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Editorial

THE MEDICAL STUDENT AND LEPROSY

Those who are committed to attempting to control leprosy with the means currently available are in little doubt that case-finding and chemotherapy are of fundamental importance. Despite the exciting advances which are being made towards the development of a vaccine and to procedures which may permanently improve the immune status of patients with lepromatous leprosy, recent publications from the World Health Organisation[1, 2] have underlined the continuing need to find and diagnose as many cases as possible and to treat them with multiple drug regimens.

Since the WHO publication on such regimens in 1982, virtually all leprosy-endemic countries have implemented, or are in the process of implementing, multiple drug therapy, but in a recent Report from WHO of a consultation on the implementation of multiple drug therapy (MDT) for leprosy control[3] it is disconcerting to read that '. . . this has in general been on a limited scale and there is an imperative need to hasten and expand the pace of implementation of the revised strategy.' This comment could appropriately be linked and considered with the fact that only 5·3 million cases of leprosy are actually registered worldwide[4] leaving at least that number—possibly more—who are estimated to have the disease, but have been neither detected nor offered treatment. The 1985 WHO Report on MDT referred to above goes on to consider some of the practical problems which have been revealed in different countries in implementation and draws attention to the shortage of qualified staff as one of the main constraints. Yet this problem is far from new; it was recognized repeatedly during the era of dapsone monotherapy and its increasing importance was predicted by experienced leprologists all over the world when MDT was first discussed, some even expressing the view that safe implementation would prove impossible, or dangerous, if urgent attention could not be given to the upgrading of health personnel concerned in the diagnosis, classification, treatment, management and follow-up of patients with this disease. These views have been upheld in countless meetings, discussions, *ad hoc* working groups and resolutions of the International Federation of Anti-Leprosy Associations (ILEP) whose member organizations are responsible, directly or indirectly, for a considerable percentage of the total of

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registered leprosy patients. Furthermore defects in the total numbers of people available for leprosy control, or their quality, or both, are plain to see for anyone who travels regularly in most leprosy-endemic countries, where it is also apparent that there is a lack of motivation, supervision, enthusiasm and 'drive' from people at the top.

Why are these defects still with us in 1986? Does the fault lie with Ministers or Ministries of Health? Health planners? Schools of training? ILEP or WHO? Should the non-government organizations have given greater emphasis to the training of personnel for leprosy control, when they began to realize, as they did some years ago, that the total of known, registered cases under their care was not rising satisfactorily? There is almost certainly no simple answer, but one possibility which has attracted attention in recent years centres on the observation that in leprosy (perhaps more than in other diseases) it is medically qualified doctors who exert enormous influence, not only on health planning and policy, but also, perhaps more importantly, on the attitude of the medical and lay community to leprosy patients and to the whole matter of leprosy control. Any leprologist of experience can testify to the disastrous effect of a locally qualified doctor, posted to take charge of a district hospital, who turns out to know nothing about leprosy and to be manifestly afraid of touching a patient. Post-graduate or 'continuing' education is of course greatly to be commended, if only as a means of keeping qualified doctors up to date with advances or changes in aspects of leprosy, such as chemotherapy, and those who have made systematic efforts to contact general practitioners in leprosy-endemic areas, as for instance in Bombay,[5] have already observed improvement in standards of case-detection and treatment. But we have to remember that many doctors become extremely busy almost from the moment of qualification; they scatter to different parts of the country and often have to earn money in order to repay debts incurred during their training. To some extent, their ideas about many diseases, including leprosy, are already formed. But behind every new doctor there is a medical student and it is the purpose of this editorial to suggest that we have, in the thousands of students who are constantly passing through medical schools in all leprosy-endemic countries of the world, a vast and important 'captive audience'. Their basic training in leprosy, including the formation of positive attitudes to the disease and clinical contact with patients, can surely no longer be ignored.

Looking only at those pages relating to leprosy-endemic countries, a glance at the World Directory of Medical Schools[6] shows only too clearly how difficult it would be to get to grips with the input of leprosy in the curriculum of universities in so many different countries. It must however be recorded that in some centres impressive advances in the teaching of leprosy to medical students have already been made. In a previous communication to this journal,[7] Warndorff drew attention to the contribution made by the All-Africa Leprosy and Rehabilitation Training Centre (ALERT) to the training of medical students from the medical faculty in Addis Ababa, over a period of many years, and Ganapati,[5] working

mainly in the slums of Bombay, has described the active involvement of medical schools, including teaching staff and students in the leprosy programme. Furthermore, we have recently received an account[8] of a potentially very important 'Leprosy Teaching Module' which is in use at the University of Calabar, Cross River State, Nigeria. At the beginning of their final year of study, students spend $3\frac{1}{2}$ months working in the field in community health and the leprosy component is linked to primary health care. The final year examinations include compulsory questions on leprosy. Such initiatives, together with those which have already been taken in various other parts of India, indicate what can be accomplished with a certain amount of determination and planning. This makes it all the more deplorable to record that, in contrast to these excellent examples, the general situation with regard to the teaching of this subject to medical students is far from satisfactory.

