adopted FDT. It is possible that behind such decision there are bureaucrats and desk-doctors.

An analysis of all the data published is beyond the scope of this letter; at any rate most of the data so far available are based on small samples or a short follow-up or both. So one can say that FDT is based on insufficient scientific data, it does not respect any of the principles of 'ars therapeutica' mentioned above and it is against the psychology of the patient and of the doctor alike.

Moreover it is *legally questionable*. A few points will give credit to my views:

1 Waters[2] has given a fair evaluation of relapses following various regimens. He says: 'Both from experience with WHO–MDT and from other regimens, a follow-up of 8–10 years appears essential.' So reports based on a shorter period cannot be considered as indicative and/or conclusive.

2 A group of thorough and reliable scientists has found viable *Mycobacterium. Leprae* (30%) in the peripheral nerves of MB patients treated with WHO regimen.[3]

3 The therapeutic regimen is, usually, based on clinical diagnosis and, in some cases, on the bacteriological index. It has been found that there is often a discrepancy between the clinical classification and the nerve biopsy report even when the diagnosis is made by an experienced clinician. Usually the nerve biopsy shows a higher BI then the skin,[4,5] so what appears as a PB is in fact a MB case.

4 Every patient is a different case and we, the clinicians, know too well that patients do not respond in the same way to the same drug: the variations in clinical response and the side effects are unlimited.

5 To my knowledge there is no disease where FDT is advocated. No doubt there are diseases for which 'protocols' have been *suggested by experts*; yet such protocols give a lot of freedom to the attending doctor.

6 As far as India is concerned, collection of statistics and treatment is done, by and large, by para-medical workers (PMWs). Without pointing the finger at anybody, we have to admit that the collection of data is faulty in a large number of cases and the way the treatment is given is not what I would desire for my son. There are good and bad reasons for it. Difficult terrain, mountainous areas and no transport facilities; at times a PMW has to walk a few miles to contact a single patient. The bureaucrats have set some targets like 'three new cases to be detected per month…,' and they want to see nice-looking statistics, in other words they like reports that show a constant decline in new cases, complete cure with the WHO regimen and no-relapses. Understandably a PMW may be tempted to please the 'boss'—after all his/her bread is at stake. It follows, I know it for sure, that: 1, If a PMW finds 12 new cases in his area, he will register only 3 (because this is the target!); and 2, at the end of the prescribed 6 or 24 months of therapy he will cancel the patient from the 'active register'; whether the patient has received only one capsule of rifampicin or 6 or 24 it is immaterial; the point is 'the *statistics* have to be in order and pleasing'.

7 What will happen when, at the end of 6 months, a PB patient thinks that he is not cured? It is very difficult to convince an educated patient that he is cured when the clinical signs are still visible. In the case of illiterate patients it is an impossible task. If the attending doctor tells the patient that he is cured and does not need any further therapy what will happen next is easy to guess. The patient will go to another doctor, who, on clinical evidence, will put the patient on another 6 months therapy. The patient may go to an Ayurveda or homeopathic doctor or even a 'quack', who will prescribe 4–8 drugs (I have seen such prescriptions!).

Eventually the patient will be treated for 2–3 years by various doctors and 'quacks'. So why not let the first doctor keep the patient under therapy for 1 year or so?

8 A doctor is legally responsible for his/her prescriptions. I, as a practising clinician, can and must take responsibility for all my actions. What about a young doctor working in a Governmental set-up? He is told what to prescribe and he has to obey orders or else … Who is legally responsible for complications, relapses, re-activation? So far our patients have been too good to us (and we too lucky). The day will come when a smart patient will take the doctor to court for complications and/or relapse. Who is going to take the blame and face the legal consequences?

In all fairness the directors of all the units (voluntary or governmental) who adopt, and impose, FDT should sign a document wherein they exonerate their doctors from any complications/relapse arising from FDT.

The practical question however is another one: do we need to have FDT?

If one single doctor had to care for ten thousand patients, a standard regimen might be practical though not ideal. But take the case of Bombay; last year there were—as per official statistics[6]—about 4600 active cases and more than 30 doctors engaged in this field. Under these circumstances the only scientific way to go about it is to personalize the treatment.

A personalized treatment is the rule in medical practice. It respects the patient and the doctor too. If you advocate FDT the role of the doctor is reduced to a 'rubber stamp': once the diagnosis is made you do not need doctors any longer but clerks.

FDT is the most frustrating thing for any real clinician who cares for his patients and likes to have a direct rapport with them. As a matter of fact hardly any dermatologist, in Bombay, follows the guidelines of WHO and least of all the FDT. Almost none of them is happy with the clinical results of WHO regimen. You cannot convince a doctor to adopt a therapy which, according to him, is not good enough or sufficient; after all he has to care for his good name too.

My suggestions:

1 Have guidelines, but let the doctors follow their knowledge and experience and take full responsibility for their prescriptions. And if the attending doctor feels that a particular patient needs 3–4 drugs he should be allowed to exercise his judgment.

2 Make it clear that the WHO regimen is the 'minimum' therapy and not the 'maximum'. Even the advocates of FDT admit that of the BI, at inception, is more than +4, a much longer period of treatment may be required.[7]

3 It is my experience extending over 20 years (and many thousands of patients) that when the patient is told about the remote possibility of relapse even the poorest will insist on having as many drugs as necessary and for as long as possible. Unfortunately, given the present trend, hardly anybody takes the trouble of explaining anything to the patients. The patient has to be explained the pros and cons of various regimens.

In conclusion I say that as a responsible doctor I am ready to take advice from my peers and elders but, in the final analysis the type of treatment and the duration is my decision and mine alone. I cannot and will not allow a bureaucrat to dictate to me.

One last work. One day I asked one of those doctor-bureaucrat: 'If your son had a TT type of leprosy, would you give him the WHO regimen?' 'Certainly not!' was the candid and prompt reply and my rejoinder: 'If 6 months therapy is not good for your son how can it be good for a poor man's son?'

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FELT THERAPY FOR LEPROSY PATIENTS WITH AN ULCER IN A PRESSURE AREA

Editor,

As a podiatrist in The Netherlands I have used felt cutouts to treat plantar ulcers in diabetics with anaesthetic feet. Whilst visiting ALERT I used this experience to experiment with self-adhesive felt cutouts for treating ulcers in leprosy patients. The purpose was to see if there was a difference in the healing of ulcers, between patients treated with felt therapy and those treated with conventional dressings.

Twenty patients of ALERT were taken into the study, and divided into two groups of 10 matching ulcers.

Group A: treated by using felt therapy of 7 mm thickness;

Group B: was the control group and received standard treatment.

All ulcers were trimmed and dressed. All patients had canvas shoes. The patients receiving felt therapy soaked the parts of the foot without felt. The control group soaked the whole foot. All patients were followed up every week, to measure the ulcer, and for trimming and dressing. Ulcer size was measured at each visit and the area of ulceration was calculated according to the following formula: $0{\cdot}785 \times \text{length} \times \text{width}$.

Temporary felt therapy

An ulcer heals optimally in a resting position after the ulcer is proper trimmed. Because some patients cannot rest, an alternative approach could be to give them felt therapy. Felt therapy is a temporary therapy to decrease the stress on the ulcer. Felt therapy is most useful for ulcers which have continuous pressure, therefore preventing healing.

Felt is pressed wool material with a sticky back so that it can be glued onto the skin. It stays in place when a patient walks. I used 7 mm thick felt. In general the felt has a useful life of no more than 10–14 days. Most ulcers were localized on the plantar aspect of the foot, all were in different places but had the same cause—pressure because of foot deformities. Each felt pad was made for the individual foot, the shape of every pad was different. Every pad had the same purpose—to relieve pressure on the ulcer.

The following steps should be followed when using felt therapy after you have trimmed and cleaned the ulcer. In my example I draw an ulcer under the 2nd metatarsal head (Figure 1).

1 Measure the ulcer and decide what size of felt is required.
2 Cut an appropriate piece of felt (Figure 1(a)).
3 Cut an opening, the size of the ulcer (Figure 1(b)).
4 Cut the rest in the shape you need.
5 Make the borders of the felt smooth, the opening around the ulcer is left straight (Figure 1(c)).
6 Put a sticky plaster over the felt (the felt will remain longer with a sticky plaster), with the same opening in it as in the felt (Figure 1(c)).
7 Dress the ulcer with a piece of gauze (Figure 1(d)).

Results

Over 4 weeks, I followed 10 ulcer patients treated with felt and 7 patients managed in the traditional way. After 4 weeks there was a big improvement with the felt, all improved and some dramatically. For

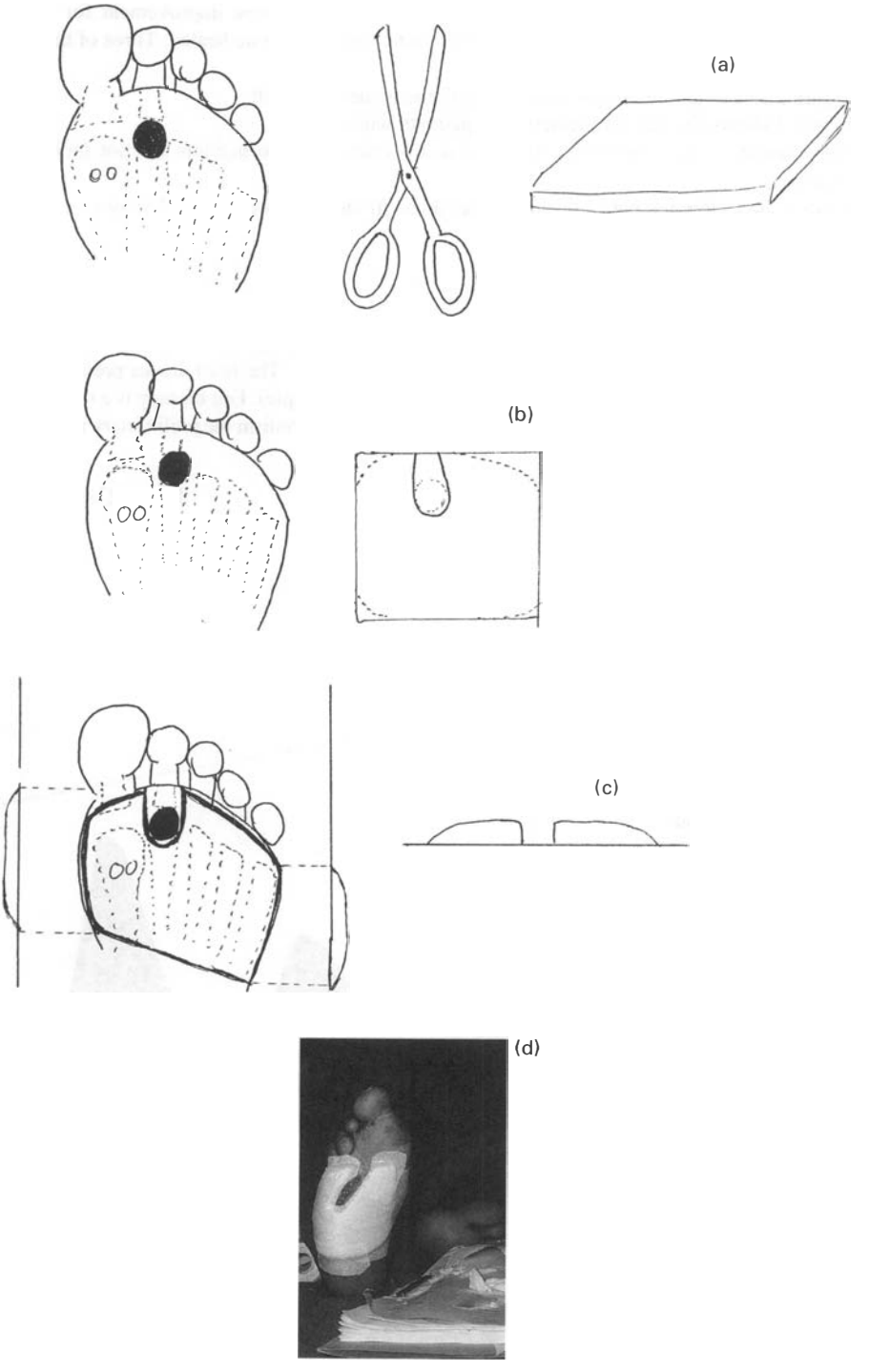

Figure 1.

