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Leprosy Review

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

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LEPRA

Editorial Office: Lepra, Fairfax House, Causton Road, Colchester CO1 1PU, England
Assistant Editor: Jennet Batten, 94 Church Road, Wheatley, Oxon OX9 1LZ, England

Leprosy Review is published by the British Leprosy Relief Association (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.

British Leprosy Relief Association
Registered Offices: Fairfax House, Causton Road, Colchester CO1 7PU

CONTENTS

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Editorial

ASSURING THE QUALITY OF DRUGS USED FOR THE TREATMENT AND CONTROL OF LEPROSY

Improvements in case-finding can make a significant contribution to reducing the prevalence and transmission of leprosy and the efficiency with which diagnosed patients are treated with the multidrug regimens recommended by the World Health Organization (WHO).[1–7] In 1988 it was estimated that only about 5 million of the 10–12 million leprosy cases in the world had been diagnosed and registered for treatment.[8] By 1990, about 3 million patients had been placed on multidrug treatment.[5] Currently, largely as a result of the continuing implementation of such treatment, the number of estimated cases has fallen to about 5·5 million.[9] However, over 2 million of these estimated cases are as yet undiagnosed.

In tuberculosis, there is compelling evidence that the effective treatment of infectious, highly bacilliferous smear-positive patients is a more efficient method of controlling transmission than mass vaccination.[10–13] It is likely that this is also true for leprosy.[11,12] Chemotherapy diminishes the risk of infection by reducing the period during which patients are infectious, and so prevents some infections that would otherwise have occurred. Vaccination, by preventing cases of active disease following infection, eliminates the risk of further infections arising from the prevented cases. However, there are two important differences in the way in which chemotherapy and vaccination reduce the risk of disease transmission, and both favour chemotherapy as being more effective.

First, there is rapidity. Thus Shepard *et al.*[14,15] showed that giving a single dose of 600 mg rifampicin to previously untreated lepromatous patients killed over 99% of the viable leprosy bacilli in their skin lesions within a week. An abrupt reduction in the infectiousness of lepromatous patients can therefore be expected as soon as they are started on WHO multidrug treatment. By contrast, future infectious cases prevented by vaccination of individuals at risk of infection would otherwise have arisen over many years since incubation periods for lepromatous leprosy are known to extend to at least 17 years.[16]

Secondly, there is practicality; the question of the relative feasabilities of delivering effective chemotherapy or vaccination to communities at risk. Thus it can be envisaged that the diagnosis and effective treatment of a high proportion of all active cases of multibacillary leprosy arising in a community each year can be achieved, especially when

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the availability of free or readily affordable effective multidrug treatment is well known.[7] By contrast, large vaccination coverages are required to significantly reduce the transmission of leprosy or tuberculosis, because of their relatively slow transmission rates in even highly endemic situations, their long incubation periods, and the rarity of the most infectious (highly bacilliferous) forms of the diseases among children.[10,17,18] Thus it has been calculated that giving a highly potent vaccine neonatally to all children in a highly endemic situation would reduce the transmission of tuberculosis by less than 2% per annum over a 15-year period.[10] In accord with such a prediction, similar declines in the morbidity and mortality of tuberculosis occurred over a 40-year period in Scandinavia, where widespread BCG vaccination was employed, and in the Netherlands, where it was not.[10] Furthermore, the introduction of effective chemotherapy resulted in markedly increased rates of decline of disease transmission.[11]

Although multibacillary patients form only a small fraction of all leprosy patients, their identification and effective treatment is a major objective of leprosy control efforts; first because lepromatous patients are the major source of transmission of the disease, and secondly, since their huge bacterial populations have the potential for allowing the selection of rifampicin- and high-level dapsone-resistant strains of *Mycobacterium leprae*[19–23] that could eventually undermine the efficacy of available treatment.

Effectiveness of the multidrug treatment recommended by the WHO

The treatment recommended by the WHO for multibacillary patients is a combination of monthly supervised doses of rifampicin and clofazimine, and daily self-administered clofazimine plus dapsone given for at least 2 years, and if possible to smear negativity. When the recommendation was first published in 1982,[24] there was convincing evidence to suggest that if the drug regimen is delivered and ingested as recommended, it should prevent failures caused by the emergence of drug-resistant *M. leprae* and be effective irrespective of the patients' past treatment histories. It was also believed that any relapses that might occur after stopping treatment would be with fully drug-sensitive organisms so that patients would respond to further treatment with the same regimen, as is the case in pulmonary tuberculosis.[25] It was also anticipated that because of the extremely marked bactericidal activity of rifampicin, such treatment should be capable of affecting a lasting cure in the great majority of patients, something that had never been achieved previously with dapsone monotherapy. It was therefore hoped that relapse rates after terminating treatment would be less than 1% per annum.[19]

These expectations have been more than fulfilled. Over 3 million patients have been treated with the recommended multidrug regimens whose acceptability has been highly satisfying. The pigmentation caused by clofazimine has not been a major obstacle to the treatment of light-skinned patients. There has also been a high level of patient satisfaction with their clinical response to the treatment and a significant reduction in the frequency and severity of ENL reactions, probably resulting from the inclusion of clofazimine in the regimen for multibacillary patients.[26]

Among more than 2000 patients whose treatment has been terminated for at least 6 years after achieving smear negativity in the 2 THELEP-supported Field Trials carried out in Karigiri and Polambakham in South India, not a single relapse has occurred.[15,27,28]

This indicates that persisting drug-sensitive bacilli, the so-called 'persisters' which appear unsusceptable to killing by rifampicin, dapsone and/or clofazimine,[29] do not pose a significant threat of relapse following treatment termination. Apparent relapse rates among paucibacillary patients treated with 6 months daily dapsone and monthly rifampicin according to the WHO Study Group recommendations[24] have also been very satisfactory.[5,30]

Operational considerations—improving treatment allocation and delivery and shortening the length of treatment

It has become increasingly clear that because of the unsatisfactory way in which skin smears are often taken and stained, it would be both simpler and much less hazardous to initially classify multibacillary and paucibacillary patients on clinical grounds.[31,32] Similarly it would be much simpler to give all multibacillary patients a total of 26 4-weekly treatments within a period of 3 years than to base treatment termination on achieving apparent smear negativity.[31,33] The results of a study carried out in China strongly support such recommendations since termination of multidrug treatment after 2 years was followed by a steady continuing decrease in the bacterial indices.[34] Excellent results have also been obtained with such fixed duration treatment in the THELEP-supported trials in South India and other parts of the world.[35]

Another important development has been the mass manufacture of blister–calendar packs for dispensing monthly allocations of dapsone, rifampicin and clofazimine.[36–39] These are often made of robust triple laminated pvc polymer with aluminium foil backing so that they have very low moisture diffusion rates. They therefore protect the drugs from humidity, physical damage and dirt. They also discourage pilfering (particularly of rifampicin) since it is more difficult to remove large numbers of capsules and it is more noticeable than if they were taken from a large stock in bottles or tins. It is believed calendar packs may also encourage patient compliance, and dispensing drugs in this way makes it possible to check at a glance how many tablets have been removed at any time.

Future chemotherapeutic developments

It is evident that the potent antileprosy activity of the fluoroquinolones[3] will enable highly effective multidrug regimens of much shorter duration to be designed for the treatment of multibacillary patients that will be considerably less vulnerable to the effects of poor patient compliance than standard multidrug therapy.[23] Thus a recent controlled clinical trial showed that some 99·99% of the viable leprosy bacilli present in the skin lesions of previously untreated lepromatous patients were killed by just under 1 month's daily treatment with 400 mg ofloxacin.[40] Furthermore, the excellent bioavailability of orally administered ofloxacin has already been demonstrated by two studies in which serum levels and urinary excretion were compared after giving oral and intravenous doses of the drug.[41,42] It therefore seems highly likely that 1 month's daily treatment with rifampicin plus ofloxacin could be at least as effective as 2 years standard multidrug treatment. A large multicentred trial to explore this possibility has recently been initiated.[43,44] However, since it is based on relapse rates following treatment termination, it will probably be at

least 4 years before the first significant results become available. Such a regimen would simplify treatment still further since it could be used for all patients and so obviate the need to classify patients on either bacteriological or clinical grounds prior to starting chemotherapy. In the meantime, standard multidrug therapy based on the use of dapsone, rifampicin and clofazimine will remain the sheet anchor of leprosy treatment.

Quality control of antileprosy drugs: magnitude of potential bioavailability problems, their importance for the treatment and control of leprosy, and the assessment of their bioavailability

For details of officially recommended methods for establishing the identity and drug contents of dapsone, rifampicin and clofazimine formulations, appropriate pharmacopoeias should be consulted.[45,46] Informative monographs concerning their physicochemical properties, determination and pharmacology are also available.[47–49] The key issue considered in this Editorial is how to ensure that tablets or capsules of dapsone, rifampicin or clofazimine containing the correct amounts of pure drug have been formulated in such a way as to secure optimal oral absorption.

DAPSONE

Despite the millions of patients that have been treated with dapsone since it was introduced in the early 1950s, there appears to be no evidence of any problems concerning its absorption. Recently the completeness of the absorption of orally administered dapsone has been formally confirmed in a cross-over study in which healthy volunteers were given both oral and intravenous doses of the drug. Identical dapsone serum concentration curves ('Areas under the curve—AUCs') were obtained.[50]

Daily treatment with 100 mg dapsone leads to serum and tissue concentrations that are over 500 times its minimal inhibitory concentration against *M. leprae*.[51–53] As a consequence even substantial reductions in dapsone bioavailability should be expected to have only the most minimal influence on the potency of multidrug treatment, since dapsone's ability to inhibit and kill dapsone-sensitive rifampicin-resistant mutants of *M. leprae* would be virtually unimpaired.[19]

The occasion might of course arise when it is necessary to confirm that a given batch of tablets did indeed contain the requisite amount of dapsone. This could readily be done by crushing the tablets and extracting the dapsone with an appropriate solvent such as acetone, ethyl acetate or methanol.[48] The identity of the dapsone and the drug content of the tablets could then be established using either officially recommended ultraviolet or ampometric titration methods[45] or alternative colorimetric,[54] thin-layer chromatographic (TLC),[55] fluorometric,[56] or high-pressure liquid chromatographic (HPLC) procedures.[57] TLC and HPLC methods have also been described for the identification and quantitation of impurities in dapsone preparations.[58]

RIFAMPICIN

The study undertaken by Levy *et al.*[59] provides clearcut evidence concerning the marked influence of rifampicin dosage on its bactericidal activity against *M. leprae*. It compared

the ability of single doses of 600 mg rifampicin, with that of a series of consecutive daily 300 mg doses of the drug, to render inocula from skin biopsies of previously untreated lepromatous patients noninfectious for mice. Leprosy bacilli from 11 of the 12 patients treated with a single 600 mg dose of rifampicin lost their infectivity, indicating reductions in numbers of viable organisms of about 99%. By contrast bacilli from 5 of 17 patients treated with either 3–5 or 7–9 daily doses of 300 mg rifampicin retained their infectivity for mice. These results indicate that the bactericidal activity of a single 300-mg rifampicin dose must be considerably inferior to that displayed by a standard 600-mg dose, and provide convincing evidence that the efficacy of the WHO-recommended multidrug treatment would be greatly impaired if rifampicin formulations with substantially reduced bioavailability were used.

The absolute bioavailability of rifampicin was demonstrated in 2 fasting subjects by giving simultaneous 300-mg doses of ^{14}C-labelled rifampicin orally and ^{3}H-labelled drug intravenously and measuring the areas under the serum concentration curves and cumulative urinary excretion of the 2 labels (Riess *et al.*, cited in references 60 and 61). Absorption was, however, significantly impaired if rifampicin was ingested with or shortly after a meal (Riess, cited in references 60, 61 and 62).

The major route of elimination of rifampicin is by biliary excretion of the unchanged drug and its desacetyl metabolite.[60] Rifampicin's serum half-life and the proportion of the dose excreted unchanged in the urine increases steadily as individual dose sizes are increased from 300 to 900 mg, probably as a result of the biliary excretion route becoming saturated.[60] Daily rifampicin treatment for periods of a week or more results in the induction of a hepatic enzyme which deacetylates the drug. Since deacetylrifampicin is rapidly eliminated in the bile and not reabsorbed,[63] such induction results in significantly reduced rifampicin half-lives.

Rifampicin's physicochemical properties and analytical methods for its determination have been reviewed.[49,57,64] Rifampicin capsules or tablets should be kept in tightly closed containers, protected from heat, light and moisture. They have a shelf-life of 4 years.[2]

In the studies reported by Buniva *et al.* from Lepetit in Milan,[65] serum rifampicin profiles are shown for 3 rifampicin formulations with impaired bioavailability that had been marketed by unlicenced manufacturers. A comparison of their peak rifampicin serum concentrations with those of Lepetit's own control formulations suggested that 2 had bioavailabilities of about 60%, while that of the 3rd was only about 25%. If the first 2 formulations had been used with dapsone and clofazimine for treating multibacillary leprosy patients, it would be anticipated that they would have resulted in suboptimal bactericidal activity, although they should still have killed *M. leprae* faster than a combination of dapsone and clofazimine. However, if the 3rd formulation had been used, all benefit of using rifampicin would probably have been lost. In many treatment settings the chances of noticing a slower than normal initial response to antileprosy chemotherapy would be very slight. It is also probable that the most important consequences of treatment with substandard rifampicin would be a higher risk of relapse after treatment termination.

At the end of their paper, Buniva *et al.*[65] described an extreme example of an unsatisfactory rifampicin capsule formulation that had been marketed by a non-licenced manufacturer, which had been brought to their attention because of its failure when used in the treatment of some leprosy patients. The capsules not only contained less than their stated amounts of rifampicin, they also had a 'high level of impurity' and an excipient

(probably bentonite) which had previously been shown to impair rifampicin absorption.[66] Unfortunately the paper did not reveal how long this rifampicin formulation had been used to treat the 7 patients concerned, the clinical or bacteriological evidence for its lack of efficacy, or whether it had been given with other antileprosy drugs. Similarly no information was provided concerning how extensively this particular rifampicin formulation had been marketed, whether its manufacturers were informed about its probable poor bioavailability, and if they were, whether it was then promptly withdrawn.

Buniva *et al.*[65] also presented evidence of the poor bioavailability of several 'experimental' rifampicin formulations with either non-standard particle sizes, altered excipients or manufacturing processes. It appears that rifampicin's crystalline structure can also critically influence its bioavailability[67] and that while dissolution testing can provide a guide as to likely bioavailability, sometimes formulations with good dissolution properties are found to be poorly absorbed and *vice versa*.[68]

A recent report by Acocella from Lepetit[69] described bioavailability studies on a series of single and combined rifampicin formulations. All the formulations containing rifampicin alone were shown to be satisfactory. However, 1 of 3 formulations containing rifampicin plus isoniazid was found to be unsatisfactory as were all 4 formulations containing rifampicin, isoniazid and pyrazinamide. Thus it appears that the difficulties of ensuring rifampicin's bioavailability are greatly increased when it is given in combined formulations with other drugs.

The implications of these findings for the treatment of tuberculosis with combined formulations of rifampicin, isoniazid and pyrazinamide of unproven bioavailability are serious[70–73] since even small reductions in rifampicin dosage (from 600 to 450 mg daily) are known to result in considerably slower sputum conversion rates.[74] It should, however, be mentioned that satisfactory fully bioavailable combined formulations of rifampicin, isoniazid and pyrazinamide have been manufactured for either daily or intermittent tuberculosis treatment.[75,76]

Since combined rifampicin-containing formulations have so far not been marketed for the treatment of leprosy, it is likely that the bioavailability of the great majority of rifampicin formulations that have been used for its treatment has been satisfactory. However, if control programmes are considering purchasing large stocks of rifampicin from a new manufacturer in the field, they should first insist on obtaining evidence of its satisfactory bioavailability.

In the studies carried out in Milan by Lepetit,[65,69] the bioavailability of the rifampicin formulations were compared by giving 600 mg doses of test and control capsules or tablets separated by at least a week to groups of 6–12 healthy volunteers on an empty stomach using a balanced cross-over design. Serum or plasma rifampicin concentrations were determined over a 9- to 12-hour period either by a microbiological plate diffusion assay using *Sarcinea lutea* or by high pressure liquid chromatography.[76]

In the investigations of the bioavailability of the 2 triple drug formulations referred to above,[75] rifampicin plasma concentrations were measured by a plate diffusion method using *Staphylococcus aureus*[77] and urinary concentrations of rifampicin and deacetylrifampicin were determined colorimetrically after extraction into isoamyl alcohol.[78] Some 14–15% of the rifampicin doses of the standard and combined formulations were recovered in the urine. These findings clearly confirm the evidence obtained over a decade ago by Brechbühler *et al.*[79] at Ciba-Geigy in Basle, that colorimetric estimates of the renal elimination of rifampicin plus deacetylrifampicin provide a reliable and much more

convenient method of assessing rifampicin bioavailability than estimating areas under serum or plasma concentration curves.

The kinetic studies of Brechbühler *et al.*[79] also suggest that rifampicin bioavailability studies could be conducted using urine samples collected over just the first 8 hours following dosage, since 78% of the total urinary excretion occurs during this time. Furthermore, such studies could be carried out with the help of leprosy patients being treated with multidrug therapy and using the laboratory facilities and expertise readily available in many endemic countries.[72,73]

CLOFAZIMINE

Unlike rifampicin, the pharmacology of clofazimine has been inadequately investigated and is poorly understood.[24,47,80,81] As a consequence it is difficult to predict the likely impact of using clofazimine formulations of impaired bioavailability on the efficacy of multidrug treatment.

Clofazimine, which is an orange-red dye, can readily be determined in tissues and body fluids by a variety of colorimetric,[82,83] fluorometric,[84] TLC[85] and HPLC[86] methods. Since it is extremely water-insoluble,[82] ensuring satisfactory absorption of the drug is difficult to achieve. Initial studies of its human pharmacology suggested that it was poorly absorbed; over 90% of the dose being recovered from the faeces. It was then found that absorption could be improved if it were given in a micronized form, or in olive oil or with fat-rich meals (W A Vischer, personal communication cited in reference 82). According to Yawalkar and Vischer[88] of Ciba-Geigy, clofazimine absorption varies appreciably from one patient to another and is more complete from micronized material and from oily preparations. When it is given in the form of coarse crystals, only about 20% of the dose is absorbed, whereas if it is taken orally in the form of a microcrystalline suspension in an oil-wax base (as 'Lamprene'), 'an absorption rate of about 70% has been achieved'.[87,88] Presumably these estimates were based on faecal elimination studies, but details appear not to have been published. Since clofazimine capsules are made of gelatin, they should be protected from humidity and heat, and are supplied in humidity-resistant containers which should be closed again immediately after use. The capsules may stick together, if improperly stored, but remain usable. They have a shelf-life of 5 years.[88]

There are many remarkable features concerning clofazimine's pharmacology, including its extremely slow elimination and marked tissue accumulation which results in the characteristic skin pigmentation of multibacillary patients undergoing treatment with the drug. Schaad-Lanyi *et al.*[89] gave either single 200 mg doses or 8 consecutive 50 mg daily doses of the drug to 12 volunteers and measured plasma clofazimine concentrations over periods of 8–18 days. After giving single doses, the peak plasma clofazimine concentrations were achieved between 8 and 12 hours. They then declined bi-exponentially, suggesting a distribution of clofazimine from the central compartment to a peripheral compartment, followed by a slow re-equilibration to the central compartment from where it was eliminated. The terminal half-life of the clofazimine after giving a single or 8 consecutive daily doses of the drug was about 10 days.

Less than 1% of the dose of clofazimine is eliminated in the urine as unchanged drug together with the 3 metabolites that have so far been identified.[83,90–92] Unless significant

amounts of other as yet unidentified metabolites of the drug are formed, it is therefore possible that the effective terminal elimination half-life of clofazimine could be considerably longer than 10 days. Levy[90] has suggested a value of at least 70 days.

The steady accumulation of the drug when ingested on a daily basis is therefore readily understandable and long-term treatment of both patients and experimental animals leads to crystals of the drug being deposited in the tissues.[82,83,93–95]

Because crystalline clofazimine clearly cannot exert an immediate antileprosy effect and because of its uneven tissue distribution, it is impossible to determine clofazimine's minimal inhibitory against *M. leprae* using the mouse foot-pad system. The only controlled clinical trial to compare the efficacy of different regimens of clofazimine (when given as monotherapy) was primarily concerned with the effects of intermittency on antileprosy activity.[96] Patients were treated for 24 weeks with 5 alternative clofazimine regimens; 200 mg daily 6 days a week, or a total of 1200 mg a month given either 3 times a week, weekly, fortnightly or on 2 consecutive days every month. The daily regimen resulted in more rapid killing of *M. leprae* than the 4 intermittent regimens, showing that increasing the average daily dose from about 43 to 170 mg resulted in a significantly enhanced therapeutic effect. Among the 4 intermittent regimens, therapeutic efficacy decreased as spacing between the doses was increased, despite the fact that all 4 intermittent regimens appeared to give similar skin pigmentation. It was therefore suggested that the accumulated drug did not appear available to exert an antimicrobial effect.

Since the mean daily dosage of clofazimine in the WHO-recommended multidrug treatment is about 59 mg, it is likely that if formulations of impaired bioavailability were used, they would be less efficacious. The risk of encouraging eventual relapses through the selection of rifampicin-resistant *M. leprae*[22] would, however, only be serious if patients were already infected with strains with a high level of dapsone resistance.[19]

The issue of whether or not the absorption of clofazimine is dose-dependent has still not been conclusively settled. With such a water-insoluble drug it might be anticipated that smaller proportions of larger doses would be absorbed and that correspondingly greater proportions of the dose would be eliminated unchanged in the faeces. Banerjee *et al.*[83] measured the clofazimine serum concentrations of 17 patients on long-term treatment with the drug and found mean levels of 0·5 μg/ml among those on treatment 3 times a week with 100 mg clofazimine, and values of 0·7, 1·0 and 1·4 μg/ml when daily doses of 100, 300 or 400 mg, respectively, were given. Thus serum clofazimine concentrations did not increase in proportion to the mean daily dose. By contrast, Lanyi and Dubois[85] found peak clofazimine plasma concentrations of 0·07 μg/ml and 0·16 μg/ml after giving single doses of 200 and 400 mg clofazimine, respectively, to a healthy volunteer.

There have been 2 small-scale investigations of the potential dose-dependence of the faecal excretion of clofazimine. Levy[90] gave single doses of 100, 300 and 600 mg clofazimine to 2 volunteers. The percentages of the doses recovered in 3-day faecal collections were 11, 8 and 12 from the first, and 61, 41 and 74, respectively, from the second volunteer. Thus while clofazimine absorption did not appear to be dose dependent, it clearly differed very significantly in the 2 subjects. By contrast, Mathur *et al.*[97] found that such increases in individual clofazimine dose-size resulted in average 3-day faecal drug recoveries increasing from 38 to 57%. In the single healthy volunteer studied by Banerjee *et al.*[83] 50% of a 300 mg dose of the drug was recovered unchanged in

the faeces over a period of 11 days. In these 2 last studies, clofazimine doses were given on an empty stomach.

The subsequent plasma level study of Schaad-Lanyi *et al.*[89] from Ciba-Geigy showed that the absorption of clofazimine can be significantly enhanced if capsules are ingested with food, but provided no evidence concerning the proportion of the dose that is absorbed when the drug is taken in this way. Under field conditions it would be impracticable to try to give monthly supervised clofazimine doses with food, and in any case this would be counterproductive since it would interfere with the absorption of the key supervised rifampicin dose.[60–62] Nevertheless, it should be recommended that patients take their daily self-administered clofazimine doses with food.

