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Editorial

THE ORGANIZATION AND MANAGEMENT OF CHEMOTHERAPY IN THE FIELD

In the 1950s, the effectiveness of the sulphones led to the facile assumption that the control and ultimate eradication of leprosy could be realized merely by distributing the drug to all who sought treatment. This assumption proved illusory, not only—or indeed mainly—because of the emergence of drug resistance but because of the failure to give due attention to the planning and organization of the leprosy control programme within the existing health service infrastructure, the motivation and training of the staff and the cooperation of the patient, his family and the community at large. These matters are no less important when one replaces dapsone monotherapy by a multidrug regimen and, if we are to avoid failure again, we should learn from our past mistakes.

It is generally accepted that the basic principles of leprosy control are the detection and treatment of all the cases in the area at as early a stage in their disease as possible and the continuation of effective treatment for the period required to ensure non-infectivity and cure. Experience with dapsone monotherapy has taught us that there are many factors acting as constraints against the successful application of these principles in practice, and before embarking on a new policy of multidrug chemotherapy it may be helpful to consider some of these factors and their implications.

1 Factors affecting early case detection

1.1 Probably the most important in most endemic areas is the attitude of the community to the disease and to those who suffer from it. This is reflected in the attitude of the health staff responsible for the care of leprosy patients, which frequently presents a major problem. An appropriate health education programme must in all cases be reinforced by an efficient and sympathetic service to the patients, leading to the recognition of its value by the community and so to their cooperation and participation.

1.2 Such a service can be provided and maintained only if it is carefully planned

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and organized, if the clinical and laboratory facilities for diagnosis and treatment are adequate and if the staff are highly motivated, well-trained and properly supervised.

1.3 In the early days of the sulphone era, regular 'Discharge Ceremonies' were a feature which had a marked effect on public opinion concerning the curability of leprosy and resulted in the voluntary presentation of large numbers of new, early cases. It can therefore be confidently expected that if the regimen recommended for paucibacillary leprosy can be implemented and many patients discharged after only 6 months' treatment, the level of case detection can be raised to a point where it has an appreciable effect on the transmission of the disease.

2. Factors affecting the continuation of effective treatment for the period required

2.1 The most serious constraint has been poor patient compliance. Every effort must be made *before* multidrug chemotherapy regimens are introduced to ensure the acceptance by both patients and staff, as well as by the community at large, that the period of treatment required is now finite. Possibly this activity should combine something of aggressive advertising with the more conventional methods of health education, particularly since we are asking that discharge from treatment be accepted even before signs of overt, active disease have disappeared.

2.2 We all know, however, that effective treatment in leprosy comprises more than chemotherapy. Disability must be prevented and alleviated, all complications must be cared for, both in the periphery and at selected referral centres, and due place must be given to the socio-economic needs of the patient and his rehabilitation. It must be constantly emphasized that *discharge from chemotherapy* is not to be equated with *discharge from care*, but that continued attendance at the treatment centre—for the preventive care of disability and plantar ulceration, as well as for routine surveillance to monitor relapse—is to be encouraged.

2.3 Administrative factors of importance include the need for an appropriate system of recording and reporting, the logistics of drug supply and drug delivery and the whole question of the relationship between the leprosy control service and the basic health services infrastructure and the primary health care approach.

It is only with properly planned organization and skilled management that the currently recommended chemotherapy regimens will succeed where dapsone monotherapy has failed.

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Report of the SEARO/WPRO/IMMLEP/THELEP Joint Scientific Meeting on Leprosy Rangoon, Burma, 18–19 November 1981*

A scientific meeting on the chemotherapy and immunology of leprosy was held, 18–19 November 1981, at the Department of Medical Research of the Ministry of Health of Burma in Rangoon, jointly sponsored by the South-East Asian and Western Pacific Regional Offices of the World Health Organization, and the Immunology of Leprosy (IMMLEP) and Chemotherapy of Leprosy (THELEP) Scientific Working Groups of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Those participating were:

Dr M Abe, National Institute for Leprosy Research, Tokyo, Japan,
Dr A B Adiga, Ministry of Health, Pachali, Nepal,
Dr Anan C Pakdi, SEARO, New Delhi, India,
Dr Aung Win Thien, Department of Medical Research, Rangoon, Burma,
Dr Ayele Belehu, Armauer Hansen Research Institute, Addis Ababa, Ethiopia,
Dr Bencha Petchclai, Ramathibodi Hospital, Bangkok, Thailand,
Dr V N Bhatia, Central Leprosy Teaching and Research Institute, Chingleput, South India,
Dr B R Bloom, Albert Einstein College of Medicine, Bronx, New York, USA,
Dr C J G Chacko, Schieffelin Leprosy Research and Training Centre, Karigiri, South India,
Dr S Chan, National University of Singapore, Singapore,
Dr M C Christian, Schieffelin Leprosy Research and Training Centre, Karigiri, South India,
Dr J Convit, Instituto Nacional de Dermatologia, Caracas, Venezuela,
Dr E Daulako, Twomey Memorial Hospital, Suva, Fiji,
Dr K V Desikan, Central JALMA Institute for Leprosy, Agra, India,
Dr G A Ellard, National Institute for Medical Research, London, England,
Dr C A P Ferracci, Institut Marchoux, Bamako, Mali,
Dr P Fine, London School of Hygiene and Tropical Medicine, London, England,
Dr T Godal, Norwegian Radium Hospital, Oslo, Norway,
Dr G le Gonidec, Institut Pasteur, Noumea, New Caledonia,

* In addition to this report, 5 papers presented at the Rangoon meeting appear in this issue of *Leprosy Review*. It is our understanding that this report, together with other papers presented at the meeting, will appear in a forthcoming issue of the *International Journal of Leprosy*. EDITOR.

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Dr R S Guinto, Leonard Wood Memorial, Cebu, Philippines,
Dr J Guld, Copenhagen, Denmark,
Dr Huan Ying Li, Beijing Friendship Hospital, Beijing, China,
Dr Ji Baohong, Zeng Yi Hospital, Shanghai, China,
Dr Kinh Due, Hôpital Bach Mai, Hanoi, Vietnam,
Dr Kyaw Lwin, Ministry of Health, Rangoon, Burma,
Dr L Levy, Hebrew University-Hadassah Medical School, Jerusalem, Israel,
Dr L Lopez-Bravo, WPRO,
Daw Mar Mar Nyein, Department of Medical Research, Rangoon, Burma,
Dr Maung Maung Ghi, Department of Health, Mandalay, Burma,
Dr P N Neelan, Central Leprosy Teaching and Research Institute, Chingleput, South India,
Dr S K Noordeen, World Health Organization, Geneva, Switzerland,
Dr S R Pattyn, Prince Leopold Institute for Tropical Medicine, Antwerp, Belgium,
Dr J M H Pearson, Dhoolpet Leprosy Research Centre, Hyderabad, India,
Dr M Pinto, University of Sri Lanka, Peradeniya, Sri Lanka,
Dr K Rajagopalan, National Leprosy Control Centre, Sungei Buloh, Malaysia,
Dr R J W Rees, National Institute for Medical Research, London, England,
Dr N M Samuel, Anadaban Hospital, Kathmandu, Nepal,
Dr H Sansarricq, World Health Organization, Geneva, Switzerland,
Dr P S Seshadri, Central Leprosy Teaching and Research Institute, Chingleput, South India,
Dr J K Seydel, Borstel Research Institute, Borstel, Federal Republic of Germany,
Dr C C Shepard, Centers for Disease Control, Atlanta, Georgia, USA,
Dr G P Talwar, All-India Institute of Medical Sciences, New Delhi, India,
Dr Than Win, Department of Health, Rangoon, Burma,
Dr R Utji, University of Indonesia, Jakarta, Indonesia,
Dr Vicharn Vithayasai, Chiang Mai University, Chiang Mai, Thailand,
Dr M F R Waters, Hospital for Tropical Diseases, London, England,
Dr Ye Gan Yun, Chinese Academy of Medical Sciences, Taizhou, China,
Dr Y Yuasa, Sasakawa Memorial Health Foundation, Tokyo, Japan.

The meeting was opened with welcoming speeches by Dr Kyaw Lwin, Deputy Director (Leprosy), Department of Health, Ministry of Health of Burma, Dr Aung Than Batu, Director, Department of Medical Research, Dr H Sansarricq, Chief Medical Officer, Leprosy Unit, WHO, and Dr S Pattanayak, Acting WHO Programme Coordinator, Rangoon.

The first day was devoted to papers on the chemotherapy of leprosy. Dr L Levy described the goals of the THELEP programme, and the strategy that had been adopted to achieve these goals. This paper was followed by 2 papers devoted to the THELEP controlled clinical trials of the chemotherapy of lepromatous leprosy. Dr M F R Waters discussed the background of the trials, sketching the

historical development of the concept of trials in which the attempt is made to detect 'persisting' *Mycobacterium leprae* by inoculation of immunosuppressed mice, and describing the design of the trials. Dr R J W Rees presented the available results from inoculation of mice, with particular emphasis on the unexpectedly high prevalence of primary resistance to dapsone in both the Central Leprosy Teaching and Research Institute, Chingleput, South India, and the Institut Marchoux, Bamako, Mali, sites of the current trials.

Dr S R Pattyn described the design of the THELEP field trials of chemotherapy of lepromatous leprosy, in which lepromatous patients are to be treated with largely intermittent, multidrug regimens for 2 years after achieving smear-negativity, after which chemotherapy will be stopped and the relapse rate measured. This paper was followed by a description of the SEARO-sponsored Burma Rifampicin Trial, presented by Dr Maung Maung Ghi. This latter trial involves an attempt to interrupt transmission of *M. leprae* from infectious source to contact by the addition of a brief (*2-week*) course of daily rifampicin to the standard dapsone monotherapy; the hoped for result is a decreased attack rate, compared to that in the control population in which only standard dapsone monotherapy is employed. Dr G A Ellard then discussed the problem of the generally poor compliance of leprosy patients with the prescribed therapy.

There followed 7 papers on various aspects of resistance to dapsone. Dr J M H Pearson presented the problem as it was understood at the time THELEP activities began, and described the strategies adopted by THELEP further to elucidate the problem. Dr M C Christian presented an up-date of the continuing prevalence survey of secondary dapsone resistance in Gudiyatham Taluk. Dr R S Guinto presented the results of the recently completed survey of primary resistance to dapsone in Cebu. Dr P N Neelan and Dr Kyaw Lwin described the on-going surveys of secondary resistance in, respectively, Trivellore Taluk, South India and Myingyan Township, Burma. Dr Ji Baohong presented the results of a virtually completed survey of secondary resistance in Shanghai Municipality. Finally, Dr Robert Utji presented the first results of an informal survey of dapsone resistance in Jakarta, including those of 1 patient with primary resistance.

The second day of the meeting was devoted to presentations on the immunology of leprosy. The research plans and progress of IMMLEP were summarized by Drs Bloom, Godal, Rees and Shepard. Dr Bloom spoke on the rationale for vaccination in leprosy, Dr Godal on immunological mechanisms in leprosy, Dr Rees on the production of *M. leprae* from armadillos, the IMMLEP Bank for *M. leprae*, and the purification procedures, and Dr Shepard on the animal vaccination studies with various preparations and on the animal models for immunological tolerance. This was followed by 3 papers on studies carried out on human beings with 'vaccine' preparations. Dr Convit presented his data on vaccinotherapy of a large number of lepromatous and borderline patients with a mixture of killed *M. leprae* and live BCG. Dr Bapat presented data on studies

carried out by his group on patients using the ICRC bacillus. Dr Talwar presented data on human studies using *Mycobacterium W* and also a preparation of hapten modified *M. leprae*. Following these, Dr Fine presented a paper on the epidemiology of leprosy, and Dr Noordeen spoke on epidemiological consideration in vaccine trials. The operational problems in vaccine trials were discussed by Dr Guld, particularly in relation to the BCG trial in South India. The formal presentations were followed by a Round Table on epidemiological studies in leprosy with Drs Maung Maung Ghi, Guinto, Ye, Samuel, Vicharn, Neelan, Christian and Noordeen participating. The discussion at the Round Table brought out the various field studies being carried out by scientists from the developing endemic countries and opportunities for their participation in the IMMLEP/THELEP supported activities.

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THELEP controlled clinical trials in lepromatous leprosy*

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

Summary The events leading to the development of the THELEP Standard Protocol for controlled clinical trials in lepromatous leprosy are recounted, and the structure of the Standard Protocol is described. Trials of multidrug regimens including dapsone, rifampicin and clofazimine or prothionamide have been undertaken in Bamako and Chingleput.

Members of the THELEP Clinical Trials Subcommittee are:

Dr G A Ellard, National Institute for Medical Research, London, England,
Dr C A P Ferracci, Institut Marchoux, Bamako, Mali,
Dr C G S Iyer, Central Leprosy Teaching and Research Institute, Chingleput, South India,
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Dr L Levy, Hebrew University-Hadassah Medical School, Jerusalem, Israel,
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* This report was prepared by Dr L Levy.

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Introduction

Modern chemotherapy of leprosy may be said to have begun in 1941, when the first effective antimicrobial drug, glucosulphone (Promin®), was employed in the treatment of patients with leprosy.[5] During the next 20 years, a number of other sulphones were introduced into the therapy of leprosy. However, despite the lack during this period of a precise means of measuring the efficacy of chemotherapy, the potency of sulphones became firmly established, and dapsone became accepted as the drug of choice.

MORPHOLOGICAL INDEX

The scientific basis of modern leprosy chemotherapy depends upon the development of 2 laboratory techniques that made it possible to measure the rate at which *Mycobacterium leprae* were killed during treatment. After earlier workers had called attention to morphological changes of *M. leprae* during treatment of leprosy patients, quantitive assessment of the bacterial morphology was introduced as a means of measuring the response of patients to treatment, and employed in a series of clinical trials carried out at Sungei Buloh, Malaysia.[10–12, 23–26] Although the efficacy of treatment by several drugs was demonstrated by observing the decrease of the morphological index (MI), as this measurement came to be known, this decrease of the MI appeared to be a rather insensitive measure of the response to antimicrobial chemotherapy. For example, the rate of decrease of the MI was no more rapid during treatment with dapsone or clofazimine in full dosage than during treatment by much smaller dosages of these drugs. In fact, there is evidence that killing of *M. leprae* is not the rate-determining step in the morphological changes that accompany death of the organisms.[19]

MOUSE FOOT-PAD INOCULATION

The second laboratory method that contributed uniquely to the development of modern chemotherapy was Shepard's mouse foot-pad technique.[16] Application of this technique to the measurement of the rate at which *M. leprae* are killed during effective antimicrobial treatment of the patient with lepromatous leprosy provided a more sensitive and discriminating means of assessing the efficacy of antimicrobial chemotherapy. Employing this technique, a series of clinical trials was carried out in San Francisco and in Cebu.[1, 2, 7, 8, 17–20] These trials established that *M. leprae* recovered from the lesions of patients with lepromatous leprosy lost their infectivity for immunologically normal mice after treatment for an average of 100 days with 50–100 mg dapsone daily; after an average of 150 days with clofazimine, 100–200 mg daily or 100 mg 3 times weekly; after more than 150 days of treatment with acedapsone, 225 mg intramuscularly every 77 days, or

clofazimine, 600 mg every 2 weeks or 1200 mg every 4 weeks; and within a few days of single 600–1500 mg or daily 300–600 mg doses of rifampicin.

Immunologically normal mice appear to mount an effective immune response, causing multiplication to cease when the number of *M. leprae* approaches $1–2 \times 10^6$ per foot-pad. *M. leprae* fail to multiply when 10^5 or more are inoculated into the foot-pad of the normal mouse, and inocula must contain no more than 10^4 organisms per foot-pad, if multiplication is to be recognized reliably. Therefore, failure of multiplication in mice inoculated with 10^4 *M. leprae* implies only that the inoculum included fewer than 1 viable organism per 10^4 inoculated. Because a patient with lepromatous leprosy who has not been previously treated may harbour as many as 10^{11} *M. leprae*, of which 10% (10^{10}) may be viable, he may harbour a great many viable organisms when, in the course of effective treatment, the first 99·9% of the patient's organisms have been killed, and his *M. leprae* are no longer capable of infecting normal mice.[3]

Thus, although application of the foot-pad technique employing immunologically normal mice to the measurement of chemotherapeutic efficacy produced much important information, the technique possessed important limitations. Thus, whereas this technique showed that single doses of rifampicin killed *M. leprae* as rapidly as could be measured, it was not sensitive enough to show how much more rapidly a combination of rifampicin with another bactericidal drug would kill the organisms, or the rate at which *M. leprae* would be killed, once the patient's organisms were no longer infective for normal mice.

RECOGNITION OF PERSISTING *M. LEPRAE*

At least a partial answer to the second question was given by studies employing T-cell depleted (adult-thymectomized, whole body-irradiated, and bone-marrow-reconstituted, 'TR') mice, which had been shown by Rees[13] regularly to permit multiplication after inoculation of 10^5 *M. leprae* per foot-pad. The first clinical trials undertaken, at Sungei Buloh, with inoculation of T900R mice demonstrated the presence of 'persisting' *M. leprae*.[6, 14, 27] (Briefly, persisting *M. leprae* are organisms that survive treatment by ordinarily effective dosages of drugs, despite being fully susceptible to the antimicrobial effects of the drugs; this subject has been recently reviewed by Toman.)[22] Viable *M. leprae* were detected by inoculation of TR mice with organisms recovered from the tissues of patients after 10 years of supervised treatment with dapsone in full dosage, after 5 years of treatment with rifampicin, 600 mg daily, and after treatment for 6 months by rifampicin, 600 mg daily, administered in combination with dapsone in a daily dose of 100 mg.

BEGINNINGS OF THE THELEP PROGRAMME

Thus, the situation confronting the committee convened in April 1976 to plan the THELEP programme[28] was as follows. As the result of a number of clinical trials

employing inoculation of normal mice, dapsone, acedapsone, clofazimine, rifampicin and ethionamide had all been shown, in various dosages, to be effective antimicrobial drugs for the treatment of patients with lepromatous leprosy. Moreover, by the use of TR mice, the ubiquity of persisting *M. leprae* had been demonstrated. It appeared that, in the course of effective chemotherapy of lepromatous leprosy, *M. leprae* were initially killed more or less rapidly; after the initial kill, however, there remained a number of persisting organisms, which was too small to be detected by inoculating normal mice with 10^4 organisms per foot-pad, but could sometimes be detected by inoculating TR mice with 10^5 organisms per foot-pad. It was not clear whether the number of persisters was smaller after treatment by some regimens than it was after treatment by others.

Another problem confronting the THELEP planning committee was that of resistance to dapsone,[9] the scope of which had been revealed as a result of an application of the mouse foot-pad technique. It was clear that treatment of patients with combinations of drugs was required to prevent the emergence of drug resistance. Whether some combinations would be more effective than others in decreasing the size of the subpopulation of persisting *M. leprae* was not clear. Therefore, the planning committee recommended that THELEP undertake controlled clinical trials of various combined drug regimens, in the course of which trials TR mice would be inoculated in an attempt to detect persisting *M. leprae*. In April 1977, at the first meeting of the THELEP Scientific Working Group (SWG), a draft *Standard Protocol for Chemotherapy Trials in Lepromatous Leprosy* was revised and adopted.[29]*

Standard Protocol

The Standard Protocol envisages trials among 3 groups of lepromatous (LL and LI) patients: 1, those without prior treatment; 2, patients who have relapsed, and whose *Mycobacterium leprae* have been proved resistant to dapsone; and 3, patients who have responded to dapsone monotherapy, and who may therefore be presumed to harbour dapsone-resistant subpopulations larger than those in previously untreated patients. The trials must comply with the ethical requirements of the World Health Organization;[4] approval of governmental or institutional authorities and consent of the patients are to be obtained, and patients are to be closely monitored for the occurrence of adverse reactions to the drugs employed in the trials.

Enough patients of the appropriate group are to be recruited into the trial so that complete data will be available on at least 30 per regimen. Patients should have LL or LI leprosy, may be of either sex, and should be at least 15 years of age. To be excluded from the trial are pregnant women, patients with a Mitsuda

* Copies of the *Standard Protocol for Chemotherapy Trials in Lepromatous Leprosy* may be obtained by application to the Leprosy Unit, World Health Organization, Geneva, Switzerland.

reaction equal to or greater than 3 mm in diameter, patients with tuberculosis requiring treatment, and those with a recent history of erythema nodosum leprosum (ENL), which may indicate recent, effective treatment, and which is often associated with failure of the patient's *M. leprae* to infect mice.

EXAMINATIONS AT INTAKE

When the patient is first considered for admission into a trial to be conducted among previously untreated patients, he is examined for the presence of lesions suggesting previous treatment, interrogated with respect to prior treatment, and a urine specimen is obtained for dapsone assay to exclude recent intake of the drug. Upon admission, two skin lesions, each large enough to permit repeated biopsies, are biopsied, and the specimens are divided, 1 portion of each being immediately fixed and submitted for histopathological examination; the remaining portions are placed at 0–4°C, and submitted within 1 week for enumeration of *M. leprae* and inoculation of mice; the organisms from the specimen containing the larger number of *M. leprae* are to be inoculated into mice for determination of viability and of susceptibility to dapsone. The patient is then assigned by random allocation to a treatment regimen.

Following admission to the trial, a complete medical history is obtained, and a physical examination is performed, with emphasis on those points of the examination that are particularly relevant to leprosy. A lepromin test is performed, employing a standard preparation of lepromin. Smears for measurement of the bacteriological index (BI) are made from both ears and from other sites, and a 'nose blow' is obtained. Finally, specimens of urine, faeces and blood are obtained, and haematologic studies, studies of liver function and other laboratory tests are performed. Patients with syphilis or heavy burdens of parasites are to be treated prior to initiating treatment of leprosy by the trial regimen.

EXAMINATIONS DURING THE TRIAL

At intervals during treatment, a number of tests are carried out, as shown in Figure 1. Every 4 weeks the patient is examined briefly by the clinical investigator, note is made of any changes in the patient's lesions, and he is interviewed for symptoms suggesting adverse reactions to drugs. At this same interval, specimens of urine and blood are obtained for laboratory investigation. A 'nose-blow' specimen is obtained after 4 weeks of treatment. Finally, the occurrence of ENL and other leprosy reactions is recorded, and the reactions are treated appropriately.

After treatment for 12 weeks, a formal clinical assessment is performed. A biopsy is performed from the lesion found earlier to yield the larger number of *M. leprae*, for histopathological examination and for inoculation of both immunolo-

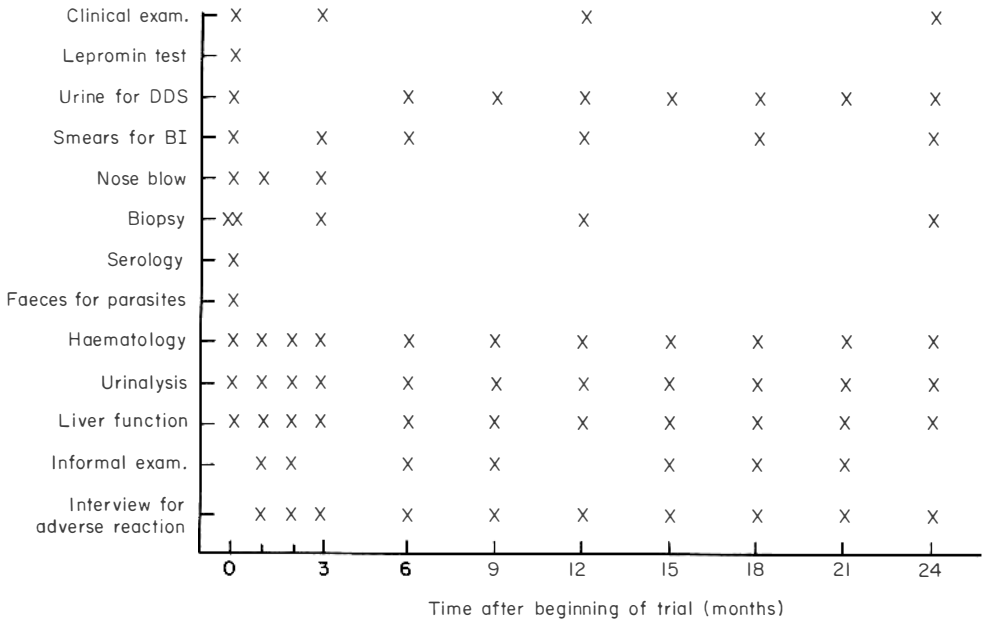

Figure 1. Schedule of examinations required by the Standard Protocol, showing minimal frequency.

gically normal mice (with 5000–10,000 organisms per foot-pad) and thymectomized-irradiated (TR) mice (with 100,000 *M. leprae* per foot-pad). Skin smears are made from the same 6 sites employed earlier, and a 'nose-blow' specimen is obtained.