Ironically, where the leprosy problem is most severe, it is often the fact that it is virtually neglected in the medical student curriculum. Some years ago, in a letter to the *International Journal of Leprosy*,[9] attention was drawn to the totally inadequate amount of time allocated to this subject in many medical schools and it is still the case that an adequate, regular, teaching–learning module, including clinical experience, has not been established in most schools where leprosy is endemic. It would, however, be wrong to imply that this has not been recognized in the past by WHO, ILEP and various other agencies, who have attempted to draft recommendations for a suitable module. In fact a Workshop on the training of undergraduate medical students in leprosy, sponsored by the Gandhi Memorial Leprosy Foundation and the Medical Council of India, was held in Calcutta in February 1979, and a detailed syllabus was described in a (restricted) WHO document later that year, covering activities and studies in clinical medicine, pathology, microbiology, pharmacology, surgery, preventive and social medicine. In 1980 a symposium was held at the MKCG Medical College, Berhmapur, Orissa on 'Intensification of Teaching of Leprosy to Medical Undergraduates',[10] again giving a fairly detailed account of the main training required. The importance of the medical student in leprosy was further emphasized in Report of Task Force 'D' on mass communications, health education and people's participation.[11]

But the truth is that neither in India, nor elsewhere, have such recommendations been generally accepted and applied, possibly because of the inherent difficulty of making recommendations for schools in so many different parts of the world, with varied resources. Foremost amongst these are the *human* resources in terms of teachers, motivators, specialists in various subjects who can, at least in theory, be either nominated or called upon to assist. But the plain truth of the matter is that enthusiastic teachers with a basic knowledge of leprosy (and an interest in the subject) simply do not exist and it may be unhelpful to continue stating that they 'should be identified'. However, in another recent publication from WHO,[12] the basic, practical steps to be taken in order to provide

'. . . teachers competent to assist the students to reach their objectives' have now been outlined by authors with long experience in this field and one wonders if this is perhaps the moment to consider a meeting of representatives of WHO, ILEP, ministries of health and other agencies interested in leprosy control, to discuss the medical student and leprosy? In this context it may be helpful to keep in mind that most medical students are more than accustomed to self-instruction and that the potential of distance-learning techniques[13] is very considerable. It could also be valuable to establish appropriate health-learning materials, including transparencies, video tapes and a full range of written material, in appropriate sections of teaching 'laboratories' or demonstration centres in the medical school.

Medical students are often hard-working, interested and receptive people. Experience shows that, if given the chance, they will write essays on leprosy subjects, go to work in leprosy hospitals and control projects, assist in research and support voluntary agencies. It would not cost much money to radically upgrade their involvement with leprosy at the undergraduate stage. Is there not a case for improving our approach to such potentially valuable members of the profession?

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References

[1] WHO. Chemotherapy of leprosy for control programmes. Report of a WHO Study Group. Technical Report Series 675. World Health Organisation, Geneva, 1982.
[2] WHO. Epidemiology of leprosy in relation to control. Report of a WHO Study Group. Technical Report Series 716. World Health Organisation, Geneva, 1985.
[3] WHO. Report of a consultation on implementation of multidrug therapy for leprosy control. WHO/LEP/851. World Health Organisation, Geneva, 1985.
[4] WHO. Report of a meeting on action plans for leprosy control. New Delhi, 23–25 August 1982 (Unpublished WHO document WHO/LEP/83.1 Corr 1).
[5] Ganapati R. Personal communication 1985.
[6] WHO. World Directory of Medical Schools, World Health Organisation, Geneva, 1979.
[7] Warndorff JA. Training in leprosy of medical students in Ethiopia. Letters to the Editor. *Lepr Rev*, 1981; **52:** 284–5.
[8] Brightmer MI. Personal communication, 1986.
[9] McDougall AC, Weddell AGM. The Teaching of Leprosy in Medical Schools: Four and One-Half Hours in Three Years. Correspondence. *Int J Lepr*, 1980; **48:** 329
[10] Intensification of Teaching of Leprosy to Medical Undergraduates. Report of a Symposium at MKCG Medical College, Berhampur, India, 1980.
[11] Mass Communications, Health Education and People's Participation. Report of Task Force 'D' Convenor R.H. Thangaraj. Working Group, Goverment of India, 1981.
[12] WHO. Training in leprosy. WHO document WHO/CDS/LEP/86.2. World Health Organisation, Geneva, 1986.
[13] Morley D, Savage-King F. Appropriate teaching aids. *Br Med J*, 1984; **289:** 1057–8.