5 out of 10 patients, their ulcers completely healed. There was some improvement for the patients without felt therapy, but none of the ulcers of the control group patients healed. Three of these patients were not seen at the final follow up.

*Figure 2 shows the ulceration in the 10 patients treated with felt.

*Figure 3 shows the area of ulceration in patients without felt.

Note: Patients 1, 6, 7 were not examined at 4 weeks, so these patients are not included in the results.

Figure 4 shows the geometric mean of ulcer areas in the two groups over 4 weeks.

Discussion

Ulcer healing consists of proper trimming, shows which fit properly, the condition of the patient and rest. If it is difficult for patients to rest, felt therapy can be useful. The felt relieves pressure so that the ulcer is unstressed even if the patient walks a little (1 km for example). Felt therapy is a therapy which is easy and quick to make. A carefully-controlled trial is needed to confirm the preliminary results reported here.

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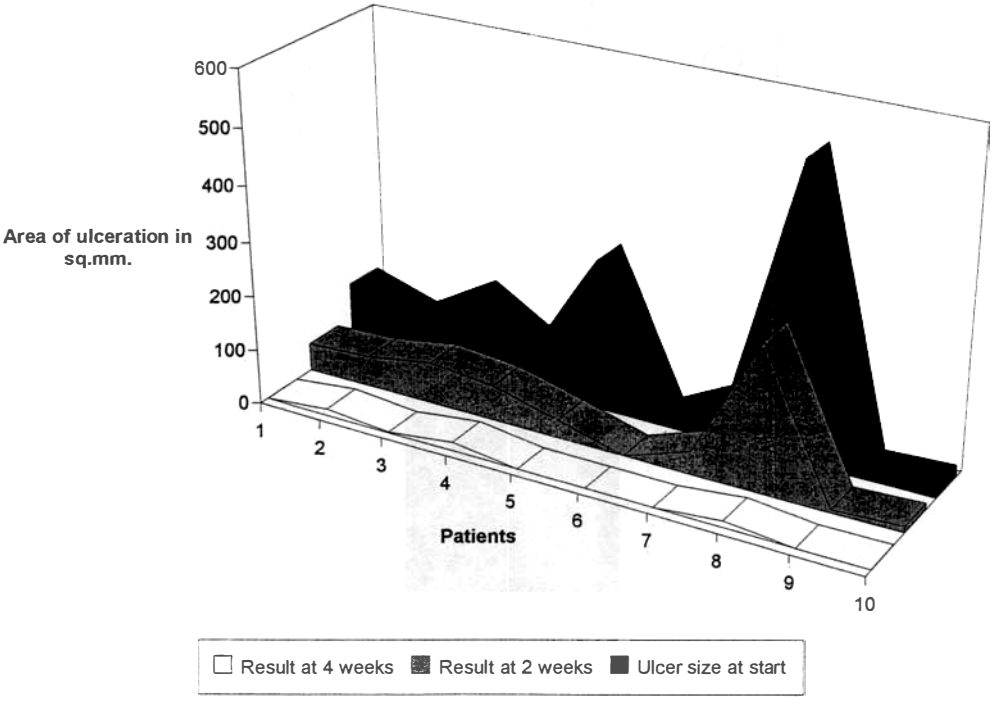

Figure 2.

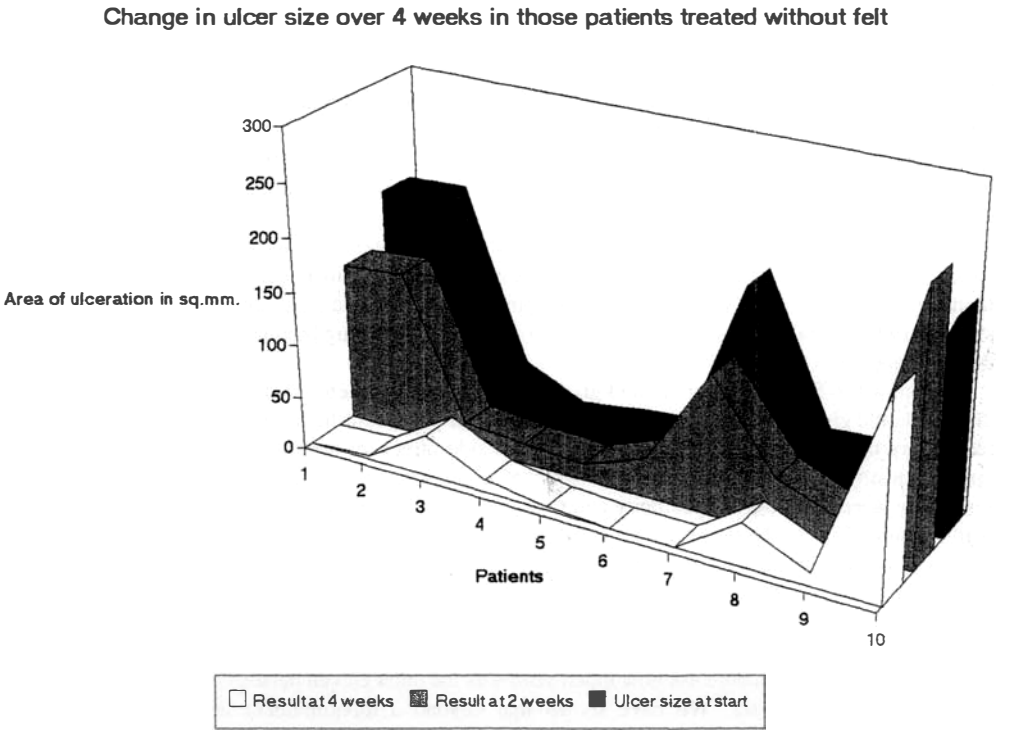

Figure 3.

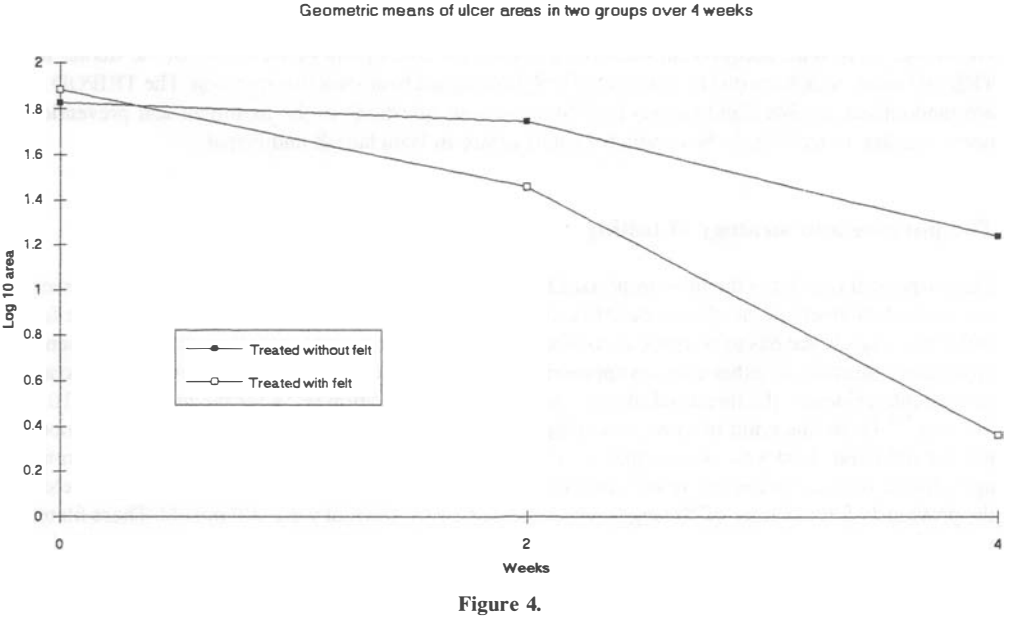

Figure 4.

COMMENT. SENSORY TESTING OF THE HANDS IN LEPROSY

Editor,

We would like to respond to the interesting letter of colleagues Saunderson *et al.* in the September 1997 issue of *Leprosy Review*, **68**, 252. Both our groups clearly have the same goal of preventing permanent nerve damage in persons affected by leprosy. For this, we believe that we need a robust test that will detect neural impairment reliably and as early as possible, and that can be used under field conditions. This is a tall order for any test.

Like Saunderson and colleagues, we believe that graded monofilaments are currently the tools most suited to the task. We introduced sensory testing using monofilaments in our project in early 1992. This filament was only used in Green Pastures Hospital, not in the field programme. Since our normative study in 1993, we have been advocating the use of only two screening filaments for the field, 200 mg for the hand and 2 g for the foot.[1]

In contrast to Saunderson *et al.*, and given that neural impairment is not always reversible, we feel that we should give treatment as early as possible, even if this means treating some patients who may not really have needed treatment. The low incidence of side-effects of the current steroid regimens, in our opinion, justifies such an approach.[2] In terms of diagnostic test design, we demand a test of high sensitivity, accepting loss of specificity and treatment of false positives. Two questions therefore arise: Is this assumption of a better prognosis with early detection valid, and is sensation loss detected with a thinner filament—'mild sensory impairment', the same as early sensory impairment?

Saunderson and colleagues show that among 12 out of 15 patients with mild sensory impairment, who were available for follow-up after 6 years, only one person had developed secondary impairment. While this may be considered a 'good long-term result', no conclusions can be drawn for such a small sample. In addition, one could ask how much *disability* the other eleven persons experienced because of their sensory impairment?[3] We have shown that beyond a monofilament level of 2 g, functional sensibility of hand is likely to be affected.[4] In a further study, we found that sensory impairment at this level is a major disabling factor in activities of daily living among persons affected by leprosy (van Braker *et al.*, submitted).

Saunderson *et al.* conclude from their study that, had a more sensitive test been used, through the use of a different diagnostic cutoff, a large number of patients would have been treated for neuritis, 'many of whom may not really need it'. At present we have to accept this difference of opinion, since to our knowledge there is no unequivocal scientific evidence for either point of view. One of the studies in the TRIPOD trials, which are due to start early 1998, is designed to answer this question. The TRIPOD trials are randomised, double-blind studies looking at various questions in the treatment and prevention of nerve damage in leprosy, to be conducted multi centre in Bangladesh and Nepal.

The purpose and strategy of testing

The purpose of our test is the most important factor in the choice of filaments to use. If it is a screening test, a single filament at the chosen cutoff can be used. One filament for the hand and one for the foot is sufficient. The choice has to be made as to whether to screen for normal sensation or for the presence of protective sensation. In either case, an appropriate monofilament threshold should be chosen. According to available evidence, the threshold of (residual) protective sensation is 2 g for the hand,[5,6] and 10 g for the foot.[7–9] From this point of view, screening with a 10-g filament seems reasonable for the foot, but not for the hand. Last year we completed a large normative study ($n = 697$), aimed at determining age-specific normal values for monofilament testing. Except in young children and among the elderly, the previously found values of 200 mg for the hand and 2 g for the foot were still upheld. These filaments were felt by 95% of the (mostly rural) healthy volunteers tested. (Anderson *et al.*, in preparation). It is interesting that the normal thresholds found in Nepal very closely match those found in India.[10] Choosing a filament giving a pressure many times the normal threshold, or the threshold of protective

sensation (such as the 10-g filament used by Saunderson and colleagues) increases the specificity of the test, at the cost of sensitivity.

If the purpose of testing is monitoring of nerve function in a patient who we are testing for sensory impairment, a test using several 'levels' of graded filaments is preferable. This allows assessment of whether the patient is improving or, sometimes, deteriorating further. If only one filament is used, changes are hidden once the patient can no longer feel that particular threshold.