At intervals of 3 months, beginning after 6 months of treatment, a urine specimen is obtained for dapsone assay as a guide to the regularity with which the patient takes his prescribed medication, the patient is examined for evidence of ENL and a change in his disease process, and he is interviewed for symptoms suggesting adverse reactions to his drugs. In addition, at intervals of 6 months, beginning after 6 months of treatment, smears are obtained for measurement of the BI, and specimens of urine and blood are obtained for laboratory study.

After 12, and again after 24 months of treatment, in addition to those procedures carried out at intervals of 3 and 6 months, a complete examination is performed, and a biopsy is performed for histopathologic examination and to provide organisms for inoculation of TR mice.

Patients may be removed from the trial by the responsible clinician for only a limited number of reasons: 1, onset of an important intercurrent illness; 2, evidence of clinically important drug allergy or toxicity; 3, ENL so severe as to require cessation of therapy; 4, pregnancy; and 5, the patient's desire to withdraw from the trial.

The patient may be removed from the trial, or the results of his study may be excluded from analysis by the THELEP Clinical Trials Subcommittee because

the *M. leprae* recovered from the pretreatment biopsy specimen either fail to infect mice, or are shown to be resistant to dapsone, or because of clinical worsening or relapse of his leprosy.

COMPARISON OF REGIMENS

In essence, the THELEP Standard Protocol for Chemotherapy Trials in Lepromatous Leprosy calls for treatment by a combined drug regimen for a period of 2 years. Normal mice are inoculated with *M. leprae* recovered before the start of treatment, and again after treatment for 3 months, providing an opportunity to measure the initial rate at which the patient's *M. leprae* are killed. The single biopsy performed after 3 months' treatment obviously cannot permit a precise estimate of this rate, but should suffice to exclude the possibility that members of the drug combination so antagonize each other as greatly to decrease this initial rate of bacterial killing. TR mice are inoculated after treatment for 3, 12 and 24 months, thus providing 3 opportunities for the detection of persisting *M. leprae*. The trial regimens will be compared in terms of the frequency with which persisting *M. leprae* are detected.

THELEP controlled clinical trials

At the time that it reviewed the THELEP Standard Protocol, the SWG suggested a number of combined-drug regimens to be tried among patients of the 3 groups. At its first meeting, immediately after the meeting of the SWG, the steering committee of the THELEP SWG selected the Institut Marchoux, Bamako, Mali, and the Central Leprosy Teaching and Research Institute, Chingleput, South India, as the sites of the first 2 trials. The trials themselves were to be carried out as a collaborative effort with participation of several investigators from different parts of the world. The trials were to be carried out among previously untreated patients with leprosy classified as LL or LI according to the Ridly–Jopling classification.[15]

Recruitment of patients for the trials was begun in Chingleput in August 1977, and in Bamako in November of that year. The regimens under trial are, at Chingleput: 1, regimen A_1—dapsone, 100 mg, rifampicin, 600 mg, and clofazimine, 100 mg, each drug administered daily for 2 years; 2, regimen C—a single initial 1500-mg dose of rifampicin, together with dapsone, 100 mg, administered daily for 2 years; and 3, regimen D_1—as for regimen C, with the addition of clofazimine administered in a daily dose of 100 mg for the first 3 months.

In Bamako, the regimens under test are: 1, regimen A_2—as for regimen A_1, but with prothionamide, 500 mg, in place of clofazimine; 2, regimen C—as for Chingleput; and 3, regimen E_2—dapsone, 100 mg daily for 2 years, rifampicin, 900 mg once weekly for the first 3 months; and prothionamide, 500 mg daily for the first 3 months.

At the same time, the steering committee elected to defer controlled trials of chemotherapy among patients of groups 2 and 3. It would have been difficult to assemble numbers of lepromatous patients who had relapsed with the emergence of dapsone-resistant *M. leprae*, and who had not been started on treatment with alternate drugs. Patients who had responded well to dapsone monotherapy were undoubtedly available in larger numbers even than previously untreated patients. However, their *M. leprae* were certain to be non-infective for mice, even before treatment with a combined drug regimen had been initiated, and they would not have formed a homogeneous group with respect to duration of prior treatment.

The regimens to be studied in the 2 trials were selected, not because they were felt to be the most suitable for use in leprosy control programmes, but because it was believed important to study the effects on persisting *M. leprae* of treatment by these regimens. Moreover, although it is clear that elimination of persisting *M. leprae* may not be identified with 'cure' of lepromatous leprosy, the THELEP SWG thought that trials of combined chemotherapy in which persisting *M. leprae* were sought would more quickly provide answers to the very urgent questions about combined-drug regimens than would trials having relapse of the patient as their end-point. Moreover, the SWG did not believe it ethical in 1977 to plan trials in which chemotherapy of patients with lepromatous leprosy was deliberately stopped.

Data attesting to acceptably low relapse rates of lepromatous leprosy following many years of dapsone as supervised monotherapy, or a few years of chemotherapy with a combination of drugs that included rifampicin and prothionamide, became available in early 1979. And at its second meeting, in April 1979, the SWG decided to undertake trials of combined chemotherapy among large numbers (500–1000) of lepromatous patients whose BI's had fallen to 0 after at least 5 years of dapsone monotherapy. Intensive combined-drug regimens are to be administered for 2 years, after which, active therapy is to be withdrawn and the patients observed for evidence of relapse. Such trials will require much more time than those described in this report. But they possess the advantage of having cure of lepromatous leprosy as their end-point.

An entirely unexpected result of these 2 trials has been the demonstration of high prevalences of primary dapsone resistance among lepromatous patients at both trial sites. This is described in detail in the accompanying paper.[21] Other publications of the results of these trials are planned.

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Primary resistance to dapsone among untreated lepromatous patients in Bamako and Chingleput*

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

Summary More than one-third of the patients with lepromatous leprosy, presumed previously untreated, who have thus far been admitted into the THELEP controlled clinical trials in Bamako and Chingleput, have been found to harbour dapsone-resistant *Mycobacterium leprae.*

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Introduction

Until 10 years ago, virtually all strains of *Mycobacterium leprae* isolated from patients with previously untreated multibacillary* leprosy by inoculation of mice were inhibited from multiplying by administering dapsone to the mice in a concentration of 0·0001 g per 100 g mouse diet.[2,5,9] Strains of *M. leprae* capable of multiplying in mice administered this or a higher concentration of dapsone were defined as resistant. Strains that multiply in mice administered 0·0001 g dapsone per 100 g diet, but are inhibited by dapsone administered in a concentration of 0·001 g per 100 g diet are said to exhibit a low degree of resistance; strains that multiply in mice administered 0·001 g dapsone per 100 g diet but not in mice administered dapsone in a concentration of 0·01 g per 100 g exhibit an intermediate degree of resistance, whereas strains of *M. leprae* that multiply even in mice administered 0·01 g dapsone per 100 g diet exhibit a high degree of resistance.

The isolation of a resistant strain of *M. leprae* from a patient with multibacillary leprosy who has not received prior treatment indicates primary resistance to dapsone, i.e. the patient was infected *ab initio* with dapsone-resistant organisms. Primary resistance to dapsone may also occur in patients with paucibacillary leprosy; however, resistance of the *M. leprae* to dapsone cannot be demonstrated by inoculation of mice, because too few organisms can be recovered from the skin-biopsy specimens of paucibacillary patients. Secondary resistance to dapsone is now a widespread phenomenon.[3] As the frequency of relapse with secondary dapsone resistance increases, so must the likelihood of transmission of dapsone-resistant *M. leprae*, with primary resistance as a consequence.

Recognizing that dapsone resistance represents a major threat to leprosy control efforts that depend so heavily on the efficacy of dapsone, the Scientific Working Group on the Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases undertook to support surveys for primary resistance to dapsone in various parts of the world. The results of two surveys—one in Ethiopia[4] and one in the Philippines[1]—have been published. In addition, susceptibility to dapsone was measured routinely of the *M. leprae* isolated from patients with previously untreated multibacillary leprosy recruited into THELEP-sponsored controlled

* Multibacillary leprosy includes lepromatous (L) and borderline (B) leprosy in the Madrid classification,[13] and LL, BL and BB leprosy in the Ridley–Jopling classification.[7] Paucibacillary leprosy includes indeterminate (I) and tuberculoid (T) leprosy in the Madrid classification, and I, TT and BT in the classification of Ridley and Jopling.

trials of chemotherapy in Bamako, Mali and Chingleput, South India;[11] the results of these measurements have provided estimates of the prevalence of primary dapsone resistance in these 2 areas.

Materials and methods

With their consent, patients with LL, LI or BL leprosy who denied prior treatment, and in whose urine no dapsone could be detected, were admitted into the controlled clinical trials at Bamako and Chingleput. As described in the accompanying paper,[11] two skin lesions were biopsied, and portions of each biopsy specimen were immediately placed in a vacuum flask filled with ice and sent by air to London. In the Department of Medical Microbiology, St George's Hospital Medical School, the specimens were homogenized, and the *M. leprae* recovered and counted.[5] The organisms recovered from the specimen providing the larger number were diluted so as to provide an inoculum of 10^4 *M. leprae* per foot-pad, and 27 locally bred female CD-1 mice were inoculated each in the right hind foot-pad. Beginning on the day of inoculation, one group of 8 mice was fed ordinary mouse diet, whereas other groups of 5–7 mice were fed diet into which had been incorporated dapsone in a concentration of 0·0001, 0·001 or 0·01 g per 100 g diet.

Six months later, several mice from the untreated group were sacrificed, and harvests of *M. leprae* were performed from the right hind foot-pads. If at least 5×10^5 organisms were harvested from 1 mouse, harvests were performed from the right hind foot-pads of the remaining untreated mice, and from the foot-pads of the mice administered dapsone in the lowest concentration. If *M. leprae* were found to have multiplied in the latter mice, harvests were performed also from mice of the groups administered dapsone in higher concentrations. If, on the other hand, the number of organisms harvested from the untreated mice was less than 5×10^5 per foot-pad, dapsone administration was continued for an additional 3 months, at which time additional untreated mice were sacrificed and harvests of *M. leprae* performed. At this time also, additional harvests were performed if at least 5×10^5 organisms were harvested from at least 1 mouse. If fewer than 5×10^5 organisms per foot-pad were harvested from the untreated mice, treatment was continued for an additional 3 months, at which time *M. leprae* were harvested from all remaining untreated mice, from the mice administered the lowest concentration of dapsone, and depending on the results of these latter harvests, from mice administered higher concentrations of dapsone.

Results

The results of mouse foot-pad inoculation with *M. leprae* recovered from the pretreatment specimens of 2 patients are presented in Table 1 as examples of the

Table 1. Data exemplifying those encountered in study

Treatment centre	Patient no.	No. *M. leprae* inoculated ($\times 10^4$)	Time of harvest (days)	Dapsone concentration (g%)	No. *M. leprae* recovered ($\times 10^5$)
Chingleput	002	1·0	183	0	<0·1, <0·1
			268	0	0·72, 1·4, 2·9
			359	0	0·20, 2·5, 6·8
				0·0001	<0·1, <0·1, <0·1
					<0·1, <0·1, <0·1
Chingleput	028	1·0	189	0	0·18, 0·66, 0·66
			282	0	1·2, 2·6
				0·0001	0·52, 0·80, 2·7, 4·0, 6·9
				0·001	<0·1, <0·1, <0·1, <0·1,
					<0·1, <0·1, <0·1

data analysed for this study. Shown first are the data from Chingleput patient No. 002, whose organisms are susceptible to dapsone. Considering only those harvests performed 268 and 359 days after inoculation, *M. leprae* are noted to have multiplied in 5 of the 6 untreated mice harvested (the criterion of multiplication in a foot-pad is an increase of at least 5-fold, i.e. to 5×10^4 organisms per foot-pad). On the other hand, no evidence of multiplication was found in any of the 6 mice administered dapsone in a concentration of 0·0001 g per 100 g diet.

The results obtained from Chingleput patient No. 028 indicate resistance at the lowest dapsone concentration. *M. leprae* had multiplied in the 2 control mice harvested after 282 days. At this time *M. leprae* were found also to have multiplied in all of 5 mice treated with dapsone at the lowest concentration, and in none of 7 mice treated with dapsone at the concentration of 0·001 g per 100 g mouse diet.

Table 2. Results of study

	Bamako	Chingleput
Not tested	5	11
Fully susceptible	26	35
Resistant (g% DDS)		
0·0001	10	16
0·001	3	5
0·01	1	0
% resistant	35·0	37·5

The results of this study, summarized in Table 2, show that in a number of instances, representing 11% of the patients in Bamako and 16% of those in Chingleput, the susceptibility to dapsone could not be measured. The *M. leprae* recovered from 10 pretreatment biopsy specimens (3 from Bamako, 7 from Chingleput) failed to multiply in untreated mice. In 6 instances (2 from Bamako, 4 from Chingleput), *M. leprae* multiplied in some of the untreated mice, and in none of the mice to which dapsone had been administered; however, the proportions of treated and untreated mice in which multiplication occurred did not differ significantly, when compared by the exact probability calculation.

The *M. leprae* isolated from 35 and 37·5% of the patients in Bamako and Chingleput, respectively, multiplied both in untreated mice and in mice administered dapsone in a concentration of 0·0001 g per 100 g mouse diet, and more than one-fourth of these strains multiplied in mice administered dapsone in a higher concentration. However, only 1 patient was found to harbour *M. leprae* capable of multiplication in mice administered dapsone in the highest concentration.

Discussion

The requirement for testing the susceptibility to dapsone of the *M. leprae* isolated from the pretreatment biopsy specimens of all the patients admitted to the THELEP controlled clinical trials in Bamako and Chingleput was included in the THELEP Standard Protocol for Chemotherapy Trials in Lepromatous Leprosy[11] to ensure that patients with primary dapsone-resistant leprosy would be recognized, and the data resulting from their participation in the trial would be analysed separately from those of the majority of the patients, whose *M. leprae* were expected to be fully susceptible to dapsone. The demonstration that more than one-third of the patients, presumed to have received no prior treatment, admitted to the trials in both treatment centres harboured dapsone-resistant *M. leprae* was unexpected.

One may question whether patients found to harbour dapsone-resistant *M. leprae* had not in fact received prior treatment. Because of its grave importance to a leprosy control programme, every effort must be made to identify primary resistance correctly. Some patients may relapse with secondary resistance but be considered instances of primary resistance because no evidence of previous treatment is discovered. When, however, there has been close contact with a patient known to have relapsed with secondary resistance,[8] or the patient's youth appears inconsistent with the long period of time required for diagnosis, treatment, response and relapse,[12] primary resistance appears likely. Considerable effort was expended to ascertain that the patients admitted to the trials in Bamako and Chingleput had not been previously treated. The patients' urine, obtained as soon as admission to the trials was considered, contained no dapsone,

and the patients steadfastly denied having received prior treatment. There was no record of their having been previously treated at either of the 2 centres, nor was the appearance of the patients' lesions suggestive of prior treatment followed by relapse. Moreover, in only 3 of 21 instances was there history of contact with a patient known to have relapsed with dapsone resistance. Finally, one might expect to be able to distinguish primary from secondary resistance on the basis of the patient's age. Because of the time required for emergence of secondary resistance—usually from 10 to 20 years,[3] patients relapsing with secondary resistance to dapsone should have suffered from leprosy much longer and should therefore be older than multibacillary patients who have not been previously treated. In fact, as shown in Table 3, the age distribution of patients from whom dapsone-resistant *M. leprae* were isolated is not different from that of patients whose pretreatment isolates were susceptible to dapsone.

Surveys for primary resistance to dapsone have been carried out in Ethiopia, where a prevalence of 67 per 100 was found,[4] and in the Philippines, where a much lower prevalence—3·6 per 100—was encountered.[1]

This present report, only the third published description of the results of a systematic study of the susceptibility to dapsone of *M. leprae* isolated from previously untreated patients, should be taken as cause for alarm and remedial action. The prevalence of primary resistance to dapsone encountered in Bamako and Chingleput signals the extensive transmission of dapsone-resistant *M. leprae* within these communities, and represents evidence that the epidemiologic background of leprosy in those communities has been transformed. Sources of new infections with *M. leprae* are no longer confined to previously untreated patients with drug-susceptible, multibacillary leprosy, but now include patients who have suffered relapse with secondary dapsone resistance. The more general ocurrence of leprosy resulting from infection with dapsone-resistant organisms portends additional difficulties for programmes of leprosy control, threatening as it does seriously to reduce the potency of one of the few effective drugs available.

On the other hand, the discovery of primary dapsone resistance of low degree does not imply that dapsone therapy will not benefit the patient. On the contrary, the patient may be expected to respond to treatment with dapsone in the full

Table 3. Age distribution of patients

Age (years)	Bamako		Chingleput	
	Susceptible	Resistant	Susceptible	Resistant
< 20	4	1	2	5
20–39	18	11	30	13
> 39	2	1	3	3

dosage of 100 mg per day. However, because resistance to dapsone appears to develop in stepwise fashion—that is, low-resistant *M. leprae* give rise to mutants of a higher degree of resistance, multibacillary patients are likely to relapse in time with fully-resistant *M. leprae* (a strain not inhibited by dapsone administered to the mice in a concentration of 0·01 g per 100 g diet) if dapsone is employed as monotherapy.[6]

Finally, the combined drug regimens recommended by the WHO Study Group on Chemotherapy of Leprosy for Control Programmes[10] clearly were designed with the increasing frequency of dapsone resistance—both primary and secondary—in mind. The data presented in this report point to the urgency of adopting the Study Group regimens, and demonstrate the need to employ combined chemotherapy for treatment of paucibacillary as well as of multibacillary leprosy.

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Studies on dapsone-resistant *Mycobacterium leprae* in leprosy patients of Gudiyatham Taluk, the leprosy control area of the Schieffelin Leprosy Research and Training Centre, Karigiri. 2. A progress report

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Summary The 1580 LL and BL leprosy patients in a community of 480,000 persons in South India were studied for the occurrence of dapsone-resistant *Mycobacterium leprae*, between March 1978 and February 1981. Patients with a BI $\geqslant 2+$ were biopsied for mouse inoculation, even if they were improving on dapsone monotherapy. Between 89 and 116 patients per 1000 patients screened were estimated to harbour dapsone-resistant *M. leprae*.

Introduction

Gudiyatham Taluk of North Arcot District in Tamil Nadu, the leprosy control area of the Schieffelin Leprosy Research and Training Centre, covers an area of approximately 1320 sq km with a population of 480,000 (1981 Census). The region is hyperendemic for leprosy, and in December 1977, 6880 patients were on the treatment register at 44 peripheral clinics within the control area. Dapsone monotherapy has been extensively used in this area since 1963, and fairly accurate records of patients have been maintained systematically throughout this period.

The objectives of the study were: 1, to determine the number of registered patients who harbour dapsone-resistant *Mycobacterium leprae*; and 2, to identify risk factors associated with the occurrence of dapsone-resistant *M. leprae*.

Materials and methods

The denominator chosen for the study was all LL and BL cases on the treatment register maintained by the Department of Epidemiology and Leprosy Control of

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this institution at the end of December 1977, who resided within the control area. Every patient in the denominator was clinically examined by a medical officer, and skin smears were taken from 4 routine sites as well as from other sites at which there was evidence of activity.

Patients with a BI $\geqslant 2+$ at any one site were biopsied, preferably from the site with the highest index (avoiding the face). In order not to underestimate the number of patients harbouring dapsone-resistant *M. leprae*, biopsy was performed on all patients with a BI $\geqslant 2+$, and not only on those showing evidence of active disease, as in the studies reported to date.[1–13] It must be emphasized that those biopsied included patients improving on dapsone monotherapy, who would not ordinarily be suspected of harbouring dapsone-resistant *M. leprae*. Biopsies were usually taken in the field and transferred to the base laboratory on wet ice for mouse foot-pad studies, which were performed by methods already described.[14, 15]

The patients whose *M. leprae* failed to grow even in untreated mice, and those in whom the test did not detect resistant *M. leprae*, were rescreened and biopsied again if eligible.

Results and interpretation

All 1580 registered LL and BL patients residing within the area were enumerated in December 1977. The screening began in March 1978, and the activities undertaken during the next 3 years are summarized in Table 1. Of the total, 1431 patients were screened in the first year, forming a cohort that was subjected to annual screening, and biopsied when eligible.

In the first year 149 patients evaded screening. A 10% random sample of these patients were subsequently screened, and none was found eligible for biopsy. The

Table 1. Numbers of patients screened annually

	Year of survey		
	1978–79	1979–80	1980–81
Enumerated	1580	1431	1320
Migrated or died during the previous year	—	56	48
Resistant bacilli demonstrated in previous year	—	33	27
Eligible for screening	1580	1342	1245
Acutally screened	1431 (90·6%)	1320 (98·4%)	1208 (97·1%)

149 patients were therefore not included in any subsequent procedures or analysis.

As shown in Table 2, 9 patients among the 1431 screened had been shown earlier by mouse inoculation to harbour dapsone-resistant *M. leprae*. Table 2 also shows the number of patients found eligible for biopsy (BI $\geqslant 2+$) during each year of the study, and the number of patients subjected to biopsy. The large proportion of biopsies done during the third year of survey did not reflect an increase in the number of patients attaining eligibility for biopsy during that year, but resulted from an improved operational capacity for handling biopsy specimens. A total of 188 patients were found eligible for biopsy, of whom 142 have thus far been subjected to the procedure.

The results of biopsy and mouse inoculation are presented in Table 3. Of the 188 patients eligible, 46 escaped biopsy for a variety of reasons. Of the 142 mouse foot-pad studies carried out, the results of 17 are still not available. In 26 studies the inoculated *M. leprae* failed to multiply in both control and dapsone-treated mice. Dapsone-resistant *M. leprae* were detected in 89 studies. The resistant *M. leprae* in 81 of these studies manifested resistance to the highest concentration of dapsone used (0·01 g%). 10 studies did not detect any dapsone-resistant *M. leprae*. It is of great interest to note that an eleventh study, which on one occasion did not detect dapsone-resistant *M. leprae*, was repeated on the same patient after a period of 12 months. On the second occasion, dapsone-resistant *M. leprae* were detected, that manifested resistance to the highest concentration of dapsone used.