The bioavailability of clofazimine is clearly problematic. The single-dose plasma concentration protocol used by Schaad-Lanyi *et al.*[89] to demonstrate the impaired absorption of clofazimine when taken on an empty stomach could obviously be used for cross-over studies to compare the bioavailabilities of different clofazimine formulations. However, studies with much larger numbers of subjects would first be required to assess how sensitive such an approach would be to detecting differences in relative bioavailability. Because of the minute elimination of clofazimine and its metabolites in the urine, the only other approach to estimating clofazimine bioavailability is on the basis of faecal elimination.

Large scale cross-over studies involving the analysis of complete faecal collections would be a formidable undertaking. An alternative approach would be to give 50 mg daily doses of clofazimine together with other capsules containing a non-absorbable faecal marker such as chromium sesquioxide,[98,99] and determine the ratios of unchanged clofazimine to chromium in samples from consecutive faecal collections until they reached an equilibrium value. Whichever approach was used to compare the bioavailability of different clofazimine formulations, it would be important to control concomitant dietary intakes as closely as possible.

Conclusion

The treatment of leprosy with the WHO-recommended multidrug therapy would be seriously threatened if rifampicin formulations of impaired bioavailability were used. Fortunately such formulations can readily be identified using relatively simple methods. The consequences of treating patients with substandard clofazimine formulations are less certain and the difficulties of assessing their relative bioavailability formidable. Problems of dapsone bioavailability have never been encountered and if they did occur they would be unlikely to be of significant importance.

National Institute for Medical Research G A ELLARD
London NW7 1AA

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Lepr Rev (1992) **62,** 317–318

Editorial

REVISED ESTIMATES OF GLOBAL LEPROSY NUMBERS

The introduction and promotion of multidrug therapy (MDT) in the early 1980s[1] gave new life to efforts to control leprosy.[2] Two more recent events have generated increased optimism with respect to that objective. The first was setting of the goal by the World Health Assembly to eliminate leprosy as a public health problem by the year 2000, defined as reducing the prevalence of the disease to less than one case per 10,000 population. The second has been the dramatic downwards revision of the estimated number of leprosy cases in the world, from the figure of 10–12 million that was used in the mid-1980s to a new figure of 5·5 million.[3]

At first sight, this seems to be rapid progress indeed towards the elimination goal, but considerable caution must be exercised in interpreting the apparent fall in cases of the disease. In revising the figures the definition of an individual with leprosy has also been changed and this is responsible, in considerable part, for the reduced number of cases reported. The new figure of 5·5 million is the estimated number of patients still in need of chemotherapy. In addition, it is estimated that there are another 2–3 million individuals who no longer require chemotherapy but who have been left with residual deformities and who may require medical treatment and care. These individuals were not considered separately in the previous global estimate of leprosy burden and, indeed, many of them would still have been receiving dapsone monotherapy. Even so, the revised figure for the number of persons with active disease means that there has been a substantial reduction in the estimated *prevalence* of leprosy. It should be emphasized, however, that the decline in prevalence does not necessarily correspond to a fall in the *incidence* of the disease.

In situations where the rates of a disease are not changing very much over time there is a simple epidemiological relationship between prevalence (the number of cases of disease at a given point in time) and incidence (the number of *new* cases of disease arising in a given time period), which is that: prevalence = incidence × average duration of disease. Thus a fall in prevalence may be brought about either by reducing the number of new cases or by reducing the length of time individuals have the disease. The major change in the WHO estimates of leprosy prevalence is due to the latter effect. Because a large proportion of leprosy patients are cured within 1 or 2 years with multidrug therapy, they cease to be classified as prevalent cases after that time, whereas with monotherapy they may have been classified as a case for many years. It has been possible, therefore, to remove many old cases from leprosy registers.

The 'elimination' goal requires that there must be a marked fall in the incidence of leprosy. It is hoped that high coverage and prompt treatment of prevalent and new cases

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of leprosy with multidrug therapy will rapidly render them non-infectious to others and thus prevent the secondary cases they would otherwise have caused. While this seems a reasonable expectation, the direct evidence that such therapy reduces the incidence of leprosy in a population is scanty and more time will have to pass before a definitive assessment can be made of the impact of multidrug therapy on transmission. There have been undoubted falls in the incidence of leprosy in some, though not all, parts of the world, but chemotherapy is certainly not the only possible explanation for the declines.[4] Many of the falls started before multidrug therapy was widely available. Changing socioeconomic circumstances were major determinants of leprosy declines in the now developed countries[5] and this is likely to be a component in the declines in incidence in some developing countries. It is also likely that the great expansion in the coverage of BCG vaccination in most developing countries has had important effects in those situations in which it appears to offer substantial protection against leprosy, such as in Africa[6,7] and Latin America.[8,9]

The optimism that the 'end' of leprosy is in sight has both good and bad aspects. It has encouraged a new enthusiasm for widespread employment of effective chemotherapy and strenuous efforts are being made to expand the application of multidrug therapy. Between 1986 and 1990 the number of patients on multidrug therapy increased from under half a million to over 2 million.[2] A more negative aspect is the possible diminution of the importance attached to leprosy as a long-term health problem. A consequence of this may be that both private and public support for research on leprosy may fall. This will affect particularly those types of research which are unlikely to bear fruit until after the year 2000, such as work on new vaccines. If leprosy does indeed cease to be a public health problem by that year, reduced support for long-term research may well seem wise in retrospect. But not all are convinced that the WHO target will be achieved. It now seems clear that the much more ambitious WHO target of health for all by that year is likely to have a very hollow ring. The more specific target for leprosy may be achievable but it is too soon to loose sight of the fact that a longer term perspective to control may be required.

Department of Epidemiology and Population Sciences
London School of Hygiene and Tropical Medicine
Keppel Street, London WC1E 7HT

P G SMITH

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Lepr Rev (1992) **63,** 319–328

Bactericidal action at low doses of a new rifamycin derivative, 3′-hydroxy-5′-(4-isobutyl-1-piperazinyl) benzoxazinorifamycin (KRM-1648) on *Mycobacterium leprae* inoculated into footpads of nude mice

M GIDOH,* S TSUTSUMI,* T YAMANE,†
K YAMASHITA,† K HOSOE† & T HIDAKA†
**National Institute for Leprosy Research, Aoba-cho 4-2-1, Higashimurayama, Tokyo 189, and †Biochemical Research Laboratories, Kanegafuchi Chemical Industry Co., Ltd, Takasago, Hyogo 676, Japan*

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Summary Among a series of newly-synthesized benzoxazinorifamycins, 2 of the 3′-hydroxy-5′-(4-alkyl-1-piperazinyl) derivatives, named KRM-1648 and KRM-2312, whose respective alkyl residues are isobutyl and isopropyl, were examined for efficacy against nude mouse-model leprosy. KRM-1648 completely inhibited the growth of leprosy bacilli inoculated into nude mouse footpads, even 6 months after the medication had been stopped, when given orally at a daily dose of 0·6 mg/kg, 5 or 6 times weekly, during 3–5 months postinoculation. In comparison, the growth inhibition by KRM-2312 was incomplete under the same conditions, though it was still stronger than that by rifampicin. Complete growth inhibition by KRM-1648 was also observed when it was given orally at a dose of 1 or 3 mg/kg twice weekly during the same period. In contrast, the growth inhibition by rifampicin was only slight at 1 mg/kg and partial at 3 mg/kg under the same condition.

Introduction

Rifampicin is a representative antileprosy drug as well as an antituberculosis drug. To search for a compound with stronger antimycobacterial activity, a series of rifamycin derivatives were synthesized, and as a result several newly-synthesized benzoxazinorifamycins were found to have potent antimycobacterial activities.[1–3] Of these compounds, two 3′-hydroxy-5′-(4-alkyl-1-piperazinyl)benzoxazinorifamycins, KRM-1648 (alkyl residue: isobutyl) and KRM-2312 (alkyl residue: isopropyl) (Figure 1), were selected for further study based on their excellent activities against *Mycobacterium tuberculosis* and *M. avium* complex. In this paper we report the therapeutic activities of KRM-1648 and

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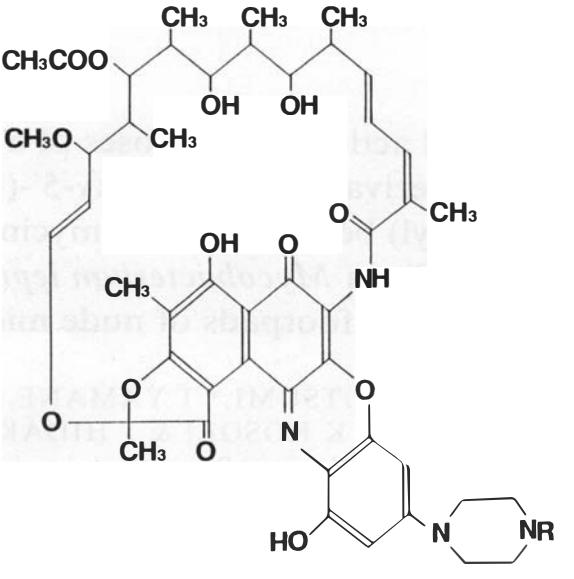

R : $CH_2CH(CH_3)_2$ KRM-1648

$CH(CH_3)_2$ KRM-2312

Figure 1. Chemical structures of KRM-1648 and KRM-2312.

KRM-2312 against an *M. leprae* infection model in nude mice, as compared with rifampicin.

Materials and methods

DRUG ADMINISTRATION

KRM-1648 and KRM-2312 were synthesized by Biochemical Research Laboratories, the Kaneka Corporation, Takasago, Japan. The rifampicin (RMP) used was Rifadin capsules (1 capsule is equivalent to 150 mg of RMP), purchased from Daiichi Pharmaceutical Co., Ltd, Tokyo, Japan. For the *in vivo* study, all the drugs were aseptically homogenized in sterilized distilled water containing 0·001% Tween 80 and kept at −80°C until use. Each nude mouse orally received $\frac{1}{10}$ ml of the drug suspension through a catheter. The treatments followed Shepard's kinetic method.[4] In the 1st experiment, each of the drugs was given continuously 5 or 6 times a week, at a dose of 0·6 mg/kg, and in the 2nd experiment, it was given intermittently twice weekly at doses of 1 and 3 mg/kg.

MICE

BALB/c (nu/nu) female mice, aged 5 weeks, were purchased from Clea Japan Inc., Tokyo, Japan. They were randomly grouped into 10 mice per group (5 mice per cage) in a vinyl isolator (Sanki Scientific Arts Co., Tokyo, Japan) and kept at 22 ± 1°C, being fed on a

sterilized heat-stable pellet from diet, MB-6E (Funabashi Farm Co., Chiba, Japan), and sterilized drinking water.

MYCOBACTERIUM LEPRAE INFECTION

We used the *M. leprae* strain Thai-53, which had been isolated from a subcutaneous leproma of a Thai lepromatous patient in 1980[5] and passaged through the nude mouse footpads 7 or 8 times. Inocula were prepared as follows: several infected swollen footpads were aseptically homogenized with chilled physiological saline (PS), centrifuged at $330 \times g$ for 3 min at 4°C, and the supernatant was treated with alkali and centrifuged. The bacilli were resuspended in 0·1% Tween 80-containing PS (pH 3)[6] and washed. The washed bacilli were suspended in PS at a cell density of above 6×10^8 bacilli/ml. A 0·05 ml-portion was inoculated into each of both hind footpads of nude mice.

COUNTING OF ACID-FAST BACILLI

We treated 4 or 6 footpads of 2 or 3 mice taken at specified times, as described above, and the supernatant after centrifugation at $330 \times g$ was diluted appropriately with PS. Acid-fast bacilli (AFB) were counted in duplication according to the method of Shepard *et al.*[7]

DETERMINATION OF HIND FOOTPAD VOLUME

The volume below *malleolus lateralis* of hind footpad in terms of the weight of water displaced by immersion was measured by a digital volume meter, Model MK-550 (Muromachi Kikai Co., Tokyo, Japan).

DETERMINATION OF UNCHANGED RMP AND KRM-1648 IN MICE BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

Plasma (0·2 ml) was loaded onto a Bond Elute Column (C_{18} for RMP or C_8 for KRM-1648, Analyt. Internat. Co., Harbor, USA). The column was washed with 3 ml of 30% methanol (RMP) or 30% acetone (KRM-1648) and then the drug was eluted with 2 ml of methanol (RMP) or methanol-ethyl acetate (1 : 1) (KRM-1648). Each eluate was evaporated to dryness by a centrifugal concentrator (Model VC-960, Taitec Corp. Koshigaya, Japan) and the residue was dissolved into 200 μl of methanol saturated with sodium ascorbate (RMP) or methanol (KRM-1648), and loaded onto a column. For the determination of drug concentration in mouse footpads and organs, 2 ml of 10% liver homogenate (in a phosphate-buffered PS containing sodium ascorbate, pH 7·4 (RMP), acetate-buffered PS, pH 4·0 (KRM-1648)) or an appropriate volume (based on the amount of homogenized spleen or footpads) of 5% tissue homogenate was extracted with a total 20 ml of methanol (RMP) or acetone (KRM-1648), filtered and then the filtrate was evaporated to dryness by a rotary evaporator. The residue was dissolved in 0·5 ml of methanol (RMP, KRM-1648), mixed with 9·5 ml of phosphate-buffered PS and loaded onto the Bond Elute Column C_{18} and treated similarly to that of plasma, except that the last dissolution from liver and spleen specimens was done with 400 μl of solvent. Analytical systems for RMP and KRM-1648 were: columns, Shim-pack CLC-ODS, internal diameter 4–6 mm, length 250 mm (Shimadzu Corp.); mobile phases, a mixture of

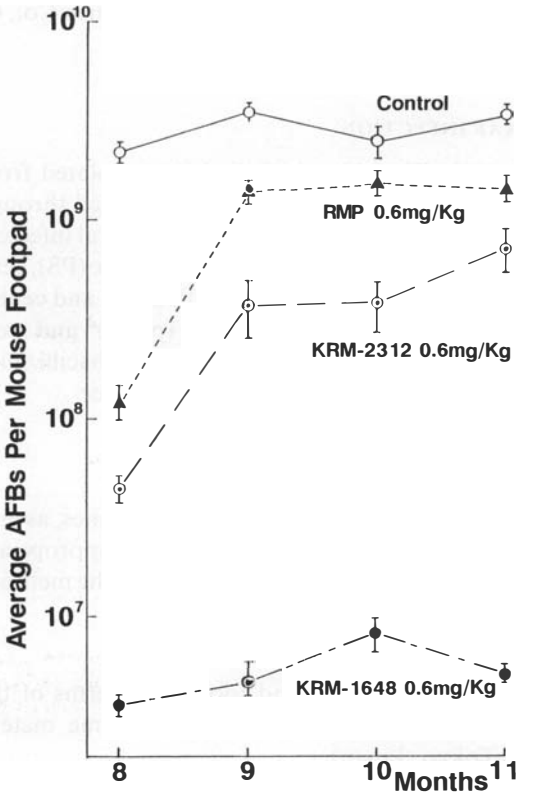

Figure 2. Growth inhibition of leprosy bacilli inoculated into nude mouse footpads by serial treatment with KRM-1648, KRM-2312, or rifampin (RMP). Groups of 10 nude mice were infected with *M. leprae*, strain Thai-53, by inoculating 3×10^7 bacilli into each of both hind footpads, followed by oral treatment with KRM-1648, KRM-2312, or RMP, given once a day, 5 or 6 times weekly, between 3 and 5 months postinfection at a daily dose of 0·6 mg/kg. We took 4 or 6 footpads of 2 or 3 mice at the indicated months postinfection, and acid-fast bacilli (AFBs) in the footpads were counted.

a solution A and acetonitrile (1 : 1) for RMP and (1 : 2) for KRM-1648, where the solution A (pH 4·4) contained 14·05 g of $NaClO_4 \cdot H_2O$, 1·92 g of anhydrous citric acid and 2·94 g of sodium citrate $\cdot 3H_2O$ per litre of deionized water; column temperatures, at 40°C; flow rates (ml/min), 0·5 (RMP) and 1·0 (KRM-1648); column pressures (kg/cm^2), 52 (RMP) and 72 (KRM-1648); pumps, Tri Rotar Model SR (Japan Spect. Co.); detectors, Model SPD-10A UV-VIS (Shimadzu Corp.) at 475 nm for RMP and Model T-4200 UV-VIS (Hitachi, Ltd) at 643 nm for KRM-1648; injectors, an autoinjector Model SIL-9A (Shimadzu) for RMP and an auto sample processor (Waters) for KRM-1648; data processors, Models Chromatopac C-R3A and C-R4AX (both Shimadzu) for RMP and KRM-1648, respectively. Both the systems were always used in parallel. The peaks of unchanged RMP and KRM-1648 were found at retention times (Trs, min) of 11·4 and 22·7 with extinction coefficients of $1{\cdot}49 \times 10^4$ (at 475 nm) and $5{\cdot}93 \times 10^4$ (at 643 nm) and with detection limits (S/N = 30) of 8·2 and 9·5 ng/ml, respectively.

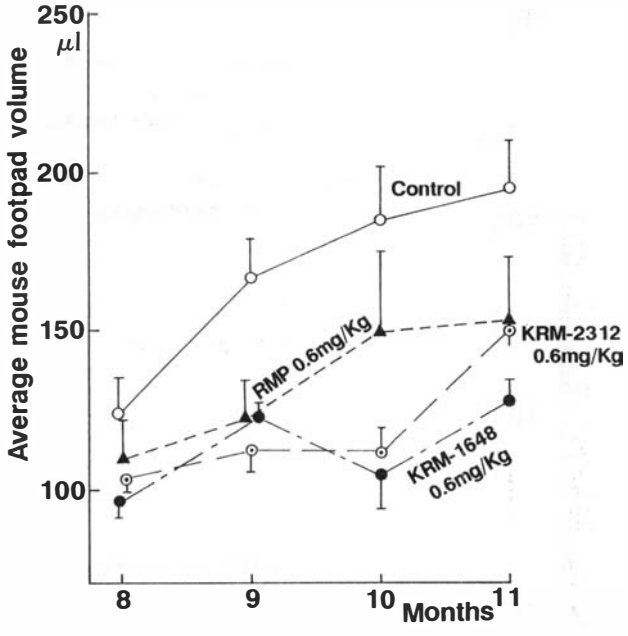

Figure 3. Suppression of footpad swelling of nude mice infected with *M. leprae* by serial treatment with KRM-1648, KRM-2312, or RMP. Mouse footpad volumes were measured in the mice used in the experiment shown in Figure 2. Each point indicates a mean value of 4 or 6 footpads of 2 or 3 mice, and the bar is the standard error.

Results

Efficacy with serial treatment

The results are shown in Figures 2 and 3. In the control nude mice inoculated with 3×10^7 leprosy bacilli per footpad, the average number of AFB had already reached above the 10^9 level at 8 months after inoculation and it remained at that level until the 11th month.

When the treatment with drugs at a dose of 0·6 mg/kg was performed 5 or 6 times weekly from the 3rd to the 5th months, after inoculation, KRM-1648 was the most active antibiotic: it reduced the average numbers of AFB to a 10^6 level, which was less than the inoculated number of AFB, between 8 and 11 months after inoculation, indicating that KRM-1648 inhibited the multiplication of leprosy bacilli in the nude mouse footpads. KRM-2312 and rifampin (RMP) were also effective in reducing the number of AFB. However, the activity of KRM-2312 seemed to be somewhat greater than that of RMP. In both groups, a gradual increase in the numbers of AFB was observed between 8 and 11 months after inoculation.

In the control group, the footpad volume increased to nearly double between 8 and 11 months after inoculation.

All the examined drugs suppressed the swelling of footpads, and a significantly stronger suppression in the KRM-1648 group than in the other 2 treated groups was seen at the 11th month (versus RMP group, $P < 0{\cdot}01$; versus KRM-2312 group, $P < 0{\cdot}001$).

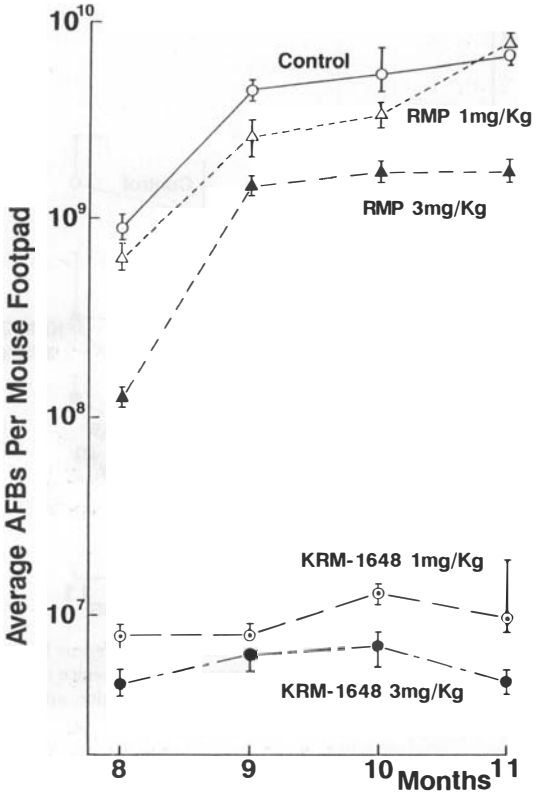

Figure 4. Growth inhibition of leprosy bacilli inoculated into nude mouse footpads by intermittent treatment with KRM-1648 or RMP. Groups of 10 nude mice were infected with *M. leprae*, strain Thai-53, by inoculating 3×10^7 bacilli into each of both hind footpads, followed by oral treatment with KRM-1648 or RMP, given once a day, twice weekly, at a dose of 1 or 3 mg/kg, between 3 and 5 months postinfection. We took 4 or 6 footpads of 2 or 3 mice at the indicated months postinfection, and AFBs in the footpads were counted.

Efficacy with intermittent treatment

The activity of KRM-1648 against nude mouse-model leprosy in comparison with that of RMP was examined by intermittent dosing with a 2- or 3-day interval. Nude mice inoculated with 3×10^7 leprosy bacilli per footpad were administered orally with KRM-1648 or RMP at a dose of 1 or 3 mg/kg, twice weekly between 3 and 5 months after inoculation. As shown in Figure 4, the average number of AFB in the control group reached nearly 10^9 at 8 months after inoculation and increased gradually thereafter at every specified time. In contrast, the average numbers of AFB in both the KRM-1648 1-mg/kg and 3-mg/kg groups were below the inoculated number of AFB throughout the specified times, demonstrating that KRM-1648 inhibited the multiplication of leprosy bacilli also by the intermittent dosing. The growth inhibition observed in RMP groups was only partial, even at the higher dose of 3 mg/kg, and the inhibition was slight at 1 mg/kg.