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The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy

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Summary In July 1970, 362 leprosy patients, all long-term residents of Sungei Buloh Leprosarium, who had been classified as lepromatous (LL and BL according to the Ridley–Jopling classification), and who had commenced treatment with sulphones as inpatients during the years 1948–1951, were 'released from control'. During a period of follow-up observation extending over 8–9 years, 25 of these patients relapsed clinically, giving an overall relapse rate of 8·6% and an average risk of relapse of 1·04 per 100 patient-years of observation. This risk did not change significantly from year to year during the period of observation. Of eight strains of *Mycobacterium leprae* isolated from patients in relapse, five were found to exhibit some level of dapsone resistance in mice. That the risk of relapse of lepromatous leprosy after long-term monotherapy with dapsone is so small is surprising, considering the deficient immune response to *M. leprae* characteristically displayed by these patients. Despite the small risk of relapse, it is recommended that smear-negative lepromatous patients who have received long-term monotherapy with dapsone receive a course of multidrug therapy before release from control.

Introduction

Early in the history of sulphone therapy, it was accepted that lepromatous

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patients whose treatment was interrupted subsequently relapsed.[1] Nevertheless, no assessment had been made of the risk of relapse following completion of long-term treatment of lepromatous leprosy, continued for many years after smear-negativity had been achieved. Therefore, when the decision was taken to stop the administration of dapsone to 362 lepromatous patients who had received well-supervised treatment for 18·5–21 years, we undertook to conduct a long-term follow-up. It proved possible to investigate a proportion of the patients who subsequently relapsed by histopathologic examination, and by assessing the susceptibility of their strains of *Mycobacterium leprae* to dapsone. This report presents the findings upon completion of an 8- to 9-year period of observation.

Materials and methods

In 1970, all surviving permanent residents of the Sungei Buloh Leprosarium (SBL) who had been admitted between 1929, the year of its founding, and the end of 1951 were reviewed. Patients were selected who: 1, had commenced sulphone treatment during the period 1948 (when sulphones had been introduced to SBL[2]) to the end of 1951; 2, were maintained on therapy with dapsone; 3, had been clinically inactive and smear-negative for at least 5 years; 4, were not known to be dapsone resistant; and 5, had received no antileprosy drugs other than dapsone, thiacetazone, thiambutosine and streptomycin. These patients had initially been treated with one of several sulphone regimens; the majority had received dapsone, 200 mg once or twice weekly by injection for the first two months, after which the dosage was increased gradually to 300–500 mg twice weekly, whereas some patients had been treated initially with solapsone (Sulphetrone^{R}) by injection in a twice-weekly dose of as much as 5 ml (1·5 g), and some with oral solapsone, 500–1000 g during the first year.[2] Between 1952 and 1963 or 1964, the majority had been maintained on dapsone, 300–400 mg twice weekly by injection for 10–12 months each year; almost every injection had been recorded.[3] After 1963 or 1964, most patients received supervised dapsone orally in a dosage of 200 mg twice weekly; a few continued treatment with parenteral dapsone.

A total of 362 lepromatous patients, whose treatment had been stopped in July 1970, met the enumerated criteria. One-third of these patients had completed 8 years, and two-thirds 9 years of follow-up at the time the records were assembled for this analysis.

These patients had been classified as lepromatous (LL and BL)[4] according to the following criteria: 1, their pretreatment classification, recorded in 1947–1952; 2, their current clinical classification; 3, their admission smears (or immediate pretreatment smears, for those admitted before 1947); and 4, the time required to become smear-negative, according to the results of the smears that were made annually on all residents of SBL.

Records of pretreatment classification and the results of smears were available

for almost all patients, and the results of serial smears were available for most. In general, patients classified as lepromatous had been classified before treatment as 'L' or 'N?L'. Clinically, they appeared to be patients with fully treated, quiescent LL or BL leprosy. Their pretreatment smears (routinely made from both ear lobes and one additional active skin site, and scored as negative, ±, 1+, 2+ or 3+[2]) were scored as 2+ or more at all 3 sites, suggesting LL, or those from one ear and the skin site were scored as 2+ and 3+, respectively, or both were 3+, with the other ear scored as negative or weakly positive, suggesting BL leprosy.