Thus, of the 188 patients eligible for biopsy and mouse inoculation, the results of mouse foot-pad studies have so far been obtained for only 99. Because 89 patients for whom no results are available comprise so large a fraction of the total, it is necessary to make some assumptions regarding them, in order to estimate the number of patients harbouring dapsone-resistant *M. leprae*. It appears reasonable to assume that among the 46 patients not subjected to biopsy and the 17 for

Table 2. Numbers of patients with positive smears and numbers biopsied annually

No. of patients	Pre-1978*	Year of survey 1978–79	1979–80	1980–81	Cumulative†
Smear positive	—	336	330	179	—
BI $\geqslant 2+$	9	114	86	82	188
BI $\geqslant 2+$ with clinical relapse	9	46	49	34	87
Biopsied for mouse inoculation	9	26	28	80	142

* 9 patients among the 1431 screened had already been shown by mouse inoculation to harbour dapsone-resistant *M. leprae*.

† A patient who appears to more than 1 year is counted only once in the cumulative total.

Table 3. Results of biopsies and mouse inoculation

	Number of specimens				
		Year of survey			
	Pre-1978	1978–79	1979–80	1980–81	Cumulative
Biopsied	9	26	28	80	142
No growth of *M. leprae*	—	—	—	26	26
No DDS-resistant *M. leprae* detected	—	2*	1	8	10
DDS-resistant *M. leprae* detected	9	24	27	29	89
Resistant to DDS, at mouse diet concentration of:					
0·0001 g%	—	—	—	1	1
0·001 g%	—	2	2	3	7
0·01 g%	9	22	25	25	81
Study in progress	—	—	—	17	17

* One of these patients was later biopsied again and shown at that time to harbour resistant organisms; he is included only once in the cumulative totals.

whom results are awaited, the proportion who harbour dapsone-resistant *M. leprae* is the same as among those for whom results are available. The 26 patients whose organisms failed to multiply in control mice are problematic, however. It could be argued that these patients harbour no dapsone-resistant *M. leprae*, because such a large proportion of the organisms from these patients had been killed during dapsone treatment that no organisms grew even in untreated mice. However, it is possible that viable dapsone-resistant *M. leprae* were present, although the inoculum contained too few to produce growth in the mouse foot-pad. To allow for this uncertainty, a separate estimate of the total number of patients harbouring dapsone-resistant *M. leprae* has been made for each of the alternative possibilities.

It has already been pointed out that some patients who showed improvement on dapsone monotherapy were biopsied only because they had a BI $\geqslant 2+$; these patients would not ordinarily have been suspected of harbouring dapsone-resistant *M. leprae*. They differ markedly from the rest of the patients biopsied, in showing a decrease in BI in successive smears at the time of biopsy. Until the significance of this difference is more fully understood, it appears important to maintain the distinction between this group of patients and the rest. Therefore, the 188 patients eligible for biopsy have been divided in 2 groups: 142 who showed an increase in BI in successive smears at the time of biopsy; and 46 who showed a decrease in BI.

Table 4 shows the estimation of the total numbers of patients harbouring

Table 4. Estimation of total number of patients harbouring dapsone-resistant *M. leprae*

	Number of patients		
	Successive smears show increasing BI	Successive smears show decreasing BI	Total
Eligible for biopsy	142	46	188
No results available*	27	36	63
No growth of *M. leprae*	22	4	26
Resistant *M. leprae* detected	84	5	89
No resistant *M. leprae* detected	9	1	10
Predicted additional number with resistant *M. leprae*:			
alternative no. 1†	$\frac{84}{(93+22)} \times 27 = 20$	$\frac{5}{(6+4)} \times 36 = 18$	38
alternative no. 2‡	$\frac{84}{93} \times 49 = 44$	$\frac{5}{6} \times 40 = 33$	77
Total number with resistant *M. leprae*:			
alternative no. 1	$84+20=104$	$5+18=23$	127
alternative no. 2	$84+44=128$	$5+33=38$	166

* Includes patients not biopsied, and those whose results are pending.

† *M. leprae* that failed to grow in mice assumed not resistant.

‡ *M. leprae* that failed to grow in mice assumed susceptible and resistant in same proportions as those that multiplied in mice.

dapsone-resistant *M. leprae* in each of the 2 groups. The assumption has been made that none of the 26 patients whose *M. leprae* failed to multiply in mice harbours dapsone-resistant organisms, whereas, among the remaining 63 patients for whom no results are available, the proportion who harbour resistant organisms is the same as among the 99 patients for whom results are available. With these assumptions, a total of 104 patients from the first group and 23 patients from the second group, altogether 127 patients, were estimated to harbour dapsone-resistant *M. leprae*.

Instead, if among the 26 patients whose *M. leprae* failed to grow in control mice, the proportion who harbour resistant bacilli is considered to be the same as the proportion among the 99 patients whose results are available, then, by similar calculations, an alternative estimate is obtained. According to this alternative estimate, 128 patients from the first group and 38 patients from the second group, altogether 166 patients, were estimated to harbour dapsone-resistant *M. leprae*.

The number of registered LL and BL patients residing in Gudiyatham Taluk,

who harbour dapsone-resistant *M. leprae*, is therefore estimated to be between 127 and 166 patients, of a total of 1431 patients screened annually. Expressing these figures as fractions, between 89 and 116 per 1000 patients screened are estimated to harbour dapsone-resistant *M. leprae*. It appears reasonable to assume that the true figure must fall somewhere between these two estimates.

Discussion

As reported earlier,[15] the crude estimate of the prevalence of dapsone-resistant leprosy in Gudiyatham Taluk after the first year of this study was 23 per 1000. This may be explained partly by our earlier inability to test in mice the *M. leprae* of all the patients eligible for biopsy during a given year, and partly by the fact that biopsy during the first year was done only on patients who were deteriorating, by smear and clinical criteria.

The unexpected finding that patients who were improving on dapsone monotherapy were also shown by the mouse foot-pad test to harbour dapsone-resistant *M. leprae* raises problems of interpretation. It would appear premature to make a decision on this until a detailed analysis of our data can be completed.

Analysis of risk factors has also been deferred. However, careful records have been kept of the treatment and progress of all the patients screened, from their date of diagnosis. An analysis of the prevalence of dapsone resistance, and its causation and consequences in the individual and in the community, will be undertaken in subsequent publications.

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Dapsone-resistant leprosy in Jakarta: a preliminary report

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Summary In a first effort to demonstrate the emergence of dapsone-resistant *Mycobacterium leprae* in Indonesia, 1 case of secondary resistance and 1 of primary resistance were demonstrated by inoculation of the mouse foot-pad.

Since 1969, it has been the practice in Indonesia to treat leprosy patients with dapsone as monotherapy. Considering the increasing prevalence of resistance to dapsone now being reported from many leprosy endemic areas,[1] it was to be expected that strains of *Mycobacterium leprae* resistant to dapsone would already have emerged in Indonesia. There appeared an urgent need to attempt to identify Indonesian patients with leprosy who harboured dapsone-resistant *M. leprae*, both to assist in the care of the patients, and to bring the problem to the attention of the authorities responsible for leprosy control. Therefore, at the end of 1980, the mouse foot-pad technique for cultivation of *M. leprae* was established in the Department of Microbiology of the Medical Faculty of the University of Indonesia, and a programme of dapsone-susceptibility testing was begun. Reported here are the results of the first 6 studies completed.

Materials and methods

Biopsy specimens were obtained from lesions of patients with multibacillary leprosy attending the Skin Clinic of the Central General Hospital in Jakarta, who were suspected of secondary or primary resistance to dapsone. Employing the technique described by Shepard,[2,3] *Mycobacterium leprae* were recovered from each specimen, and 5×10^3 were inoculated into each right hind foot-pad of 40 CBA mice; 1 group of 10 mice was held as untreated controls, whereas the mice of the other groups were administered dapsone in the diet in concentrations of 0·0001, 0·001 and 0·01 g per 100 g diet. Beginning 5 months after inoculation, *M.*

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leprae were harvested at intervals of 1 month from the right hind foot-pads of 2 control mice, and from the right hind foot-pads of 2 mice of each treated group, when the average number of organisms per foot-pad reached 5×10^5 in control mice.

Results

The characteristics of the patients, and the results of inoculation of mice with *M. leprae*, are summarized in Table 1. These data demonstrate that the organisms of 1 patient—patient A—failed to infect mice, and might therefore have been susceptible to dapsone, i.e. they had been killed in the patient in the course of treatment. Those of 3 additional patients—S, M and R—multiplied in untreated but not in treated mice, and may therefore be concluded to have been fully susceptible to dapsone.

The *M. leprae* of 2 patients were resistant to dapsone. Those of patient T multiplied as well in all groups of treated mice as in the untreated mice, and may be considered to show a high degree of resistance. The *M. leprae* of patient 'I' may be seen to have multiplied only in untreated mice, and in the mice administered the lowest concentration of dapsone, whereas they did not multiply in the mice treated with dapsone in higher concentration.

Table 1. Characteristics of the patients, and the fate of their *M. leprae* in mice

Patient	Sex/age (years)	Class	BI	Date mice inoculated	Time of harvest (days)	Average no. *M. leprae* per foot-pad ($\times 10^5$) Dapsone concentration (g%) 0	0·0001	0·001	0·01
S	F 22	BL	3+	8.12.80	248	8·7	0·20	NM*	0·03
T	M 35	BL/LL	5+	26.2.81	184	9·7	14·0	8·3	16·0
A	M 29	Histoid	5+	26.2.81	216	NM	NM	NM	NM
I	M 14	Histoid	3+	20.3.81	188	6·8	2·1	NM	NM
M	M 35	Histoid	6+	5.5.81	322	3·1	NM	NM	NM
R	M 52	Histoid	3+	1.9.81	188	4.8	0·60	0·50	0·20

* No multiplication.

Discussion

In a first attempt to demonstrate the presence of dapsone-resistant *M. leprae* in Indonesia, the susceptibility to dapsone was measured of the organisms of 6 patients clinically suspected of resistance to dapsone. The organisms of 3 patients

were fully susceptible, and those of an additional patient failed to infect mice, and may therefore be considered also to have been susceptible to dapsone. *M. leprae* of a high degree of resistance were isolated from 1 patient who had initially responded and subsequently relapsed after treatment with dapsone as monotherapy for years; this appears clearly to be an example of secondary resistance. Finally, low-degree resistance to dapsone was demonstrated in the case of a 14-year-old boy who denied previous treatment, and who therefore appears to represent an instance of primary resistance. Although one may be reluctant to base a diagnosis of primary resistance on the statement of a patient that he has received no previous treatment, the patient's statement is in this case reinforced by his youth; he does not appear to have lived long enough to have been treated with dapsone, responded and subsequently relapsed with secondary resistance.

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Secondary dapsone-resistant leprosy in Shanghai Municipality

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Summary A formal survey of the prevalence of secondary dapsone-resistant leprosy, conducted in Shanghai Municipality according to the THELEP Protocol, has revealed an estimated prevalence of from 5·66 to 8·62 per 100 patients at risk.

Secondary resistance to dapsone has been detected with increasing frequency among patients with multibacillary (LL, LI and BL) leprosy in many countries.[4] In order to assess the severity of the problem in the Shanghai area and measure the magnitude of the threat to leprosy control activities, we undertook a survey of the prevalence of secondary dapsone resistance in Shanghai Municipality according to the THELEP Protocol for Surveys of Dapsone Resistance.[1]

In Shanghai Municipality, which includes a total population of about 11·5 million in an area of 6185 km^2, a leprosy control programme has been active since 1956. At the end of 1979, 5326 patients of all types were registered, of whom 1195 (22·4%) had been classified lepromatous according to the Madrid classification.[6] Patients with multibacillary leprosy are usually hospitalized until smears become negative, after which treatment is continued on an out-patient basis. Case records have been maintained with reasonable accuracy since 1956.

Sulphone therapy was introduced into this area in the early 1950s. Dapsone, which soon became the sulphone of choice, is routinely administered to leprosy patients in a daily dosage of 100 mg. Thiacetazone, 100–200 mg daily for 0·5–4 years, and thiambutosine, 2–3 g daily for 1–2 years, have been administered to some lepromatous patients, usually in combination with dapsone. In addition, some patients, the majority of whom had relapsed, were treated with other 'first-line' drugs, among them clofazimine, B628, rifampicin, AF-MO (the methyloxime of 3-formylrifamycin SV), *iso*butylpiperazinylrifamycin, ethionamide and prothionamide, for 0·5–2 years.

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Materials and methods

A team of 8 physicians, nurses and laboratory technicians was organized for this survey. Analysis of the records of all registered patients revealed that 795 lepromatous patients—573 males and 222 females—who had been treated with dapsone for at least 5 years were still living. Of these, 777 (97·7%)—560 males and 217 females—were found by the team and assessed clinically and by skin smears. These 777 patients comprise the denominator—the patients at risk of dapsone resistance. Ninety-two (11·8%) of the patients yielded positive smears of whom 67 (8·62% of the total) were found to have a bacterial index (BI) $\geqslant 3$ in at least 1 skin lesion, and were therefore suspected of harbouring dapsone-resistant *Mycobacterium leprae*. All but 6 of these patients were subjected to skin biopsy and measurement of the susceptibility of their *M. leprae* to dapsone.

The susceptibility of *M. leprae* to dapsone was measured by published methods.[5] Briefly, 10^4 *M. leprae* were inoculated into each hind foot-pad of a number of locally bred Swiss mice. One group of 14–20 mice served as untreated controls, and groups of 7–14 mice were administered dapsone incorporated into the mouse diet in a concentration of 0·0001, 0·001 or 0·01 g dapsone per 100 g diet. Harvests of *M. leprae* were performed from both hind foot-pads of 2 to 4 untreated, control mice at intervals of 45–60 days, beginning 8–10 months after inoculation, until evidence of multiplication (an average yield of at least $10^{5·7}$ *M. leprae* per foot-pad) was observed. At this time, the remaining control mice and all of the treated mice were harvested individually. If, by the end of 14 months, control harvests had yielded an average of less than $10^{5·7}$ but at least $10^{5·0}$ organisms per foot-pad, harvests of *M. leprae* from the dapsone-treated mice were carried out at that time. However, if the yield of *M. leprae* after 14 months was fewer than $10^{5·0}$ organisms per foot-pad, no further harvests were carried out, and the patient's *M. leprae* were considered to have been non-infective for the mouse foot-pad. A strain of *M. leprae* was considered resistant to a given concentration of dapsone if more than half of the mice treated with dapsone in that concentration yielded at least $10^{5·0}$ organisms per foot-pad.

Results and interpretation

RESULTS OF SCREENING

The results of screening the 777 patients at risk are summarized in Table 1, in which the patients are divided between 2 groups. The patients in Group I had received no treatment other than dapsone, or had received additional treatment with thiacetazone or thiambutosine, both weak, bacteriostatic drugs. The patients of Group II, most of whom had exhibited clinical evidence of relapse or deterioration after a period of dapsone as monotherapy, had all received

Table 1. Results of screening

Group	Treatment	Number of patients	Relapse or deterioration	BI 0	BI 1–2	BI ⩾3
I	Dapsone + bacteriostatic drugs	718	48	665	12	41 (5·71%)
II	Dapsone + other first-line drugs	59	52	20	13	26 (44·1%)

additional treatment with first-line drugs. Fewer than 6% of the patients of Group I were suspected of harbouring dapsone-resistant *M. leprae*, whereas 44% of the patients of Group II met the criteria for biopsy and mouse inoculation. On the other hand, it is clear that some of the Group II patients had responded to therapy with first-line drugs in addition to dapsone; most of them had been found to have BI ⩾ 3 at the time that the additional treatment had been instituted.

RESULTS OF MOUSE FOOT-PAD INOCULATION

The results of the measurements of susceptibility to dapsone of 61 strains of *M. leprae* are summarized in Table 2. The organisms of 15 strains failed to infect mice. Seven of these strains, representing patients of Group I, may be concluded to have been fully susceptible to dapsone, which was being administered as monotherapy to these 7 patients at the time of the survey. Presumably, the *M. leprae* had been killed in the patient, but the BI had not yet decreased to < 3. The

Table 2. Results of dapsone-susceptibility testing

Group	Number of specimens: Number tested	Not infective	Fully susceptible	Resistant to dapsone (g%): 0·0001	0·001	0·01	Uncertain
I Relapse	26	2	2	2	5	14	1
No relapse	13	5	6	1	0	1	0
Not biopsied	2*	—	—	—	—	—	—
II Relapse	22	8	4	0	0	10	0
No relapse	0	0	0	0	0	0	0
Not biopsied	4*	—	—	—	—	—	—

* Refused biopsy.

patients among 777 at risk, for a prevalence of 8·62 per 100; the 95% confidence limits are 6·79 and 10·88 per 100.

Discussion

Although cases of secondary resistance to dapsone had been previously reported from China,[3] no estimate of prevalence was available. Prevalence surveys among leprosarium patients may well result in biased estimates, because patients who do not do well on treatment are likely to remain longer in and around treatment centres, whereas those who have responded to treatment are more likely to return to their homes. Therefore, in order to obtain an unbiased estimate of the prevalence of secondary dapsone resistance, it is necessary to examine all of the patients at risk; this is the basis of the THELEP protocol.[1] Such a prevalence survey was possible in Shanghai Municipality.

This first survey of the prevalence of secondary dapsone resistance in China has yielded evidence that secondary resistance to dapsone may already be an important problem in Shanghai, affecting as many as 10% of the patients at risk. Because one consequence may be the transmission of dapsone-resistant *M. leprae* in the community, an on-going survey of primary dapsone-resistant leprosy has recently been initiated. In addition, it may appear reasonable to treat all of the patients who remain at risk of secondary resistance with a combination of two first-line drugs in addition to dapsone; such a programme is now being actively considered.

It is interesting to note that, of the 34 strains of dapsone-resistant *M. leprae* isolated, all but 4 were of intermediate and high degrees of resistance. This testifies to the excellence of the leprosy control programme in Shanghai Municipality in the past,[5] and serves warning that an intensive programme of leprosy control based on dapsone monotherapy will not protect a community against secondary resistance to dapsone.

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Antigens of *Mycobacterium leprae* and anti-*M. leprae* antibodies in the urine of leprosy patients

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Summary Forty-six newly diagnosed untreated leprosy patients and 11 control persons were examined for acid-fast bacilli, *Mycobacterium leprae* antigen(s) and anti-*M. leprae* antibody-like activity in concentrated urine samples. No acid-fast bacilli were found. Two of 23 paucibacillary and 11 of 23 multibacillary patients had detectable antigen(s) in the urine. The antigen(s) was/were absorbed by anti-BCG in 7 out of 8 examined samples. A significant correlation between maximal bacteriological index and antigen concentration was found. Extensive differences in the anti-*M. leprae* antibody-like activity were seen within the group of control persons and the different groups of patients throughout the spectrum of leprosy. The results of examinations of the antibody-like activity after absorptions with Cowan I staphylococci, Sepharose–anti-human IgG, heat treatment and assays for total IgG, IgA and IgM gave good evidence that most of the activity was due to anti-*M. leprae* antibodies of the IgG class.

Introduction

Clinical leprosy is recognized by the clinical signs and symptoms, the documentation of acid-fast bacilli in slit-skin smears and histopathologically. Sometimes *in vivo* or *in vitro* immunological tests can be helpful in the diagnosis of clinical leprosy.

The diagnosis of subclinical leprosy (defined as infection without clinical signs and symptoms at any time after infection) and preclinical leprosy (defined as the

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stage of infection before the clinical signs and symptoms have developed; this corresponds to the incubation period) can be done by documenting the bacilli and/or the histopathological changes these may cause. This is, however, difficult when the location of the infection is unknown. The use of immunological methods to measure these responses to the infection offers one possibility for diagnosis of sub- and preclinical leprosy.

Tests for cell-mediated immunity include, for example, lepromin test lymphocyte transformation test and leukocyte migration inhibition test.[1,2] The problems with these tests are, however, that (a) persons who will develop lepromatous leprosy probably have a bad response to *Mycobacterium leprae* antigens already in the preclinical period; (b) positive results are difficult to interpret with respect to the time that an individual was infected, unless prospective studies are conducted with repeated tests; (c) subclinical infections that have been spontaneously cured cannot be differentiated from preclinical infections; and (d) the tests lack specificity and cross-react with other mycobacteria, for example *M. tuberculosis* and BCG.[3]

Tests for anti-*M. leprae* antibodies have also been tried in the diagnosis of sub- and preclinical leprosy.[4–9] This approach overcomes some of the disadvantages listed above. For example, most lepromatous patients develop anti-*M. leprae* antibodies[4,10] in spite of their low or lacking cell-mediated immune response to *M. leprae*. The antibody tests have also been refined to decrease the cross-reactivity with other mycobacterial infections.[4,6] The drawbacks mentioned under (b) and (c) above are, however, still attached to these tests.

Another diagnostic method would be to document the presence of *M. leprae* antigens. This has been done in tissue biopsies from patients with diagnosed leprosy.[11] In other infectious diseases like bacterial meningitis,[12] pneumococcal pneumonia[13] and *Schistosoma mansoni* infections[14] microbial antigens have been found in body fluids like blood and urine. If *Mycobacterium leprae* antigens could be found in body fluids like urine it may offer a better method for diagnosing sub- and preclinical leprosy. The theoretical advantages would be that detection of antigen ought to be closely correlated to active infection and that urine is a much easier sample to collect than blood, skin smears and biopsies, especially in epidemiological field surveys.

The present study was initiated due to the theoretical advantages of antigen detection discussed above with the primary aim to see if *M. leprae* antigens were to be found in urine or not. Since untreated newly diagnosed patients with clinical leprosy were thought to be the ones most likely to have detectable levels of *M. leprae* antigens, the study was focused on this group. It was also realized that the anti-*M. leprae* antibody-like activity, found in many urine samples in pilot studies that were conducted by us, needed to be further explored. The results of these studies are also included in the present paper.

Material and Methods

PATIENTS

Forty-six untreated leprosy patients attending the out-patient clinic of ALERT between March and July 1982 were included. Their ages ranged from 9 to 51 years (mean 28 years) and the history of clinical signs and symptoms varied between 3 months and 9 years (mean 2 years and 9 months). The diagnosis was based on the clinical findings, the results of examining slit-skin smears for acid-fast bacilli (Ziehl–Neelsen staining) and in most cases by histopathological examination of skin biopsies. The classification was performed according to the Ridley–Jopling scale.[15] Reversal reactions were seen in 2 borderline tuberculoid (BT) and 2 borderline lepromatous (BL) patients. None of the patients was suffering from erythema nodosum leprosum.

Four healthy Ethiopian laboratory technicians, who have been working extensively with *Mycobacterium leprae* for several years, and 7 patients admitted to the ALERT hospital without leprosy but with the diagnosis of pemphigus vulgaris, diffuse cutaneous leishmaniasis, cataract, glucoma and keratitis due to onchocerciasis were included as controls.

URINARY SPECIMENS

One hundred to three hundred millilitres of urine was collected from each patient before start of antileprosy treatment. The urine was stored at +4°C for 1–3 days after addition of sodium azide (final concentration 1 mg/ml). Tests for blood, glucose, protein and nitrite was carried out using Ames N-multistix. The urine was centrifuged at 17,000 ***g*** for 20 minutes. The sediment was examined for cells, cylinders and bacteria after staining with crystal violet (0·1%) and safranin (0·2%). Staining for acid-fast bacilli was performed with the Ziehl–Neelsen technique and by the fluorochrome auramine.[16] At least 100 high-power fields were examined in each slide. The supernatant was concentrated about 10 times in an ultrafiltration cell (Amicon model 402) with a Diaflo ultrafilter YM 10 (cut-off 10,000 MW). The source of pressure (4·5 bar) for operating the cell was dried nitrogen gas. Double distilled water was added to reach the original volume which was again reduced to one-tenth of the original in the cell. This volume was lyophilized. The dry powder was dissolved in 'RIA-buffer' (0·01 M phosphate-buffered saline pH 7·4 = PBS, with 0·2% bovine serum albumin—Sigma Chemical Co, USA—and 0·2 mg NaN3/ml) to a volume 1:100 the original, and stored at −20°C until assayed.