The average footpad volumes at each specified time are shown in Figure 5. It shows that while KRM-1648 completely suppressed the swelling of footpads, the suppression by

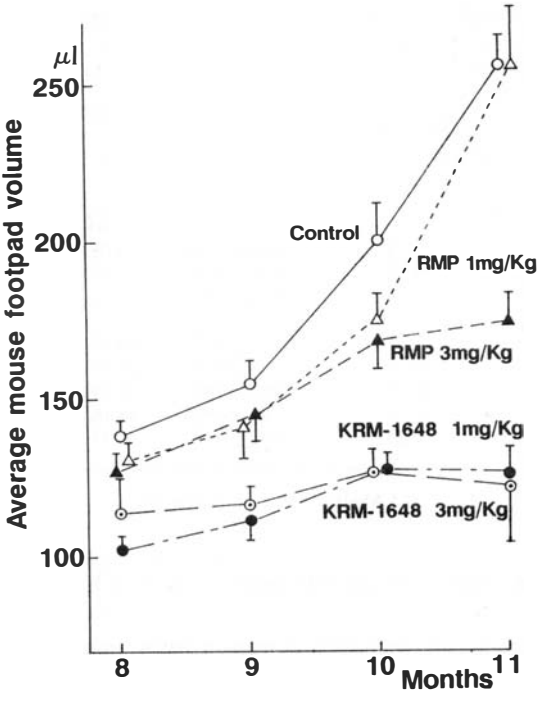

Figure 5. Suppression of footpad swelling of nude mice infected with *M. leprae* by intermittent treatment with KRM-1648 or RMP. Mouse footpad volumes were measured in the mice used in the experiment shown in Figure 4. Each point indicates a mean value of 4 or 6 footpads of 2 or 3 mice, and the bar is the standard error.

RMP was weak. In this experiment, the degree of the swelling suppression by a drug was well correlated with the inhibition of bacillary growth by the drug.

All these results indicated that the bactericidal action of KRM-1648 was more potent than that of RMP on leprosy bacilli inoculated into nude mouse footpads.

Discussion

The importance given to rifampicin for the treatment of leprosy followed the report by Rees *et al.*[8] on the bactericidal action of the drug at a minimal inhibitory dose of 5 mg/kg on *Mycobacterium leprae* inoculated into footpads of normal mice, and the demonstration by Shepard *et al.*[9] that *M. leprae* was eradicated from the footpads of mice given intermittently 2 doses of 25 mg/kg body weight.

Since then we, like many others, have attempted to develop derivatives with still greater antimycobacterial activity than rifampicin. Our first objective was to administer and assess the fate and the antileprosy activity of the metabolites of rifampicin (^{14}C-labelled) we had synthesized from [3-^{14}CH=] RMP. All the metabolites were found to be more rapidly excreted and their tissue levels lower than rifampicin. In particular the rifampicin 1,4-quinone metabolite was inactive against the *M. leprae* footpad infection in mice fed 0·0005% in their diet, while rifampicin was very active at this dose.[10] However, it seemed reasonable to conclude that protection of rifampicin from 1,4-oxidation, as well

Table 1. Distributions of unchanged KRM-1648 and RMP in BALB/c (nu/nu) female mice after a single oral administration of 10 mg/kg

Drug	Time after administration (hr)	Concentration (μg/ml or g)		
		Plasma	Liver	Spleen
KRM-1648	1	0·01 ± 0·01*	3·13 ± 0·71	1·38 ± 0·62
	3	0·05 ± 0·00	3·40 ± 0·31	2·19 ± 0·36
	5	0·29 ± 0·02	5·08 ± 0·94	5·45 ± 1·05
	8	0·18 ± 0·05	3·48 ± 0·42	5·56 ± 1·39
	24	0·01 ± 0·01	0·21 ± 0·10	0·18 ± 0·12
RMP	1	9·37 ± 0·45	49·88 ± 2·65	3·85 ± 0·30
	3	7·38 ± 0·26	43·15 ± 0·39	2·61 ± 0·11
	5	7·62 ± 0·65	51·89 ± 3·71	2·90 ± 0·10
	8	7·01 ± 0·67	48·16 ± 0·91	1·97 ± 0·16
	24	0·42 ± 0·01	6·15 ± 0·53	0·19 ± 0·01

* Mean ± SEM of 3 animals.

as from desacetylation, might enhance its activity, at least by prolonging the tissue half-life.

Therefore, in addition to the more common approach used for developing more potent rifampicin analogues by modifying the 4-methyl-1-piperazinyl moiety,[11] more stable rifampicins were developed by protecting the ring 4-hydroxy group from oxidation. Unfortunately this modification, as exemplified by rifabutin,[12] and in spite of improved antimycobacterial activity *in vitro* and pharmacokinetics,[13–15] failed to be of clinical use in leprosy.[16]

In addition to the potent activity of KRM-1648 against *M. leprae* in the footpads of nude mice inoculated with 3×10^7 bacilli/footpad, both KRM-1648 and KRM 2312 showed potent and mutually comparable *in vitro*[17,18] and *in vivo* activities[19] against cultivable mycobacteria, such as *Mycobacterium avium* complex infection in female beige mice, and their therapeutic effects were superior to those of rifampicin and rifabutin.

Before considering pilot trials of KRM-1648 in man extensive pharmacokinetic studies are planned. In one such experiment, carried out by the Kaneka Corp. using ddY male mice, it was found that the plasma concentration ratio (%) of KRM-1648/rifampicin was only between 1·9 and 22·7 at specified time points during the 24 hr following a single oral dose of 20 mg/kg body weight. However, at 48 hr, KRM-1648 retained a plasma concentration 11 times higher than that of rifampicin and from which its plasma half-life was presumed to be at least longer than 8 hr. According to a report by Bruna *et al.*,[20] the plasma half-life of rifabutin in mice after a single oral dose of 50 mg/kg body weight is about 8 hr. The results also showed that, despite a far lower hepatic concentration of KRM-1648 than that of rifampicin, the splenic concentration of KRM-1648 was higher at every determination time throughout 24 hr post administration (data to be published elsewhere by the Kaneka Corp.).

The concentrations of KRM-1648 and rifampicin in BALB/c (nu/nu) female mice were also examined. As shown in the Table 1, after a single oral dose of 10 mg/kg body weight, the splenic concentration of KRM-1648 was again observed to be higher than that of rifampicin, though, in this case, only at 5 and 8 hr postadministration. The dosage was

half that given to ddY male mice, and so an accurate comparison at 24 hr between these 2 experiments cannot be made. But, in general, the retention of KRM-1648 seemed to be shorter than that observed in the normal mouse experiment on ddY mice.

Although the pharmacokinetic characteristics are not consistent with the extremely potent activity of KRM-1648, further studies will be carried out, particularly on the unexpected and sustained levels of KRM-1648 in spleen tissues.

In the meantime, the new rifampicin derivative, KRM-1648, has all the potentials of an even more powerful antileprosy drug when compared to rifampicin, and which can be given intermittently.

Acknowledgment

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Lepr Rev (1992) **63,** 319–328

Action bactéricide à faibles doses d'un nouveau dérivé de la rifamycine, 3′-hydroxy-5′-(4-isobutyl-1-pipérazinyl)benzoxazinorifamycine (KRM-1648) sur *Mycobacterium leprae* inoculé dans la plante due pied de la souris "nude".

M Gidoh, S Tsutsumi, T Yamane, K Yamashita, K Hosoe et T Hidaka

Résumé Sur une série de benzoxazinorifamycines récemment synthétisés, nous avons examiné, sur la souris "nude" utilisée comme modéle, l'action anti-lèpreuse de 2 des dérivés 3′-hydroxy-5′-(4-alkyl-l-piperazinyl) appelés KRM-1648 et KRM-2312, dont les résidus alkyl sont respectivement isobutyl et isopropyl. En prises orales à la dose journalière de 0,6mg/kg, 5 ou 6 fois par semaine, pendant les 3 à 5 mois suivant l'inoculation, KRM-1648 a complètement inhibé la croissance des bacilles lépreux dans la plante du pied de la souris "nude", jusqu'à 6 mois après l'arrêt du traitement. En comparaison, l'inhibition de croissance obtenue avec KRM-2312 dans les mêmes conditions a été incomplète, bien que plus forte que celle obtenue avec la rifampine. L'inhibition de croissance complète obtenue avec KRM-1648 a été également observée aux doses orales de 1 et 3 mg/kg deux fois par semaine pendant la même période. Par contre, l'inhibition de croissance obtenue avec la rifampicine a été faible seulement à la dose de 1 mg/kg et partielle avec 3 mg/kg dans les mêmes conditions.

Acción bactericida a dosis bajas de un nuevo derivado de la Rifamicina, 3′-hidroxi-5-(4-isobutil-1-piperazinil)-benzoxazinorifamicina (KRM-1648), sobre *Mycobacterium leprae* inoculada en la almohadilla plantar de ratones desnudos

M Gidoh, S Tsutumi, T Yamane, K Yamashita, K Hosoe y T Hidaka

Resumen Se examinaron 2 de los derivados de 3′-hidroxi-5′-(4-alquilo-1-piperazinilo) con un residuo alquílico de isobutilo o isopropilo con los nombres KRM-1648 y KRM-2312 respectivamente, de una serie de benzoxazinorifamicinas recientemente sintetizadas, para eficacia contra la lepra en un modelo de ratón desnudo. La KRM-1648 inhibió por completo el crecimiento de los bacilos de la lepra inoculados en la almohadilla plantar de ratones desnudos, mismo 6 meses después de descontinuar la medicación, cuando se la administraba por via oral a una dosis diaria de 0,6 mg/kg, 5 o 6 veces por semana, durante los meses 3 a 5 después de la inoculación. En comparación, bajo las mismas condiciones, la inhibición del crecimiento por KM-2312 fue incompleta, aunque el efecto era más marcado que con la rifampicina. Se observó una inhibición total del crecimiento mediante la KRM-1648 cuando se administraba en una dosis oral de 1 a 3 mg/kg dos veces por semana durante el mismo periodo. Vuelta en cambio, la inhibición de crecimiento por la rifampicina fue solamente leve a 1 mg/kg y parcial a 3 mg/kg, bajo las mismas condiciones.

Lepr Rev (1992) **63,** 329–336

Persistence of *Mycobacterium leprae* in the peripheral nerve as compared to the skin of multidrug-treated leprosy patients

V P SHETTY, K SUCHITRA, M W UPLEKAR & N H ANTIA*
The Foundation for Medical Research, 84, A.R.G. Thadani Marg, Worli, Bombay 400018, India

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Summary Skin and nerve biopsies obtained from 18 multibacillary (MB) and 16 paucibacillary (PB) cases of leprosy who had been fully treated by the WHO regimen were assessed for bacterial load using different staining techniques. In addition skin and nerve homogenates of 10 MB cases were tested for 'persistor' *Mycobacterium leprae* using immunosuppressed mice.

While significant amounts of integral bacilli and BCG cross-reactive antigen of *M. leprae* were detected both in skin and nerve tissues of all the MB cases (100%), 56% of skin and 62% of nerve biopsies of PB cases also showed the presence of BCG cross-reactive antigen.

Detection of 'persistor' *M. leprae* in 2/10 skin biopsies (20%) and 3/10 nerve biopsies (30%) of MB cases was thought to be unexpectedly high after 2 years of MDT.

Introduction

Although the peripheral nerves, and the Schwann cells in particular, are well recognized to be the seat of disease in leprosy,[1] decisions regarding diagnosis and therapy are based largely on skin manifestations and the presence or absence of bacilli within the skin lesions. This is chiefly because of the ease of investigation and also because skin lesions do provide a good indication of the activity of the disease process. However, it has been demonstrated in histopathological studies that in the same patient, nerves generally show lesions which are more advanced and also harbour bacilli exhibiting solid forms which indicate a higher degree of viability.[2,3] This is believed to be because nerves, being immunologically protected, are favoured sites for bacillary survival and multiplication,[4,5] It is possible that after prolonged chemotherapy, while skin lesions may not have viable bacilli, some viable bacilli may persist within the nerves and may cause a relapse at a later stage after therapy has stopped. THELEP trials with MDT at Bamako and Chingleput showed the presence of persistor *M. leprae* in 9% of cases.[6]

* Corresponding author.

0305-7518/92/063329+08 $01.00

The present study was undertaken in order to determine and compare the bacterial load as well as the viability within the peripheral nerves and the skin of leprosy patients who had been treated with the WHO recommended multidrug therapy.

Patients and method

A total of 18 multibacillary cases (BL–LL) treated for a minimum of 2 years and 16 paucibacillary cases (BT–TT)[7] treated for a minimum of 6 months with the WHO recommended multidrug regime[8] were studied for bacterial load in the skin and nerve using different staining techniques. Additionally skin and nerve biopsies from 10 of the multibacillary cases were studied for bacterial viability using the mouse footpad technique.

Where possible, skin biopsies of all the cases were taken from lesions that appeared most active, but in the absence of any active lesions, the choice of biopsy in lepromatous patients was either earlobe. In tuberculoid patients with healed lesions, the biopsy was taken from a clinically inactive lesion. The selection of the peripheral nerve for biopsy was based on the amount of clinical and electrophysiological involvement. An involved sural nerve was biopsied in all except 1 of the lepromatous patients, the biopsy in the tuberculoid patients varied according to the site of involvement and included the sural (6),

Table 1. Bacterial load in skin and nerve of treated MB cases using different staining techniques

		Skin			Nerve		
No.	Rx doses MDT–MB	Smear BI (Avg) (+)	Histo BI (+)	Anti BCG. (+)	Histo BI (+)	Anti BCG. (+)	EM BI (+)
1	32	3·3	3	3	3	3	4
2	24	0·2	0	1	0	2	2
3	24	0	0	2	0	1	2
4	30	4·2	2	2	3	ND	ND
5	24	0	2	1	2	1	2
6	24	0·5	3	2	3	2	3
7	24	0·3	2	1	0	2	2
8	24	2·0	2	3	2	2	2
9	24	4·3	3	2	3	2	3
10	24	2·1	3	3	3	3	3
11	24	1·0	3	3	ND	ND	2
12	24	0	0	1	0	2	2
13	24	0·3	0	0	0	2	2
14	24	2·1	3	3	2	3	3
15	24	0·2	2	2	0	2	2
16	24	0	2	2	0	3	3
17	24	0	2	1	0	2	2
18	24	0	2	2	2	2	2
+VE staining		12/18	14/18	17/18	9/17	16/16	17/17

ND, not done; semiquantative grades: BI = 0 to 6+ (Ridley DS 1964, 1985); AntiBCG = 0 to 4+.

the cutaneous branch of the radial (7), the cutaneous branch of the ulnar (1), the lateral thoracic (1) and the superficial peroneal (1).

Determination of the bacterial load

The following methods were employed for the determination of the bacterial load:

a Multiple slit-skin smears were obtained from all the patients before biopsy. Smears stained with Fite-Farraco were scored for their bacterial index (BI) using Ridley's scale.[9]

b Paraffin sections of skin and nerve biopsies were stained with Trichrome modified Fite-Farraco (TRIFF) and the bacterial index was determined on tissue sections using Ridley's method.[10]

c Paraffin sections of skin and nerve tissues were also stained with anti-BCG antibody (from DAKO) for cross-reactive Mycobacterial antigen using the peroxidase–antiperoxidase (PAP) technique.

d Araldite embedded ultrathin transverse sections of the nerve were scanned for the presence of osmiophilic bacilli using electron microscopy (EM). We determined the bacterial index (BI) at EM level for a given cross-section on the following grounds.

1+ = 1 or 2 cells carrying few bacilli (< 10);
2+ = few cells carrying single to small clusters of bacilli (> 10 to < 100);
3+ = several cells carrying clusters of bacilli (> 100), and so on.

All these are well standardized, routinely used techniques in our laboratory.

Table 2. Bacterial load in skin and nerve of treated PB cases using different staining techniques

		Skin			Nerve		
no.	Rx doses MDT–PB	Smear BI (+)	Histo BI (+)	Anti BCG. (+)	Histo BI (+)	Anti BCG. (+)	EM BI (+)
1	12		0	1	0	+	0
2	12		0	1	0	+	0
3	7		0	0	0	1	0
4	10		0	2	0	1	0
5	12		0	0	0	+	0
6	6		0	1	0	1	0
7	12		0	1	0	1	2
8	10	−ve	0	+	0	1	0
9	18		0	1	0	0	0
10	6		0	0	0	2	1
11	7		1	1	1	2	2
12	6		0	0	0	1	0
13	9		2	1	2	1	2
14	6		0	1	0	0	0
15	6		0	0	0	3	2
16	6		0	0	0	+	0
+ VE staining		0	2/16	9/16	2/16	10/16	5/16

+, Doubtful.

Determination of bacterial viability

Skin and nerve homogenates from 10 of the above-treated multibacillary cases only, were studied for bacterial viability. Skin and nerve homogenates were prepared immediately after biopsy using sterile measures. The bacterial load per gram weight of skin and nerve tissues was determined using WHO guidelines and 0·03 ml of the homogenate containing not more than 10^5 bacteria were injected into both hind footpads of Swiss white mice thymectomized and irradiated with 5 graded doses of 200 rad each of 'X' irradiation at bi-weekly intervals.[11] A minimum of 8 mice were used for each inoculum. Footpad harvests were done at the end of 12 months.

Summary of results

BACTERIAL LOAD USING DIFFERENT STAINING TECHNIQUES

Multibacillary cases (MB): (Table 1)

Of the 18 MB cases studied, 6 scored negative in all the smears and the remaining 12 cases (66·6%) (Table 3) were positive with bacterial indices ranging from 1+ to 5+ in the skin.

On paraffin sections stained with TRIFF, 4 of the skin biopsies scored negative for acid-fast bacilli (AFB), whereas 1 skin biopsy showed negative anti-BCG staining. In the case of nerve biopsies, 8 out of 17 did not show AFB in TRIFF stained longitudinal and transverse (LS & TS) sections, whereas all the nerves (both LS & TS) were positive for anti-BCG.

In spite of the small sample size used for electron microscopy, all the nerve biopsies showed the presence of osmiophilic bacilli in the endoneurium (Tables 1 and 3).

Paucibacillary cases (PB): (Table 2)

None of the treated PB cases (BT–TT) showed any bacilli in the smear, whereas 2 of the skin biopsies stained with TRIFF showed a few bacilli in the deep dermal nerves. However 9 of the skin biopsies (56·2%) showed significant BCG positivity in the epithelioid cells.

Of the nerve biopsies, 2 showed bacilli in TRIFF, whereas 10 out of 16 nerve biopsies (62·5% Table 3) showed BCG positivity mainly in the Schwann cells. It was interesting to note that 5 of the nerve biopsies showed the presence of osmiophilic bacilli mostly in Schwann cells at the ultrastructural level.

Table 3. Percentage of skin and nerve tissues of MB and PB cases showing bacterial positivity after full MDT

	Skin			Nerve			
	Smear (%)	Histo (%)	BCG (%)	Histo (%)	BCG (%)	EM (%)	Total No. of cases
BL–LL c > 2 years of MDT	66·6	77·7	94·4	56·9	100	100	18
BT–TT c > 6 month of MDT	0	12·5	56·2	12·5	62·5	31·2	16

Table 4. Number of skin and nerve homogenates showing *M. leprae* growth in the FP of T200 × 5R mice

	Fold increase			
	> 10	> 5	< 1	Total
Skin	2/10 (20)*	2/10 (20)	6/10 (60)	10
Nerve	3/10 (30)	5/10 (50)	2/10 (20)	10

* Numbers in parentheses are percentages.

Table 5. *M. leprae*-fold increase in the FP of TR mice with skin and nerve homogenates

	Skin		Nerve	
Fold increase	No. of FP counts	%	NO. of FP counts	%
10	4	6·7	10	19·2
5	5	8·3	7	13·5
2	15	25·0	12	23·1
1	30	50·0	14	26·9
0 (no growth)	6	10·0	9	17·3
Total	60		52	

BACTERIAL VIABILITY USING T200 × 5R MICE

Both skin and nerve homogenates of 2 patients and only nerve homogenate of 1 patient showed over 10-fold growth in the mouse footpad (Table 4).

One of the patients, where both skin and nerve homogenates showed > 10 fold growth had completed 32 doses of MDT and he was on treatment during biopsy. The bacterial index of his smears ranged from 2+ to 4+. The other 2 patients had completed 24 doses of MDT, were smear negative and were off treatment for 2 months before biopsy.

In 5 out of 10 nerve homogenates (50%) and 2 out of 10 skin homogenates (20%) there was more than a 5-fold increase in footpad count which requires reconfirming to satisfy the WHO protocol.

Even though the bacterial load per gram weight of skin tissue was higher than that of nerve tissue (Table 6) the number of footpads showing over a 10-fold growth with nerve homogenate was twice more (10/52, i.e. 19·2%) than that of the skin homogenate (4/60, i.e. 6·7%) suggesting the presence of a higher number of viable organisms in the nerve (Table 5). By applying the χ^2 test for goodness of fit the difference was found to be of borderline significance of $p < 0{\cdot}05$.

Table 6. AFB count per gramme weight of the tissue

No.	Skin AFB count/gramme weight of tissue	Nerve AFB count/gramme weight of tissue
1	$6{\cdot}2 \times 10^7$	$2{\cdot}21 \times 10^7$
2	$3{\cdot}6 \times 10^7$	$0{\cdot}16 \times 10^7$
3	$50{\cdot}4 \times 10^7$	$13{\cdot}2 \times 10^7$
4	$3{\cdot}8 \times 10^7$	$10{\cdot}8 \times 10^7$
5	$25{\cdot}25 \times 10^7$	$3{\cdot}45 \times 10^7$
6	$33{\cdot}65 \times 10^7$	$1{\cdot}344 \times 10^7$
7	$4{\cdot}004 \times 10^7$	$3{\cdot}904 \times 10^7$
8	$22{\cdot}36 \times 10^7$	$< 1 \times 10^4$
9	$16{\cdot}85 \times 10^7$	$1{\cdot}130 \times 10^7$
10	$0{\cdot}286 \times 10^7$	$0{\cdot}709 \times 10^7$

Discussion

A semiquantitative analysis of the results reveal that detection of the BCG cross-reactive antigen using the PAP technique is far superior and more sensitive than the detection of acid-fast organisms using TRIFF staining in tissue sections, which in turn is superior to the smear technique. This is in accordance with the findings of Mshana *et al.*[12] Interestingly, detection of osmiophilic bacilli using an osmium-fixed araldite embedded ultrathin section is similar to the BCG cross-reactive antigen detection system in spite of the small sample size.

It is noteworthy that among the paucibacillary cases there is no concordance between BCG positivity of skin and nerve biopsies even though both biopsies were obtained simultaneously from the most active site of involvement.

The continued presence of both integral and BCG cross-reactive antigen of *M. leprae* in skin and nerve biopsies of MB cases after completion of treatment is not surprising since it is expected that the dead bacteria and its residues may take longer to clear from intracellular locations. However, 56% of skin and 62% of nerve biopsies of PB cases showed a persistence of bacterial antigen which is surprising. It is assumed that the initial load of bacteria in these cases is not more than 10^6. This low load combined with 2 highly potent bactericidal drugs taken for a period of 7–18 months in some cases (Table 2) clearly raises questions regarding the ability of these individuals to mount a better immune response that facilitates faster bacterial clearance. It is worth mentioning that 4 of the patients (Nos 4, 7, 9 and 13, Table 2) who were showing a significant amount of antigen in both skin and nerve had not only taken 7–18 months of treatment but the biopsies under study were obtained 6–11 months after stopping the treatment. This is in contrast to the expectations that the clearance of bacterial products would be faster after the withdrawal of antileprosy drugs which are partially immunosuppressive.[13,14] Alternative strategies need to be worked out to neutralize these antigens.

The presence of these antigens in any form of leprosy (PB or MB) can pose a potential danger in bringing about reversal reactions. The study of how and where these antigens are located in relation to the activity of the lesion might have an important bearing on any impending reaction, and this is also being studied and will be reported elsewhere.