All of the patients were followed by means of an annual full clinical examination for leprosy. Smears were taken from those found at the time of an annual examination to have clinical evidence of relapse, or who presented between annual examinations with clinical evidence of relapse. Biopsies were taken from patients who consented to the procedure, one portion of tissue being fixed for histopathological examination and the other employed fresh for isolation of *M. leprae* and testing of dapsone susceptibility by inoculation of mice.[5] The diagnosis of relapse was based on clinical findings, supported by the results of smears from the relapse lesions.

For the purpose of this analysis, the risk of relapse was calculated as the number of relapses per 100 patient-years of observation. In calculating the number of man-years of observation, patients withdrawn from follow-up because of relapse, reinstitution of treatment, or death were considered to have been withdrawn from the study in the middle of the year in which these events occurred (*i.e.* the number of man-years of observation during any year was taken as the average of the number of patients at risk of relapse at the beginning of the year and the number remaining at risk at the end of the year). Patients who were still under observation were finally assessed during the 8th or 9th year of follow-up and appear under 'Withdrawn from observation' in Table 1.

Results

The outcome of the 362 lepromatous patients studied is presented in Table 2. Twenty-five patients relapsed; 29, who were uneasy without treatment after so many years of therapy, or who were friends of patients who relapsed, insisted upon resuming dapsone treatment; 3 of these patients died during the period of follow-up, and none relapsed. Sixty-eight of the remaining patients died from intercurrent disease during follow-up.

Relapse occurred during each year of follow-up, as shown in Table 1; the risk of relapse did not vary significantly from year to year during the 8 to 9 years of observation. The cumulative rate of relapse was 1·04 per 100 patient-years of observation.

Eight of the patients who relapsed were female (32%), as were 141 (39%) of the 362 patients studied. Twenty-two of the patients who relapsed were Chinese, 3

Table 1. Sungei Buloh Leprosarium 'Release from Control' (July 1970) Lepromatous Patients—Annual incidence of relapse and other outcome during the nine-year follow-up period.

Year of follow-up	Number of patients under observation at beginning of year	Relapsed	Died	Withdrawn from observation	Patient-years of observation	Relapse rate (per 100 patient-years)
1	362	2	8	13	350·5	0·6
2	339	3	8	2	332·5	0·9
3	326	2	14	5	315·5	0·6
4	305	4	9	0	298·5	1·3
5	292	6	8	1	284·5	2·1
6	277	3	6	2	271·5	1·1
7	266	2	7	0	261·5	0·8
8	257	2	10	73*	214·5	0·8
9	172		1	1 170*	86	0·6
Total		25	71*	266	2415	
mean						1·04

* Patients analysed after 8th and 9th years of follow-up (see text).

Table 2. Sungei Buloh Leprosarium (SBL) 'Release from Control' Lepromatous Patients—Outcome at end of follow-up period.

Outcome	Number of patients for each outcome according to treatment status		
	Patients who remained off treatment	Patients who without relapsing insisted on going back onto treatment	Total
Relapsed	25	0	25
Under SBL treatment	0	24	24
In SBL, not under treatment	222	2*	224
Died	68	3	71
Discharged (not under treatment)	18	0	18
Total	333	29	362

* Two patients insisted on returning onto dapsone treatment, but then stopped for the second time.

were Indian, and none was Malay, yielding proportions that did not vary significantly from those in the entire group of patients studied. Twenty-one of the patients who subsequently relapsed had been treated initially with dapsone by injection, and 4 with solapsone. One patient initially treated with dapsone, and another with solapsone had also been treated with thiacetazone.

Most of the relapses presented clinically as a small number of asymmetric lepromatous (LL or BL) lesions, showing various degrees of activity; the clinical presentations were not dissimilar from those of relapses with dapsone resistance during dapsone monotherapy. One patient (No. 5077) developed several annular BT lesions,[6] although he had been classified as advanced lepromatous (LL_s)[7] leprosy in 1948. In the cases of those patients who underwent biopsy, histopathological examination fully supported the clinical evidence of activity. The bacteriological index of smears made from the relapse lesions varied widely from patient to patient, ranging from 0 to 5 on Ridley's logarithmic scale.[8] The morphological index (MI) varied from 0 to 33%; in general, more active lesions were associated with higher values of the MI.

Ten of the 25 patients who relapsed agreed to undergo biopsy in the Leprosy Research Unit. The susceptibility to dapsone of 7 of the strains was subsequently assessed; 3 proved to be fully susceptible, 2 were resistant at the lowest level (the organisms multiplied in mice administered 0·0001% dapsone in the diet), 1 was of intermediate resistance (multiplication occurred in mice fed 0·001% dapsone in the diet), and 1 strain was fully resistant (the organisms multiplied in the mice fed

Table 3. Clinical, histological and bacteriological findings, and their dapsone sensitivity in mice of nine lepromatous patients subjected to biopsy on relapse following 'release from control' after 19–22 years of sulphone therapy.