Practical considerations

One cannot always easily get the monofilaments one would like to use. We have no stock of 1-g filaments and have therefore not used these routinely. Having a filament of ~100 g would also be desirable, to replace the 300 g filament, which has less than ideal buckling properties. It would be a great advantage if someone could make monofilaments available cheaply and in bulk. Perhaps ILEP could help in this?

The thinner filaments are more likely to become permanently bent. However, in our experience, the 200-mg filament can be used, provided the handle is constructed so that it can serve as a protective cover for the filament when not in use. In our field programme we use handles made of cheap ballpen shafts.

The choice of filaments may also be dependent on the skill, workload and motivation of the staff. In our experience, specialist leprosy staff of almost any level can learn to use the pocket monofilament set reliably. In the integrated field programme, where leprosy work is done by multipurpose health workers, nerve function assessment still leaves much to be desired. This is probably due to a combination of general patient work load, lack of motivation and low priority given to leprosy work. It is unlikely that this has anything to do with the thickness of the filaments used. Most can use the two-filament threshold test acceptably well, when they leave our Comprehensive Leprosy Training course.

In conclusion, it is acceptable to differ between projects in the diagnostic threshold chosen, because of local requirements. The sensitivity and specificity of the diagnosis 'sensory impairment' does not only depend on the choice of filament. It is the combination of factors that needs careful consideration in the light of the purpose of the test. Let us continue to work on this together, to save as many people as possible from permanent nerve damage.

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ALISON M. ANDERSON

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REPLY: SENSORY TESTING OF THE HANDS IN LEPROSY

Editor,

Thank you for the opportunity to reply on this topic. It seems likely that our differing points of view reflect the different environments in which we are working.

In Ethiopia, and in much of the rest of Africa, leprosy control activities are being integrated into the general health services, which are themselves undergoing major structural reform. At the same time, the routine treatment of neuritis with steroids in the field is just being established in many countries. Thus policies which are ideal and those which are feasible may be rather different.

There are two technical matters on which we would disagree with van Brakel and Anderson. Firstly, although steroids do indeed have a low incidence of side effects, these are not negligible. In our pooled experience of steroid use in leprosy (which extends to about 35 person-years), we have seen enough benefit to advocate the wider use of steroids in the field, but we have also seen a sufficient number of adverse effects to be very reluctant to advocate a policy which treats a significant number of patients unnecessarily.

Secondly, van Brakel and Anderson state that they know of no evidence to suggest that the finer filaments are less reliable than, say the 10 gm filament. In the study done here and referred to in our letter, the 10 gm filament was found to be more reliable (there was less inter-observer variation) than in the 1 gm filament (1).

Under present conditions in Africa, therefore, we advocate a screening test for use in the field that:

is simple and feasible to apply by busy, non-specialised staff,
is not time consuming,
gives an unequivocal and reliable result, and
does not lead to many false positive cases being treated.

We feel that the 10 gm filament best fulfills these criteria for sensory testing in the hand, while the next best option may be the ball-point pen, which is even less sensitive, but which is advocated in many national programme manuals in Africa as the most feasible approach.

We feel that the simpler the method, even if it is less sensitive, the more likely it is to be actually used by busy junior staff and therefore the more cases of neuritis will be picked up and treated. It is not just a question of what junior staff can be trained to do, it is really a matter of what they will be willing and motivated to do amidst their other work.

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Reference

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Lepr Rev (1997) **68,** 386–397

Teaching Materials and Services

Schieffelin Leprosy Research & Training Centre, Courses 1998*

I Courses Recognized by The Government of India

	Courses	Qualifications	Duration	Commencing Date
1	Medical Officer	Medical Personnel engaged in Leprosy work	6 weeks	Jan. 19–Feb. 28 Jul 27–Sep. 05
2	Non Medical Supervisor	Qualified Para Medical Workers with a minimum of 5 years experience	3 months	Apr. 01–Jun. 30
3	Physiotherapy Technician	+2 passed or P.U.C. (with science subjects)	12 months	Jul. 01–Jun. 30
4	Laboratory Technician	+2 passed. Science graduates preferred	12 months	Jul. 01–Jun. 30
5	Smear Technician	+2 passed (with science subjects)	3 months	Jan. 12–Apr. 11 Sep. 07–Dec. 05
6	Para Medical Worker	+2 passed. Graduates preferred	6 months	Jul. 01–Dec. 31
7	Shoe-Maker	V-standard with knowledge of English preferred	6 months	Jan. 02–Jun. 30 Jul. 01–Dec. 31
8	Diploma in Prosthetic & Orthotic Engineering	+2 passed. Graduates preferred (with science subjects)	30 months	Jul. 01–Dec. 31 (2000)
9	Opthalmic aspects in leprosy	Medical Personnel	1 week	Mar. 02–07 Sep. 07–12
10	Eye care in Leprosy	Non Medical Personnel	1 week	Sep. 14–19

II Other Courses Offered by the Institution

	Courses	Qualifications	Duration	Commencing Date
1	Training of Trainers	Personnel involved in teaching	2 weeks	Mar. 16–21
2	Medical Records Technologist (CMAI)	+2 passed	15 months	Jul. 01–Oct. 31
3	Community Based Rehabilitation Worker		12 months	Jul. 01–Jun. 30
4	Refresher Course in Skin Smear	Trained Laboratory Technician	2 weeks	Apr. 20–May 02 Aug. 17–29

* Similar courses are run every year.

	Courses	Qualifications	Duration	Commencing Date
5	Condensed Course in Leprosy	Medical Personnel Non-Medical Personnel	1 week 1 week	Nov. 02–07 Nov. 23–28
6	Research Methods in Leprosy		1 week	Nov. 09–14
7	Programme Management issues in Leprosy Control	Project Officers & Supervisory level in Leprosy Control Project	1 week	Nov. 23–28

3, 6, 7—New courses

III In-Service Training

	Courses	Qualifications	Duration	Commencing Date
1	In-service training in Medical Surgery, Surgery rehabilitation, Pathology, Laboratory Technology, Ophthalmology & Epidemiology and Leprosy Control	For qualified Medical personnel/ Health professionals	3 months	By arrangement
2	Medical Students Course	Clinical Medical Students	1 week	By arrangement
3	Medical Record Keepers	+2 passed with proficiency in typing and good English	2 months	By arrangement
4	Basics of Physiotherapy in Leprosy	Under graduates in Physiotherapy	1 week	By arrangement
5	Basics of Occupational therapy in Leprosy	Undergraduates in Occupational therapy	1 week	By arrangement
6	Psycho-social aspects in Leprosy	Medical/Non-Medical Personnel working in leprosy field	1 week	By arrangement
7	Ophthalmic Nursing Care	Nursing Technician students/ Staff Nurse	2 weeks	By arrangement

Courses:- English fluency essential. Recognized by WHO and Indian Government (all Paramedical & Technical courses are fully recognised by the Indian Government).

Contact: Mr T Jayarajan, Registrar, Schieffelin Leprosy Research & Training Centre, Karigiri-632 106, Vellore District, Tamil Nadu, India.
Telephone: 91-(0)416-74227, 74229, 74251, 74221 (Director) Fax: 91-(0)416-74274, 25035, 32103, 32788.

Training Programme for 1998 in Tuberculosis and Leprosy, ALERT

ALERT'S Training Philosophy

Our courses are all modular and seek to reflect the change in leprosy work by being combined with tuberculosis. Management and supervision of programmes are emphasized. Our teaching philosophy is learner centred; all the courses use participatory methods with opportunity to practice in the 240 bed hospital and the field programme. Group work and problem solving exercises are also used. Self study facilities are available using the video, slide and textbook libraries.

In-service training

ALERT offers excellent in-service training opportunities in physiotherapy, surgery, laboratory, dermatology, ophthalmology, etc. The duration and content of the in-service training period will be arranged according to the experience and the interest of the individual trainee. Students attending courses may opt to stay on for in-service training after the course has finished.

*International Courses offered in 1998**

January 12–February 20
Prevention and management of disabilities
Target group: physiotherapists, occupational therapists, podiatrists as well as experienced leprosy workers involved in POD. Emphasis on both the patient (early detection of nerve damage, health promotion, problem solving) and the programme (POD management, home based care and rehabilitation).
March 9–March 20
Introduction to leprosy for physicians
Highly recommended for those participants in the following 'Management of Combined Programmes' course who need to refresh their knowledge of clinical leprosy. The course can also be taken on its own.
March 23–April 24
Management of combined leprosy and TB control programmes for physicians
Target group: experienced physicians responsible for managing a leprosy and TB control programme at the regional level or above. Emphasis on programme management: needs analysis, action plan, implementation of activities, supervision, evaluation, management of resources, training, health promotion and POD. A brief review of the essentials of TB is included, but leprosy expertise is a prerequisite. Participants lacking the latter should also take the preceding 'Introduction to Leprosy' course.
May 11–May 27
Essentials of leprosy and TB for administrative and programme support staff
Target group: non-medical managers and administrative staff working in leprosy and TB programmes and donor agencies. Objectives: to gain a better understanding of the two diseases, to be able to communicate more effectively with the medical staff, and to contribute more efficiently in decision making and priority setting.
September 21–October 30
Essentials of leprosy and TB for physicians
Target group: physicians with limited experience in either leprosy or TB. Emphasis on clinical aspects of leprosy and TB, individual patient care and its application in the context of a combined programme, with an introduction to managerial issues, paying special attention to health promotion, POD and supervision.
November 2–November 13
Introduction to leprosy for senior field staff
Highly recommended for those participants in the following 'Management of Combined Programmes' course who need to refresh their knowledge of clinical leprosy. The course can also be taken on its own.
November 16–December 11
Management of combined leprosy and TB control programmes for senior field staff
Target group: experienced nurses, paramedical workers and supervisors responsible for leprosy and TB control at the district (or equivalent) level. Emphasis on planning, implementation, supervision and evaluation of control activities, with special attention to POD, health promotion and support functions. A brief review of the essentials of TB is included, but leprosy expertise is a prerequisite. Participants lacking the latter should also take the preceding 'Introduction to Leprosy' course.

* Similar courses are held every year.

Training fees

Basic training fees amount to US$ 460 per week. This covers tuition, full board and lodging, laundry facilities, airport service, weekend transportation and Ethiopian Birr 30 per day pocket money. Field trips are an additional US$ 25 per day. This covers transportation, facilitation and living expenses. Special rates are available for long-term in-service trainees. Please note that ALERT does not provide any sponsorship.

Visa formalities

As soon as you are accepted for the course, we will send you a letter of acceptance which you may use to obtain the visa for Ethiopia. Because administrative formalities can be time consuming, we advise you to apply as early as possible.

If your country has no Ethiopian embassy, please send your full name, passport number and nationality to ALERT at least three weeks before you are due to leave. We will then fax your entry permit number. You need this to get on the plane. At Addis Ababa airport immigration, you will be issued with an entry visa which you will have to pay for personally in hard currency. You should bring US$ 25 for this.

Upon departure, you need US$ 20 to pay for your airport tax.

Health

ALERT does not provide health insurance. Please make sure that you are suitably insured before coming to Ethiopia.

You need a valid yellow fever vaccination certificate. Malaria prophylaxis is recommended. Although there is no malaria at ALERT, you may be exposed during field visits.

If you are interested in any of these training opportunities, you need to send an application form (available upon request from the Training Division of ALERT) to the address given on the back of this leaflet. Applications should ideally be submitted 3 months before the starting date of the course.

For further information please contact: The Training Division, ALERT, P.O. Box 165, ADDIS ABABA, ETHIOPIA Tel: +(251) 1 711524 or +(251) 1712792; Fax: +(251) 171 1199 or +(251) 1711390; email: AHRI@TELECOM.NET.ET.

Health information for the developing world

Writing in the *British Medical Journal*, **309**, 8 October 1994, Rajendra Kale examines the inherent problems of transferring information effectively from one part of the world to another. The *summary* reads as follows:

> Doctors and other health professionals in developing countries are missing out on relevant information about health. A lot of the information they need is available in the developed countries, and those who have it are happy to share it with them. But transporting information, like food or medicines, from one part of the world to another is not an easy task nor is it the complete answer to the information drought. It is one thing to ferry books and journals from Europe to Africa and another to make relevant information available to the right person at the right time at an affordable cost.

