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Leprosy Review

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

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LEPRA

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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.

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Editorial

RECENT ADVANCES IN THE CHEMOTHERAPY OF LEPROSY

The classical strategy of leprosy control, based on early detection and effective chemotherapy, is likely to remain unchanged for many years.[1,2] Effective chemotherapy will still be necessary for the treatment of millions of leprosy patients even after a leprosy vaccine with proved effectiveness becomes available.

The most important progress made in the history of leprosy control was the development and implementation of multidrug therapy (MDT) for both paucibacillary* (PB) and multibacillary* (MB) leprosy. Due to MDT, new hopes of controlling leprosy as a major public health problem have been raised. Around the topic of MDT we are trying to review the recent advances in the chemotherapy of leprosy.

Basic concept of multidrug therapy

By the end of the 1970s it was clear that attempts to control leprosy by life-long dapsone monotherapy were failing, because of the rapid increase of dapsone-resistance. Multiple surveys conducted in a number of leprosy-endemic areas clearly demonstrated that both secondary and primary dapsone-resistant leprosy have been found wherever they have been sought;[1,3] the prevalence of secondary dapsone-resistance increased with time if dapsone monotherapy continued, even if patients were treated regularly and were well supervised; the prevalence of primary dapsone-resistant leprosy, which was virtually nonexistent before 1977,[4] had become alarmingly high, about one-third of newly diagnosed MB patients were resistant, although the majority of the primary resistance was of a low degree.[5–7] It must be assumed that primary dapsone resistance, unlike secondary resistance, occurs in at least as high a proportion of PB leprosy as of MB leprosy. By analogy with what was known about the treatment of tuberculosis, it gradually became understood that selection of resistant mutants by monotherapy was involved in the emergence of drug resistance in MB leprosy; and the only way to prevent

* To classify leprosy patients into PB and MB leprosy is essentially an operational categorization for purposes of MDT [1] The WHO Expert Committee (1988) has recommended that : (1) PB leprosy includes only smear-negative indeterminate (I), polar–tuberculoid (TT) and borderline–tuberculoid (BT) cases in the Ridley–Jopling classification; or indeterminate (I) and tuberculoid (T) cases in the Madrid classification. Any case belonging to these types but showing smear positivity will be classified as MB; and (2) MB leprosy includes all midborderline (BB), borderline–lepromatous (BL) and polar lepromatous (LL) cases in the Ridley–Jopling classification or borderline (B) and lepromatous (L) in the Madrid classification, as well as any other smear-positive types [8]

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the emergence of dapsone resistance and the spread of the dapsone-resistant leprosy was to use multidrug therapy. It was recommended that combined therapy with rifampicin and dapsone should be used for all PB leprosy; and at least two additional drugs should be combined with dapsone for the treatment of MB leprosy, and one of the two additional drugs should always be rifampicin because of its great potency.[1] Another problem that was particularly worrying was that the persisting viable, drug-susceptible *Mycobacterium leprae* (persisters) had been detected in MB patients even after treatment of many years.[1] It was feared that after the therapy had been withdrawn, persisters would cause relapse in a large proportion of patients, and it was hoped that the multidrug therapy might be able to eliminate such persisting organisms.

During the dapsone-monotherapy era, poor compliance with the patients' self-administration of dapsone had been a serious problem in most leprosy control programmes; typically, only about half of the prescribed doses were ingested,[9] and irregular treatment appeared to predispose the development of dapsone resistance.[1] The unsupervised, self-administered chemotherapy simply could not be enforced for long periods of time. Many control programmes continued to have high drop-out rates. To improve the compliance and the case-holding, MDT should be administered only for a limited period of time, and whenever feasible the regimens should contain a high degree of supervised drug administration.

Based on these reasons, and the knowledge regarding the sizes and the compositions of the bacterial populations in PB and MB leprosy, the efficacies of available antileprosy drugs and the immunological status of the patients, the following standard MDT regimens were recommended by the WHO Study Group:[1]

PB leprosy—Rifampicin 600 mg once-monthly for 6 months, supervised, plus dapsone 100 mg (1–2 mg/kg body weight) daily, self-administered, for 6 months.

MB leprosy—Rifampicin 600 mg once-monthly, supervised, plus dapsone 100 mg daily, self-administered, plus clofazimine 300 mg once-monthly, supervised, and 50 mg daily, self-administered. The duration of treatment should be at least two years and be continued, wherever possible, up to smear negativity. Where clofazimine is totally unacceptable owing to the coloration of skin lesions that it caused, its replacement by 250–375 mg self-administered daily doses of ethionamide/protionamide should be considered.

The two standard regimens have been endorsed by the WHO Expert Committee on Leprosy (1988),[8] except that substitution of ethionamide/protionamide for clofazimine was not recommended because of potential serious toxic side-effects.

Overall achievements of multidrug therapy

Since the recommendation of MDT in 1982, many leprosy endemic countries have accepted and introduced, or are in the process of introducing, the MDT regimens. By the end of 1989, 1·8 million patients in the world were being treated with MDT and 900,000 patients had completed their treatment.[10] In 1988, for the first time in the history of leprosy control, the number of registered leprosy cases showed a slight decline, to 5·1 million,[8] and the number of registered cases further declined to 3·9 million by the end of

1989.[10] Although such decline could be partly due to the discharging of inactive patients during screening of all cases at the preparatory phase of implementing MDT,[11] there is no doubt that the effectiveness of MDT and shortening of the duration of treatment also played an important role.

Both regimens are very effective, as the clinical response during treatment is satisfactory, and so far the relapse rate after stopping treatment is low: in control programmes, less than 0·1% per year among 85,000 PB cases and less than 0·06% per year among 22,000 MB cases;[10] in field trials, 4·17 per 1000 person years in PB leprosy during the first year after completion of MDT,[12] and no relapse in more than 8000 person years of follow-up in MB cases.[13] It is important to point out that no relapse due to a drug-resistant strain, especially resistant to rifampicin, has yet been reported. With respect to the persisters, the results of a clinical trial has suggested that they were present in virtually all MB patients and did not respond to any of the 5 rifampicin-containing combined regimens;[14] the very low relapse rate in MB leprosy after stopping MDT strongly indicated that the presence of persisters did not carry a high risk of relapse following the termination of treatment. In Karigiri, India, the incidence rate in a population of 35,000 has been monitored annually since 1980 and MDT was introduced into the area in 1982. The incidence rate was 1·46/1000 during 1982–84 and 0·85/1000 in 1985–87; the 40% reduction suggested that effective interruption of transmission may be achieved much earlier by community-wide treatment of patients with MDT than with dapsone monotherapy.[15]

Both MDT regimens were well tolerated by the patients except that the coloration of skin caused by clofazimine has been a problem in certain light-skinned patients,[17] and side-effects were extremely rare and mild. High motivation of patients as well as health workers has also been reported; in terms of attendance rate, the regularity of treatment has been excellent.[8]

The needs for improved multidrug regimens

In order to minimize relapse after stopping treatment, it was recommended that the duration of MDT for MB leprosy should be at least two years, because it was thought that this is the minimum period of treatment to ensure the elimination of drug-resistant mutants, especially rifampicin-resistant mutants, and to reduce the number of drug-susceptible viable organisms to a low level which will not cause an unacceptable relapse rate. A recent clinical trial demonstrated that the number of viable organisms have been reduced to no more than 10^6 after a single dose of rifampicin.[14] By definition, the response of the dapsone- and clofazimine-resistant mutants to rifampicin should be the same as drug-susceptible organisms and to be killed rapidly during the course of rifampicin treatment. The major problem is that the necessary duration of treatment with MDT to eliminate rifampicin-resistant mutants is still unknown. Failure to isolate rifampicin-resistant mutants from nude mice infected with a large number of *M. leprae* suggested that the frequency of such mutants might be smaller than 10^{-7} (unpublished observation), thus, the average size of the rifampicin-resistant *M. leprae* in an untreated lepromatous patient is no more than 10^4. However, rifampicin-resistant mutants can only be killed by dapsone plus clofazimine in the combined regimens. A clinical trial is being undertaken with lepromatous patients aiming to assess the necessary duration of treatment for the

killing of 4 logs of *M. leprae* by dapsone plus clofazimine. The other approach is to investigate the efficacy, measured by relapse rate, of fixed duration (two years) MDT among previously untreated MB patients though field trials.[13,17] Before such information becomes available, there is no justification in reducing the duration of the current MDT regimen for MB leprosy to less than 2 years in any control programme. From an operational point of view, the recommended duration is still relatively long and the monthly supervised treatment for 24 months or even longer cannot always be applied in certain areas. It is likely that the coverage of MDT may be significantly improved if the duration of MDT can be substantially reduced.

There are more complaints of the MDT regimen for PB leprosy. The major concern is the persistence of active lesions at the end of 6 months treatment, which ranged from 4·3[12] to 27·8%.[18] Although the active lesions may gradually resolve and finally disappear within 1 to 2 years after stopping MDT,[17] the details of such regression have not yet been well documented. A certain number of health workers and patients wish to continue the treatment until the lesions are inactive. It was claimed that the inactivation rate of the lesions had significantly improved and that relapse after stopping treatment might be prevented if the 6 months MDT was continued by an additional 6 months dapsone monotherapy,[18,19] but the observations still require further investigation and independent verification. Another concern is reversal reaction, especially the late reaction which appears after stopping MDT, because it may cause irreversible deformities. The incidence rate of late reversal reaction ranged from 5%[12] to 9%.[19] Due to a lack of well documented baseline data and well planned controlled studies, no definite conclusion can be drawn as to whether or not reversal reaction has become more common since the introduction of MDT. The claim that an additional 6 months' dapsone treatment might prevent the late reversal reaction[19] should be verified. The question that remains to be answered is whether or not the inactivation of PB lesions and the development of reversal reaction are correlated with the bactericidal effect of chemotherapy. It is desirable to develop regimen(s) which may accelerate the inactivation rate of lesions and reduce the reversal reaction, although the approaches may not necessarily be chemotherapy.

The need for new bactericidal drugs against *M. leprae*

One of the basic concepts of MDT is that the treatment be administered for only a limited period, and therefore only bactericidal drugs should be considered as candidates for MDT regimens.[1] To date only four antileprosy drugs, i.e. dapsone, rifampicin, clofazimine and thioamide (ethionamide/protionamide), with bactericidal activities that act by different mechanisms, are available. Because thioamides may cause hepatotoxicity especially when combined with rifampicin, neither thioamide should be used as a component of MDT under field conditions unless absolutely necessary.[8] Consequently, apart from the combination of rifampicin, dapsone and clofazimine, the choice for an alternative MDT regimen for MB leprosy is practically nil. If a MB patient does not accept clofazimine because of skin coloration, he/she has no chance to be treated with MDT. In addition, in view of the fact that both dapsone and clofazimine are only weak bactericides against *M. leprae*, it is very unlikely that the current composition of MDT allows for a substantial reduction in the duration of treatment for MB leprosy without introducing another strong bactericidal drug into the regimen. Furthermore, rifampicin

was employed in certain areas for the treatment of leprosy before the introduction of MDT, usually for patients who had relapsed after prolonged dapsone monotherapy, and adding rifampicin to such patients probably represented a change of dapsone monotherapy to monotherapy with rifampicin. We have observed that at least 5% (22 out of 404) of such patients have relapsed with secondary rifampicin resistance, and 90% of the rifampicin-resistant strains were also resistant to dapsone.[20] The treatment of these doubly resistant patients is extremely difficult. A recent study demonstrated that close to 30% of patients in Karigiri, one of the best leprosy control programmes in the world and where clofazimine is well accepted by the patients because of their dark-skin, did not take their prescribed dapsone and clofazimine properly,[9] suggesting that, simply because of noncompliance, it is still possible for rifampicin resistance to be developed in a programme where MDT has been implemented. Although the magnitude of this threat to the success of MDT is still unclear, the problem of rifampicin resistance must not be ignored. For these reasons, new antileprosy drugs with bactericidal mechanisms entirely different from those of existing drugs are urgently needed.

Ideally, a new antileprosy compound should possess the following characteristics: strong bactericidal mechanisms against *M. leprae* without antagonism to available drugs; safe and well accepted by the patients; can be administered orally, and its pharmacokinetic properties allow the treatment to be given no more than once daily. The prospect is bleak for a compound if it requires to be given by injection, because it is difficult to implement under field conditions, and the recent epidemiological trend of HIV infection further hampers the application of multiple-injection treatment in rural areas.

Strategies of developing new drugs

Before 1960, the only approach to the search for an antileprosy drug was to conduct clinical trials. The progress was extremely slow, and the results were difficult to interpret. Now, there are two different approaches for the development of new antileprosy drugs: 1, synthesis of new compounds; and 2, the screening of existing compounds.

With the development of experimental infection in armadillo[21] and the method of purification of *M. leprae* from infected armadillo tissue,[22] a limited amount[23] of purified *M. leprae* has been obtained for studies of the metabolism and physiology of *M. leprae*. The scientific progress in the understanding of the metabolism and physiology of *M. leprae*,[23–26] and the techniques for producing and studying the structures of the potential target enzymes have made it possible to exploit such knowledge and capabilities for synthesizing new compounds in a systematic fashion—the process becoming known as rational drug development. In order to provide a large amount of *M. leprae*-derived enzymes that are supposed to be the targets of antileprosy drugs for screening, the genes encoding the dihydrofolate reductase, RNA polymerase and DNA gyrase are being cloned, and new inhibitors of several target enzymes are being synthesized. Unfortunately, rational drug design for leprosy is certainly not a high priority of the pharmaceutical industry because of the lack of commercial viability.

The laboratory screening of antileprosy drugs was started only after the mouse footpad model of *M. leprae* infection[27] became available. Huge amounts of different classes of antimicrobials are being developed every year. The recent discovery of strong bactericidal activities of pefloxacin,[28,29] ofloxacin,[30,31] minocycline[32] and clarithromycin[33]

clearly demonstrate that the screening of existing compounds is still the most practical approach. Of course, random screening is not possible due to limited facilities and it is also uneconomic. The candidates should focus on compounds which show strong activity, in terms of MICs, against Gram-positive organisms and particularly against cultivable mycobacteria. Favourable pharmacokinetic properties, e.g. better absorption rate or longer half-life, are also critical in selecting the analogues of active compounds, e.g. newer fluoroquinolones and macrolides, for screening.

Methods in screening antileprosy drugs

The mouse footpad technique is by far the only universally accepted experimental system for the study of drug activity against *M. leprae*. Three methods are employed for drug screening by this technique: 1, the continuous method;[34] 2, the kinetic method;[35,36] and 3, the proportional bactericidal method.[37] The methods and their applications have recently been reviewed.[38] All of the effective antileprosy drugs have been demonstrated to exert at least bacteriostatic activity in this system, whereas no compound shown to be inactive in mice has been demonstrated to exert definite therapeutic effects in leprosy patients. Nevertheless, the mouse footpad technique possesses several disadvantages. It is time consuming, requires many mice and gramme amounts of the compounds to be tested, and can therefore be employed to investigate only limited numbers of compounds that represent a very few selected classes.

The search for active compounds representing a wide variety of classes requires a rapid primary screening method that will yield results within days or, at most, a few weeks, and that requires only milligrammes rather than gramme amounts of the tested compounds. Ideally, drugs should be screened *in vitro*.

Despite the fact that *M. leprae* cannot be cultivated *in vitro*, and taking the advantage that viable organisms still retain many of their metabolic functions for a limited period of time outside the host,[39] within the last decade many systems have been reported to be capable of rapidly demonstrating the *in vitro* activity of a compound to kill or to impair the key metabolic processes of *M. leprae*. These techniques include the use of radiolabelled substrates to investigate the incorporation by *M. leprae* of dihydroxyphenylalanine (DOPA),[40] thymidinein,[41,42] hypoxanthine[43,44] and uracil;[45] measurement of changes of the adenosine triphosphate (ATP) content of *M. leprae*[46] and the changes of intrabacterial ratio of sodium and potassium;[47,48] changes of Fc receptors and sialic acid on the surface of macrophages[45] and changes of the ratio of cholesterol to cholesterol esters within macrophages[49] which have phagocytosed *M. leprae*; and changes of staining by fluorescein diacetate and ethidium bromide.[45,50] Recently three different *in vitro* screening systems have been developed by the scientists at Carville. It has been reported that the incorporation of ^{14}C-palmitic acid into phenolic glycolipid-1 (PGL-1), the *M. leprae*-specific antigen, has been suppressed in the presence of all known antileprosy drugs as well as other compounds in both intracellular[51] and extracellular *M. leprae*.[52,53] Another method is based on the measurement of intracellular ATP of *M. leprae* incubated in an axenic modified Dubos medium. Over 25 antimicrobial agents have been evaluated, and, except dapsone, 3 of the 4 most commonly used antileprosy drugs (rifampicin, clofazimine and ethionamide) demonstrated activity in this system.[54] The system appeared suitable for assessing comparative activity of new structural analogues of

clofazimine.[54,55] The third method is based on the measurement, by radiorespirometry with the Buddemeyer-type counting system[56] or with the BACTEC 460 system,[57] of the oxidation of ^{14}C-palmitic acid to $^{14}CO_2$ by *M. leprae*. It was reported that these are the simplest systems described to date and all established antileprosy drugs displayed significant activities by the method.[56,57] Its simplicity has facilitated screening of a variety of macrolides,[33] fluoroquinolone derivatives[58] and clofazimine derivatives.[55,59]

Because so many *in vitro* screening methods have been reported, it is of great urgency that highly specific and sensitive methods be identified. It is possible that in future more than one method will be employed simultaneously, such as a combination of palmitic acid oxidation and ATP measurements.[33,56] The evaluation of the methods must be conducted 'blindly', by testing a series of coded compounds by the respective investigators who developed the techniques. At the same time, independent assessments and verifications by other investigators are also needed.

The *in vitro* method may serve the purpose of primary drug screening and in the detection of secondary drug resistance,[42,56,57] but certainly the compounds found to be active *in vitro* should not yet be tested in humans. Besides the study of pharmacokinetics and toxicities, the activity against *M. leprae* must be firmly established in the mouse footpad system prior to the initiation of a clinical trial.

New drugs with bactericidal activity against *M. leprae*

FLUOROQUINOLONES

The fluoroquinolones inhibit bacterial DNA gyrase, a target which had never been exploited in leprosy chemotherapy. In view of the strong activities against Gram-positive microorganisms and the pharmacokinetic properties, we have tested, in the mouse footpad system, the activities against *M. leprae* of three major commercially available derivatives: ciprofloxacin, pefloxacin and ofloxacin. It turned out that ciprofloxacin was inactive even in the dosage of 150 mg/kg daily by continuous method, mainly because of its unfavourable pharmacokinetic properties;[28] pefloxacin 150 mg/kg daily displayed bactericidal activity;[28] ofloxacin 50 mg/kg daily exerted the same effects as pefloxacin 150 mg/kg daily, and ofloxacin 150 mg/kg daily displayed profound killing activity.[30] These observations, confirmed by other investigators,[58,60,61] represented the first lead to an important new antileprosy drug in many years.

As a first clinical trial of a fluoroquinolone derivative in leprosy, 10 previously untreated lepromatous patients (two-fifths of them with primary dapsone resistance) were treated with pefloxacin 400 mg twice daily for 6 months.[29] Definite clinical improvement was observed in all 10 patients as early as 2 months after beginning treatment, and the morphological index (MI) has also drastically decreased to the baseline during the same period. The rapid bactericidal effects, as measured by serial mouse footpad inoculations with organisms recovered from biopsies taken before and at different intervals during treatment, were demonstrated to the extent that about 99% of the bacilli were killed during the first two months of treatment. However, the bacterial load (in terms of the bacterial index (BI) and the number of acid-fast bacilli per mg of tissue) of the patients was only moderately reduced. The side-effects were mild, and the patients tolerated the treatment well.

The second clinical trial was to compare the therapeutic effects and side-effects

between pefloxacin 800 mg and ofloxacin 400 mg once daily among 21 previously untreated lepromatous cases.[31] The trial consisted of two parts: monotherapy from Day 1 to Day 56 except stopping treatment from Day 2 to Day 6; and combined with WHO/MDT regimen for MB leprosy from Day 57 to Day 180. The clinical improvement, and the evolution of MI and BI during monotherapy with either compound were virtually the same as had been observed in the first trial. The most important observation was the demonstration of rapid bactericidal activities of both treatments by serial mouse footpad inoculations with immunologically intact (normal) and congenitally athymic (nude) mice. Although a single dose of pefloxacin or ofloxacin only displayed a modest degree of bactericidal effect, about 99·99%, or 4 'logs', of organisms viable on Day 0 were killed by 22 doses of either treatment, and no significant difference could be detected between the two regimens.[31] Except for rifampicin, no other drugs thus far tested in humans have demonstrated such a degree of bactericidal activity. The side-effects were rare and mild, except one patient who developed a psychic disorder after 21 doses of pefloxacin monotherapy. All patients tolerated extremely well the combination of fluoroquinolone plus WHO/MDT.

As it has been demonstrated that 4 'logs' of viable *M. leprae* (more or less the same amount of rifampicin-resistant mutants present in a lepromatous patient before treatment) have been killed after 22 daily doses of either pefloxacin or ofloxacin; and by definition, rifampicin-resistant mutants should be killed by fluoroquinolone at the same speed as rifampicin-susceptible organisms, thus, all the rifampicin-resistant mutants may be eliminated after 22 doses of either pefloxacin or ofloxacin. It is, therefore, possible that the combination of ofloxacin and rifampicin may considerably shorten the required duration of MDT. A multicentric field trial is being organized to test the hypothesis.

The fluoroquinolones are rapidly developing,[62] with many new compounds appearing that might be more active against *M. leprae* than pefloxacin/ofloxacin. It is important to be on the alert for new compounds with lower MICs against Gram-positive organisms, or those with favourable pharmacokinetic properties. Recently it was reported that 7 newer fluoroquinolones, i.e. AT-4140, OPC-17100, OPC-17066, PD-117596, PD-124816, PD-127391 and WIN 57273, were more active against *M. leprae in vitro* than ofloxacin.[58] Further *in vivo* evaluations of these agents are required to determine their potential for the treatment of leprosy.

MINOCYCLINE

Among the tetracyclines, minocycline is unique in being active against *M. leprae*,[32,63] probably because its lipophilic properties allow it to penetrate the cell wall of *M. leprae* more effectively than other tetracyclines. Two tetracyclines, doxycycline and minocycline, have been tested in the mouse footpad system because of their greater *in vitro* activities against certain microorganisms included slow-growing mycobacteria. Doxycycline was inactive. However, by kinetic method and proportional bactericidal method, 0·01% (wt/wt) dietary minocycline was bacteriostatic, and higher dietary concentrations of minocycline, i.e. 0·02% to 0·04%, were bactericidal; minocycline combined with dapsone, kanamycin and rifampicin resulted in 'additive' antimicrobial activity against *M. leprae*; and the minimal inhibitory concentration (MIC) of minocycline against *M. leprae* was estimated at about 0·2 μg/ml, which is considerably less than levels (2–4 μg/ml) easily obtained in plasma and tissues of patients treated with customary doses.[32] We have also

demonstrated strong bactericidal activity in mice treated with 20 daily doses of 25 mg/kg minocycline by a proportional bactericidal test (unpublished observation). Because minocycline is an established antimicrobial and it seems to be safe in the long-term therapy of acne,[32] clinical trials are being conducted, aiming to evaluate the bactericidal activity of minocycline 100 mg daily in previously untreated lepromatous patients.

MACROLIDES

It was reported that erythromycin at ≥ 2 μg/ml was active against *M. leprae* by several *in vitro* methods,[33,53,54,56] but failed to inhibit the multiplication of *M. leprae* in mouse footpads probably due to its poor pharmacokinetics in mice.[33] In any case, erythromycin has no future in the treatment of human leprosy because of the need for daily multiple dosing due to its short half-life. Recently several semisynthetic macrolides, included azithromycin, clarithromycin, roxithromycin, M-119-31 and M-119-49, have been tested by *in vitro* methods, radiorespirometric assay of palmitic oxidation[56] and ATP assay.[54] These newer macrolides have superior acid stability and serum half-life as compared with erythromycin. Azithromycin was less active than, and M-119-49 had similar activity to, erythromycin; M-119-31 and roxithromycin appeared somewhat more active; whereas clarithromycin was the most active compound, causing significant inhibition at 0·125 μg/ml. When the drugs were administered at 0·01% (wt/wt) in the diet by kinetic method, probably also due to poor pharmacokinetics, roxithromycin was unable to inhibit the multiplication of *M. leprae* in mouse footpad as erythromycin, whereas clarithromycin demonstrated strong bactericidal activity against *M. leprae*. We also demonstrated the bactericidal activity in mice treated with 20 daily doses of 12·5–50 mg/kg clarithromycin by proportional bactericidal test (unpublished observation). It was estimated that the dietary concentration of 0·01% clarithromycin in mice corresponds to 100 mg daily in humans,[33] which is far lower than the clinically tolerated doses, 250 to 500 mg twice daily. Because clarithromycin is well tolerated in phase II and III clinical trials for various clinical conditions, clinical trials with different doses of clarithromycin among previously untreated lepromatous cases are being conducted.

PHENAZINE DERIVATIVES

Clofazimine, a phenazine derivative, is one of the important components of MDT regimen for MB leprosy because of its bactericidal activity against *M. leprae* and its anti-inflammatory effects in preventing and controlling type 2 reaction (erythema nodosum leprosum). A problem is the skin coloration it caused. Recently, a series of phenazine derivatives have been synthesized that do not result in skin coloration. Structure-activity relationships of 12 phenazines against *M. leprae* have been investigated by using *in vitro* radiorespirometric assay.[55] Most of the chlorinated phenazines were considerably more active *in vitro* than clofazimine. Because the most active compounds, such as B4019 and B3786, contained a 2,2,6,6-tetramethylpiperidine (TMP) substitution at the imino nitrogen,[55] the effect of substitution at the para position of phenyl and anilino groups in TMP-substituted phenazines was further assessed.[59] All of the tested TMPs were clearly more active *in vitro* than clofazimine, and the most active compound was the bromine-substituted TMP (B4076) and a trichlorinated analog (B4090). The efficacies of the highly active derivatives require *in vivo* confirmation. A few compounds have already been tested

in mice and the preliminary results were not very encouraging.[59] Although B4019 has completely inhibited the multiplication of *M. leprae* when administered at 0·01% (wt/wt) in the diet, clofazimine remains the only phenazine to inhibit *M. leprae* at 0·001% by kinetic method. It was thought that the disappointing results were largely due to pharmacokinetic properties, in particular low lipophilicity, and the lipophilicity of phenazines was responsible for skin coloration. If the assumption has been confirmed, it seems difficult to develop a nonpigmented phenazine with superior *in vivo* activity against *M. leprae* which may substitute for clofazimine in the treatment of leprosy.

RIFAMYCIN DERIVATIVES

In the mouse footpad system, strong bactericidal activities have been demonstrated by several rifamycin derivatives included rifabutin (LM 427),[64–66] rifapentine (DL 473)[66–69] and R-76-1 (isobutylpiperazinylrifamycin SV).[69] All these derivatives were more effective on a weight for weight basis than rifampicin. The greater activity of rifapentine is apparently due to its much longer half-life; and the favourable results of rifabutin and R-76-1 are probably due to their greater intrinsic activities. A pilot clinical trial has demonstrated that R-76-1150 mg daily was very active among 20 lepromatous cases.[69] However, because no difference on bactericidal activity could be detected between rifampicin 600 mg daily or intermittent therapy,[14] the new derivatives could contribute significantly to the treatment of leprosy only if they are active against rifampicin-resistant strains of *M. leprae*. Although it was reported earlier that rifabutin was active against rifampicin-resistant *M. leprae*,[65] unfortunately, this has not been confirmed in further experiments (unpublished data). Therefore, it is unlikely that the available rifamycin derivatives may further improve the efficacy of the current MDT regimen.

OTHER ANTIBIOTICS

Among beta-lactam antibiotics, cephaloridine, cephaloglycin, 7-aminocephalo-sporanic acid, cefuroxime and cefoxitin displayed various degree of bactericidal-type activity against *M. leprae* by kinetic method in the mouse footpad system.[70,71] It was thought that these antibiotics interfere with the cell-wall synthesis of *M. leprae*. However, except cephaloglycin (a drug no longer produced), most of the active beta-lactams must be administered by injection, and the injections have to be repeated frequently because of their short half-lives. Therefore, the prospect of applying the beta-lactam antibiotics for the treatment of leprosy is bleak.

With respect to aminoglycosides, streptomycin was found to be purely bacteriostatic[35] or to have varying degrees of bactericidal activity[72,73] against *M. leprae* in mice. An intraperitoneally injection of kanamycin or amikacin 100 mg/kg daily also showed impressive killing, but a 20 mg/kg daily injection of gentamicin or tobramycin were much less active.[73] Recently, because the high doses of aminoglycosides might be toxic the efficacy of lower dosages and intermittent therapy was evaluated. It was reported that reducing the dosage to 12·5 mg/kg 5 times a week or reducing the frequency of administration to 100 mg/kg once a week, streptomycin exerted a decreased but still significant bactericidal activity, and kanamycin no longer displayed bactericidal activity. In addition, once-monthly rifampicin plus streptomycin was more active than either drug alone.[74] Nevertheless, because streptomycin has to be administered by injection, it is unlikely that it might be used as a component of an MDT regimen in the field.

Clinical trial in measuring the therapeutic effect of new antileprosy drugs and new MDT regimens

The major objectives of a clinical trial are to evaluate the efficacies and side-effects of the treatment. Here, we are focusing on the techniques related to the monitoring of the therapeutic effects.