Patient number	Initial treatment	Year of relapse	Classification		Smears		Dapsone sensitivity of *M. leprae* in mice
			Clinical	Histological	Bacterial index	Morphological index	
10614	Solapsone	1	BL	BL	2·7	27	0·01% dapsone
6281	Inj. dapsone	3	LLs	LLs	3·0	2	NT*
10853	Inj. dapsone	4	LLs	LLs	3·1	2	Sensitive
9534	Inj. dapsone	4	LLs	BL	1·9	15	Sensitive
10027	Inj. dapsone	4	LLs	BL	1·7	0	0·0001% dapsone
8660	Inj. dapsone	4	LLs	LLs	4·0	1	0·001% dapsone
5077	Inj. dapsone	5	LLs/BT	BT	0·3	0	0·01% dapsone†
6466	Inj. dapsone	7	LLs	LLs	2·0	26	Sensitive
6978	Inj. dapsone	9	LLs	LLs	3·5	5	0·0001% dapsone

*NT = No multiplication of *M. leprae* in control mice.

† This strain of *M. leprae* was eventually isolated in 1979 and found to be resistant to 0·01% dapsone in the mouse diet.

0·01% dapsone). An additional strain (that from patient No. 5077), isolated 4 years after relapse, was also found to be fully resistant (see Table 3).

Discussion

In 1947, following his introduction of sulphones to the chemotherapy of leprosy,[9] Faget reported[10] the achievement of negative skin smears in some treated lepromatous patients. By that time, he had already learned that a smear-positive patient who stopped treatment could relapse, although the relapse sometimes occurred only after many months or years.[1] For this reason, he adopted a policy of continuing treatment for a full 12 months after the patient achieved smear-negativity. In that same year, Muir suggested[11] a similar policy, *i.e* that treatment should be continued at least until the patient had remained smear-negative for a period of 6–24 months, depending upon the severity of disease at the beginning of treatment, and upon the duration of treatment required to produce the first negative smears.

Those of Faget's patients whose smear-results are presented in the publication[10] became smear-negative after 0·5–5 years of treatment; in retrospect, therefore, the majority may be considered to have suffered from borderline-lepromatous (BL) or mild (L_1) lepromatous leprosy. (The majority of the patients in the present study suffered from moderately advanced or advanced lepromatous or BL leprosy.) Nevertheless, Erickson reported[12] that the outcomes of these patients were disappointing. Five of 11 lepromatous patients whose treatment had been stopped became smear-positive again after 0·5–3 years, of whom three showed clinical as well as bacteriological evidence of relapse, whereas none of 22 similar patients who continued treatment after becoming smear-negative showed clinical evidence of relapse, and only 1 exhibited mild bacteriological relapse 6 months after becoming smear-negative. (The possibility that sampling error might have accounted for this bacteriological relapse was not discussed.) The difference of relapse rates, 24·4 per 100 patient-years among those stopping treatment, to be compared with 1·7 per 100 patient-years among those continuing treatment, was striking. The patients who relapsed responded well to resumption of treatment. Erickson therefore recommended[12] that treatment of lepromatous patients should be continued indefinitely, although the dosage might safely be reduced once the patients had become smear-negative. His advice was accepted by Chaussinand,[13] at least for patients with advanced lepromatous leprosy, whose smears were still positive after 4–5 years of treatment.

Larger series from Africa failed to confirm Erickson's disappointing results. In 1954, Lowe reported[14] that, in a follow-up of 139 lepromatous patients, the majority of whom did not have severe involvement, who were treated with sulphones for 24–82 (mean 41) months, there were minimal clinical signs of relapse (neuritis) in only 2. Thirteen others showed only minimal bacteriological

evidence of relapse, and none exhibited both bacteriological and clinical evidence. The bacteriological findings were of doubtful significance: 5 of 6 smear-positive patients, who remained untreated, later became smear-negative again. It is difficult to interpret Lowe's findings, because, although all of the relapses occurred within the first 2 years without treatment, the mean duration of follow-up was only 22 months, and was in no case longer than 61 months. Both Davey, reporting in 1958,[15] and Browne in 1966,[16] confirmed that relapse was rare among discharged lepromatous patients, Davey stating that the relapse rate was 2·3% in 'unequivocal lepromatous cases', and higher in borderline leprosy patients.