The article addresses the questions 'What is wanted?', 'What is happening now?', 'What can librarians do?', 'What problems do commercial publishers face?', 'How can the distribution of information be improved?' and 'What is the role of electronic publishing and distribution?'

Key messages are interspersed in the text:

Sending appropriate information:

- Ask people what material they want, and let them know what material is available
- Use core library catalogues that have been identified by the WHO and others
- Encourage recipients to be constructively critical. They may be afraid to criticise the quality of material for fear of being thought rude or that donations may stop
- Establish personal contacts and use carefully phrased evaluation forms
- Include international reply coupons to pay for the return of evaluation forms
- Consider offering training in critical appraisal to donors and recipients

Donation and distribution schemes:

Info-med project is run by the Health Foundation of New York and is based in Ghana and Zambia. It prepares and distributes to doctors a quarterly digest based on information contained in bibliographic and full text databases that are accessed on CD-ROM.

African Index Medicus was created by the Association for Health Information in Libraries in Africa with technical support from the WHO. It believes that giving visibility to locally published material prevents redundant research and duplication of materials for training.

African Books Collective has 42 African publishers as members and a stock of 1200 different journals and books.

Swedish Agency for Research and Co-operation has active library support programmes in Eritrea, Ethiopia, Tanzania, Mozambique, and Zimbabwe.

American Association for the Advancement of Science supplies up to 191 different publications to 250 institutions in 38 countries.
East and central Europe journal donation project offers 600 different journals to its regional network of 200 libraries.

Intra-African book support scheme, launched in 1991, ensures that books from the African Books Collective reach 12 main academic libraries in Africa.

African Publishers Network, established in 1992 and comprising publishers throughout Africa, supports and promotes indigenous publishers.

International campus book link, run by Book Aid International, is entirely led by recipients. This means that it will not send out a journal unless it is asked for by a recipient.

Barriers faced by publishers in developing countries

- Language is a major barrier in countries outside the new Commonwealth
- The cost of subscribing to journals from the developed countries is too expensive for almost all health professionals from developing countries. Funds generated from advertising are inadequate to support publishing in developing countries
- Distribution systems in developing countries are inefficient compared with those in the developed world
- Information about the market for books and journals is inadequate because of poor market research
- In some countries doctors are unwilling to pay for information and expect it to be supplied free, whereas in others information sent free is not valued highly
- Publishers' costs need to be recovered even if profit is not a consideration

Useful Addresses:

Appropriate Health Resources and Technologies Action Group, Three Castles House, 1 London Bridge Road, London SE1 9SG

Association for Health Information and Libraries in Africa, WHO Regional Office for Africa, Library, BP6 Brazzaville, Congo

Bireme Centre for Health Information, Rua Bolucatu 862, Vila Clementino, CEP 04023-901, São Paulo—SP, Brazil

Book Aid International, 39–41 Coldharbour Lane, London SE5 9NR

ExtraMED, Informania Limited, PO Box 1359, London W5 3ZP

International Network for the Availability of Scientific Publications, PO Box 2564, London W5 1ZD

East and central Europe journal donation project, New School for Social Research, 65 Fifth Avenue, New York, NY 10003, USA

World Health Organisation, Office of Publications and Library, CH 1211 Geneva 27, Switzerland

The author's current address is 'Laxmi-Kunj', 37 Shanwar Pune 411 030, India.

Leprosy Elimination Campaigns (LEC) and Special Action Projects for the Elimination of Leprosy (SAPEL)

The Action Programme for the Elimination of Leprosy has recently published a booklet of above title (WHO/LEP/97.3) recording questions and answers on LEC and SAPEL. The following are typical examples:

Q.2
What are the essential elements of LEC?

A: *LEC is a combination of three elements, namely: capacity building measures for local health workers to improve MDT services; increasing community participation to strengthen elimination activities at the peripheral levels; and diagnosing and curing patients, particularly 'cases of consequence'.*

Q.3
What do you mean by leprosy of consequence?

A: *Leprosy of consequence is a term used to denote cases with more than five skin lesions and skin-smear positive cases (where facilities are available and reliable). These cases are regarded to be of consequence because they are acting as a source of infection in the community and are likely to be suffering from disability/impairment or have a high potential to become disabled in the future.*

Q.18
What is SAPEL?

A: *SAPEL is an initiative aimed at providing MDT services to patients living in special difficult-to-access areas or situations or to those belonging to neglected population groups. These underserved groups have been neglected so far mainly because of the limited resources available and the difficulties foreseen in reaching them in a cost-effective manner. Now that the accessible areas have been reached, some resources can be made available to address this problem or, where this is not the case, additional assistance sought. The most important thing is for the elimination programme to reach everyone who needs MDT services.*

Note: for more details please refer to the document on 'Special Action Projects for the Elimination of Leprosy'.

Q.19
What are the essential elements of SAPEL?

A: *The essential elements of SAPEL are, firstly, to find cases living in difficult situations who are in need of treatment and, secondly, to cure them. Innovative and practical strategies involving mainly operational solutions will be used in order to provide MDT to these patients. Since the project operates in situations where the health infrastructure is weak or does not exist, the strategies used should promote self-reliance and self-help, and must involve the community so that the activities began under SAPEL can be sustained.*

Summary. Essential differences between LEC and SAPEL

Aims: LEC aims to detect 'hidden' (back-log) cases present in an area and to strengthen on-going activities. SAPEL is aimed at providing MDT services to patients who for various reasons are not yet reached by routine services.

Area: LEC is to be conducted in high endemic areas where a large pool of undetected cases exists in spite of the availability of a reasonably adequate health infrastructure. SAPEL is focused on reaching patients living in difficult areas or under 'special' situations where MDT services and even general health services are non-existent.

Activities: LEC activities are basically routine programme activities which are being intensified for a short period. On the other hand, SAPEL activities are innovative because routine activities are not feasible or practical.

Duration: LEC is for a limited period, on average 3 months, whereas SAPEL could last for up to 12 months.

Local resources: LEC will make use of all existing health personnel, either specialized or integrated, who are available in the area. SAPEL will identify community-resource persons to support and maintain MDT services in a given area.

Additional resources: Additional financial support for LEC will be minimal, due to the short duration and the presence of an existing health infrastructure. External resources needed for SAPEL could be larger in relation to the number of patients reached, due to lack of health infrastructure and difficult logistics. Additional trained personnel from outside the area will be needed to support and supervise SAPEL activities.

Nongovernmental organizations: WHO 'Liaison'. Office of Library + Health Literature Services

The following information about international Nongovernmental Organizations (NGO's) is reproduced from the August 1996 issue of *Liaison*, Office of Library + Health Literature Services, WHO, 1211 Geneva 27, Switzerland:

Sources

IRED (Innovations et réseaux pour le Développement)

IRED represents a network of some 1000 NGOs working at grassroots level in development, women's

groups and organizations for action in urban surroundings. It has regional centres in Niger, Zimbabwe, Sri Lanka, Colombia and Italy; national representatives manuals, directories and their bulletin **IRED Forum** are published in English, French and Spanish. The special issue no. 50–51, 1994, is particularly useful as it gives a full overview of the history, goals and strategies of IRED as well as lists of its members and publications. IRED's aim is to help local NGOs to manage and organise their activities, create or join local networks, as well as providing the necessary documentation, training and tools to do so. *For further information, contact IRED, 3 rue Varembé, 1211 Geneva 20, Switzerland or 64 Horton Place, Colombo 7, Sri Lanka.*

ODI (Overseas Development Institute)

Briefing Paper, 1995, no. 4 is entitled 'NGOs and Official Donors'. This four sheet paper gives an excellent picture of the ways in which NGOs interact with official donors and discusses possible new directions in their relationship. *Published by the ODI, Regent's College, Inner Circle, Regent's Park, London NW1 4NS, UK. e-mail: odi@odi.org.uk or Internet on http://www.oneworld.org/odi.*

United Nations Non-Governmental Liaison Service (NGLS)

Established in 1975, the NGLS is a voluntarily funded, inter-agency unit of the UN system which seeks to promote enhanced dialogue and cooperation between the UN system and the broad development NGO community. It works with NGOs in developing countries, with North-South NGO networks and increasingly with southern NGOs seeking access to UN system events, processes and resources. They publish a regular newsletter entitled 'Go-Between' and several useful books, including ''@t ease with e-mail: a handbook on using electronic mail for NGOs in developing countries', the 'NGLS Handbook' and 'Economic and social development in the UN system: a guide for NGOs'. *For further information contact UN-NGLS, Palais des Nations, 1211 Geneva 10, Switzerland.*

Afri-CAN: Africa Community Action Network for Health

A new initiative launched with the support of the International Federation of Red Cross and Red Crescent Societies and the World Council of Churches for networking NGOs working in the area of community-based health care. Groups on training, advocacy, resource mobilization and monitoring and evaluation are important elements for the development of the network. *For further information, contact Dr Dan Kaseje, IFRC, PO Box 372, 1211 Geneva, Switzerland.*

Directory of Nongovernmental Organizations in Official Relations with the World Health Organization

This is a valuable source of information on some 180 international health-related NGOs which meet the criteria for the admission to official relations with WHO. The type of information found under each entry relates to the NGO's history, objectives and aims, structure and policy, finance, membership, activities, publications, etc. Examples of NGOs included are: Medicus Mundi Internationalis, the International Hospital Federation, the International Conference of Deans of French Language Faculties of Medicine, Network of Community-Oriented Educational Institutions for Health Sciences, AMREF, etc.

The printed edition of the Directory, published in 1990 (WHO document ECO/NGO/1990), is now superseded by an updated version on the Internet on WHO's home page (http://www.who.ch). The printed version of this update is in preparation. *For further information, contact the Division for Interagency Affairs, WHO, 1211 Geneva 27, Switzerland.*

Reseau d'Information Tiers-Monde des Centres de Documentation pour le Developpement (RITIMO)

This network links 36 documentation centres in France with collections of material on all aspects of

development, including health. It has a database of some 26,000 references to periodical articles, grey literature, theses, mission reports, etc., mainly in French but also Arabic, English, Portuguese, Spanish, etc. The primary documents are available in RITIMO documentation centres. *For further information, contact RITIMO at 14, rue de Nanteuil, 75015 Paris, France.*

Newsletters

Contact

Published six times a year in English, French, Spanish and Portuguese (circulation: 15,000), it deals with varied aspects of community health, health promotion and integrated development; each issue has a specific theme and lists useful contacts and publications. *Contact: Churches' Action for Health, World Council of Churches, PO Box 2100 1211 Geneva 2, Switzerland.*

The Health Exchange

A bi-monthly magazine which explores issues, ideas and practical approaches to health improvement in developing countries and provides a forum for health workers to share viewpoints in this area. *Contact: International Health Exchange, 8–10 Dryden St, London WC2E 9NA, UK).*

HAI News (Health for all now)

Reports on developments in the international campaign for more rational and fairer health and drug policies worldwide. It is the communication tool of Health Action International, an informal network of NGOs and individuals striving for 'health for all now'. *Contact: HAI Clearinghouse, CIROAP, PO Box 1045, 10830 Penang, Malaysia.*

Inter-African Committee on Traditional Practices affecting the health of women and children. Newsletter

The network affiliates NGOs in 26 African and three Western countries. The Committee is sponsored by a wide variety of international donors such as the Dutch government, DANIDA, UK/ODA, UNICEF, OAU and many others.