Clinical assessment and evolution of BI during chemotherapy were the most important parameters in earlier trials. Although a definite clinical improvement was observed in previously untreated lepromatous patients during treatment with all established antileprosy drugs and other new compounds such as pefloxacin,[29,31] ofloxaxin[31] and R-76-1,[69] the assessment of clinical improvement is very much subjective and difficult to quantify for comparison. The BI reflects the total bacterial load including both dead and viable organisms. Because the great majority of bacilli were dead even before treatment,[29,31] and also because the dead organisms persisted in the tissue and were eliminated by a process unrelated to the antimicrobial activity of the treatment; the reduction of BI did not differ significantly between dapsone monotherapy and MDT or other rifampicin-containing regimens although it is well known that rifampicin is far more bactericidal than dapsone. The MI was a major development in measuring the proportion of viable *M. leprae* in the host, and clinical trials based on changes of MI permitted identification of effective drugs after treatment of small numbers of patients for only a few months. Nevertheless, the technique is difficult to standardize and to perform with accuracy; also because it is difficult to examine more than 50–100 organisms, it may monitor a decrease in proportion of viable organisms by no more than 90%, or one 'log'.[75,76] These parameters are still useful in clinical trials, but they are not sensitive enough to evaluate more accurately and precisely the bactericidal activities of treatments.[76]

Serial mouse footpad inoculations have been applied as one of the most efficient techniques, in the sense that it needs the fewest patients for monitoring the rate of the 'initial killing' of *M. leprae* during treatment with individual drugs or combinations of drugs in short-term trials among MB leprosy.[75] *M. leprae* are recovered from biopsies taken at different intervals before and during treatment from a skin lesion and are inoculated into normal mice for assessing their viability. Because the technique involves examination of a much larger number of organisms than does measurement of the MI, if the proportions of viable organisms in the bacterial population have been carefully titrated on different occasions by inoculating groups of mice with several 10-fold diluted inocula prepared from each biopsies, it allows to measure the bactericidal activity of the treatment up to 99% to 99·9%, two or three 'logs' depends upon the proportion of viables before treatment.[29,31] The sensitivity of measuring the killing cannot be further improved by using normal mice because of the limited inoculum size, i.e. 5×10^3 to 1×10^4 organisms per footpad. To improve the sensitivity, one has to inoculate more organisms into immunocompromized rodents: thymectomized-irradiated (TR) mice,[77] neonatally thymectomized (NT) rat[78] and nude mice.[79,80] Up to now, these immunocompromised rodents have been employed only in a limited number of trials,[14,31,81–84] but their superiority in detecting a small proportion of viable organisms have been clearly demonstrated. Because nude mice are extraordinarily susceptible to infection by *M. leprae*,[85] as many *M. leprae* as are available can be inoculated. In our recent clinical trial for testing pefloxacin and ofloxacin,[31] we inoculated both normal and nude mice with

different dilutions of bacterial suspensions prepared from biopsies taken on several occasions. It was possible to measure the killing rate up to four or even five 'logs', depending upon the proportion of viables in the pretreatment biopsies and the maximum available amounts of organisms for nude mice inoculation.

Nevertheless, the disadvantages in applying the serial footpad inoculations are evident. It is time-consuming, it takes at least 12 months to obtain the results; it requires many animals to monitor a single trial, and the application of nude mice enormously increases the costs because the purchase and maintenance of nude mice are very expensive. In addition, because no more than 10^6 organisms per mg of tissue can be recovered from biopsies of advanced lepromatous patients, and the small size of mouse footpads severely restricts the volume of inoculum, even with nude mice, at best one can measure the initial five 'logs' killing among lepromatous patients who may have 10^{10} viables organisms before treatment.[31] It has already been proved that TR mice[14] and NT rats[82] are not sensitive enough to evaluate precisely and to compare the extraordinarily rapid and strong bactericidal effects of various rifampicin-containing regimens; although nude mice have not been used for such comparison but, based on the available knowledge, they are unlikely to be able to detect any difference after a few doses of treatment with rifampicin. It seems none of the existing rodent systems are able to monitor the therapeutic effects of any regimen containing more than one strong bactericidal drug, such as the combination of rifampicin and ofloxacin. Apparently, more rapid, simple and sensitive systems should be developed for measuring the killing of *M.leprae* by the treatment. It is unclear whether or not any of the above mentioned *in vitro* systems can meet the requirements because, to our knowledge, none of the systems has been tested in a clinical trial for monitoring the bactericidal effects of the treatment. Nevertheless, in view of the rationales and the procedures of these methods, it is unlikely that the available *in vitro* methods may be as sensitive as mouse inoculation in detecting a tiny proportion of viables among dead organisms. Recently, it has been reported that small numbers of *M. leprae* ($\sim 10^2$) can be detected by a simple procedure based on polymerase chain reaction (PCR).[86] In comparison with serial mouse (normal and nude) footpad inoculations, studies are being carried out by us to determine whether or not the *M. leprae* detected by PCR are viable organisms.

The other method for monitoring the therapeutic effects of treatment is to follow-up the relapse rate after stopping treatment. In MB leprosy, the relapse rate is thought to be proportionally correlated with the number of viable organisms at the time when the treatment is stopped, and therefore the relapse rate may reflect the bactericidal activity of the treatment. Under present circumstances, this seems to be the most reasonable approach to evaluate new combined regimen(s) containing more than one strong bactericidal drug. Unlike the footpad inoculation which requires a certain amount of organisms and therefore can be applied only for the trials of MB leprosy, this approach may also be employed for monitoring the therapeutic effects of treatment in PB leprosy; although it is still unclear whether or not the relapse in PB leprosy does reflect the treatment failure and is caused by the remultiplication of viable organisms.

The trials should be conducted as a double blind. Because the relapse rate after completion of MDT is already low and the relapse in MB leprosy after treatment with rifampicin-containing regimens may occur late,[20] in order to prove that the new combined regimen(s) is as good as or even better than the current MDT regimens, the sample size must be sufficiently large and the follow-up should be long enough. Patients should be

allocated randomly, and each regimen should have at least 500 patients which will be followed-up after 7 years in MB trials and 5 years in PB trials after completion of the treatment. The MB patients should have active, skin-smear positive lesions, and must be either previously untreated or only treated with dapsone monotherapy for a limited period, say, less than 12 months; the PB patients should be previously untreated, and with active skin lesions. Because it is unlikely that such amounts of patients may be recruited by any single centre within a reasonable period, e.g. 24 months, the trial is bound to be multicentric. Besides monitoring the relapse rate, the tolerance, side-effects and feasibility of the regimens will also be evaluated during the trials.

Since the assessment of the therapeutic effects of the regimens heavily depends upon the relapse rate, the criteria of relapse must be well defined in advance. In MB leprosy, relapse refers to the evidence of remultiplication of the organisms. Whenever a BI increase of at least 2+ from any single site over the previous value is detected, with or without new lesions, relapse should be suspected and a biopsy should be taken from the site for mouse footpad inoculation. Relapse will be confirmed only after viable organisms have been demonstrated in the mouse. In PB leprosy, because of the difficulties in distinguishing relapse and reversal reaction,[8,87] and also because the rapid response of reversal reaction to treatment with corticosteroid whereas relapse does not; unless the PB patient has become skin-smear positive, all suspected relapsed cases should be confirmed by corticosteroid therapeutic trial. Patients who respond well by the end of 4 weeks of corticosteroid treatment are diagnosed as having suffered from reversal reaction, and those who do not respond properly are diagnosed as relapse.

Future research activities related to chemotherapy in leprosy

Within the next five years, a substantial increase of information about the long-term therapeutic effects of the current MDT regimens will be accumulated, screening and synthesizing of new drugs will be continued and expanded, clinical trials of various new antileprosy drugs and field trials of new combined regimens will be mounted. However, the development of more powerful regimens does not necessarily result in better disease control, the key factor is to apply the effective regimens properly under routine field conditions. There is still a large gap between the number of cases who have been or are being treated with MDT and the total number of registered cases, needless to mention the gap between the former figure and the total number of estimated cases, which is probably still between 10 and 12 million in the world.[8] The gap is particularly wide in Africa, only 19% of the registered cases are under MDT as compared to 50% of cases for the rest of the world,[10] although the problem of leprosy on the African continent is significant. To control leprosy eventually, the gap should be reduced to the minimum. The weakness in the operational aspects are always the reasons that MDT cannot be implemented successfully. It appears that operational research, including health systems research and social-economic research, may provide a better understanding of the reasons of and the possible approaches to cope with the weakness in operational aspects. Unfortunately, this has been a neglected area in leprosy research,[88] therefore, all efforts should be made to promote operational research. The other important research area is related to leprosy reactions and nerve damage, which may occur during or even after MDT. Within the last two decades, there has been almost no progress either in prevention or in treatment of

these two important clinical events. Basic research leading to a better understanding of the mechanisms are needed, and appropriate animal models should be established.

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Relationships between PGL-1 antigen in serum, tissue and viability of *Mycobacterium leprae* as determined by mouse footpad assay in multibacillary patients during short-term clinical trial

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Summary In connection with a 56-day controlled clinical trial for comparing the therapeutic effects between pefloxacin and ofloxacin in 21 lepromatous patients, we have studied the relationships between PGL-1 antigen level in serum and in skin and serum PGL-1 antibody titre on the one hand, and the viability of *Mycobacterium leprae*, as measured by serial mouse footpad inoculations, and other bactericidal parameters on the other. Before and during treatment, significant correlation was found between serum PGL-1 level and the morphological index (MI), and with the number of viable organisms per mg skin tissue. However, neither serum PGL-1 antibody titre nor skin PGL-1 antigen level showed significant change during the 56-day trial. Because the reduction of serum PGL-1 level was well correlated but less pronounced as compared with the evolution of viable organisms during treatment, the serum PGL-1 antigen assay may be useful as an early indicator of response to chemotherapy in short-term clinical trial, but it is unlikely to replace mouse footpad inoculation for the evaluation of viability of *M. leprae*.

Introduction

Serial mouse footpad inoculations have been applied as the most efficient technique for monitoring the chemotherapeutic effects of antimicrobials in leprosy research.[1] Nevertheless, the system is time-consuming and expensive. In addition, even using nude mice, at best one can measure only the initial 5 to 6 logs of killing[2] far in advance, previously untreated lepromatous leprosy patients which may have 10^{10} to 10^{11} viable organisms before treatment. Obviously, a more sensitive, more rapid, and preferably more simple

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technique for measuring the changes of viability of *Mycobacterium leprae* should be developed. Several *in vitro* systems[3–6] have been reported to be able to demonstrate the viability of *M. leprae*. However, all of these methods require further investigation and independent verification on their specificity and sensitivity.

In view of the following facts: 1, phenolic glycolipid I (PGL-1) is a *M. leprae*-specific antigen[7]; 2, the techniques to measure PGL-1 antibody[8, 9] as well as antigen[10, 11] are available; and 3 high levels of PGL-1 antigen can be found in serum[10] as well as in skin[12, 13] in untreated lepromatous patients, and it was reported that the serum PGL-1 antigen decreased rapidly after commencing effective chemotherapy,[11] it is likely that PGL-1 antigen assay may be applied as an indirect index on the viability of *M. leprae* during a short-term clinical trial. In connection with a controlled clinical trial in comparing the therapeutic effects between pefloxacin (PEFLO) and ofloxacin (OFLO) among lepromatous patients,[2] we have studied the relationships between PGL-I antigen in serum and in skin on the one hand, and the viability of *M. leprae* as measured by serial mouse footpad inoculations and other bacteriological parameters on the other.

Materials and methods

1 PATIENTS

Twenty-one previously untreated lepromatous leprosy patients attending the R. Follereau Institute at Adzope, Côte d'Ivoire, were selected for the trial. The characteristics of these patients have been described elsewhere.[2] These patients were allocated randomly into two groups: 11 were treated with PEFLO and 10 were treated with OFLO.

2 PROTOCOL OF TREATMENT

The patients were treated with a single dose of 800 mg of PEFLO or OFLO on day 1, a daily dose of either 800 mg of PEFLO or 400 mg of OFLO from day 7 to day 56. At the end of the trial, they were prescribed the standard WHO multidrug therapy.[14]

3 BIOPSIES AND SERA COLLECTION

The sera and biopsies were collected on day 0 (before treatment) and on day 7, 14, 28, 56 after starting the treatment.

Prior to the treatment, for each patient 2 biopsies (biopsy 1 and 2) were taken from 2 different lesions. The biopsy containing the higher number of acid-fast bacilli (AFB) per mg of tissue and MI was selected for mouse inoculation and referred to as biopsy 1. The further sequential biopsies were taken from the same lesion of biopsy 1. All of the biopsies were sent as fresh tissues to Paris (Faculté de Médecine Pitié-Salpétrière) in refrigerated containers for inoculation.

The sera and the pieces of biopsies remaining after mouse inoculation, were kept frozen before being sent in refrigerated containers to Tahiti, for PGL-1 antigen and antibody determination.

4 MEASUREMENT OF VIABILITY OF *M. LEPRAE* BY MOUSE INOCULATION AND OTHER BACTERIOLOGICAL PARAMETERS FROM SKIN BIOPSIES

The procedure for measuring the proportion of viable organisms by inoculation into footpads of normal mice with serial dilutions of the bacterial suspension have been described.[15] In the present trial, the organisms recovered from pretreatment specimen (day 0) were inoculated into normal mice with four different dilutions (5×10^3, 5×10^2, 5×10^1, 5×10^0 AFB) per footpad; with organisms recovered from day 7 and day 28 specimens one dilution (5×10^3) was inoculated into normal mice and one dilution (maximum available number of organisms) into nude mice; whereas only one dilution (5×10^3) was used in inoculating normal mice with organisms recovered from day 14 and day 56 specimens. The proportion of viable bacilli was calculated by the analysis of median infectious dose (ID50).[1]

Before mouse inoculation the concentration of *M. leprae* in each biopsy was determined and reported as the total number of acid-fast bacilli (AFB) per mg of tissue. The morphological index (MI) of these bacilli was determined as the percentage of solid-staining bacilli.[16]

The number of viable bacilli per mg of wet tissue was calculated by multiplying the proportion of viables with the number of AFB per mg of tissue.

5 PGL-1 ANTIBODY AND ANTIGEN ASSAYS

Anti-PGL-1 IgM antibody was detected by standard ELISA test,[8] and using the synthetic trisaccharide (NTP) (Nara University, Japan) as antigen. The antibody titre was determined as the reciprocal of the last dilution of the serum giving a positive result according to a cut-off of 0·200 optical density unit determined previously.[11]

PGL-1 antigen detection in the serum was assessed according to a methodology already described.[10, 11] Briefly after extraction from 0·5 ml of lyophilized serum with a mixture of chloroform and methanol 2:1, the PGL-1 was purified by chromatography on a small florisil column and the extract issued from the column quantitated by DOT–ELISA on nitrocellulose membrane. Purified PGL-1 (Colorado State University, Fort Collins, USA, through NIAD contract No. A1 52582) was used as a standard for quantitative assay. The results were expressed in nanograms (ng) of PGL-1 per ml of serum. The sensitivity (detectability) of the test was of 6 ng/ml of serum.

The procedure of PGL-1 antigen detection in the biopsies was as follows: each biopsy was weighed wet, homogenized in phosphate saline buffer pH 7·2 and the suspension lyophilized. The following procedure of extraction and purification was the same as for the sera and the results were expressed in ng of PGL-1 per mg of tissue. The specificity of the assay was such that all the skin tissues from 5 non-leprosy individuals, obtained during plastic surgery, were negative. The sensitivity (detectability) of the test was of 0·3 ng/mg of tissue.

6 STATISTICS

The results were analysed using the software 'Statgraphics' (Uniware Products, USA). Since the sample size was relatively small and the data did not conform to a normal distribution, nonparametric methods were used.[17]

The decrease of the PGL-1 in serum and tissue for each patient during the treatment was expressed by the percentage of reduction as compared to their respective initial PGL-1 level before treatment. The comparison between the 2 groups of patients was performed using the Mann and Whitney's two-tailed U test.

The relationships between the different parameters studied were analysed using the Spearman's rank correlation coefficient r' tested by the t test of Student.

Results

1 PGL-1 ANTIGEN AND ANTIBODY BEFORE THE TREATMENT

Two sets of pretreatment results related to the number of AFB per mg of tissue and MI were available. The mean number of AFB per mg tissue and the mean MI were calculated and used for the correlation analysis.

Anti-PGL-1 IgM antibody

All 21 patients were anti-PGL-1 IgM positive before treatment, and the antibody titres varied from 2000 to 128,000. The geometric mean titre for those patients was 14,020. The correlations between anti-PGL-1 antibody and the number of AFB per mg tissue, MI and the number of viable bacilli per mg of biopsy were analysed. The Spearman's coefficient r' was respectively 0·35 ($p=0·11$); 0·26 ($p=0·24$) and 0·34 ($p=0·12$). None of these correlations was statistically significant.

PGL-1 antigen in the serum

The results of PGL-1 antigen levels in the serum are presented in Table 1. The PGL-1 concentration for the 21 patients ranged from 125 to 8000 ng/ml, and the geometric mean level was 1357 ng/ml. In 4 of these patients the organisms recovered from their pretreatment biopsies failed to infect normal mice, but still low levels of PGL-1 could be demonstrated in their serum (125 to 500 ng/ml). We have studied the correlations between PGL-1 versus number AFB per mg tissue, MI and the number of viable bacilli per mg tissue, respectively. The Spearman's rank coefficient r' was calculated and corresponded respectively to 0·45 ($p=0·043$), 0·63 ($p=0·0044$) and 0·82 ($p=0·0003$). The correlation between the level of PGL-1 in the serum and the number of viable bacilli was of highest significance as compared to the correlation with the MI or the AFB per mg tissue.

No correlation was found between circulating PGL-1 antigen and anti-PGL-1 IgM in these 21 patients ($r'=-0·12$, $p=0·587$).

PGL-1 antigen in the skin biopsies

The PGL-1 antigen was determined on a small piece of skin tissue remaining after mouse inoculation. It could be done for 17 of the 21 patients studied. Two biopsies at day 0 were available for 14 of these 17 patients, a total of 31 samples were then tested, and their wet weight ranged from 7 to 25 mg. Table 2 showed that all of the pretreatment biopsies tested were positive for PGL-1 antigen ranging from 5 to 8889 ng/mg, the geometric mean level was 200 ng/mg. Two (from patients nos 4 and 13) of the 4 biopsy specimens which failed to

Table 1. PGL-1 in serum, mean morphological index (MI), mean AFB/mg and number of viable bacilli in 21 MB patients before treatment

Patient no.	PGL-1 ng/ml	Mean* MI %	Mean* AFB/mg	Number viable† bacilli/mg
1	1250	25·5	$5{\cdot}5 \times 10^5$	10380
2	4000	17·5	$2{\cdot}5 \times 10^6$	55000
3	500	6	$1{\cdot}1 \times 10^6$	< 70
4	125	5·5	$1{\cdot}1 \times 10^6$	< 70
5	1000	6	$2{\cdot}1 \times 10^6$	2760
6	125	6	8×10^4	< 5
7	2000	7	$1{\cdot}5 \times 10^6$	340
8	8000	38	$1{\cdot}5 \times 10^6$	4350
9	1000	6	$2{\cdot}7 \times 10^6$	450
10	2000	36	3×10^5	69000
11	4000	19·5	$7{\cdot}5 \times 10^5$	173000
12	5000	21	$2{\cdot}5 \times 10^5$	690000
13	156	4	3×10^5	< 18
14	8000	14·5	$5{\cdot}7 \times 10^5$	173000
15	833	12	9×10^5	1384
16	1333	25·5	1×10^6	13800
17	2666	5·5	$1{\cdot}5 \times 10^6$	34600
18	3333	16	$1{\cdot}8 \times 10^6$	8400
19	666	24·5	$3{\cdot}5 \times 10^4$	87
20	375	1·5	3×10^5	2760
21	8000	30·5	$1{\cdot}5 \times 10^6$	275000

* Mean values obtained from biopsies 1 and 2.

† Derived from mouse footpad inoculation results of biopsy 1.

Spearman's coefficient of correlation:

PGLS/Mean MI 0·62 ($p = 0{\cdot}0044$)

PGLS/Mean BI 0·45 ($p = 0{\cdot}043$)

PGLS/No. viable bacilli 0·82 ($p = 0{\cdot}0003$).

infect mice were available for PGL-1 testing and they showed a significant amount of PGL-1. The AFB per mg tissue of these 2 biopsies were respectively 2×10^6 and 4×10^5.

The correlations between the skin PGL-1 and the AFB per mg tissue and the number of viable bacilli per mg tissue were statistically significant: the Spearman's coefficient r' was respectively 0·56 ($p = 0{\cdot}002$) and 0·659 ($p = 0{\cdot}01$). There was also a significant correlation between the level of PGL-1 antigen found in the skin and in the serum: $r' = 0{\cdot}68$ ($p = 0{\cdot}008$). Conversely, the PGL-1 level in the tissue was not found to be correlated with the MI of the bacilli recovered from the same biopsy specimen ($r' = 0{\cdot}198$, $p = 0{\cdot}276$).

2 EVOLUTION OF PGL-1 ANTIGEN AND ANTIBODY LEVELS DURING TREATMENT

The 4 patients (nos 3, 4, 6 and 13) in which no detectable viable organisms were demonstrated in their pretreatment biopsies were removed from the study. Therefore the analysis included the data obtained from 9 patients treated with PEFLO and 8 patients treated with OFLO.

Table 2. PGL-1 in skin biopsy, morphological index (MI), AFB/mg and viable bacilli in 17 MB patients before treatment

Patient No.	PGL-1 ng/mg		MI %		AFB/mg		Number viable bacilli/mg biopsy 1*
	Biopsy 1	Biopsy 2	Biopsy 1	Biopsy 2	Biopsy 1	Biopsy 2	
1	238	109	26	25	6×10^5	5×10^5	10380
2	870	500	28	7	2×10^6	3×10^6	55000
3	ND	52	4	8	2×10^6	2×10^5	< 70
4	294	62	5	6	2×10^6	2×10^5	< 70
7	250	227	8	6	2×10^6	1×10^6	340
9	952	526	5	7	5×10^6	4×10^5	450
10	416	278	47	25	5×10^5	1×10^5	69000
11	8889	147	18	21	1×10^6	5×10^5	173000
12	869	113	26	16	2×10^6	3×10^6	690000
13	73	139	5	3	4×10^5	2×10^5	< 18
14	588	125	15	15	1×10^7	4×10^5	173000
15	119	200	15	9	8×10^5	1×10^6	1384
17	455	108	5	6	2×10^6	1×10^6	34600
18	104	ND	9	23	3×10^6	3×10^5	8400
19	5	12	23	26	1×10^4	6×10^4	87
20	16	192	3	0	4×10^5	1×10^5	2760
21	2857	ND	40	21	1×10^6	2×10^6	275000

ND, not done.
* Derived from mouse footpad inoculation results of biopsy 1.
Spearman's coefficient of correlation:
PGLB/MI 0·198 ($p = 0·276$)
PGLB/BI 0·56 ($p = 0·002$)
PGLB/No. viable bacilli 0·659 ($p = 0·01$).

Evolution of Anti-PGL-1 IgM antibody

As compared to the initial level, no significant change of anti-PGL-1 IgM titre was observed in any of the patients during the 56 days of the trial.

Evolution of PGL-1 antigen in the serum

The evolution of the PGL-1 levels are represented in Table 3. The percentage of decrease of the PGL-1 level on days 7, 14, 28 and 56 was calculated for each patient, as compared to their level before treatment. Then the median of the percentage of reduction for each group was obtained. For both groups of patients this median of reduction decreased gradually, and reached 87% for PEFLO and 85% for OFLO on day 56. No significant difference in the PGL-1 reduction was found between the 2 groups using the Mann–Whitney's U test ($\Sigma < 0·01$, $p > 0·99$).

Evolution of PGL-1 antigen in the skin

Table 4 presents the individual results of the PGL-1 from sequential biopsies in 14 patients (8 treated with PEFLO and 6 treated with OFLO) from whom enough skin tissue was available after mouse inoculation. The percentage of decrease of the PGL-1 was calculated for each patient, as compared to the level before treatment. The medians of the

Table 3. Evolution of PGL-1 antigen in the serum of multibacillary patients treated either with ofloxacin or pefloxacin

Patient No.	PEFLO (P) or OFLO (O)	PGL-1 in ng/ml (percentage of reduction as compared to level before treatment)				
		Before treatment	Day 7 1 dose	Day 14 8 doses	Day 28 22 doses	Day 56 50 doses
1	O	1250 (0)	—	4000 (−220)	2000 (−60)	500 (60)
2	P	4000 (0)	—	1000 (75)	1000 (75)	500 (87,5)
5	P	1000 (0)	—	—	1000 (0)	280 (72)
7	O	2000 (0)	—	—	1000 (50)	375 (81,25)
8	O	8000 (0)	—	—	2000 (75)	500 (93,75)
9	P	1000 (0)	500 (50)	250 (75)	125 (87,5)	125 (87,5)
10	P	2000 (0)	500 (75)	250 (87,5)	250 (87,5)	—
11	P	4000 (0)	4000 (0)	2000 (50)	1000 (75)	190 (95,25)
12	P	5000 (0)	4000 (20)	8000 (−60)	4000 (20)	1000 (80)
14	O	8000 (0)	1000 (87,5)	4000 (50)	1000 (87,5)	333 (95,85)
15	O	833 (0)	500 (40)	500 (40)	416 (50)	292 (64,95)
16	O	1333 (0)	500 (62,5)	1000 (25)	333 (75)	141 (89,4)
17	P	2666 (0)	4000 (−50)	4000 (−50)	500 (81,25)	333 (87,5)
18	P	3333 (0)	1000 (70)	2000 (40)	500 (85)	250 (92,5)
19	O	666 (0)	1000 (−50,15)	500 (24,9)	125 (81,2)	62 (90,7)
20	O	375 (0)	250 (33,3)	250 (33,3)	125 (66,7)	125 (66,7)
21	P	8000 (0)	8000 (0)	8000 (0)	8000 (0)	833 (89,6)
Median of % reduction for PEFLO ± CL*		0%	−20 ± 42%	45 ± 56%	75 ± 34%	87 ± 4%
Median of % reduction for OFLO ± CL*		0%	40 ± 20%	29 ± 10%	71 ± 16%	85 ± 15%

* Confidence limit of median.

Difference of PGL-1 reduction between the 2 groups using the Mann–Whitney U-test was not significant.

percentage of reduction for both groups of patients were obtained: these figures were found to fluctuate with large confidence limits. It should be noted that the number of samples tested was small for each series (4 to 6 samples). The PGL-1 level in the skin tissue was not likely to decrease in both groups of patients during the 56 days' trial. Simultaneous testing of different parts of a same biopsy showed a great variability of PGL-1 concentration from one part to another part of a lesion (results not reported), and probably explained some extensive variations observed in sequential biopsies of the same patient.

3 RELATIONSHIPS BETWEEN THE REDUCTION OF PGL-1 IN SERUM, THE REDUCTION OF MI AND THE KILLING RATE OF *M. LEPRAE* DURING THE TREATMENT

The complete clinical and bacteriological results of this study are reported elsewhere.[2]

Relationships between the reduction of PGL-1 in the serum and the reduction of the MI

In the current trial, the MI fell gradually and significantly during the treatment in both groups of patients.[2] Because the relationships between the reduction of PGL-1 and the

Table 4. Evolution of PGL-1 antigen in the skin tissue of multibacillary patients treated either with ofloxacin or pefloxacin

		PGL-1 in ng/ml (percentage of reduction as compared to level before treatment)				
Patient	PEFLO (P) or OFLO (O)	Before treatment	Day 7 1 dose	Day 14 8 doses	Day 28 22 doses	Day 56 50 doses
1	O	238 (0)	192 (19,3)	208 (12,6)	—	113 (52,5)
2	P	870 (0)	588 (32,4)	1176 (−35,2)	—	—
7	O	250 (0)	—	104 (58,4)	250 (0)	192 (23,2)
9	P	952 (0)	1000 (−5)	357 (62,5)	—	—
10	P	416 (0)	—	—	—	54 (87)
11	P	8889 (0)	1176 (86,8)	555 (93,8)	625 (93)	—
12	P	869 (0)	—	—	500 (42,5)	—
14	O	588 (0)	250 (57,5)	769 (−30,8)	192 (67,3)	—
15	O	119 (0)	217 (−82,3)	89 (25,2)	—	108 (9,2)
17	P	455 (0)	454 (0,2)	178 (60,9)	400 (12,1)	—
18	P	104 (0)	192 (−84,6)	119 (−14,4)	147 (−41,3)	—
19	O	5 (0)	166 (−33,20)	—	3 (40)	15 (70)
20	O	16 (0)	18 (−12,5)	—	—	12 (25)
21	P	2857 (0)	1666 (41,7)	—	138 (95,2)	—
Median of % reduction for PEFLO ± CF*		0%	16 ± 30%	61 ± 54%	42 ± 57%	—
Median of % reduction for OFLO ± CF*		0%	−12 ± 71%	19 ± 40%	40 ± 61%	25 ± 20%

* Confidence limits of median.

Difference of PGL-1 antigen reduction between the 2 groups using the Mann–Whitney U-test was not significant.

reduction of the MI were independent from treatment, the data from the 17 patients were pooled for analysis. The Spearman's rank coefficient of correlation so obtained was $r' = 0{\cdot}46$ ($p = 5 \times 10^{-4}$).

Relationship between the decrease of PGL-1 in the serum and the reduction of number of viable bacilli

The number of viable *M. leprae* defined by their ability to multiply in mice before and during treatment and the median of the killing rate (percentage of viables killed) were calculated for each group of patients.[2] As the killing rate obtained from the OFLO group was not significantly different from that obtained from the PEFLO group, the data from all the 17 patients were gathered. The evolution of the number of viable organisms per 10^6 AFB during the course of treatment with PEFLO or OFLO was summarized in a single regression equation: $Y = -0{\cdot}175X + 3{\cdot}9168$. Similarly, the regression equation of the evolution of PGL-1 per ml of serum was obtained as below: $Y = -0{\cdot}0172X + 3{\cdot}286$. According to the slopes of these two equations, the speed of reduction of the viable *M. leprae* was about 10 times higher than the speed of reduction of the PGL-1 in the serum. Figure 1 presents the evolution of the number of viables (in $\log_{10}$) and the evolution of PGL-1 (in $\log_{10}$) in the serum from 8 doses (day 14) to 50 doses (day 56) of PEFLO or

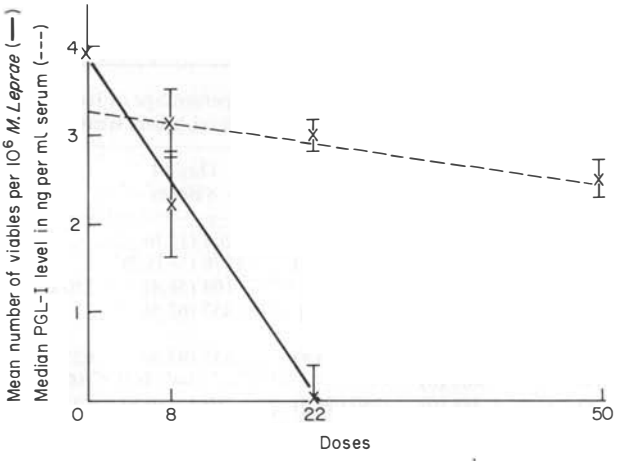

Figure 1. Evolution of the PGL-1 antigen in the serum and of the number of viable *M. leprae* in multibacillary patients, according to the number of doses of pefloxacin or ofloxacin. Equation for PGL-1 regression line: $Y = -0{\cdot}0172x + 3{\cdot}286$. Equation for number of viables regression line: $Y = -0{\cdot}175x + 3{\cdot}916$.