Few other series have been published. The two best known, those of Rodriguez[17] and Quagliatto *et al.*,[18] were based only on bacteriological findings, and the majority of their patients were on continuing, if often irregular, treatment. Nevertheless, the general experience was that lepromatous patients frequently relapsed upon cessation of treatment.[19] In 1966, therefore, the World Health Organization recommended[20] that lepromatous patients becoming clinically inactive and smear-negative should be continued on full treatment for 5 years before they were 'released from control'. In 1970, influenced largely by the results of Quagliatto *et al.*,[18] the WHO recommended continuing treatment for at least 10 years.[21]

The decision, by Dr M K Bhojwani, as Director of the National Leprosy Control Centre, Sungei Buloh, to carry out the recommendation made by the WHO Expert Committee on Leprosy at its third meeting,[20] by releasing from control (*i.e.* stopping treatment of) a large group of long-treated and smear-negative lepromatous patients, provided a unique opportunity to observe the subsequent rate of relapse. Follow-up was greatly facilitated because the patients had made their homes in the SBL in the days of long-term segregation, and only 18 of the 362 moved away during the 8- to 9-year period of observation. In addition, because of their fear of leprosy, and because they had much earlier been provided with permanent homes in the SBL, the patients had no incentive to take treatment irregularly. Moreover, during the period 1948–1963, during which a majority of the patients received dapsone twice weekly by injection, irregular attenders had been quickly noted and reprimanded. Thus, these patients had, as a group, received unusually regular and well-documented treatment.

Although a word of caution appears to be in order, the significance of our findings is clear. A relapse rate of 1·04 per 100 patient-years of observation among patients with advanced lepromatous leprosy, who had been treated for about 20 years with regularly administered dapsone as monotherapy is considerably smaller than that expected, considering the persisting inability of such patients to mount an effective immune response to *M. leprae*. Of course, these results were obtained from a group of patients who had received exceptionally regular, well supervised treatment, the majority commencing treatment with dapsone in full dosage. The patients were among the first to receive dapsone in Malaysia, and therefore primary dapsone resistance was then nonexistent. Moreover, a number

of their peers had already relapsed while on treatment from the development of dapsone resistance before the institution of release from control, and had been changed to alternative treatment.[3,22] One should perhaps not expect so low a rate of relapse among similar patients whose treatment was administered in the context of the average leprosy control programme. On the other hand, the risk of relapse after release from control might well be smaller among patients who had received a course of multidrug therapy according to the recommendations of the WHO Study Group on Chemotherapy of Leprosy for Control Programmes.[23] In fact, the results of this study encourage the belief that a course of finite duration of a chemotherapeutic regimen more effective than dapsone monotherapy, especially a regimen including rifampicin, might suffice to prevent relapse in the great majority of lepromatous patients, and make achievable the goal of control of leprosy.

A final consideration is the desirability of administering an end-phase of multidrug therapy to the smear-negative patients who have been treated only with sulphones; such patients are well known to nearly all leprosy control programmes. We recommend that such patients, many of whom may have been irregularly treated in the past, should be administered a multidrug regimen for some period prior to their release from control. As the present study has demonstrated, these patients are at some risk of relapse; and some of the relapses are likely to be associated with the emergence of dapsone-resistant *M. leprae*. This has, in fact, been attempted in the Malta trial, with virtual freedom from relapse.[24]

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References

[1] Wolcott RR. Erythema nodosum in leprosy. *Int J Lepr*, 1947; **15:** 380–8.

[2] Molesworth BD, Narayanaswami PS, Simpson IA. The treatment of lepromatous leprosy with 4:4′-diaminodiphenyl sulphone in oil. *Int J Lepr*, 1949; **17:** 197–210.

[3] Meade TW, Pearson JMH, Rees RJW, North WRS. The epidemiology of sulphone-resistant leprosy. *Int J Lepr*, 1973; **34:** 684.

[4] Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr*, 1966; **34:** 255–73.

[5] Rees RJW. Drug resistance of *Mycobacterium leprae* particularly to DDS. *Int J Lepr*, 1967; **35:** 625–36.

[6] Waters MFR, Ridley DS. Tuberculoid relapse in lepromatous leprosy. *Int J Lepr*, 1979; **47:** 350.

[7] Ridley DS. Histological classification and the immunological spectrum of leprosy. *Bull World Health Organization*, 1974; 451–65.

[8] Ridley DS. Bacterial indices. In *Leprosy in Theory and Practice*. Cochrane RG, Davey TF eds, Baltimore: Williams and Wilkins, 1964; 620–2.

[9] Faget GH, Pogge RC, Johansen FA, Dinan JF, Prejean BM, Eccles CG. The promin treatment of leprosy. A progress report. *Pub Hlth Rep*, 1943; **58:** 1729–41. Reprinted in *Int J Lepr*, 1966; **34:** 298–310.

[10] Faget GH. Chemotherapy of leprosy. *Int J Lepr*, 1947; **15:** 7–14.