Développement et Santé: revue international de perfectionnement médical et sanitaire

This periodical was started in 1975 by the NGOs Frères des hommes and Medicus Mundi to fill a gap in francophone information available to health personnel in Africa. It is intended for health workers working at district level and in community services. *For further information, contact Développement et Santé at 15, rue de l'Ecole de Médecine, 75006 Paris, France.*

Quarterly newsletter of Action in International Medicine

AIM is an international consortium of some 100 health and health-related professional organisations and spans 35 countries. It strives towards the establishment of locally appropriate and intercommunicating health services and sets out to champion the cause of district health systems in developing countries. Examples of member institutions include the Academia de Medicina del Paraguay, Academy of Medicine of Malaysia, Polish Academy of Sciences, Institute of Medicine, Tribhuvan University, Nepal. The newsletter covers activities at country level and the links being created between them. *For further information, contact AIM, 125, High Holborn, London WC1V 6QA, UK.*

Ecoforum

Published bimonthly by the Environmental Liaison Centre International (ELCI) in Nairobi, it enables NGOs to share information and strategies relating to environment and substainable development issues, and facilitates networking. Arabic, French and Spanish editions are also available.

Comtaps

Published in Portuguese by the Associacao Brasileira de Technologia Alternative na Promocao da Saude (Caixa Postal 20396, 04034 Sao Paulo, Brazil) it is aimed at health workers and NGOs, covering issues of interest in Latin America.

NB *Many newsletters published by NGOs for NGOs appear in several language editions, often English, French and Spanish; sometimes also in Arabic, Chinese and Portuguese.*

The World Guide 1997–98; *New Internationalist*, UK

The publishers description runs as follows:

The World Guide, published regularly since 1979, has earned its place among the essential reference volumes that no outward-looking home, school or library can be without. It is highly informative, with easy-access A–Z listing of all countries and a wealth of development information unavailable elsewhere. *The World Guide* is researched and edited by the Third World Institute in Uruguay in collaboration with a range of development and campaigning organizations throughout the South.

Their view of the world carries the distinctive stamp of an institute operating in the South able to view the West and its Euro-centric perspective of the world in a refreshing and often challenging way. This book prioritises the facts and issues that are central to the lives of people in Africa, Asia, the Middle East, Latin America and the Caribbean. It gives you everything you will find in a conventional reference work, plus a whole lot more.

The World Guide contains more than 600 pages of global information with over 250 maps, 650 diagrams, 10,000 references and an-easy-to use index. It divides into 85 pages on special development themes accompanied by 520 pages with country-specific information.

Up-to-date information is available on 217 countries, arranged alphabetically for easy reference, with supporting charts, statistics and maps. Profile of each country including its environment, history, politics, economics and social setting. A large fold-out colour world map 420 mm × 270 mm (16'' × 10 1/2'') plus a map per country.

Special development themes include:

◆ Demography ◆ Labour ◆ Childhood ◆ Habitat ◆ Food production
◆ Overseas Aid ◆ Debt ◆ Communications ◆ Refugees
◆ Social Development ◆ Health ◆ Deforestation ◆ Education ◆ Women
◆ Trade ◆ Arms ◆ Indigenous people ◆ Global Warming ◆ Water
◆ Transnational Corporations

Confession

The World Guide 1997/98 is explicitly biased:

✔ in favour of the poor ✔ in favour of women ✔ in favour of social and political liberty
✔ in favour of the environment

× against militarism × against external financial controls × against hamburgers and disposable chopsticks ...

Also available on CD-ROM. The UK paperback version of the book costs £27.94; CD-ROM £52.45. Further details, including prices for purchasers in the European Community and elsewhere: *New Internationalist*, PO Box 79, Hertford, SG14 1AQ, United Kingdom.

The Cochrane Library

The *Cochrane Library* is a regularly updated electronic library designed to give you the evidence you need for informed healthcare decision making. Launched in April 1995 under the name *The Cochrane Database of Systematic Reviews* it has now been renamed to reflect the inclusion of further important related databases, making it the most comprehensive source of evidence for all those with an interest in evidence based health care.

The Cochrane Library now contains four databases:

The Cochrane Database of Systematic Reviews (CDSR)

The York Database of Abstracts of Reviews of Effectiveness (DARE)

The Cochrane Controlled Trials Register (CCTR)
complete register only available on CD ROM

The Cochrane Review Methodology Database (CRMD)

Now updated every quarter, each database provides a mine of information to assist in the health care decision making process.

A new simplified interface allows users to enter a search term and with one key-stroke retrieve all reviews on that topic, plus the most complete list of trials available on any database.

The Cochrane Library is available in two formats:

CD ROM for Windows
$3^1/_2$ inch disk for Windows

Annual subscription (four issues): Personal £95.00 plus £16.53 VAT:
Institutional £120.00 plus £21.00 VAT
Non EC customers please add £15.00 postage and insurance

SYSTEM REQUIREMENTS The following specifications are required to run *The Cochrane Library*: PC with 386SX processor or higher, both with 4 MB RM minimum and a hard disk with at least 15 MB of free space.

Further information: BMJ Publishing Group, PO Box 295, London WC1H 9TE Fax: 0171-383-6662

Leprosy Control in Myanmar, 1948–1973

This booklet describes the intensive leprosy control activities during the first twenty-five years of independence, when Myanmar was confronted with one of the worst leprosy problems in South-East Asia.

Copies are available free from: B. Zuiderhoek, Medical Officer, Leprosy, Fideliolaan 103, 1183 PP Amstelveen, The Netherlands.

Treatment of Neuritis in Leprosy, A. Salafia and G. Chauhan

Neuritis is the most challenging problem in leprosy. The authors of this book with their wide experience extending over many years and hundreds of operated cases, illustrate the normal anatomy of the nerves,

the mechanism of nerve oedema and damage; the contributory factors, ischemia, compression and stretching.

The medical treatment and its limitations are highlighted; so is the surgical treatment.

Microsurgical techniques are illustrated for each of the commonly affected nerves. Surgery is emphasized because, in the authors view, it is far superior to medical treatment in many ways. The protocol suggested for the treatment of neuritis gives the right place to drugs and surgery.

It has 48 colour plates (most intra-operational) and copies can be obtained from Dr A. Salafia: Head of the Reconstructive Surgery at Vimala Dermat. Centre, Bombay. Cost USA $ 25/- inclusive of Seamail: USA $ 28 by Airmail. Kindly sent a Bank Draft to Banca Commerciale Italiana of Ragusa (Italy) to account n. 98.99.4640.157 or ask your Bank to send the money to: CIN: F, ABI: 02002, CAB: 1700, Account N. 98.99.4640.157.

Kindly send/fax of the counterfoil of the remittance, and the book will be posted to you.

Phone: 00.91.22.6264702—Fax: 00.91.22.6261988 (Attention Dr Salafia) Res.: 203/B, Denzil Apts., Cross Road No. 3, Lokhandwala Complex, Andheri (W), Bombay—400 053, India.

Lepr Rev (1997) **68,** 398–411

News and Notes

Indian research doesn't reflect country's needs'

The following is taken from the *British Medical Journal*, **315**, 2 August 97:

Most medical research in India is unrelated to the country's major health problems, says a new report which has sparked off a debate on the priorities and relevance of biomedical research.

The report, based on an analysis of research publications from India indexed in the Medline database says that achievements in research have 'little influence' on healthcare delivery. Medical research seems to be concentrated in the fields of tertiary health care and new biology, says the study published in *Current Science*, a journal of the Indian Academy of Sciences (1997;72:912–22).

Government statistics show that diarrhoea diseases, respiratory illnesses, and infections, including malaria and tuberculosis, are the leading causes of morbidity in India. But the highest number of research publications were in general medicine (2602), paediatrics (1420), pharmacology (1367), immunology (928), oncology (821), surgery (750), and cardiovascular research (663), according to the analysis of Indian research published between 1987 and 1994.

The analysis by Subbiah Arunachalam, an information scientist with the Swaminathan Research Foundation in Madras, also suggests that India is doing little research in opthalmology (362 papers published), although the country has the world's biggest blind population—10 million—and has a high incidence of cataract and glaucoma. He says that doctors in tertiary care centres are 'better endowed' to do research and publish findings than their overworked counterparts in less expensive public hospitals, which are overcrowded with patients.

The analysis also showed that more than 14,000 of the 19,952 papers published during the period were in journals with an impact factor of less than 1·0 while only 58 papers were published in journals with an impact factor higher than 8·0.

The report's conclusions as well as its methodology have, however, been criticised. A spokesman for the Indian council of medical research said that research with a direct impact on health care is not always published. Also the Medline database covers less than a quarter of the English language medical journals published in the country.

Critics also say that the government neglect of public health is responsible for the persistence of many of India's major health problems, and not researchers focusing on the wrong areas. Political and administrative action is needed to fight infections and nutrition related problems, said B Ramamurthy, a neurosurgeon in Madras.

Some analysts, however, say that the mismatch between India's healthcare needs and research carried out cannot be denied. MS Valiathan, a former director of a government funded medical sciences and technology centre, said: 'Successive waves of tools and methods from the West, not societies' needs, have determined the medical research agenda in the country.

Gender and Leishmaniasis in Colombia: inequality in access to health services for women

This important report from WHO and the Special Programme for Research and Training in Tropical

Diseases (WHO/TDR/GTD/RP/97·1) draws attention to distortions in the epidemiological patterns of leishmaniasis in Colombia and inequalities in access to health services for women. The *Abstract* reads as follows:

> Leishmaniasis in Colombia has traditionally been seen as a health risk for adult males, as they become infected when they enter the biotopes of the vector in order to utilize the natural resources. National health statistics seem to confirm this theory. During field studies, however, the PECET observed equal proportions of men and women with active leishmaniasis, and delayed skin testing also showed equal proportions of both sexes having had contact with the parasite from early childhood. Some factors, up until now never seriously analyzed in Colombia, seem to distort the epidemiological pattern of the disease in the country, and gender-linked differentials in access to health care appear to exist. As a consequence, human suffering is not alleviated, and the socio-economical repercussions for the household are significant. The preventive measures of the Ministry of Health (MOH) systematically underestimate the magnitude of intra- and peridomicialiary transmission, and active case detection is omitted for female patients. Further research should be devoted to this phenomenon. The MOH should be encouraged to improve programmes of leishmaniasis control, especially with regard to active case detection, training and teaching, so that the diagnosis can be made more rapidly. In the meanwhile, the MOH should retrain its health workers.

The *Conclusions* read:

In this study we have presented arguments to demonstrate that women and children are as much affected by cutaneous leishmaniasis as men in foci where transmission is domestic and peridomiciliary (an epidemiological situation observed increasingly in Colombia) but that women who are resident in these rural areas have less access to health care. It has been shown that the statistics of the MOH do not really reflect the true epidemiology of leishmaniasis in rural areas. Because women consult official services less than do men, women are under-represented in the incidence of the disease, and a false estimation of the number of cases by sex.

This problem is often ignored; a better strategy on the part of the MOH is needed to correct the inequalities in access to treatment for woman, as well as a strategy for control of the disease oriented towards domestic and peridomiciliary transmission. One would also want to help the MOH to see that the inequality in access to health services that exists for women with respect to leishmaniasis might also exist with regard to other problems and situations in rural health. This report seeks to sensitize health personnel to the possibility of diagnosing cutaneous leishmaniasis in women when they meet them, even if they come to the services for other reasons (e.g. with sick children for vaccination or pre- and post-natal care).

Genetic engineering reverses antibiotic resistance

The following appeared in the *British Medical Journal*, **315**, 16 August 97:

Researchers have developed a genetic engineering technique that for the first time allows drug resistant bacteria to be rendered drug sensitive. This may prove to be a cheaper method of negating antibiotic resistance than the current approach of developing new drugs.

A team of biologists from Yale University in the United States, led by Nobel prize winner Professor Sidney Altman, has used plasmids that contain synthetic genes coding for small oligoribonucleotides, called external guide sequences (EGSs), to infiltrate drug resistant strains of *Escherichia coli* (*Proceedings of the National Academy of Science* 1997:94:8468–72).

Once inside, the external guide sequences facilitate the cleavage and inactivation of messenger RNA associated with the bacteria's drug resistant genes. In this way the bacteria are transformed from drug resistant to drug sensitive. In this study the bacteria were originally resistant to chloramphenicol and ampicillin, but the technique should be just as effective for bacteria resistant to other antibiotics.

Professor Altman said: 'This is a different approach to antibiotic resistance from the usual pharmaceutical company approach, It takes a shorter time and is less expensive. In a couple of months we can develop EGSs against particular genes.'