OFLO. The data after 1 dose (day 7) were not presented because both parameters were not significantly different from before treatment.

Discussion

Before starting chemotherapy, the IgM antibody titre to PGL-1 antigen varied widely in the 21 lepromatous patients, and therefore confirmed what we have observed previously.[11] The variation was not correlated with the bacterial load in the hosts, and was neither correlated with MI nor with the number of viable organisms measured by mouse footpad inoculation. The wide variation of antibody titre probably reflects the significant variation of antibody response to *M. leprae* among lepromatous patients. The anti-PGL-1 antibody titre did not show significant changes during treatment, obviously this is due to the short-term nature of the trial. As demonstrated in patients under multidrug therapy[11,18] significant reductions of PGL-1 antibody titre might be observed only after more than one year's treatment.

Prior to the treatment, the PGL-1 antigen level in the serum of lepromatous patients was also widely distributed (125 to 8000 ng/ml), however, the level was well correlated with the number of AFB/mg tissue, the MI and the number of viable organisms in the skin. Serum PGL-1 antigen could still be detected in 4 patients whose bacilli, recovered from skin biopsies, failed to infect normal mice. Nevertheless, their antigen levels (125 to 500 ng/ml) were in the lowest range of the 21 patients tested.

The detection of PGL-1 antigen in the tissue of leprosy patients or *M. leprae*-infected armadillo has been previously reported,[7,12,13] but usually required several hundred milligrammes or even grammes of the specimen and used thin layer chromatography or high pressure liquid chromatography for characterization and quantitation. In the current study we used a modified method, consisting of rapid purification on a florisil column, followed by DOT–ELISA. As small as 10 to 20 mg of skin biopsy can be

examined for PGL-1 quantitation with the modified method. Using our method we were able to detect PGL-1 in all 31 pretreatment biopsies taken from 17 lepromatous patients, including the biopsies from 2 patients in which no viable organisms could be detected by mouse footpad inoculation. The concentration of PGL-1 in the 31 samples varied from 5 to 8889 ng/mg, and it was significantly correlated with the number of AFB/mg tissue ($r' = 56, p = 0{\cdot}002$). Similar to the elimination of AFB from the tissue, the preliminary data suggested that the complete clearance of PGL-1 antigen from the tissue may take several years after starting effective chemotherapy[12] (and unpublished data). However, up to now no systematic study has been carried out to follow-up simultaneously the clearance of organisms and PGL-1 antigen from the tissue. Such a study may well be useful in providing a better understanding of the potential value of PGL-1 antigen detection and the kinetics of PGL-1 in the hosts.

Contrary to the skin PGL-1 antigen, the PGL-1 antigen levels in the serum steadily decreased during treatment with 800 mg PEFLO daily or 400 mg OFLO daily. Similar to the reduction of viable organism as measured by mouse footpad inoculation,[2] the percentage of PGL-1 reduction after 56 days' treatment, i.e. 50 doses, did not show a significant difference between the two groups (87% and 85% respectively). Because both PEFLO and OFLO displayed strong bactericidal activity against *M. leprae*,[19, 20] the decrease of PGL-1 in the serum during a few weeks of treatment with either drug was consistent with our previous observation[11] during treatment with rifampicin, another strong bactericidal agent against *M. leprae*. Moreoever, during treatment the evolution of the viable organisms and the evolution of the antigenemia showed similar trends. However, the slope of the regression line for the reduction of viable organisms was about 10 times greater than that for serum PGL-1 reduction. As compared with the reduction of viable organisms, the delay of the clearance of serum PGL-1 antigen probably related to the involvement of different mechanisms in release and elimination of the metabolite.

Although it is unclear whether or not the detected serum PGL-1 was due to the presence of *M. leprae* in the blood, or bacillemia, the relatively rapid clearance of PGL-1 from the serum and the disappearance of bacillemia during the course of effective chemotherapy was quite similar.[21, 22] Both phenomena occurred when a sufficiently large amount of PGL-1 and *M. leprae* were still available in the tissue, suggesting that the mechanisms involved in the clearance of PGL-1 and bacillemia may have some similarities. To the best of our knowledge, up to now, no study has simultaneously measured the evolution of serum PGL-1 antigen level and bacillemia. Probably this is a reasonable approach for a better understanding of the relationship of the two different phenomena.

In conclusion, because of the correlation with the viability of *M. leprae*, the serum PGL-1 antigen assay may be useful as an early indicator of response to chemotherapy in short-term clinical trial; nevertheless, it is unlikely to replace mouse footpad inoculation for the evaluation of viability of *M. leprae*.

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Anti-phenolic glycolipid 1 IgM antibodies in leprosy patients and in their household contacts

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Summary Though they have no apparent protective action, the specific antibodies are important markers of the infection with *Mycobacterium leprae*. For their detection we employed an ELISA method using as substrate a synthetic immunodominant disaccharide of phenolic glycolipid 1 antigen of *M. leprae*, conjugated with bovine serum albumin (D-BSA). Increased levels of anti-D-BSA antibodies of the IgM class were detected in 61·5% of the 13 leprosy patients and in 13·3% of their 53 household contacts, whereas they were not found in any of the 37 normal blood donors. A strong correlation ($r = -0{\cdot}846$) was found between the antibody levels and the duration of the disease among the 12 patients with lepromatous leprosy.

These preliminary data demonstrate the usefulness of this method for epidemiological studies and for the detection of cases with subclinical infection.

Introduction

The better understanding of the immune response to *Mycobacterium leprae*, the causative agent of leprosy, is very important not only in view of the production of a possible vaccine but also for the development of more sensitive serological tests.[1]

The antigenic structure of *M. leprae* has been extensively studied in the last years and a phenolic glycolipid, called the phenolic glycolipid 1 (PGL-1), has been characterized to be one of the major antigens of this microorganism.[2] The unique trisaccharide portion of this antigen, containing an immunodominant terminal 3·6-di-methylglucose residue has been found to elicit both a B cell response and a T cell suppression *in vitro*.[3]

A sensitive enzyme immunoassay has been recently developed that detects specific antibodies to the PGL-1 antigen[4] and this test has been used for epidemiological studies in different countries.[5] We applied a similar study in Albania and our preliminary data have confirmed the usefulness of this method for epidemiological purposes revealing on the other part a strong negative correlation between the antibody levels and the duration of the disease among the patients with lepromatous leprosy.

0305-7518/90/061341+06 $01.00

Materials and methods

PATIENTS

103 individuals, all from Albania, have been studied for anti-PGL-1 IgM antibodies, 58 were male and 45 female, aged from 5 to 78 years.

Among these were 12 with lepromatous leprosy (LL), 1 with tuberculoid leprosy (TL) and 53 were their close household contacts, 37 healthy blood donors were taken as a control group.

The duration of the disease in all the leprosy patients from the time of the diagnosis, until the moment of blood collection for anti-PGL-1 antibody determination varied from 1 to 33 years, mean 19·9 years (Table 1).

In all the patients treated before 1981, the treatment was started with DDS and CIBA 1906 and since 1981 multidrug therapy (MDT) was introduced, composed of rifampicin, DDS and clofazimine. This therapy has been continued for at least two years, and thereafter, every two years, the patients have received MDT for 1–3 months for the prevention of relapses. At the time of the study all the patients were negative for *M. leprae* in skin biopsies

The index cases of all the household contacts were either their first degree relatives or their consorts with whom they had been living in close contact for many years.

METHODS

Anti-PGL-1 antibodies of IgM isotype were determined using an indirect enzyme-linked immunoassay (ELISA). For antigen we used a synthetic disaccharide that is the immunodominant epitope of PGL-1. The disaccharide was conjugated with bovine serum albumin (D-BSA). The unconjugated BSA was used in parallel as a negative control. The antigens and the negative and positive reference sera were kindly provided by Dr H D Engers (WHO Immunology Research and Training Centre, Geneva, Switzerland).

Table 1. Leprosy patients studied for anti-PGL-1 IgM antibody levels

Patient No.	Age	Duration of disease (years)	Type of leprosy	ELISA results (%)
1	62	33	LL	11·6
2	47	20	LL	10·6
3	50	22	LL	7·6
4	65	15	LL	100·0
5	73	23	LL	9·6
6	58	32	LL	8·3
7	38	24	LL	32·5
8	48	24	LL	28·4
9	46	9	LL	162·9
10	36	18	LL	93·7
11	42	24	LL	28·9
12	78	14	LL	123·0
13	47	1	TL	25·5

The polystyrene plates were coated for 14–18 hr at 37°C with either D-BSA or BSA diluted in pH 9·6 0·1 M carbonate-bicarbonate buffer. After saturating with PBS-Tween-1% BSA for 1 hr at 37°C and washing, 100 microlitre of a 1/300 serum dilution were incubated in quadruplicate for 1 hr at 37°C. The IgM antibodies were detected using a peroxidase-labelled goat anti-human μ chain (Institute Pasteur, Paris) and revealed with orthophenylenediamine in citrate buffer pH 5·1 and in presence of H_2O_2. The reaction was stopped with H_2SO_4 and the optic densities were read on a Titertek Multiscan at 492 nm.

All the sera were run in parallel with the conjugated antigen and as well with BSA alone, and the differences of the two results were taken into consideration. The absorbances obtained with 1/300 dilution of test sera were converted and expressed in percentage in relation to the same dilution of the positive reference serum that was placed on the same plates.[6] Those sera which gave an optical density higher than 20% of the reference serum were considered to be positive.

The differences between the antibody levels of different groups were analysed using Student's *t*-test after logarithmic transformation of data. *R* coefficient was calculated for linear regression.

Results

A graphic representation of absorbances obtained with serial dilutions of a positive and a negative reference serum is shown in Figure 1. These curves and others obtained with different positive sera (data not shown) allowed us to choose a dilution of 1/300 for the anti PGL-1 IgM antibody detection since this dilution was generally found in the linear portion of the curves.

Raised levels of anti-PGL-1 IgM antibodies were observed in 61·5% of the leprosy patients, in 13·3% of their household contacts and in no one of the normal blood donors (Figure 2). The geometric means of the antibody levels in the three groups were respectively $49{\cdot}4 \pm 52{\cdot}0$, $7{\cdot}7 \pm 9{\cdot}5$ and $2{\cdot}0 \pm 3{\cdot}1$. A significant difference ($P < 0{\cdot}1$) was found between the patient's group and the group of healthy contacts, and on the other side between the last group and the normal blood donors ($P < 0{\cdot}01$).

The seven household contacts with raised levels of anti-PGL-1 IgM antibodies were found in four families where the index cases also resulted with high levels of these antibodies (Table 2). The duration time of the disease among these index cases varied from 1 to 14 years, mean 8·5 years, that is lower than the mean duration time of the disease (19·3 years) of all the leprosy patients.

We also studied the correlation between anti-PGL-1 IgM antibody levels and the duration of the disease among the 12 patients with lepromatous leprosy (Figure 3) and a strong correlation ($r = -0{\cdot}846$; $P < 0{\cdot}005$) was found between these two parameters.

Discussion

The ELISA method that we applied for the detection of antiphenolic glycolipid 1 IgM antibodies enters in the last generation of the serological tests used for the study of the *M. leprae* infections.[3] The antigen used is a synthetic disaccharide which constitutes the antigenic determinant of the phenolic glycolipid 1, one of the principal antigens of

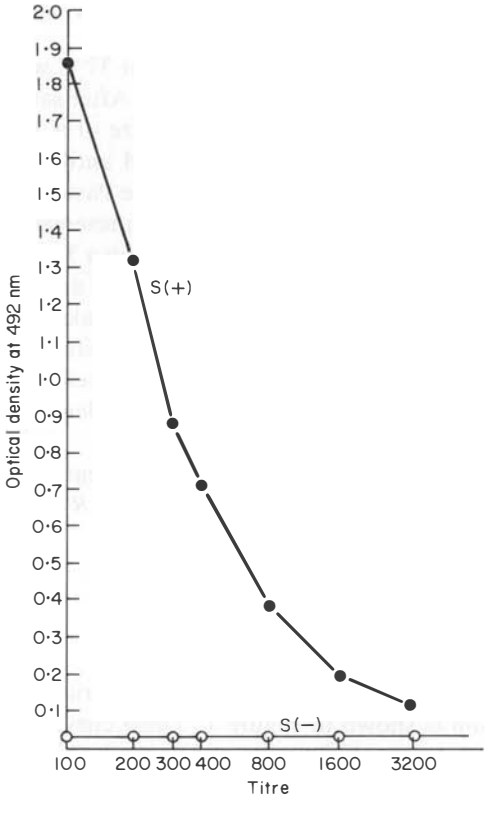

Figure 1. Titration curves of a positive S(+) and a negative S(−) reference serum.

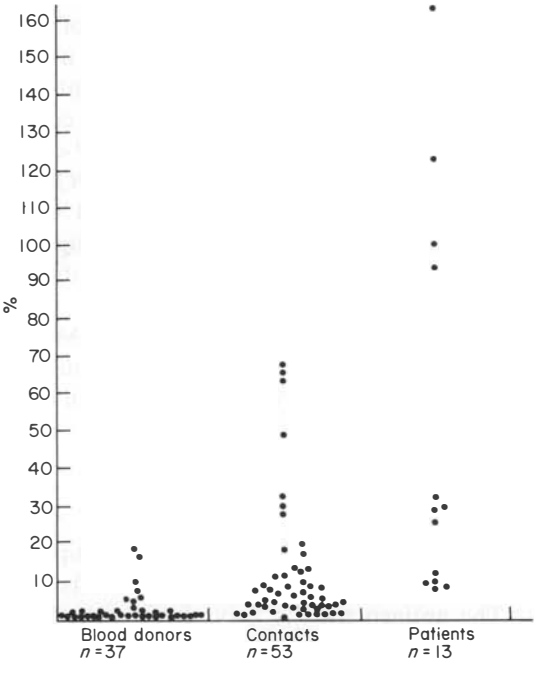

Figure 2. Anti-phenolic glycolipid I IgM antibody levels in the 3 groups of individuals studied. The data are presented in percentages in relation to the positive serum of reference estimated as 100%.

Table 2. The household contacts with raised levels of anti-PGL-1 IgM antibody and their respective index cases

Contacts				Index Cases			
Nr	Age	ELISA results (%)	ELISA results (%)	Diagnosis	Family relation with the contact	Duration of disease (years)	Patient No.
1	36	66·4	162·9	LL	husband	9	9
2	8	27·6	162·9	LL	father	9	9
3	32	49·5	—	LL	father	10	deceased
4	14	32·2	—	LL	mother	10	deceased
5	12	30·4	25·0	TL	father	1	13
6	9	65·7	25·0	TL	father	1	13
7	20	66·8	123·0	LL	father	14	12

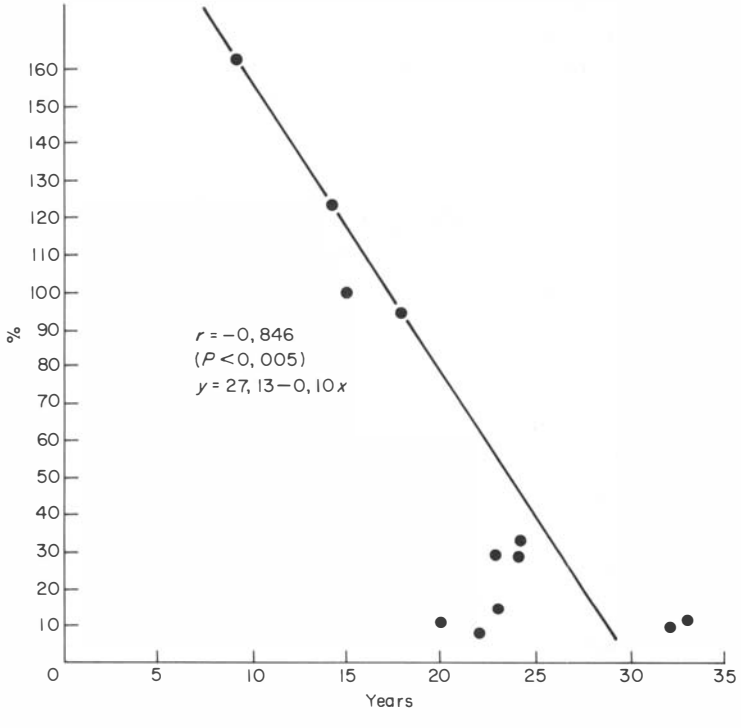

Figure 3. The correlation between anti-phenolic glycolipid I IgM antibody levels and the duration of the disease in the lepromatous patients.

M. leprae.[7-9] Its specific antibodies are mainly of the IgM class and are specific markers for this infection.[10] The specificity of this method is confirmed by the fact that we did not find detectable antibody levels in any of the normal blood donors.

The seropositivity of 61·5% in our patients that were all under treatment is comparable with the data of other authors that have found a seropositivity of 68% in

treated patients.[5] Among the household contacts the seropositivity was 13·3%. These data are lower than the frequencies of 25–35% reported from other authors in studies performed in hyperendemic areas.[11] This may be due to the fact that in our study, all the index cases were under long term treatment and with negative results for *M. leprae* from skin biopsies at the time of the study. On the other part in hyperendemic areas the household contacts may have multiple contacts with leprosy in addition to the identified index cases, whereas in Albania where the prevalence of leprosy is rather low, with a rate of 0·016 per thousand in 1988,[12] the identified index cases are probably the only source of infection.

We found a strong correlation between the antibody levels and the duration of the disease among the patients with lepromatous leprosy. This may reflect the antigen load of the patients and the effect of chemotherapy since a decrease in antibody levels during treatment has been reported.[5] This is also supported by our finding of raised levels of anti-PGL-1 antibodies only among those contacts whose index cases resulted with high antibody levels and with a mean duration of the disease that was much lower than the mean duration of all leprosy patients.

Our data support the usefulness of this method for epidemiological studies and for the detection of cases with subclinical infections.

Acknowledgments

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Positive Mitsuda lepromin reactions in long-term treated lepromatous leprosy

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Summary Twenty-four lepromatous (LL) patients, treated for 22 to 40 years with chemotherapy, including sulphones and with multidrug therapy, were tested with standard Wade–Mitsuda lepromin. Thirteen gave weak positive (3–4 mm) Mitsuda reactions, confirmed histologically in the ten whose reactions were biopsied. Six of the eleven negative reactors were partly accounted for by a history of relapse, and two others had probably taken dapsone irregularly. Eleven control LL patients, treated for less than 20 years, were uniformly lepromin negative. Spontaneous lepromin conversion appears to occur around 24 years after commencing successful chemotherapy. The late Mitsuda conversions are attributed to delayed clearance of the reservoir of bacterial antigen, but a poor correlation between Mitsuda and Fernandez positivity is not explained.

Introduction

It is generally agreed that provided a lepromatous patient, classified as LL on the Ridley–Jopling spectrum,[1] does not undergo a marked reversal (upgrading, Jopling type 1) reaction whilst receiving successful chemotherapy, he or she remains Mitsuda-negative for life.[2,3] Hitherto, this had been our own experience in following up LL patients for 10 to 12 years after commencing treatment.[4] Old LL patients who had relapsed were also invariably lepromin negative.[5] However, from 1975 onwards, we have observed a small number of undoubted LL patients who relapsed with borderline–tuberculoid (BT) lesions and in whom the lepromin test was positive.[6–8]

Therefore, it seemed important to discover whether such positive lepromin tests were only associated with fresh, though very limited, bacterial multiplication and relapse, or whether they represented a more general phenomenon. We took the opportunity, in initiating a study of immunotherapy in lepromatous leprosy, to include Wade–Mitsuda lepromin testing. Here we report on our finding that a majority of LL patients, successfully treated for about 23 years without relapse, are indeed weakly lepromin positive.

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Materials and methods

Twenty-four long-treated LL patients with no known history of reversal reaction were selected for lepromin testing during the period 1987–89 (Group 1). All had received at least 20 (range 22–40) years of chemotherapy, initially with a sulphone drug, usually dapsone, although most had recently received triple drug therapy with rifampicin and either clofazimine or a thioamide for two years. All had come under the care of the Hospital for Tropical Diseases and/or the Leprosy Study Centre, London between 1950 and 1966 and their original London biopsies were available, confirming their LL classification, although seven had commenced treatment overseas. Six had a history of relapse, 22, 22, 15, 12, 8 and 5 years before testing, although the last two consisted only of a few papules of erythema nodosum leprosum (ENL) with transitorily weakly positive smears, and smear-negative neuritis respectively. All but two relapse cases had been skin-smear negative for at least 10 years.

Two control groups were also selected. One (Group 2) consisted of 11 LL patients, of whom nine had received less than 20 (range 3 to 18) years' treatment without either reversal reaction or relapse, and two had presented with gross dapsone-resistant relapses one and eight years earlier. All 11 had completed or were receiving multidrug therapy (MDT). Two were also receiving thalidomide in low dosage to suppress mild chronic ENL. Eight of the 11 were skin smear positive.

The second control group (Group 3) consisted of six borderline–lepromatous (BL) patients of whom four had undergone mild reversal reactions. Four had received 3 to 6 years of effective MDT, including one who had relapsed with dapsone-resistant leprosy, and two had commenced treatment 14 and 22 years earlier, and were off antileprosy chemotherapy. Only one was still skin-smear positive.

The patients received a full clinical examination for leprosy, skin-smear examination from six sites including both earlobes, and lepromin testing on the flexor surface of the forearm, the site being identified by recording the distance (in mm) from the crease of the elbow. The Wade–Mitsuda lepromin was supplied by the WHO Reference Laboratory for the Microbiology of *Mycobacterium leprae*, London. All save three patients also underwent skin biopsy, and additional immunological investigations, including lymphocyte transformation tests (LTT) on their peripheral blood monocytes (to be reported elsewhere) and Mantoux skin tests. The Fernandez and Mantoux reactions were read at 48–72 hrs, and the Mitsuda reactions at 20–28 days (save for two read at two weeks and one at five weeks).

Results

1 THE MITSUDA REACTION

Of the 24 LL patients who had received 22 or more years of chemotherapy, 13 (treated for 24–40 years) gave a Mitsuda lepromin reading of 3–4 mm and were considered to be weakly positive. None of the six patients who had relapsed 22 years or less from the time of lepromin testing was positive, although the patient who had had the milder relapse 22 years earlier gave a doubtful result (a 2 mm tiny papule). A further patient who had received 22 years' treatment for mild to moderately severe disease also gave a doubtful (2

Table 1. The size of the Mitsuda reaction (diameter of area of induration) related to the type of leprosy (LL or BL), duration of treatment and history of relapse

	Number of patients			
	Size of Mitsuda reaction (mm)			
Patient group	0	2	3–4	Total
Group 1; LL, 22 or more years of chemotherapy; skin smear negative				
No history of relapse	4	1*	13	18
History of relapse	5	1†	0	6
Group 2; LL, less than 20 years of chemotherapy; or gross relapse within 20 years and skin smears positive	11	0	0	11
Group 3; BL	2	3	1*	6

* 22 years of successful treatment.
† Mild to moderate relapse 22 years earlier.

mm) result. Of the remaining four lepromin-negative patients, one had undoubtedly, and a second had probably taken treatment irregularly for many years while on dapsone monotherapy; whilst a third had suffered from chronic cholangitis and had recently undergone major bile-duct surgery.

Six of the thirteen positive (3 mm or greater) Mitsuda reactions were biopsied, and all revealed epithelioid-cell granulomas. Four other positive patients were subsequently retested; their reactions were biopsied and confirmed positive on histological examination. Patient number 12 was of particular interest, although it was 31 years since he had commenced treatment for severe LL disease, as his skin biopsy revealed empty foamy macrophages, while his 4 mm Mitsuda reaction histologically revealed epithelioid cells and Langhans giant cells.

Not one of the 11 LL control (Group 2) patients gave any detectable response to lepromin when read between 21 and 38 days. The patient who had received 18 years effective chemotherapy, including MDT, developed an episode of ENL following a single vaccination with live BCG and dead *M. leprae*. Biopsy of an ENL nodule revealed foamy macrophages with scanty granular acid-fast debris.

In the BL controls (Group 3), the lepromin responses were graded negative in five of the six patients, although in three there was a 2 mm (doubtful) reaction. The sixth, who had commenced treatment 22 years before testing, gave a 4 mm positive response, confirmed histologically.

2 THE FERNANDEZ REACTION

Of the 24 Group 1 patients, only four were Fernandez-positive with readings (diameter of induration) measuring 5 mm or greater. Of these, two had positive Mitsuda reactions and two were Mitsuda negative (including the 22-year-treated patient with a 2 mm Mitsuda reaction). In this group there appeared to be no correlation between the Fernandez and the Mitsuda readings.

In Group 2, three of the eleven patients were Fernandez positive, including one patient

who had suffered a relapse one year earlier, and whose smears were strongly positive. None of the six BL (Group 3) patients was Fernandez-positive.

3 THE MANTOUX REACTION

Of the 21 LL patients in Group 1, who were tested with 'new' tuberculin[9] containing 2 μg protein per ml, five gave completely negative reactions, including two who produced 4 mm positive Mitsuda reactions. Four gave giant tuberculin reactions[10] with readings greater than 40 mm, of whom three were Mitsuda negative.

In group 2, two patients gave no response to tuberculin, seven yielded positive responses (5–40 mm), whereas two had giant reactions; both of the last patients were receiving thalidomide to suppress chronic ENL.

All of the six BL patients (Group 3) gave a response to tuberculin, five being in the range 7–27 mm, the sixth having a 4 mm reaction.

Discussion

Leprosy has for long been considered peculiar, if not unique, among mycobacterial diseases in that specific immunodepression, once attained, was normally irreversible. This view was based on the persistence over a very long period, despite successful chemotherapy and the attainment of 'bacteriological negativity' in smears, of: 1, the lepromatous state;[5] 2, lepromin negativity;[2–4] and 3, the nonresponsiveness of lymphoproliferative assays against *M. leprae*[11] and the persistence of negative skin-test responses to *M. leprae* soluble cytoplasmic antigens.[12] The only exceptions to this general rule were the minority of lepromatous and borderline-lepromatous patients who upgraded markedly during the course of overt reversal reactions. Claims of rare lepromin conversions on attainment of clinical inactivity in the pre-sulphone era[13] almost certainly refer to borderline (probably borderline–tuberculoid) patients, and reflect the historically unavoidable lack of precision in classification at that time.

The results suggesting permanent specific anergy were based on experience of dapsone monotherapy for periods of up to 20 years. With even longer experience, and the introduction of MDT, these conclusions are shown to be valid no longer. We first noted that very long treated and bacteriologically negative patients might show clinical and histological signs of upgrading and lepromin conversion upon relapse.[6–8] Lymphocyte responsiveness was recently found to have been regained in five out of eight lepromatous patients treated for more than 20 years, being associated with the appearance of CD3+CD8− T cells, some of which appeared to be specific for *M. leprae*.[14] Here we report weak Wade–Mitsuda lepromin conversion in 13 out of 24 LL patients who had been treated for periods of 22 years or more. The conversions were confirmed histologically in six cases and on retesting in four others, the Mitsuda reaction showing marked tuberculoid features that were lacking from the old skin lesions. In such lepromin studies, it would appear important not only to biopsy the lepromin reaction,[15] but also a residual skin lesion[16] to confirm that the patient had been and had remained LL.

These indications of delayed spontaneous upgrading of the lepromin reaction were found predominantly in LLs[17] patients who had previously downgraded from borderline. There is so far no definite evidence of such upgrading in polar LL patients. Our decision to

divide the LL patients into two groups, depending on whether they had received more (Group 1) or less (Group 2) than 20 years of chemotherapy proved nearly correct. In practice, the cut-off point appeared to be 22 to 25 years of effective chemotherapy, taken with good compliance and without relapse. Around the 22-year mark, we obtained some doubtful (2 mm) lepromin reactions. It is noteworthy that in two somewhat less precise studies, positive lepromin reactions were obtained in small numbers of 'lepromatous' patients who had been skin-smear negative for more than 11[18] and 16[19] years. We conclude that a weak-positive Mitsuda conversion is not a rare, but a common occurrence.

The persistence and eventual reversion of the immunodeficient state in its various manifestations referred to above, could be accounted for by a single explanation. Insufficient allowance has been made for the immunological consequences of the prolonged persistence of a reservoir of mycobacterial antigen in lepromatous patients,[20] as discussed in the previous paper.[8] There is no direct measure of this antigenic mass in old lesions and the reticuloendothelial organs, of which acid-fast stains give little indication. But since recovery of specific immunoresponsiveness occurs only at a very late stage, our results suggest that the Mitsuda reaction will not convert to positive in LL leprosy until the great bulk of leprosy antigens has been removed from the skin and peripheral nerves. We cannot, however, explain the lack of correlation between the Fernandez and the Mitsuda reactions. In addition, we have demonstrated that giant tuberculin reactions, which we assume to be due to allergy to species-specific antigens of *M. tuberculosis*,[10] can occur at this stage.

These recent results of ourselves and of Gill *et al.*[14] suggest that immunological unresponsiveness in leprosy may not be the primary and irreversible feature of the disease that was at one time thought. They encourage the prospect that the defect might be at least partly reversible if some way could be found to hasten the substantial elimination of degraded bacterial products. It is interesting that claims have recently been made that immunotherapy may increase the rate of fall of the bacterial index, for example, in sites locally injected with interleukin-2.[21] But if, as we have found, specific immunological responsiveness may return spontaneously with time, great care will be needed in the design and the interpretation of immunotherapy trials in LL leprosy.

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Tuberculoid relapse in lepromatous leprosy

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Summary It is commonly accepted that the attainment of bacteriological negativity fails to restore the immune state of leprosy patients who have downgraded to lepromatous. We report six patients who had been lepromatous (LLs), and who, after many years of chemotherapy and bacteriological negativity, were found upon relapse to have upgraded to borderline–tuberculoid (BT). Five had become Mitsuda lepromin positive. The relapses could be accounted for by proven or suspected dapsone resistance. The upgrading was associated with minimal signs of reaction, which was attributed to the low level of antigen in the almost resolved lesions. The manner of development of the new high immune lesions resembled the onset of a primary infection, clinically and histologically. The development of a positive Mitsuda reaction in longstanding LL leprosy is not necessarily an indication of cure.