The concentrations of total IgG, IgM and IgA in the concentrated urine samples were measured by the Mancini technique (standard solutions from Behringwerke AG).

KIDNEY FUNCTION

This was evaluated in each patient by the history and general physical examination including blood pressure, the serum creatinine level (Créatinine-kit Bio Mérieux) and the urine tests noted above.

RADIOLABELLING OF ARMADILLO *M. LEPRAE* ANTIGENS

Freeze-dried armadillo *M. leprae* batch CD12, prepared according to Protocol 1/79, was provided by IMMLEP component of UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The bacilli were sonicated twice in 0·15 M NaCl, first with 50 W for 5 minutes and a second time, after storage of the suspension over night at +4°C, with 100 W for 5 minutes. The sonicated suspension was centrifuged at 20,000 ***g*** for 20 minutes and the supernatant concentrated to 0·3 mg protein/ml. This preparation was named the armadillo *M. leprae* sonicate (AMlS) and was radiolabelled ^{125}I by the electrolytic iodination method described by Harboe and Fölling.[17]

In short 400 μl of AMlS was mixed with 40 μl 5×10^{-5} M NaI, 160 μl distilled water and 1 m Ci ^{125}I (supplied as sodium iodide in dilute sodium hydroxide by Amersham International, England) in a stirred platinum beaker. A current of 15–25 mA was run for 15–25 minutes between the beaker and a platinum electrode dipped into the AMlS. 200 μl of 1×10^{-2} M NaI was added and the solution dialysed extensively against RIA-buffer. After centrifugation at 20,000 ***g*** for 20 minutes the supernatant was tested for antigenicity and stored at +4°C. The method of radiolabelling has been shown to give a strong labelling of *M. leprae* antigen 7.[18]

RADIOIMMUNOASSAY (RIA) FOR DETECTING ANTI-*M. LEPRAE* ANTIBODY-LIKE ACTIVITY IN CONCENTRATED URINE SAMPLES

Samples were run in duplicate. Each tube contained 50 μl of concentrated urine, that had been cleared of sedimenting particles by centrifugation at 2300 ***g*** for 10 minutes after thawing; 50 μl of RIA-buffer; and 50 μl of (^{125}I)-AMlS diluted to give 125,000 counts in 400 seconds. The mixture was incubated for 30 minutes at room temperature (Rt). Controls without urine and (^{125}I)-AMlS were run at the same time. For reference values of anti-*M. leprae* antibody-like activity different concentrations of a high titre patient anti-*M. leprae* serum (no. 625 in ref. 18) was also run in the assay.

(^{125}I)-AMlS bound to antibodies, or antibody-like substances, was separated from free AMlS by formalinized staphylococci (1 ml of a 1% suspension) strain Cowan I (Pharmacia Diagnostics AB, Sweden). The staphylococci (CI) were pelleted by centrifugation at 2300 ***g*** for 20 minutes, the supernatant aspirated and the pellet counted in a LKB-Wallac 1270 rackgamma II gamma counter for 400 seconds.

In order to get some idea of the nature of anti-*M. leprae* antibody-like activity, the concentrated urine samples were treated in different ways before the RIA. Samples were absorbed with different amounts of CI; heat treated in boiling water (+92·5°C at the altitude of Addis Ababa) for 5 minutes; absorbed with different amounts of Sepharose 4B (Pharmacia Fine Chemicals AB)-conjugated rabbit anti-human IgG (DAKO-immunoglobulins a/s, lot 110B).

INHIBITION RIA FOR DETECTING *M. LEPRAE* ANTIGENS IN CONCENTRATED URINE SAMPLES

Samples were run in duplicate. Each tube contained 50 μl of a 10^{-3} dilution of patient anti-*M. leprae* antiserum 625. In addition to being present in a high titre the antibodies had previously been shown[18] to be blocked by the mycobacterial polysaccharides arabinogalactan (AG) and arabinomannan. Fifty microlitres of concentrated urine was added after inactivation of the antibody-like activity by absorbing 100 μl of urine with 20 mg wet weight CI for 5 minutes at Rt and heat treatment. Fifty microlitres of properly diluted (^{125}I)-AMlS was added and the further steps in the assay were run as for antibody-like activity. Controls without anti-serum 625, urine and (^{125}I)-AMlS were included. Different concentrations of a crude AG preparation from *M. tuberculosis*, prepared as previously described,[18] were assayed at the same time to give reference values to inhibiting substances in the urine samples.

In order to see if inhibition in the assay was due to the presence of mycobacterial antigens in the urine, absorptions were made before the assay with coagglutination reagents made by mixing 100 μl of anti-BCG antiserum (DAKO, lot 068C) or 100 μl of normal rabbit serum (NRS, DAKO lot 109B) with 1 ml of a 10% suspension of CI.[19,20] The mixture was kept at Rt for 5 minutes, centrifuged at 2300 ***g*** for 10 minutes, the supernatant aspirated and the pellet resuspended in PBS with 1% tween 20.

Results

KIDNEY FUNCTION IN NEWLY DIAGNOSED UNTREATED LEPROSY PATIENTS

All the 46 patients included in the study except 1 showed normal renal function (as evaluated by the clinical examination, serum-creatinine, the negative findings of blood and protein in urine and normal urine sediment). One patient with LL for 3 years without inflammatory complications had microscopic haematuria but no proteinuria. No patient had evidence of urinary tract infection as evaluated by the history, physical examination, nitrite test and urine sediment. No case of glucosuria was found.

URINE SEDIMENT EXAMINED FOR ACID-FAST BACILLI

Acid-fast bacilli were not seen in the stained urinary sediments from any of the 46 patients.

ANTI-*MYCOBACTERIUM LEPRAE* ANTIBODY-LIKE ACTIVITY IN CONCENTRATED URINE SAMPLES

Figure 1 shows that almost all the urine samples showed higher antibody-like activity than a 10^{-5} dilution of the high titre patient serum 625. Some urine

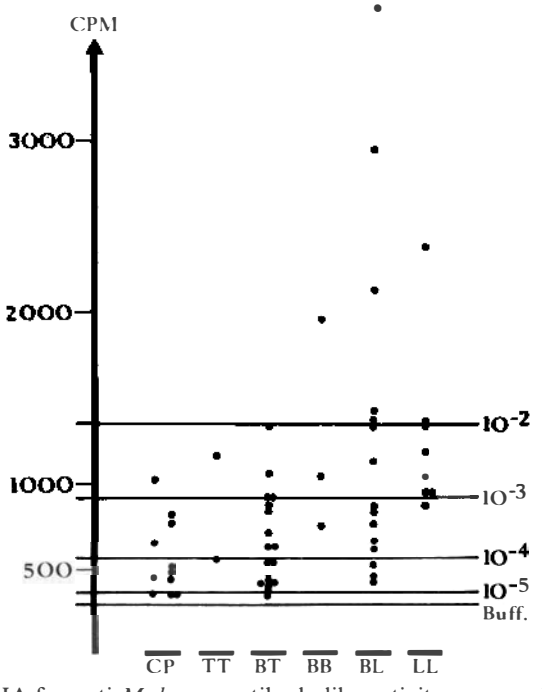

Figure 1. Results of RIA for anti-*M. leprae* antibody-like activity expressed as counts per minute (CPM) for individual concentrated urine samples in different groups of leprosy patients and control persons (CP). The horizontal lines represent the CPM with different dilutions of the high titre anti-*M. leprae* patient serum 625 (see 'Material and methods').

samples had very high antibody-like activity. In order to further explore the nature of this activity additional tests were performed and the following results were observed:

1 Binding to the gamma-vial wall of a urine-(^{125}I)-AMlS complex was ruled out by resuspending counted pellets, repelleting them in new gamma-vials and recounting the pellet and the empty vial. Only background values were obtained from the empty vial.

2 Formation of precipitates between some urine components and (^{125}I)-AMlS that pelleted together with CI could not be ruled out.
3 Direct binding of (^{125}I)-AMlS to CI was not found since the controls with just these two components gave low counts (300 CPM in Figure 1). In addition absorptions of (^{125}I)-AMlS with CI (100 μl with 20 mg) did not affect the results of the assay for antibody-like activity in the urine.

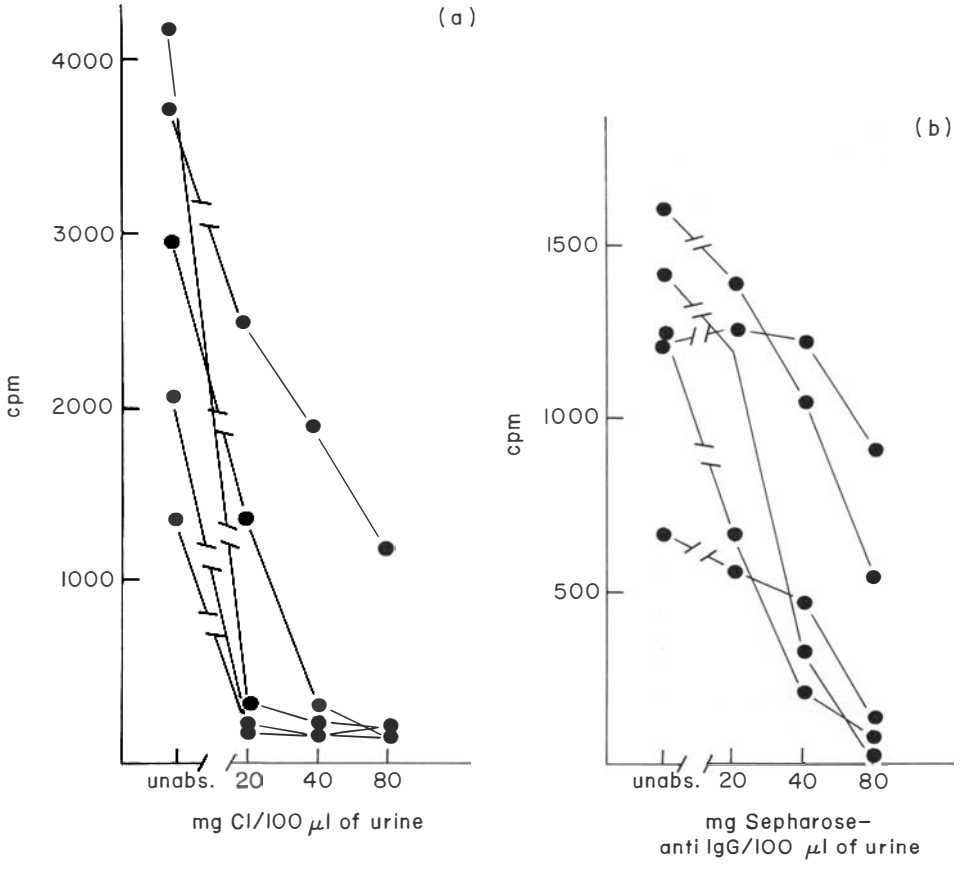

Figure 2. Results of RIA for anti-*M. leprae* antibody-like activity expressed as CPM for the 5 concentrated urine samples from leprosy patients with the highest anti-*M. leprae* antibody-like activity after (a) absorptions with different amounts of Cowan I (CI) staphylococci per 100 μl of urine, and (b) absorptions with different amounts of Sepharose–anti-human IgG per 100 μl of urine.

4 Binding of (^{125}I)-AMlS to CI by anti-mycobacterial antibodies or by a non-specific component in urine was documented by absorbing urine samples before the assay with CI. Twenty milligrams CI wet weight per 100 μl of urine absorbed all anti-*M. leprae* antibody-like activity completely except in the 5 samples with the highest antibody-like activity. The results obtained by absorptions with 20, 40, and 80 mg CI (wet weight) per 100 μl urine is shown in

Figure 2a. In 4 of the samples all activity was absorbed by 80 mg CI while the activity was substantially reduced in the fifth sample.

In order to see if antibodies or non-specific components were responsible for the coupling of (^{125}I)-AMlS to CI the concentrated urine samples were absorbed with Sepharose 4B–anti-human IgG before the assay. The urine samples were also examined for total immunoglobulin G, M and A.

The 5 concentrated urine samples with the highest anti-*M. leprae* antibody-like activity, the same as in Figure 2a, were absorbed by different amounts of Sepharose–anti-IgG (Figure 2b). In 4 of the samples the antibody activity was markedly reduced while the fifth showed a slight decrease in activity after absorption with 80 mg Sepharose–anti-IgG (wet weight). The dilution of a sample by the absorption procedure came to 4–9% so the results are not explained by dilution of the samples.

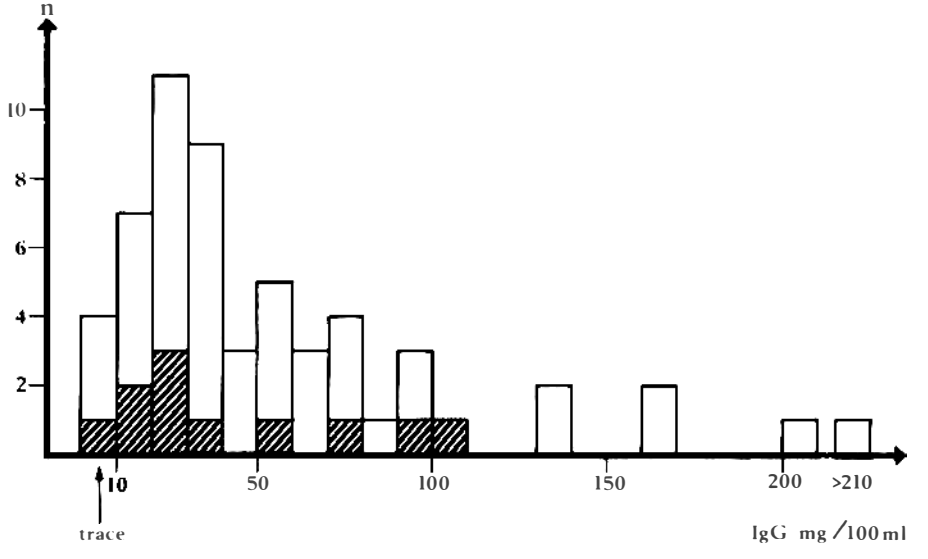

Figure 3. Results of examination of concentrated urine samples for IgG. Open bars represent leprosy patients and hatched control persons. n = number of persons.

All the samples from patients as well as control subjects contained IgG (Figure 3), or fragments of IgG, as shown by a Mancini test. There was no correlation between total IgG and anti-*M. leprae* antibody-like activity. IgA was found in trace amounts (less than 10 mg/100 ml) in 47 concentrated urine samples. In 7 samples no IgA was documented and in 3 the concentrations were 19, 73 and 106 mg/100 ml respectively. IgM was found in trace amounts (less than 30 mg/100 ml) in 6 samples while the remaining were negative.

Heat treatment completely destroyed all the anti-*M. leprae* antibody-like activity.

M. LEPRAE ANTIGENS IN CONCENTRATED URINE SAMPLES

Figure 4 shows the results of inhibition RIA for detection of *M. leprae* antigens. The relation of a urine sample count to the mean buffer value (1003 CPM) is expressed as a percentage, after subtraction of the mean background value (369 CPM) from each of them. The inhibition by different concentrations of AG is also indicated in Figure 4. Using Student's *t*-test (one tail) after square root

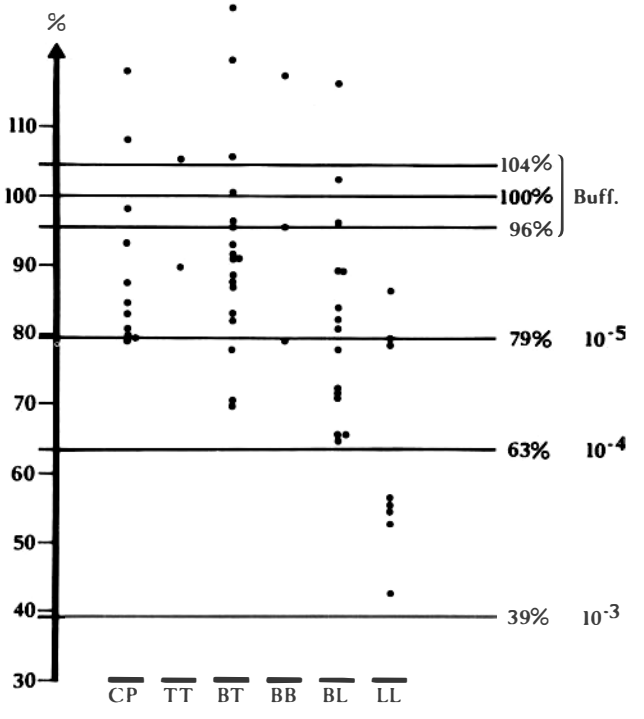

Figure 4. Results of inhibition RIA for *M. leprae* antigen in concentrated urine samples from different groups of leprosy patients and control persons (CP). The radioactivity in a sample is expressed as a ratio (%) calculated as follows:

$$100 \times \frac{\text{CPM for sample} - \text{CPM of background}}{\text{CPM for buffer} - \text{CPM of background}}$$

The horizontal lines represent the ratio for different concentrations of arabinogalactan (AG).

transformation of the results for the control persons only 1% of these could be calculated to get values lower than 79·6% by chance. The same level of inhibition was seen by 10^{-5} mg AG/ml.

It can be seen that 2 out of 18 (11%) urine samples from BT patients, 6 out of 15 (40%) samples from BL patients and 5 out of 8 (63%) samples from LL patients showed a markedly higher inhibition than the inhibition by 10^{-5} mg AG/ml.

Three of the urine samples from BL patients and 5 from LL patients with the

highest inhibition were selected for absorptions with CI–anti-BCG and CI–NRS co-agglutination reagents in order to study if anti-BCG could absorb the AG-like inhibition.

It was found that in 7 of the 8 urine samples absorption with CI–anti-BCG gave a reduced inhibition as compared to absorption with CI–NRS. The reduced inhibition corresponded to an absorption of $1{\cdot}6 \times 10^{-4}$ to $3{\cdot}4 \times 10^{-3}$mg AG/ml urine (mean $8{\cdot}0 \times 10^{-4}$) by the CI–anti-BCG reagent. This absorption study thus suggests that most of the urine samples with a high inhibition contained mycobacterial antigen(s) that could be absorbed with a CI–anti-BCG reagent.

Heat treatment of dilutions of AG and concentrated urine samples did not alter the inhibitory effect in the present assay.

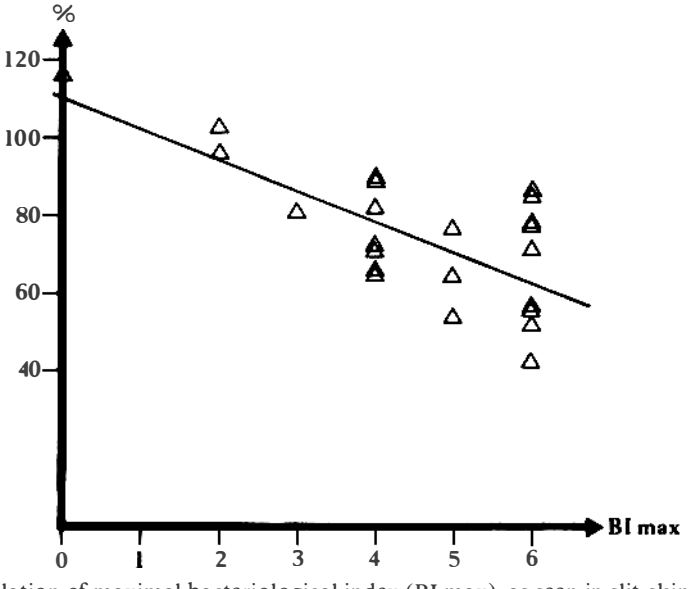

Figure 5. Correlation of maximal bacteriological index (BI max), as seen in slit-skin smears from 6 different sites, with the inhibition RIA for *M. leprae* antigen in concentrated urine samples from BL and LL patients. The ratio (%) is calculated as presented in Figure 4. For interpretation of BI numbers see.[21] The equation for the regression line is $Y = 109{\cdot}9 - 7{\cdot}64.\ X$.

The correlation between inhibitory activity and the highest bacteriological index (BI) found in 1 site out of 6 in the BL and LL patients (Figure 5) was significant (correlation coefficient 0·71, $P < 0{\cdot}1\%$, 21 degrees of freedom) for a linear average relationship between the 2 parameters.

Discussion

The approach of antigen detection for the diagnosis of an infectious agent has definite advantages over measurements of antibodies or cell-mediated immune

response. The presence of antigens is, for example, more closely related to active infection. In leprosy antigens may, however, also be found in the body for a long time after the bacilli are dead as suggested by the slit-skin examinations of treated patients.[22]

The antigen detection is a theoretically interesting possibility for the diagnosis of leprosy before clinical signs and/or symptoms develop (= preclinically). This would of course be of great value to the patient, who could get treatment earlier, perhaps without development of clinical disease, as well as for the society when contagious multibacillary cases could be diagnosed and treated earlier than at present.

Other interesting aspects of antigen detection are that quantitative measurements of antigen excretion in urine, over for example 24 hours, may be an additional way to evaluate the load of *Mycobacterium leprae* in a patient and also a way to follow the effect of treatment.

The use of urine for antigen detection is a favourable approach since the sampling is non-traumatic and urine is easily passed without hesitation by persons in most societies. These factors may prove favourable in epidemiological studies of leprosy.

The present study was conducted to see if *M. leprae* antigen(s) could be detected in urine in view of the possible advantages mentioned above. It was soon found out that the concentrated urine samples had an anti-*M. leprae* antibody-like activity that destroyed the antigen detecting assay. It is well known that Ig, mainly class G, and fragments of Ig are found in the urine from normal persons,[23] patients with non-renal infectious diseases[24] including leprosy.[25] This was also found in our patient and control urine samples which all contained IgG or at least antigenic fragments of IgG that gave precipitation with the anti-IgG antiserum used. It is also well documented that IgG (subgroup 1, 2 and 4) is the main class of human Ig that binds to CI[26] and therefore it is likely that urine IgG with antibody specificity to mycobacterial antigen(s) is responsible for the interference seen in the antigen assay.

The interfering activity was inactivated by absorption of the urine by CI–Sepharose anti-human IgG and by heat treatment. These results are expected if IgG is responsible for the interference.

Whether the anti-*M. leprae* antibodies found in urine can be of any diagnostic/epidemiological use or not is an open question.

In multibacillary leprosy patients acid-fast bacilli can be found in peripheral blood.[27] In spite of this sign of systemic spread of the bacillus there are few reports of acid-fast bacilli and histopathological patterns corresponding to leprosy lesions in kidneys.[28–33] The reported finding of acid-fast bacilli in urine from a high proportion of leprosy patients, even after long periods of treatment[34] has not been confirmed and finds no support in the present study.

Renal damage has been reported in a high percentage of leprosy patients. The patients examined in these reports have mostly been treated for longer periods

before their kidneys were biopsied and have had complicating inflammatory reactions. They thus differ from our material from newly diagnosed and untreated patients who all, except 4, had not experienced any reactions. With the methods available only 1 patient had evidence of kidney damage by having an isolated haematuria. Causes for the haematuria other than renal disease were, however, not fully evaluated in this case.