Furthermore, the researchers showed that increasing the external guide sequences to messenger RNA ratio and targeting more sites on the messenger RNA both resulted in a higher success rate in eliminating drug resistance.

Antibiotic resistance has become an increasing clinical problem in the past 15 years, leading to the use of more expensive antibiotics that often have more side effects. Notably the eradication of tuberculosis has been complicated by the rise in drug resistant strains of *Mycobacterium tuberculosis*. Antibiotic resistance is also a problem in the treatment of *Haemophilus influenza*, a common vector in childhood meningitis, epiglottitis, and pneumonia.

Professor Altman won the 1989 Nobel prize for his discovery that RNA, as well as being a carrier of genetic material, can be involved in chemical reactions. He has been working on the problem of bacterial drug resistance for the past six years.

Although the Yale team has shown the success of their techniques in laboratory cultures, it readily admits that it will be several years before a therapeutic tool is developed. The question now is whether the development of this technique will indeed prove cheaper and more practical than the present strategy of developing new antibiotics.

Professor Altman added: 'I want to emphasise that this is purely laboratory work at present and further research will be needed in animal models, and after that humans. We will continue to refine the technique but cannot afford to take the research further ourselves.'

Human Development Report, Oxford University Press, UK, 1997

Rapid technological changes and globalisation are transforming the world economy at unprecedented pace, but the benefits are going to the rich and strong rather than the weak and poor, the United Nations says today.

Despite claims that free trade and free movement of capital would benefit all nations through a process of global 'trickle-down', the UN's latest Human Development Report found the gap between wealthy and poor growing ever larger.

The report says that free global markets have been applied selectively, with the West driving through reforms that help its exporters and financiers but being resistant to changes in agriculture and textiles that would benefit the developing world.

'Lacking power, poor countries and poor people too often find their interests neglected and undermined.' The share of world trade for the 48 least-developed nations—representing 10 per cent of the world's population—has halved to just 0·3 per cent in the past 20 years.

In measuring poverty, the report uses the broader criteria of 'human poverty', rather than just 'income poverty', taking into account the factors measured in the HDI index, such as illiteracy and short life expectancy which add up to lack of choices and capabilities, not just income. Canada has the highest HDI rating in the world, while Britain ranks 15th.

'Globalisation has its winners and its losers. With the expansion of trade and foreign investment, developing countries have seen the gaps among themselves widen. Meanwhile, in many industrial countries unemployment has soared to levels not seen since the 1930s, and income inequality to levels not recorded since the last century'.

Among the losers are the 1·3 billion people living on a dollar a day or less, the 160 million children moderately or severely malnourished, the one fifth of the world's population not expected to live beyond the age of 40, and the 100 million people in the West living below the poverty line.

The biggest globalisation winners have been multinational corporations. A list of the 100 largest economies in the world would show that half of them are nation states and the other half corporations. The 359 largest corporations now account for 40 per cent of global trade.

According to the UN, globalisation is being presented 'with an air of inevitability and overwhelming conviction. Not since the heyday of free trade in the 19th century has economic theory elicited such widespread certainty.'

The UN believes much of this optimism is misplaced, and that the rewards will not be available to all unless specific policies are identified.

The report puts forward a six-point programme for promoting pro-poor growth:

- People-centred policies to give individuals, households and communities better access to economic, social, political, environmental and personal assets.
- Work towards gender equality.
- A minimum target of 3 per cent per capita income growth in 100 poor countries.
- Improving the management of globalisation through better trade policies, fairer rules and fair terms for poor countries to enter markets.
- Creating a political environment so that poor people and poor communities can be heard rather than suppressed and oppressed.
- Special action to prevent countries sliding back into poverty, including peace-building efforts and debt relief.

Put into context, the UN puts the cost of eradicating poverty at 1 per cent of global income. Effective debt relief for the 20 poorest countries would be even cheaper with a price tag of $5·5 billion—the cost of building Disneyland Paris.

Why does HIV infection progress to AIDS?

The following appeared in the *British Medical Journal*, **315**, 30 August 97:

The answer to this deceptively simple question has aroused controversy,[1] much of it clarified recently. From the beginning of the epidemic it was clear that progression to AIDS was marked by the development of opportunistic infections or tumours, associated with immunological failure and T4 cell lymphocyte depletion. Overwhelming epidemiological evidence showed that a retrovirus, HIV, capable of infecting and destroying T cells, was the causative agent. The initial doubts expressed about HIV being the cause of AIDS[1] because of the small numbers of T cells infected have been dispelled by a clearer understanding of the dynamics of infection which was generated by mathematical modelling of changes in viral load following proteinase inhibitor therapy.[2] More than 109 viral particles are produced each day, predominantly from recently infected T cells. Although the number of T cells destroyed by this process is controversial,[3] it is likely that this high rate of destruction cannot be compensated for by increased rates of production, and T4 cell numbers therefore decline. It also seems that specific immune responsiveness to particular antigens (measured by the V beta family repertoire) is depleted as the T4 cell numbers fall, leaving the patient open to a range of opportunistic infections.

The observe of the question posed is why HIV infection does not progress to AIDS in a small proportion of patients (5–10%). This may represent the extreme of normal biological variability, but some of these individuals have deletions in the viral genome rendering it non virulent and others have a relatively vigorous and, more importantly, broad spectrum cytotoxic lymphocyte response to the virus which may keep replication in check for long periods.

Brian Gazzard, *consultant physician, London*

References

[1] Duesberg PH. Is HIV the cause of Aids? *Lancet,* 1995; **346:** 1371–2.
[2] Ho DD, Newmann AV, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*, 1995; **373:** 123–6.

[3] Effros RB, Allsopp R, Chui CP, Hausner MA, Hirji K, Wang L, *et al.* Shortened telomeres in the expanded CD28-CD8+ cell subset in HIV disease implicate implicative senescence in HIV pathogenesis. *AIDS* 1996; **10:** F17–22.

Tuberculosis infection process pinpointed

The following appeared in the *British Medical Journal*, **315**, 30 August 1997:

Mycobacterium tuberculosis, the bacterium that causes tuberculosis, uses an underhand trick to invade cells, researchers announced last week.

The body's immune system normally tags any invading bacteria with proteins that alert macrophages to consume it. One of these proteins, C2a, then floats in the blood with no known function.

The researchers from Washington University School of Medicine in St Louis showed that *M tuberculosis* manages to associate with this discarded C2a protein and use it to create a new label that helps the bacteria adhere to the macrophage and enter it. Once inside the macrophage, the mycobacteria multiply until the cell ruptures and the bacteria are then released to repeat the process (*Science* 1997;277:1091–3).

Previous studies have described other invasion techniques used by mycobacteria, but this strategy stands out because it is used only by the types of mycobacteria that cause disease. Jeffrey Schorey, one of the lead authors, said: 'Understanding how the bacterium invades cells may be an important first step towards developing a vaccine to prevent tuberculosis.'

Tuberculosis is a growing problem, with eight million new cases of pulmonary tuberculosis a year and three million deaths. As many as one third of the world's population is infected with *M tuberculosis.*

Thalidomide ban to be lifted in the USA

The following appeared in the *British Medical Journal*, **315**, 20 September 1997.

A scientific advisory committee to the Food and Drug Administration has recommended that thalidomide, which has never been licensed in the United States, should be allowed to be used to treat serious inflammatory conditions associated with leprosy.

Once approved, the drug could also be prescribed, under certain restrictions, to treat other diseases, including some forms of cancer, lupus, chronic host-graft disease, and some complications due to AIDS.

Thalidomide was used widely throughout Europe during the 1950s and 1960s as a sedative for pregnant women. But after about 8000 babies were born with severe deformities to mothers who had taken the drug its use was stopped. Thalidomide was never licensed in the United States, but it can be prescribed under certain circumstances, under a special dispensation that allows rare or controversial drugs to be used for 'compassionate' purposes in individual patients. Women who are given the drug, however, must agree to make all efforts possible to avoid getting pregnant; men must agree to wear condoms or abstain from sexual intercourse because it is unknown whether thalidomide can be found in semen.

The scientific committee was set up to review the drug after reports that buyers clubs in San Francisco were obtaining the drug illegally from Brazil to give to patients with AIDS. Celegene, an American pharmaceutical company that manufactures thalidomide, was asked to review the data on the drug and submit an application to the Food and Drug Administration.

The administration said that there was renewed interest in the drug because of its ability to lower the body's concentrations of tumour necrosis factor α, a chemical mediator which increases in response to infections such as tuberculosis, sepsis, and cancer. There has also been interest in the fact that thalidomide stunts new blood vessel growth, which would make the drug useful in treating macular degeneration.

The Thalidomide Victims Association of Canada referred to the possibility of thalidomide's approval as 'extremely distressing'.

Reaching undetected leprosy patients in endemic countries Joint ILEP–WHO Workshop, 1997

1 Introduction

The Workshop, held at WHO Headquarters, Geneva, Switzerland, 18–19 July 1997, opened with welcome addresses by Dr J-P. Schenkelaars, President of ILEP, the International Federation of Anti-Leprosy Associations and Dr S. K. Noordeen Director, WHO Action Programme for the Elimination of Leprosy. Both speakers stressed the importance of this occasion, the first joint workshop ever to be held between ILEP and WHO and also the first time there has been a global tripartite collaboration between national programme managers, ILEP Member Associations and the WHO Action Programme for the Elimination of Leprosy.

Dr Schenkelaars described ILEP Member's commitment to getting Multi drug Therapy to all those who need it. Members are currently supporting a number of projects which aim to bring treatment to hard to reach patients. However, there is always more that can be done. Much of the work of ILEP Members is carried out through support to national programmes and Members are keen to work with national programmes in the development and implementation of strategies to reach undetected patients. The discussions between national programme managers, technical experts and ILEP Members in this workshop should pave the way for action in the field.

Dr Noordeen stressed the very focused and practical nature of the workshop. From the perspective of WHO, reaching undetected patients in endemic countries is extremely important to attain the leprosy elimination goal to which all member countries of WHO are formally committed. The significance of case detection and treatment with MDT was emphasised. This is now a critical point in the global effort against leprosy and there is a need to intensify and adjust anti-leprosy activities in order to reach undetected leprosy patients.

Dr Noordeen recommended that any strategies which are adopted should have a nationwide coverage in order to bring about the maximum benefit.

2 The current situation of undetected patients

Dr D. Daumerie of the WHO Leprosy Elimination Programme described the current situation regarding undetected patients. The global number of leprosy cases in 1997 is estimated by WHO to be around 1·15 million of which 890,000 are registered by health services. In many endemic countries, leprosy continues to be under detected. In 1997, an estimated 260,000–300,000 patients have no access to diagnosis and treatment. This number represents about one quarter of all existing cases and is unacceptably high.

Undetected cases are at risk of developing complications and are likely to transmit the disease. The majority of the undetected cases live in the 'major' leprosy endemic countries. India has more than 120,000 undetected cases, mainly living in Assam, Bihar and Orissa. It is estimated that 20,000 cases remain undetected in Bangladesh and Indonesia. Other endemic countries, notably Cambodia, the Democratic Republic of Congo, Guinea, Laos, Liberia, Madagascar and Nepal may have 2000–5000 cases each. Dr Daumerie explained that the widest gaps between the number of registered cases and the estimated number of cases are in countries where leprosy elimination programmes are non-existent. In highly endemic countries which have a well functioning national leprosy elimination programme, the absolute number of undetected patients is high even though the gap between registered and estimated cases is small. The need to improve the reliablity of estimating the number of leprosy cases was stressed.

3 Why are patients undetected?

Dr W. C. S. Smith, Chair of the ILEP Medico-Social Commission, outlined some of the reasons why

patients remain undetected. In 1994, respondents to an ILEP questionnaire survey (covering programmes which totalled 250,000 registered patients) identified groups of people with leprosy who were not yet detected. The problems in reaching such people are either of a geographical nature, related to the community or related to the health services.

Geographical problems include difficult terrains (e.g. mountains, rivers, scattered islands, poor or non existent roads) or inclement climates (e.g. monsoons, heavy snowfalls).