Introduction

Before the advent of multidrug therapy (MDT), when long-treated, smear negative lepromatous patients relapsed, from whatever cause, their relapse lesions almost invariably retained lepromatous (LL) or borderline–lepromatous (BL) characteristics, and they remained lepromin negative.[1,2] Occasional BL patients have relapsed as borderline–tuberculoid (BT), but usually as a consequence of reversal (upgrading, Jopling type 1) reactions during treatment. In 1978, we reported[3] for the first time three subpolar lepromatous[4] (LLs) patients who had relapsed with BT leprosy without having undergone any marked reaction. We report here three further patients, together with a follow up of our original cases. In addition, we have performed control lepromin studies, with unexpected findings, which we report in an associated paper.[5]

Case reports

1 PATIENT 5077

This Chinese patient was admitted to Sungai Buluh Leprosarium, Malaysia, in 1937,

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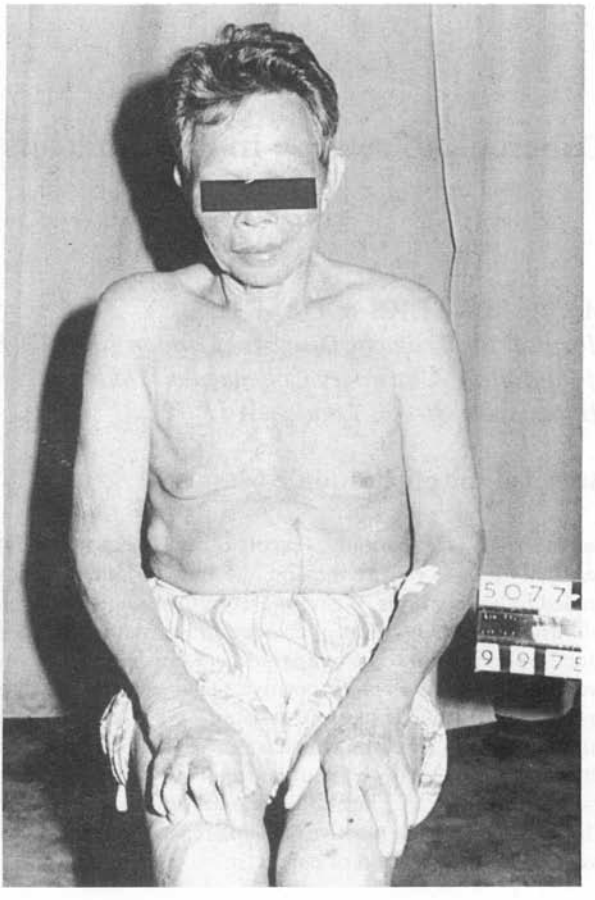

Figure 1. Patient No. 1. Front view showing the typical features of well-treated, advanced LL leprosy. There is clawing of the right hand.

when aged 35. In 1947, he was graded 'L3' with failing vision due to lepromatous infiltration and iritis. He was treated with dapsone from 1948 to 1970. His smears were negative from 1959 to 1974.

Annual examinations were satisfactory until 1975, when erythematous patches were noted on his trunk. On referral to the Leprosy Research Unit three months later,[6] his general appearance was considered consistent with well-treated, advanced LLs leprosy (Figure 1). The skin was wrinkled, madarosis was almost complete, nerves were enlarged and there was widespread anaesthesia over the limbs and trunk, with a right ulnar and median claw hand. Yet there were fading erythematous raised annular tuberculoid lesions on both flanks, two on the left and three on the right (Figure 2). Smears from these lesions gave a bacterial index (BI) on the Ridley scale of 1+; elsewhere they were negative. The Mitsuda reaction (standard Wade–Mitsuda lepromin) measured 9 mm at three weeks and 6 mm with ulceration at four weeks. Two annular lesions were biopsied, revealing a rather nondescript mass of lymphocytes. A year later, after parenteral dapsone, 400 mg twice weekly, he was graded histologically as BT (Figures 3 and 4).

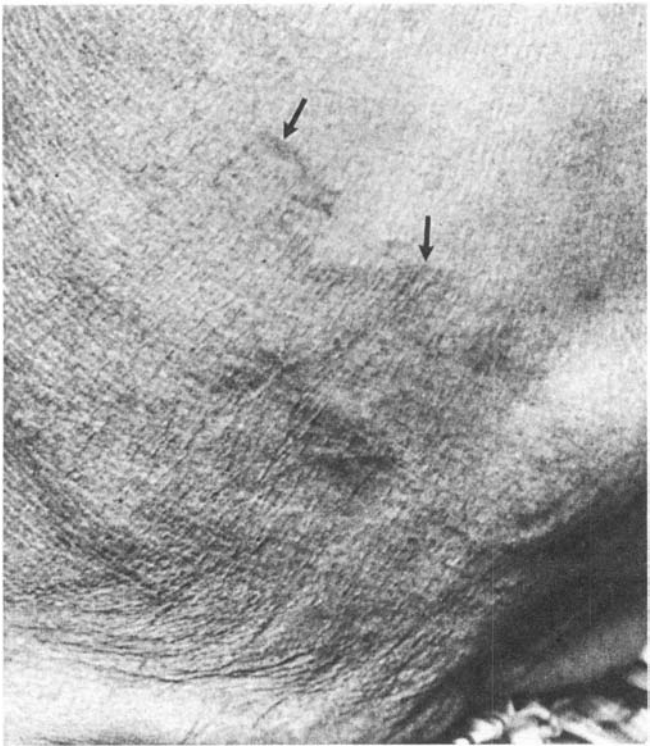

Figure 2. Patient No. 1. Right flank showing (arrowed) irregular-edged, annular lesions typical of BT leprosy.

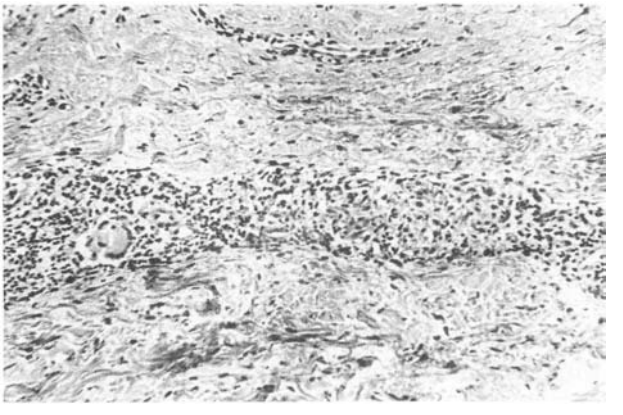

Figure 3. Patient No. 1. Biopsy of annular lesion, taken one year after recommencing dapsone therapy. The appearances are of a BT leprosy granuloma with many lymphocytes.

From 1976 to 1981, chemotherapy was continued unchanged owing to severe gastric ulcer symptoms, with little change in his condition save for some fluctuation in the degree of erythema and induration in the annular edges of the lesions. Repeat skin biopsy in 1979 again revealed the histological appearances of BT leprosy with mild reaction but no signs

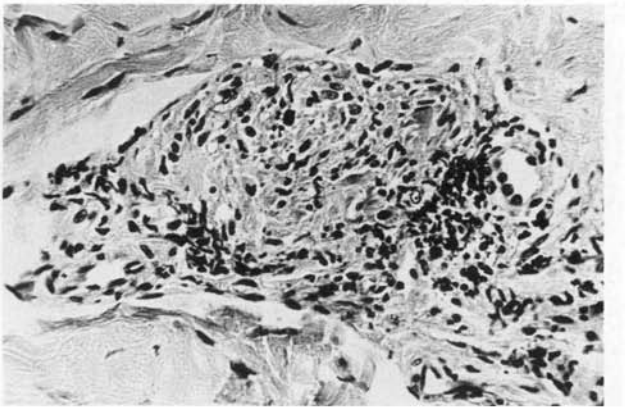

Figure 4. Patient No. 1. Infiltration and disorganization of a dermal nerve. From the same lesion as Figure 3.

of downgrading or active spread; a few granular acid-fast bacilli (AFB) were noted. A fresh biopsy homogenate yielded a BI of 3+ with a morphological index of 10. Mouse footpad inoculation showed the strain to be fully resistant to dapsone (at 0·01% concentration in the mouse diet) but sensitive to thiambutosine (at 0·1% concentration). A repeat lepromin test in 1980 was still strongly positive, and skin smears from his relapse lesions were negative.

2 PATIENT 8715

This male Chinese patient was admitted to Pulau Jerejak Leprosarium, Malaysia, in 1939 when aged about 16 years. His voice became hoarse in 1945, and his right eye blind in 1946. He commenced treatment with dapsone around 1950 and became skin smear-negative around 1960. He was transferred to Sungai Buluh Leprosarium in 1969, and remained smear negative until June 1974, when new lesions were observed.

When he was referred to the Leprosy Research Unit in May 1975, his clinical appearance was consistent with treated, advanced LLs leprosy, with 'rat-bitten ears', madarosis and a deformed nose and soft palate. Nerves were slightly and symmetrically enlarged. New erythematous, dryish papules and plaques with irregular edges were present on the arms, trunk and lower limbs (Figure 5). One lesion on the right thigh was more borderline with a hollowed-out centre. His smears gave a BI of 1·2; the Mitsuda reaction measured 5 mm at four weeks and histological examination of lesions on the back and arm revealed BT in reaction.

On treatment with dapsone 400 mg by injection twice weekly, he initially improved. But 15 months later further new lesions were more lepromatous in character and histologically BL. His strain of *Mycobacterium leprae* was shown to be fully resistant to dapsone (0·01% concentration in the mouse diet).

3 PATIENT RS

A 60-year-old Punjabi was referred to Dr Jopling in 1966, complaining of epistaxes and swelling of the ankles. On examination (Figure 6), there was widespread diffuse

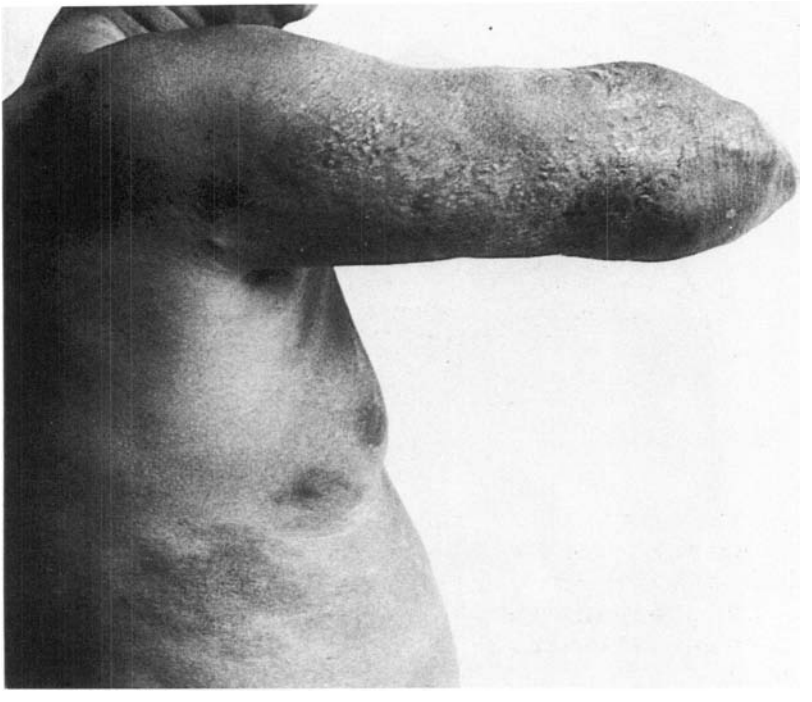

Figure 5. Patient No. 2. Right arm and chest showing erythematous plaques (on chest) and coalescing papules (on arm), suggestive of BT or BT/BB leprosy.

lepromatous infiltration with some mild erythema nodosum leprosum (ENL), complete madarosis, mild symmetrical nerve enlargement, and anaesthesia of the feet and ankles. The lepromin test was negative and the smear BI 4·2. Histologically, he was graded as typical LLs (Figure 7), which was mildly active with low grade ENL. He responded well to treatment with dapsone (plus Vadrine for the first six months) becoming smear negative in 1973. In 1975, a biopsy showed an infiltrative, mainly lymphocytic lesion which was now almost indeterminate but with some tuberculoid features: erosion of the epidermis and destruction of sweat glands. There was also mild reactional oedema, and one short solid-staining bacillus. He was smear negative in May 1977, when clinically he resembled well-treated, inactive, polar or near-polar lepromatous leprosy. He admitted to taking little if any dapsone during the previous six months owing to chronic bronchitis.

Three months later he was found to have developed erythematous, raised, annular lesions in both lumbar regions. Histologically, the lesions were now BT with many lymphocytes and not far removed from TT (Figure 8). There was no active spread and no AFB; smears were negative. His Fernandez reaction measured 5 mm at 3 days; no Mitsuda reading was then possible. The lesions subsided steadily on dapsone 50 mg daily. After one year they were virtually invisible, though smears were 1+ positive. A repeat lepromin test in October 1978 gave a Mitsuda reading of 3 mm at 4 weeks. In 1979, his treatment was changed to clofazimine, with rifampicin initially, for fear of dapsone resistance. Three of six mouse footpads inoculated with a homogenate from a new lesion

Figure 6. Patient No. 3. View of face, on first diagnosis in 1966, showing typical appearances of advanced untreated LL leprosy.

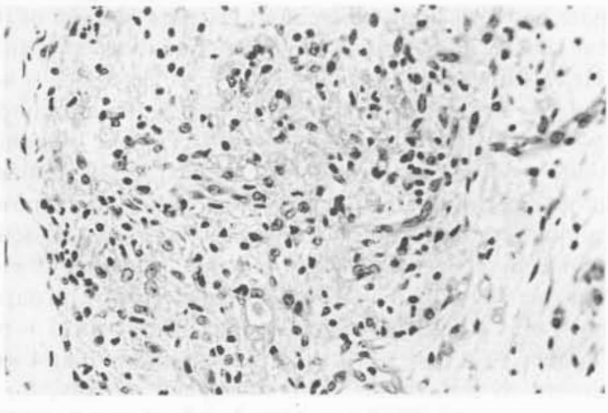

Figure 7. Patient No. 3. Histological appearances of skin on first diagnosis in 1966, showing mildly active LLs leprosy.

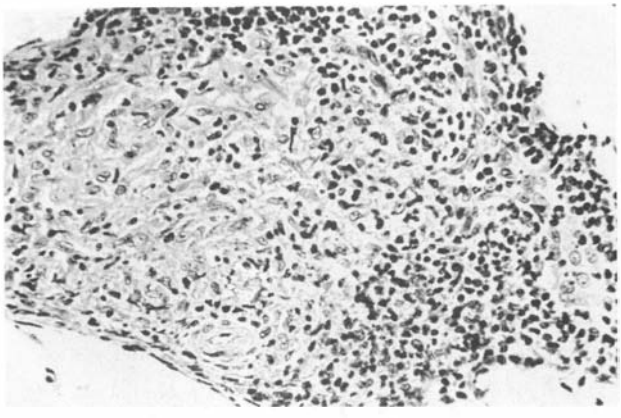

Figure 8. Patient No. 3. Histology of a relapse skin lesion in 1977; the appearances are of BT leprosy with many lymphocytes, not far removed from TT.

taken in August 1977 had become positive for *M. leprae*, and subsequent passage confirmed full dose dapsone resistance. He died of intercurrent disease in 1980.

4 PATIENT TB

This Anglo-Indian patient, aged 25, developed a severe ulcerating ENL reaction, progressive deformity of his fingers and hands and left foot drop, following treatment with sulphoxone sodium (Diasone) in 1950. Chemotherapy was changed to thiacetazone, and then stopped altogether in 1953. The ENL ceased around the same time. He arrived in England and was admitted to the Hospital for Tropical Diseases in 1954. In addition to the deformities noted above, he had 'rat-bitten' ears and a large nasal septal perforation, clawed toes, and numerous whitish scars chiefly on his limbs, compatible with past severe ulcerations. There was widespread enlargement of nerves. His eyebrows were intact. Skin smears were weakly positive for AFB (overall BI 1·0, with the densest site 3+). The Mitsuda reaction was negative. Histologically, his skin biopsy was classified as LLs; the lesion was small but with some solid AFB. It was considered that his treatment in 1950 had commenced shortly after downgrading from borderline to lepromatous. He was restarted on dapsone and within a month episodes of mild ENL recurred and these continued for about five months. After that the lesions regressed, and he became skin-smear negative by November 1956. He stopped taking dapsone in 1962, but recommenced in 1963, because of bilateral iridocyclitis, for which he received corticosteroids almost continuously for the next 15 years. From 1965 to 1970, he received low dose thiambutosine and then restarted dapsone, the dose being raised to 100 mg daily in 1977. His urine was repeatedly positive for dapsone. In August 1978, the lepromatous leprosy was clinically completely quiescent and his smears (6 sites) were negative for AFB.

Two months later he developed erythematous plaques over his right forehead and his face, which increased slightly in size; their edges were indurated and raised (Figure 9). Clinically they were BT. Histologically, a lesion was characterized by many lymphocytes and undifferentiated histiocytic cells, but no granuloma or AFB; it was classified as indeterminate, but tuberculoid rather than lepromatous. Smears were negative. The

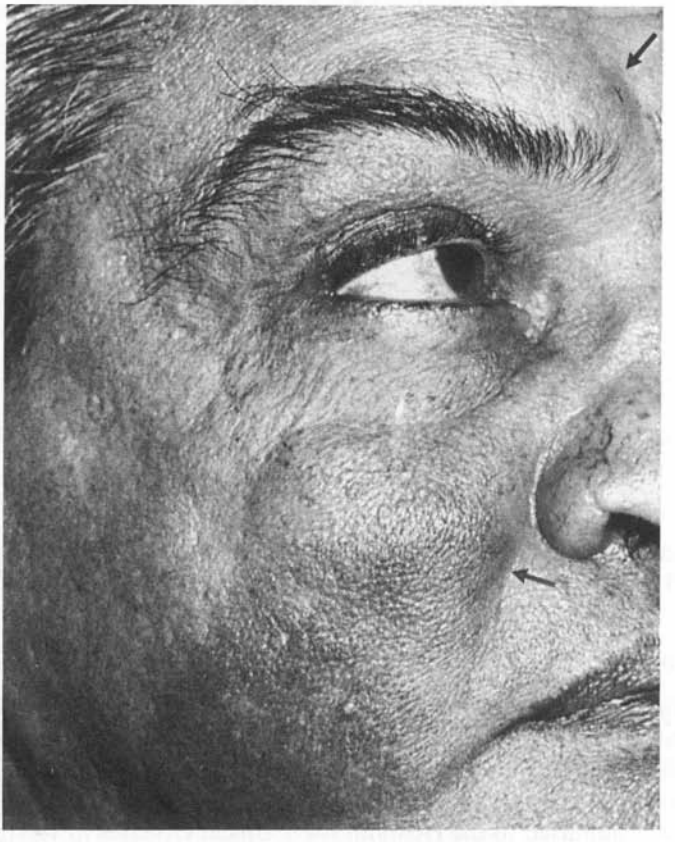

Figure 9. Patient No. 4. Relapse lesions in 1978; raised, sharp-edged plaques (edges arrowed) are present on the face and forehead.

Mitsuda reaction measured 4 mm, but histologically it showed the same tuberculoid but rather non-specific features as the skin lesion. Peripheral blood lymphocytes responded positively to stimulation with *M. leprae* (Dr G A W Rook). An attempt to isolate his strain of *M. leprae* was unsuccessful.

The facial lesions slowly settled with rifampicin and ethionamide, becoming completely inactive after 16 months. In 1988, his lepromin Mitsuda reaction measured 5 mm, a biopsy showing epithelioid cell granulomas (Dr S Lucas). He died of intercurrent disease.

5 PATIENT SN

This patient, aged 29, was classified as lepromatous in Cyprus in 1950, his skin smears being strongly positive. He commenced treatment with solapsone sodium and thiacetazone. On referral to the Hospital for Tropical Diseases in 1953, he was noted to have a resolving leonine facies, prominent eye brows and no rash or nodules. Although smears contained only 'scanty bacilli', histology revealed several masses of globi and he was classified by Dr R G Cochrane as resolving leproma. This was confirmed by subsequent

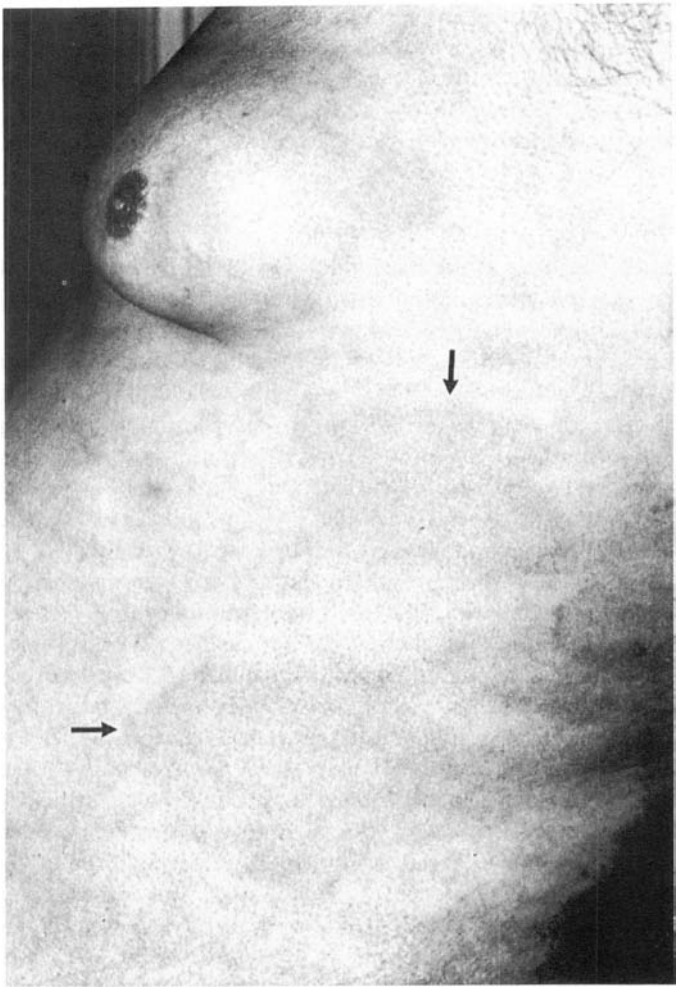

Figure 10. Patient No. 5. Right flank in 1984, showing dry erythematous plaques (edges arrowed) consistent with BT leprosy. Note the gynaecomastia.

re-examination of the section, which showed a resolving lesion with many lymphocytes, being classified LLs, almost BL. Dapsone therapy was continued, but another biopsy in 1956 was more active. He suffered from ENL in 1957 and became smear negative in 1960. His smears became weakly positive in 1975, and his dose of dapsone, previously around 50 mg twice weekly for many years, was raised to 50 mg and then 100 mg daily. Nevertheless, several urine tests were negative for dapsone in 1978–79, although subsequently compliance improved. His smears were negative again in 1983. He remained clinically quiescent until June 1984, when erythematous anaesthetic macules and plaques developed on his back and chest, which over the course of weeks faded and then relapsed (Figure 10). Smears from the new lesions were negative (left elbow site was 1+). Histological examination revealed typical BT leprosy, quiescent or mildly active, with fairly numerous lymphocytes and scanty granular AFB. There was no sign of reaction and

the lesions appeared to be in a moderately late stage of relapse with upgrading. His Mitsuda reaction was negative on two occasions. His treatment was changed to MDT (rifampicin, ethionamide and dapsone) in September 1984, and the skin lesions flattened and faded over the next four months. The Mitsuda reaction, repeated in 1989, remained negative. Organisms obtained prior to MDT were not infectious to mice.

6 PATIENT DD

This Cypriot patient was seen at the Hospital for Tropical Diseases in 1954, aged 18. She gave a history of having been treated with injections for leprosy for eight years. On examination, she had signs of early active lepromatous leprosy, with a few small nodules on her face and erythematous areas on her limbs and buttocks; her ears were not enlarged and the eyebrows were intact. Her BI was 4·0, with solid-staining bacilli present. Skin biopsy revealed active lepromatous (LLs) leprosy. A lepromin test was negative. She was treated with silver sulphone for six months, and then with dapsone by injection. By 1957 she showed no stigmata of leprosy, and had only one small area of anaesthesia on the foot. She continued treatment with oral dapsone 100 mg daily. Her skin smears became negative in 1959 and the dapsone was reduced to 25 mg twice weekly.

In 1979 there was mild clawing of her left toes, with anaesthesia of the left foot and the lateral side of the left leg. Granular AFB (2+) were found in a finger smear. The Mitsuda reaction was negative. In 1982, when clinically her disease was completely inactive, she agreed to take dapsone 50 mg daily, plus rifampicin 600 mg for two consecutive days each month, but refused clofazimine and ethionamide. Seven months later she began to suffer from neuritic pains, and developed a dry, erythematous plaque over her right index and mid-fingers and the associated part of her right palm, a similar plaque over her left lower chest posteriorly, as well as faint erythematous lesions on the left buttock and both calves. The two plaques were anaesthetic. The dorsal branch of the right superficial terminal ulnar nerve was considerably enlarged, and the right superficial radial and ulnar nerves had increased in size. Skin smears from the new lesions and earlobes were negative for AFB. Biopsy of the left back plaque revealed a small BT lesion with signs of reaction. Scanty (2+) granular AFB were present in a nerve bundle. Her Mitsuda reaction measured 3 mm at four weeks. It was thought that she had developed a very early subclinical relapse, probably due to dapsone resistance, before commencing rifampicin and standard dapsone therapy, and that a reversal reaction had occurred after seven months. She was treated with prednisolone, chemotherapy was continued, including ethionamide which she now accepted, and the lesions became quiescent after 18 months.

Table 1 summarizes the time scale and salient points of the six patients.

Discussion

We submit that all six patients were suffering from subpolar lepromatous (LLs) leprosy when first they commenced treatment with effective chemotherapy. Patients 1 and 2 showed the stigmata of old LL leprosy and their classification is confirmed by the time taken to become skin smear negative. The remaining four patients all had their classification confirmed histologically. All became bacteriologically negative and, at the time of their relapses, five of the six had been negative on skin smear for 14 years or more.

It is reasonable to suppose that relapse was accounted for by dapsone resistance in all

Table 1. Details of the six lepromatous patients, timing, histological classification, lepromin results and dapsone sensitivity at time of relapse

Patient number	Year of commencing sulphone therapy	Year skin smears became negative	Relapse histology	Relapse year	Relapse (years) since starting sulphones	Relapse (years) since smears became negative	Dapsone resistance	Lepromin (Mitsuda) reading at relapse
1 (5077)	1948	1959	BT Mild Reaction	1975	27	16	Proven	6 mm (ulcerated)
2 (8715)	1950	1960	BT Reaction	1974	24	14	Proven	5 mm
3 (RS)	1966	1973	BT	1977	$11\frac{2}{12}$	$3\frac{8}{12}$	Proven	3 mm
4 (TB)	1950	1956	Ind/Tuberculoid	1978	28	22	Prima facie	4 mm (histology BT)
5 (SN)	1950	1960	BT mildly active	1984	34	24	Prime facie	0
6 (DD)	1954	1959	BT Reaction	1983	28	23	Prima facie	3 mm

cases. In the first three patients, resistance was proved by the mouse footpad technique. It is noteworthy that it took up to four years after the initial relapse to obtain a satisfactory inoculum; and in the two subsequent patients mouse footpad inoculation of their strains of *M. leprae* was unsuccessful, mainly because it was considered unethical indefinitely to delay changing treatment. Patent No. 6 had already commenced treatment with rifampicin before her clinical relapse and isolation of her strain of *M. leprae* was not attempted. Patients Nos 4, 5 and 6 had commenced chemotherapy with early, substituted sulphones, and Meade *et al.*[7,8] reported that the risk of relapse from dapsone resistance was three times greater in lepromatous patients commencing treatment with solapsone than with dapsone in full dosage. The incubation period of up to 34 years presents no problem; we have observed patients relapse with proven dapsone resistance as late as 33 and 37 years after commencing sulphone therapy.[9]

In our experience, the majority of lepromatous patients are histologically of the sub-polar LLs type that have downgraded from BB or even BT.[10] Observations in the pre-sulphone era suggest that perhaps 5% of BT patients downgraded across the spectrum.[11] Therefore it is surprising that reversion to BT on relapse has not been reported earlier. The account of the development of BT lesions, 12 years after commencing sulphones in a 'borderline–lepromatous' patient reported in 1962[12] (Fernandez *et al.* case no. 2) is suggestive of a late reversal (upgrading, Jopling type 1) reaction in a LLs patient and not necessarily of a bacterial relapse. The case reported by Jonquieres *et al.*[13] in 1963, who stopped sulphone therapy after 11 years because of intercurrent disease and who developed a BT relapse two years later, with a 3 mm Mitsuda reaction, appears very similar to our third patient. But very late relapses with Mitsuda conversion do not appear to have been reported.

The observation that relapse might follow the restarting (case 3) or increasing (case 6) of chemotherapy suggests that chemotherapy may help to uncover, or make clinically apparent, a relapse. Similarly tuberculoid leprosy may follow prophylactic sulphones.[14,15] In case 3, however, a biopsy had shown the evolution of certain tuberculoid features 21 months before the clinical onset of relapse. This was associated with slight histological reaction and one short solid bacillus. It seems probable that in these very long treated patients, a clinically silent upgrading had taken place that might never have been detected but for the accident of a relapse. But it cannot be excluded that late stage relapse might help to trigger upgrading after the manner of a vaccine.

The role of reactions in the upgrading process may be questioned. There were no overt reactions, although in one case there were neuritic pains. Histological signs of reaction were reported in three cases, but they were mild and more in the nature of incipient reactions which are often clinically silent. There was some enhancement of delayed hypersensitivity, as indicated by the development of Mitsuda reactivity, and the low level of reaction in the lesions is probably explained by the low level of mycobacterial antigen present. It is noteworthy that five of our six patients developed their BT relapses 24 to 34 years after commencing effective chemotherapy, and 14 to 24 years after becoming smear negative. As discussed in our associated paper,[5] we consider that residual antigen is only slowly removed from the dermis and may persist for many years (perhaps 10 or more) after an LL patient has become negative for AFB by slit-skin smear examination. During this time a patient might be expected to remain lepromin negative. The relapses which we report appeared, both clinically and histologically, to follow a course similar to that of an initial infection prior to the development of delayed hypersensitivity: even the Mitsuda

reaction in one of the two cases that were biopsied showed a predominantly lymphocytic response. Such relapse, with limited bacterial multiplication in almost resolved lesions, would increase the ratio of dermal to systemic antigen, since any residual antigen from old lesions would, after this duration of time, have mostly drained to the reticulo-endothelial system. It would also increase the ratio of live to dead bacilli in the host, and the ratio of surface and secreted antigen to exposed cytoplasmic antigen. If residual antigen is, as we suggest, quantitatively minute in such long-term treated patients, two of these three factors would also apply to their lepromin tests and could account for the finding of positive (3 mm or greater) Mitsuda lepromin reactions.