Preliminary data in the second part of the study reveal that 2 out of 10 skin biopsies and 3 out of 10 nerve biopsies harboured significant numbers of viable bacteria, which is unexpectedly high. Our results also reveal that the viable number of bacteria in the nerve is twice that in the skin tissue. This observation calls for a fresh look at the efficacy of MDT which is the major tool in leprosy eradication programmes. We are inclined to believe that for cessation of therapy, the clinical evidence of disease inactivity and slit-skin smear negativity should be viewed with caution. Indeed a larger investigation including MB as well as PB cases needs to be undertaken, keeping in mind the possibility of multidrug resistance and bioavailability of antileprosy drugs.

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Lepr Rev (1992) **63,** 329–336

Comparaison de la persistance de *Mycobacterium leprae* dans les nerfs périphériques et dans la peau de patients sous traitement multidrogue

V P Shetty, K Suchitra, M W Uplekar et N H Antia

Résumé A l'aide de diverses techniques de coloration, nous avons déterminé le taux de contamination bactérienne de biopsies de la peau et des nerfs obtenues chez 18 cas de lèpre multibacillaires (MB) et 16 cas de lèpre paucibacillaires (PB). De plus, nous avons recherché le *Mycobacterium leprae* 'persisteur' dans des homogénats de peau et de nerf de 10 cas MB en utilisant la souris immuno-déprimée.

Des quantités significatives d'antigène des bacilles intégraux et du BCG en réaction croisée ont été décelées dans les tissus épidermiques et nerveux chez tous les cas MB (100%); par contre, 56% des biopsies de peau et 62% des biopsies de nerf des cas PB ont montré la présence d'antigène du BCG en réaction croisée.

La détection de *Mycobacterium leprae* 'persisteur' dans 2/10 biopsies de peau (20%) et 3/10 biopsies du nerf (30%) chez les cas MB semble plus élevée que prévu après 2 années de traitement multidrogue.

La persistencia del *Mycobacterium leprae* en el nervio periferico comparada a la piel de los leprosos tratados con multi-drogas

V P Shetty, K Suchitra, M W Uplekar y N H Antia

Resumen Biopsias de la piel y de nervios obtenidas de 18 leprosos multibacilares (MB) y 16 paucibacilares (PB) que habían recibido un tratamiento completo con el régimen de la OMS, fueron evaluadas para carga bacteriana utilizando diferentes técnicas de coloración. Además, productos homogenizados de piel y nervios en 10 casos MB fueron probados para *Mycobacterium leprae* 'persistor' mediante ratones immunosuprimidos.

Aunque se detectaron cantidades significativas de bacilos integros y antígeno BCG de reactividad cruzada de *M. leprae* tanto en tejidos de piel como de nervios, en todos los casos MB (100%), 56% de las biopsias de piel y 62% de las de nervios en los casos PB tambien mostraron la presencia de antígeno BCG de reactividad cruzada.

Se cree que la detección de *M. leprae* 'persistor' en 2/10 de las biopsias de la piel (20%) y en 3/10 biopsias de nervios (30%) en los casos MB fue inesperadamente alta después de 2 años de MDT.

Lepr Rev (1992) **63,** 337–344

The international classification of impairments, disabilities and handicaps in leprosy-control projects

J W BRANDSMA, Y F HEERKENS,
K LAKERVELD-HEYL &
C D MISCHNER-VAN RAVENSBERG
National Institute for Research and Postgraduate Education in Physiotherapy, Postbus 1161, 3800 BD Amersfoort, The Netherlands

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Summary The use of a uniform language, which includes definitions of terms, is very important in the field of health care. It is important to have a common language for educational, research and communication purposes. Classifications can play a major role in the development of uniform reporting and registration systems. The purpose of this article is to familiarize leprosy workers with two classifications that are in common use in health care, a classification of diseases and a classification used to describe the overall health status of a person, and to relate the 3 terms that are used in the latter classification, impairments, disabilities and handicaps, to leprosy.

The importance of uniform language and the use of classifications within health care

The quality of communication depends largely on the quality of the message. The message must be clear, understandable and uniform. Communication fails when the message, verbal or non-verbal, is misinterpreted or misunderstood by the receiver. Within health care much effort is spent to realize a uniform language which is necessary to manage the rapidly increasing growth and flow of data.

This has resulted in the development of uniform terminology/nomenclature and classifications to handle different types of data, e.g. personal data, causes of diseases, pathology of diseases, consequences of diseases and characteristics of treatment modalities.

A classification can be generally described as a systematic arrangement of similar entities on the basis of certain different characteristics.[1] The Dutch Classification and Terminology Committee (WCC) for Health of the National Council for Public Health (NRV) gives the following definition: 'a system of terms connected by generic relationships'.[2]

The use of a uniform language facilitates recent developments, e.g. quality care, quality assessment and the compilation of reliable epidemiological data. It will promote research of, and insight into the effects of treatment for categories of patients. In this way the use of a uniform language will enhance the quality of health care as a whole.

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The International Classification of Diseases (ICD) and the International Classification of Impairments, Disabilities and Handicaps (ICIDH)

In 1980 the International Classification of Impairments, Disabilities and Handicaps (ICIDH) was published by the World Health Organization (WHO) for trial purposes as a classification of the consequences of disease.[3]

The classification was primarily developed as a complementary classification to the International Classification of Diseases (ICD). The ICD is the oldest of all medical classification systems in current use and now is undergoing its 10th revision which will be introduced in 1993. Whereas the ICD is the classification used to classify diseases, the ICIDH is the classification used to classify manifestations and sequelae of diseases and disorders, be they transient or permanent. With the 10th edition of the ICD it has become possible to classify all clinical types of leprosy: indeterminate, tubercuoid, borderline and lepromatous.[4] *All* sequelae, however, that can occur as a result of leprosy and leprosy neuropathy will have the same ICD code. To differentiate between these sequelae the ICIDH could be used.

The ICIDH consists of 3 separate classifications: a classification of impairments, a classification of disabilities and a classification of handicaps.

In the ICIDH these terms are defined as follows:[3]

Impairment: an impairment is any loss or abnormality of psychological, physiological or anatomical structure or function.
Disability: a disability is any restriction or lack of ability (resulting from an impairment) to perform an activity in the manner or within the range considered normal for a human being.
Handicap: a handicap is a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual.

Impairments occur at the organ level (function or structure). Loss of protective sensation, hoarseness of voice, loss of eyebrows, clawhand, amputation, and absorbtion of digits are all examples of impairments which can occur in leprosy patients secondary to peripheral nerve damage or as a late result of advanced lepromatous leprosy.

Impairments may result in disabilities and information on the latter tells us what the patient is not able to do. Dis-ability leads to the meaning 'not being able to' (compare: dis-ease, not being at ease). Disabilities represent 'objectifications' of an impairment, and as such they reflect disturbances at the level of the person (functioning as a person; self-care and interaction with the environment). The current chapter divisions for both the classification of impairments and the classification of disabilities in the present ICIDH are given in Table 1.

Impairments and disabilities in turn may lead to handicaps. A handicap represents the effect of the consequences of disease at the level of the society for that individual in cultural, social, economical and environmental dimensions. A handicap is a disadvantage for a given individual that limits or prevents the fulfilment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual.[3] It should be mentioned that the diagnosis of leprosy alone, without the obvious impairments/disabilities, in many countries may lead to a handicap if the diagnosis is known to the society (stigma).

Table 1. Chapter division impairment and disability classification in the present ICIDH

Impairments	Disabilities
1 Intellectual	1 Behaviour
2 Other psychological	2 Communication
3 Language	3 Personal care*
4 Aural	4 Locomotor*
5 Ocular*	5 Body disposition
6 Visceral*	6 Dexterity*
7 Skeletal*	7 Social integration*
8 Disfiguring*	8 Economic self-sufficiency*
9 Generalized, sensory, and other*	9 Other

* Chapters containing impairments, disabilities commonly encountered in leprosy patients.

A leprosy patient who cannot work because of his/her impairments, disabilities or even the stigma of the disease has a handicap in occupation. Similarly a patient who is housebound because of the impairments/disabilities has a handicap in mobility. A patient that is partially or totally dependent on others for his/her existence has a handicap in the dimension of physical dependency.

The 'handicap classification' in its present form is not a true classification. It is more a severity scale that can be used to grade the patients in the different dimensions of his/her (non)functioning in society.

'Disability' grading and 'disability' prevention in leprosy

In light of the above-mentioned definition of disability, the commonly used terms 'disability grading' and 'disability prevention' by leprosy workers, will have to be used with caution.

The grading of disabilities has been practised for a long time in leprosy. The WHO has suggested and advocated the use of a disability grading in official publications.[5,6] In many publications suggestions have been made to modify the disability grading as suggested by the WHO in 1980.[7–9] When 'disability' grading is performed regularly and conscientiously it is for example possible to assess whether patients do develop 'disabilities' while on treatment, how many new patients are reporting with 'disabilities' and whether certain types of leprosy are more prone to develop 'disabilities'.[10–17] However, what is actually graded with the suggested scales are impairments, impairments that may or may not result in disabilities. For the eye it could be argued that even diseases are graded that can be classified with the ICD, e.g. iritis and keratitis. Disabilities as defined above are not listed on the various disability grading scales including the official WHO disability grading scales (Tables 2, 3).

It should be emphasized that the grading of disabilities is a means to gather epidemiological data and to evaluate an individuals health status over time. It is not to be used to monitor the nerve function status of patients.

Table 2 lists the 'disabilities' from the 1980 leprosy disability grading form which is

Table 2. Leprosy 'disability' grading 1980

Impairment	Code	Description
Absorbtion	86·8	Other structural disfigurement
Blindness	51·9	Both eyes
	54·9	One eye
Clawhand	73·2	Other paralysis of upper limb
Conjunctivitis		
Dropfoot	73·4	Other paralysis of lower limb
Injury	??	
Insensitivity	58·2	Anaesthetic eye
	97·0	Sensory impairment upper limb
	98·0	Other sensory impairment
Iritis		
Keratitis		
Lagophthalmos	70·2	Facial palsy
Stiff joints	71·4	Mechanical impairment of finger
	71·7	Mechanical impairment of ankle and foot
Ulcer	??	
Wristdrop	73·2	Other paralysis of upper limb

The first number of the impairment code refers to the chapter in the classification of impairments. As can be seen from the table with the present ICIDH, the impairments commonly seen in leprosy patients can often only be classified under broad headings (class: other . . .); others cannot be classified. No disabilities are listed.

Table 3. Leprosy 'disability' grading 1988

Hands and feet:
Grade
0: no anaesthesia or visible deformity or damage.
1: anaesthesia, but no visible deformity or damage.
2: visible deformity or damage.

Eyes
Grade
0: no eye problems due to leprosy; no evidence of visual loss.
1: eye problems due to leprosy present, but vision not severely affected.
2: severe visual impairment.

Comment: anaesthesia and visible deformities or damages are impairments.
Eye problems due to leprosy are corneal anaesthesia, lagophthalmos and iridocyclitis; corneal anaesthesia and lagophthalmos are also impairments.

still in use in some control projects.[5] Table 3 lists the 'disabilities' from the suggested disability grading form as revised in 1988.[6]

It would be possible to talk about prevention of disabilities in leprosy only indirectly. Loss of protective sensation and paralysis (impairments) are not likely to occur when patients are diagnosed early, nerve function loss is detected in time and when patients comply with the drug treatment. Impairments due to nerve involvement will then not occur and therefore the patients will not develop disabilities.

Without nerve function loss in the hand, disabilities, e.g. in eating and selfcare, will not develop. The ultimate goal of patient education (health education) is that patients will not develop ulcers, injuries and burns (impairments) that may result in disabilities.

A surgeon who corrects a clawhand deformity or a footdrop corrects impairments and thereby restores the ability to turn a key or eat properly with the hand or enables a patient to walk properly again (these are classified as disabilities when this is not possible).

Updating/revision of the ICIDH

The conceptual framework of the ICIDH is becoming more and more well known and accepted especially in the fields of rehabilitation and social medicine. The number of publications in which the concept of impairment, disability and handicap is used either descriptively or in epidemiological studies is vastly increasing.[18] Many authors have also criticized parts of the ICIDH, especially the handicap classification.

Based on the comments given by a great number of ICIDH-users the WHO started a revision procedure for the ICIDH in 1990. There are two WHO collaborating centres for the ICIDH and each of the centres has been asked to co-ordinate work for one of the classifications of the ICIDH. The collaborating Centre in France will co-ordinate the suggestions and/or comments for the impairment classification, and the Netherlands (WCC) for the disability classification. The United Nations Statistical Office and the Canadian Society for the ICIDH are jointly entrusted with the handicap 'classification' and the role of environmental and social factors that determine disability and handicap. At the last international meeting about the ICIDH with the collaborating centres in March 1992 it was decided to first publish an update of the current ICIDH.[19] There will only be a few minor changes. With the update, the ICIDH will no longer have the status of classification for trial purposes and a formal revision procedure for the classification can be initiated.

As already stated the ICIDH is a very important classification for health professionals, including paramedical professionals. As the present ICIDH does not meet the need for paramedical professionals the Dutch Institute for Research and Postgraduate Education in Physical Therapy (SWSF) started a project to formulate proposals for improvements in the ICIDH, both for the classification of impairments and the classification of disabilities, in co-operation with representatives of 5 paramedical professions: physiotherapy, occupational therapy, chiropody, and exercise therapists

Table 4. Proposed chapter division of impairments

Impairment classification	Examples in leprosy
1 Intellectual and other mental impairments	
2 Voice, speech and language impairments	Hoarseness
3 Ear, hearing and balance impairments	
4 Eye and visual impairments	Loss of eyebrows, lagophthalmos, loss of vision
5 Internal impairments	Gynaecomastia
6 Impairments of the locomotor system	Absorbtion, clawhand
7 Skin and sensibility impairments	Ulcus, scar, anaesthesia
8 Pain	Nerve pain
9 Generalized, other sensory and other impairments	

according to the systems of Mensendieck and Cesar.[20] The project is subsidised by the Ministry of Welfare, Public Health and Cultural Affairs. The final report has been submitted to the Dutch Collaborating Centre for the ICIDH, the WCC and through seminars and publications the proposals are made known to generate interest in the ICIDH and invite reactions.[21,22]

Tables 4 and 5 list the proposed chapters for a revised ICIDH with examples of impairments and disabilities commonly seen in leprosy patients. New, suggested definitions for impairment and disability are given in Table 6.

Conclusions and recommendations

In leprosy there is a long tradition of classifying the disease and grading the consequences of the disease. To enhance the quality of communication with other workers within the health care system, nationally and internationally, it is important that leprosy workers are familiar with the classifications that are used by workers in related fields, e.g. rehabilitation medicine. If possible they must adapt their own terminology to these internationally used standards. The use of a common language will not only facilitate communication but will also enhance the quality of research and eventually the quality of care to the patients. For record keeping and for reporting purposes it is mandatory that a common language/terminology is used. This terminology should be in accordance with suggested terminology.

Because the ICIDH terminology is becoming more and more popular when describing a patient's 'health status', it is important that leprosy workers become familiar with the ICIDH and the 3 classifications contained therein. This will enable them to describe a patients' health status on 3 levels of functioning: organ, person, society.

Table 5. Proposed chapter division of disabilities

Disabilities in	Examples relevant for leprosy patients
1 Basic sensory motor skills	Grasping, carrying
2 Psycho-social skills	
3 Communication skills	Writing
4 Locomotion and transfers	Walking
5 Personal care	Bathing, dressing, eating
6 Domestic activities	Cleaning, preparing meals, washing cloths
7 Work	Handling working conditions, work output
8 Recreation	Visiting friends/relatives, playing musical instrument
9 Other	

Table 6. Suggested definitions

Impairment:	In the context of health experience, an impairment can be defined as the loss or abnormality of an anatomical structure or physiological or psychological function.
Disability:	In the context of health experience a disability can be defined as the reduction or absence of the ability of a person to perform activities or to show behaviour in accordance with normally expected activities/skills/behaviour both in a quantitative and a qualitative sense.

For practical purposes and field use we would like to recommend the use of the 1988 WHO 'disability' grading which makes it possible to score the impairments of the patient. The 1988 grading scale could be expanded, where practical, with a few items to indicate/assess the presence of disabilities that are common in leprosy patients, e.g. in selfcare, eating; and in locomotion, walking. Depending on the purpose for which impairments and/or disabilities are graded it may at times be more important to know what the patient is unable to do (disability) rather than what the patient has (impairment).

Invitation

The authors are extremely interested to receive comments and suggestions regarding the use of classifications in leprosy control work and the proposed definitions and chapter divisions.

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La classification internationale des deficiences, incapacités et handicaps dans les projets de contrôle de la lèpre

J W Brandsma, Y F Heerkens, K Lakerveld-Heyl et
C D Mischner-van-Ravensberg

Résumé L'usage d'un langage uniforme, comprenant des définitions de termes, est très important dans le domaine des services de santé. Il est important d'avoir un langage commun à des fins d'éducation, de recherche et de communication. Les classifications peuvent jouer un rôle majeur dans l'établissement de systèmes uniformes de reportage et d'enregistrement. Le but de cet article est de familiariser ceux qui travaillent sur la lèpre avec deux classifications utilisées couramment dans les services de santé, une classification des maladies et une classification utilisée pour décrire l'état de santé générale d'une personne. Le second but est d'appliquer à la les 3 termes qui sont utilisés dans cette dernière classification: détériorations, invalidités et handicaps.

La clasificación internacional de deterioro, incapacitación y minusvalidez, en los proyectos del control de la lepra

J W Brandsma, Y F Heerkens, K Lakerveld-Heyl y
C D Mischner-van Ravensberg

Resumen El uso de un lenguaje uniforme que incluye la definición de vocablos, es de suma importancia en el campo de la asistencia sanitaria. También es importante tener un lenguaje común para propósitos educacionales, de investigación y de comunicación. Las clasificaciones juegan un papel principal en el desarrollo del reportaje y de los sistemas de registración uniformes. La intención de este artículo es familiarizar los trabajadores en el campo de la lepra con las dos clasificaciones que se usan comunmente en la asistencia sanitaria, una clasificación de enfermedades y una clasificación que se utiliza para describir el estado general de salud de la persona, y relacionar los 3 vocablos, deterioro, incapacitación y minusvalidez, que se utilizan en ésta, a la lepra.

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Risk factors among defaulters in the urban leprosy control centre of Thaketa Township in the City of Yangon, Myanmar, 1986

T MYINT, M T HTOON, M WIN & C YIN
Leprosy Control Programme, Department of Health, Ministry of Health, Myanmar

Summary A total of 884 registered cases from the city of Yangon were retrospectively analysed. The defaulter proportion among cases registered for treatment at the Thaketa Health Centre was 34·16%. It was established that patient sex and occupation are not a factor in defaulting. Paucibacillary cases and cases with no disability are more likely to default.

Introduction

Leprosy in Myanmar is one of the major health problems in both the rural and urban communities. The City of Yangon is made up of 27 townships and has a registered leprosy prevalence of 4·61 per 1000 population.[1] A total of 12,107 cases were treated in 1986 by special leprosy clinics opened at the various health centres in the City of Yangon. The major problem encountered in most of these clinics is the high defaulter rate. Since the urban leprosy control programme is based on delivery of treatment services through stationary clinics where patients come in for treatment on their own, the defaulter rates are presumed to be high. This is especially a problem in Yangon City where the majority of the health workers' time is spent on opening clinics at the various health centres with very little time left for tracing defaulters. In the rural leprosy control programme, patients are being treated on a domiciliary basis where drugs are being distributed at each patient's house. Because the drugs are delivered to the patient's door-step in rural areas, the problem is not defaulting but whether the drugs are used.

Thaketa Township has a population of 206,000 and is one of the most densely populated townships in Yangon. It had a total of 884 registered leprosy cases in 1986. A leprosy clinic is open, manned by a leprosy inspector (paramedical health worker) at the township health centre. During 1986, paucibacillary cases were given dapsone monotherapy and multibacillary cases were given a monthly single dose of rifampicin 1200 mg for 6 months along with the daily dapsone therapy.

The study was undertaken to discover the defaulter proportion and factors causing defaulters among leprosy patients attending the leprosy clinic at Thaketa Health Centre

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during 1986. This would serve as baseline data for any future comparison with MDT defaulters.

Methods

The treatment charts of 884 registered leprosy cases at the Thaketa Health Centre for 1986 were analysed retrospectively. There were 581 patients taking regular treatment and 303 cases were found to be defaulters. Out of these 303 defaulters 147 cases could not be traced at the address given at the time of treatment. From the treatment records information on age, sex, occupation, classification and the deformity state of the patient was collected.

A defaulter was defined as a leprosy case who did not collect the recommended drugs for 12 consecutive months. The remaining cases were then just categorized as cases under treatment. Out of these cases under treatment, cases getting dapsone on a monthly basis, 9 months in a year (calender year) are then defined as leprosy cases obtaining regular treatment.

Cases classified as tuberculoid and indeterminate at initial registration were grouped as paucibacillary cases and the lepromatous and borderline cases were classified as multibacillary.

Findings

Table 1 shows that the defaulter proportion is seen to be the highest in the 15- to 29-year age group, amounting to 39·27%, and the lowest is seen in the 0- to 14-year age group, amounting to 21·43%.

The overall defaulter proportion among cases registered for treatment at the Thaketa Health Centre is 34·16% (95% CI 31·03–37·29%).

As seen in Table 2, the defaulter proportion among males and females is similar (risk ratio 1·05, 95% CI of RR 0·95–1·16).

Table 3 shows that paucibacillary cases default more than the multibacillary cases (RR 1.62, 95% CI 1·47–1·78).

Table 4 shows that the risk of defaulting among the different occupational categories is the same.

The risk of defaulting is the highest among cases without disability (RR 1·52, 95% CI of RR 1·38-1·68), and the lowest is among those leprosy cases wth Grade II disability (Table 5).

Discussion

In 1986 out of a total of 884 registered leprosy cases at the Thaketa Health Centre 34·16% (95% CI 31·03%–37·29%) of them were defaulters. This was similar to that of Hertroij's[2] study where 32·4% were defaulters. In Koticha's[3] study, which was conducted in Bombay, the defaulter percentage was 71%. The highest defaulter proportion was in the

Table 1. Age distribution of patients taking treatment regularly and that of the defaulters

Age (yr)	Regular treatment	Defaulter cases	Total	Defaulter proportion	Risk ratio	95% CI of RR
0–14	22	6	28	0·02143	1·0	
15–29	183	119	302	0·3927	1·83	1·48–2·27
30–44	170	80	250	0·32	1·49	1·21–1·84
45–59	143	64	207	0·3092	1·44	1·16–1·78
60	63	34	97	0·3505	1·64	1·29–2·09
Total	581	303	884	0·3416		0·3103–0·3729

Table 2. Sex distribution of patients taking regular treatment and that of the defaulters

Sex	Regular treatment	Defaulter cases	Total	Defaulter proportion	Risk ratio	95% CI of RR
Male	372	189	561	0·3368	1·0	
Female	209	114	323	0·3529	1·05	0·95–1·16

Table 3. Defaulter proportion among paucibacillary and multibacillary cases

Type leprosy	Regular treatment	Defaulter cases	Total	Defaulter proportion	Risk ratio	95% CI of RR
Paucibacillary	323	218	541	0·403	1·62	1·47–1·78
Multibacillary	258	85	343	0·2478	1·0	

Table 4. Occupation of patients taking regular treatment and that of the defaulters

Occupational status	Regular treatment	Defaulter cases	Total	Defaulter proportion	Risk ratio	95% CI of RR
Unemployed	42	19	61	0·3115	1·0	
Students	119	64	183	0·3497	1·12	0·92–1·24
Government workers	99	52	151	0·3444	1·11	0·90–1·36
Private sector workers	159	78	237	0·3291	1·06	0·88–1·28
Housewife	154	82	236	0·3475	1·12	0·92–1·36
Others (monks and pensioners)	8	8	16	0·5	1·61	0·95–2·70

Table 5. Disability occurring among patients taking regular treatment and that of defaulters

Disability grading (grades)	Regular treatment	Defaulter cases	Total	Defaulter proportion	Risk ratio	95% CI of RR
O	376	228	604	0·3775	1·52	1·38–1·68
I	51	24	75	0·3210	1·29	1·08–1·54
II	154	51	205	0·2488	1·0	

15- to 29-year age group (39·27%), which is also the peak age of onset of leprosy in Myanmar.