The presence in concentrated urine of substance(s) inhibiting the binding of (^{125}I)-AMlS to a reference serum with anti-*M. leprae* antibodies was documented in 11 of 23 multibacillary cases and in 2 of 23 paucibacillary patients. Support for the idea that the inhibition was due to mycobacterial antigen(s) was found by the markedly reduced inhibition seen after absorption of 7 out of 8 urine samples with CI–anti-BCG and by the significant correlation of the BI to the inhibition. The nature of this/these antigen(s) has not been revealed so far but work is in progress to clarify this by immunological and biochemical techniques.

A significant linear average relationship between inhibitory activity and the highest BI was found (Figure 5). Since the BI scale is logarithmic the inhibition is not directly proportional to the number of bacilli found in a slit-skin smear but to the logarithm of this number. The same linear relation was found for the inhibition and the logarithm of different concentrations of AG. This can to some extent be seen from results presented in Figure 4 where 10^{-5}, 10^{-4} and 10^{-3} mg of AG per millilitre gave ratios of 79%, 63% and 39% respectively. The inhibition RIA thus seems to give a linear relationship of the inhibition to the logarithm of the antigen concentration within the interval of concentrations here studied.

Acknowledgements

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Immune responses to bovine neural antigens in leprosy patients. II. Absence of *in vitro* lymphocyte stimulation to peripheral nerve myelin proteins*

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Summary Nerve damage is common in leprosy although the mechanisms involved are poorly understood. We have isolated myelin proteins from bovine sciatic nerves and used them to detect sensitization to these antigens as a possible mechanism for nerve damage in leprosy patients. These proteins as well as *Mycobacterium leprae* sonicate were used in an *in vitro* lymphocyte stimulation assay and data from leprosy patients compared to healthy contacts who served as controls. Furthermore, for each patient a correlation between the lymphoproliferative response to the myelin proteins and clinical parameters of nerve damage was looked for.

Our results do not show any differences between the patients and control subjects in their responses to myelin proteins. There was also no correlation between these responses and any clinical parameter of nerve damage or classification of the patient. Myelin basic protein, P_1, stimulated lymphocytes from all individuals studied and behaved like a mitogen. A significant positive correlation was found between lymphocyte stimulation to *M. leprae* and the number of enlarged peripheral nerves.

It is felt that unlike experimental allergic neuritis or encephalomyelitis, leprosy neuropathy is most likely not mediated via an autoimmune sensitization to myelin proteins. Our negative findings could, however, be due to lymphocyte trapping in nerve lesions. Furthermore, the possibility that autosensitization to other nerve components, e.g. non-myelin, may be involved in the pathogenesis of some nerve lesions in leprosy cannot be ruled out. Our studies, however, offer further support to the concept that hypersensitivity to intraneurally located *M. leprae* antigens is the main mechanism whereby nerve damage is produced in leprosy.

* Part I of this paper will appear in *Int J Lepr*, 1983; in press as: Mshana RN, Harboe M, Stoner GL, Hughes RAC, Kadlubowiski M, Belehu A. Immune responses to bovine neural antigens in leprosy patients. I. Absence of antibodies to an isolated myelin protein.

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Introduction

In animals the involvement of cell-mediated immune responses to myelin proteins in the pathogenesis of peripheral neuropathy has been studied.[1–3] In this model, experimental allergic neuritis (EAN), the antigen involved has been shown to be a myelin basic protein called P_2.[4–6] Injection of this protein with complete adjuvant (although even without adjuvant: Hughes RAC, personal communication) usually leads to EAN in susceptible animals.[6] Histologically, EAN lesions are characterized by perivascular lymphocytic and macrophage infiltration accompanied by demyelination.[1–7] Myelin basic protein, P_1, has been shown to be encephalitogenic in animals inducing a disease of the central nervous system. Although electrophysiological changes in peripheral nerves can be seen in this disease,[8] the peripheral nerves are not the primary target of the inflammatory cells. Since leprosy seems to spare the central nervous system, it seems unlikely that an autoimmune attack to P_1 might be involved in the pathogenesis of leprosy nerve damage. Myelin protein, P_0, is the major protein component of the peripheral nerves. Its role in the induction of autoimmune peripheral neuropathies has not been well studied.

Segmental demyelination is a frequent finding in leprosy especially early in the disease evolution.[9–12] In these instances, demyelination has been reported even in the absence of morphologically definable *Mycobacterium leprae in situ*.[9,10,12] Failure to detect definable *M. leprae* in nerves which show changes consistent with early leprosy might indicate that either intact bacilli are not absolutely necessary for the pathogenesis of the early changes or that some factors produced at a distance, e.g. autoantibodies or enzymes, are involved.

In established leprosy, especially in the tuberculoid end of the spectrum, lymphocytic infiltration and granulomatous destruction of the nerve tissue in the extreme paucity of *M. leprae* is the characteristic finding. So far it has been assumed that the cellular infiltration is a result of hypersensitivity to intraneural bacillary antigens.[13,14] Since *M. leprae* has powerful adjuvant activity,[15] it has been suggested that autosensitization to myelin proteins might perpetuate nerve damage in these patients.[10,16–18] To date no work has been done to confirm this.

This paper describes results of studies on the role of cellular responses to isolated myelin bovine proteins in the pathogenesis of leprosy neuropathy.

Materials and methods

ANTIGENS

Mycobacterium leprae were isolated from a single subcutaneous nodule of an untreated lepromatous leprosy patient.[13] After washing, the bacilli were suspended in 0·1 M NaCl at a concentration of 1×10^7 bacilli/ml before being sonified

for 1 hour. The sonicate was centrifuged at 45,000 ***g*** for 30 minutes and the supernatant used for the study.

Myelin proteins, P_1, P_0 and P_2 were isolated from freshly dissected bovine sciatic nerves. Nerves were collected in ice-cold isotonic saline containing 800 KIU/ml Aprotonin (Trasylol®; Bayer, Leverkusen, Germany) and cleaned of fat and connective tissue. They were then minced and homogenized in 0·31 M sucrose to give a 5% w/v homogenate which was layered on 0·85 M sucrose and centrifuged at 10^5g for 1 hour. Myelin proteins in the interphase were collected and resuspended in 0·31 M sucrose and again layered on 0·85 M sucrose and centrifuged to purify them. Myelin proteins were then separated by the method of Uyemura *et al.*[19]

LYMPHOCYTE TRANSFORMATION TEST

Lymphocytes were isolated from venous blood using Böyum's technique.[20] Lymphocytes were then resuspended in RPMI-1640 containing penicillin, streptomycin, glutamine and fortified with 20% normal human serum to a final concentration of 5×10^5 cells/ml. 200 μl aliquots were then pippetted out into microtitre culture plates and incubated with the antigens in an incubator at 37°C with a 5% CO_2, 100% humidity atmosphere. Eighteen hours before harvesting cultures were pulsed with ^{3}H-thymidine. Cells were then harvested and counted in a liquid scintillation counter.

CLINICAL EXAMINATION

Prior to intake, patients were thoroughly examined and special attention paid to peripheral nerve enlargement and/or tenderness. The nerves examined in each patient were ulnar nerve immediately above the elbow, the posterior tibial nerve between the internal malleolus and the point of the heel, the common peroneal nerve where it winds round the neck of the fibula and the great auricular nerve. These were all done by one examiner. All patients were untreated prior to intake.

STATISTICS

Results of radioactivity in cultures without antigen were subtracted from those with the antigen. The resulting figures were then $\log_{10}$ transformed and statistical analysis done by the unpaired Student's *t*-test.

Results

Fifteen normal healthy leprosy contacts and 29 leprosy patients participated in the study. The normal contacts were either institute or hospital staff and have had

more than 5 years of direct contact with leprosy patients. None of these, however, on clinical examination, had any signs or symptoms of leprosy. The leprosy patients consisted of 14 borderline tuberculoid (BT) and 15 patients with either borderline lepromatous or lepromatous leprosy. The diagnosis was confirmed by histological examination of skin biopsies according to the Ridley–Jopling scale.[21] The ages of the patients and controls were matched and ranged from 18 to 40 years.

Myelin proteins were all used on a fixed concentration giving 20 μg protein/ml of culture and harvested on day 6. This was based on the dose response curves (Figure 1a) and time response curves (Figure 1b) of normal healthy contacts.

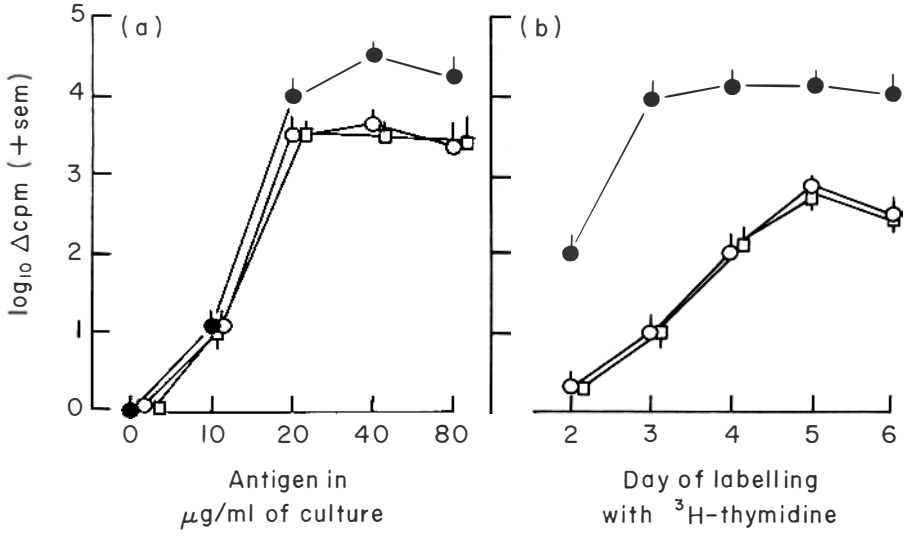

Figure 1. (a) Dose response curves for *in vitro* lymphocyte stimulation to bovine peripheral nerve myelin proteins in healthy individuals ($n=15$). All cultures harvested at day 6. (b) Time-response curves for *in vitro* lymphocyte stimulation to bovine peripheral nerve myelin proteins in healthy individuals ($n=15$). All tests done with 20 μg antigen/ml of culture. ●, P_1, ○, P_0, □, P_2.

Note that the response of the normal lymphocytes to myelin protein, P_1, is significantly higher than the rest starting from day 3 when using 20 μg/ml (Figure 1b). The response attained at this time shows only slight increase with prolonged culture. No newborn cells were used to confirm whether this protein actually is mitogenic or not. Figure 2 shows that there are no significant differences between the different study groups in response to individual myelin proteins, whereas patients with lepromatous type of leprosy had a significantly lower response to *Mycobacterium leprae*. The correlations between the major neural findings and individual responses to the antigens studied are shown in Figure 3. The only correlation was found to be between *in vitro* lymphoproliferative response to *M. leprae* and the number of enlarged peripheral nerves, so that patients with high

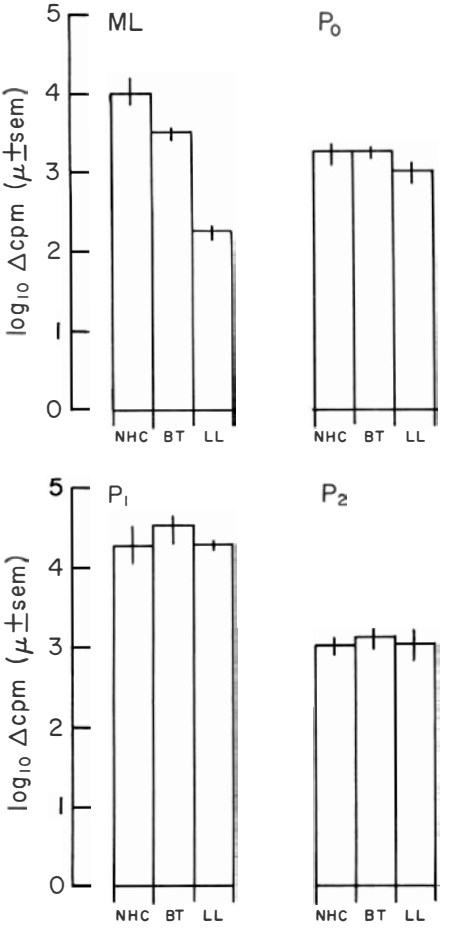

Figure 2. *In vitro* lymphocyte stimulation test to various antigens in healthy controls and leprosy patients. Myelin proteins were used at final concentration of 20 μg/ml of culture while the *Mycobacterium leprae* antigen was a sonicate preparation of 1×10^7 bacilli/ml. ML, *M. leprae*; P_0, P_1 and P_2 are bovine peripheral nerve myelin proteins; NHC, normal healthy controls; BT, borderline tuberculoid leprosy patients; LL, lepromatous leprosy patients.

responses tended to have more enlarged peripheral nerves ($r = 0{\cdot}8$; $t = 6{\cdot}9$; $P < 0{\cdot}001$). No correlation exists between *in vitro* lymphocyte stimulation to myelin proteins and number of enlarged peripheral nerves. Figure 4 shows that no correlation exists between *in vitro* lymphocyte stimulation to *M. leprae* and stimulation to the various myelin proteins.

Discussion

Proof had already been produced to show that in susceptible animals, peripheral

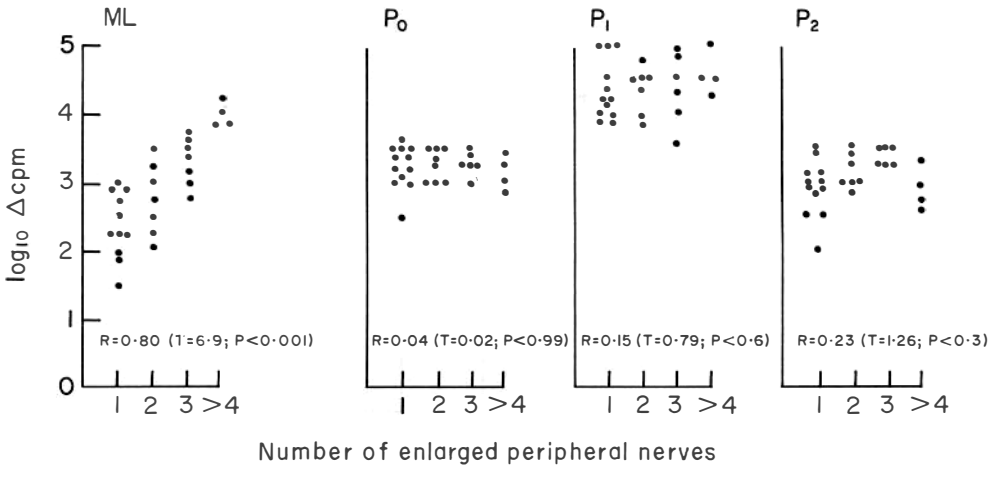

Figure 3. Correlation between lymphocyte stimulation to various antigens and the number of enlarged peripheral nerves judged by clinical examination in leprosy patients. Each dot represents an individual patient. (Abbreviations are as in Figure 2.)

neuropathy could be induced via autoimmune mechanisms. Although the exact role of each component of the immune response has not been clearly delineated, the consensus of opinion at the moment indicates that the main pathology is mediated by cellular mechanisms. Histologically this neuropathy is characterized by florid perivascular lymphocyte and macrophage infiltration with marked myelin loss. Macrophages can be seen to strip myelin sheaths and destroy them by extracellular vesiculation. How macrophages do this is not known with certainty, but release of enzymes is thought to be involved.[22,23] A conspicuous feature is that in this disease intraneural granuloma formation is not seen; perhaps because of the acute nature of the disease. In borderline tuberculoid and tuberculoid leprosy, the involved nerves show typical features of well matured epithelioid cell granulomas. Although perivascular infiltration can be seen in some areas, it is not a prominent feature except during acute reversal reactions (unpublished observations). Although the granulomas are thought to be directed towards *M. leprae*, in certain sites areas of segmental demyelination can be seen in the absence of morphologically definable *Mycobacterium leprae*, the intensity of demyelination being roughly proportional to the cellular infiltrate.[11] In these instances it is tempting to suggest that an autoimmune cellular reaction is propagating the nerve damage.[10,16–18] In order to shed light into this problem, however, techniques to demonstrate *M. leprae* antigens rather than the whole bacillus will have to be employed. This is especially important since Bjune *et al.*[13] have indicated that *M. leprae* cytoplasmic antigens rather than the whole bacillus may be more important in the pathogenesis of leprous neuropathy. It must be stated that the conventional techniques to stain *M. leprae* do not stain released antigens. By using an immunologically based technique, we were able to detect mycobacterial

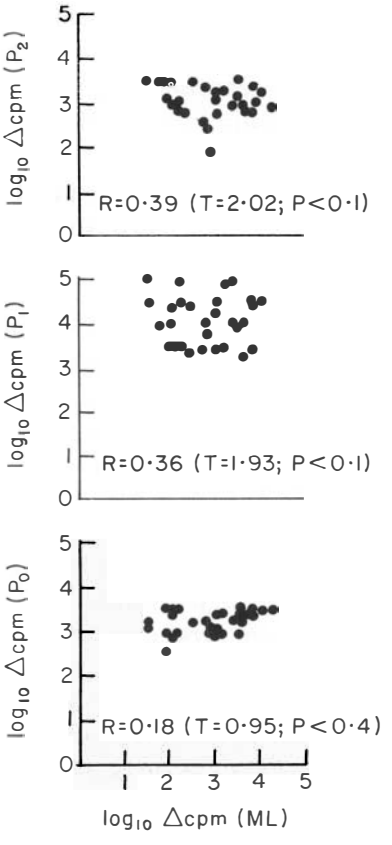

Figure 4. Correlation between lymphocyte stimulation to *Mycobacterium leprae* (ML) and stimulation to various myelin proteins (P_0, P_1 and P_2) in leprosy patients. Each dot represents an individual patient. (Abbreviations are as in Figure 2.)

antigens in a number of biopsies which had no morphologically identifiable acid-fast bacilli.[24] By applying the technique to peripheral nerve biopsies we have found similar findings (submitted). These findings thus support the concept that peripheral nerve damage in leprosy is a result of immunological recognition of intraneural *M. leprae* antigens. Furthermore, in the present study a correlation could only be seen between *in vitro* lymphoproliferative response to *M. leprae* and the number of enlarged peripheral nerves (Figure 4). Repeated delayed type hypersensitivity reactions to intraneural antigens could explain these findings. It is unlikely that this correlation was due to the duration of the disease.

Myelin proteins or their fragments are expected to be released and come into contact with the immune system in a disease where demyelination is frequent. In leprosy, one would then expect autosensitization to these proteins since *M. leprae* has powerful adjuvant activity.[15] Our data, however, do not indicate this to be the case. The possibility of lymphocyte trapping at lesional areas can, however, not be easily ruled out. Indeed a discrepancy between disease severity and *in vitro*

lymphoproliferative responses to P_2 can be seen in animals with experimental allergic neuritis, and in earlier studies similar observations had been reported in animals with experimental allergic encephalomyelitis (EAE).[25] Absence of the *in vitro* correlate of cell-mediated immunity to myelin proteins, therefore, does not offer absolute or conclusive evidence for lack of involvement of autoimmune mechanisms in the perpetuation of leprosy neuropathy. Patients with the Guillain–Barré syndrome have been shown to have cell-mediated immune response against peripheral nerve extracts[27,28] but unexpectedly not to P_2[29] indicating that an antigen not yet described might be the target of the immune attack. A similar situation could very well be operating in leprosy neuropathy. Although determinant(s) for cell-mediated immune responses to myelin proteins might differ from species to species as has been suggested for the humoral response to myelin protein, P_2,[26] it is unlikely that this could be the reason for our negative findings since both EAE and EAN belong to the group of autoimmune diseases which are organ specific but species non-specific.

Degeneration of unmyelinated nerve fibres is an essential feature of nerve damage in leprosy. In EAN demyelination is the characteristic finding but there is little or no involvement of unmyelinated fibres. Both granulomas and unmyelinated fibre degeneration have been produced by skin testing rabbits previously sensitized with human sensory peripheral nerve.[30,31] The skin-test antigen producing unmyelinated fibre degeneration and granuloma formation resides in the non-myelin fraction of the sensory nerve and seems to be a component of Schwann cell membrane.[32] It is thus possible that nerve damage in leprosy, especially the sensory nerve damage, may be due to an autoimmune response to a non-myelin component in sensory nerves.[33]

Although lymphocyte stimulation test cannot strictly be used to assess immunological relatedness between antigens, it is interesting to note that no correlation was found between responses to *M. leprae* and those of myelin proteins. Indirectly, this would suggest that no cross-reactions, at least as far as this system is concerned, can be found between *M. leprae* and myelin proteins. This implies that an immune response directed against *M. leprae* could not damage myelin proteins in the absence of intraneural *M. leprae*. Indeed this observation explains the clinical findings of healthy nerves in individuals in leprosy endemic areas despite their having hypersensitivity to *M. leprae*. Our data thus contradicts previous findings which were based on using skin testing and reporting cross-reactions between mycobacteria and myelin proteins[34] and supports those of Stoner *et al.*[35] who found no such cross-reactions.

Myelin protein, P_1, stimulated lymphocytes from both leprosy patients and healthy contacts (Figure 2). This finding is in line with that reported previously.[36] This would indicate that either there is a low level of sensitization to this antigen[37] or that P_1 is mitogenic.[36] Our data on studies of the kinetics of this reaction where a definite response is seen after 3 days of culture would tend to support the latter (Figure 1b). Further studies on this protein are, however, needed especially in

view of the fact that this protein causes EAE which is a disease with certain similarities to multiple sclerosis.

Other mechanisms have been proposed to be involved in the pathogenesis of leprosy neuropathy. Peri- and intraneural inflammation secondary to intraneural antigen has been shown to lead to primary demyelination.[38] In high-resistant leprosy, hypersensitivity to and intraneural *M. leprae* co-exist, thus closely mimicking an experimental animal model.[38] Hypersensitivity to these antigens may thus be responsible for part of the nerve damage.[13, 14] We have recently been able to produce direct evidence for this mechanism by injecting *M. leprae* intraneurally into animals made hypersensitive to *M. leprae*.[39] The histology of the nerve damage seen was strikingly similar to that of human nerves during reversal reaction.

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Deformity prevention in the field: a systematic approach

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Summary The importance of preventing deformity among our patients by detecting and treating neuritis is stated. The process of 'silent neuritis' which leads insidiously to deformity in a number of leprosy patients is defined, and the importance of its recognition and early treatment in the field situation is stressed. An approach adopted primarily for this purpose, consisting of simple motor, sensory and nerve palpation tests repeated at varying intervals, whose results are recorded briefly and acted upon appropriately, is described. The benefits observed and problems encountered in implementing this approach are described, and areas of training and management on which its success depends are discussed.

Introduction

Prevention or reduction of deformity is important for the personal, economic and emotional welfare of leprosy patients. It may contribute to the effectiveness of the leprosy control programme, and also be of value in changing the public image of leprosy. It has been well stated that 'the control of leprosy depends as much on the effective prevention and treatment of disability (which is the patient's primary concern) as on the reduction of the mycobacterial load in the community by chemotherapy'.[1]

CAUSE OF DEFORMITY

The deformities considered in this paper are those resulting from nerve damage. Loss of sensory and/or motor function leads initially to anaesthesia and/or muscle paralysis in the area supplied by the nerve, and subsequently, if neglected, to tissue injuries and joint stiffness, these being the visible and stigmatizing evidence of leprosy. Such nerve damage occurs in two particular phases of the

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disease,[2] namely in untreated leprosy, and during the course of both Type I and Type II reactions. Many deformities will therefore be prevented by early diagnosis of leprosy, followed by regular and adequate treatment with anti-leprosy drugs, but in the presence of reaction, treated patients remain at risk of developing deformity. Also women may be at special risk of nerve damage during pregnancy and lactation,[3] when they may develop new deformity in the absence of reaction. We are therefore convinced that special care must be given to patients registered at our clinics, to minimize deformity occurring during reaction, pregnancy, etc.