If this explanation is correct, we might expect that many similarly long-term treated LL patients, with no history of relapse, might also with time become lepromin positive, as indeed we have found.[5] Nevertheless, it is clear from the five of our six relapse patients who became lepromin positive, that the development of a positive Mitsuda test is, of itself, no test of cure in LL leprosy, nor necessarily an indication of adequate protective immunity.

Acknowledgments

We particularly thank Dr W H Jopling for access to his meticulous clinical notes of patients 3–6, and Dr A B G Laing for supplying follow-up details of patient no. 1. We also thank Drs R J W Rees and M J Colston for attempting to isolate strains of *M. leprae* from three of the patients. The Leprosy Research Unit, Sungai Buluh, where we studied patients Nos 1 and 2, was (until 1981) jointly sponsored by the Malaysian Ministry of Health and the British Medical Research Council.

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Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malawi

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Summary This paper describes the pattern of disability among 1654 leprosy patients ascertained between 1973 and 1987 in Karonga District, Northern Malawi. Approximately 20% of patients identified prior to 1980 had some disability at registration, but this percentage fell to approximately 10% with the introduction of total population surveys in the Lepra Evaluation Project. The proportion of patients with disabilities at registration increased with age, was higher among males than females, was higher among borderline and lepromatous than tuberculoid patients, and was higher for passively than for actively detected patients. The risk of developing disabilities among patients without any disabilities at registration was approximately 5 per 1000 person years, and appeared to be slightly higher after the completion of treatment than during treatment.

Introduction

If leprosy is a public health problem, it is because of the disabilities it causes. Given this fact, it is surprising how little is known of the extent of leprosy-attributable disabilities in endemic populations. Published estimates vary widely, and are difficult to interpret. These estimates are typically expressed as percentages of leprosy 'cases', but the leprosy case definitions, and their representativeness of all leprosy cases in the population, are more often than not unclear. Twenty years ago, Bechelli *et al.* gave estimates of percentages disabled ranging from 7·6% in Cameroon and 23·4% in Nigeria to 48·7% in Burma and 80% in Taiwan.[1,2] Noordeen & Srinivasan reported an overall 'deformity' rate of 19·4% among leprosy patients in South India, and noted increasing deformity associated with increasing age and duration of disease.[3] They also found deformity rates higher in lepromatous than in tuberculoid patients, and higher rates among males than females.

§ Address for reprint requests.

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Several other authors have discussed disability or deformity in specific groups of patients—often in institutionalized patients or urban leprosy clinics.[4–13] Except for the WHO surveys carried out in Nigeria and Cameroon[14] and a small study carried out in Kenya,[15] there is little published information on the pattern of leprosy-attributable disabilities in African populations.

Very few studies have attempted to relate disability figures to population denominators, let alone to relate leprosy to other causes of disability in the populations concerned. Another fundamental problem is the definition of disability appropriate for leprosy studies. The so called 'WHO-scales' were first proposed almost thirty years ago for this purpose[16,18] but they have been revised repeatedly and there are still very few examples of their use in an epidemiological context. Though the WHO scales have been incorporated into OMSLEP reporting forms, they have never been validated rigorously; and thus many workers have derived alternative schemes for use in various studies around the world.[19–22] We are aware of no attempts to describe leprosy disabilities in the context of the international classification system for impairments, disabilities and handicaps.[23]

We present here a study of disabilities associated with leprosy in Karonga District, Northern Malawi, based on detailed records of patients ascertained over the years 1973–87. The work was carried out in the context of the Lepra Evaluation Project (LEP).

Background

Karonga District is a rural area with a population of approximately 120,000 people in 1980. It has long been known to have a relatively high prevalence of leprosy. The first targeted leprosy control programme was started in 1973 as the Lepra Control Project (LCP). Except for school surveys, the LCP relied entirely upon passive case detection. Large scale active detection of cases began only in 1980 with the onset of the LEP. All households except those in the southern tip of the district were included in the project during the years 1980–84, and more than 112,000 persons were examined for leprosy. The methods of the LEP have been described in detail elsewhere.[24]

The history of leprosy control policies in Malawi and trends in incidence and prevalence of the disease have been described in previous publications.[25,26] Routine treatment policies changed over time, and are described in detail in Table 4 of reference 25. Type I reactions were treated routinely with a 12 week course of prednisolone.

Materials and methods

Several types of records were available for the purposes of this study:

(a) *LCP records made out at registration of patients.* These records include a pictorial representation of lesions, enlarged nerves and disabilities at the time each patient was registered.
(b) *LCP treatment records.* These include a record of all treatment received, of reactions, and of clinical changes during the course of treatment.
(c) *LCP discharge records.* These include a description of lesions and disabilities at time of discharge.

(d) *LEP general and detailed examination forms.* These include independent detailed clinical descriptions prepared each time an individual was met by the LEP survey teams.
(e) *MDT surveillance records* prepared for patients included in a study of WHO-recommended multiple drug therapy regimens in paucibacillary leprosy.[27]
(f) *Repeat examinations* carried out by the principal investigator of this study (IP).

Only individuals who were seen by the LEP at least once, and whose leprosy diagnosis was confirmed by published criteria ('narrow' or 'middle' group—see reference 28) were included in this study. This criterion was chosen as the diagnosis of leprosy prior to the

Table 1. Classification of disabilities into mild, moderate and severe categories, as used in this study

	Comparable WHO classifications		
Malawi disability study definitions	1960 grade	1970 grade	1988 grade
Minor			
Any of the following:			
Face—paresis of eyelids, corneal anaesthesia paresis of mouth, partial collapse of nose	—	—	0 or 1
Hands—median, ulnar or radial paresis, indefinite (doubtful) median, ulnar or glove anaesthesia	—	—	—
Feet—paresis of toes or foot indefinite anaesthesia, dorsum, or plantar anhydrosis with cracking of skin	—	—	—
Moderate			
Any of the following			
Face—lagophthalmos (without loss of vision) collapsed nose mouth drop	2 or 3	1 or 2	1
Hands—definite median, ulnar or glove anaesthesia definite median, ulnar or radial paralysis (but not fixed)	1 or 2	1 or 2	1 or 2
Feet—definite anaesthesia, dorsum or plantar definite paralysis toes or foot	1 or 3	1 or 2	1 or 2
Severe			
Any of the following			
Face—definite lagophthalmos plus loss of vision in various combinations	4 or 5	2 or 3	1 or 2
Hands—definite anaesthesia and/or paralysis on both hands plus ulcer or partial loss of any finger loss of an entire finger	3 to 5	2 or 3	2
Feet—bilateral anaesthesia plus any ulcer or paralysis loss of an entire toe	2 to 5	2 or 3	2
Combination of disabilities in any two extremities			

Table 2. Correspondence between classification employed in this study and the 1960, 1970 and 1988 WHO scales

	WHO scale		
Malawi study	1960	1970	1988
Not included	Grade 1 (on face)	Not included	Not included
'Minor'	Not graded	Not graded	Grade 1 (corneal anaesthesia)
'Moderate'	Grades 1 to 3	Grades 1 and 2	Grades 1 and 2
'Severe'	Grades 2 to 5	Grades 2 and 3	Grades 1 and 2

LEP was not routinely subject to the same rigour as it was thereafter.[28] In addition, this study excludes all individuals with a history of initial antileprosy treatment given either outside Karonga District, or prior to 1973. This criterion was established as there are no good records of the disability status of these individuals at the time of their initial diagnosis and treatment. The exclusion of these groups may have important implications, as will be noted in the discussion.

All records were coded on specially designed forms and entered onto a microcomputer for analysis. Information coded included descriptions of all enlarged peripheral nerves, of doubtful (indefinite) or definite anaesthesia in extremities, of paresis, of paralysis, of diminished vision, and of present or past ulcers and loss or absorption of digits as well as information on the history and treatment of reactions in the past.

For the purposes of this study, disabilities were classified as being either 'minor', 'moderate' or 'severe', according to the schedule presented in Table 1. It will be noted that the disabilities here classified as 'minor' are less than those included on the 1960, 1970 or 1988 WHO scales. Grade 1 disabilities of the face as defined by the 1960 WHO scale (i.e. 'permanent stigma, loss of eyebrows, or deformity of ear') were not included in our study as we do not believe that they represent real disabilities or cause stigma in this Malawian population. On the other hand, the WHO 1988 Grade 1 only includes disabilities of the eyes. Other facial disabilities are not included at all within this scale. Our 'moderate' group comprises items classified as grade 1 or 2 on the WHO 1970 and 1988 scales, or as grades 1 to 3 on the WHO 1960 scale. The correspondence between the classification employed in this study, and the 1960, 1970, and 1988 WHO scales, is summarized in Table 2.

Results

1654 confirmed leprosy patients satisfied the criteria for inclusion in this study. These include 968 females and 686 males. Figure 1A shows the distribution of numbers of patients, by year of registration. The numbers registered per year varied from a high of 160 in 1975, soon after the initiation of LCP activities, to a low of 40 cases ascertained by passive detection during 1985, the year between LEP surveys. The total numbers

registered by the LCP fell during the years 1974–79, reflecting gradual ascertainment of patients which had accumulated in the district prior to the appearance of LEPRA. High numbers of cases were detected during the years 1980–84 and again in 1986–1987, reflecting active case detection by the LEP. The relatively low number recorded in 1982 reflects temporary interruption of fieldwork due to staff illness.

Figure 1(B) presents a breakdown of these patients by their disability status at registration. The percentage disabled at registration fell from approximately 20% during the era of passive case detection, to approximately 10% during the LEP survey, reflecting the early detection of cases by active case finding. It is notable that the percentages disabled at registration were highest in 1978, 1979 and in 1985, coinciding with small total numbers of patients, almost all of whom self-reported.

Figures 2(A)–(D) show the percentage breakdown of disability status by age at registration, sex and mode of ascertainment. Each of these variables is seen to have an important relation to the distribution of disabilities. First, there is a clear increase of percentage with disabilities with age at registration. Out of 114 children under age 10, only 2 had any disability at registration. Second, there were higher disability rates among males, for both the passively and the actively detected groups. Third, disability percentages were much higher among passively detected (self-reporting) cases than among those actively detected in the epidemiological survey. The percentage with any disability among actively detected females did not exceed 10% for any age group, whereas it rose to over 40% among the oldest group of self-reporting females. This difference is less marked among males than females.

Figure 3 shows disability status at registration by classification, for females and males separately. There is a tendency in each sex for the percentage with severe disabilities at registration to rise as one moves across the spectrum from tuberculoid to lepromatous groups.[17] The proportions with moderate disabilities were highest among the borderline

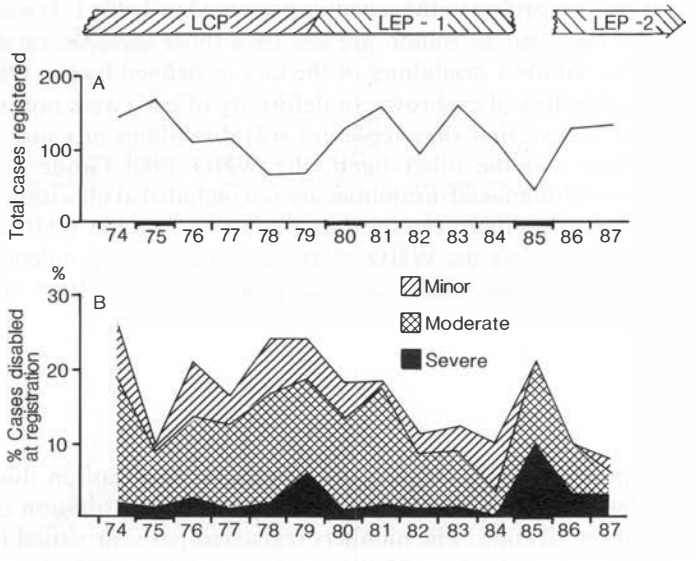

Figure 1. Annual numbers registered (A) and disability status (B) of 1654 confirmed leprosy patients registered in Karonga District, Northern Malawi, 1973–87.

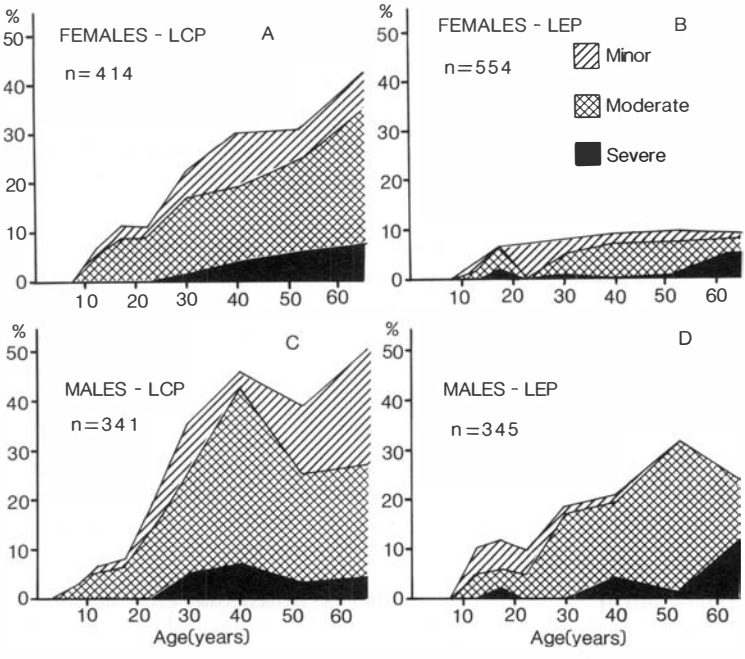

Figure 2. Percentages of leprosy cases with minor, moderate or severe disabilities, by age at registration, sex and mode of ascertainment. (LCP = Lepra Control Project, passive detection; LEP = Lepra Evaluation Project, active detection).

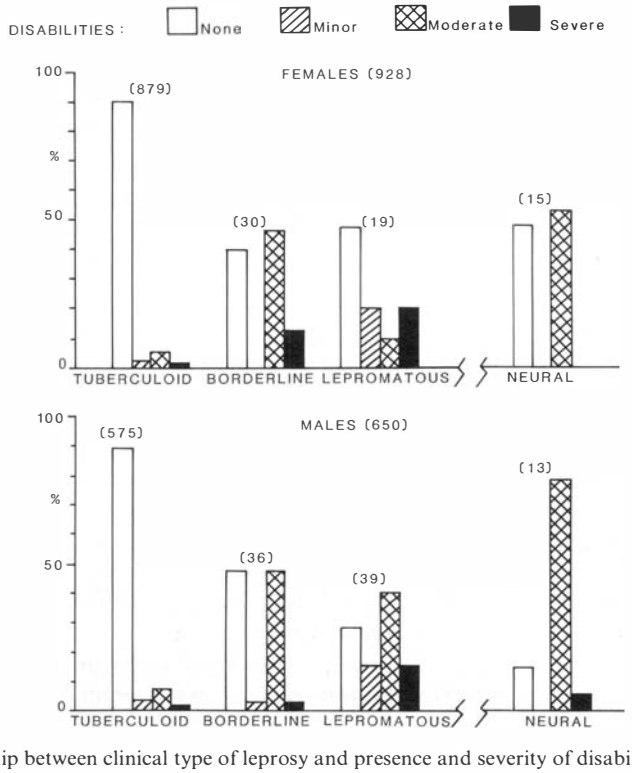

Figure 3. Relationship between clinical type of leprosy and presence and severity of disabilities at registration, separately for males and females. The Figure excludes 48 patients of uncertain classification.

Table 3. Risks of developing disabilities during and after treatment.

Sex	Number	Person years at risk	Numbers of new disabled (and rate per 1000 person years)	
			All disabilities	Moderate and severe
During treatment				
Females	750	2596	9 (3·5)	2 (0·8)
Males	479	1872	4 (2·1)	4 (2·1)
Total	1229	4468	13 (2·9)	6 (1·3)
After completion of treatment				
Females	498	1340	12 (9·0)	6 (4·5)
Males	329	916	6 (6·6)	5 (5·5)
Total	827	2256	18 (8·0)	11 (4·9)

patients, in particular in females. It may also be noted that although there were larger numbers of female patients overall, there were twice as many lepromatous males as lepromatous females (39 compared to 19). Out of 28 patients with neural leprosy, 19 (68%) had moderate or severe disabilities.

Table 3 presents the risks of developing disabilities either during treatment, or after discharge, among individuals with no recorded disabilities at time of initial registration, or at time of discharge from treatment, respectively. Incidence rates of disabilities after discharge were based upon new disabilities between discharge and the first recorded subsequent examination, and thus relate to a period of time during which the individuals were on no antileprosy treatment whatsoever. These data show a low risk of developing any disabilities during treatment—approximately 3 per 1000 persons per year (1·3/1000 for moderate and severe disabilities), but slightly higher risks, in the order of 8 per 1000 person years (4·9/1000 for moderate and severe disabilities) after completion of treatment. Each of these differences between pre- and post-treatment rates is statistically significant ($p < 0{\cdot}02$).

Discussion

This analysis of data on 1654 confirmed leprosy patients diagnosed in Karonga District, Northern Malaŵi, between 1973 and 1987, shows several clear patterns. The proportions with disabilities were appreciably higher for cases who self-reported than for actively detected cases. The actual differences observed necessarily reflect many things: the history and classification (e.g. proportion multibacillary) of leprosy in the population; cultural factors (e.g. health care seeking behaviour), availability of routine health services and the history and intensity of active case ascertainment.

Interpretation of the time trend in disability rates prior to the LEP, as shown in Figure 1, is complicated by the fact that our analysis has excluded individuals who were not seen, and hence not diagnostically confirmed, by the LEP. This criterion has probably meant the exclusion of some (severe?) leprosy cases who were registered by the LCP but

who died prior to being seen by the LEP, and perhaps also some (mild?) cases who were registered and treated by the LCP but whose lesions had so totally resolved by the time they were seen by the LEP that their original diagnosis could no longer be confirmed. As these potential biases are of unknown magnitude, and in opposite directions, their overall impact on the observed severity distribution (Figure 1(B)) is unclear. Such difficulties frequently arise in attempting to interpret data from routine control programmes.

The sex differences seen in these data are particularly interesting. Though leprosy is more frequent among females than males in this population,[26] it is more severe among males. These differences are seen in terms of percentages disabled (Figure 2) and also in the numbers and percentages of multibacillary forms of the disease (Figure 3). Though a general male predilection for lepromatous disease has been noted by other authors,[2,3,29,30] these data are unusual in that the overall prevalence of leprosy is appreciably higher among females in this population. A similar pattern was also found in a small study carried out in Kenya.[15] Consistent with the association of more severe and disabling forms of the disease with males we may also note a tendency for disability rates to fall among older males, but not older females (see Figure 2). This may be a chance observation, but it could also reflect selective mortality among more severely affected elderly males. We plan to explore this hypothesis in future analyses of LEP data.

The incidence rates of disability presented in Table 3 represent unusual statistics, as there are few comparable data in the leprosy literature. Several authors have reported incidence rates of disabilities during the course of treatment. For example Keeler & Ryan[31] reported onset of disabilities in 2 (0·6%) of 335 patients after several years of treatment on the islands of Trinidad and Tobago. More impressive are analyses presented by Radhakrishna & Nair on the incidence rates of 'deformities' among almost 6000 leprosy patients on dapsone therapy in Polambakkam, South India.[32] These authors found incidence rates of 'deformity' in the order of 14 per 1000 person years among nonlepromatous cases. Each of these studies used different criteria for disabilities or deformities, and neither reported on disabilities arising after the completion of chemotherapy. Of particular interest in our data is the suggestion of higher incidence rates of disabilities *after* rather than *during* treatment (e.g. 4·9 compared to 1·3 per thousand person years for disabilities classified as moderate or severe). We plan in the future to compare these data with ongoing follow-up studies of patients during and after discharge from short course multiple drug regimens.[27]

It should be emphasized that we have described the disabilities in this population in a manner which is analogous but not identical to systems used by other authors or to any of the WHO scales. This has been necessary because of the nature of the data available to us, and has seemed preferable in that it allowed us to adjust the severity grading to what appears to us to be appropriate for this African population. The concordance between our system and the various WHO scales is illustrated in Tables 1 and 2. Given that the literature now contains many different systems for classifying leprosy-attributable disabilities, there is a need for a critical review of these systems, preferably with reference to the International Classification of Impairments Disabilities and Handicaps as recommended by the World Health Organization.[23]

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Preliminary observations on myiasis in leprosy patients

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Summary Out of 3350 leprosy patients attending the surgical outpatient department for various ulcerative lesions, 18 patients had typical symptoms of myiasis. Maggots were collected in 5 cases from the nose, in 3 cases from ulcers of the hand and in 10 cases from ulcers of the foot. It was possible to rear the maggots into flies in 8 out of 18 cases. The flies were identified as *Sarcophaga ruficornis* and *Chrysomyia bezziana*.

Introduction

Myiasis is more prevalent in the tropics and subtropics where leprosy is also prevalent. It is known that about 65% of lepromatous leprosy (LL) patients have ulcerative lesions of the nose[1] and about 10 to 20% of leprosy patients have ulcers in the foot and hand.[2] The anaesthesia caused by leprosy leads to small injuries and recurrent injuries produce ulcers and suppuration. The anaesthetized suppurative ulcers become congenial for the flies for laying eggs or larvae. The tiny first instar maggots invade the wounds and living tissues and increase the size of the ulcers, thereby complicating the injury. Therefore, myiasis, when it occurs, should be considered as a serious problem.

The literature of myiasis in leprosy patients is scanty. A few to quote are the reports by Rao,[3] Bose[4] and Tin Shwe[5] who reported myiasis in leprosy patients and observed that suppurative leprosy wounds inside the nose provided an attractive site for flies to breed.

During the course of our observations at the Central JALMA Institute for Leprosy, about 40 to 50 leprosy patients came for treatment for myiasis every year. In most of the cases maggot infection was in the nose, plantar ulcers and in a few cases in the wounds of hands. Leprosy patients pose a specific problem of anaesthesia and ulceration with suppuration. This makes them more prone to myiasis than non-leprosy patients. Therefore this study has been undertaken to screen the leprosy patients attending the surgical OPD for various ulcer treatments for myiasis and to determine the incidence of myiasis and the causative dipteran fly. This report presents the preliminary observations.

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Materials and methods

Leprosy patients attending the surgical outpatient department of the Central JALMA Institute for Leprosy, Agra, during the year 1986–87 for various ulcerative lesions were screened for myiasis. Patients with specific symptoms of nasal myiasis such as sensation of gnawing or crawling in the nose, irritation, sneezing and maggots ejected while sneezing, intense facial cellulitis, headache, nasal obstruction, frank epistaxis and foul-smelling discharge mixed with blood and mucus, were examined for myiasis. Similarly patients with ulcers on hand and foot with considerable swelling, foul-smelling discharge of thick pus, crawling sensation in the wound and maggots falling out, were screened.

From the patients with myiasis in the nose, the maggots were collected by washing the nasal cavity with saline and also by asking the patient to blow his nose into a clean Petri dish. The nose of maggot infected patients was irrigated with a turpentine–water mixture (1:10) twice daily and plugged with paraffin soaked ribbon gauze after applying a few drops of liquid paraffin. This procedure was continued and maggots were picked up manually until the discharge from the nose subsided.

The maggots from infected wounds of the hand and foot were picked up manually by using a pair of blunt forceps and transferred to a clean Petri dish. The infected wounds were cleaned and dressed with gauze soaked in a turpentine–water mixture (1:10) twice a day. Maggots were removed manually until the wound became clean.

Maggots thus collected in Petri dishes were transferred to a beaker containing meat, and the beaker was covered with a cloth and kept at room temperature away from other flies. Fresh meat was substituted periodically when the larvae were found moving out from the old meat. A few of the 3rd stage larvae moving out for pupation from each sample were treated with 10% menthol solution for 10 min, fixed in chloroform vapour and preserved in 70% alcohol for identification. The remaining 3rd stage larvae were transferred to a bowl containing sand and sawdust and allowed to pupate at room temperature. For identification later flies emerging from the pupae were held for 24 hr for the cuticle to harden, killed by etherization and preserved by pinning in glass tubes impregnated with a thin layer of naphthalene.

Results

A total of 3350 leprosy patients attending the surgical OPD for various ulcerative lesions

Table 1. Incidence of myiasis on various body parts of the patients

Type of leprosy	Nose	Hand	Foot	Total
LL	5	1	3	9
BT	0	2	6	8
Neuritic	0	0	1	1
Total	5	3	10	18

Table 2. Incidence of myiasis cases during the year 1986–87

Month	Number of cases
July and August 1986	2
September and October	9
November and December	6
January to June 1987	1
Total	18

were screened for myiasis and 18 were found positive. Sites of infection in the various types of leprosy are shown in Table 1.

Myiasis sex ratio was 1F:17M. The ages of patients ranged from 18 to 75 years and their history of leprosy ranged from 3 to 26 years. Monthly incidence of myiasis coincided with the prevalence of flies (Table 2).

It was possible to rear the maggots into flies in 8 out of 18 cases. The flies were identified as *Sarcophaga ruficornis* Fab. (Sarcophagidae—Flesh Flies) in one case and *Chrysomyia bezziana* Villeneuve (Calliphoridae—Blow Flies) in the other seven cases.

Discussion

Myiasis is defined as the parasitism of living mammalian tissue by larvae of dipteran flies. The flies responsible for myiasis are grouped as specific (obligatory), semi-specific (facultative) or accidental parasites.[6] This classification is based on the ovi-or larviposit-ing habits of the fly. Depending on the affected organ, the myiasis can also be classified as nasal, intestinal, aural, ocular, anal, vaginal, bladder or urinary tract.[7]

Rev. F W Hope[8] was the first to coin the term myiasis. Goldstein[9] was probably the first to report on myiasis in humans. The commonest genera causing myiasis in humans are *Sarcophaga, Lucilia, Calliphora* and *Chrysomyia.* Occasionally the common house-flies belonging to the genus *Musca* are also responsible for accidental myiasis in humans.

The maggots of certain species of dipteran flies are merely scavengers and sometimes found to be beneficial. These 'surgical maggots' are said to help in healing wounds. However it is very difficult to predict circumstances under which they act as scavengers or as serious parasites.

In leprosy maggot infestation is rare with an incidence of 0·5% in this report, but it can cause much distress, pain and increased tissue damage. In the present study the maggots that were identified were not the larvae of the common house-fly, and they were not even found beneficial in curing the ulcers. They were the flesh-eating ones responsible for specific and semi-specific myiasis. It was observed that myiasis in ulcers of the foot was more common than that of ulcers of the nose and hand. Occupation, age and sex were not seen as a major factor responsible for myiasis. The reason for getting more cases of myiasis during the post-monsoon season appears to be climatic and due to the increased prevalence of the flies. Poor personal hygiene as well as environmental conditions are the other compounding factors for myiasis. Flushing the ulcerative lesions with a turpentine–water mixture and manual removal of maggots were found to be the only way of treating

these cases. Myiasis is an avoidable problem which can be prevented primarily by early treatment of leprosy and prevention of ulcers. Even if ulcers have occurred, myiasis can be prevented by proper ulcer care and preventing flies from settling on the ulcers by keeping them regularly covered with dressings.

Acknowledgments

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Leprosy in Saudi Arabia, 1986–89

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Summary This study on leprosy includes information obtained from the Ibn Sina Hospital, a specialized centre established 27 years ago for treatment and management of the disease in Saudi Arabia. A total of 792 patients with leprosy were reported during the period of the study (1986–89). A steady decline was observed in the number of patients reported: 432 (54·55%) were non-Saudi and 360 (45·45%) were Saudi. Patients were reported from a total of 22 different countries. The majority of the non-Saudi patients were from the Yemen, 286 (36·11%). The male-to-female ratio was 3·83:1. The age groups comprised: 133 (16·79%), 51 to 80; 575 (72·60%), 21 to 50; and 84 (10·61%), under 20 years of age. The disease was classified into five categories (Ridley and Jopling classification): 295 (37·25%), lepromatous type; 238 (30·05%), tuberculoid type; 146 (18·43%), borderline–tuberculoid type; 29 (3·66%), borderline type; and 84 (10·61%), borderline–lepromatous type.

Although the number of registered patients is decreasing, this trend does not suggest an overall decline in the disease in the country. It is recommended, therefore, that the services being provided to patients with leprosy must be integrated with the nationwide network of the Primary Health Care Centres to implement effective control and prevention, including health education for the general population. Furthermore, mutual agreements must be developed with adjacent countries to study the geographic distribution of the disease.

Introduction

In Saudi Arabia it is estimated that roughly 6000 cases of leprosy occur in the population of approximately 10 million.[1,2] Most of the cases have been reported from the southern and western regions of the country.[3–5] At the time this study was compiled, 2200 patients with leprosy had received treatment at the Ibn Sina Hospital in Hadda, located about 35

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km from Jeddah. This Institution, established 27 years ago, is the only facility in Saudi Arabia for the treatment of leprosy.

Beginning in 1985, an infectious and communicable disease case reporting system was established by the Ministry of Health, which also required that all patients with leprosy identified elsewhere in Saudi Arabia be reported or transferred to the Ibn Sina Hospital for registration, treatment, and rehabilitation. Since then, records (including a treatment register and an individual patient file, modified from the OMSLEP recording and reporting system for patients with leprosy that provides all the necessary information for patient evaluation) have been maintained.[6] During the study period, about 792 patients registered for treatment, rehabilitation, and follow up at the Ibn Sina Hospital.

This study includes information on the patients who entered Saudi Arabia from the southern borders (Yemen), solely for specialized treatment at the Ibn Sina Hospital. In addition, a considerable expatriate population exists in the country. Patients from this population who have developed leprosy are also reported. This study explores the implication and significance of the number of patients with leprosy in the Saudi and non-Saudi population.

Subjects and methods

The subjects of this study were all patients with leprosy reported to the Ibn Sina Hospital during the period of 1986–89. The total number of reported patients was 792, which included both sexes as well as Saudi and non-Saudi patients.