Community related problems include insecurity (e.g. wars and famines), mobility (e.g. refugees, nomads, seasonal and migrant workers, pilgrims, military) beliefs (e.g. stigma, treatment refusers) women (e.g. culture, marriage, childbirth), economic (e.g. loss of wages, affluence) and special groups (e.g. tribal, minorities, language, elderly, urban slum dwellers).

Health Services problems include no leprosy programme, no healthcare infrastructure, no trained staff, traditional healers, restricted clinic time, lack of privacy, private health care).

Dr Smith reported that in many areas it was a combination of one or more factors which contributed to problems in reaching undetected leprosy patients.

4 An overview of ILEP Members assistance in reaching undetected patients

Dr S. Lacey, Scientific officer, ILEP, described the work which ILEP Members are doing to bring MDT to all who need it. ILEP Members are currently supporting leprosy work in more than 90 countries. Members work in partnership with National and Local Governments, Non-Governmental Organisations, both local and international, as well as communities. A survey by ILEP in 1994 highlighted the resources needed by individual projects to reach undetected patients. As a result of this information many of the leprosy treatment programmes sponsored by ILEP Members were strengthened.

More than 40 special initiatives aimed at reaching undetected cases are currently being supported by ILEP Members and their partners in 15 countries. Activities are being carried out in 7 of the top 16 leprosy endemic countries. Half of the initiatives are located in India. A variety of solutions have been adopted illustrating the flexibility of approach. So far the focus has been on strengthening the existing leprosy programme, integration of the leprosy programme within the general health services, improving access to treatment services or involving the community in order to sustain new initiatives. Examples of special initiatives were given from various countries amongst others, India, Brazil, Sudan, Angola, Somalia, the Philippines. In scope, the projects supported ranged from working with an international NGO to support rural general health dispensaries in Angola to an extensive package of activities including health education, telephone help lines, opening of new clinics and the use of mass media in a city in Brazil. Some ILEP Members are also supporting Leprosy Elimination Campaigns (LEC) and Special Action Projects for the Elimination of Leprosy (SAPEL) initiatives.

Dr Lacey emphasised that ILEP Members have adopted a comprehensive approach. Thus, disability prevention and the reintegration of people affected by leprosy back into society are seen as significant components of a quality service to leprosy patients. Since 1996, field programmes supported by ILEP Members have been requested to report on the WHO disability grade of new patients in an attempt to monitor more closely delay in detection so that action can be taken to improve the service to those who have not yet been detected and treated.

5 An overview of the technical and operational problems of reaching undetected cases

Dr M. Leide Wan-Del Rey de Oliveira the National Co-ordinator for Sanitary Dermatology in the Ministry of Health Brazil, drew attention to the problem of detecting cases of leprosy when patients present with early symptoms. The patient's low level of awareness of early symptoms can delay detection and the health professional may have a low sensitivity in diagnostic skills. However, she stressed that all cases with cardinal leprosy signs can be diagnosed using the current technology, the

challenge is to address both the geographical and social problems which increase the difficulty of reaching patients.

People living in remote rural areas with low population density may have no access to health services. When providing leprosy services, issues such as cost-benefit and quality of the service must be taken into account. In over crowded areas and socially impaired urban pockets, poverty, violence, homelessness, family breakdown and frequent absences from home demand flexibility of treatment points in time, place and in supervision of doses. The periphery of metropolitan areas may have a combination of rural and urban problems.

In Brazil, strategies for reaching undetected patients focus on the selection of areas with high hidden prevalence, then choosing from a range of interventions such as Leprosy Elimination Campaigns (LEC) to make an impact on public awareness, and Special Action Projects for the Elimination of Leprosy (SAPEL) to improve the commitment of community agents, and to sell or 'market' the elimination target to local authorities and partners. The importance of using all of the health infrastructure was stressed.

6 Leprosy Elimination Campaigns (LEC)

In many areas where leprosy treatment services are available there is evidence that a number of patients remain undetected. Dr Myo Thet Htoon, Consultant WHO Action Programme for the Elimination of Leprosy, described how Leprosy Elimination Campaigns aim to detect these leprosy cases, particularly the 'cases of consequence' and to treat them with MDT. LEC is a combination of three elements namely: capacity building measures for local health workers to improve MDT services, increasing community participation to strengthen elimination activities at the periphery and diagnosing and curing patients. Activities carried out under LEC vary from country to country.

An example of the implementation of a LEC in Indonesia was described by Dr Y. Hasibuan Chief, Leprosy Control Division, Indonesia. Leprosy Elimination Campaigns (LECs) were carried out in Karawang, Bekasi and Subang districts in West Java Province from June–September 1996. The area covered had 39 health centres serving a population of 1.5 million people. 1142 new cases were detected in 285 villages during the four month period. This was a dramatic increase, more than 4·7 times the total number of new cases in a one year period before the LECs started. The success of the LECs was attributed to the involvement of health staff, community leaders and volunteers in preparatory and training workshops, adequate supervision of the fieldwork activities and inter sectoral cooperation between district, social, education, religious and medical departments. An increased community awareness of leprosy and the input of informal leaders also contributed to the successful outcome.

Districts with a prevalence rate of leprosy of more than three cases per 10,000 are now being targeted in a plan to extend LEC projects. The Government of Indonesia, ILEP Members and WHO have all been approached for assistance in extending LECs.

7 Special Action Projects for the Elimination of Leprosy (SAPEL)

Dr M. A. Khalafalla Director, National Leprosy Control Programme Sudan described the experience of SAPEL, a WHO initiative aimed at providing MDT services to patients living in special difficult to access areas or situations or to those belonging to neglected population groups. Most offered solutions to situations where there was geographical inaccessibility or insecurity. He stressed the need for WHO and international NGOs to be more pro-active in helping programme managers to develop SAPEL proposals.

Dr Khalafalla illustrated how SAPEL offered the possibility of reaching leprosy patients among nomadic populations by giving six months treatment in the form of blister packs to patients without supervision, provided that the patient receives full information about the treatment and the need for treatment regularity. In other difficult-to-access areas this was made possible by using the community leaders to deliver MDT treatment and trace defaulters themselves. It is therefore important to identify

SAPEL areas in all endemic countries and provide MDT services to under-served populations living there.

Dr G. Cabanos of the WHO Action Programme for the Elimination of Leprosy informed the group that, so far, in the last six meetings of the SAPEL Steering Committee, 52 projects from 22 countries have been approved and are being implemented. Twelve (75%) of the top 16 endemic countries are doing special action projects while Mozambique, Ethiopia, Madagascar and Tanzania are still in the process of developing plans for these special initiatives.

The number of new cases so far detected, based on interim and final reports, is 3396 with almost equal proportions between PB (1698 or 50%) and MB (1658 or 48.8%) cases and a small proportion of unknown cases (40 or 1.2%) cases. The projects are expected to detect about 14,000 new cases.

SAPEL projects may not contribute significantly to the elimination of leprosy as a public health problem in terms of decreasing the prevalence rate to elimination levels; however, since our battle cry is to 'reach every patient in every village', our efforts and resources must also be geared towards providing equity in health care to cover 'special' groups of people or populations. These are the under-served, unreached leprosy patients which SAPEL, as a special initiative, must cater to. A set of parameters to evaluate these projects is necessary and the Leprosy Elimination Monitoring (LEM) exercise is a good opportunity to do this.

8 Reaching the undetected and ensuring sustainability

Advice from the ILEP Medico-Social Commission was presented by Dr E. Declercq Medical Advisor to Damien Foundation Belgium and a member of the Commission. He stressed the need for all leprosy control programme managers to investigate whether they have undetected cases within their area and if so, to find out the reasons for this. Possible solutions for reaching undetected patients were described.

Dr Declercq presented a number of criteria for the critical assessment of proposals to reach undetected patients. The ILEP Medico-Social Commission had recommended that consideration should be given to the following: Is there a clear and adequate plan of action? Is the proposed solution feasible? Is it acceptable to the population? Were potential or actual partners (e.g. community members, local associations) involved in the preparation of the plan? Is it cost-effective? How will the results be evaluated? Can the project be expanded to other areas? Is it technically and financially sustainable?

Dr Declercq emphasised that many hard to reach leprosy patients could and should be adequately taken care of by the existing health services. Improving the effectiveness of these services regarding the management of leprosy patients, and their acceptability for the community should remain the first priority of leprosy control managers. Some special situations need innovative action but their feasibility, chances of success, cost-effectiveness and potential impact on the routine programme should be analysed. There should always be a medium to long term plan to integrate these actions into the routine control programme.

9 Development of workshop recommendations

Professor M. F. Lechat and Dr W. C. S. Smith, joint Chairs of the Workshop identified a number of issues for discussion. The participants of the workshop were divided into four working groups representing four different endemic zones of the world. Within the groups, each national programme manager reported on:

- the current leprosy situation in the country
- difficult areas within their country
- ongoing activities to reach undetected patients
- national plans to reach undetected patients
- collaborative activities in reaching undetected patients.

The reports from each group were discussed during a plenary session and the following Workshop Recommendations were agreed:-

RECOMMENDATIONS

1 In the effort to reach undetected cases, the primary health care system should be strengthened by:
   - training all health care staff in diagnosis, treatment and care of patients (capacity building measures for local health workers to improve MDT services);
   - involving other non-leprosy NGOs, local leaders, volunteers and their communities.

2 Initiatives and special campaigns like Leprosy Elimination Campaigns (LEC), Special Action Projects for Eliminating Leprosy (SAPEL), etc. should be implemented within the national leprosy programme, particularly in difficult areas:
   Particular emphasis should be given to sustainability on the completion of special actions:
   - all potential partners, technical and financial, should be involved starting from the early planning stages;
   - special projects need not all be directed to WHO for funding but information regarding these activities should be reported to all concerned parties.

3 Encourage the wider use of leprosy elimination monitoring (LEM) to measure access to MDT and success of the programme using indicators of:
   - drugs supply
   - patient care
   - leprosy elimination

4 Organize national leprosy campaigns involving, on a larger scale, local NGOs, media and politicians, well-known figures, as well as people affected by the disease to demonstrate that they can lead a normal life.

5 Improve information systems to identify areas needing attention, for example through the use of Geographic Information Systems (GIS).

7 The coordination of activities is essential. A regular meeting at the initiative of Governments with local and international agencies should be held at least annually.

7 In promoting collaboration and monitoring progress towards reaching undetected patients, a joint Workshop between ILEP, WHO and the National Programme Managers should be held once a year.

Further reading:

Leprosy Elimination Campaigns (LEC) and Special Action Projects for the Elimination of Leprosy (SAPEL). Questions and Answers. World Health Organisation Action Programme for the Elimination of Leprosy, WHO, Geneva, 1997.

Detecting and treating hard to reach leprosy patients. ILEP Medical Bulletin no. 11. ILEP, London 1997.

Independent evaluation of leprosy elimination activities in Bangladesh 11–23 September 1997

The World Health Organization (WHO–SEARO), in association with the combined Tuberculosis and

Leprosy Control Services of the Ministry of Health and Family Welfare, organized an *Evaluation of Leprosy Elimination Activities* in Bangladesh during the above dates. The terms of reference were: a, to assess the progress towards achieving the goal of leprosy elimination in Bangladesh by 2000 AD—nationally and subnationally; b, to review the implementation of the National Leprosy Programme in specific activities such as case detection and the provision of multiple drug therapy (MDT), case holding and support activities such as Information-Education-Communication and training; c, to review and validate available data; and d, to submit recommendations for further strengthening and accelerating elimination activities.

The evaluation was carried out by 4 teams, each consisting of 3 members and a project facilitator or representative from the Ministry, covering all 6 divisions of the country, 29 of the 64 districts (25%), 64 of the 460 'thanas' (primary health care complexes with in-patient facilities) and 10 of the 12 leprosy hospitals. This included the examination of 121 patients, review of 150 record cards, interviews with 76 leprosy staff and 156 general health staff, including 55 doctors and 159 community members. The team leaders (all from outside Bangladesh) were Drs J. P. Baral (Leprosy Control Section, Ministry of Health, Nepal), N. S. Dharmshaktu (Leprosy Division, Ministry of Health and Family Welfare, Delhi, India), A. C. McDougall (Department of Dermatology, Oxford, UK) and B. Peters (DANLEP, Delhi India).