MODE OF ONSET

Nerve damage caused by neuritis may present in either acute or silent forms. 'Silent' neuritis is defined by us as the presence of recent motor or sensory loss unaccompanied by nerve pain, of which the patient is usually unaware, and therefore does not complain. It closely resembles 'quiet nerve paralysis' as recently described by Srinivasan *et al.* from India.[4] By contrast, 'acute' neuritis, elsewhere described as 'overt',[3] is characterized by nerve pain and/or sudden, severe loss of function, which causes the patient variable but definite distress, and is therefore usually reported before deformity is established.

When recognized and treated early, a good proportion of neuritis patients show recovery, or limitation of nerve damage. In our experience, patients with acute neuritis, being easily recognized, are usually treated, whereas silent neuritis may go unnoticed and untreated, and lead to new deformity. Among lactating women, silent neuritis has been found to occur more than overt,[3] highlighting this insidious problem, which, however, is not confined to women or to the period following childbirth.

It has also been observed that there is a large 'intermediate' group of patients who have mild neuritis clinically, and who complain of limb pain, who do not actually rate as having a reaction. These too may go on to develop permanent nerve damage, in the absence of appropriate neuritis treatment. The physiotherapy worker, hereafter referred to as physiotherapist, is traditionally associated with deformity care. The government pattern of leprosy control in India now includes a physiotherapist in the field team, and many voluntary agencies do likewise. However, these workers are often totally preoccupied with visible, established deformity about which comparatively little can be done, to the exclusion of concern to prevent new deformities occurring in apparently normal patients. Reversal and adaption of the philosophy 'innocent until proved guilty' to 'potentially deformed until proved normal' has much to commend it in the search for cases of silent neuritis. The method of assessment and its application, as now described, has been developed during the past 5 years in the leprosy control programme of the Leprosy Mission Hospital at Salur, South India, in order primarily to detect such cases.

Method

Rapid but comprehensive assessment of the patient provides a baseline on nerve function. This can be used first to detect changes occurring, so diagnosing silent neuritis early, and secondly to guide the education and treatment required for existing deformity.

1 METHOD OF ASSESSMENT

(a) *Nerve palpation*

The ulnar, median, lateral popliteal and posterior tibial nerves of both arms and both legs are palpated at the sites of predilection. Nerve tenderness,[5] recognized by watching the patient's face for a wincing expression, and enlargement, are noted.

Since nerve enlargement is a cardinal sign of leprosy, and it is difficult to detect further enlargement of already enlarged nerves—a sign of neuritis—significance is attached mainly to tenderness. This is almost always a sign of neuritis in a registered leprosy patient, though other diseases can cause nerve tenderness.[1]

(b) *Movement testing*

Closure of the eye-lids, opposition of thumbs to little fingers (or separate finger and thumb abduction) and ankle dorsiflexion are checked. Where range is full, resistance to movement is applied. Weakness is noted. A note on the Voluntary Muscle Test (VMT) grading of the muscle producing any movement found to be weak is added when the tester is a physiotherapist. This, when repeated at the next visit, provides more accurate information on the state of the nerve, and response to treatment given.

(c) *Sensory testing*

The cornea is tested carefully with a cotton wisp, but the palms and soles are tested for response to light pressure, using a ball-pen. Partial or complete anaesthesia is noted. In our opinion, this test gives the least accurate information regarding new nerve damage, but shows at an early stage which patients lack protective sensation and must therefore learn to prevent secondary ulceration.

A definite order of testing each patient is adopted, either doing tests for his eyes, then his hands, then his feet; or checking first his nerves, then his movements, and then sensation. Such a system is not always adopted automatically, but it increases both the speed of testing and the reliability of the results.

2 RECORDING OF FINDINGS

A rubber stamp, covering relevant movements, sensation and nerves in the eyes, hands and feet, permits quick and accurate recording by a set of standard symbols, understood by all our team members. The deformity assessment is stamped in the patient's treatment chart beside the prescription of medicine and not separately, so that information is readily seen by all. Duration of movement weakness and sensory loss (if known) is recorded. Additional notes are written on points not covered by the stamp.

Date	Muscles R	Muscles L	Sensation R	Sensation L	Nerves R	Nerves L
Eyes						
Hands	U M	U M	U M	U M	U M	U M
Feet					P T	P T

Muscles	Sensation	Nerves
√ = normal	√ = normal	√ = normal
W = weak	P = partial	T = tender
O = paralysed	A = anaesthesia	+ = enlarged

U = ulnar M = median P = lateral popliteal
T = posterior tibial

3 FREQUENCY OF ASSESSMENT

New patients are now assessed at the first attendance, and most previously registered patients have also been assessed. Thus all have baseline data.

Undeformed or partially deformed patients are rechecked as often as possible, but the suggested ideal of monthly, or at every clinic visit, is probably unnecessary and seldom practicable. Every effort, however, is made to check the following patients, considered to be most 'at risk' of neuritis and deformity, at least every 3 months: borderline cases, patients in their first year of treatment, lepromatous patients prone to recurrent Type II reactions, patients who have been irregular, and those who have had recent complications. Those with particular complaints

are checked immediately. It must be stressed that annual reassessment will not detect silent neuritis in time for treatment to be effective.

4 ACTION TO BE TAKEN ON FINDINGS

(a) Patients with nerve tenderness, and/or movement weakness or sensory loss of recent duration (from patient's report, or by comparison with previous assessment) are given a warm wrapping for the nerve, and a rest sling for the arm or firm bandage in the leg. The patient is encouraged to rest the nerve as much as possible.

These patients are referred to the senior clinic worker present, for the treatment of neuritis by anti-inflammatory drugs in addition to antileprosy drugs.

Careful reassessment is carried out at the next clinic visit, to evaluate the response to treatment. Hospital referral is often required for proper neuritis care, but the patient is usually unwilling because he is not incapacitated.

(b) Patients with established nerve damage, having anaesthesia and/or muscle paralysis, are given specific advice on the home self-care required to prevent secondary deformities of tissue injury and absorption, and contractures. This may include acceptable skin protection methods and soaking, scraping, oiling for dry, anaesthetic hands and feet, and simple exercises to strengthen weak muscles or prevent skin or joint contractures. The minimum teaching is given, in a practical way when possible, on the patient's priority need. Advice given is recorded, and progress checked at subsequent visits, encouragement or correction being given as appropriate. When ready, the patient is given any further teaching required.

Benefits and problems

The following observations are based on our experiences in Salur, and in the leprosy control programmes of other Leprosy Mission centres in Andhra Pradesh and Western India, where this systematic approach has also been introduced. They form the basis of a preliminary, subjective evaluation.

BENEFITS

1 Neuritis has been detected at an early stage in uncomplaining patients, and treated. The proportion of such cases appears higher in more recently established programmes.

2 During assessment, patients have been educated about the early signs and symptoms of nerve damage. Immediate reporting of paraesthesia, or unusual clumsiness or tiredness, in the hands or feet is emphasized. The probable connection between irregular DDS and development of deformity is also stressed.

In addition, needs other than neuritis may be revealed during the assessment; specific individual education for such needs has been found more effective than general group health education, and the knowledge seems to spread from patient to patient!

3 The relationship between staff and patients has been strengthened during this regular contact, allowing personal problems, or less obvious but 'felt needs' to be discussed. Although repeat assessments are frequently 'negative', they are, therefore, of positive value in case-holding.

4 The physiotherapist has in several instances been transformed from a disillusioned, aimless worker into a purposeful member of the team, with a definite and important role to play.

PROBLEMS

The frequent occurrence of similar problems in different programmes suggests that there are real difficulties in implementing this approach. They appear to fall into 3 broad, but overlapping categories.

1 *Management problems*

Ideally these assessments should be done by a physiotherapist, whose main role is to minimize deformity. However, reliance on physiotherapy staff exclusively to undertake this care has resulted in no assessments being done in the following situations:

(a) At small clinics, where the presence of a physiotherapist for several hours, in order to see a handful of patients, is not justified; in programmes where domiciliary treatment is given; and in situations where for any other reason a physiotherapist is not allotted to the control programme.

(b) At clinics held concurrently with other clinics in the same programme, when the physiotherapist can only be in one place at a time; unless his tour programme is carefully planned, he will repeatedly see the same patients at a given clinic, whilst others, attending a different week or a different month, are never seen.

(c) When the physiotherapist is on leave, or withdrawn from field activities to cover staff shortages in the 'more urgent' work of the base hospital.

These problems have to do with the priority that is accorded to the early diagnosis, treatment and prevention of deformity; their solution depends on recognition by the whole team of the importance of this activity.

2 *Work organization problems*

(a) The assessment is time consuming at first and in addition there is a 'back-log' of patients to be examined.

(b) In large clinics it is necessary to select patients most 'at risk' for more frequent rechecking, and to ensure that they do not depart from the clinic unchecked. This applies particularly to irregular attenders, who may be at special risk.

In such conditions, when there is too much work for the physiotherapist, the priorities must be carefully defined, and consideration given to arranging for other staff to undertake part of the work.

3 *Training problems*

Many defects in implementation were due to lack of relevant knowledge and/or practical skills, or failure to adapt and apply these in the field situation; these, therefore, suggest deficiencies in training.

(a) *Training of physiotherapists.* (i) The training of leprosy physiotherapy staff is usually hospital and surgery orientated, and therefore many workers are afterwards assigned to field programmes with no idea of their role or goals. Specific teaching on the principles of deformity prevention in the field is needed, in addition to the detailed technique of the assessments.
(ii) The assessment is not an end in itself. The physiotherapist must be taught to exercise judgement, and in particular to decide whether, as a result of his assessment, the patient should (a) have routine assessments in the future; (b) have more frequent assessments; (c) have local treatment on the physiotherapist's advice; and/or (d) be referred to senior staff for special treatment.

If each patient is seen as an individual, the physiotherapist will escape the monotony of simple repetitive work and avoid careless mistakes.

(b) *Training of more senior staff.* At times, the staff responsible have failed to give immediate, and appropriate, neuritis treatment, though indicated. This has arisen from:

(i) Lack of understanding about the purpose of the assessment, and inability to interpret the findings—the assessment is seen as an end in itself, a duty to be performed by the physiotherapist.
(ii) Belief that neuritis always causes the patient to complain—and if not complaining, no treatment is required.
(iii) Unbelief that early nerve damage can be reversed or limited—once demonstrated possible, effort to save nerves increases dramatically.
(iv) Failure to understand that the *nerve* requires treatment when muscle weakness is recent, and that exercises are not appropriate as the main line of treatment.

It is essential that deficiencies of this sort are corrected by training. A physiotherapist who detects neuritis and gives correct physical treatment and advice to the patient is frustrated if the staff responsible do not prescribe drugs or encourage hospital referral. The fact that silent and mild neuritis, as described

above, must be taken as seriously as acute neuritis typically associated with reaction, must be emphasized to all, if deformity is to be prevented.

For supervisory purposes, it is also necessary that senior staff know which patients are most likely to develop neuritis and deformity, and so ensure their regular rechecking by the physiotherapist.

(c) *Training of more junior staff.* Since this approach does not require highly-specialized physiotherapy techniques, it can be learned by most other field workers. Deformity care is already included in the syllabus of training programmes for paramedical workers (non-medical assistants) in India, and in defining the roles of various categories of workers in the National Leprosy Control Programme of India,[6] Hasan indicates the overlap of responsibility for deformity care and prevention among different workers; though whether detection of silent neuritis is included is uncertain.

Discussion

This approach requires staff to have basic skills in assessing nerve function, and recording and interpreting results in terms of treatment needed to reverse or minimize nerve damage and therefore prevent deformity. It also needs considerable practical organization if it is to be used effectively on our many patients at widely differing clinics.

Key factors in successful implementation appear to be: 1, a changed emphasis in the teaching of deformity prevention and care to all categories of staff working in the field, not least the physiotherapist; 2, recognition of local variations in programme structure, requiring specific management decisions; and 3, good clinic organization at the local level.

Particular problems may be encountered when staff other than physiotherapists are required to undertake assessments. Our experience suggests that paramedical workers are reluctant to share in the deformity care of their patients, even when having the knowledge, and time, to do it; understandably they feel they are doing the physiotherapist's work in addition to their own duties. But to meet the types of situation listed above, and to ensure the total care of patients at all times, some flexibility is necessary. Appropriate assignment of specific tasks to each member of the control team must be made according to particular local needs, and written into the job description.

Although teaching on deformity care, or 'physiotherapy aspects', is included in training courses for various categories of leprosy staff, our experience suggests that there is need for continuing effort to clarify training objectives, especially with regard to deformity prevention in the field situation. Careful elucidation of students' learning objectives, with theoretical and practical teaching based on these, will help to change the emphasis from care of established deformities to prevention of nerve damage and new deformity, impart the necessary skills and also rectify specific misconceptions.

If a programme of this sort is to be implemented successfully, careful training, detailed management and positive supervision are required. In addition, however, changes of attitude are often needed, so that staff at all levels are positively motivated to prevent and lessen deformity in their patients. Only the interest, guidance and supervision of the senior team members can achieve this change.

Acknowledgements

I thank the physiotherapy staff at Salur for their willingness to introduce, adapt, and so refine the approach described here, as well as the leprosy control staff at Salur and other leprosy mission centres in Andhra Pradesh, Karnataka and Maharashtra for their cooperation. I also thank Dr Alexander Thomas (Superintendent, Salur) and Dr R H Thangaraj (Director, The Leprosy Mission, Southern Asia) for their encouragement and permission to write this paper. I am grateful to Dr M E Duncan, Dr J M H Pearson and Miss P J Neville for their help in the preparation of this paper.

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Dapsone-resistant leprosy in Burundi

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Summary Between 1978 and 1981 a dapsone-resistance survey was performed in 4 out of 5 regions of Burundi. Among 1791 leprosy patients, 925 were multibacillary (51%) and prevalence of dapsone resistance is 3·7%, with variations in regions between 1·2 and 6·1%. Since the selection of patients was on a clinical rather than a bacteriologic basis, this should be a minimum figure. Incubation time of dapsone resistance was from 8 to more than 20 years of monotherapy. Two cases of primary dapsone resistance were also diagnosed.

Introduction

Burundi is situated in Africa between 2°45 and 4°28 S, at an altitude varying between 775 m and 2670 m above sea level. It is 28,000 km^2 with a population of $4{\cdot}10^6$ living in families dispersed in the hills, except for some commercial or administrative centres that originated during this century.

Leprosy Control Service was initiated after the Second World War, when dapsone monotherapy was introduced. This service covered the entire country from 1976 onwards. Dapsone, thiambutosine and long-acting sulphonamides were used. There was a leprosarium from 1950 to 1972 which admitted some 2000 patients.

Between 1978 and 1981 we performed a dapsone-resistance survey in Burundi.

Materials and methods

For practical reasons the survey was done in 4 (Kiremba, Rwisabu, Bururi and Kinyinya) of the 5 regions existing. Based on the latest census (1979) these regions have a population of 3,144,340 out of a total of 4,021,910, and thus comprise 78% of the population. Prevalence of leprosy in Burundi is 0·6% but in Bururi and

‡ Reprints may be obtained from Professor Pattyn.

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Kinyinya it is 1·3–1·5%. Two hundred new cases are detected each year, 30% being multibacillary.

In the 4 regions surveyed there were 2473 patients under treatment of whom 1243 (50%) were multibacillary. Criteria for biopsy were: (a) patients with an original diagnosis of lepromatous leprosy, (b) patients treated with dapsone for at least 5 years, and (c) patients who had clinically active lesions, as judged by one of the authors (JB).

Biopsies were transported in thermosflasks on wet ice to Bujumbura and from there by air to Antwerp. Three biopsies were inoculated in 1978, 4 in 1979, the remaining 46 between January 1980 and June 1981. For each biopsy 34 mice were inoculated in both hind foot-pads with $5 \cdot 10^3$ acid-fast bacilli, 10 controls received normal food and 3 groups of 8 mice each received food containing 10^{-2}, 10^{-3} and 10^{-4} g% dapsone.

A control mouse was examined after 6 months. If the bacterial count did not reach 10^4, another control animal was examined after 8 and 10 months and 3 animals after 12 months; if it was between 10^4 and 10^5, further controls were examined at 3-week intervals. When the bacillary population reached $5 \cdot 10^5$, 3 control animals and 5 of each treated group were examined. If there was lack of time to examine the animals immediately, they were stored at $-20°C$.

Results and discussion

All biopsies except 15 were inoculated into mice within 7 days. Of those inoculated later than 7 days after having been taken, 8 were inoculated after 8, one after 9, 3 after 10, 1 after 12 and 2 after 15 days, of these 7, 1, 2, 1 and 1 respectively, multiplied in control mice. Thus the number of strains lost as a result of delay in transportation must have been minimal.

Table 1 shows the overall results. Fifty-one per cent of the patients under treatment had a multibacillary form of the disease. Of these, 53 had been treated for more than 5 years and were diagnosed as having clinically active disease. In 5 cases the biopsy did contain insufficient bacilli for mouse foot-pad inoculation. Nine strains did not multiply in mice, 4 were fully sensitive to dapsone, and 35 were resistant. The overall prevalence of proven dapsone resistance is 3·7% but varies considerably in the different regions: from 1·2% in Rwisabi to 6·1% in Kinyinya. The reasons for this variation remain unknown, but it is highest in the two regions where the disease is more prevalent. In contrast with the THELEP criteria[1] for dapsone resistance surveys, where all previously multibacillary leprosy patients treated for a minimum of 5 years are examined bacteriologically and biopsied if a skin lesion shows a bacterial index of 3 or more, in the present study, owing to lack of manpower, patient selection for mouse foot-pad testing was based on clinical impression. Therefore, patients who were incubating dapsone resistance and had not yet developed manifest signs of relapse were

Table 1. Dapsone resistance among leprosy patients in 4 regions of Burundi

Region	Population	Patients treated	Multibacillary	Suspected of dapsone resistance	Not inoculated	Results of MFI*		
						neg	S	R
Kiremba	1,274,140	291	160	5 (3·1)†	1	—	—	4 (2·5)
Rwisabi	1,020,690	281	156	6 (3·8)	1	3	—	2 (1·2)
Burundi	487,200	653	284	17 (5·9)	1	3	4	9 (3·1)
Kinyinya	362,310	566	325	25 (7·6)	2	3	—	20 (6·1)
		1791	925	53 (5·7)	5	9	4	35 (3·7)

* MFI (mouse foot-pad inoculation).

† Percentage.

S = sensitive to 10^{-4} g% dapsone in the diet; R = resistant to at least 10^{-4} g% dapsone in the diet.

probably overlooked. The real prevalence of dapsone resistance, therefore, might be higher and the figures arrived at are to be considered minimal.

The degree of dapsone resistance is shown in Table 2. Twenty-eight strains were fully dapsone resistant, e.g. they multiply in mice fed 10^{-2}% dapsone in the diet, 4 strains were median resistant, and 3 low grade resistant. In 4 cases bacillary multiplication had occurred in part of the mice receiving dapsone in the food, while multiplication had occurred in all of the control mice. This cannot be the result of inocula containing small proportions of viable bacilli and might be the result of the presence of mixed populations of dapsone sensitive and resistat organisms.

The duration of treatment when dapsone resistance was proven by mouse foot-pad inoculation varies between 8 and more than 30 years and shows a bimodal distribution, with peaks at 8–10 years and 20 years (Table 3).

However, these are most probably unreliable figures due to the patients whose files had disappeared and recall having been treated 'before independence' (1961) or not; for the latter group clinical files exist since the last 10 years (Table 3).

Finally 3 cases of suspected primary dapsone resistance were also inoculated. Two showed dapsone resistance: the results of the mouse foot-pad inoculations

Table 2. Degree of dapsone resistance

Concentration of dapsone in food:	10^{-2} g%	10^{-3} g%	10^{-4} g%
Number of strains:	28	4	3

Table 3. Number of years elapsed since start of treatment

	5	8	10	12	15	18	20	25	30	?
Number of dapsone-resistant cases		4	3	1	3	5	10	5	2	2
Number of dapsone-sensitive cases	1	1	1	1						

are presented in Table 4, one of the strains is definitely median dapsone resistant, the second has a lowered sensitivity, although it would be inhibited in man by full dosage 100 mg daily dapsone. These patients had been treated for 6–8 months.

The prevalence of dapsone resistance in Burundi (3·7%) is thus of the same magnitude as in other populations studied: 5·1% in Jiangsu Province, China, 5·0%[2] in Bamako, Mali,[3] keeping in mind that 3·7% is probably lower than reality, since patients were selected on clinical grounds.

Table 4. Results of MFI of 2 cases of suspected primary resistance

Patient No.	Dapsone concentration in mouse food		
	10^{-2} g%	10^{-3} g%	10^{-4} g%
1	1/5*	4/5	5/5
2	0/5	0/5	1/5

* Number of mice showing multiplication in the foot-pad/number of mice examined.

Acknowledgments

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Obituaries

LORD BOYD, PRESIDENT OF LEPRA 1960–1983

It is with deep regret we have to announce the tragic death of the President of LEPRA, the Viscount Boyd of Merton PC CH who died on 8 March 1983 in a motor accident at the age of 78.

As Alan Lennox-Boyd he was Minister of State for Colonial Affairs from 1951 to 1952 and Secretary of State for the Colonies from 1954 to 1959. This experience provided an excellent background for the future President of LEPRA.

Lord Boyd was an inspiring and greatly admired President who will be remembered by readers of *Leprosy Review* for the able way in which he presided at so many Annual Meetings of the Association. Despite his wide-ranging activities, Lord Boyd had time for everybody, and he never failed to convey a feeling of special interest in his dealings with LEPRA personnel and the organization itself. He once told the House of Commons, and was applauded from both sides, '. . . discrimination on the ground of colour is quite deplorable and, like all rudeness, it is both stupid and offensive'. Since most of LEPRA's work is amongst coloured people, it was particularly dear to his heart.

Shortly before his death, Lord Boyd learned of the exciting developments in the introduction of the new short-term treatment for leprosy patients with multiple drugs and the development of a possible vaccine. It was clear that he was very pleased with the contribution of the Association of which he was President to these exciting developments.

EDITOR

REV DR T FRANK DAVEY CBE

The Rev Dr Frank Davey, CBE, a world expert on leprosy and a former medical secretary of the Methodist Missionary Society, died on 24 March 1983. He was 75.

Davey qualified in medicine at Manchester University before training for the Methodist ministry at Hartley Victoria College. Following his ordination in 1935 he became a medical missionary in Nigeria and in 1939 he was appointed Director of the Methodist Leprosy Settlement at Uzuakoli.

Under Davey's leadership the settlement became one of the foremost centres for leprosy research in West Africa. It was there that Davey, with Dr John Lowe, pioneered the use of the drug dapsone in the treatment of leprosy, he also initiated leprosy surveys and control measures throughout what was then known as Iboland.

He was appointed senior leprosy officer by the Nigerian government in 1944, a post he held while remaining at Uzuakoli, and was appointed OBE in 1945.

In 1959 he returned to Britain to become medical secretary of the Methodist Missionary Society, but in 1968 he returned to field work as director of the Victoria Leprosy Hospital at Dichpalli in the Medak Diocese of the Church of South India, a post which he held for 5 years. During this period he advised the Indian Medical Service on its leprosy programme and served as chairman of the leprosy work associated with Vellore Christian Medical College.

On his return to this country Davey became Chairman of the Friends of Vellore. During his retirement he was editor of *Leprosy Review*, the international journal of leprosy medicine. He was the joint author with R G Cochrane of *Leprosy in Theory and Practice*, a standard work on the disease, and of numerous papers and articles.