Medical records at Ibn Sina Hospital were scrutinized and information regarding age, sex, nationality, area of residents, year of registry, as well as type of disease was obtained.[7] Although the 792 patients were reported at the Ibn Sina Hospital for the first time in the year shown, not all of them had been diagnosed during that year. Some of the patients had been diagnosed earlier elsewhere, and for various reasons had not been reported until the year in question. The majority of these previously unreported patients involved expatriates who had been admitted to Saudi Arabia with known disease. In addition, the majority of the 286 (36·11%) patients from Yemen came to Saudi Arabia for treatment and rehabilitation for their disease and deformities at the Ibn Sina Hospital. The data were collected only for the registered patients during the study period. The patients were categorized according to the Ridley and Jopling classification into five types: lepromatous, tuberculoid, borderline–tuberculoid, borderline, and borderline–lepromatous.[7] The data were transferred to coding sheets and entered into computer files. Data were analysed using an IBM microcomputer; SPSSPC + software package was used to analyse the data.

Results

This study showed that the number of patients with leprosy registered during the last four years (1986–1989) has declined. A high of 268 patients with leprosy was reported in 1986 and a low of 158 in 1988, with an increase to 169 patients reported in 1989 (Table 1). The average number of patients admitted was 198 per year.

Of the total 792 patients reported with leprosy during 1986 to 1989 in Saudi Arabia,

Table 1. Reported cases of leprosy in Saudi Arabia (1986 to November 1989)

	Patients registered	
Year	No.	%
1986	262	33·08
1987	203	25·63
1988	158	19·95
1989	169	21·34
Total	792	100·00

Table 2. Distribution of patients with leprosy in Saudi Arabia by gender (1986 to November 1989)

	Male		Female		
Year	No.	%*	No.	%†	Total
1986	217	34·55	45	27·44	262
1987	165	27·27	38	23·17	203
1988	122	19·43	36	21·95	158
1989	124	19·74	45	27·44	169
Total	628	100·00	164	100·00	792

* Percentage of total males, 1986 to November 1989.

† Percentage of total females, 1986 to November 1989.

Table 3. Age distribution of patients with leprosy in Saudi Arabia (1986 to November 1989)

Age range (years)	No.	%
< 20	84	10·61
21–50	575	72·60
51–80	133	16·79
Total	792	100·00

628 (79·29%) were males and 164 (20·71%) were females, for a ratio of 3·83:1 (Table 2). Of these patients, 133 (16·79%) were 51 to 80 years old, 575 (72·60%) were 21 to 50 years old, and 84 (10·61%) were under 20 years old (Table 3). Of those under 20, nine (1·14%) were less than ten years old. None of the registered patients were excluded from the study.

CLASSIFICATION OF DISEASE

According to the Ridley and Jopling classification of disease, the lepromatous type had the highest number of patients 295 (37·25%) compared to the other types. Classification breakdowns for other categories were: tuberculoid type, 238 (30·05%); borderline–tuberculoid, 146 (18·43%); borderline type, 29 (3·66%); and borderline–lepromatous type, 84 (10·61%) (Table 4).

REGIONAL DISTRIBUTION IN PATIENTS WITH LEPROSY

The largest number of patients, 306 (60·47%) was from the western region. The southern region had the next largest number of reported cases, 116 (22·92%). The number of patients reported from the central region was 44 (8·69%); those reported from the northern region were 31 (6·13%); and the remaining nine (1·79%) were reported from the eastern region (Table 5). These data demonstrate that the disease may be concentrated in the south-western region of the country.

SAUDI VERSUS NON-SAUDI PATIENTS WITH LEPROSY

Classifying the patients into Saudi and non-Saudi groups, the results of this study showed more non-Saudi than Saudi patients. Of the 792 reported patients, 432 (54·55%) were

Table 4. Classification of disease in patients with leprosy reported in Saudi Arabia (1986 to November 1989)

Type of disease	No.	%
Lepromatous	295	37·25
Tuberculoid	238	30·05
Borderline–tuberculoid	146	18·43
Borderline	29	3·66
Borderline–lepromatous	84	10·61
Total	792	100·00

Table 5. Distribution of patients with leprosy in Saudi Arabia by region* (1986 to November 1989)

Region	No.	%
Western	306	60·47
Southern	116	22·92
Central	44	8·69
Northern	31	6·13
Eastern	9	1·79
Total	506	100·00

* Does not include 286 Yemeni patients.

Table 6. Source of patients with leprosy reported in Saudi Arabia, native and foreign born (1986 to November 1989)

	Saudi		Non-Saudi		Total	
Year	No.	%*	No.	%	No.	%*
1986	127	16·04	135	17·05	262	33·08
1987	95	11·99	108	13·64	203	25·63
1988	64	8·08	94	11·87	158	19·95
1989	74	9·34	95	11·99	169	21·34
Total	360	45·45	432	54·55	792	100·00

* Percentage of total patients reported (1986 to November 1989).

non-Saudi and 360 (45·45%) were Saudi (Table 6). The non-Saudi patients came into Saudi Arabia from 22 countries. The Yemenis contributed the largest number of patients reported among the non-Saudi group—286 (36·11%) of the total. The second largest group, 95 (12%), was reported from the Asian subcontinent. Lastly, 51 (6·44%) were reported from Africa (Table 7). The total number of Saudi patients declined from 127 in 1986 to 64 in 1988, then increased to 74 in 1989, whereas the non-Saudi patients declined from 135 in 1986 to 94 in 1988, then increased by one patient in 1989. The overall total demonstrates that the trend of the patients reported with leprosy during the study period was declining, with a slight increase in the number of patients reported in 1989 (Table 6).

Table 7. Distribution of patients with leprosy in Saudi Arabia by nationality (1986 to November 1989)

Country	No.	%
Saudi Arabia	360	45·45
Yemen	286	36·11
India	40	5·05
Pakistan	24	3·03
Egypt	16	2·02
Bangladesh	15	1·89
Sudan	10	1·26
Indonesia	9	1·14
Somalia	4	0·51
Burma	4	0·51
Eritrea	3	0·38
Mali	3	0·38
Sri-lanka	3	0·38
Ethiopia	3	0·38
Other	12	1·51
Total	792	100·00

Discussion

Before 1985, medical records and a case registry were not properly maintained at Ibn Sina Hospital, hence an accurate follow-up of patients was not available. A suspected diagnosis of leprosy is the only qualification for admission to the Ibn Sina Hospital. Anyone who has or is suspected of having leprosy, and comes to the hospital requesting care for an illness, is entitled to admission. This liberal admission policy applied not only to Saudi patients, but also to all expatriates, including those who are in the country on a visitor's visa or pilgrimage visa, and aliens residing in the country illegally. Any expatriate may be hospitalized for treatment, because treatment is considered to be a control measure instituted to decrease or eliminate hazards these expatriates may present to the Saudi Arabian public health.

Accurate records of the 2200 patients who received treatment at the Ibn Sina Hospital before 1986 were not available; therefore, comparisons could not be made to reflect the average annual change of reported patients with leprosy in the country. Previous studies have not demonstrated long-term comparisons.[3–5] A recent report from the eastern region concluded that the disease was rare in this region.[5] In our study, patients reported from the southeastern region remain the highest, and those reported from the eastern region the least, which is in concordance with previous reports.[3,4]

This study showed a decline in the number of Saudi patients registered during the past four years; however, an increase is expected in the number of reported patients over the next few years. This is to be attributed to the recently established nationwide primary health services network of the Ministry of Health. It is also expected that the Ministry of Health will adopt the World Health Organisation (WHO) recommendations to integrate the primary health care service providers, and involve them in management of patients with leprosy, as well as develop awareness in the community through health education.[8,9] The decline in the number of non-Saudi patients is due to the stringent measures the Government has taken to screen expatriate workers before issuing them with work permits to enter the country; however, a few escape detection or may not have developed the disease at the time of entry. The other category of patients is from Yemen. The Yemeni patients contribute to the largest number of patients entering the country legitimately, either as expatriate workers or specifically to seek medical treatment. Accurate data were not available on the contacts with Saudi as well as non-Saudi patients.

Conclusions

The prevalence of patients with leprosy in Saudi Arabia remains less than in the neighbouring countries. With improved health services being offered to the community through the Primary Health Care Centres of the Ministry of Health, proposed integration of the management of diagnosed cases at this level, a further decline is expected in patients being reported to the Ibn Sina Hospital. The patient registration system, therefore, must be enforced rigorously to identify new patients and their contacts to promote efficient control programmes nationwide.

Although sincere efforts are made by the personnel of the Ibn Sina Hospital to maintain contact with patients throughout the duration of their treatment, loss to follow-

up remains a disadvantage for the programme. Saudi patients may return to their town and continue receiving treatment, either at the Primary Health Care Centre or in a private medical facility, whereas non-Saudi patients may return to their country of origin.

So far, no regional or nationwide surveys have been conducted to study the magnitude of the disease in Saudi Arabia, nor are there any established programmes through the government or non-government organizations for the control of leprosy in Saudi Arabia. The recent representation of Saudi Arabia in the international activities of the WHO for the prevention and control of leprosy, however, has provided an incentive to develop such programmes in the country.

Recommendations

Based on the results of this study, it is recommended that:

1 A surveillance system be developed to detect patients with leprosy using the primary health care centres.
2 Specific guidelines be established according to the WHO requirements to integrate primary health services.

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SPECIAL ARTICLE

Basic requirements for implementation of multidrug therapy—ILEP Medical Bulletin

In 1982 the World Health Organisation (WHO) officially recommended that leprosy should be treated with multidrug therapy (MDT). Experience in using the WHO recommended MDT regimens has shown that they are effective, safe and acceptable to patients and field staff.

However, only 39·5% of the 4·3 million leprosy patients registered for chemotherapy at the end of 1988 were on MDT while a cumulative number of one million patients had completed treatment with MDT. Apparently far too many leprosy patients do not have access to the benefits of MDT. To a great extent, this regrettable situation can be attributed to the fact that in many countries the health services cannot fulfil the complex and demanding requirements for the introduction of MDT which were identified some eight years ago.

A working group of the ILEP Medical Commission's Leprosy Control Expert Discipline, in which programme managers from various parts of the world participated, met in Brussels in September 1989 in order to review these requirements and to formulate recommendations which are more appropriate to the real field situation in many leprosy endemic countries. The recommendations were endorsed by the Medical Commission in December 1989 and were slightly adapted after the Interface Meeting of the ILEP member associations and the Medical Commission in June 1990. They represent the consensus of the members of the working group and the Medical Commission.

These recommendations concern basic rather than optimal requirements, which are intended especially for those programmes which otherwise could not implement MDT.

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The following are the suggested recommendations and are reprinted in full with the permission of ILEP, from a *Medical Bulletin*, Issue No. 1, revised July 1990.

1 INTRODUCTION

The current strategy for leprosy control is early diagnosis and the provision of effective chemotherapy in order to cure the patient, to interrupt transmission and to prevent leprosy-related disabilities.

At present, regular and complete course with multidrug therapy (MDT) of all known

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leprosy cases and early diagnosed new cases is the best available effective approach to achieve leprosy control and its use must be the top priority for leprosy control programmes. Using this approach will decrease the need for social, psychological and economic rehabilitation of the leprosy patient.

Until now on the global scale the coverage of MDT has been too slow. There has been hesitation to use MDT especially because the requirements proposed for its introduction were too demanding for the health services in many leprosy-endemic countries. In order to assist ILEP members to quickly expand the coverage of MDT in their own projects as well as those of national and local governments, the basic rather than the optimal requirements which should be met before MDT is implemented have been identified as follows.

2 THE MDT REGIMEN

2.1 MDT should be given to all patients in need of chemotherapy.

2.2 In principle there is no longer a place for dapsone monotherapy. Where dapsone monotherapy is used, every effort must be made to transfer the patients to MDT.

2.3 The WHO recommended MDT regimens for Multibacillary (MB) and Paucibacillary (PB) leprosy are recommended for routine field conditions. Experience has shown that they are effective, safe and operationally feasible. They are acceptable to patients and field staff.

This does not imply that where some countries have already introduced other multidrug regimens which have proven to be equally effective and safe that these are to be changed.

2.4 Experience with the WHO MDT regimens has shown that 24 monthly doses in 36 months for MB patients and 6 monthly doses in 9 months for PB patients is adequate thus continuation of treatment beyond these periods is not necessary in the vast majority of the cases.

The available evidence indicates that the risk of relapse after MDT is low. Moreover, as it is always possible to adequately retreat relapsed cases, the possibility of relapse after treatment should be accepted; this is so for other diseases.

2.5 The principle of monthly supervised intake of drugs should be adhered to and ideally supervision should be done at the peripheral health service and by a health worker. However, if a health worker is unavailable a village leader, teacher, family member, etc. could be given this responsibility.

In particular cases such as migrant workers, inaccessible roads due to the rainy season, etc., patients could be entrusted with more than one month's supply of drugs. In such cases the provision of blister calendar packs is indicated.

2.6 The following are reasons for stopping MDT:

—severe liver disease,
—severe toxic or allergic side-effects to the drugs.

In cases of leprosy patients also suffering from tuberculosis, both diseases should be treated simultaneously.

3 THE BASIC REQUIREMENTS WHICH MUST BE MET BEFORE IMPLEMENTING MDT

MDT can be introduced into and successfully implemented in all existing health infrastructures in leprosy-endemic countries if the following basic requirements are fulfilled:

3.1 Political and professional commitment

In principle, commitment at all administrative levels is essential to expand the coverage of MDT.

In practice, the commitment of one or two key professional individuals in the health service to introduce MDT at a local level is the basic requirement.

3.2 A plan of action

This can be a simple statement of objectives, main activities with targets and timetable, a statement of the finances needed and information on who is responsible for the allocation of resources.

3.3 Operational guidelines

This can be a simple document which includes information on:

—Job descriptions,
—Supervisory schedules,
—Criteria for the diagnosis and classification of patients,
—Criteria for the selection of patients for MDT, this includes criteria for screening old patients currently on register,
—Treatment regimens,
—Management of patients during treatment including periodicity of examination, absentee tracing, prevention of disability and management of complications (including referral procedure),
—Procedure at release from treatment,
—Recording and reporting of patient data.

3.4 Competent staff

Staff responsible for leprosy control should be able to diagnose leprosy, treat patients and give health education on regularity of drug intake and disability prevention to patients. Their training should be task-orientated according to appropriate job descriptions.

Well trained paramedical workers can diagnose leprosy, give treatment with MDT and give adequate health education. As treatment has a fixed duration the paramedical worker can release patients from treatment. Thus it is not absolutely necessary for every patient to be seen by a doctor.

At the regional/provincial and/or district levels, staff with adequate knowledge and skills in the field of management of leprosy control should be available for supervision, training and referral.

3.5 Availability of drugs

There must be an adequate logistical system to guarantee a secure and uninterrupted drug supply.

3.6 Collection of basic data

The following is the minimum data required:

—Number of patients registered for chemotherapy (MB and PB),
—Number of patients registered for MDT (MB and PB),
—Proportion of patients who have successfully completed MDT within the required time period (MB and PB).

Although the availability of the following data is not a pre-requisite for the introduction of MDT, collection of this information is recommended in order to monitor the effectiveness of case finding and disability prevention activities:

—Proportion of cases with disabilities (grade 2) among newly detected cases,
—Proportion of patients who developed new disabilities among those on register/or MDT.

3.7 Case detection activities

With the introduction of a good quality service, voluntary self-reporting should be the basis of conducting cases. Active case finding can be limited to the examination of the patients' contacts.

This can be a useful occasion also to improve the motivation of the patient through fostering the support of the family.

3.8 Diagnosis

The vast majority of leprosy patients who report voluntarily to the health service can be diagnosed using clinical skills only.

With the application of well-defined criteria, a number of programmes base the classification into MB and PB leprosy on clinical findings alone. (To help field programmes, the ILEP Medical Commission intends to convene a working group to define the most appropriate criteria for this purpose.)

If there is doubt about the classification of leprosy, the MDT regimen for MB leprosy should be given to the patient.

3.9 Laboratory Services

Skin smear examination is necessary in the diagnosis of early lepromatous cases and is useful in monitoring the classification which was made on clinical grounds. Therefore it is recommended that reliable skin smear services should be established.

In practice, however, skin smear services in most programmes are not reliable. As already discussed in section 3.8, almost all patients can be diagnosed using clinical skills only. The availability of skin smear services is thus not an absolute prerequisite for starting MDT on the condition that if there is doubt about the classification of leprosy, the MDT regimen for MB leprosy should be given to the patient.

3.10 Care activities

Early diagnosis and adequate treatment with MDT are the most important means of preventing disabilities.

Whilst the early detection of neuritis and the treatment of reactions is extremely important, the lack of this service should not be a block to the introduction of MDT.

The main responsibility for the prevention of new/increasing disabilities should be given to the patient. Health education in self care practices should be given to those patients at risk of developing disabilities.

Though the early detection of neuritis and the treatment of reactions are extremely important, the provision of this care is not an absolute requirement to the introduction of MDT. However, it is strongly recommended that these services should be established as soon as possible.

3.11 Surveillance after MDT treatment

It is recommended that passive surveillance only is carried out. Each patient should be aware at the time of release from treatment of the need to contact the health service if problems are experienced.

3.12 Rehabilitation services

The availability of rehabilitation services although important and desirable is not a prerequisite for introducing MDT. However, if rehabilitation services exist for the physically or socially handicapped, every effort should be made to make these services available for leprosy patients as well.

4 THE FRAMEWORK FOR IMPLEMENTATION OF MDT

ILEP Members should aim at the implementation of MDT through the General Health Services (based on the primary health care approach). This would give a wider and more comprehensive coverage and provide greater continuity of service. Where this is not yet possible, vertical services may still be appropriate but consideration should be given to combining the leprosy service with other vertical health programmes as a transition towards full integration. Within the integrated programme a specialized component should be available at the more central levels for supervision, training and referral. ILEP Members can play a crucial role in expanding the coverage of MDT. Member-Associations should consider the following proposal:

Acceptance of the global goal of **'MDT for all leprosy cases by the year 2000'.**

* * *

This document was originally produced by a working group of the Leprosy Control Expert Discipline co-ordinated by the Damien Foundation Belgium in September 1989. It was endorsed by the ILEP Medical Commission in December 1989 and revised following the 2nd ILEP Interface meeting in June 1990.

Lepr Rev (1990) **61,** 391–404

Letters to the Editor

MULTIDRUG THERAPY IN PAUCIBACILLARY LEPROSY

Sir,

Chopra *et al.* have reported some interesting results in their trial of multidrug (MDT) in paucibacillary leprosy (*Lepr Rev*, 1990; **61:** 157–62), and they took exemplary care to avoid mistaking upgrading (reversal) reaction for relapse, but a proper evaluation of their study would be facilitated if they would clarify the following points: (1) What was the numerical composition of the four types of PBL included in their trial? (2) How many patients failed to complete treatment? (3) Were all patients followed-up for three years? If so, why is a two-year period mentioned on p. 158? (4) Did any of the 723 patients relapse after taking MDT for 12 months?

Finally, from experience gained in this trial, would the authors recommend that all PBL cases should be treated for 12 months and followed-up for three years?

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W H JOPLING

ARE DAPSONE HYPERSENSITIVITY REACTIONS DOSE RELATED?

Sir,

I would be surprised if there are many leprologists who would disagree with the often repeated concern regarding dapsone hypersensitivity reactions. Numerous publications in the past five years from many countries have commented on the frequency as well as the severity of this phenomenon and most have concluded with some hypotheses as to the reason for the presumed increase in incidence of dapsone hypersensitivity in one or other of its manifestations.

I am stimulated to reply to the paper by Richardus & Smith[1] on the recent observation of the recovery of a ten-year-old boy with full blown dapsone syndrome in the south east of Nepal. He is the thirteenth case of dapsone hypersensitivity (fortunately none fatal) in the past two years from this leprosy control project, which currently has a total of 4645 patients on treatment, 59% of whom are on standard WHO multidrug therapy. With two exceptions all of these patients were started on full dose dapsone monotherapy and hence developed their problem before rifampicin or rifampicin and clofazimine were commenced. It can be seen from Smith's paper[2] that two of the three fatalities we reported to him from Zambia were in patients who were still on monotherapy at the time of their catastrophic drug reaction and this has similarly been reported over many years.[3 6]

It would therefore suggest to me that the combination of dapsone with other antileprosy drugs, as has been suggested elsewhere, is not a factor in the possible increase in dapsone hypersensitivity. The high starting dose of dapsone given almost universally to all patients is probably a more significant factor. The idea that a reduced dose of dapsone may lessen the incidence of side-effects is certainly not new.[3] Additionally it was considered that the dapsone syndrome virtually disappeared with the subsequent lowering of the initial dose, for example to 25 mg weekly.[6] A small average body

weight population, such as the Nepalese, Burmese, Thais, etc. may be even more at risk from starting on full dose dapsone.[7] Where health workers are not sufficiently alert to the problem, or where the patient stays at home, it may initially be the case that further doses of dapsone are consumed after the presenting features of hypersensitivity occur and this may also result in more serious manifestations and possibly increase the likelihood of a fatal outcome.

I think we would see fewer and less severe problems if we started adults at 50 mg per day and children at 25 mg per day and only after a period of four weeks on this dose assumed the standard WHO recommended dose.

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IMPLEMENTATION OF MULTIDRUG THERAPY FOR LEPROSY CONTROL PROGRAMMES

Sir,

In a recent article (*Lepr Rev*, 1990; **61:** 64–72) Georgiev & McDougall put forward certain important proposals that emphasized a change in the strategy of MDT in leprosy control programmes. On more than one occasion the authors have expressed concern at the inadequacy of peripheral laboratory services,[1,2] their articles bear numerous references which indicate that the functioning of smear laboratories continue to be unsatisfactory in many of the control programmes. We have been involved in organizing the smear laboratory in some of the MDT districts in India and our experience is also disappointing. In response to their correspondence we also presented certain views which appeared in a subsequent issue of the Journal.[3] Some of our proposals contained in the said correspondence were:

The replacement of inadequately staffed and equipped peripheral laboratories with one well organized laboratory at district level, where smears of only selected cases would be examined.
2 Discontinuation of routine smear examination in each and every case.
3 Identification of a cut-off point to stop treatment in multibacillary cases. These patients become clinically inactive much earlier to smear negativity. There is evidence that bacilli clearance continues even after stoppage of chemotherapy.[4,5] Hence it is recommended that clinical inactivity and the absence of solid and fragmented bacilli may be considered as the cut-off point for ceasing therapy.
4 Liberalization of the smear reporting system. It is peculiar to leprosy that:

(i) a negative smear report does not exclude the disease, since about 80% of cases are smear negative.

(ii) the extent of tissue damage is proportional to the hosts aberrent tissue behaviour rather than to bacterial load.

(iii) the number of bacilli in a microscopic field can be anything from 1 to >1000 and any count whatsoever deserves three drugs for a minimum period of two years. Hence, as in any other bacterial disease, why not concentrate our expertise on reporting only 'positive' or 'negative' with accuracy. Grading no doubt gives the density of bacteria as the source of infection. For this a less comprehensive system, which can be done by visual impression alone, as proposed below will suffice:

<100 per field	1+ or few
100–1000 per field	2+ or numerous
>1000 per field	3+ or innumerable

Such less precise grading has already been advocated and practised.[6]

5 Laboratory reports are mostly either supportive or confirmative, both in diagnosis and classification. One needs to know clinically whether a disease is generalized or localized before deciding on a particular schedule of treatment. The number of skin and nerve lesions would no doubt be an important parameter for clinically classifying the disease. Whether these lesions are produced directly due to *Mycobacterium leprae* (as in BL or LL) or indirectly due to its products (as in BT or TT) is immaterial. Two more aspects, namely the active or inactive status of the disease and the reaction proneness must also be kept in mind. They considerably influence the length of treatment.

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COMMENT: ASSESSMENT OF HISTOLOGICAL RESPONSE TO TREATMENT

Sir,

There is a striking lack of therapeutic trials in leprosy compared with other diseases of similar importance and it was encouraging to read the paper by Pattyn *et al.* (*Lepr Rev*, 1990; **61:** 151–6).

As the authors state, there is a particular problem in assessing the response of paucibacillary leprosy to treatment, since one cannot use the fall of the Bacterological Index (BI) as a measure of outcome. The use of histological resolution as an index of cure is novel and perhaps deserved greater success. However, it should be noted that histological assessment is by its nature subjective and the

failure to demonstrate differences between different therapeutic regimens may owe much to this. Disappearance of histological lesions is difficult to judge and, unlike BI, gives no information about the rate of resolution in the early stages of treatment.

In future therapeutic trials in paucibacillary patients, it would be useful to assess the granuloma fraction (GF), which falls during treatment in both paucibacillary and multibacillary leprosy. The proportion of the dermis occupied by granuloma (GF) can be assessed objectively and with a high degree of reproducibility using simple tracing devices.[1,2]

The method is easy to use and the equipment is relatively inexpensive. I would be pleased to help other centres set up the necessary equipment or to cooperate with those wishing to run clinical trials.

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EXPERIENCES WITH REPEATED QUALITY CONTROLS OF SKIN SMEARS IN DIFFERENT ROUTINE SERVICES IN LEPROSY CONTROL PROGRAMMES

Sir,

In 1987 the leprosy reference laboratory at the Armauer Hansen Institut started an evaluation of skin smears with the objective to obtain more detailed information on the actual standard of laboratory work in various leprosy control programmes. By the end of 1989, 84 laboratory technicians had participated in this quality control. The performance of 50 technicians was evaluated and reported previously.[1]

In general, laboratory technicians whose performance was unsatisfactory according to the criteria set by the reference laboratory,[1] were asked to send a second set of slides for further evaluation. Among these, those with unsatisfactory results were asked to participate a third and—if necessary—fourth time in the quality control. Each check was followed by a written assessment which analysed deviations in the results, trying to explain them to the technicians and providing suggestions for improvement. Besides the evaluation of the reliability of the results, individual feedback was given to the technicians, in the hope of stimulating motivation and self-criticism. The results of these repeated quality controls are presented in the following:

Out of the 84 participating laboratory technicians, 58 (69%) were invited to take part in further evaluations. Twenty three (39·7%) actually sent a second set of slides. Twenty of these laboratory technicians (87%) came from Asia, 2 (8·7%) from Africa and 1 (4·4%) from South America. Table 1 compares the results of the first and second quality control according to taking, staining and reading of the skin smears. Out of the 23 laboratory technicians evaluated, 10 (43·5%) were asked to send slides for a third quality check, in which 7 technicians participated.

The results of this third quality control are presented in Table 2. This evaluation was followed by a fourth one, in which 5 laboratory technicians participated. Of these 5 laboratory technicians, 2 were asked for further slides, based on the results of the third quality control, and 3 laboratory technicians participated voluntarily. The results of this fourth quality check are presented in Table 3.

Table 1. Comparison of the first and second quality control results, according to taking, staining and reading of skin smears performed by 23 laboratory technicians

Continent	No. of technicians	Quality control	Taking			Staining			Reading			
			*	†	‡	*	†	‡	§	*	†	‡
Asia	20	I	7	3	10	1	14	5	0	4	7	9
		II	15	1	4	7	4	9	0	7	8	5
Africa	2	I		1	1			2				2
		II	1	0	1		1	1	0	1	1	0
South America	1	I		1			1			1		
		II		1		1				1	0	0

* good; † satisfactory; ‡ unsatisfactory; § very good.

Table 2. Comparison of the second and third quality control results, according to taking, staining and reading of skin smears performed by 7 laboratory technicians

Continent	No. of technicians	Quality control	Taking			Staining			Reading			
			*	†	‡	*	†	‡	§	*	†	‡
Asia	6	II	5	1	0	4	0	2	0	2	3	1
		III	4	0	2	3	1	2	1	1	1	3
Africa	1	II			1			1		1		
		III			1			1		1		

See Table 1 for notation.

Table 3. Comparison of the third and fourth quality control results, according to taking, staining and reading of skin smears performed by 5 laboratory technicians

Continent	No. of technicians	Quality control	Taking			Staining			Reading			
			*	†	‡	*	†	‡		*	†	‡
Asia	5	III	3	0	2	2		3		1	0	4
		IV	3	0	2	1	2	2	1	0	3	1

See Table 1 for notation.

Qualitative data were analysed using Yates continuity corrected Chi-square or—if an expected value in any cell was less than 5—by Fisher's exact test. According to our data, only the taking of smears had improved significantly ($p = 0{\cdot}041$), when comparing the second with the first quality control. Differences in staining and reading were not significant when the results of the quality controls were compared with each other.

Repeated assessments of skin smears have been performed during the last three years. Besides the evaluation of the actual standard of laboratory work in various leprosy control programmes, we

hoped that by giving a regular feedback to the participating laboratory technicians we might be able to improve their skills. We assumed that basically the laboratory technicians were sufficiently trained and that by pointing out possible reasons for differences between their skin-smear results and ours as well as through our suggestions, we might be able to improve their performance. The evaluation of our data does not indicate that a true improvement in the overall work performance has been achieved. However, there was little participation in the third and fourth quality control, so that statistical analysis alone might be misleading.

The ability to take good skin smears improved significantly when the results of the second quality control were compared with the first one. However, in the third quality control 2 of the laboratory technicians whose performance was good or satisfactory in the second quality check had unsatisfactory results and no change in skills was found when the results of the third were compared to the fourth quality control.

After the first assessment, 6 participants changed their staining method from hot to cold staining or vice versa. Of the 5 participants who changed from hot to cold staining, 1 laboratory technician improved from satisfactory to good. One laboratory technician, whose previous stains were satisfactory, obtained unsatisfactory ones when changing staining methods from cold to hot. Seventeen participants did not modify their method, but followed the suggestions given by the reference laboratory, leading to an improvement of 6 and a worsening in performance of 2 laboratory technicians. In the third and fourth evaluation of skin smears, none of the participating technicians improved their staining convincingly.

Even though reading did not improve significantly during the various quality controls, some of the laboratory technicians were able to better their reading, leading particularly to a decrease in unsatisfactory results. During the first quality control, misclassification into paucibacillary or multibacillary leprosy was found in 8 slides (4·4%), decreasing to 2 slides (1%) out of the 184 examined.

In conclusion, we are not able to state clearly whether quality controls in the leprosy reference laboratory at the Armauer Hansen Institute lead to a definite improvement in the working skills of the participating laboratory technicians or whether this improvement occurred by chance. Nevertheless, we think that the quality control of skin smears does benefit the laboratory technicians. Whether this feedback is more important in terms of 'moral support' or is able to effectively improve performance in the long run, will have to be shown by collecting more data. Improvement as a result of suggestions based on regular evaluation of skin smears might only be of limited value, because it does not replace lack of knowledge or technical 'know-how'. How refresher courses and quality controls can be combined effectively should be discussed and evaluated further.