Following a series of meetings with WHO and the Ministry of Health on return to Dhaka, observations and recommendations were pooled to produce a preliminary report for the Health Secretary, pending the later production of a full account of all the main findings. In the South-east Asia Region (SEARO) of WHO, Bangladesh is unusual (in fact unique) in having a combined tuberculosis–leprosy programme. This was created in 1976 by the Government of Bangladesh as a separate *Mycobacterial Disease Control (MBDC)* unit, under the *Directorate of Health (Preventive)* to oversee the *National Tuberculosis and Leprosy Control Programme.* In 1985, MDT was introduced in some endemic areas and by 1990 120 had been covered in collaboration with non-government agencies, which have, over a period of many years, played an important role in leprosy control, notably in the northern and more highly-endemic parts of the country.

The present situation is that Bangladesh (population approximately 120 million) has 13,385 registered cases with 100% coverage, a national prevalence rate of 1·1 per 10,000 of the population, a total of 70,063 cases cured with MDT, 11,225 cases detected in 1996, giving a detection rate of 9·4/100,000 of the population. WHO estimate 50,000 cases to be detected and cured, 25,000 of whom are to be found through the *Leprosy Elimination Campaign (LEC)* approach, already in operation and to be extended during the remainder of this year and in 1998. Efforts are now being directed to achieving elimination levels at subnational levels, notably in the division of Rajshahi (north-western part of the country), which accounts for approximately 50% of all cases in the country.

Report of the workshop on 'Strategies for Elimination of Leprosy from Maharashtra'

The Workshop on 'Strategies for Elimination of Leprosy from Maharashtra' was held on 29 and 30 August 1997 in the premises of B. J. Medical College, Pune. The objectives of the workshop were to identify issues related to Elimination of Leprosy from Maharashtra as a preparatory phase of the forthcoming Modified Leprosy Elimination Campaign (MLEC) aiming at creating public awareness and identification of hidden leprosy cases as well as to develop academic interest among the District Leprosy Officers (DLOs) of Maharashtra State.

The workshop was organized by the Indian Association of Leprologists, Maharashtra Branch (IAL-MB) in collaboration with the Govt. of Maharashtra and Bombay Leprosy Project (BLP). The workshop was inaugurated on 29 August 1997 by Dr B. M. Dama, Addl. Director for Family Welfare, Govt. of Maharashtra. Shri Arun Ghate, Deputy Secretary, Public Health department, Govt. of Maharashtra expressed all his support towards MLEC and elimination of leprosy from Maharashtra. Dr C. V. Bapat,

Vice President of the Branch and Dr R. Ganapati, Former President of IAL and Director of BLP blessed the occasion. Dr C. R. Revankar, Hon. Secretary, IAL-MB welcomed the guests.

The Valedictory function was held on the following day. The Honorable Health Minister Dr Daulatrao Aher inaugerated the MLEC project as well as released publications of the IAL and Govt. of Maharashtra, Dr S. R. Salunke, Director of Health Services, Govt. of Maharashtra was Chief guest. On this occasion, Government of Maharashtra and IAL-MB honoured Dr R. Ganapati and Dr A. R. K. Pillai, President, Indian Leprosy Foundation for their yeoman services to the leprosy programme in the state of Maharashtra.

The 'Action plan on Modified LEC' was presented by Dr S. B. Chavan, Jt Director of Health Services (Leprosy), Govt. of Maharashtra. This plan was discussed among the delegates who also gave many valuable suggestions which was accepted.

A total of 10 papers were presented on both days. Seven papers were presented by DLOs based on their experiences with MDT programme in their respective districts. The topics discussed mainly were—Leprosy problem in hilly terrain, urban areas, tribal communities, treatment out come and identification of smear positive cases, epidemiological trend in MDT districts, community participation etc.

Out of the seven papers, one paper titled 'Identification of smear positive leprosy cases' presented by Dr B. B. Mynde, DLO of Parbhani district, was awarded 'Dr A. C. Parikh award for the best presentation.'

The following issues were stressed after extensive discussion:

Planing case detection in geographically difficult areas and difficult population groups like hilly terrain, construction workers, nomadic groups and fishing folks was considered as a priority. It was also suggested to introduce short course chemotherapy with newer drugs.

Special plan for fishing population who are available only during certain period of the year was suggested. Maharashtra has 18 lakhs fishing population. This population may not be available during MLEC operation.

There should not be any doubts about WHO/Govt. of India recommendations on FDT-24 dose treatment. The treatment has been further reduced to 12 months in MB leprosy and single dose-ROM treatment in single patch PB leprosy. This has been recommended by WHO and Govt. of India. This should be accepted as a public health programme strategy.

The principles of current chemotherapy should be understood by all the public health clinicians and programme managers specially by those in charge of training centres. A workshop has been suggested for training centre trainers to discuss further on certain issues raised by the doctors on FDT.

Apprehension regarding practising dermatologists not following WHO/Govt. of India recommendations while treating leprosy patients should be viewed from an over all context of leprosy elimination. As a small proportion of patients are managed by them, attempts should be made to orient them to see that at least the minimum period of treatment as recommended by NLEP is followed by them.

It was announced that IAL-MB will conduct orientation programmes for dermatologists in various districts of Maharashtra in due course of time.

'Princess Diana Fund to raise millions?

The following is extracted from the *Guardian*:

Charities are calling for broad distribution of the tens of millions of pounds expected to be contributed to a central fund set up yesterday in memory of the Princess of Wales.

Experts predicted that volume of donations would be such as to require professional management of the fund. One suggestion is that it should be taken under the wing of a charity, such as the Red Cross, used to handling emergency appeals.

The Charity Commission last night confirmed that it was working with legal advisors to Kensington Palace on how to secure charitable status for the fund.

The fund, named The Diana, Princess of Wales Memorial Fund, was announced by Buckingham Palace in response to overwhelming public demand for a single conduit for donations to causes with which the princess was identified.

There was an immediate expectation that contributions would be routed to the six charities with which she retained formal links, as patron or president, after last year severing of connections with more than 100 others in an attempt to reduce her public commitments.

However, charity leaders urged a far wider spread of cash. They said this would reflect the princess's wishes and avoid very large sums going only to causes already well supported by the public, such as Great Ormond Street children's hospital in London.

Stephen Lee, director of the Institute of Charity Fundraising Managers, said: 'It needs to be empathetic, sensitive and above all flexible to reflect the breadth of the princess's interests and to accommodate monies that will be given for specific causes.'

The fund looks certain to attract sums at least comparable with the biggest one-off charitable causes, such as Live Aid which raised £40 million for famine relief.

One option would be simply to disburse the cash to make a quick and concrete impact.

The 6 charities referred to above are:

- **National Aids Trust:** Promotes understanding of Aids and helps prevent spread of HIV (annual income £700,000)
- **Centrepoint:** Works with homeless young people in London (£6 million)
- **The Leprosy Mission:** Helps sufferers of leprosy and works towards its eradication (£7 million)
- **English National Ballet:** Furthers knowledge of enjoyment of classical ballet (£8 million)
- **Royal Marsden Hospital:** Cares for cancer sufferers (appeal fund £2 million; total income £61 million)
- **Great Ormond Street Hospital:** Cares for sick children (appeal fund £10 million; total income £89 million)

'Leprosy of consequence'

This term has recently appeared in the literature, particularly in the context of *Leprosy Elimination Campaigns* (LEC) as described by the *Action Programme for the Elimination of Leprosy* (see, for instance, *Status Report Updated 1997. WHO/LEP/97.4).*Leprosy cases of consequences are skin-smear positive cases and those with more than five skin lesions.

Major breakthrough in leprosy using single-dose treatment inaugurated— Treatment span slashed to half for multibacillary cases

Single-lesion leprosy cases can be treated with a single-dose combination of rifampicin, ofloxacin and minocycline (ROM) and multibacillary cases need only 12 months treatment instead of 24 months, observed Dr R. Ganapati in Mumbai on Wednesday. These treatment schedules, approved by the World Health Organisation (WHO) and the Govt. of India, is a revolutionary breakthrough in reducing the treatment cost drastically and saving manpower resources in a significant way, he added. Nearly 60% of leprosy cases in India are single-lesion cases and the new scheme will be a boon to the leprosy programme in India, Dr Ganapati remarked.

Dr R. Ganapati, Director, Bombay Leprosy Project (BLP) who had also participated in the 7th Expert Committee meeting of WHO's held recently at Geneva informed that these schedules with newer drugs could be used where there are operational difficulties in treating leprosy patients. While presiding over a workshop on 'Future Strategies for elimination of leprosy in Mumbai' and launching of single dose chemotherapy for single lesion leprosy organised by the Jt Director of Health Services (Leprosy), Govt. of Maharashtra, Dr Ganapati said that already there is an indication for further reducing the duration of treatment for multibacillary leprosy cases also. The assistant Director of Health Services (Leprosy) of

Mumbai and Thane, Medical Officers and staff involved in leprosy work in Mumbai attended the Workshop on **''FUTURE STRATEGIES FOR ELIMINATION OF LEPROSY IN MUMBAI AND LAUNCHING OF ONE DOSE CHEMOTHERAPY FOR SINGLE LESION LEPROSY''** held on 27.8.1997 at Committee Room, Advanced Training Institute, ATI Campus, Sion-Chunabhatti, Mumbai-400 022.

Dr Ganapati added that the new scheme will be an advantage to the leprosy programme and will drastically reduce the cost as well as manpower needs. The case load will come down with this short duration treatment and greatly help in reaching the goal of elimination of leprosy by the turn of the century.

Dr M. G. Singh, Assistant Director of Health Services (Leprosy), Mumbai organised the Workshop and explained the plan of implementation to medical officers and paramedical staff of Mumbai district. Dr A.R.K. Pillai, president of Indian Leprosy Foundation and Chief Guest inaugurated the function and exhorted all those involved in leprosy work to fully dedicate themselves in achieving the target. The single dose treatment was inaugurated by administering the new drugs to a child patient with a single lesion.

Dr C. R. Revankar, Deputy Director, BLP, explained the details on operational aspects of the short term chemotherapy. Dr V. V. Pai, Deputy Director, BLP, made an audio visual presentation on clinical trials on single dose chemotherapy for single lesion leprosy cases. Dr S. V. Dinni, Assistant Director of Health Services (Leprosy), Thane District, dealt with the advantages of the new scheme. Earlier Dr M. G. Singh thanked Dr S. B. Chavan, Joint Director Health Services (Leprosy), Govt. of Maharashtra for organising this workshop and welcomed the gathering. Dr S. B. Gude, Medical Officer, proposed a vote of thanks.

Handbook of leprosy, Fifth, Revised Edition, W. H. Jopling and A. C. McDougall, 1996

CBS took over the printing and distribution of this Handbook in 1995 from Heinemann Professional Publishing in the United Kingdom. A reprinting of the Fourth Edition by CBS achieved widespread distribution, mainly in India, and in 1996 a revised Fifth Edition sold over 1000 copies in a little over one year.

The Fifth Edition has now been reprinted (April 1997) and is available from medical booksellers in India and from the address above.

Erratum. The inclusion of primary amyloidosis of peripheral nerves as one of the conditions causing palpable nerve thickening, with or without muscle wasting, page 152 in Chapter 12, *Differential Diagnosis*, is an error. The clinical features described for primary amyloidosis are correct, but this condition *does not cause palpable thickening of peripheral nerves*. This will be corrected in any future edition.

Available from: CBS Publishers & Distributors, 4596/1-A, 11-Daryaganj, New Delhi 110002, India. Tel: 91 11 3271632; fax: 91 11 3276712. Price: Rs 195.

Poster notice

The poster included with this issue of the Journal is 'Staining slit-skin smears'.

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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 × 210mm) paper, with wide margins (4cm 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.

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