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He wrote also *A Medical Te Deum*, and a collection of prayers he wrote in the Ibo language became the basis of prayer books for several other language groups.

During his service as medical secretary to the MMS he became a founder member of the Christian Medical Commission, the medical wing of the World Council of Churches. He was advanced to CBE in 1960.

Davey is survived by his wife, Kay, a fellow missionary.

(Reprinted by kind permission of Mrs M Nixon, Methodist Church Press Service and *The Times*.)

Frank Davey's entire active medical career was devoted to leprosy, commencing in 1936 when he was appointed to the Leprosy Settlement at Uzuakoli, Nigeria. From the humble beginning he became recognized as one of the leading world authorities on leprosy. Frank was one of the few remaining leprologists whose knowledge of and continuing work in leprosy span the eras preceding and following the use of dapsone in the treatment of leprosy. With the availability of dapsone, by the late 1940s Frank pioneered its use in the treatment of leprosy based on the knowledge and detailed observations he had recorded by then on the clinical and epidemiological aspects of leprosy at Uzuakoli. In retrospect it is clear that Frank's eminence and that of Uzuakoli as a leprosy research centre stemmed from the management and critical assessments of his clinical trials on dapsone Throughout the 1950s Uzuakoli was considered the centre of choice for leprosy drug trials and with Frank's boundless energy he pioneered trials on thiourea derivatives, particularly thiambutosine; mercaptan derivatives, particularly Etisul and a sulphone derivative, diphenyl sulphoxide. Throughout this period Frank attempted to standardize the design of leprosy trials to ensure comparability throughout the world and introduced for the first time a group of patients on dapsone in order to rate the activity of the new drug with that of dapsone. Many of his procedures for standardizing such trials have been adopted.

In fact I first met Frank in 1958 at the time of the International Leprosy Congress in Tokyo when we were attempting to determine by electron microscopy the possible biological significance relating the variable staining properties of *Mycobacterium leprae* by carbol fuchsin. Our hypothesis was that the irregularly stained bacteria represented degenerate forms and were therefore dead. To my delight Frank presented a paper supporting our hypothesis, based already on extensive data on stained smears from patients in his various drug trials which indicated a shift from uniformly stained to irregularly stained bacteria in patients clinically responding to treatment!

For me the importance of the Tokyo Conference was my meeting Frank, who for the past 25 years has been my tireless teacher and advisor on all the clinical intricacies of leprosy. This has enabled our more laboratory orientated researches to also be applied or directed to current clinical problems.

DICK REES

Frank Davey has filled a warm and honoured niche in my affections for upwards of 40 years. His career as a Christian medical missionary began in the same year as mine—1936. He was based at Uzuakoli in Eastern Nigeria. With Kinnear Brown, who had just founded that Methodist medical centre, and then John Lowe, fresh from Bankura and Calcutta, Davey soon set about learning leprosy the hard way—by painstaking clinical observation and thorough objective investigation. While still a general physician and surgeon in the former Belgian Congo, I learned of his seminal work on the demonstration of the parent sulphone in the post-hepatic blood of patients taking the expensive sulphone derivatives. At the time, I was about to harvest the first fruits of the plantation of chaulmoogra seeds I had planted in the early 1940s. The sulphone derivatives were soon discarded, and we embarked on a general administration of the parent sulphone (dapsone) in oily suspension and of injectable solapsone. Frank Davey was our guide and inspiration.

When I was appointed to replace him as Director of the prestigious Leprosy Research Unit at Uzuakoli in 1959, I inherited from him a tradition of remarkable cooperation that he had created and fostered—cooperation between missions and government, between the academics of Ibadan University Medical School and medical officers in the whole country, between researchers and field workers, between leprosy patients and investigators. There was a bond of mutual trust and confidence between Frank Davey and the patients, who acutally vied with each other for the privilege of being included in drug trials and immunological investigations.

The 'segregation villages' which he and Kinnear Brown developed in Eastern Nigeria bore eloquent testimony to the excellent rapport between Davey and the traditional chiefs of Iboland. The prevalence of leprosy was already declining before the widespread use of dapsone.

Davey was an excellent linguist and a musician of no mean attainment. He created a Literary Society for the patients at Uzuakoli, and became 'guide, philosopher and friend' to leprosy sufferers of all ages from far and near. As Consultant Leprologist to the government of Eastern Nigeria, he was constantly in demand for advice and counsel.

Our friendship continued when, as Medical Secretary of the Methodist Missionary Society based at London (1959–68), he asked me to serve on a Medical Advisory Committee he was organizing. He was a valued member of the Leprosy Study Centre when I was appointed Director in 1966, and rejoined the Committee when he returned from India in 1973. With Dr Robert Cochrane, he was responsible for seeing through the press the second edition of *Leprosy in Theory and Practice*. As Councillor of the International Leprosy Association, he played a prominent role in several of its quinquennial congresses.

As Medical Secretary of the Methodist Missionary Society, he enjoyed the contacts with patients that his frequent overseas journeys afforded, and grasped the opportunity to resume his clinical leanings when in 1968 he was appointed to the staff of the Methodist Hospital at Dichpalli (India). Here he worked in close cooperation with Dr L M Hogerzeil, who had been his colleague in Nigeria. Here he saw a more serious side to leprosy than that to which he had been accustomed in Africa. The social overtones of the disease in the individual, the family and the community made a deep impression on him, and he entered wholeheartedly into an integrated community health programme, not neglecting his research interests. The Government of India, the Christian Medical College of Vellore and the Karigiri Leprosy Research Centre claimed his interest and expertise.

Returning to England in 1973, Frank Davey soon immersed himself in numerous professional and church activities. He was in great demand as a preacher and as an eloquent advocate of medical missions. He was indefatigable, tireless in his willingness to help.

He replaced me as Editor of *Leprosy Review*, and left his imprint in the prestige of this Journal, enhancing its reputation.

During the past 3 years, Frank Davey had been busily engaged (as co-editor with Dr William A R Thomson and myself) in amassing material for his brain-child—a multi-author account of the initiatives taken by Christian doctors in medicine. In tropical medicine particularly, the contribution of many unsung heroes deserves recognition and recording for contemporary opinion-formers and for posterity. Davey's vision and enthusiasm combined to stimulate and encourage co-editors and contributors alike.

In all his work over the years (since 1939), Frank Davey has been wonderfully helped by his wife Kay, a most loyal helpmeet and true colleague. She will miss him in a special way.

I shall miss him too. His whole life has been an inspiration of genuine outgoing Christian service. Blessed with a fine intellect and abundant energy, Frank Davey has made a unique contribution to the treatment and the well-being of sufferers from leprosy throughout the world.

STANLEY BROWNE

The Rev Dr Frank Davey, the distinguished leprologist, editor emeritus of this Journal and former medical secretary of the Methodist Missionary Society, died on 24 March 1983 at the age of 75.

Thomas Frank Davey trained initially as an industrial chemist, being awarded the MSc of London University in 1930. He then felt the call to serve as a medical missionary and qualified in medicine at Manchester University in 1935. He was ordained in the same year following ministerial training at Hartley Victoria College and proceeded to Nigeria in 1936. He assumed almost immediately the post of Director of the Methodist Leprosy Settlement at Uzuakoli in what was then known as Eastern Nigeria. In the subsequent 10 years he developed a unique system of voluntary segregation villages for leprosy patients in the southern part of Iboland. This was an admirable and timely answer to the problem of social rejection of leprosy sufferers by the community. It enabled the patients to be directly supported by the family and to retain the family link; facilitated the provision of local treatment and enabled regular supervision to be undertaken by senior staff from the Settlement and the organization of a hospital referral system. This was a pattern of care which was to be widely adopted in Nigeria. Frank Davey initiated leprosy surveys in certain of the highly endemic districts which were to prove of immense value in later assessments of leprosy prevalence. This increasing interest of HM Government in leprosy control after the Second World War and the allocation of funds under the Colonial Welfare and Development Programme led to the formation of a Nigeria Leprosy Service in which the services of senior medical and nursing staff of the pioneering mission bodies were retained and a training programme for locally recruited health workers developed. Under Frank Davey's leadership Uzuakoli Settlement became also an acknowledged research centre, particularly for drug trials, and it was here that Dr John Lowe proved the value and suitability of the drug dapsone for use in the treatment of leprosy.

During the 1950s Uzuakoli Settlement became the venue for a stream of expatriate trainees, WHO Fellows and observers, and the organization and structure of leprosy services in a number of other countries, both in Africa and SE Asia were modelled on the Nigerian pattern.

During the period 1952–59 Frank Davey was Leprosy Adviser and Senior Specialist (Leprosy) to the Government of Nigeria and the initial involvement of UNICEF in the supply of drugs and of various forms of transport to facilitate leprosy control owes much to his advocacy. In 1959 he returned to the United Kingdom to serve as medical secretary to the Methodist Missionary Society but returned to field work in 1968, serving for 5 years as Director of the Victoria Leprosy Hospital at Dichpalli in the Medak Diocese of the Church of South India. Here his organizing abilities and enthusiasm reactivated and extended the services of an institution which is now well recognized for its rural health work and research activities. During this time his advice was eagerly sought by the Indian Government Leprosy Services, and by the Vellore Christian Medical College. His interest in the latter institution was to be maintained after his return to the UK as Chairman of the Friends of Vellore.

Besides being the author of many papers and articles, particularly on the epidemiology of the disease and on chemotherapy, he was joint author with Dr R G Cochrane of the second edition of *Leprosy in Theory and Practice* (1964).

He took pride in the contribution made by Christian Missions in the field of medicine in the developing countries and was a founder member of the Christian Medical Commission of the World Council of Churches.

Awarded the OBE in 1945 he was further honoured with the CBE in 1960.

To those who had the privilege of working with Frank Davey whether in the field or in committee, the abiding memory will be of one who devoted fully his rich and diverse gifts to the service of His Master. A natural leader who needed to use no assertion of authority, he inspired a deep loyalty and love in both staff and patients. He was a man of vision who expected things to happen and who was prepared to devote all his energies and resources in the pursuit of the physical, social and spiritual welfare of his patients. He generated an atmosphere of purpose and dedication and the writer, as with many other colleagues, recall their periods of association with him as the most significant and purposeful of their lives.

A man of true humility, he had a natural gaiety and a great appreciation of the beautiful things

in the world. His lifelong interests included music and gardening and he was a lepidopterist of repute. In later years he found much joy in exercising a new skill in painting in water-colours.

Our sympathy for his wife Kay who survives him is the deeper because of the perfect partnership that Frank and Kay showed in their service and home.

KENNETH SEAL

Like everyone else working in leprosy, I knew of Frank Davey many years ago, but it was really only in the mid-1970s that I came to meet and get to know him, in the Leprosy Study Centre in Wimpole Street in London, where he came to work as the Editor of *Leprosy Review* while I was looking at slides in the room next door with Douglas Harman and Rena Waudby, analysing data from the immense collection of leprosy and other conditions.

I soon became more interested in the Journal and eventually took over his chair as Editor in late 1978, far from confident that I would be able to maintain his high standards, but fortified by his clear advise, wise counsel and a set of practical guidelines concerning the whole process of editing and publication with Academic Press. I was tremendously impressed then, and will in fact never forget, his breadth of vision, professional knowledge, kindness, optimism, and above all his unerring ability to grasp the main point of any scientific or clinical project, manuscript or discussion. He was not a man to be diverted from what he believed to be of prime importance and it is, in retrospect, not surprising that he devoted much thought in his later years to the paramount significance of the excretion of leprosy bacilli into the environment from patients with lepromatous leprosy. We have lost a former Editor of great quality and the world of leprosy has lost one of the most distinguished leprologists of this century.

A COLIN McDOUGALL, EDITOR

RICARDO S GUINTO MD, MPH 1907–1983

It is with deep regret that the Leonard Wood Memorial announces the death of Ricardo S Guinto, MD, MPH, on 9 January 1983. Dr Guinto was the Chief Epidemiologist of the Leonard Wood Memorial Laboratory for Leprosy Research and Cebu Skin Clinic in Cebu, Philippines. He had served at the LWM since 1935. Dr Guinto conducted many of the most classic studies in the epidemiology of leprosy, and was considered a foremost expert in the field.

Dr Guinto received his MD degree in 1932 from the University of the Philippines, and his CPH degree from there in 1933. He also was a graduate of the Johns Hopkins University MPH programme in 1940. Additionally, he attended extensive postgraduate courses in dermatology and general medicine in the United States and Asia. Over the years he served as a member on numerous World Health Organization Committees for leprosy, was a Counsellor to the International Leprosy Association, was elected President of the Philippine Leprosy Society, was maintained as Fellow of the Philippine Dermatological Society and most recently was active as a member of the International Coordinating Committee for the Joint Chemotherapy Trials and Lepromatous Leprosy, conducted in Korea, Philippines and Thailand with assistance from Sasakawa Memorial Health Foundation.

The records indicate that he attended more than 50 major international meetings during his extensive career, which included consideration of leprosy research problems, immunology, and epidemiology. He is credited with 59 publications, beginning in 1936 (*International Journal of Leprosy*, Volume IV), and an additional 20 miscellaneous reports.

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Domiciliary and Field Work

Save our soles

J W Brandsma and J G Andersen, All Africa Leprosy and Rehabilitation Training Centre (ALERT), PO Box 165, Addis Ababa, Ethiopia.

Damage of the posterior tibial nerve, resulting in anaesthetic feet, is very common in leprosy patients. Probably even more common than ulnar nerve damage. Foot ulcers are an unnecessary result of posterior tibial nerve damage and are often a major problem in the management of leprosy patients. We hope that the threefold S-O-S (Soak-Oil-Scrape; See-Observe-Secure; See-Organize-Sit) presented here will be helpful in the prevention of foot ulcers in the anaesthetic foot.

Soak your feet daily in soapy water. If you cannot get soap, you can use kitchen salt or even plain water. Afterwards, while the feet are still wet—

Oil them with any vegetable oil or Vaseline. This will soften the hard calluses so that you can—

Scrape the sole of the feet with the blunt edge of a knife. Do not cut your feet. You might make an ulcer yourself. You can also use your fingernails or a pumice stone.

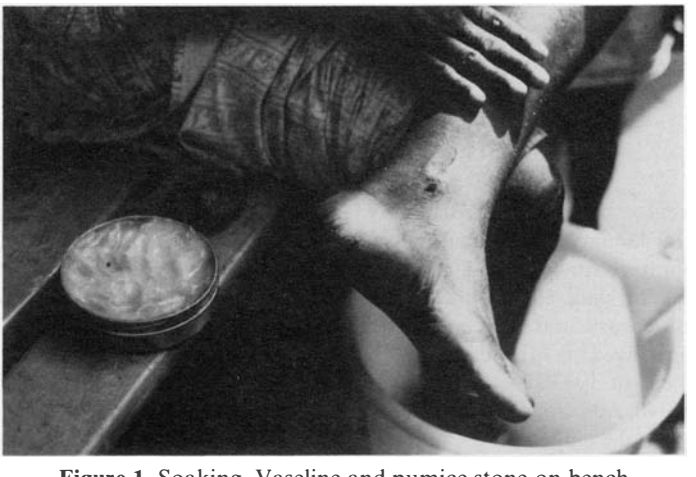

Figure 1. Soaking. Vaseline and pumice stone on bench.

See to your feet. Inspect them daily. Since you cannot feel you must see and you must think.

Observe any little danger sign. Observe the slight swelling that is so often the first sign of a developing ulcer. Observe the slightly raised temperature that indicates the beginning of a haematoma. Observe the thick callus that so often leads to deep cracks and infection.

Secure the right type of shoes. Wear them always. Keep them in good repair.

See where you walk. Avoid sharp stones and thorns. Avoid walking on hot tarmac. Do not sit too close to the fire.

Organize your daily life so that you avoid walking long distances. If possible, use the public bus, or buy yourself a bicycle or a mule.

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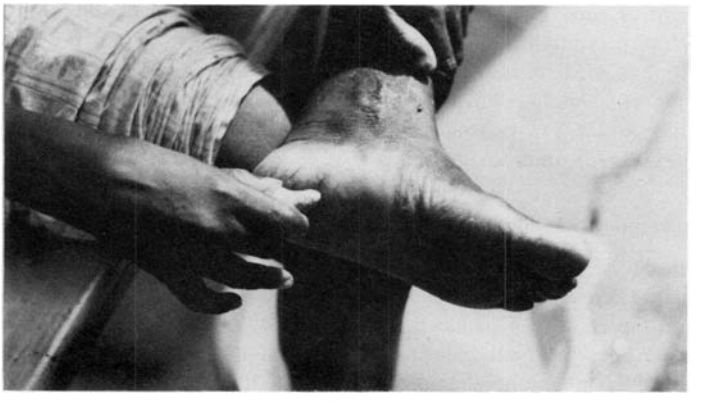

Figure 2. 'Trimming' of cracks with pumice stone.

Sit whenever you can. Your bottom is much stronger than your anaesthetic feet. Much work is traditionally done standing but could also be done sitting. Do not squat when you sit in the evening gossiping in the village. Even if it is foreign to your culture, get yourself a stool to sit on.

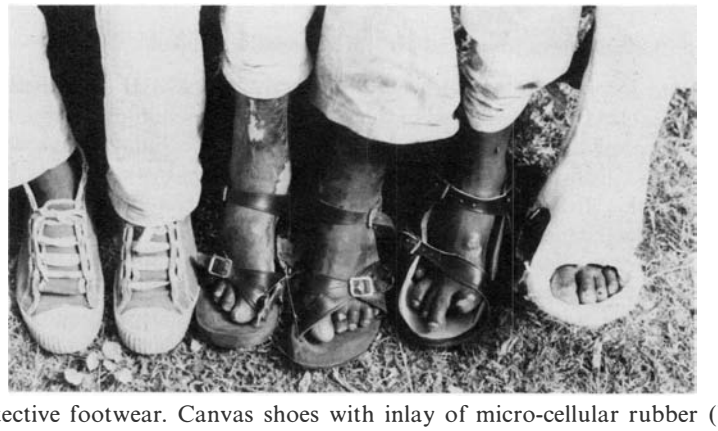

Figure 3. Protective footwear. Canvas shoes with inlay of micro-cellular rubber (MCR), open sandals with MCR and a patient with a plaztazote shoe and a plaster cast for an ulcer.

ILEP in London: A catalogue of training courses

A catalogue of leprosy training courses being offered during 1983 in a number of centres—members of the International Federation of Antileprosy Associations (ILEP)—in Africa, Asia, Europe and the US, is now available.

Requests for the catalogue, and inquiries should be addressed to: ILEP Coordinating Bureau, 234 Blythe Road, London W14 0HJ / UK.

Fontilles, Spain: training courses for doctors, missionaries and health assistants

We thank the Medical Director of Fontilles, Dr Terencio de las Aguas for sending details of two courses to be held in October–November 1983. The first is for doctors and covers all aspects of

leprosy from diagnosis, through treatment, to all aspects of management and follow up. The second has a broader base, presumably planned for some students who would not necessarily have a previous knowledge of medicine and leprosy, and it lasts for about 3 weeks, whereas the doctors' course is for 5 days. These courses have of course been held in Fontilles for many years, and it is our understanding that similar courses are planned for 1984. Apply to the Medical Director, Sanatorio de Fontilles, Fontilles, Alicante, Spain.

***Leprosy in the light-skinned;* slide set with text**

The Regional Office for Europe of WHO in Copenhagen, in cooperation with Food for the Hungry International and the Danish Order of St John have produced a set of 50 colour transparencies, with accompanying descriptive text. This has been prepared by Dr D. L. Leiker of the Royal Tropical Institute in Amsterdam, the Netherlands, and the text includes: introduction; distribution of leprosy; diagnosis; classification; chemotherapy. The opening paragraphs draw attention to important differences between the clinical manifestations of leprosy in light- and dark-skinned patients and also remind the reader that a series of slides on leprosy in the dark skin, a co-production of the Royal Tropical Institute, is available from MEDDIA, Mauritskade 63, 1092 AD Amsterdam, the Netherlands. Further information on this invaluable source of information on leprosy in light-skinned patients may be obtained from Professor B. Velimirovic, Chief Communicable Diseases, WHO Regional Office for Europe, Scherfigsvej 8, DK-2100, Copenhagen, Denmark.

***Atlas of Leprosy;* the Sasakawa Memorial Health Foundation, Japan**

Following the first edition or issue of the 'Atlas of Leprosy' by SMHF, a revised and expanded version is now available. This is dedicated to the late Dr Ricardo Guinto of Cebu, the Philippines, and contains the series of 40 clinical pictures of patients from that country, representing almost all aspects of the disease, including reactions, together with 32 pictures of leprosy histopathology, prepared by Dr Abalos. In addition, there are also 18 clinical pictures to illustrate some of the problems in differential diagnosis. Our understanding is that this atlas will be distributed to selected training centres, libraries and some medical schools, and as is traditional with this Foundation, the priority countries may be those of the Far East in which they have had a particular interest. Dr Yo Yuasa indicates however, that individuals with a bona fide interest in leprosy and its histopathology may apply for copies. Address: Sasakawa Memorial Health Foundation, the Sasakawa Hall, GF, 3-12-12 Mita, Minato-ku, Tokyo 108, Japan.

***Technical Guide for Smear Examination for Leprosy by Direct Microscopy*. D. L. Leiker and A. C. McDougall. Leprosy Documentation Service, Amsterdam, 1983, 34 pp.**

This booklet published by INFOLEP, Royal Tropical Institute, 61a Mauritskade, Amsterdam Oost, the Netherlands, is intended as a practical guide to smear examination in leprosy, similar to that for sputum examination published by the International Union Against Tuberculosis (Paris). The Foreword is by Dr H. Sansarricq of WHO and the contents are—1. Introduction: terminology and classification of leprosy; bacteriological findings in the various types of leprosy; nasal smears; numbers of and morphology of bacilli in smears; facilities for examination; supervision, standards of work and quality control. 2. Technique of smear-taking: section of patients; number of smears per session; sites and frequency of examination; equipment and materials; smear-taking; nasal smears; fixation; storage and transport. 3. Technique of staining: equipment and materials; preparation of reagents; staining of smears. 4. Examination by microscopy: equipment and materials; use of the microscope; reading of smears.

Translations from English to French, Spanish and Portuguese are being made.

ALERT, Addis Ababa, Ethiopia. Training courses for 1984

Course	Participants	Dates	Requirements
International Courses			
Doctors' course on clinical leprosy leprosycontrol and teaching methodology	Medical officers involved or going to be involved in clinical management of leprosy patients, leprosy control work or training in leprosy of health personnel	9 January–11 February (5 weeks) 24 September–27 October (5 weeks)	It is generally required that participants who will undertake leprosy control work should, prior to the course, visit and study their future project. It is also recommended that they prolong their stay by not less than 2 weeks for further in-service training in leprosy control
Tuberculosis course on TBC and TBC control	Medical officers and paramedical health staff involved in tuberculosis control	29 October–17 November (3 weeks)	
Rural area supervisor's course on clinical leprosy, leprosy control, supervision and teaching methodology	Senior rural area supervisors	19 March–19 May (9 weeks)	Senior rural area supervisors should be in charge of leprosy control activities on provincial or national level
	Junior rural area supervisors		Junior rural area supervisors should have not less than 5 years' experience in leprosy and on their return expect to be upgraded to a senior position
Physiotherapy course on assessment and management of disabilities in leprosy and pre- and postoperative case	Physiotherapists, occupational therapists, other paramedical health staff with experience in leprosy physiotherapy	10 September–20 October in conjunction with the second doctors' course (6 weeks)	
National Courses			
Medical undergraduates		9–12 weeks	Other Ethiopian and non-Ethiopian health personnel with limited responsibilites in leprosy work may be attached to these courses when places are available
Student nurses		8–10 weeks	
Health assistants		4–6 weeks Dates still to be fixed	

cont.

cont.