[11] Muir E. The sulphone treatment of leprosy. *Br Med J*, 1947; *i*: 798–801. Reprinted in *Int J Lepr*, **15:** 309–15.

[12] Erickson PT. Relapse following apparent arrest of leprosy by sulfone therapy. *Pub Hlth Rep*, 1950; **65:** 1147–57. Reprinted in *Int J Lepr*, 1951; **19:** 63–74.

[13] Chaussinand R. Aspect actuel du problème thérapeutique de la lèpre. *Bull Soc Path Exot*, 1951; **44:** 763–73. Reprinted in *Int J Lepr*, 1952; **20:** 229–38.

[14] Lowe J. The chemotherapy of leprosy. Late results of treatment with sulphone, and with thiosemicarbazone. *Lancet*, 1954; **2:** 1065–1068. Reprinted in *Int J Lepr*, 1955; **23:** 181–91.

[15] Davey TF. *In discussion*. Trans VIIth International Congress of Leprology, Tokyo, 1958, Tofu Kyokai, Tokyo; 1959, 241.

[16] Browne SG. Relapses in Leprosy: Uzuakoli Settlement 1958–64. *Int J Lepr*, 1965; **33:** 273–9.

[17] Rodriguez JN. Relapses after sulfone therapy in leprosy of the lepromatous type. *Int J Lepr*, 1958; **26:** 305–12.

[18] Quagliatto R, Bechelli LM, Marques RM. Bacterial negativity and reactivation (relapse) of lepromatous outpatients under sulfone treatment. *Int J Lepr*, 1970; **38:** 250–63.

[19] Price RB. Relapse of leprosy in American Samoa. *Amer J Trop Med Hyg*, 1959; **8:** 358–63.

[20] WHO Expert Committee on Leprosy. Third report. Technical Report Series, 1966; 319.

[21] WHO Expert Committee on Leprosy. Fourth report. Technical Report Series, 1970; 459.

[22] Pearson JMH, Rees RJW, Waters MFR. Sulphone resistance in leprosy. A review of one hundred proven clinical cases. *Lancet*, 1975; **ii:** 69–72.

[23] WHO Study Group. Chemotherapy of leprosy for control programmes. Technical Report Series, 1982; 675.

[24] Jopling WH, Ridley MJ, Bonnici E, Depasquale G. A follow-up investigation of the Malta-Project. *Lepr Rev*, 1984; **55:** 247–53.

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Implementation of multidrug therapy in the ALERT Leprosy Programme in the Shoa Region of Ethiopia. First results with paucibacillary patients

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Summary Multidrug therapy (MDT) was introduced in the ALERT Leprosy Control Programme in January 1983, using the regimens recommended by the World Health Organization (WHO). During the period 1 January–30 June 1983 1684 paucibacillary patients started their course of MDT in two districts in the north-eastern part of the Shoa Region. 1501 patients (89·1%) completed their 6-month course of treatment within a period of 9 months. Although there are some communication problems in the area the implementation of MDT with a once monthly supervised component has proved to be feasible; in only 1 of the 65 clinics which were involved did less than 70% of the patients complete their course of MDT.

This paper discusses the results of implementation of MDT for paucibacillary patients.

Introduction

The ALERT Leprosy Control programme is responsible for the leprosy control activities in the Shoa Administrative Region. This region is located centrally in Ethiopia with Addis Ababa as its capital; it covers 85,500 sq km with a population of 8·75 million.

There are 296 leprosy treatment centres in the region; 170 are attached to the general medical services and 126 are leprosy clinics which have been established in those areas where as yet no general medical service exists. Fifty percent of the leprosy centres are accessible by car throughout the year; 32% are accessible by car only during the dry season and 18% can be reached only on foot or on muleback. Almost all clinics are conducted by special leprosy staff. The majority of them are health assistants who, besides a general medical training, have received special training in leprosy. At the beginning of 1983 the number of leprosy patients registered in the region was 19,498.

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Multidrug Therapy (MDT) is being introduced gradually into the region. In January 1983 the introduction of MDT started in the north-eastern part of the region and involved both paucibacillary and multibacillary patients. In this paper the first results of implementation of MDT for paucibacillary patients are discussed. Paucibacillary patients are defined as those patients who are clinically TT, BT and I, according to the Ridley–Jopling Classification, and who have a Bacteriological Index (BI) of less than 2 at any site and at any time.

The MDT regimen recommended by the World Health Organization (WHO)[1] for paucibacillary patients is given to patients: 600 mg rifampicin, every 4 weeks under supervision, and 100 mg dapsone daily, self-administered; for 6 months. In September 1983 it was decided that the 6 months of treatment should be completed in a period not exceeding 9 months.