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ACID-FAST AND H&E STAININGS CAN BE COMBINED BETTER THAN IN THE TRIFF METHOD

Sir,

The TRIFF staining for *Mycobacterium leprae*[1] is usually considered convenient and ideal for demonstration purposes.[2,3] In some institutions this method is the main tool of the histological

diagnosis of leprosy. Compared with *M. tuberculosis* the *M. leprae* is much less acid and alcohol fast,[4] thus any treatment with alcohol and acid should be minimal. However, the TRIFF method requires six treatments with acid alcohol or alcohol as follows:

1 differentiation of the carbol fuchsin
2 differentiation of the Harris' haematoxylin
3 dehydration after eosin
4 staining in alcoholic saffron
5 rinsing after saffron
6 final dehydration before mounting

All these steps contribute to the removal of the carbol fuchsin accounting for the difficulties experienced in controlling the method. In our hands the TRIFF staining is rather capricious and invariably gives poor results on granular bacilli. For diagnostic purposes the separately stained H&E and modified Wade–Fite stainings[5] have not been surpassed. If one opts for the use of a single slide, then we would recommend an alternative stain. This method is a combination of the H&E and acid-fast stainings and it has been aimed at simplicity and reliability.

1	Dewax sections in a mixture of xylene and vegetable oil, preferably clove oil (2:1)	15 min
2	Blot, dry till opaque and wash in running water	5 min
2/a.	Remove mercury/formol pigment, if applicable	
3	Stain with filtered carbol fuchsin	25 min
4	Wash in running water	5 min
5	Differentiate in 0·5% acid alcohol or in 10% sulphuric acid	1–20 sec
6	Wash in running water	5 min
7	Stain in Mayer's or preferably Carazzi's haematoxylin[6]	20 sec
8	Blue in tap water or in tap water substitute if necessary	
9	Stain in 1% aqueous eosin	60 sec
10	Differentiate eosin in running water	1–5 min
11	Blot, dry in oven at 45°C	30 min
12	Clear in xylene and mount	

This method eliminates the last five alcoholic treatments of the TRIFF staining. The use of a progressive haematoxylin makes the second acid alcohol unnecessary, which is a major drawback of the TRIFF staining. The staining with alcoholic saffron has entirely been left out as it gives little additional information. Finally, the alcoholic dehydration has been substituted by the blot and dry method.

Following dewaxing the sections should be carefully blotted several times and then dried. Breaking this rule results in prolonged differentiation time, moreover the desirable decolourization of the background may not be reached. The only critical step is the differentiation of the carbol fuchsin. Usually every batch contains a few slides which have to be returned into the differentiating agent for a few more dips or seconds. The progress and the final result of the decolourization should be checked under the microscope. However, as experience grows the pale pink hue of the sections is a good indicator of the proper differentiation. The times for steps 7 to 10 may vary widely depending on the actual solutions and the pathologist's preference. A relatively long differentiation of the eosin is important as the strong eosin can obscure the bacilli. The rule of thumb is that the hues of both the haematoxylin and the eosin should be lighter than those of the ordinary H&E staining.

It cannot be overemphasized that each batch of slides to be stained by any acid-fast method for either diagnostic or research purposes *must* include a positive control section,[7] as false negative results are much more common than it is usually supposed. The control specimen of choice is an old regressing lepromatous case predominated by granular bacilli of decreased stainability.

The information on the bacteria furnished by this method is fully comparable with that of the

modified Wade–Fite staining.[5] On the other hand the staining may not be equal to a neatly prepared H&E due to the slight fuzziness of the cellular details resulting from the oily dewaxing.

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AMYLOIDOSIS—A POSSIBLE MINOR FACTOR CONTRIBUTING TO THE DISAPPEARANCE OF LEPROSY FROM NORTHERN EUROPE

Sir,

The disappearance of leprosy from Northern Europe even before the advent of antileprosy drugs is an epidemiological mystery. Peter Richards[1] has traced the rise and fall of the disease in Europe in his book and enumerated the various theories regarding this topic. The various factors thought to be responsible for the fall of the disease include the isolation of the patients; plague epidemics which contributed by killing the patients and by reducing the total population; increase in the prevalence of tuberculosis which conferred immunity against leprosy and, lastly, improved socioeconomic conditions which improved housing and nutrition. However, none of the theories can explain the historical facts. Richards concludes that many circumstances have contributed to differing extents at different times.[1]

One more factor that may have contributed is reactive systemic amyloidosis. It is known that Europeans are more likely to contract the lepromatous form of the disease than are Indians or Africans.[2] Also, recurrent erythema nodosum leprosum (ENL) reactions are associated with development of amyloidosis.[3] The prevalence of amyloidosis in leprosy patients is variable.[4] Renal amyloidosis is reported in 5% leprosy patients in tropical regions but a high prevalence of more than 30% is reported from the United States and Argentina.[4] Cochrane had noted that amyloidosis is rare, except in Caucasian races and to some extent in Mongolian people as a terminal complication of leprosy.[5] There are at least 3 different phenotypes of the serum amyloid A protein (SAA),[6] an acute phase protein whose levels increase during ENL reactions.[3] The amyloid fibrils are derived from the SAA. It is possible, though not yet proved, that the susceptibility to develop amyloidosis may depend on the SAA phenotype. It is likely that the leprosy patients in Europe had two

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peculiarities—high prevalence of the lepromatous form of the disease and increased susceptibility of these lepromatous patients to develop reactive systemic amyloidosis as a complication of ENL reactions which were untreated or poorly controlled. Death of lepromatous patients from amyloidosis may have reduced the infectious pool in the community thus reducing the chances of infection. Thus amyloidosis may have contributed to the disappearance of leprosy from Northern Europe along with the other factors that have been mentioned.

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EFFECT OF CALENDULA ON TROPHIC ULCERS

Sir,

We concur with Dr Srinivasan's view in his article (*Lepr Rev*, 1989; **60:** 278–82). Only immobilization of the affected part can facilitate healing and prevent repeated trauma. However, in our field areas, medical advice on immobilization went unheeded because the patients (usually illiterate farm labourers) feared loss of daily wages. Many refused plaster casts because of social reasons but preferred using topical antibiotics prescribed by obliging practitioners.

With the objective of preventing secondary infection, we tried to compare the effects of an inexpensive homeopathic ointment (calendula) and topical antibiotics. In this study, 18 patients of both sexes in the 25–45 age group were randomly divided into 3 groups using the lottery method. Only 4 patients were on multidrug therapy while the others had been 'released from treatment' following prolonged dapsone monotherapy. Calendula ointment is prepared by mixing tincture of marigold flowers (*Tagetes patula*) with 10% white soft paraffin. In order to ensure 'blindness', calendula ointment, topical neomycin (commonly prescribed by practitioners in our field area) and plain white soft paraffin were re-packed in identical containers and labelled with code numbers.

After 3–4 weeks, patients using calendula ointment showed 30–40% reduction in depth and diameter of the trophic ulcers and absence of any secondary infection, despite their refusal to immobilize the affected part. Since calendula is a natural product with no known untoward effects, we feel that our observations may be useful to field personnel facing similar problems.

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MALIGNANCY IN PLANTAR ULCERS IN LEPROSY

Sir,

Carcinomatous transformation in trophic ulcers, though not very frequent, is a potential danger to leprosy patients. After retirement from active service with TLM in India and Bhutan I (RGR) had several short-term assignments in Bhutan, Bangladesh, and Tanzania. On these occasions I came across six cases of malignancy in plantar ulcers 3 of which were proved histopathologically squamous cell carcinoma. The rest showed strong clinical evidence of malignancy though it was not possible to take a biopsy. In some cases it appeared that this possibility is not given sufficient consideration in diagnostic and therapeutic procedures and sometimes it is overlooked. This is not altogether surprising as in some of the newer textbooks on leprosy,[1] malignancy in plantar ulcers is not mentioned at all or only parenthetically.

Condensed histories of 2 of the cases are given below:

Case 1

A hill farmer from West Bhutan, male, aged 63, with lepromatous leprosy of 37 year's duration, who had received DDS monotherapy for 19 years. He was BI 4·3+, negative after 10 years. He was treated mostly as an out-patient, occasionally as an in-patient. He had had trophic ulcers on the left forefoot (MTH area) on and off for 20 years. Conventional treatment with immobilization and protective footwear was only partly successful under the constraints of village life.

In August 1986 he was admitted to hospital with a large cauliflower growth of uncertain duration, which covered the whole left forefoot. There was secondary infection with foul smelling pus and involvement of regional lymph nodes. There was no decisive improvement despite adequate treatment. On 27 August 1986 a biopsy was taken from the edge of the ulcer and lymph nodes. Six weeks later there was a spread of infection and acute haemorrhaging. On 21 October 1986 a below the knee amputation was performed. On 22 October 1986 the result of the biopsy was received: well differentiated squamous cell carcinoma; lymph nodes show no evidence of malignancy.

Postoperatively the patient developed necrosis of the skin covering the stump and then hepatitis. His death occurred on 5 November 1986.

Case 2

A farmer from Eastern Bangladesh, male, aged 59, with borderline–tuberculoid leprosy of 5 year's duration, who had received irregular multidrug therapy for 4 years. His BI was negative. Treated mostly as an out-patient in a village clinic, and occasionally as an in-patient for ulcer treatment in a central hospital—the ulcer was of the left heel and of 4 year's duration. In November 1988 the ulcer was covered with hypertrophic granulation tissue. A biopsy showed hyperplastic squamous epithelium, nonspecific infiltration of the dermis by acute and chronic inflammatory cells; no malignancy.

The patient went to another centre for excision of the ulcer and returned 2 months later. The ulcer had not healed. He received further irregular treatment at the village clinic.

On 2 March 1990 the patient was admitted to hospital with a plantar ulcer on the left heel, 5·5 × 4 cm, covered with sluggish red, partly fungating granulation tissue overhanging at the edges. On probing the rough surface of the calcaneus foul smelling pus was present. The lymph nodes were enlarged and tender. A biopsy showed well-differentiated squamous cell carcinoma infiltrating the dermis.

Discussion

Duration of the ulcer is an important factor in the aethiopathogenesis of cancer in trophic ulcers. Constant tissue irritation due to frequent traumatization and/or chronic infection with or without osteomyelitis needs time to have its effect. The great majority of leprosy patients receive domiciliary or village clinic treatment, where they are sometimes seen irregularly, and ulcers do not receive much attention. It is essential that plantar ulcers are checked regularly and carefully by the drug delivery team so that the beginning of malignant degeneration is not overlooked.

Even though this happens in only a small percentage, those who get it face a fatal outcome. Epidemiologically this does not matter. But besides trying to control the endemicity of leprosy we should continue to care for the afflicted individual. The size of the problem is difficult to estimate. In Bhutan, e.g. I know of 3 cases out of a total of about 6000 leprosy patients. Assuming that 12% of all patients have ulcers this means that among 720 ulcer patients 3 develop malignancy, i.e. 0·4%. Applied to India with 4 million leprosy patients this would mean 480,000 ulcer patients with approximately 2000 cases with malignant degeneration. Even if this guess is grossly off the mark it merits closer scrutiny.

Further it would be worthwhile to investigate the following:

1 Duration of disease, duration and type of treatment.
2 Type of disease—does immune deficiency play a role?
3 Quality of nervous damage—Superficial, deep sensation? Loss of autonomous function? Loss of motor function?
4 Duration and location of ulceration. Type of ulcer treatment.
5 Other aspects of aethiopathogenesis.
6 Development of secondaries.
7 Consequences regarding prevention and treatment.
Is wide excision still advisable, or rather below the knee amputation?
Are prosthesis available, and what of rehabilitation?
For prevention every plantar ulcer should receive early attention and consistent treatment. Better still is the prevention of disability. The best prevention, of course, is early detection and treatment of every leprosy patient before disability can develop.

The possibility of malignant degeneration should be thought of and taught at every level of staff dealing with leprosy patients.

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PACHYDERMOPERIOSTOSIS AND LEPROSY

Sir,

I write to propose that pachydermoperiostosis be given a recognized place in the differential diagnosis of lepromatous leprosy (LL). Apart from my references to this disease[1,2] there has been no mention of it in leprosy literature, and it is time leprosy workers were given a description of it. In the *Textbook of Dermatology*, 4th edition, it is called 'a rare developmental defect which has been reported in many races, and occurs predominantly in males. The condition has been attributed to an autosomal dominant gene of variable expressivity'.

Physical signs of primary pachydermoperiostosis. These are largely confined to skin and bones. There is thickening of the skin of the scalp, forehead, and to a lesser extent, of the face, with a pattern of folds and fissures simulating the leonine facies of LL. There is thickening of the skin of the hands and feet, and clubbing of fingers and toes. Thickening of upper eyelids gives an expression of somnolence, and the nose may enlarge. Facial skin is shiny because of sebaceous activity, and sweating may be excessive. There have been reports of gynaecomastia and impotence. X-rays show periosteal thickening (proliferative periostitis) of limb bones. Skin and bone changes develop soon after puberty, progress for the next 5–10 years, then remain unchanged (see Table 1). Secondary pachydermoperiostosis causes no confusion with leprosy as skin changes are mild or absent, and the patient has chronic pulmonary disease.

A Case Report. An Indian male in his early 30s was referred to me at the Hospital for Tropical Diseases in 1973 with a provisional diagnosis of LL. On examination he looked older than his years. The skin of his forehead was thickened and thrown into folds, and his upper eyelids were thickened

Table 1. Similarities between pachydermoperiostosis and lepromatous leprosy

Pachydermoperiostosis	Lepromatous leprosy
It may appear in families	It may appear in families
Patients look prematurely old	Patients look prematurely old
Forehead is furrowed	Forehead is furrowed
Upper eyelids thickened	Upper eyelids thickened
Face appears shiny	Face appears shiny
Nose may be enlarged	Nose may be enlarged
Legs and feet become thickened	Legs and feet become thickened
Gynaecomastia and impotence may develop	Gynaecomastia and impotence may develop
Hyperhidrosis common	Hyperhidrosis (compensatory) common
Peripheral nerves thickened	Peripheral nerves thickened in late stage
Periostitis of long bones	Periostitis of long bones in neglected cases

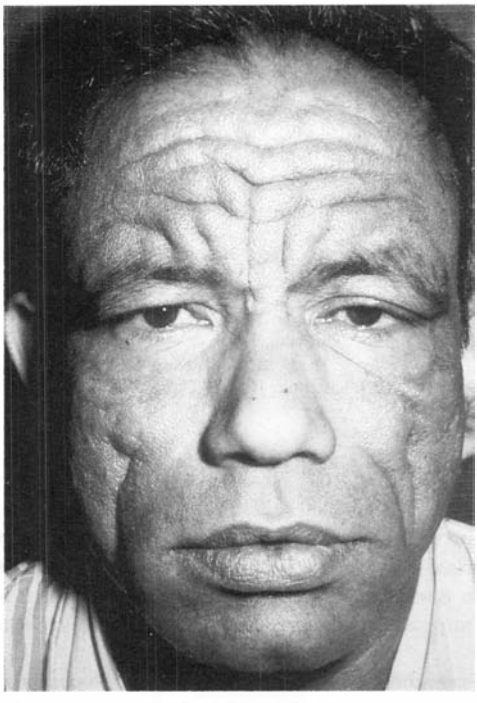

Figure 1. The patient.

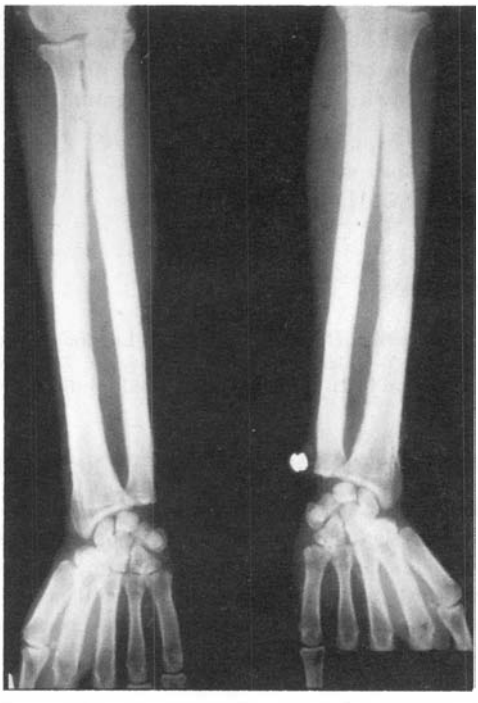

Figure 2. Proliferative periostitis of radius and ulna.

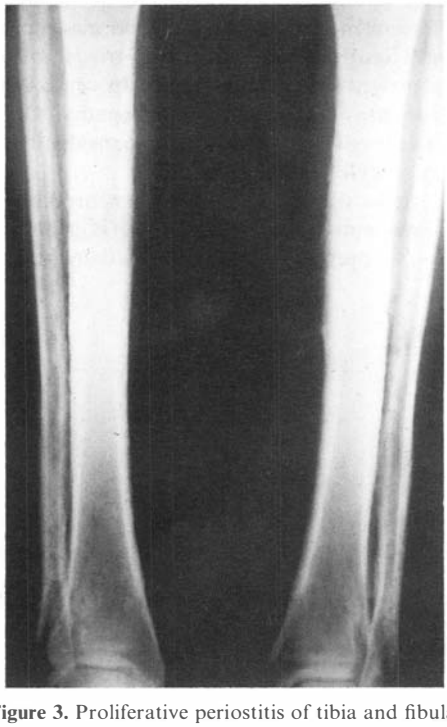

Figure 3. Proliferative periostitis of tibia and fibula.

(Figure 1). The skin of his hands and feet was thickened and there was clubbing of fingers and toes. X-rays of bones of forearms and lower legs showed periosteal thickening (Figures 2 and 3). Palpation of his peripheral nerves revealed generalized thickening—a feature which had not previously been recorded in the literature. Skin smears were negative for AFB.

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PREVENTION OF PERIPHERAL NERVE DAMAGE IN LEPROSY

Sir,

Peripheral nerve damage is the most important problem in leprosy, leading to the disabilities we are so familiar with. Apart from treatment with corticosteroids during the active phase of neuritis, very little can be done once peripheral nerves are damaged. The only hopeful development at present is a microsurgical technique of nerve decompression pioneered by Dr W J Theuvenet at Anandaban Leprosy Hospital in Nepal.[1]

I would like to draw attention to the potential possibility of a medical approach. Recently an article appeared in the *New England Journal of Medicine* describing the positive results of an ACTH (4-9) analogue, Org 2766, in the prevention of cisplatin induced neuropathy in patients treated for ovarian cancer.[2] Although the exact mechanism is not known, evidence suggests that the presence of melanocortins (such as Org 2766) in nerve tissue may trigger off or facilitate neural repair. Melanocortins have already proved beneficial in rats with crush injuries, cut injuries, diabetic neuropathy, acrylamide neuropathy and cisplatin neuropathy. Org 2766 showed no adverse reactions in humans in the trial described and the authors consider it as promising in the treatment of other forms of neuropathy as well.

At present there is no experience with Org 2766 at all in neuropathy caused by leprosy.[3] In view of the potential of this drug, I recommend that full attention is given to it by researchers in the field of leprosy. Every possibility to prevent or treat nerve damage in leprosy is of paramount importance.

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Chiang Mai 50000
Thailand

J H RICHARDUS

References

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Lepr Rev (1990) **61,** 405–413

Teaching Materials and Services

Neuropathic foot in leprosy, Poona, India—best film award

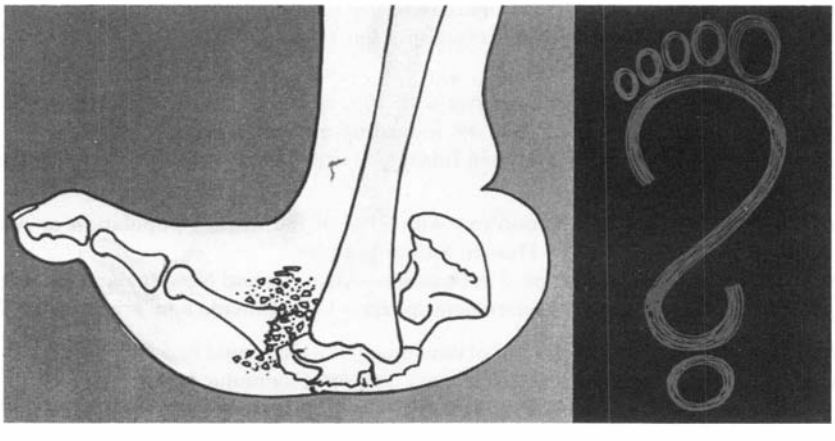
This film received the highest award of Best Scientific Film at the 37th National Film Festival 1990, New Dehli. This documentary was filmed mainly at the routine foot clinics of the Dr Bandorawalla Leprosy Hospital, Kondhawa, with special emphasis on the research work on tarsal disintegration.

The evolution of the foot, its unique features, and certain innovative procedures of 'graded weight bearing' and 'auto-correction of gait' are described. In this work, commendable contributions have been made by Dr Sanjay Sane, Mr Vivek Kulkarni and Mr Anjay Dey. The scientific direction, commentary and overall features were prepared by Dr Mehta, while on the technical side, Director: Mr Vishram Revankar, Cameraman: Mr Vijay Deshmukh and Artist: Mr S Phansalkar have made worthy contributions. The animation sequences explain well the function and pathological changes of the foot. The advantages of bare-foot walking and the better development of the foot without restrictive footwear have been studied in the Indian context. The Producer's Award was conferred on Dr Mehta and the Director's Award on Mr Revankar.

The principles of foot management enunciated in the film are applicable to foot conditions in other peripheral nerve disorders and diseases like diabetes mellitus. The film is ideally suited for medical training.

The film is 25 mins in length. Price: 16 mm film, Rs 9900; for video VHS format of the PAL system, Rs 1600. Postage and packing extra. Enquiries: Dr Jal Mehta, Poona District Leprosy Committee, 35, 'Manisha', 2-A Moledina Road, Pune 411 001, India.

[The 1989 Award was also received by Poona and was reported in *Lepr Rev*, 1990, **61,** 201.]



Eye health at village level

Hanyane: a village struggles for eye health by Erika Sutter, Allen Foster and Victoria Francis is 'a useful, colourfully illustrated book on eye health directed at various categories of community health

workers and their trainers. Presents problems in the area of community eye care and simple, practical ways of solving them using stories, questions, and discussions.

Includes lecture notes on eye diseases, their diagnosis and management at both the village health worker and the ophthalmic assistant levels.' Available from Teaching-aids At Low Cost (TALC) for £3.25, plus postage and handling, at the following address: Teaching-aids At Low Cost (TALC), PO Box 49, St Albans, Herts AL1 4AX, United Kingdom.

The International Human Suffering Index—poster/brochure

The Human Suffering Index statistically rates living conditions in 130 countries. It was created to measure, in a single figure, differences in living conditions between countries. The presentation also allows a side-by-side comparison of rates of population increase and human suffering.

Each individual country index is compiled by adding 10 measures of human welfare related to economics, demography, health and governance: (1) income, (2) inflation, (3) demand for new jobs, (4) urban population pressures, (5) infant mortality, (6) nutrition, (7) clean water (8) energy use, (9) adult literacy and (10) personal freedom.

Each of the 10 measures of well-being is ranked from 1 to 10—the most distressful being 10. For example, Ethiopia receives a rating of 10 in the Infant Mortality Index because 152 Ethiopian children under one year of age die out of every 1000 born, one of the highest rates in the world.

The 10 measures are added together to obtain The Human Suffering index. Those countries with high infant mortality rates, low gross national product per capita, poor supplies of clean drinking water, etc., scored high on the index—close to 100.

Living conditions are worst in Mozambique, followed by Angola, Afghanistan, Chad, Mali, Ghana, Somalia, Niger, Burkina Faso, Central African Republic, Zaire, Benin and Malawi. The most comfortable countries to live in are Switzerland, West Germany, Luxembourg, the Netherlands and the United States, in that order.

Countries rated in The Human Suffering Index were grouped in the following quadrants:

Extreme Human Suffering: The 30 countries with 11% of the world's population or 519 million people registered 75 or greater on The Human Suffering Index.

Of these countries, 24 are in Africa; 6 are in Asia. None is in Europe or the Western Hemisphere.

High Human Suffering: The 44 countries with 58% of the world's population or 2·85 billion people registered between 50 and 74 on The Human Suffering Index.

Of these countries, 16 are in Africa; 16 are in Asia; 11 are in Latin America; 1—Papua-New Guinea—in Oceania; none is in Europe.

Moderate Human Suffering: The 29 countries with 10% of the world's population or 491 million people recorded an index between 25 and 49, indicating moderate levels of suffering.

Of these countries, 10 are in Asia; 7 are in Europe; 11 are in Latin America. Mauritius is the only African country in this category.

Minimal Human Suffering: The 27 countries with 21% of the world's population or one billion people recorded 24 or lower on The Human Suffering Index.

Of these countries 20 are in Europe; 2 in Oceania—Australia and New Zealand; 2 are in Asia—Japan and Singapore; 3 are in the Western hemisphere—U.S., Canada and Trinidad and Tobago.

This publication carries a vast amount of data much of which could be used to further document the association between the prevalence of leprosy and socioeconomic status.

Apply: Human Suffering Index, Population Crisis Committee, 1120 19th Street, NW #550, Washington DC 20036, USA. Price: US $5.00, pre-paid, per copy.

INFOLEP: Leprosy Information Services

Until 1987 the Leprosy Documentation Service (INFOLEP) aimed at providing international coverage of documentary information concerning mycobacterial diseases to users throughout the

world for the purposes of research, education and policy-making. INFOLEP was a joint project of the Netherlands Leprosy Relief Association (NSL) and the Royal Tropical Institute (KIT).

In October 1987 NSL and KIT terminated the contract of cooperation with regard to INFOLEP and activities were suspended. The aim of becoming a worldwide oriented information centre was not reached because of insufficient personnel, organizational and management problems and a too broad scope of goals. During the period April 1987 till May 1988 external experts provided reports on possible future tasks of INFOLEP. In November 1987 and in July 1988 the Board of NSL took decisions on the future of INFOLEP. It was resolved that INFOLEP should shift from a passive documentation service to a pro-active approach.

INFOLEP restarted as INFOLEP Leprosy Information Services in September 1989 with the following general objective: to strengthen the capacity of the countries with which NSL cooperates, to locally develop, produce and distribute teaching and learning materials in leprosy.

Objectives

To find possibilities to locally develop, produce and distribute teaching and learning materials in leprosy, primarily in countries with which NSL cooperates. If such possibilities are identified and considered feasible, INFOLEP will support such activities, through pilot projects, starting in Indonesia. To make the TLM (available in a given NSL-project) accessible and applicable to other NSL-projects. INFOLEP will have to occupy a linking position between different projects and serve as a back-up centre by setting up and maintaining an information-network for developing, producing and distributing TLM in the various projects.

Means

INFOLEP has an extended collection in the fields of leprosy and leprosy control consisting of journal articles, books, journals, brochures, reports, slides, films and other audiovisual material, which can be consulted and/or borrowed. The greater part of the collection consists of scientific medical material, the smaller part teaching and learning material. Due to the new objective of INFOLEP more attention will be given to this material from now on. The collection is accessible to visitors and students, enquiries by letter will be dealt with.

INFOLEP also offers to NSL-projects the possibility to order, copy and/or borrow literature by inter library loan as well as to arrange literature searches.

Services to TALMILEP

Keeping up-to-date all publications on leprosy available at all ILEP-projects in the form of a bibliography.

INFOLEP Leprosy Information Services being a project of NSL, belongs to the project department of NSL and is based in the NSL office at Wibautstraat 135, 1097 DN, Amsterdam, The Netherlands. Project leader: Ir D J Ponsteen. Information officer: Ms H M Dietrich, librarian/documentalist. Medical adviser: Drs R Verduin, Royal Tropical Institute/Leprosy Unit, Amsterdam.

A consultative expert group has been installed to advise INFOLEP in setting up and maintaining its task. The members represent the following disciplines:

Leprology:	Drs R Verduin (Royal Tropical Institute, Amsterdam).
Library/documentation:	Ms E R M Spruit (Centre for Health Education, Utrecht).
Health education:	Dr H R Folmer (Royal Tropical Institute, Amsterdam).
Information/education:	Dr A Kater (Centre for the Study of Education in Developing Countries, The Hague).
Secretariat:	Ir D J Ponsteen.

African Leprosy Aid

African Leprosy Aid is a small, Midlands-based charity which aims to help leprosy patients and leprosaria in Africa. It is mainly geared to the provision of simple aids to prevent damage and disability, but has also supplied transport, sewing machines, water systems, electric pumps and hospital equipment. One of the trustees, Mr Alfred Foster, became interested in disability prevention for leprosy patients after retiring from his work as an engineer. He was invited to Liteta Leprosarium in 1986 by Dr Richard de Soldenhoff and is due to go to Sierra Leone early in 1991, accompanied by his grandchildren, who are gifted musicians. They will give concerts there to raise more money for the work.

Instructions and illustrations of a method for making footwear, using thin rubber, bonded with a neoprene based adhesive, for the soles, together with more information about African Leprosy Aid, are available from Mr Alfred Foster, 6 Foster Road, Woodville, Burton-on-Trent, Staffordshire, England.

TDR: Tropical diseases on the increase

The following is extracted from *TDR News*, No. 32, June 1990:

'Governments are becoming deeply concerned about tropical diseases, to judge by the 43rd World Health Assembly in Geneva this May—the first time since 1980 that the Assembly has considered TDR, at length, as a separate agenda item.

In a resolution on TDR (see p. 3), delegations requested WHO Director-General, Dr Hiroshi Nakajima, 'to ensure the continuation of the Special Programme's global leadership role in tropical disease research', and appealed to the pharmaceutical industry to increase research and development in tropical diseases and step up collaboration with TDR.

During technical discussions, many delegations listed increasing problems with tropical diseases, which dramatically underlined the need for research to improve the delivery of existing tools, and to provide better drugs and treatments.

The Cameroon delegate expressed 'extreme urgency' to find new tools to control malaria. TDR, pleaded Malawi, should intensify its research into vaccines and drugs that could be 'available to everyone'.

In Nigeria, even existing drugs are not getting to those who need them. Under 5% of leprosy patients there are receiving multi-drug therapy. In the resulting vacuum, patients are suffering from illicit trade in fake and substandard drugs, emphasizing the urgent need to develop new cost-effective and practical means of delivering tools that work.

The Congo is seeing a 'resurgence' of parasitic diseases, with two major foci of sleeping sickness, a nearly 3% prevalence of leprosy, increasing schistosomiasis and drug-resistant falciparum malaria. In Zaire 'all diseases are rife in their most severe forms'.