As also demonstrated in Hertroij's[2] and Koticha's[3] studies, sex does not seems to be a factor in defaulting. The risk of defaulting is seen to be much higher among paucibacillary cases (RR 1·62, 95% CI 1·47–1·78). Because of their infiltrated lesions multibacillary cases may be more conscious of their appearances and this might motivate them to take treatment more regularly. As for the paucibacillary cases, because the disease apparently looks so benign, they may even doubt the diagnosis and therefore may be less willing to take treatment regularly. In Hertroij's[2] study it was also observed that tuberculoid cases defaulted more, but in Koticha's[3] study BB and BL cases were found to be more regular than LL or BT cases. In Koticha and Nair's[4] study smear-positive cases, particularly borderline types, were seen to be more regular.

The occupation of patients is not a factor for defaulting, but it is surprising to note that out of 151 cases who were government employees, 34·44% of them were defaulters, and out of 183 students registered for treatment 34·97% of them were defaulters'. These 2 categories of people should be highly motivated to obtain treatment, and finding a similar proportion of defaulters among them as compared to other occupations denotes that proper health education to each individual patient is much in need.

Table 5 shows that the risk of defaulting is seen to be the highest among leprosy cases with no disabilities (RR 1·52, 95% CI 1·38–1·68). Patients with grade II disability are seen to be less likely to be defaulters. Cases without deformity may be less motivated to obtain treatment, whereas for those leprosy patients with disabilities, they may be coming for treatment as a result of these disabilities. This was also found in both Hertroij's[2] and Koticha's[3] studies, where deformed cases are more regular in their treatment. This finding refutes the previous thinking that deformed cases, due to their difficulty in travelling, are more prone to default.

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Facteurs du risque d'abandon du traitement au centre urbain de contröle de la lèpre de la commune de Thaketa, dans la cité de Yanton, Myanmar, 1986

T Myint, M T Htoon, M Win et C Yin

Résumé Nous avons analysé rétrospectivement un total de 884 cas recensés provenant de la ville de Yangon. La proportion des abandons parmi les cas inscrits pour un traitement au Centre sanitaire Thaketa était de 34,16%. Nous avons établi que le sexe et l'occupation des patients ne sont pas un des facteurs de l'abandon. Les cas paucibacillaires et les cas sans invalidité sont plus susceptibles d'abandonner le traitement.

Los Factores de Riesgo en los Incomparecentes en el Centro Urbano de Control de la Lepra en el término municipal de Thaketa, en la ciudad de Yangon, Myanmar, 1986

T Myint, M T Htoon, M Win y C Yin

Resumen Se analizaron retrospectivamente un total de 884 casos registrados de la ciudad de Yangon. La proporción de incomparecentes entre los casos registrados para tratamiento en el Thaketa Health Centre fue 34,16%. Se estableció que ni el sexo ni el oficio erán causas de incomparecencia. Los casos con mayor probabilidad de incomparecencia eran los paucibacilares y los sin incapacidad.

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Initial intensive therapy for multibacillary leprosy patients—in retrospect

P S RAO,* B N REDDY,† P KRISHNAMURTHY,* B RAJA RAO,‡ M V SASTRULU§ & A DUTTA*

**Central Leprosy Teaching and Research Institute, Chengalpattu 603 001, Tamil Nadu, India, †Regional Leprosy Training and Research Institute, Raipur, Madhya Pradesh, India, ‡Nalgonda, Andhra Pradesh, India and §Srikakulam, Andhra Pradesh, India*

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Summary We analysed the results of 4845 multibacillary (MB) patients being treated with multidrug treatment (MDT) in the Srikakulam District of Andhra Pradesh, India. Of these, 2309 (47·7%) patients were given an initial 14-day intensive therapy with rifampicin, clofazimine and dapsone, followed by the WHO recommended pulse therapy. The rest of the cases were given only pulse therapy. The improvement in terms of bacteriological clearance and the proportion of cases declared released from treatment (RFT) was found to be significantly higher among patients treated with only pulse therapy. Clinic attendance was found to be better and more regular in patients treated with intensive therapy, and no relapses were seen with either therapy. The implications of these findings on the operational aspects of programme implementation are discussed.

Introduction

The WHO study group on chemotherapy for leprosy control programmes recommended multidrug, pulse regimens with rifampicin, clofazimine and dapsone for multibacillary patients and rifampicin and dapsone for paucibacillary patients.[1] A number of countries where leprosy is endemic incorporated the treatment regimens into their control programmes either exactly as recommended by the WHO or with various modifications. The National Leprosy Eradication Programme in India adopted the WHO recommended regimens but modified the MB regimen by the addition of a 14-day initial, intensive therapy of rifampicin (600 mg), clofazimine (100 mg) and dapsone (100 mg) daily.[2] The modified regimen was advocated only for MB patients who were eligible for MDT on medical screening at the start of the MDT project in an area. Multibacillary patients detected after the start of the MDT project were given direct pulse therapy for operational convenience. Srikakulam District in Andhra Pradesh is one of the districts where the

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MDT project has been implemented since 1983. The purpose of the present analysis is to identify any advantages/disadvantages of the modified regimen compared with the direct pulse therapy.

Materials and methods

Srikakulam District in Andhra Pradesh was selected for the study because MDT has been used there since 1983 and the maintenance of medical records is good. The study population was 4485 MB patients who started MDT between 1983 and 1988. Of these, 2309 (47·7%) patients were given an initial, 14-day supervised, intensive therapy, followed by pulse therapy (IIT Group) and the remaining 2536 (52·3%) were treated with direct pulse therapy (DPT Group).

Bacteriologically negative cases were outnumbered at intake, in the DPT group (Figure 1) because certain borderline–tuberculoid (BT) cases, depending on the number of skin and nerve lesions (which changed over time) were given MB MDT, following the National Programme Guidelines. Also a large chunk of MB cases who were on dapsone monotherapy, and became bacteriologically negative in the last 2 years, were required to be given a minimum dose of 24 pulses, as in the programme guidelines, have become DPT group *de facto*.

As the treatment regimens under study include antibiotics, the bacteriological index (though crude) is considered to be the most important prognostic factor. It also has the advantage of being hard data. The reduction/deterioration in BI and the proportion of cases released from treatment (RFT) were taken as the criteria of response and regularity in treatment and relapses were considered as subsidiary criteria for this study.

The IIT Group was followed-up for 5 years and the DPT Group for 4 years. Hence the analysis is restricted to the initial 4 years only for both groups. Bacteriological positivity was recorded using Dharmendra's method. Patients put on either of the regimens were declared as RFT when they became clinically inactive and bacteriologically negative or had received 24 pulses in 36 months, whichever was later.

Results

INITIAL BACTERIOLOGICAL PROFILE

Figure 1 shows the bacteriological profile of the patients in the IIT and DPT groups at the commencement of MDT. The 2 groups are significantly different and if analysed for the groups as a whole the differences may mask the beneficial effects of IIT. To avoid this and to make comparison possible, the analysis was done for each group separately.

RFT RATE

The multiple bar diagram (Figure 2) shows that a significantly higher proportion of cases were RFT from the DPT group when compared with the IIT group. This difference is consistently seen after the 24th, 36th and 48th pulses. However, the high percentage of bacteriologically-negative patients at intake in the DPT group might have resulted in a better RFT rate at the 24th pulse.

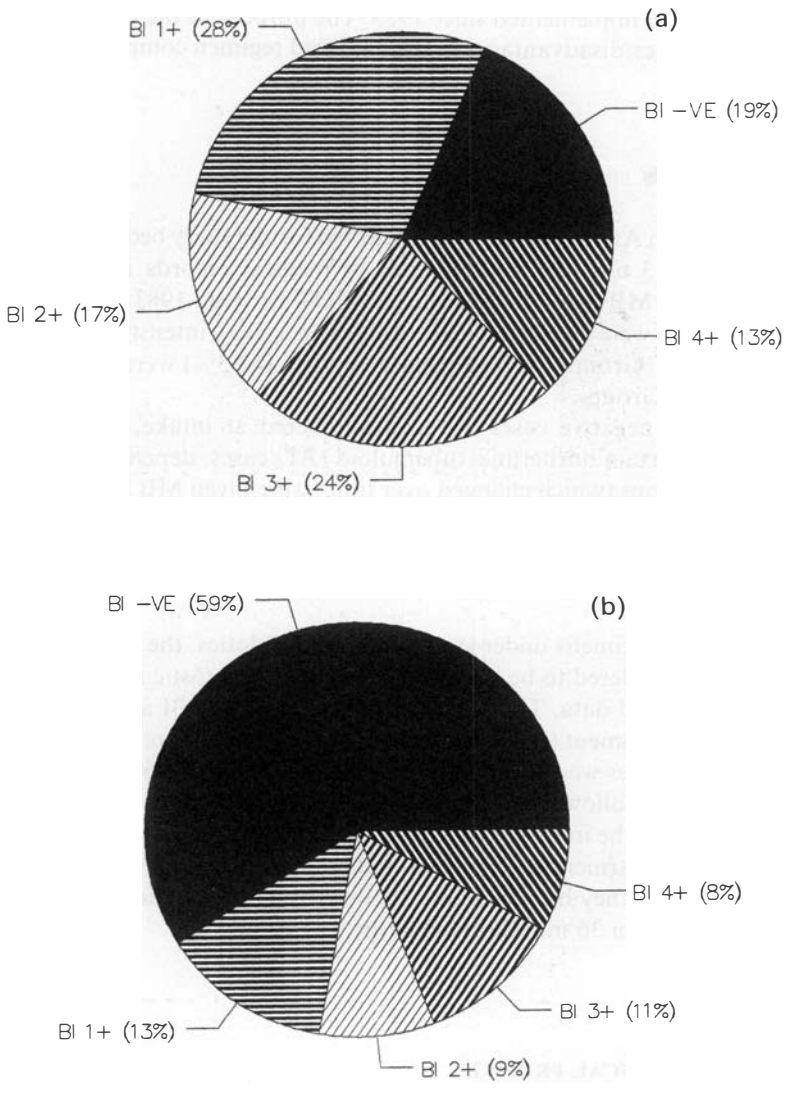

Figure 1. Bacteriological profile at intake: (a) IIT (2125); and (b) DPT (2347).

BACTERIOLOGICAL POSITIVITY

Tables 1, 2 and 3 show the bacteriological positivity in patients to be positive at the start of treatment and at the 24th, 36th and 48th pulses. The percentage of cases remaining bacteriologically positive was found to be directly proportional to the initial BI and was inversely proportional to the duration of the treatment. In this respect, in both the IIT and DPT groups, the response is comparable, but the actual figures were consistently and significantly lower for the patients belonging to DPT group.

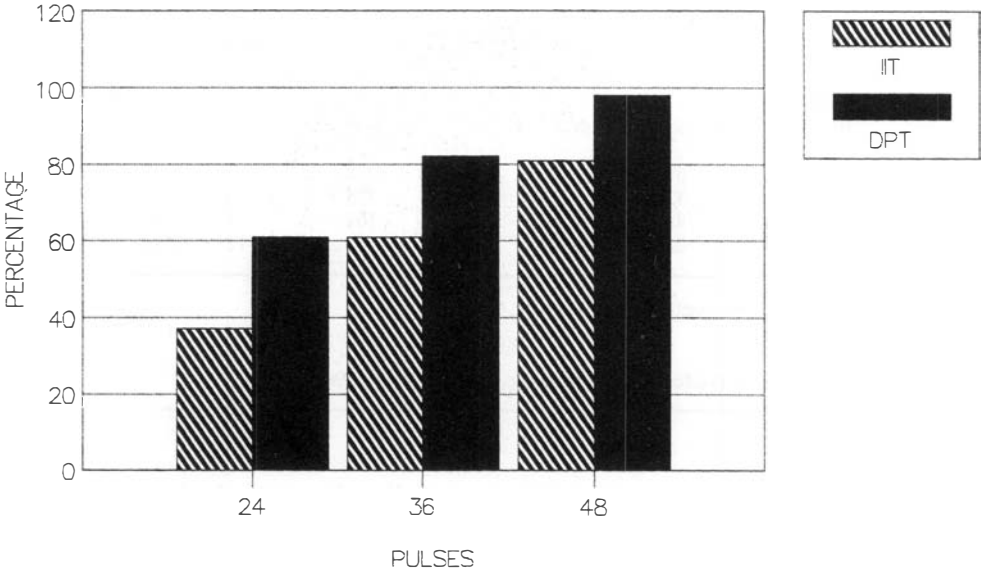

Figure 2. Proportion of cases released from treatment.

Table 1. Bacteriological positivity after the 24th pulse

Initial BI	IIT			DPT		
	No. examined	No. +ve	%	No. examined	No. +ve	%
>0–≤1+	579	197	34·0	305	52	17·0
>1–≤2+	345	225	65·2	197	102	51·8
>2–≤3+	494	432	87·4	240	186	77·5
>3–≤4+	263	251	95·4	166	150	90·3

($P < 0{\cdot}05$.)

Table 2. Bacteriological positivity after the 36th pulse

Initial BI	IIT			DPT		
	No. examined	No. +ve	%	No. examined	No. +ve	%
>0–≤1+	577	67	11·6	262	11	4·2
>1–≤2+	338	83	24·6	149	28	18·8
>2–≤3+	488	287	58·8	160	65	40·6
>3–≤4+	241	179	74·3	104	65	62·5

($P < 0{\cdot}05$ for all groups except for 2+.)

Table 3. Bacteriological positivity after the 48th pulse

Initial BI	IIT			DPT		
	No. examined	No. +ve	%	No. examined	No. +ve	%
>0–≤1+	571	16	2·8	238	1	0·4
>1–≤2+	338	27	8·0	125	0	0·0
>2–≤3+	458	105	22·9	101	4	4·0
>3–≤4+	223	96	43·0	52	12	23·0

($P < 0{\cdot}05$ excepting 2+ Group.)

Table 4. Bacteriological progress after the 24th pulse

	IIT			DPT		
	No.	No. examined	%	No.	No. examined	%
Improved*	1278	1681	76·0	764	908	84·1
Static	745	2080	35·0	1499	2293	65·3
Worsened†	57	1817	3·1	30	2127	1·4

* Initial BI negative cases are excluded from both the groups as improvement beyond negativity cannot be measured.

† Initial BI 4 plus cases are excluded from both the groups as BI worsening beyond 4 plus cannot be measured under Dharmendra's method ($P < 0{\cdot}001$).

Table 5. Bacteriological worsening under two regimens

Pulse	No. showing worsening	No. examined	%
24th			
IIT	57	1817	3·1
DPT	30	2127	1·4
36th			
IIT	9	1801	0·49
DPT	5	1831	0·27
48th			
IIT	2	1766	0·11
DPT	0	1698	0·00

Differences are statistically significant at the 24th Pulse only ($P < 0{\cdot}001$).

BACTERIOLOGICAL PROGRESS

Bacteriological progress made by these 2 groups as assessed at the end of 24th pulse are given in Table 4. Overall progress made was significantly better for DPT group. Similar

analysis at the 36th and 48th pulse could not be undertaken due to logistic problems and the non-availability of data. However, bacteriological deterioration alone was studied at the 36th and 48th pulses and the results (Table 5) show that deterioration is comparable in both groups.

CLINIC ATTENDANCE

At the end of the 36th month, only 1·2% of the cases had not completed the required 24 pulses in the IIT group and 16·5% had not completed in the DPT group.

RELAPSES

No relapses were reported in either group during the periods they were under surveillance following RFT.

Discussion

From the analytical results, it appears that the only advantage of the initial 14-day supervised therapy when compared with direct pulse therapy is the regularity of treatment compliance. Even this might be due to the fact that the majority of IIT group patients were under dapsone monotherapy and the change of therapy to better drugs and the initial enthusiasm of the MDT project implementation might have motivated them to be regular attenders. On the other hand, the DPT group showed better results in terms of BI reduction at the 24th pulse, the proportion of RFT, BI deterioration and comparable results with regard to relapses. The better response of the group without intensive therapy has been reported by others.[3,4] It is also reported that a regimen consisting of daily, initial administration of rifampicin for 21 days did not show distinct advantages over the WHO regimen.[5]

Rifampicin kills *Mycobacterium leprae* with exceptional speed—99% a few days after a single dose of 600 mg or 1500 mg.[6] It has been shown that daily administration of 600 mg of rifampicin is no more effective than monthly administration of 600 mg on each of 2 consecutive days.[7] Studies proved that with both 600 mg daily rifampicin and 600 mg as a single dose, the proportion of infective organisms fell to undetectable levels within 1 or 2 weeks after initiating treatment.[8,9] There is no experimental evidence in support of the 14-day initial intensive therapy. Perhaps it is based on the theroretical assumption that the generation time of *M. leprae* is about 14 days, and therefore coverage of the entire generation time by a powerful bactericidal drug, namely rifampicin, will kill most of the organisms, thereby causing source reduction and a decline in the spread of infection. This needs to be substantiated by controlled studies.

However, the implementation of 14-day initial supervised therapy is operationally cumbersome and financially burdensome—costing about Rs. 100,000 for an average leprosy control unit with a prevalence rate of 10 per 1000, including the cost of drugs, petrol, oil and lubricants, travelling allowance/daily allowance for staff, etc. It is also time consuming since it would take 8 months to 1 year to complete the intensive therapy in a given leprosy control unit and ethically questionable because it exposes the patients to the added risk of the toxic side-effects of rifampicin. It is often argued that by visiting the

villages daily for 14 days, the medical teams will help to build the confidence of the patients and have a positive impact on new case detection, community education and participation. This may be true to some extent. Again, these arguments need to be confirmed by further studies. Even if the above arguments were true, the same result could probably be achieved by a 14-day, intensive, health education campaign in the treatment circuits. This would save the patients from exposure to the possible toxic side-effects of an additional 13 pulses of rifampicin and also reduce the exhorbitant cost of the drugs.

Recommendations

Since many districts have completed their intensive phase of NLEP in the country, it is suggested that:

(i) data be collected and analysed so that a reasonable conclusion on the value of 14-day initial intensive therapy can be reached; so, also, data from control programmes may be collected and analysed in other countries, where initial intensive therapy is in vogue; and
(ii) since the WHO recommended MDT regimens are being implemented unmodified in some other countries, the experiences of those countries might help us in reviewing the necessity for initial, intensive therapy for MB cases.

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Lepr Rev (1992) **63,** 350–357

Thérapeutique d'attaque intensive chez les patients lépreux multibacillaires—étude rétrospective

P S Rào, B N Reddy, P Krishnamurthy, B Raja Rau, M S Sastrulu et A Dutta

Résumé Nous avons analysé les résultats obtenus chez 4845 patients multibacillaires (MB) en cours de traitement multidrogue (MDT) dans un district Srikakulam de Andhra Pradesh, Inde. Parmi ceux-ci, 2309 (47,7%) ont reçu une thérapeutique d'attaque intensive de 14 jours de rifampicine, clofazimine et dapsone, suivie de la thérapeutique intermittente recommandée par WHO. Les autres cas ont reçu seulement la thérapeutique intermittente. L'amélioration, exprimée par la clearance bactérienne et la proportion des cas déclarés comme libérés de traitement (RFT), s'est révélée significativement plus élévée chez les patients traités seulement par la thérapeutique intermittentee. Les patients traités par la thérapeutique d'attaque étaient plus assidus et réguliers dans leurs visites à la clinique, et aucune rechute n'a été observée avec les deux thérapeutiques. Les implications de ces observations sur les aspects opérationnels du programme sont discutées.

Terapia intensa inicial para los pacientes leprosos multibacilares—en retrospectiva

P S Rao, B N Reddy, P Krishnamurthy, B Raja Rau, M S Sastrulu y A Dutta

Resumen Análizamos los resultados de 4.845 pacientes multibacilares (MB) que recibían tratamiento multidroga (TMD), en el Distrito de Srikakulam de Andra Pradesh, India. 2309 (47,7%) pacientes recibieron una terapia inicial intensa con rifampicina, cloazimina y dapsona, seguidos por la terapia por pulsación recomendada por la OMS. Los demás casos solamente recibieron solamente la terapia por pulsación. La mejora expresada como aclaramiento bacteriológico y la proporción de casos declarados librados de tratamiento era significativamente más alta en los pacientes tratados solamente con la terapia por pulsación. Asistencia a las clínicas era mejor y más regular en el caso de los pacientes tratados por terapia intensa, y no se observaron relapsos con cualquier terapia. Se discuten las implicaciones de estos resultados sobre los aspectos operativos del programa.

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Immunotherapeutic potential of ICRC vaccine: a case control study

W S BHATKI & R G CHULAWALA
Acworth Leprosy Hospital, Wadala, Bombay 400 031, India

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Summary A bacteriological follow-up of 16 lepromatous patients with a high initial Bacteriological Index (BI) showed that in 8 randomly selected patients who received single doses of ICRC Vaccine (C44) at the onset of multidrug therapy, the average reduction of BI was from 4·4+ to 1+ in 2 years—3 of these patients became negative and 3 showed BI 1+ or less. Comparable bacteriological assessments in 8 non-vaccinated but otherwise similar patients showed an average reduction of BI from 4·7+ to 2·6+, i.e. consistent with the expected response to MDT in lepromatous patients. Here we discuss the role of immunotherapy and the selection of a desirable antileprosy vaccine in the context of fixed-duration MDT.

Introduction

Rapid bacterial clearance from skin smears and histopathology sections have been reported in patients given ICRC Vaccine.[1,2] However, these observations were made on patients who had not been standardized by classification, drug regimen and duration of past treatment and illness.

Multidrug therapy (MDT) based on rifampicin, clofazimine and dapsone (DDS), used at present for the treatment of multibacillary (MB) leprosy, kills viable *Mycobacterium leprae* rapidly. However, the fall in the Bacteriological Index (BI) in lepromatous patients on these drugs is at the rate of 0·6 to 1 Index per year, the same as patients who are on DDS monotherapy.[3] Due to persistent bacterial positivity, MDT is often continued by clinicians for more than 2 years. It would therefore be advantageous to have a therapy which would not only kill the bacilli but also rapidly clear their debris.

In the present study, the ICRC Vaccine was used to see if it could supplement conventional MDT to achieve early bacillary clearance.

Methods and materials

The present study included 16 lepromatous patients (13 males and 3 females) admitted to the Acworth Leprosy Hospital, Bombay.