In-service Training

NB The in-service training programmes are generally intended for further specialized training in specific fields. Applicants for programmes listed under 1–5 are therefore required to possess prior experience in leprosy or to have participated in an appropriate formal course.

Programme	Required qualifications	Recommended duration
1 Clinical leprosy	Medical officers Qualified nurses Medical assistants	Minimum of 2 months
2 Clinical leprosy and leprosy control	Medical officers Qualified nurses Medical assistants	Minimum of 4 months
3 Septic surgery and amputation surgery	Qualified general surgeons Surgical residents, medical officers with good experience in surgery	3 months
4 Reconstructive surgery	Qualified plastic, orthopaedic or general surgeons Surgical residents, medical officers with good experience in leprosy	Dependent on extent of training required and basic qualifications
5 Physiotherapy	Physiotherapists Occupational therapists	3 months
	Other paramedical health personnel	4–6 months. Good command of English
6 Laboratory techniques in leprosy	Laboratory Technicians Laboratory Assistants	1 month. Good command of English 2 months. Good command of English
7 Dermato-histo-pathology techniques (in Armauer Hansen Research Institute)	Laboratory Technicians	3 months. Good command of English
8 Orthopaedic workshop techniques. Making of protective foot-wear (sandals, plastozote)	Standard—8	6 months. Good command of English
9 Prosthetics	Orthopaedic workshop technicians	12 months. Good command of English

Apply to the Director of training, ALERT, PO Box 165, Addis Ababa, Ethiopia.

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Reports, News and Notes

Leprosy Scientific Memoranda: Leonard Wood Memorial

After a lapse of time, this Memoranda is now once again available as '. . . a means for scientists working on the chemotherapy of leprosy, the pharmacology of antileprosy drugs, culture techniques, and the bacteriology of immunology of leprosy, to exchange information informally and quickly with their colleagues throughout the world'. The appearance of findings in this Memoranda does not constitute publication. Further details may be obtained from the address below.

Contributions must be typed on standard size paper; an original and a good copy should be submitted. Pages should be typed single-spaced and in a compact format. The width of the reproducible area must not exceed 7 inches (17·8 cm). Because the pages will be photographically reduced to 1/2 size, large size type should always be used. It is important that you sequentially number every page of each submission, including tables and figures. Complete manuscripts or contributions resembling manuscripts cannot be accepted.

The *LSM* is sponsored solely by the Leonard Wood Memorial, with a partial contributing grant from the CIBA-GEIGY Co. (Basle, Switzerland). Closing dates for the *LSM* are scheduled bi-monthly so communications should be submitted, whenever ready, to Dr. Jay Sanford, Chairman, Scientific Advisory Board, Leonard Wood Memorial (American Leprosy Foundation) 11600 Nebel Street, Suite 210, Rockville, Maryland, USA 20852. No responsibility is assumed for the content of communication exchanges through the *LSM*.

WHO: Report of the Meeting on Action Plans for Leprosy Control, New Delhi, 1982

A meeting on the practical implications of the recommendations of the WHO Study Group on Chemotherapy of Leprosy for Control Programmes (1981) was held at the WHO Regional Office for South-East Asia, in New Delhi, 23–25 August 1982. Dr Sansarricq, Chief Medical Officer, Leprosy Unit, WHO Headquarters, outlined the scope and objectives of the meeting.

He emphasized that this was a unique occasion, since representatives of important voluntary organizations with a long history of involvement in leprosy control, were for the first time invited together with those responsible for leprosy activities in WHO, to discuss appropriate ways for implementation of the new multidrug therapy in order to formulate a uniform approach to achieve the common objectives. He stressed the need to implement extensively and expeditiously the new regimens recommended by the WHO Study Group at its meeting in Geneva in October 1981. Any further delay could be disastrous, with increasing dapsone resistance and the development of multiple drug resistance. The need for increased funding to support the substantially increased costs in order to promote the implementation of this strategy was therefore imperative. The long-term cost-effectiveness ratio and the substantially increased benefits to patients would adequately justify this sound technical approach. He emphasized that efficient planning, sound managerial concepts, strengthening of the infrastructure and periodic evaluation will be essential prerequisites for effective implementation of the new strategy. Appropriate training for all categories of personnel commencing at the managerial levels will be necessary, to ensure greater efficiency in the effective

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utilization of available resources. Better and more effective treatment could be the most important factor in reducing defaulter rates and substantially improving case-finding.

He then briefly outlined the main objectives of the meeting which were closely interlinked:

1 To prepare an outline plan of action for implementation of multidrug therapy at the regional level with appropriate financial requirements.

2 To explore the intentions of collaborating agencies regarding their participation, particularly in financial terms, in national leprosy control programmes, for the implementation of the new regimens.

This document, WHO/LEP/83.1, is essential reading for all concerned with leprosy control.

Raoul Follereau Grant for Leprosy Research, 1984

The Italian Leprosy Relief Association "Amici di Raoul Follereau", an organization for international health cooperation, offers a grant of U.S. $20,000 for leprosy research, named after Raoul Follereau, to a young research worker in a European department. The object of the grant is to stimulate the undertaking of original research in the field of leprosy in a research department in Europe.

The precise conditions were finalised at the recent meeting of the Federation of Anti-Leprosy Associations (ILEP) in Berne, Switzerland in June 1983, and will shortly be distributed to all ILEP members, leprosy journals and appropriate institutions, including universities and research centres, in Europe. Meanwhile, further details may be obtained from "Amici di Raoul Follereau", via Borselli, 4—40135 Bologna, Italy. Tel. 051/423809—433402.

ALERT, Annual Report, 1982

We are most grateful for this very full report (virtually 90 pages) of activities at ALERT in Addis Ababa, Ethiopia. The courses for 1984 are listed under 'Domiciliary and Field Work' in this issue. The work is described under the headings of organization, general information, summary of activities, training department, department of hospital services, leprosy control, Armauer Hansen Research Institute, finance and appendices. It is extremely encouraging to read this account of continuing activities at ALERT, which have been maintained often under conditions of considerable difficulty. Address: ALERT, PO Box 165, Addis Ababa, Ethiopia.

Malaysia: Annual Report of National Leprosy Control, 1981

This is a remarkably comprehensive account of control activities (200 pages) from the National Leprosy Control Centre, Pusat Kawalan Kusta Negara, Sungai Buloh, Selangor, Malaysia, with detailed information on all aspects of control in various parts of the country. Special sections cover the Regional Working Group meeting on drug policy in the Philippines in February 1981; the WHO Study Group on Chemotherapy in Geneva in October 1981; and the Asian Seminar on Vocational Rehabilitation of Leprosy Patients, Bombay, October 1981.

XII International Leprosy Congress, New Delhi, 20–25 February 1984

The Final Information Brochure has now been issued. Details are given of the necessary Registration and Hotel Accommodation Forms, Scientific Sessions, Workshops, Teaching Sessions, Social Events and Tours. Enquiries *in the UK* to Dr S.G. Browne, Secretary, the International Leprosy Association, 16 Bridgefield Road, Sutton, Surrey, SM1 2DG and *in India* to Dr R.H. Thangaraj, Organising Secretary, XIIth International Leprosy Congress, 1, Red Cross Road, New Delhi-110 001, India.

***Handbook of Leprosy* by W H Jopling now in Portuguese**

In view of the very considerable success of this booklet in English-speaking (and many other) areas, it is a pleasure to record that it has been translated, and is now available in Portuguese. The UK publishers (William Heinemann Medical Books Ltd, 23 Bedford Square, London WC1B 3HH) have kindly confirmed that the Portuguese edition has been published by Livraria Atheneu Ltda, Rua Bambina 74, Loja A/B, Rio de Janeiro, Brazil, South America. Apart from Macao, our understanding is that the need may be mainly in Brazil, Portugal, Mozambique, Angola, Cape Verde Islands, Guinea Bissau and East Timor. (Note: Fig. 14, p. 45, needs a correction. Polar LL + TT are printed as 'instavel' (meaning unstable) but this should of course read 'stavel' (meaning stable).)

INFOLEP: Materials for Teaching and Learning in Leprosy, November 1982

The Leprosy Documentation Service (INFOLEP) in Amsterdam has recently produced and circulated a 103-page document (A4 size) on teaching and learning and leprosy in pursuance of its objective to collect analyse and document all relevant material for teaching in leprosy. The purpose is to act as a 'clearing house' in collection, analysis, definition of needs and dissemination of information in the form of an annual report/bibliography.

The present document lists the materials so far examined under appropriate headings; adds an index of personal names; summarizes the material by language; and gives the addresses of distribution agencies. It should be noted that INFOLEP does not intend to actually stock and distribute the materials described. The final green pages give details of such materials as are already already distributed by The Leprosy Mission (International), OXFAM, TALC, MEDDIA, VHAI, Hind Kusht Nivaran Sangh, Gandhi Memorial Leprosy Foundation, Carville, the Sasakawa Memorial Health Foundation and others. Address: Leprosy Documentation Service (INFOLEP), Royal Tropical Institute, Mauritskade 63, 1092 AD Amsterdam, The Netherlands.

Workshop on Reconstructive Surgery of the Hand in Leprosy, Kumbakonam, South India, 1982

A workshop on reconstructive surgery of the hand in leprosy was held at the Sacred Heart Leprosy Centre, Kumbakonam, 18–20 October 1982. This workshop was fully sponsored by LEPRA, all the expenses being given through the 'ring' fund.

The aim of this workshop, the first of its kind held in recent years, was to establish a communication between the young and old surgeons working in this field and to bring their knowledge up-to-date in all branches of reconstructive surgery of the paralytic hand deformities.

Twenty-two doctors from various parts of India participated in this workshop. The internal faculty consisted of Dr D D Palande, Dr A Subramanian (Surgeons), Mr Vasant L Naganore (OT), Mr Simon (PT), and Mr Gopal (Social Welfare Officer), while the external faculty consisted of Dr H Srinivasan, Senior Surgeon, CLT & RI Chingleput, Dr A Beine, Surgeon, Sivananda Rehabilitation Home, Hyderabad, and Dr G D Sundararaj, Surgeon, CMC Hospital, Vellore. A complete account of this workshop may be obtained on application to Dr D Palande, Chief Surgeon, Sacred Heart Leprosy Centre, Sakkottai 612 401, Kumbakonam, RS, Thanjavur District, South India.

INTERLINK: International network for disadvantaged and disabled people

Mr A D Askew, International Director of the Leprosy Mission (International) in London has kindly drawn our attention to this organization. INTERLINK is an international network for the

exchange of arts opportunities for disadvantaged and disabled people of all nationalities and cultures.

Elderly people or children with severe mental or physical limitations everywhere can extend themselves through drawing, playing music, sculpting or puppetry and dance. Programmes of rehabilitation can include creative activities.

INTERLINK has a developing free advisory service. This service can arrange for the visit of a consultant who has had considerable experience of working with disabled or severely disadvantaged people and who is specialized in a particular aspect (for example, crafts, visual art, drama, music, etc.). The consultant will work closely for a few weeks with local artists and staff, demonstrating the value of creative involvement. New arts programmes could be set up which would be continued by the clients after the initial visit. Advice about continued funding for the creative projects will be part of the consultancy.

Exchange visits can be organized to other countries for those wishing to investigate creative activities for recreation or rehabilitative purposes.

Three-month introductory training courses can be arranged for staff wishing to learn about arts activities for rehabilitation or recreational purposes. INTERLINK is interested to discuss the possibility of developing projects with leprosy patients overseas. For more information, contact Gina Levette, 358 Strand, London WC2R 0HS.

BOMS: Bureau for Overseas Medical Service, London—Health Workers for the Third World

The Bureau for Overseas Medical Service (BOMS) is a charity for health workers who are interested in working in the Third World countries of Asia, Africa, the Caribbean and South America. We offer career advice and can tell you about jobs in hospitals, clinics, missions, primary health care units and teaching establishments. We welcome enquiries from doctors with provisional or full registration in the UK. We recently enlarged our register to include all health workers and would like to hear from paramedical workers with state registration and 2 years' working experience. Nurses must be SRN with a higher teaching qualification. We are particularly interested in health workers with leprosy experience. Anyone interested in joining our register or who knows of a vacancy for a health worker in the Third World is invited to contact Colin Jacobs, Secretary, Bureau for Overseas Medical Service, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, Telephone 01-636 8636, ext. 232.

OXFAM–LEPRA: a pack of 25 documents for teaching-learning in leprosy

In late 1981, OXFAM in Oxford, in cooperation with LEPRA, drew up a list of 25 documents for teaching-learning in leprosy, with the object of providing an 'immediate' source of information for medical students, medical officers (with and without experience of leprosy), leprosy control officers, tutors, nurses and other potential teachers. The pack includes: two short paperback 'textbooks' on leprosy; 2 colour transparency self-teaching sets, with text; various essential WHO publications; documents and reprints on laboratory work, prevention of disability, adverse immunological reactions, essay competitions on leprosy for medical students and social aspects.

One hundred packs were assembled in Oxford in early 1982, and all sold out within 7 months to individuals, teaching units, universities and research institutes in various parts of the world. Later in 1982 a further 100 packs were made up of which over half were sold before March 1983. Although an assessment of the value of these packs in the field has not yet been attempted, the demand from many different countries has far outstripped the original expectations and this is interpreted as indicating—at the very least—a significant level of professional interest. (A similar pack for

tuberculosis is in preparation.) Enquiries on current cost of the leprosy pack and postal charges to: Medical Unit, Oxford, 274 Banbury Road, Oxford OX2 7DZ, England.

Histopathology Services for Developing Countries

Professor Michael Hutt will be retiring from St Thomas's Hospital in London in September this year and has recently issued the following letter concerning histopathology services, which include the examination of biopsies for leprosy:

'For the last 15 years the department of Histopathology at St Thomas' Hospital has provided a free, postal, diagnostic service for a number of hospitals, both government and mission, in developing countries. It was originally envisaged that the need for such services would decrease as they were built up locally. For a variety of reasons, differing from country to country, this has not happened and the need is still there and likely to continue. To meet these problems and to provide histopathological expertise in parasitic, communicable and other tropical diseases in the UK a new consultative histopathologist post has been created jointly with the London School of Hygiene and Tropical Medicine and University College Hospital Medical School. This post has just been filled by the appointment of Dr S B Lucas who has spent 2 of the last 4 years in this unit and 2 in the Pathology Department at Nairobi. My own full-time post will terminate in September when I retire, though I will continue my involvement with developing countries on a part-time basis.

'Dr Lucas is keen to maintain or increase the diagnostic services for tropical countries and we hope to raise funds to cover the expenses of such work.

'As from 6 April 1983, I would be grateful if you could re-route your postal specimens to him:

Dr S B Lucas, Department of Morbid Anatomy, School of Medicine, University College London, University Street, London WC1. Telephone 01-387 9300.

'I hope to remain in contact with you through my association with Dr Lucas and I am sure that he will provide you with an excellent service.'

M S R HUTT, *Professor of Geographical Pathology*

Editorials for 1984

At a meeting of the Editorial Board of *Leprosy Review* in February 1983, it was proposed that editorials for 1984 would include the subjects of immunotherapy, monoclonal antibodies, and a review of the International Leprosy Congress in Delhi (1984).

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Book Reviews

Bitter Pills: Medicines and the Third World Poor by Dianna Melrose. Published by Oxfam.

'A woman was crying. We found her with a dead baby in her arms and a collection of medicine bottles beside her. She had spent all her money on these expensive drugs. . . . The baby had become severely dehydrated from diarrhoea. Her death could have been prevented with a simple home-made solution of water, salt and sugar.'

Millions of people in the Third World die or suffer from curable or preventable conditions because of problems in making effective drugs available to the world's poor. Problems abound, solutions are far more elusive. The demands of market forces dictate the drugs which are available—more than a third of the drugs on the market in Nepal in 1980 were multivitamin tonics—profit margins, rather than need, determine who gets what; sales promotion is the major source of medical information. Dianna Melrose documents the case-histories of abuse, greed and ignorance, but while the pharmaceutical industry receives most of the criticism, one is left to ponder why governments, both developed and developing, have not taken a more assertive role. Thus, if the Third World regulatory agencies' reliance on manufacturers' information on toxicity has proven, not surprisingly, unsatisfactory, why hasn't the extensive information generated by the agencies of developed countries been utilized? If the interests of the drug companies and the interests of the poor cannot both be satisfied by commercial pressures, then it is the poor who need legislative protection. It is to be hoped that the leads taken by the governments of Bangladesh, Sri Lanka and Mozambique in controlling the numbers of drugs available and in limiting the freedom of the prescriber, are seen to be successful and are followed elsewhere.

Bitter Pills is a thought-provoking book which demonstrates that while the gap between the laboratory and the pharmacy shelf may be large, the gap between the pharmacy shelf and the provision of essential medical help to the Third World poor can be even larger. The book provides a voice for the sick and poor which, if we are to prevent the sale of anabolic steroids as appetite stimulants for children, the over-the-counter sale of toxic anti-cancer drugs as 'safe cures for all cancer', or any of the other abuses which are eloquently described in *Bitter Pills,* we would all do well to hear.

M J COLSTON

The Biology of the Mycobacteria. Volume 1. Editors C Ratledge and J Stanford. Academic Press, 1982.

This is the first part of a 2-volume publication. This first volume deals with mycobacterial physiology, identification and classification, while the second volume is concerned with immunological and environmental aspects. The book brings together a wealth of information on basic and laboratory aspects of the mycobacteria, and should be of great benefit to those working in this field. It is likely to be of less value to those whose primary interest is in the clinical aspects of mycobacterial diseases, unless they are seeking to increase their basic knowledge of the mycobacteria.

The book is a multi-author publication, with chapters on the anatomy of mycobacteria, lipids (2 chapters), nutrition and physiology, *Mycobacterium leprae*, genetics, antimycobacterial agents, diagnostic bacteriology, and taxonomy. The coverage by each of the authors is very comprehensive, providing an excellent reference text for each of the areas covered. The mycobacteria emerge from this book as being essentially similar to other groups of bacteria,

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but the importance of the lipid-rich cell envelope is attested for, not only in the chapters dealing specifically with mycobacterial lipids, but also in those dealing with the structure, physiology and taxonomy of the mycobacteria, and with the development of antimycobacterial chemotherapeutic agents. No doubt Volume 2 will provide even more compelling evidence on the importance of the bacterial cell surface in the evolution of mycobacterial pathogenicity.

M J COLSTON

British National Formulary (BNF), Number 5, 1983, 456 pp., paperback.

This publication, jointly from the British Medical Association and the Pharmaceutical Society of Great Britain, has just appeared in the UK and will no doubt prove as invaluable to general practitioners, hospital doctors, specialists and medical students as the numerous previous issues. It is, however, now somewhat larger and certainly heavier than previous versions, which used to slip easily into the doctor's pocket, to be consulted inconspicously and without too much loss of face. A glance at this Number 5 will, however, confirm the enormous breadth and complexity of pharmacology and therapeutics in 1983, and it must surely be only the exceptional doctor who can keep abreast of new developments, including side-effects and incompatabilities. The BNF includes useful pages on prescription writing; prescribing for children; the elderly; those with liver and renal disease; pregnancy and lactation. There are also sections on adverse reactions to drugs and drug dependence. Most of the basic tropical disease drugs, including those for leprosy, are well covered. Available from the BMA, Tavistock Square, London, WC1H 9JP or the Pharmaceutical Press, 1 Lambeth High Street, London SE1 7JN.

EDITOR

The Scientific Working Groups on Immunology of Leprosy (IMMLEP) and Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) wish to undertake a series of trials of immunotherapy of lepromatous leprosy. The first trials are designed to compare the efficacy of three vaccines—BCG, heat-killed *Mycobacterium leprae* (HKML), and the combination BCG + HKML—in terms of the proportions of treated, smear negative lepromatous patients who develop skin-test reactivity to a soluble antigen prepared from *M. leprae*. A protocol* has been prepared, which calls for four groups, each of 100 such patients. The patients are to be skin-tested and vaccinated on eight occasions at intervals of three months, and followed thereafter for a period of five years. Leprosy treatment centres interested in participating in such trials are invited to write to Dr S.K. Noordeen, Secretary, IMMLEP and THELEP Steering Committees (TDR), World Health Organization, 1211 Geneva 27, Switzerland.

* "Protocol for a trial to determine the capacity of several vaccines to produce skin-test reactivity to a soluble *M. leprae* antigen in treated smear-negative patients with lepromatous leprosy."

Abstracts

MANUNGO J, THOMAS JEP (1982) A Comparison of the incidence of type 2 reactions in lepromatous leprosy with two regimens of treatment. *Central African Journal of Medicine*, **28** (9), 208–11.

On the principle of giving combined chemotherapy for the first year in treating lepromatous leprosy, followed by dapsone alone, this trial was devised to compare 2 combined regimens as regards the incidence of type 2 lepra reactions (ENL reactions). Fifty-four African patients in Harare, Zimbabwe, were divided in 2 groups: group 1 received clofazimine 100 mg/day together with standard dosage of dapsone, and group 2 received isoniazid 300 mg/day, thiacetazone 150 mg/day, and standard dosage of dapsone.

Two patients in group 1 developed reactions, and counting recurrences, had 5 bouts of reaction between them, 1 mild and 4 severe. Six patients in group 2 experienced reactions, and as there was 1 recurrence, there were 7 bouts of reaction all told, 3 graded mild and 4 severe. The authors concluded that in both groups there was no significant relationship of type 2 reactions to age or sex, to the duration of disease, or to the length of treatment. As the regimen in group 1 was twice as expensive as that in group 2, and as reactional episodes were only slightly less common, it is concluded that group 2 treatment regimen is the most cost/effective in Zimbabwe during the first year of chemotherapy for lepromatous leprosy.

[No mention is made of clinical and bacteriological progress in the two groups, nor of any drug toxicity.]

W H JOPLING

MANUNGO J, THOMAS JEP (1982) A study of type 2 reactions in lepromatous leprosy. *Central African Journal of Medicine*, **28** (9), 211–13.

This is a report on laboratory studies during the reactional episodes of the patients described in the previous paper. Investigations included Hb estimation, leucocyte count, platelet count, and examination of urine for protein, together with the response of the reactions to various drugs. These results are shown in a series of tables.

A mild anaemia, a leucocytosis, and a thrombocytosis were common findings; the highest white cell count was 41,300 per mm^3 and the highest platelet count was 849,000 per mm^3. The degree of proteinuria was variable and unpredictable. As regards response to treatment, the best and most consistent results were obtained with prednisolone; response to chloroquine and to aspirin was variable, and phenylbutazone proved unsatisfactory.

[This study has highlighted a little-known complication of type 2 reaction, namely, thrombocytosis. In speculating why this increase in platelets is not associated with thromboembolism, especially as decreased fibrinolytic activity has been demonstrated during type 2 reactions,[1] two possible explanations should be considered: 1, impairment of platelet adhesiveness and of platelet aggregation to collagen;[2] 2, increased prothrombin time due to a circulating anticoagulant.[3]

References

[1] Sharda DP, Parvez M, Jain AK, Bhargava NC, Misra SN. A study of serum fibrinolytic activity in leprosy. *Lepr India*, 1979; **51:** 203.

[2] Gupta M, Bhargava M, Kumar S, Mittal MM. Platelet function in leprosy. *Int J Lepr*, 1975; **43:** 327.

[3] Cole FS, Brusch JL, Talarico L. A circulating anticoagulant in lepromatous leprosy. *Int J Lepr*, 1979; **47:** 121.]

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