Operational research to find ways to reduce the cost of drug delivery and other control tools is being undertaken in collaboration with WHO's Action Programme on Essential Drugs and the Division of Control of Tropical Diseases (CTD).

There is also urgent need for social research in the field, said Dr Godal, for example, to determine health care and control priorities of the communities themselves. But too few social scientists are prepared to undertake the work'.

TDR: Call for Applications for Support of Research Training (1991)

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), established in 1976, has two objectives:

(1) research and development of new tools to control the TDR target diseases: malaria, filariasis, trypanosomiasis, leishmaniasis, schistosomiasis and leprosy.
(2) strengthening of research capabilities in countries where these diseases are endemic.

As an important way to achieve its second objective, TDR provides funding to train research workers from disease-endemic countries. TDR support enables research workers to acquire research skills related to one or more of the TDR target diseases or in a discipline related to these diseases, such as molecular and cell biology, immunology, entomology, parasitology, epidemiology, clinical pharmacology, and the social sciences. Funding is available for opportunities in established training programmes for studies leading to a doctoral level Degree, or for an individualized post-graduate programme in a centre which conducts research in tropical diseases. Support for Masters level courses will be considered in exceptional cases.

The maximum duration of TDR support for research and training is three years. Those eligible to apply for research training include:

- staff members of (i) institutions currently receiving one of the TDR institution strengthening grants, and (ii) other institutions where TDR support for such grants ended two to three years ago;
- scientists from other institutions who are already engaged in research or committed to doing research on one or more of TDR's target diseases, and whose home institution is equipped with required research facilities;
- staff members of Ministry of Health disease control services who are involved in planning, executing and evaluating disease control programmes related to TDR's target diseases;
- scientists who have had appropriate postgraduate training in epidemiology, social sciences, and other field-oriented subjects and who require practical, hands-on (postdoctoral) training in a research project or suitable institution doing field research in one of TDR's target diseases;
- scientists with postgraduate research training who have been actively involved in clinical, field or laboratory research in one of TDR's target diseases for a minimum of five years and who now want to spend a period of time in a suitable research centre or laboratory to upgrade their skills or to carry out specialized experiments or data analyses.

Further enquiries: Dr J A Hashmi, Special Programme for Research and Training in Tropical Diseases, WHO, 1211 Geneva 27, Switzerland.

Water, Engineering and Development Centre, Loughborough, UK

The Water, Engineering and Development Centre (WEDC) is a self funding unit within Loughborough University of Technology devoted to training, research, consultancy and other activities related to the planning, provision, operation and maintenance of water supplies, sanitation and physical infrastructure in developing countries.

WEDC is especially concerned

- with all that is appropriate for rural areas and low income communities;
- with site preparation, water supply, disposal of liquid and solid wastes, roads and communications, buildings, and other services that improve the health and well-being of people living in towns and cities;
- with small-scale irrigation, rural water supply and sanitation and technological facilities for the economic and social development of rural areas;
- with refugees and the relief of natural and man-made disasters;
- with appropriate technology, cost effective design and construction, sustainability through good operation and maintenance, the optimization of institutional support, and health education, mobilization and participation of communities;
- with the integration of technological, social and management inputs for development.

For further information: Information Officer, WEDC, Loughborough University of Technology, Leicestershire LE11 3TU, England.

Leprosy poster from ALM International and Wellcome

There are available 150 sets of Wellcome Tropical Institute posters on leprosy consisting of 9 main themes, which cover all aspects of the disease, in colour together with text. ALM is prepared to send a set free of charge to any *bona fide* applicant but they reserve the right to exercise judgement with regard to appropriate recipients. A covering letter from ALM will accompany each set, together with a questionnaire which should be completed by each recipient and which will greatly aid assessment of the value of these posters for teaching and other purposes. The language is English only. Apply to the Medical Consultant, American Leprosy Missions International, 1 ALM Way, Greenville, South Carolina 29601, USA.

WHO publications 1986–1990

The latest edition of the WHO Publications Catalogue (240 pp) of new books (1986–1990) summarizes WHO policy with regard to publications as follows:

Reliable information is the cornerstone for building the awareness, expertise, and practical strategies necessary to improve the world at its heart: the health—physical, mental, and social—of humanity.

For 40 years the development of reliable information has been one of the functions of the World Health Organization. Charged to act as the world's directing and coordinating authority on questions of human health, WHO has developed a host of networks and mechanisms for generating data, applying facts to problems, and recommending solutions that will lead to sustained improvements in health.

Much of the information developed by WHO is made available to the world through an extensive programme of publications, now numbering 7 periodicals and close to 80 new books each year. Some are practical manuals for use in preventing and controlling disease or developing quality health care. Others are unique guides to internationally accepted procedures, standards, or practice, introducing uniformity to world medical care. Still others attack urgent technical problems with advice formulated and agreed upon by international groups of experts.

Action Health 2000, Cambridge, UK

Based at Bath House, Gwydir Street, Cambridge, UK, this organization is concerned with various aspects of health care in Third World countries, but has given emphasis to elective periods abroad for medical students, nurses and other health paramedical workers. In association with the Bureau for Overseas Medical Services (Africa Centre, 38 King Street, London WC2E 8JT), AH 2000 has produced an 'electives booklet', which deals with all aspects of preparing for an elective overseas, including practical organization, communication, the role of an elective student and personal health care. The booklet is available from BOMS.

The spring meeting of AH 2000 was held in Sheffield and the programme included talks on: Sheffield University's Third World Community Health Research Programme; primary dental care in India; facing up to AIDS and the Economic Crises in Zambia; action on disability and development; programmes with disabled people; ageing in developing countries.

Tuberculosis skill book, Marie Adelaide Centre, Karachi, Pakistan

This 202 pp book, of typed format, is published by the Training Department of the Marie Adelaide Centre. The introduction modestly describes the objectives as helping the reader to learn skills needed to diagnose and cure individual tuberculosis patients and control the disease, whilst at the same time, '... enabling you to become a competent and successful tuberculosis technician, who knows his job and loves his work and his patients'. (The term technician in this context describes a health or paramedical worker.) The whole subject is covered extremely thoroughly and the book is well illustrated throughout with line drawings. Although essentially for use in Pakistan, this book is exceptional in its range and quality and could, with some modification, be valuable in many other tuberculosis-endemic countries.

For further details write to: Marie Adelaide Centre, Mariam Manzil, AM 21, off Shahrah-e-Liaquat, POB No. 8666, Karachi-03 Pakistan.

TALMILEP—Catalogue of teaching and learning materials

Health workers in leprosy endemic countries are faced with a shortage of suitable teaching and learning materials. Printed materials do exist, but often do not reach the people who need them. In order to overcome this problem, The Leprosy Mission International operates a distribution service, and is in contact with health staff in 112 countries. This service is carried out in co-operation with other member associations of ILEP (International Federation of Anti-Leprosy Associations).

A revised catalogue is now available, and contains information about 31 titles in English, selected for those involved in leprosy control, patient care and training activities.

Copies of the catalogue may be obtained from: Teaching and Learning Materials, The Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex, TW8 0QH United Kingdom.

Colour transparency teaching sets for India

Glindia Ltd (formerly Glaxo Laboratories (India) Ltd), Dr Annie Besant Road, Bombay 400 025, India, now have 18 colour transparency slide sets, with written text, on a wide range of subjects in clinical medicine, sexually transmitted diseases and dermatology. The set of 48 slides on leprosy has been updated recently and is composed entirely of Indian patients. The authors are Dr V D Parekh, Dr R Ganapati and Dr Chetan Oberai, all from Bombay. A price list is available on application from Dr Pritam Phatnani, Head of Medical Education at the above address.

Steam sterilization 'slide set'

Steam sterilization of reusable syringes and needles has been adopted as the preferred global policy of the Expanded Programme on Immunization and over 100,000 portable steam sterilizers have been distributed to the field in the last two years. The most recent addition to the range of training materials available from the EPI unit in Geneva is the 'Sterilization Slideset'.

The set of 48 slides, packed in an A5 size plastic folder with an English and French commentary, is intended to be used during the practical training of health workers in the use of steam sterilizers and reusable plastic syringes. The first 26 slides are focused on the process of loading the sterilizer and conducting a sterilization cycle. The remainder of the slides show the sterile techniques to be followed when assembling syringes for use and the mechanical cleaning of the syringes and needles.

The slideset was prepared by the EPI using funds and facilities provided by Prestige Medical, United Kingdom.

(Source: *Essential Drugs Monitor*, No. 8, 1989, WHO, CH-1211, Geneva 27, Switzerland.)

Clinical guidelines: diagnostic and treatment manual

A therapeutic guide for nurses, medical assistants and doctors in hospitals, health centres, dispensaries and refugee camps. It summarizes etiology, prevention, diagnosis and treatment of approximately 200 common diseases and complaints and is based on many years of practical field work.

The book is very successful in combining recommendations by technical organizations, such as WHO, and standard specialist handbooks with the practical experience of organizations, such as Médecins sans Frontières, UNICEF and UNHCR. The result is a highly practical manual which can serve for both training and reference. Its size and price make it as essential as the drugs it is intended to accompany.

Available in French, English and Spanish from Médecins sans Frontières, 68 Bd. St-Marcel, 75005 Paris, France. Price FFr 87 (approximately $15.00). Add postage FFr 10 (Europe), FFr 20 (outside Europe).

(Source: *Essential Drugs Monitor*, No. 8, 1989, WHO, CH-1211, Geneva 27, Switzerland.)

Making low-cost spectacles

Christoffel Blindenmission (CBM) have come up with a system for producing spectacles locally in most African countries. They are based in Germany and have so far set up 25 workshops in more than 15 countries.

It trains local indigenous workers, the training takes about four weeks and trainees need little previous formal education.

80% of demand for spectacles in many African countries south of the Sahara can be met with spherical lenses, mainly for people with long-sightedness in old age and those who had cateract operations. The demand for glasses to correct short sight is currently low.

Christoffel Blindenmission has a set of guidelines for setting up optical workshops, the approximate cost of setting up a workshop is US$625–875. Some tools need to be imported, but others will be available locally.

The workshops can easily produce two pairs of glasses per hour of work which can add up to 3000 pairs a year. This is enough to keep the average eye clinic or mobile unit well stocked. Most of the workshops soon become self supporting and even return a profit if properly managed.

Details are available from: Program for the prevention of Blindness, World Health Organization, 1211 Geneva 27, Switzerland.

(Source: *Health Lines* a quarterly newsletter concerning general and personal health matters. OXFAM, 274 Banbury Road, Oxford OX2 7DZ, England.)

Leprosy; a guide for professional workers; TLM, South Africa

This booklet was originally compiled by Dr E McCabe, former consultant at Westfort Hospital, South Africa. The 15 pages cover definition, world distribution, aetiology, spread, types of leprosy, clinical signs, chemotherapy, reactions, rehabilitation, surgery, care of the hands and eyes, control schemes and research. The initiative in the production of special shoes made of canvas, deepened for Plastazote or sponge rubber, with Velcro straps, is particularly interesting. Further details of this approach have been published elsewhere in this Journal (**60,** 332 and **61,** 291).

Further enquiries to: The Reverend L A Wiseman, The Leprosy Mission (Southern Africa), PO Box 890527, Lyndhurst 2106, Republic of South Africa.

Chemotherapy of leprosy for control programmes. Video

This video describes the recent regimens of drug treatment for leprosy, based on the Report of a WHO Study Group. The intended audience includes—medically qualified doctors, senior personnel in ministries of health in leprosy-endemic countries, tutors and teachers in medical and para-medical schools, programme planners, leprosy control officers and supervisors, senior staff in pharmacies, drug supply and distribution.

The subject matter covers the classification of leprosy according to both Madrid and Ridley–Jopling systems; definition of pauci- and multi-bacillary leprosy; unit dosage and regimens of dapsone, rifampicin, clofazimine and the thioamides for the treatment of both pauci- and multi-bacillary cases. In order to ensure the safe and effective implementation of multiple drug therapy for as many patients as possible and with the minimum of delay, repeated emphasis is given to the importance of the training, retraining and supervision of the health personnel concerned.

Available from: Department of Medical Illustration, John Radcliffe Hospital, Headington, Oxford OX3 9DU, England. Cost: £16 (US$25) plus postage.

Leprosy—the misunderstood disease. Film

The above colour film has been produced by the Katharina Kasper Leprosy Control Scheme, Bangalore. It runs for 21 minutes and was directed by Mr T S Ranga. The medical expertise in the production of this film was provided by Dr M S Nilakanta Rao (who has also written the script), Dr E Vomstein and Mr H Meermeier. At present the film is available in three languages: English,

Kannada and Tamil. Production in other languages, e g Telegu, Urdu, Hindi and Marathi are also contemplated.

Further enquiries about cost and despatch to: Project Officer, Katharina Kasper Leprosy Control Scheme, 16 Hutchins Road, Cooke Town, Bangalore 560 005, Karnataka, India.

Transmission of HIV in health-care settings

The following is the summary of an article published in the *Bulletin of the World Health Organization*, **67**(5): 577–82 (1989), entitled, 'Transmission of human immunodeficiency virus (HIV) in health-care settings worldwide':

Based on the information available, transmission of human immunodeficiency virus (HIV) can and does occur in health-care settings. No cases of such transmission have been reported from an infected health-care worker to a patient. Transmission of HIV from an infected patient to a health-care worker has been documented after parenteral or mucous-membrane exposure to blood. However, this risk is $< 1\%$, is limited to exposure to blood, and can be further minimized through adherence to routine infection control measures. Patient-to-patient transmission through invasive equipment or through HIV-infected blood, blood products, organs, tissues, or semen also occurs but can be prevented by proper sterilization of instruments and through donor-deferral, donor screening, and heat treatment of Factors VIII or IX to inactivate the HIV. In health-care settings, prevention of HIV transmission requires education of all heath-care workers and ancillary staff, provision of necessary equipment, and strict adherence to general infection control practices.

Health Technology Directions; Immunisation

Health Technology Directions (**Vol. 9**, No. 2, 1989) gives an excellent account of the subject of immunization with an emphasis on: (1) the continued use of current vaccines, as well as the introduction of new, more effective and more stable ones; (2) the development and improvement of cold chain technologies to safely transport, store and distribute vaccines; (3) the development and improvement of injection technologies to ensure proper administration of vaccines and safe handling of injection equipment; and (4) efficient programme management that strive to achieve and sustain expanded coverage and service delivery through improved training, supervision, evaluation and community mobilization. The main vaccines in common use are described in detail. With regard to BCG, the correct storage temperature is between $+2^{\circ}C$ and $+8^{\circ}C$; maximum storage times are up to 8 months in central store; up to 3 months are regional level; up to 1 month at health centre level and up to 1 week in transport. Expiry dates should always be checked before use. As usual this issue contains much of practical value. PATH (Program for Appropriate Technology in Health) is, '. . . a non-profit, international organization devoted exclusively to the development and application of appropriate health technologies for primary health care programmes in developing countries'. Address: 4 Nickerson Street, Seattle, WA 98109-1699, USA.

Community Health Support Services (CHESS)

The Department of International Community Health, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, England provides up-to-date information, useful literature and practical advice. It is developing a new service for field workers in health, nutrition and population programmes in developing countries.

Appropriate Health Resources and Technologies Action Group (AHRTAG)

AHRTAG provides an information and enquiry services to health workers in developing countries. It also publishes practical manuals and newsletters about a variety of topics, including AIDS, disability, dental and diarrhoeal diseases. There is a resource centre and courses and workshops are organized for health workers. Address: 1 London Bridge Street, London SE1 9SG, England.

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News and Notes

A model system for drug supply

In the early seventies a small country in Northern Europe reorganized its pharmacy system, and the National Corporation of Swedish Pharmacies 'Apoteksbolaget' was founded. This has developed into one of the main resources of Swedish health care, providing pharmaceutical services to the public, doctors and institutions throughout the country.

Apoteksbolaget not only has the sole right to retail drugs in Sweden, but through a subsidiary, also covers 80% of the wholesale market. It operates under the same rules as any other Swedish incorporated company and is committed to providing a good pharmaceutical service and objective information about drugs, in close cooperation with the medical services. A first evaluation of the new system in 1983–84 showed it to be highly successful.

The principal advantage of the Swedish model is that it provides a comprehensive view of the drug supply problem and includes the means to carry out all the basic activities necessary for the efficient and safe distribution of drugs. Its size has also enabled the pharmaceutical system to be established on a sound economic basis.

In discussions on drug supply in developing countries the idea of using Apoteksbolaget as a model has been mooted. This led to a project aimed at developing a 'model system', for initial field testing in a few countries, which could then be used as a training ground for others interested in the system. The first phase of the project—the outlining of the model system—has now been completed and its further development is under discussion.

(Source: *Essential Drugs Monitor*, No. 8, 1989, WHO, CH-1211, Geneva 27, Switzerland.)

Care of patients with chronic renal failure in the Third World—International Workshop

The first International Workshop on the above topic is to be held in Havana, Cuba, 5–8 February 1991 together with the Second International Seminar on Dialysis and Transplant, the Fifth National Congress of Nephrology and the Second National Conference on Nephrology Nursing.

The main objective of these simultaneous events is to provide the highest level of scientific discussion on such topics as epidemiology, primary care, prevention and progression of chronic renal failure and its treatment through dialysis and transplant in Third World countries.

For further details write to: Palacio de las Convenciones, Calle 146 e/11y 13, Playa Apartado 1646, La Habana, Cuba.

Moniaya Tuberculosis and Leprosy Control Services Report, 1989, Nigeria

Part I of this report gives an outline history of the services together with details of the hospital's development, TB and Leprosy Advisory and Co-ordinating Committee, training, transport, health education, objectives and challenges. Part II consists of tables giving data on, e.g. leprosy patients on treatment; case detection activities; rehabilitation units and mobile clinics. A copy of the full report (9 pp) is available from: Sr (Dr) Cecily Bourdillon, Moniaya TBL Control Services, PO Box 183, Ogoja, Cross River State, Nigeria.

Drug labelling study

After concern expressed about the adequacy of information provided with products sold in developing countries—during the debate on the 1986 Drug Export Act—the US Office of Technology Assessment was called upon by Congressional and Senate committees dealing with health, the environment and human resources to investigate the situation. Its interim report on the first phase of the resulting study gives basic information on health and pharmaceuticals for Panama, Brazil and Kenya; presents observations from a field visit to Kenya; covers the development and operation of the multinational pharmaceutical industry, and describes the international organizations actively concerned with issues of drug information in developing countries.

Preliminary findings for the initial 85 products (from Panama and Brazil) examined in the study were that the labelling for 10 was considered adequate; relatively minor questions were raised for 20; for a further 10 the questions were considered serious, while the rest of the products fell in between the last two categories.

Further information about the study can be obtained from the Health Programme, Office of Technology Assessment, US Congress, Washington DC 20510-8025.

(Source: *Essential Drugs Monitor*, No. 8, 1989, WHO, CH-1211, Geneva 27, Switzerland.)

Leprosy in the People's Republic of China

Mrs Sufei Ma Haide, President, China Leprosy Foundation, The Ma Haide Foundation, 24 Ho Hai Bei Yan, Beijing, China 100009, has confirmed that the total number of patients in the country (population over 1000 million) is now about 50,000 and that the number of active cases has declined considerably since the introduction of WHO multiple drug therapy. The number of provinces reporting basic eradication is increasing. The overall costs of MDT in China are relatively high, particularly in view of the clofazimine element. The Pingzhou Centre in Guangdong (South China) continues to contribute as a guiding centre for treatment and research work, programme planning, the training of personnel, national and international meetings.

WHO *Liaison*—Newsletter of the WHO Office of Library and Health Literature Services

Following the cessation of the *WHO Health Literature Programme Newsletter* in 1987, this publication takes its place, and is intended as a link between health libraries and documentation services worldwide. A continuous exchange of information between editors and readers will be greatly encouraged. Apply: WHO Office of Library and Health Literature Services, 1211 Geneva 27, Switzerland.

Thinking about computers?

A recent entry in the *New Internationalist*, 55 Rectory Road, Oxford OX4 1BW, reads as follows:

'We are a small consultancy specialising in advice to small businesses and voluntary organizations. We can also supply you with all necessary equipment and services.' Appropriate Technology (UK) Ltd., 99–101 Pixmore Avenue, Letchworth, Herts., SG6 1QX, UK. Tel: (0462) 481888.

Glucose-6-phosphate dehydrogenase deficiency, sulphonamides and sulphones

The *Bulletin of the World Health Organization*, Volume 67, No. 6, 1989 carries an up-to-date article on G6PD deficiency, including a map (Figure 2) showing the distribution of this condition worldwide. As with many other conditions in the Third World the areas affected, expressed in this case as a percentage of the male population that is homozygous, bear some resemblance to those affected by leprosy and it may therefore be helpful to note that Table 3 of the article, 'Drugs to be avoided in G6PD deficiency' includes all the sulphonomides, together with dapsone, glucosulphone sodium (Promin) and sulphoxone. (Dapsone and sulphoxone may, of course, cause haemaolysis in some normal individuals.)

Acworth Leprosy Hospital Research Society, 20th Anniversary

Acworth Leprosy Hospital Research Society celebrated its 20th Anniversary day on 9 June 1990 and published *Indian Leprologists Look Back*, The 16 prominent Indian Leprologists who have actively taken part in antileprosy work in India for more than 30 years, tell of their experiences that gave them an interest in leprosy. Their contributions and views about future leprosy programmes are also documented. The book gives a panoramic view of the historical aspects of the strategies and methodologies adopted and evolved by Indian leprologists for antileprosy work in India. Some of them have been accepted on an international level.

Eminent leprologists such as Drs N H Antia, D K Dastur and R Ganapati were present at the celebrations and took part in the 'question and answer' session with the audience. 'The day on which the leprosy patient was admitted in the ward of the general hospital was the happiest moment in my life' Dr Antia said. Dr Ganapati rejoiced when he saw that leprosy patients were allowed in the workshop of the institutes run for disabled persons other than leprosy persons. Topics such as, the results of multidrug therapy; the possibility of a leprosy vaccine in the near future; and participation of the community in leprosy control programmes were discussed and the information obtained from the leprologists was enlightening. Mr S S Naik, Honorary Secretary of the Acworth Leprosy Hospital Research Society gave a resumé of the work carried out by the Society over the last 20 years and proposed the vote of thanks.

The unquiet eye; a diagnostic guide

We have been advised that the above title, advertised in the June issue of this Journal is now out of print and therefore no longer available.

N D Diwan Memorial Award Fund

The objective of the N D Diwan Memorial Award Fund is to make annual awards to workers: 'whose contribution to work for the handicapped in the fields of education, training, rehabilitation or placement, administration of services for the welfare of the handicapped, prevention and cure of handicapping conditions or any other programme or field related to the welfare of the handicapped, has been outstanding.

The N D Diwan Memorial Award will be awarded to workers for the handicapped selected on an all India basis for his/her outstanding contribution as a professional worker to the welfare of the handicapped.'

Dr R Ganapati was one of those to receive this Award in March 1990 for, among other things, 'working ceaselessly towards establishing community based deformity prevention programmes integrated with the general health programmes in both urban and rural areas'.

The Fund is administered by the National Society for Equal Opportunities for the Handicapped in India.

Bombay Leprosy Project, Report 1976–89

This report, provided by Dr Ganapati, covers the Project's activities since its inception in 1976. Its headings include: Current objectives; achievements; health education; research; training; rehabilitation; management; and future action.

For a complete copy (8 pp) write to Dr R Ganapati, Vidnyan Bhavan, 11 VN Purav Marg, Sion-Chunabhatti, Bombay 400 022, India.

Handbook of Leprosy on sale in India

Five hundred copies of the '*Handbook of Leprosy*' by W H Jopling and A C McDougall, 4th edition, published by Heinemann, have been placed with CBS Publishers and Distributors, 485 Jain Bhawah, Bhola Nath Nagar, Shahdra, Delhi 110032, India, at 175 Indian rupees per copy, which includes the cost of packing and postage to anywhere in India.

BCG vaccination in leprosy; final results from Papua New Guinea

The following is the summary of an article published in the *Bulletin of the World Health Organization*, **67,** (4), 389–99 (1989), entitled, 'BCG vaccination in leprosy: final results of the trial in Karimui, Papua New Guinea, 1963–79':

The efficacy of BCG vaccine in preventing the clinical manifestations of leprosy in a tuberculosis-free area of Papua New Guinea is reported. Between 1963 and 1966 a total of 5356 subjects, randomized to receive BCG or saline inoculations, were examined for leprosy before the vaccination and surveillance was continued until 1979.

BCG afforded 48% protection against clinical leprosy, being most effective against borderline tuberculoid leprosy and in children vaccinated when under 15 years old. Protection was evident within 12 months in those vaccinated between the ages of 10 and 15 years but was delayed in other age groups. There was evidence for accelerated manifestations of tuberculoid leprosy in children vaccinated when under 5 years of age. Tuberculin sensitivity was more likely to be sustained following multiple BCG inoculations; vaccinees with sustained tuberculin sensitivity had the lowest incidence of leprosy, but protection was also evident in tuberculin-negative vaccinees. These results may have implications for ongoing trials of leprosy vaccine incorporating BCG.

Leprosy profiles, Sasakawa Memorial Health Foundation, Japan

The Sasakawa Memorial Health Foundation, Sasakawa Hall, 3-12-12 Mita, Minato-ku, Tokyo 108, Japan, has recently published a report, *Leprosy profiles*, of a 'coordinating meeting' involving 6 countries (China, Thailand, Vietnam, Indonesia, The Philippines and Zambia) held in Singapore, June 1988. The meeting gave particular emphasis to the implementation of multiple drug therapy (MDT) as recommended by WHO in 1982. The Report is a valuable source of information on the progress in the countries listed.

Erratum

The address for Letter to the Editor 'Comment: Value of thermal sensibility testing in leprosy diagnosis in the field—field trial of a pocket device' (*Lepr Rev*, 1990; **61:** 295) was printed incorrectly and should read: Central Leprosy Teaching & Research Institute, Division of Epidemiology & Statistics, Chengalputtu, Tamil Nadu, India 603 001.

We apologize for any inconvenience this may have caused.

Wellesley Bailey Scholarship

We wish to inform readers that the Wellesley Bailey Scholarship fund is now closed. The General Director, The Leprosy Mission International.

Leprosy—Third World edition

Leprosy, edited by R C Hastings and published by Churchill Livingstone is now available as a paperback edition in Third World countries only. The contents and the quality of the paper are the same as the first edition (1985) which was priced at £55.00. Copies may be ordered from: Teaching and Learning Materials, The Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex, TW8 0QH, United Kingdom. Price £4.00 per copy—plus packing and postage.

Customers in India should order from: DAHW, 4 Gajapathy Street, Shenonagar, Madras 600 030, South India.

Medication monitoring

Medication Monitoring (MEMO) is produced and circulated free of charge by Aprex Corporation, Bundesstrasse 3, CH-6304 Zug, Switzerland, dealing with various aspects of compliance monitoring. Emphasis is given to devices, developed by this company, which incorporate a microprocessor into the lid of tablet/capsule bottles or other containers, so that opening and closing

can be recorded as a presumptive dose. Data are later retrieved by connecting the device to a microcomputer communication port. The current issue highlights the proceedings of a 2-day workshop held in Philadelphia, sponsored by the Drug Information Association of the USA. The subject matter covered includes: partial compliance, measurement of compliance by pill counts, serum levels, interviewing and electronic data. Aprex offer regular mailing of information and a selection of reprints on compliance monitoring, free of charge.

Social research methods for the study of tropical diseases (leprosy), Workshop Report, Hyderabad, India

The Centre for Social Science Research on Leprosy (CSSRL) Wardha, India in collaboration with the Department of Medical Sociology of the University of Hyderabad, held a three-day workshop, 12–14 October 1989 which was attended by a multidisciplinary group of over 50 participants drawn from different disciplines of social and health sciences.

Inaugurating the Workshop Dr Dharni P Sinha, Principal, Administrative Staff College of India, a noted social scientist and management expert, pleaded for a national policy on Social Science Research. Prof Bh Krishnamoorthy, Vice Chancellor, University of Hyderabad, who chaired the meeting underlined the importance of social science in identifying the psychosocial implications of human ailments in the process of disease eradication, particularly of leprosy.

Social scientists and health scientists delivered keynote addresses-covering a wide spectrum of methodological issues relating to the study of tropical diseases, including leprosy. The themes of papers related to: The challenge and the promise of social science research on tropical diseases (Dr V Kochar); Methodological issues: Social science approach to leprosy (Prof L B Valencia); Social science research on leprosy and the Indian National Leprosy Eradication Programme (Dr A M Kurup); Sociological aspects of communicable diseases (Dr D N Kakkar); Attitude: concepts, study and methodology (Dr P Rama Rao); Personality erosion in leprosy: the sociocultural horizon (Prof N S Chouhan); Methods for the evaluation of disease control programmes (Dr D C S Reddy): Methods for evaluation of leprosy programmes under primary health care (S P Tare); Review of social science research in communicable diseases (Dr A B Hiramani); Problems and short-comings in epidemiological investigations (Dr N S N Rao); Relevance of anthropological research methodology for studying health behaviour (Dr J Ramakrishna): Research methods for the study of changing health behaviour (Prof R K Mutatkar); Problems and methods for the study of treatment compliance among leprosy patients (Dr C R Revankar); Economics, health and leprosy (Dr E Max); Methodological problems of health services research (Dr C A K Yesudian); and Health organizations: structural issues in delivery systems (Dr G Nayarana).

Chairing the valedictory session Prof M S Gore high-lighted the need for organizing such workshops on the most critical micro areas relevant to health programmes using a multidisciplinary approach and suggested dissemination of the results.

Essays on leprosy

Some copies of this collection of essays by UK medical students remain and are available from: The Department of Dermatology, The Slade Hospital, Headington, Oxford OX3 7JH, England. Price: £10.00 including postage and packing. The contents include: The mode of transmission of human leprosy; The *in vitro* cultivation of *M. leprae*; Factors in delayed hypersensitivity in leprosy; Immunosuppression and immunodeficiency; The mechanism of nerve damage in leprosy; Hypopigmentation in leprosy; Are lymphatics important in leprosy?; The mode of action of dapsone in leprosy; The efficacy of Duoderm ulcer dressings; Factors influencing patient compliance to drugs.

Bureau for Overseas Medical Service (BOMS)

This Bureau, located at Africa Centre, 38 King Street, London WC2E 8JT, England, coordinates health workers, jobs and information in support of health care programmes in developing countries.

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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.

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

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