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Table 1. Average pretreatment BI of both groups and after 1 and 2 years' treatment

	No. of patients	Average BI		
		Pretreatment	1 year treatment	2 year treatment
Group I (Vaccinated patients)	8	4·4+ (SD = 0·69)	2·8+	1+ (SD = 1·29)
Group II (Control patients)	8	4·7+ (SD = 0·46)	3+	2·6+ (SD = 0·84)

Pretreatment BI—Group I *vs* Group II: $t = 1{\cdot}18$, $p > 0{\cdot}05$ (not significant).
2 year treatment BI—Group I *vs* Group II: $t = 2{\cdot}58$, $p < 0{\cdot}05$ (significant).

All these patients had active, disseminated, infiltrating lesions with occasional nodules. The skin smears, collected by slit and scrape method, from at least 2 sites, including 1 earlobe, showed a BI of 4+ to 6+ (Ridley's scale). From the patients without obvious thick infiltration and nodules, additional smears were collected from 1–2 additional sites, including the other earlobe. The classification was further confirmed by skin biopsies which showed histology to be consistant with LL leprosy. All the patients were late lepromin reaction negative.

A total of 10 out of the 16 patients had no past history of any treatment, while 6 patients had received dapsone monotherapy with gross irregularity for periods of 3 months to 1 year in the preceding 3 years.

The patients were randomly divided into 2 groups of 8 patients each. Their initial BI was as follows:

Group I —1 patient = 6+, 4 patients = 5+, 3 patients = 4+
(18 smears, Average BI = 4·4+, SD = 0·69)
Group II—1 patient = 6+, 5 patients = 5+, 2 patients = 4+
(19 smears, Average BI = 4·7+, SD = 0·46)

All the patients were kept on daily supervised MDT along with other in-patients of the hospital, i.e. rifampicin 600 mg once a month, clofazimine 50 mg daily and dapsone 100 mg daily. All the patients were hospitalized throughout the 2 years and except for the few earlier patients the clofazimine 300 mg booster dose wsa given every month.

At the onset of therapy, the patients belonging to group I were given ICRC Vaccine (C44 strain, 1×10^8 bacilli/0·2 ml) as intradermal injection, 0·1 mg on each deltoid region. The ICRC Vaccine was obtained from the Cancer Research Institute, Parel, Bombay. The patients belonging to group II were given saline in a similar manner.

All the patients were clinically and bacteriologically monitored every 6 months. Skin smears were collected from most active lesions and from one of the earlobes and the slides were sent to the laboratory together with the slides from other in-patients on MDT.

The bacteriological results were analysed after completion of 2 years of therapy.

Results

The initial average BI of the patients (i.e. Group I (18 smears) = 4·4+ and Group II (19

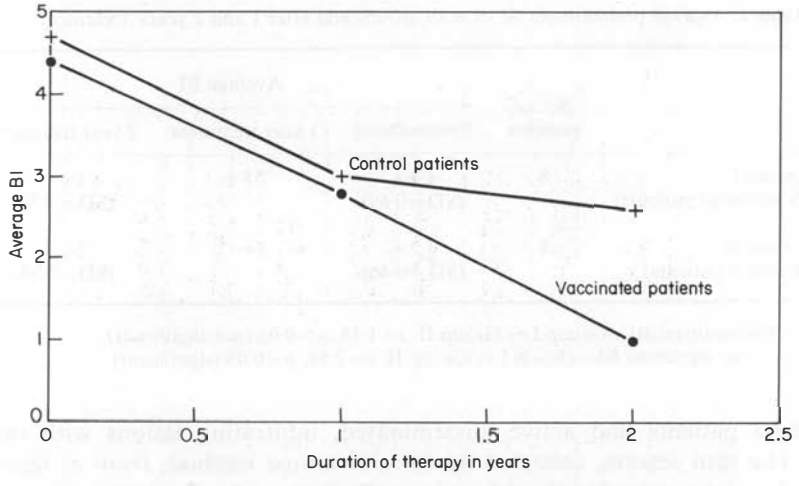

Figure 1. Average BI of vaccinated and control patients.

smears) = 4·7+) indicated that the 2 groups had comparable bacteriological status ($t = 1{\cdot}18$, $P > 0{\cdot}05$, Table 1).

Bacteriological responses observed in the patients showed that at the end of the 1st year, there was no significant difference in the average BI of the 2 groups (Figure 1). However, at the end of the 2nd year, the average BI in Group I (1+) was found to be significantly lower than that seen in Group II (2·6+), i.e. $t = 2{\cdot}58$, $P < 0{\cdot}05$ (Table 1).

For analysing the bacteriology of individual patients at the pretreatment stage and at the end of 1 and 2 years' treatment, the maximum BI reported in each patient was considered (Figure 2 and Tables 2 and 3). Analysis of patients' BI showed (Table 2) that in Group I, 3 out of 8 patients had become smear negative and 3 had a BI of 1+ at the end of 2 years' therapy. The corresponding BI in Group II showed that 5 out of 8 patients had a BI of 3+ or more. It is clearly seen that significantly higher numbers of ICRC vaccinated patients (i.e. 6 out of 8 patients from Group I) showed a BI of 1+ or less than control patients (i.e. none out of 8 from Group II).

Bacteriological response of individual patients in relation to their initial BI (Figure 2, Table 3) showed that the 3 patients from Group I who became smear negative in 2 years had an initial BI of 4+. In comparison 2 patients with an initial BI 4+ from Group II, however, showed BI 2+ and 3+ at the end of 2 years' therapy. The patients with an initial BI 6+ showed falls to 1+ and 3+ in Groups I and II, respectively. The patients with initial BI 5+ showed that in Group I 3 out of 4 patients showed a BI 2+ or less while in Group II, 3 out of 5 patients had BI 3+ or more after 2 years' therapy. This shows that the fall in the BI was related to the initial BI and it was comparatively faster in the ICRC vaccinated patients on MDT.

Discussion

Antileprosy drugs presently used for multibacillary patients kill *M. leprae* and render them nonviable in 1–3 months[3] but their ultimate clearance from the body depends upon

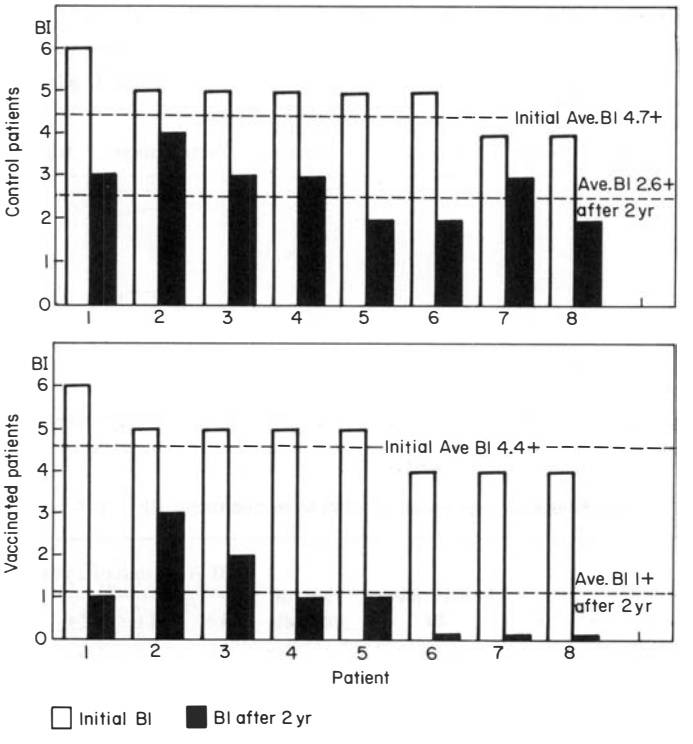

Figure 2. BI—initial and after 2 years of individual vaccinated and control patients.

the status of immunity. Thus skin smears bacteriology in the patients on MDT shows a lowering of the Morphological Index (MI) to 0% much earlier, while the BI continues to remain high for a much longer period.[4,5]

According to the Government of India Guidelines on MDT, the treatment should be continued for 2 years or till smear negativity.[6] Kiran Katoch *et al*,[7] reported that for BL/LL patients, it took 5 years of regular MDT to bring down the average BI from 4·45+ to 0·03+ with 86% patients showing smear negativity. It is also reported that in the initially highly bacillated BL–LL patients, viable bacilli are present in 9–16% tissue biopsies even after 2 years of MDT.[8] On the other hand, in multibacillary patients, the relapse rate after 2 years of MDT is very low in spite of persisting BI[3]. We (in unpublished observations) and other experienced leprologists (personal communication) have observed that the BI continues to fall progressively even in the absence of any therapy beyond 2 years, thus supporting fixed-duration therapy. In the midst of these confusing reports, the clinicians in the routine MDT programme will never have enough confidence to stop MDT after 2 years in patients with BI 3+ or 4+. The morale and the enthusiasm of the control team would increase if their therapy was able to clear substantially bacilli from the skin smears in about 2 years.

Earlier reports on various antileprosy vaccine candidates suggested that the ICRC, MW and BCG with *M. leprae* have immunotherapeutic values because besides inducing lepromin conversion, they were able to bring about faster bacterial clearance and induce

Table 2. Distribution of patients according to BI

BI	Group I (Vaccinated patients)			Group II (Control patients)		
	Pretreatment	1 year treatment	2 years treatment	Pretreatment	1 year treatment	2 years treatment
6+	1			1		
5+	4			5	1	
4+	3	2		2	2	1
3+		2	1		3	4
2+		3	1		2	3
1+			3			
0		1	3			
No. of patients	8	8	8	8	8	8

Table 3. Bacteriological response in relation to pretreatment BI

	Pretreatment BI	No. of patients	BI at the end of 2 year treatment				
			4+	3+	2+	1+	0
Group I (Vaccinated patients)	6+	1				1	
	5+	4		1	1	2	
	4+	3					3
Group II (Control patients)	6+	1		1			
	5+	5	1	2	2		
	4+	2		1	1		

reversal reactions in BL–LL patients.[1,2,9–11] Though these studies require wider multicentric trials with proper case control as regards past treatment, duration of illness, classification, initial BI etc, all the reported evidence since 1980 suggests that antileprosy vaccines do have a place in the therapy of leprosy.

The present case-control study, though based on a small sample of 16 lepromatous patients, certainly shows that ICRC vaccine given as a single dose is synergistic with the conventional MDT, and 6 out of 8 ICRC vaccinated patients showed a lowering of BI from 4–6+ to 1+ or less (3 patients were smear negative) within 2 years of therapy as against none out of 8 comparable lepromatous patients on MDT only (Table 2).

The bacteriological followup showed a significant difference in the average BI of vaccinated and non-vaccinated patients in the 2nd year of therapy but not in the 1st year (Table 1, Figure 1). This is quite consistent with our past experience with ICRC vaccine. Earlier trials showed lepromin conversion in a considerable number of patients as late as 8–12 months after vaccination.[1,2] Furthermore 3 out of the 5 ICRC vaccine-induced reversal reactions developed 12–15 months after vaccination.[9] It was also observed in our earlier studies that lepromin conversions were more frequent among the lepromatous patients who had been treated for a long time and who had a low bacillary load, i.e. BI less than 3+.

In view of this, it is possible to postulate that the immunotherapeutic action of ICRC vaccine on bacterial clearance is exhibited only after the BI is reduced to around 3+ (which usually occurs by the second year of MDT). This also suggested that the vaccine will have to be used in combination with MDT and not as a replacement for MDT.

Thus it may be concluded that an antileprosy vaccine, if used with MDT, might significantly reduce the period of treatment, thus reducing the consumption of antileprosy drugs (which are often in short supply) and lowering the leprosy morbidity substantially. However, such a vaccine has to be safe, acceptable and easy to administer under field conditions. The vaccine that has prolonged activity following a single dose is preferable to those that have to be given frequently and in multiple doses.

Acknowledgment

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Lepr Rev (1992) **63,** 358–364

Potentiel immunothérapeutique du vaccin ICRC: une étude de cas avec témoin

W S Bhatki et R G Chulawala

Résumé Un suivi bactériologique de 16 lépreux avec un index bactériologique (BI) initial élévé a démontré que chez 8 patients choisis au hazard, ayant reçu une dose unique de vaccin ICRC (C44) au début d'une thérapeutique multidrogue, la réduction moyenne de BI était de 4,4+ à 1+ en 2 ans; 3 de ces patients sont devenus négatifs et 3 ont présenté un BI de 1+ ou inférieur. Des évaluations bactériologiques comparables chez 8 patients non vaccinés, mais par ailleurs similaires, ont révélé une réduction moyenne du BI de 4,7+ à 2,6+, c'est-à-dire conforme à la réponse attendue à la thérapeutique multidrogue chez des patients lépromateux. Nous discutons le rôle de l'immunothérapie et la sélection d'un vaccin antilépreux satisfaisant dans le contexte de la thérapeutique multidrogue de durée fixe.

El potencial immunoterapéutico de la vacuna ICRC: un estudio del control de casos

W S Bhatki y R G Chulawala

Resumen Un estudio bacteriológico posterior de 16 pacientes lepromatosos con un elevado Indice Bacteriológico (IB) inicial demostró que, en 8 pacientes seleccionados al azar y tratados con una sola dosis de Vacuna ICRC (C44) al comienzo de la terapia multidroga, el promedio de reducción de IB fue de 4,4+ a 1+, en 2 años. Evaluaciones bacteriológicos comparables de pacientes similares no vacunados mostró un promedio de reducción de IB, de 4,7+ a 2,6+ es decir, la respuesta que se anticiparía mediante terapia multidroga en los pacientes lepromatosos. Se discute el papel de la inmunoterapia y la selección de una vacuna antileprosa conveniente en un entorno de terapia multidroga de duración fija.

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Healing rates of plantar ulcers in leprosy and diabetes

J A BIRKE,* A NOVICK,* C A PATOUT* & W C COLEMAN†

**Gillis W Long Hansen's Disease Center, Carville, LA 70721; USA, and †Attending Staff Podiatrist, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121, USA*

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Summary Comparison was made of wound healing time in a consecutive series of leprosy and diabetic patients with plantar ulceration. In the leprosy group, 66 of 70 (94%) ulcers healed in a mean time of 42·7 (±36·1) days, and in the diabetic group, 75 of 80 (94%) ulcers healed in a mean time of 39·7 (±32·1) days. Analysis of all healed ulcers using a general linear model found wound depth ($p < 0{\cdot}03$), and wound diameter ($p < 0{\cdot}05$) significantly related to ulcer healing time. Diagnosis, healing devices (cast, splint and cut-out sandal), age and sex were not significant. In diabetic subjects a regression model including depth, diameter and age explained 36% of the variation in healing time. A meaningful regression model was not found in leprosy patients.

Introduction

Plantar ulceration is a major cause of disability in patients with leprosy and diabetes mellitus. Sensory loss secondary to peripheral neuropathy and mechanical stresses (pressure) are considered the primary causes of plantar ulceration.[1–5] In patients with diabetes, angiopathy may also be a factor contributing to tissue breakdown and delayed healing.

Motor neuropathy results in atrophy and deformities in the feet which causes in abnormal patterns and increased stresses on the foot.[1] Autonomic neuropathy results in dry inelastic skin due to loss of sweating mechanisms, and abnormal blood flow due to alterations in vasomotor control.[6]

Based on animal studies and observational data, repetitive stresses are believed to be the most common mechanism of injury in the neuropathic foot.[7,8] Repetitive stress also contributes to delayed healing in plantar ulcers because patients with sensory loss will walk on an unprotected, ulcerated foot.

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AETIOLOGY OF FOOT PROBLEMS IN LEPROSY AND DIABETES MELLITUS

While neuropathy is the major complication of leprosy, generalized disease can also effect the respiratory tract, eyes, liver, testes, muscles and bones. Invasion of the nerve by *Mycobacterium leprae* can result in injury secondary to inflammation and/or compression. The deformities and ulcerations of the feet and hands that so heavily stigmatize leprosy patients are secondary to neuropathy.[9]

Diabetes mellitus is a metabolic disorder of uncertain aetiology characterized by hyperglycaemia resulting from diminished secretion or ineffective action of insulin. Neuropathy or angiopathy are frequent complications which together may be contributing factors to the delayed wound healing in diabetic patients.[10] Altered nerve metabolism associated with hyperglycaemia and nerve ischaemia may lead to the distal, symmetrical, primarily sensory polyneuropathy most commonly seen in diabetes.[11]

Patients with diabetes have a higher incidence of both microangiopathy and macroangiopathy than nondiabetics. Microangiopathy is characterized by thickening of the capillary basement membrane resulting from hyperglycaemia. This pathology may alter the capillary diffusion of cell nutrients and lymphocytes which could prolong healing and promote infection.[12] Macroangiopathy results from accelerated atherosclerosis commonly involving the tibial and peroneal arteries, but uncommonly the small vessels of the feet.[13–14] Angiopathy is the primary cause of painful ischaemic lesions or gangrene generally affecting the nonweightbearing areas of the feet, but is an unlikely cause of the painless lesions associated with callous formation which develop over the plantar surface of the foot.[3,12,15,16]

ULCER TREATMENT

Several methods of treatment which reduce the mechanical stress on the foot have been recommended for the treatment of plantar ulcers.[12,17–23] These include bedrest, crutches, walking casts, walking splints, prefabricated walkers and splints, patellar tendon braces, foam pads, cut-out sandals and healing footwear. The effectiveness of methods such as bedrest, crutches, and easily removable appliances is highly dependent on patient compliance.

Brand found the total contact cast (TCC) to be the most effective method of treating plantar ulcers in leprosy and recommended their use in both leprosy and diabetes mellitus. The TCC promotes healing by reducing mechanical stress on the foot.[18] Walking casts

Table 1. Ulcer grades

Grade	Definition
0	Intact skin
1	Superficial ulcer
2	Deep ulcer (involvement of tendon, bone, ligament, or joint)
3	Deep abscess or osteomyelitis
4	Gangrene of toes or forefoot
5	Gangrene of whole foot

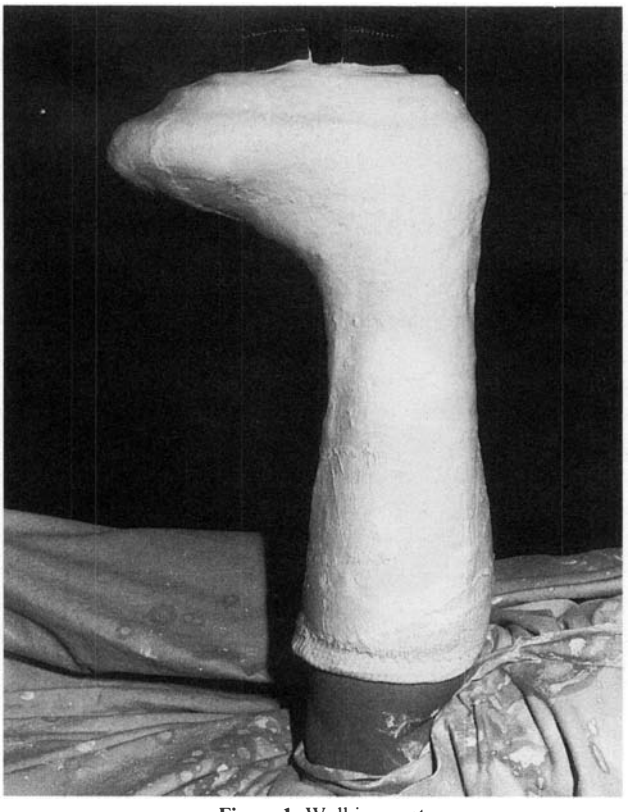

Figure 1. Walking cast.

have been shown to be effective in reducing pressure on the plantar surface of the foot during walking.[24–26] Novick *et al.*[27] found no meaningful differences in the reduction of plantar forces between walking casts and walking splints. Mooney & Wagner[28] proposed that the TCC promoted healing in the diabetic patients by reducing oedema and thereby improving the microcirculation.

The effectiveness of walking casts in the management of plantar ulcers in both leprosy and diabetic patients has been well reported.[29–36] The median and average healing time of these studies collectively is approximately 6 weeks. Several studies using control groups found a much higher percentage of the healed ulcers, as well as significantly decreased healing time of plantar ulcers using casting.[31,33,35] There is limited data on the effectiveness of other wound healing devices in leprosy and diabetic patients.

This study compares the healing rates of leprosy and diabetic patients utilizing several devices designed to reduce plantar stresses.

Method

Subjects included all patients with leprosy and diabetes treated for plantar ulcerations by the Foot Program of the Gillis W Long Hansen's Disease Center during a 2-year period.

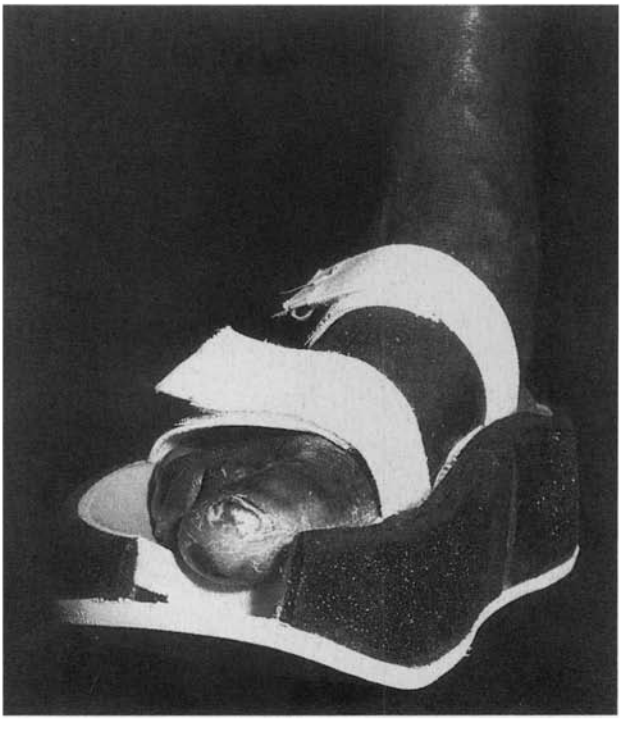

Figure 2. Cut-out sandal.

Patients with a history of both leprosy and diabetes mellitus were not included in the study.

Initial recordings were made on a tracking form including patient's age, sex, duration of ulcer, wound diameter and depth. Diameter was determined by tape measurement of maximum wound length. Depth was determined by measuring the depth with a sterile probe. Wound probing was also used to classify the wound into an ulcer grade as described by Wagner (Table 1).[37]

TREATMENT

Wounds were debrided of necrotic tissue unless such removal would result in further injury to underlying viable structures. Callous and overlying wound edges were cut back to expose the basal cell layer of the epidermis in order to promote epithelialization. Wound care following debridement included cleansing with hydrogen peroxide and flushing with saline. Povadine iodine solution was often used to clean intact skin areas but was not used topically on wounds. Antibiotic therapy was only used in the treatment of acute infection.

Wounds were protected from walking stresses using 1 of 3 devices (treatments 1–3): walking casts, cut-out sandals or walking splints (Figures 1–3). The fabrication technique for each device has been previously described by Birke *et al*.[38] Patients who were treated with more than one treatment device, or required surgical treatment were included in

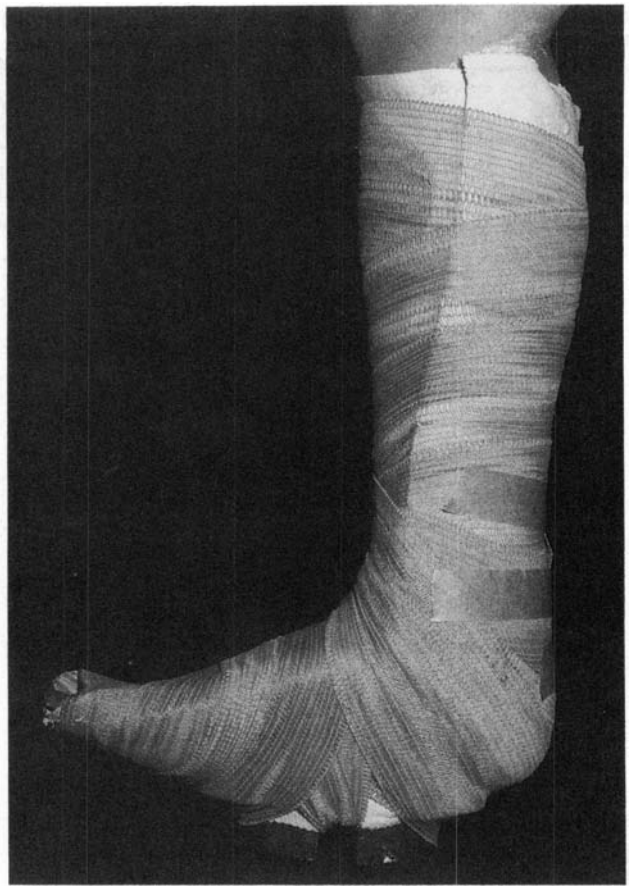

Figure 3. Walking splint.

treatment group 4. All patients were instructed in partial weightbearing ambulation using crutches or a walker.

Healing devices were selected in a nonrandomized manner based on ulcer grade, location and in some cases patient preference. Generally, walking casts were the recommended treatment for Wagner grade 1 and 2 ulcers. Deep abscess, purulent drainage, heavy drainage, systemic signs of infection and dermatosis were contraindications for casting in this study. Suspected Grade 3 ulcers were evaluated for surgery. Cut-out sandals were used for toe ulcerations. Walking splints were the alternate method when casting was not indicated or patients were not amenable to a cast.

Healing time (measured in days) was determined by clinical observation of wound closure. Wound closure was defined as complete epithelialization of the wound. Differences in healing time between diagnostic groups and the relationship of secondary variables including healing device, age, wound diameter, depth and duration on healing time were analysed using a general linear model (SAS System, SAS Institute Inc, Cary, NC, USA) and multiple regression.

Table 2. Mean healing rates and wound characteristics between diabetic and leprosy patients

	n	Rate (days)	Age (years)	Diameter (mm)	Depth (mm)	Duration (days)
Diabetic	75	39·7	51·8	17·4	7·4	328·6
Leprosy	66	43·2	54·8	11·4	6·1	244·1

Table 3. Data on ulcers not healed or lost to follow-up (LTFU)

	Not healed	LTFU
Diabetic	2	3
Leprosy	3	1

Table 4. Mean healing rates and wound characteristics for healing devices

	n	Rate (days)	Diameter (mm)	Depth (mm)	Age (years)
Walking cast	68	37·7	16·4	7·2	50·2
Cut-out sandal	25	34·8	7·7	4·1	55·9
Walking splint	27	43·0	20·0	7·0	55·6
Other*	21	58·7	10·0	8·5	56·5

* Includes surgery cases.

Results

In the leprosy group 66/70 ulcers (94%) healed in a mean time of 42·7 ($\pm$ 36·1) days and 75/80 ulcers (94%) in the diabetic group healed in a mean time of 39·7 ($\pm$ 32·1) days (Table 2). The number of cases which did not heal or were lost to follow-up were similar in both groups (Table 3). There was no significant difference in healing time between leprosy and diabetic patients ($p > 0{\cdot}05$).

Analysis of secondary variables using a general linear model showed a significant relationship between wound depth ($p < 0{\cdot}03$), and diameter ($p < 0{\cdot}05$) and the dependent variable healing time. Age, duration of ulceration, treatment devices (Table 4) and sex were not significant. A stepwise regression model including depth, diameter and age explained 36% of the variation in healing time for diabetics (Table 5). Depth was found to be a highly significant predictor of healing time. A meaningful prediction model ($p > 0{\cdot}15$) was not found for leprosy patients.

Table 5. Stepwise regression procedure for dependent variable rate

Step	Variable	Partial R2	Model R2	F ratio	Probability
1	Depth	0·3191	0·3191	34·208	0·0001
2	Diameter	0·0214	0·3404	2·332	0·1311
3	Age	0·0215	0·3619*	2·387	0·1268

* 36·19% is the total variation in rate explained by the model rate = −1·8337 + depth (2·32334) + diameter (0·34087) + age (0·35414).

Discussion

It has been thought that delayed healing of ulcers in diabetic patients may be the result of vascular disease. Since leprosy patients are at no greater risk of vascular disease than the general population, it might have been expected that the diabetic group in this study would have healed at a slower rate. The finding of no difference in healing time between leprosy and diabetic patients supports loss of protective sensation and mechanical stress as the primary aetiology for plantar ulceration in both groups.

Delbridge *et al.*[4] characterized neuropathic ulcers as being painless, circular, calloused, pink lesions and localized over bony areas on the plantar surface of the foot. In contrast he notes that vascular lesions tend to be painful, irregular, noncalloused, pale and nonplantar. Additionally, ulcers in leprosy and diabetic patients seem to be located at the same sites of the foot.[41,42] The first metatarsal head, the great toe, and fifth metatarsal head have been shown to be the most common sites of ulceration in both groups. These sites represent areas of highest pressure on the foot and ulceration has been shown to occur where pressure is highest.[1,39,40] The patients' inability to protect their feet due to sensory loss results in delayed healing of plantar ulcers.

Both leprosy and diabetes are major international health problems. Leprosy has an estimated 12 million cases and diabetes mellitus 100–120 million cases worldwide.[43,44] In the USA foot complications account for 20% of annual hospital admissions of diabetic patients, and foot injuries caused by neuropathy have been found to be 3 times more common than ischaemia.[45,46] Diabetes is the leading cause of lower extremity amputation in the USA (50,000 diabetic foot amputations yearly), and it has been reported that this rate could be significantly reduced by implementation of programme emphasizing preventive care of insensitive feet.[47–50]

There are limited resources to provide healing devices, protective footwear and orthotics for the tens of millions of leprosy and diabetic patients likely to develop foot problems in most parts of the world. Since there is a common aetiology in plantar ulceration in leprosy and diabetes, the pooling of resources could result in more effective management and reduction of disability in both groups.

This study shows that both leprosy and diabetic patients can obtain satisfactory ulcer healing with proper wound protection. While not randomly assigned, device selection showed no relationship to healing time between the 3 devices used. Also, the average healing time in this study (using the cast, sandal or splint) was similar to the cast groups in other studies where walking casts were shown to be more effective than traditional methods.[31,33,35]

Wound depth was found to be the strongest predictor of healing time. Deeper wounds may heal more slowly because of involvement of subdermal tissues such as tendon, joint, capsule and bone. These lesions may also be more septic. Wound diameter and age were also found to affect healing time. As expected, healing time was longer for larger diameter wounds and in older patients.

Of note is the absence of a meaningful prediction model for the leprosy patients, where ulcer size and age accounted for an insignificant percentage of the variation in healing time. In this study, leprosy patients were primarily residents of the Center, while the diabetic patients were exclusively outpatients. The treatment of ulcers should be easier in a controlled environment, but in this situation, familiarity of patients with both staff and treatment procedures may have had a negative impact on patient compliance. For example, in contrast to the diabetic group, leprosy patients were more likely to direct their treatment or miss appointments. We speculate that compliance, or lack of it, may have accounted for much of the unexplained variation in healing time in the leprosy group. Research has been lacking on the measurement of compliance, the effect of compliance on treatment outcome in neuropathic patients, and the benefit of patient education on improving treatment compliance.

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Lepr Rev (1992) **63,** 365–374

Taux de cicatrisation des ulcères plantaires dans la lèpre et le diabète

J A Birke, A Novick, C A Patout et W C Coleman

Résumé Nous avons comparé le temps de cicatrisation des plaies dans des séries consécutives de patients lépreux et diabétiques souffrant d'ulcération plantaire. Dans le groupe des lépreux, 66 des 70 ulcères (94%) se sont cicatrisés dans un temps moyen de 42,7 ($\pm$ 36,1) jours, et dans le groupe des diabétiques, 75 des 80 ulcères (74%) se sont cicatrisés dans un temps moyen de 39,7 ($\pm$ 32,1) jours. L'analyse de tous les ulcères cicatrisés, à l'aide d'un modèle linéaire général, a révélé que la profondeur de la plaie ($p < 0{,}03$), et son diamètre ($p < 0{,}05$) étaient en relation significative avec le temps de cicatrisation. Le diagnostic, les systèmes d'aide à la cicatrisation (plâtre, attelle et sandale découpée), l'âge et le sexe n'étaient pas significatifs. Chez les sujets diabétiques, un modèle régressif comprenant profondeur, diamètre et âge a expliqué 35% de la variation du temps de cicatrisation. Pour les lépreux nous n'avons pas trouvé de modèle régressif ayant un sens.

Velocidades de curacion de las ulceras plantares en la lepra y la diabetes

J A Birke, A Novick, C A Patout, y W C Coleman

Resumen Se realizó una comparación del tiempo de curación en una serie consecutiva de pacientes de la lepra y diabéticos sufriendo de ulceración plantar. En el grupo leproso, 66 de las 70 úlceras (94%) se curaron en un tiempo medio de 42,7 días ($\pm$ 36,1 días), y en el grupo diabético, 75 de las 80 úlceras (94%) se curaron en un tiempo medio de 39,7 días ($\pm$ 32,1 días). Un análisis de las úlceras curadas utilizando un modelo general lineal reveló una profundidad de herida ($p < 0{,}03\%$) y un diámetro de herida ($p < 0{,}05$) significativamente relacionados al tiempo de curación de la úlcera. El diagnóstico, dispositivos de curación (escayola, tablilla, sandalia recortada), edad y sexo not eran sifnificativos. En los pacientes diabéticos, un modelo de regresión que incluía profundidad, diámetro y edad explicó 36% de la variación del tiempo de curación. No se encontró un modelo de regresión válido para los pacientes leprosos.

Lepr Rev (1992) **63,** 375–376

SPECIAL ARTICLE

Global estimates of the number of people needing medical treatment and care as a result of leprosy*

Introduction

The new global estimates of the world leprosy problem recently published by WHO are the first formal revision of such figures since 1983. These estimates are important as a measure of the task before us. The figures, however, must be interpreted carefully.

Comments

1 It is extremely difficult to arrive at an accurate estimate of the size of the leprosy problem in the world. For the countries with the largest numbers of patients, the new estimates result from both evaluation of available statistics and the views of programme managers.

WHO while admitting that the methods used are crude, feels that the estimates are reasonably adequate for planning purposes.

2 Any errors in the estimates for individual countries other than India have little importance for the overall global figures. They should be treated, however, with considerable caution for national planning purposes.

Because of possible inaccuracies in the figures for individual countries, it is the intention of WHO to regularly revise these estimates. The knowledge of ILEP Co-ordinators will be helpful in corroborating national figures.

3 It is relevant that detailed figures have been derived only for the top 25 countries as these represent almost 95% of all registered cases.

4 We strongly welcome the distinction made between estimates of people with leprosy who require chemotherapy and estimates of those who have disabilities as a result of leprosy. Previous global estimates have blurred this difference. It is more appropriate to cite global estimates of the leprosy problem in terms of *people who require medical treatment and care as a result of leprosy* with the two components of chemotherapy and disability clearly expressed.

5 It means, however, that care must be taken over comparisons with the previous global estimates of 10–15 million. Although there is some overlap between the two figures of 5·5 million people requiring chemotherapy and 2–3 million people with disabilities, it is reasonable to take the two together in order to compare with the earlier figure.

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6 We consider that the figure of 2–3 million people with Grade 2 disability is most likely to be an underestimate and could be almost double this figure.

There is a need for more accurate figures in order to arrive at a more sophisticated picture of the needs for continuing care caused by leprosy.

7 The reduction to 5·5 million people requiring chemotherapy is partly due to the introduction of MDT. It is also due to reviews of existing patient registers and stricter adherence to the definition of a case of leprosy—i.e. those people in whom the bacillus is active and who therefore require chemotherapy.

Compared with the figure given for registered patients (1), it suggests that approximately 40% of those who suffer from leprosy are so far not being reached.

8 The number of new cases arising each year, at present estimated by WHO as about 600,000 to 800,000, will become an increasingly important statistic as the total number of cases reduces. Until this figure shows steady decline, **it is too early to say that leprosy has been brought under control**.

Implications for ILEP Member-Associations

The new global estimates of leprosy in the world put two important challenges in context:

(A) The ILEP target of achieving MDT for all leprosy patients by the year 2000. While about half the registered cases are currently receiving MDT, these new data show that this only represents a quarter of all estimated cases.

(B) The needs of people with disabilities as a result of leprosy. Once implementation of MDT for all is assured, further goals for meeting these needs will have to be set.

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[Endorsed by the ILEP Medical Commission, June 1992]

Lepr Rev (1992) **63,** 377–380

Letters to the Editor

LEPROSY CONTROL IN THE GHARBIA GOVERNORATE OF EGYPT

Sir,

At the International Conference of Leprosy, held in Cairo, Egypt, 1–2 March 1992, Professor Wafaa Ramadan, from the Department of Dermatology and Venereology, Tanta University, described the epidemiological features of leprosy in the Gharbia Governorate over a period of 19 years (1973–91). This important presentation has stimulated us to re-examine and submit for publication a summary of data collected from a survey in the same part of Egypt many years ago. The 'Gharbia Project' as it was then called, set out to: 1, provide information on the prevalence of leprosy in selected areas of the Governorate; 2, evaluate the importance of early case detection by active, as opposed to passive methods; 3, identify the level of survey of the population which might be effective in detecting the majority of all cases, and 4, generate data which could contribute to plans for control of leprosy in Egypt. We take this opportunity to record the information gathered and to comment on the extent to which these objectives were realized.

Planning. As Director of Skin Disease Control in the Ministry of Public Health at that time, one of us (RM) developed an outline proposal and protocol, to include survey methods, staff equipment, personnel involved and a budget. The CIBA-GEIGY Company in Egypt very kindly approved the proposals and agreed to give considerable financial support, including the provision of free drug supplies equal to those purchased by the World Health Organization (WHO) for the duration of the project. Additional financial backing was received from the Le Petit Company, Caritas-Egypt and the Gharbia Ministry of Public Health.

Survey methods. We selected 3 areas: 1, an urban area around Tanta Health Centre; 2, a rural area to include 4 villages known to be endemic for leprosy; and 3, another rural area with 9 villages in which, on the basis of all previous records, very few cases had been recorded. The work was carried out by 2 mobile teams, consisting of a general practitioner and a nurse. Staff training for the project started in December 1981, with practical sessions on clinical diagnosis, classification, management, laboratory work, for both paramedical and medical staff. Some of the teaching was done locally but there were also sessions in the Abu Zaabel leprosarium, about 25 km from Cairo. Using a prepared master list of the populations concerned, together with detailed maps of the villages and houses, the team interviewed the head of each household to obtain information about general attitudes to leprosy and the presence of any patient known to have leprosy in the house, or nearby. From patients a wide range of information was collected, including attitudes and knowledge about leprosy, any history of previous treatment, marital status, income, literacy level, diet, smoking, water supply and toilet facilities. Detailed notes were also made of domestic and community cleanliness and socioeconomic conditions generally.

Results. In summary, during the period 1982–86 a total of 135,425 people were examined out of a recorded total population of 143,567 in the survey areas. We were aware of the absentees, but co-operation was extremely good throughout the period of study and it is likely that the difference in the above figures could be mainly accounted for by deaths, those who had moved to another part of Egypt or left the country. A total of 144 cases were discovered during the survey period, giving an overall prevalence of approximately 1·1 per thousand. Some of the cases gave a history of having been diagnosed and treated previously, either by the health services or in private practice, but the

majority were new, first-time presentations, often in quite an advanced stage of disease, with grade 1 or 2 deformities. Over 50% of all cases were in the age group 20–50; 40% were over 50 and there were remarkably few cases under the age of 20 (less than 7%). There were no cases in children below the age of 14 years. With regard to classification, 66·7% were borderline, 20·7% lepromatous, 9·2% tuberculoid and 3·5% indeterminate. No fewer than 76% of all patients were illiterate, with relatively higher rates in females. Many patients described progression of disease at the time of our diagnosis, but none presented in reaction of any kind. All patients with active disease were treated with multiple drug regimens, as recommended by WHO in 1982, including supervised monthly dosage and monitoring for the prescribed periods of time in pauci- and multibacillary groups. The cost of discovering a patient under these circumstances, including transport, equipment and administration worked out at 538 Egyptian pounds (approximately USA $534 at that time) per patient.

Comments. From the outset, it was abundantly clear that on a daily basis we were working with a seriously disadvantaged section of the community. The villages were dirty and the roads of poor quality. Flies abounded in the vicinity of many houses. Modern toilet facilities were available in only 20% of the houses and a clean water supply in only 22%, many had indoor cattle and poultry sheds. As already noted above, literacy levels and education were poor and over 90% of all patients interviewed thought that leprosy is due to mere chance, unknown causes, or a variety of factors beyond their control; hardly anyone mentioned a 'germ' or infective cause. With regard to social status and acceptance by the community, it was noteworthy that the vast majority of patients, even those with advanced disease and deformity, were well accepted by the family, the neighbours and the community, apparently without any element of rejection or stigma.

As the Gharbia Project came to an end, a considerable number of patients were referred for continuing treatment and care to the local health services, or—in the case of those who could afford it—to private practitioners. Partly due to the difficulty of recruiting and training staff to pursue the work, the entire project took much longer than had been envisaged and this no doubt contributed to the difficulty of collecting and analysing results. The unexpectedly high cost in terms of each patient discovered also became a matter of mounting concern. We realize that the data presented above could be considered as 'dated' and it has also to be recognized that the study covered only a relatively small proportion of the total population of the Governorate, possibly weighted towards areas of low socioeconomic standing. Nevertheless we believe that a number of broad conclusions can be drawn: 1, socio-economic conditions, environmental and personal hygiene were at a remarkably low level in all villages and it may be significant that they were worst in 2 villages (Shendelet and Marhoum) which had the highest incidence of cases; 2, the vast majority of patients were illiterate; 3, the majority of patients were in advanced stages of disease; 4, the incidence of leprosy below age 20 was low; and 5, there was no evidence of rejection or stigma on the part of family members of the community. The findings from a project carried out in Lower Egypt in the 1980s may still have relevance for the attempts which are currently being made to proceed towards, '. . . a future free of leprosy in Egypt'. Surveys of the type described here are clearly time-consuming and expensive and the yield may be disappointing. In reviewing the data, our strongest impression centres on the need for a sustained programme of health education, taking into account the low literacy level in many parts of the country, so that the early signs of leprosy and the potential of multiple drug therapy are widely understood by the population at large.

Acknowledgments. We are indebted to Dr A Colin McDougall, Department of Dermatology, the Slade Hospital, Oxford, for his encouragement to present this information for publication. We would like also to thank Dr M Bakhoum, the head of CIBA-GEIGY Scientific Office Egypt at that time, Dr H Tawfik head of the Medical Department of Le Petit Egypt and Dr Parisi, EMRO of the WHO Alexandria for their active role in the financial and technical support of the project.

PO Box 469
Maady, Cairo
Egypt

R MOHAREB,
N SALAMA, M EI-AKKAD &
S KAMEL

RAPID HEALING OF A CHRONIC WOUND SURROUNDED BY HYPERKERATOSIS IN A LEPROSY PATIENT AFTER HYDROCOLLOID OCCLUSIVE DRESSING

Sir,

One of the commonest problems in the care of leprosy patients is the treatment of chronic wounds originating as small skin injuries or burns. In leprosy patients, a characteristic form of wound healing often occurs, which leads to the development of a chronic wound with incomplete epithelization surrounded by hyperkeratosis. Since leprosy patients have sensory loss caused by peripheral nerve involvement, infection of wounds sometimes leads to serious inflammation which often goes unnoticed.

A 69-year-old male lepromatous leprosy patient had a chronic wound on his thumb for 10 years. The wound was an ulcerative lesion with surrounding hyperkeratosis, appearing like tylosis or warts (Figure 1(a)). Although conventional treatment such as topical use of ointments or the removal of hyperkeratosis was not effective, the lesion was rapidly healed by hydrocolloid occlusive dressing (DuoDerm). This dressing, changed every 7 days, is a compound of gelatin, pectin, carboxymethylcellulose sodium and polyisobutylene; 1 week after the start of the treatment, incomplete epithelization was observed on the surface of the ulcerative lesion, and in the following week, the surrounding hyperkeratosis showed slight collapse. Epithelization was completed and the surface of the whole lesion became flat and smooth within 1 month (Figure 1(b)).

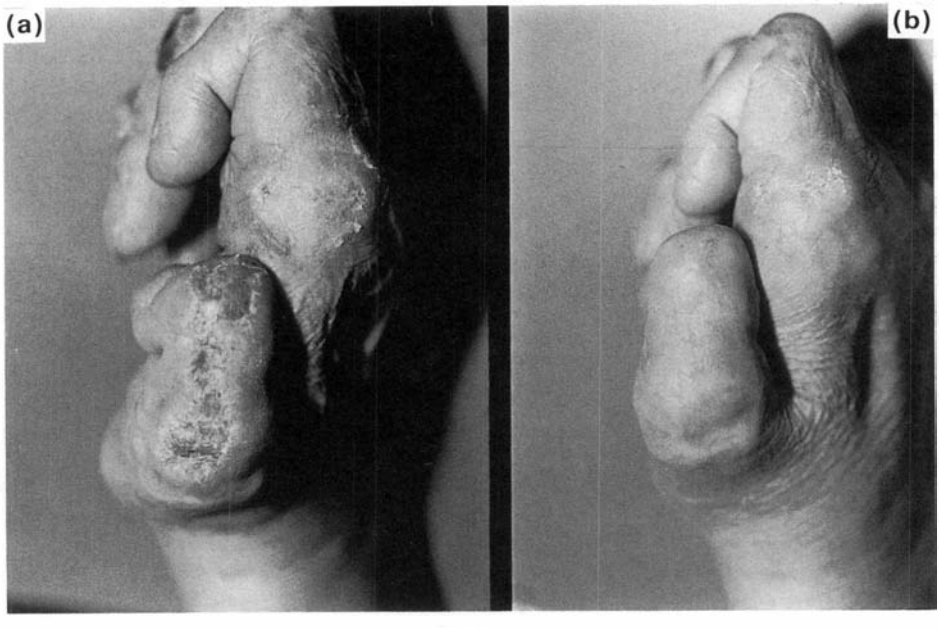

Figure 1.

The precise mechanism of wound healing by occlusive dressing is unclear, but it is thought that the environment of the wound is modified to a condition conducive for wound healing.[1-3] Although

follow-up of this patient showed that scratches on the healed surface could cause skin roughness again, this simple dressing treatment may prove extremely valuable for the healing of chronic wounds in leprosy patients.

National Sanatorium Tama-Zenshoen
Tokyo 189, Japan

Y SUGITA,
M KOSEKI &
M NARITA

Department of Dermatology
Yokohama City University
School of Medicine
Yokohama 236, Japan

S KIM &
H NAKAJIMA

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Lepr Rev (1992) **63,** 381–382

Book Review

Social Science Research and Social Action for Better Leprosy Control
Editor: D H Srinivasan

This book is a record of an attempt made in India to help leprologists and social scientists work together to solve the extramedical problems of leprosy. Sponsored by the Indian Association of Leprologists, this workshop consisted of 30 Indian leprologists and social scientists from different disciplines and took place over 2 days in March 1991 at Karigiri, India.

While some leprologists think social science research 'a waste of time from a practical viewpoint', Dr Srinivasan in his introduction feels that co-operation between leprologists and social scientists can and must be established if we are to deal effectively with the problem of leprosy in all of its dimensions.

Papers presented included subjects like 'Problems of leprosy and leprosy control', 'Social sciences and social action for leprosy control', 'Self concept and coping with illness', 'Patient-health service contact in the context of NLEP', and 'Towards developing social action for comprehensive leprosy work in local community systems'. The report also includes background information on leprosy, a short introduction to the research methods and concerns of social scientists and a bibliography on social science research between 1979 and 1990 taken from 3 of the main leprosy journals.

Participants at the meeting concluded that many of the problems confronted by the National Leprosy Eradication Programme (NLEP) in India are because it operates on a 'biomedical' perception of leprosy, while society and patients have a 'biosocial' view of the disease. For these reasons health education, imposed from the top down on passive recipients, has not been successful in changing society's and patients' negative views of leprosy and persuading them to co-operate with professional staff in leprosy control programmes.

On the other hand, experiences in several Indian districts have shown that when patients and community members are involved by leprosy workers as equal participants in the process of identifying and solving leprosy-related problems, their views of the disease and their level of co-operation with the programme changes for the better.

Because of this positive experience in 'social action', the participants in the meeting urged that NLEP staff should be trained to promote similar community and patient involvement elsewhere in order to eradicate fear and a sense of despair, and to encourage voluntary reporting, prevention of deformities, rehabilitation and integration. Likewise, social scientists were encouraged to become involved in more practical 'action-research-action' schemes. Together with medical scientists, they would jointly define problems, design research programmes and carry them out as partners.

This report on the workshop is a timely one and helps to bring to the forefront a number of issues which are being thought about and acted on in many parts of the world: (1) leprosy is the cause of at least as many psychosocial problems as physical ones; (2) nonmedical problems are often more important to patients and to members of their communities than medical problems and certainly effect the success or failure of medical treatment; (3) to solve these nonmedical problems in a systematic way, we need the input, co-operation and leadership of others outside the medical field who are affected by or have experience in dealing with the problems we are facing. These are not

only the wide array of persons covered by the term 'social scientists' but also patients, family members, and the leaders of the medical and socioeconomic institutions whose support we need to solve our problems.

Perhaps the time has come to put as much effort into planning and implanting practical, efficient programmes on the social side of leprosy as on the medical side. The Indian workshop is certainly a sign that concern is growing that we need to do much more than we are now doing. It also provides some practical proposals for action.

Thomas F Frist

Indian Association of Leprologists, 245 TTK Road, Madras 600 018, India. 168 pp.

Lep Rev (1992) **63,** 383–386

Teaching Materials and Services

'Action Kit'; facts and information on leprosy, AHM, Germany

Aussätzigen-Hilfswerk München e.V., Zenettistrasse 45, D-8000, München 2, Germany, have produced an 'Action Kit' of basic information on leprosy in the form of a ring binder, with the following main aims:

1 To give the correct and recent scientific facts about leprosy to people at large.
2 To stimulate interest in people to accept leprosy as a normal physical sickness.
3 To promote decisively the role and importance of medication and therapeutic effectiveness.
4 To overcome the deep-rooted stigma and unnecessary bias still attached to leprosy.
5 To integrate the leprosy afflicted within the community.

The main headings are: the leprosy problem; basic information on leprosy; prevention and care of deformities in leprosy patients; involvement of community groups; list of educational and training material; names and addresses of agencies, for local preparation.

(Section 1 on the global perspective gives 'around 12 million' as the WHO estimate for the number of people, worldwide affected by leprosy, but this should be corrected to 5·5 million—see 'Estimated number of leprosy cases in the world' by S K Noordeen *et al.*, *WHO Bull*, 70, (1992), 7–10 or *Lepr Rev*, 63 (1992), 282–7.)

On page 2.4 under 'How leprosy can be detected and treated', the daily dose of clofazimine should be 50 mg daily and **NOT** 150 mg daily.

ELBS—low-priced book scheme, UK

The Educational Low-Priced Books Scheme (ELBS) is funded by the Overseas Development Administration as part of the British Government overseas aid programme and administered by International Book Development Ltd. It makes available specially selected, unabridged editions of British textbooks to students in developing countries. The books are produced and marketed by their original publisher with the aid of a subsidy which enables them to be priced at between *one-fifth and one-third the price of the cheapest standard edition*. A reasonable mark-up is agreed by local booksellers' associations to cover postal and freight charges.

Booksellers should order through the usual book trade channels from stockists in those countries where they have been appointed, from the publisher, the publisher's agent or from a United Kingdom exporting wholesaler.

Academics and students should order books from their local bookseller or from a United Kingdom exporting retailer. Academics requiring specimen copies should write direct to the publishers.

All orders should include the International Standard Book Number (ISBN) given in the catalogue.

Books cannot be ordered direct from the Educational Low-Priced Books Scheme.

Academic staff are invited to suggest additions to the ELBS list. Only British books published for the first time or with a new edition within the last 5 years are eligible for consideration. Please state whether the books are recommended at universities, polytechnics, technical colleges, or other education or professional training institutes.

Annotated subject catalogues can be obtained from ELBS Administration at the address below or, in some instances, from the local British Council office. Copies of ELBS books may also be found in some British Council libraries. Complete sets of ELBS texts can be seen and consulted in the British Council Libraries.

Books cannot be supplied free of charge by ELBS Administration, who also regret that they cannot answer students' letters. The address is:

ELBS Administration, International Book Development Ltd, 10 Barley Mow Passage, London W4 4PH.

The following titles are included in the Tropical and Communicable Diseases Section:

Bryceson ADM, Pfaltzgraff RE	*Leprosy.* £3·35 ISBN 0 443 04370 1 (Churchill Livingstone, 3rd edn 1990)
Emond RTD, Rowland HAK	*A Colour Atlas of Infectious Diseases.* £7·50 ISBN 0 7234 0986 2 (Wolfe Publishing, 2nd edn 1987)
Manson-Bahr PEC, Bell DR	*Manson's Tropical Diseases.* £16·50 ISBN 0 7020 1197 5 (Baillière Tindall, 19th edn 1987)
Parry EHO (editor)	*Principles of Medicine in Africa.* £17·50 ISBN 0 19 442383 2 (Oxford University Press, 2nd edn 1984)
Peters W Gilles HM	*A Colour Atlas of Tropical Medicine and Parasitology.* £11·00 ISBN 0 7234 1598 6 (Wolfe Publishing, 3rd edn 1989)

Association for Medical Education in Europe (AMEE)

1 Members of AMEE are teachers in medicine or the healthcare professions, and organizations or national bodies committed to high standards in medical education.
2 AMEE is concerned with the continuum of education from undergraduate or basic training through postgraduate, specialty or vocational training to continuing education.
3 AMEE is concerned with the facilitation of high quality research in medical education and with the dissemination of the findings.
4 AMEE recognizes the need to appraise, and where necessary, improve the quality of teaching.
5 AMEE serves as a source of advice on matters relating to medical education in a national, European and worldwide context.
6 AMEE encourages students and junior staff to take an interest in medical education and assists with the development of the skills required by medical teachers.
7 AMEE assists physicians and teachers in the health-care professions to keep up-to-date with current developments in medical education.
8 AMEE encourages and offers assistance with the development of high quality learning resources and assessment materials.
9 AMEE facilitates the exchange of information on medical education.
10 AMEE is concerned with the development of medical education to meet current and future needs, particularly in the European context.

Association for Medical Education in Europe, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, United Kingdom; Telephone 0382 60111; Ext 3141 Fax 0382 645748.

Centre for Medical Education, University of Dundee, UK

Since the Centre for Medical Education was established in 1972 it has developed into a leading international centre in undergraduate, postgraduate and continuing education. It has pioneered new approaches in teaching methods, including distance learning, assessment and curriculum planning. The staff come from a wide range of backgrounds and bring together a unique blend of expertise in medical education.

The Centre runs numerous courses and workshops throughout the year, many of them are

appropriate for applicants from Third World countries. Apply: Cource Director, Centre for Medical Education, at the above address.

Research Training Grants, 1993, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

TDR invites applications for research training grants to be awarded in 1993 to researchers from countries where TDR 'target diseases'—malaria, leprosy, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis, African trypanosomiasis and Chagas disease—are endemic. (As a matter of policy, TDR cannot provide funds for the training of scientists who are nationals of developed countries.) These grants are awarded to enable researchers to acquire skills related to one or more of the above diseases, such as molecular and cell biology, immunology, parasitology, epidemiology, clinical pharmacology and the social sciences.

Applications for training in research on the following topics are particularly welcome:

- Molecular entomology, aimed at introducing molecular genetic approaches and technologies to medical entomology, especially for the study of plasmodium behaviour in vectors and the possible genetic modification of the mosquito so as to disrupt the malaria parasite's life cycle.
- Product development in such areas as synthetic chemistry, novel systems for screening compounds against the above TDR target diseases, process development and different genetic vector expression systems.
- Health economics, related—for example—to direct and indirect costs imposed by the TDR target diseases, the cost-effectiveness of different control strategies, the impact of changes in health care financing on the control of tropical diseases, innovative financing of programmes for controlling the TDR target diseases, etc.
- Women and tropical diseases, especially in relation to (a) women's health-seeking behaviour and decision-making within their households; (b) gender differences in clinical manifestations; and (c) interventions, using formal and informal educational systems, that might increase women's knowledge of tropical diseases.

The research training grants can be used to help a researcher join an established training programme (whether or nor in the applicant's own country) culminating in a doctoral degree or an individualized training programme in a centre for research and training in tropical diseases. Support for attendance at a master's degree course abroad will be considered in exceptional cases. Grants supporting research training for a doctoral degree are awarded for a maximum of 3 years; grants supporting other types of research training are generally awarded for 6 months to a year.

Those eligible to apply for TDR research training grants include:

- staff members of an institution that is currently receiving a TDR institution-strengthening grant or that has ceased receiving such support within the past 3 years;
- scientists from other institutions in countries where a TDR target disease is endemic, who are already engaged in research or committed to undertaking research on one or more of the TDR target diseases and whose home institution possesses the necessary research facilities;
- staff members of health ministries who are involved in the planning, implementation or evaluation of programmes set up to control a TDR target disease;
- scientists with postgraduate research training who are actively involved in postdoctoral clinical, field or laboratory research on a TDR target disease and who wish to spend up to a year in a research centre or laboratory ungrading their skills or conducting specialized experiments or data analyses;
- scientists who are registered in their own country for a PhD, whose thesis is related to a TDR target disease and who wish to spend 6 months to a year in a research centre or laboratory upgrading their skills in conducting specialized experiments or data analyses.

For further information apply: Dr J A Hashmi, TDR, WHO, 1211 Geneva 27, Switzerland.

MSc Course, Heidelberg, Germany—Community health and health management in developing countries

The Institute of Tropical Hygiene and Public Health, University of Heidelberg, offers a 1-year English language, postgraduate course in Community Health and Health Management in Developing Countries. The course aims to provide specialized training in those skills (planning, communication, organization and administration, implementation and evaluation) required to manage health care in developing countries successfully.

The course is open to medical doctors and other graduates in the health and social science sectors who have at least 2 years' working experience in community health care/management of health services in developing countries. The university reserves the right to make exceptions to this general requirement. It is expected that participants return to this type of work after the course to put their newly-acquired skills and knowledge into practice and they will be encouraged to maintain links with the Institute.

A high standard of spoken and written English is required and has to be proved by a standard test (TOEFL, minimum requirement: 550; ELTS, British Council, minimum requirement: 'band 6'). Applicants can only be exempted from this standard test if they come from a country in which English is the administrative language and/or if their higher education was in English.

A maximum of 25 participants will be accepted each year, drawn from a wide range of countries. It is intended to achieve a balance between participants from industralized and developing countries.

The course begins 1 October each year and continues until September the following year. The application deadline is 31 December of the year preceding the course.

The curriculum is divided into 4 modules plus an introductory period. An essential additional part of the curriculum is a field-study project in a developing country in which participants will work on an actual problem faced by the health system, using methods developed during the modules. The results of this work are to be presented as a thesis which will form part of the final examination.

Enquiries to: Institut für Tropenhygiene und Öffentliches Gesundheitswesen (ITHÖG) SAI, Universität Heidelberg—Postgraduate Studies—Im Neuenheimer Feld 324, D-6900 Heidelberg 1, Germany.

Teaching and learning materials for leprosy; TALMILEP

An English language booklist of teaching and learning materials for leprosy is available from the Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex TW8 0QH, UK. A wide range of materials is listed for leprosy specialists, general practitioners, medical students, paramedical professionals, senior health workers, nurses, junior health workers, programme managers and trainers.

Manual of training; multiple drug therapy for leprosy; The Philippines

Amongst many manuals produced by national programmes, the above one from the Philippines (1987) is notably comprehensive and well written and could be used as an example for other countries. Apart from standard, basic information, there are chapters on operational aspects of multidrug therapy, monitoring, supervision and evaluation. It is distributed by TALMILEP by the Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex TW8 0QH, England.

Major equipment for peripheral laboratories, PATH, USA

In the series *Health Technology Directions*, the Program for Appropriate Technology for Health (PATH), 4 Nickerson Street, Seattle, WA 98109–1699, USA, has recently produced an issue on the above subject, which discusses major pieces of laboratory equipment used in district and health centre laboratories in developing countries. The information is very practical and there is a list of materials available, other resources of supply and information. Previous issues cover such topics as leprosy, tuberculosis, anaesthesia, venereal diseases, essential drugs and blood transfusion.

Lepr Rev (1992) **63,** 387–390

News and Notes

Reconstructive Surgery Fund, Lepra, UK

Lepra's (The British Leprosy Relief Association) Reconstructive Surgery Fund (formerly the 'Ring Fund') gives priority to early leprosy case-finding and treatment before the nerves become involved or damage ensues. Nevertheless, Lepra wishes to encourage reconstructive surgery for leprosy patients who have suffered nerve damage. This surgery should: remobilize clawed hands; reactivate eyelid closure; rebuild collapsed nose bridges; and restore dorsiflexion to dropped feet or correct clawed toes. Lepra has therefore established a fund for reconstructive surgery. Grants will be given on a per capita basis towards the cost of surgery, pre- and post-operative physiotherapy, equipment and temporary hospitalization for the patient. The grants apply to India and will usually be paid in rupees at rates which are decided by Lepra, allowing for inflation. Applications for grants should be submitted to: Lepra-India-Society, PB No. 1518, Plot No. 37, Asbestos Colony, Vikrampuri, Secunderabad 500 003, India.

WHO Model Prescribing Information; *Drugs used in Mycobacterial Diseases*

This 40-page publication provides model prescribing information for some 13 essential drugs used for the prevention and treatment of tuberculosis, and for the treatment of leprosy, and for the treatment of diseases caused by nontuberculous mycobacteria, including localized cutaneous lesions, pulmonary disease, lymphadenitis, and disseminated disease.

The first chapter, devoted to tuberculosis, opens with a detailed overview of the disease, its clinical features, and the main principles of prevention, tuberculin testing, and chemotherapy. The special problems of diagnosis and treatment in HIV-infected patients are briefly discussed. Readers are also given detailed information on the properties of antituberculosis drugs, preferred treatment regimens, monitoring of patient compliance and therapeutic response, and the treatment of relapsing and unresponsive disease. Against this background, model prescribing information is presented for 10 drugs used in vaccination, chemoprophylaxis, and chemotherapy. Each drug is profiled in terms of its clinical uses, dosage and mode of administration, contra-indications and precautions, use in pregnancy, adverse effects, and possible interactions with other drugs. Drugs used in the treatment of leprosy are covered in the second chapter, which also features background information on the disease and the main principles of multi-drug therapy. The final chapter provides prescribing information for drugs used to treat nonspecific mycobacterial infections.

Apply to: Office of Publications, WHO, 1211 Geneva 27, Switzerland. Price: Sw. fr. 9; US $8.10. In developing countries; Sw. fr. 6.30. Order no. 1150363.

Actionaid Disability News, Bangalore, India

Actionaid Disability News is a bi-annual newsletter of the Disability Division, ActionAid, India. The newsletter is meant for private circulation only, for planners, administrators, professionals, funding organizations and implementing agencies involved in disability and rehabilitation programmes.

The major emphasis of the newletter is on articles related to policy development, concept

clarification, development of methodology in areas of service delivery, training of manpower and programme evaluation, and development of technology related to rehabilitation.

Other information related to rehabilitation of disabled people that may be of use to funding organizations and implementing agencies are also welcome.

The views expressed in the newsletter are those of contributors and not necessarily of ActionAid.

Copies of the newletter are mailed free of cost on request.

We are interested in exchanging copies of this newletter on a reciprocal basis, with other rehabilitation publications and in gathering information on programmes and research findings related to disability and rehabilitation.

Articles sent to use will be published subject to their suitability and may also be published elsewhere if so desired. Two copies each (typewritten, double spaced, on bond paper) of articles, letters, comments and other communications meant for publication may be sent to the address given below:

Disability Division, Actionaid, P.B. 5406, 3, Resthouse Road, Bangalore-560 001, India.

A fresh look at Hansen's Disease, M J de Mallac

The above book (162 pp) written by Dr M J de Mallac, previously of Westfort Leprosy Institute, Pretoria, South Africa and with extensive experience from Nigeria, Gambia, Burma, India and Zaire, is described by the publisher as:

Although a good deal remains unclear or imperfectly understood, incomplete, or inconclusive about Hansen's disease (leprosy), major considerations in M J de Mallac's *A Fresh Look at Hansen's Disease* give cognitive evidence that the dignity and integrity of the patient are central to an issue awaiting redress; that it is no longer possible to envisage the disease as other than a fundamental immunological reality; that, neural in its inception, the disease assumes its true status from cause to effect, not the other way round as has been hitherto the case in both clinical and didactic practice.

Taking in the facts about Hansen's disease to see them whole calls for a sharper focus, since they equally spell a multi-leveled challenge at its scientific and humanitarian best.

It is available from Vantage Press Inc. 516 West 34th Street, New York, NY 10001, USA. Price US $25.00 plus postage.

Action in International Medicine; First World Assembly, 1992

Action in International Medicine (AIM), an organization of 76 colleges and academies of medicine and other health professions based in 27 countries, held its first world assembly in Toronto, 25–28 August 1991, at the Koffler Institute hosted by the University of Toronto. Although only founded as a charitable organization in November 1988, under the able leadership of its chairman, Sir Gordon Wolstenholme, former Director of the Ciba Foundation, AIM has attracted the membership of many professional organizations interested in world health, especially those involved in training and education. The objective of the AIM Assembly was to agree upon plans to promote the infrastructure development for the delivery of health care around the world. AIM's focus, as differing from other organizations working in the field, is upon the frontline professional health worker at the district level in developing countries.

The 87 Assembly participants came from 23 countries (Argentina, Bangladesh, Brazil, Canada, Colombia, Ecuador, Ghana, India, Jamaica, Kenya, Malaysia, Nepal, Nigeria, Philippines, Sri Lanka, Switzerland, Thailand, United Kingdom, United States of America, Western Samoa, Yugoslavia, Zaire and Zambia). Representatives of the World Health Organization and UNICEF also attended.

The conference was addressed by a number of speakers reporting on the status of worldwide health care delivery and the prospects for its future. Margaret Catley-Carlson, Deputy Minister of Health and Welfare of Canada, pointed out that many developing countries are facing economic

recession and a debt crisis, both of which eat into government spending. Major demographic shifts, such as growing urbanization, international migration and an ageing population, are contributing to the affordability and sustainability of health systems worldwide. She stated that there had been some gains in the 13 years since the Alma-Ata Declaration on Primary Health Care. During that period, infant mortality rates had fallen from 83 per thousand live births to between 65 and 70. By 1988, access to local health services and immunization coverage had increased globally to about 70%, and in the last 3 decades under the age of 5 mortality rates had been halved. Against this, major gaps remained between rich and poor, with more than a billion people living in absolute poverty and a fall-off in per capita GDP of 10% in Latin America between 1980 and 1990, and twice that amount in Africa. Women's literacy was still only two-thirds of men, and childhood diseases still killed 14 million children a year. Dr Catley-Carlson emphasized the importance of the participation of communities in designing and evaluating health services tailored to local needs. The arch-enemy to progress was poverty, which she interpreted as the lack of choice—choice of food, fuel, education and the opportunities for individual and collective development. Poor people's efforts to survive in turn ravage the environment.

Professor Olikoye Ransome-Kuti, Minister of Health for Nigeria, emphasized the need to complement activities from primary health care with improvements in staff, resources and training of those working in district hospitals. He advocated a bottom-up approach to counteract the tendency towards centralization of management, called for standardization of equipment for general hospitals, and regretted that because the performance of hospitals in many countries had been discredited, there were now very few sources of financial and other forms of assistance for their development.

Further information: Action in International Medicine, Windeyer Building, 46 Cleveland Street, London W1P 6DP.

Handbook of Leprosy, 4th edition, Indian distributor

The *Handbook of Leprosy*, eds W H Jopling and A C McDougall, is now available in India from CBS Publishers and Distributors, 485 Jain Bhawan, Bhola Nath Nagar, Shahdra, Delhi 11032. Price: 150 rupees, postage free in India.

The Heiser Program for research in leprosy and tuberculosis

This well known Program, previously for leprosy only, now includes grants for tuberculosis under the headings of Postdoctoral Research Fellowships and Research Grants. Further details from: Mrs Barbara Hugonnet, Director, Heiser Program for Research in Leprosy and Tuberculosis, 450 East 63rd Street, New York, NY 10021, USA.

Clinical tuberculosis, John Crofton, Norman Horne and Fred Miller, TALC/WHO

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

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

The 3 authors have had many years' experience of dealing with tuberculosis and of teaching both undergraduates and postgraduates. They have advised in many countries in Asia, Africa and South America. The final text incorporates constructive comments on an earlier draft by experienced consultants from the IUATLD, WHO and consultants working in several countries in Asia, Africa and the Pacific. The book therefore represents much collective wisdom.

Price: £3.00, plus postage and is being distributed by TALC, PO Box 49, St Albans, Herts AL1 4AX, U.K.

The All Africa Leprosy and Rehabilitation Training Centre (ALERT)

seeks a

Senior Field Research Medical Officer (SFRMO)

Who should continue an important longitudinal research project on reactions, neuritis and nerve function impairment in leprosy patients treated with the WHO-MDT regimen.

The successful candidate must have:

* a basic medical degree;
* a postgraduate diploma/degree in public health preferably in epidemiology;
* at least 4 years experience in leprosy control, preferably with research activities in that field.

OR

Substantial experience with field studies of another chronic disease and at least 2 years experience in leprosy control.

* teaching experience;
* a record of publications in reputed journals.

Candidates are requested to submit detailed CVs, with the names and contact details of three international referees, within 6 weeks of the appearance of this announcement, to:

The Executive Director, ALERT, P.O. Box 165, Addis Ababa, Ethiopia. Telephone: +251 1 71 11 10. Fax: +251 1 71 11 99. Telex: 21821 ALERT ET.

Internationally competitive salary and benefits, including furnished accommodation, are available to the successful candidate.

Contract Period: 3 years, renewable.

Leprosy Review Index

VOLUME 63 (1992)

Instructions to Authors

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

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

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

Proofs are submitted to authors for immediate return by air.

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