The MDT programme in the Debre Berhan area

The Area

The Debre Berhan area consists of Tegulet & Bulga, Yifat & Timuga and Menz & Gishe districts. In January 1983 the MDT programme was launched in the 37 clinics of Tegulet & Bulga, the 27 clinics of Yifat & Timuga and in 1 clinic of Menz & Gishe districts. The population of the area covered is about 920,000; geographically most of the people live in the depths of the valleys.

The 65 clinics are 2 hospital clinics, 3 health centres, 27 health stations and 33 leprosy clinics. Thirty clinics are accessible by car throughout the year; 18 clinics (7 health stations and 11 leprosy clinics) are accessible by car only during the dry season and 17 clinics (3 health stations and 14 leprosy clinics) can be reached only on foot or on muleback. Twenty-eight clinics are conducted at weekly intervals, 31 clinics at fortnightly intervals and 6 clinics once every 4 weeks.

The resources

The following resources were available in the area.

Manpower: 1 field coordinator, in charge of the programme; 1 senior supervisor; 2 acting supervisors; 9 health assistants, 3 staff of the Extended Programme of Immunization (EPI); 1 clerk; and 2 drivers.

In November 1983 the field coordinator was withdrawn from the area after he had initiated and supervised the initial phases of implementation of the programme. In March 1984 1 acting supervisor and 1 driver were transferred to Addis Ababa.

Transport: At the start of the programme 3 cars were available; after a few months 2 additional cars were made available. One of the additional cars was withdrawn with the field coordinator and one with the acting supervisor.

The patients

Two-hundred-and-two patients were excluded from MDT, mainly due to old age, severe disabilities or working conditions, or because they were unable to attend every 4 weeks for the supervised treatment. Two patients were excluded because of irregular attendance for anti-tuberculosis treatment.

Twenty-six patients were released from dapsone monotherapy prior to the introduction of MDT. Release criteria were based on the recommendations made by the WHO Expert Committee in its fourth report (No. 459, 1970).[2] However, as many patients had not been reviewed regularly, it appeared impossible to apply these criteria. It was then decided to put all paucibacillary patients, who were able to attend the clinics every 4 weeks, on MDT.

During the first 6 months of 1983 1766 paucibacillary patients started their 6-months' course of MDT. Due to positive skin smear results, 82 patients who were initially classified as paucibacillary, were reclassified as multibacillary patients, 2–4 months after the start of MDT. Their treatment was changed accordingly. For the remaining 1684 patients the period of dapsone monotherapy prior to MDT is given in Table 1.

Patients who were noncompliant were pursued by contact with the Farmers' Associations and personal visits by other patients. Patients who had completed their course of MDT before September 1983 were given a release from treatment certificate and were told to come back at any time if they experienced problems or developed a new activity of the disease. From October 1983 patients were given appointment dates for follow-up examinations after release from MDT. Patients who were released prior to this date were instructed through other patients to come for regular follow-up examinations.

Reorganization of the leprosy control activities in the area

Before MDT was introduced all patients were clinically examined and for those

Table 1. Period of dapsone prior to MDT

Period of dapsone	No. of patients
None	95/74 BT, 21 TT
−2 yr	212
2–5 yr	341
> 5 yr	804
Unknown	232

who did not have a clinical record card one was filled in with the clinical signs noted at the time of assessment.

The clinical classifications which were available were checked with previous recorded and present signs. Patients classified as B were reclassified BT or BL. In order to be on the safe side a small number of B patients who could not be reclassified were classified BL.

Skin smears from paucibacillary patients were only taken 2–4 months after the start of MDT. Because of positive skin smear results 82 patients were reclassified as multibacillary patients. A central register was prepared in which all patients who were put under MDT were entered. Treatment register, patients record cards and other recording systems which were already in use in the dapsone monotherapy programme were adapted for the MDT programme.

At the start of MDT detailed instructions for implementation had not been formulated. In October 1983 a 'Manual for implementation of Multiple Drug Therapy (MDT) in Ethiopia'[3] was prepared by senior staff of the National Leprosy Control Programme and the ALERT Leprosy Control Programme; in cooperation with a short-term WHO consultant. After the manual was finalized the recording and reporting systems described in the manual were introduced. The staff received additional training concerning the new regimens, organizational, recording and reporting aspects. It was decided that only a limited number of the staff, the supervisors and a few experienced health assistants, should be made responsible for giving out the supervised treatment. A small stock of drugs was given to all staff in order to ensure that patients would receive their treatment if a supervisor or one of the other assigned staff could not attend the clinic. In all clinics the supervised treatment is given out once every 4 weeks. Patients who fail to attend during those days can still receive the rifampicin up to 2 weeks after the scheduled clinic days and the dapsone at any time. In weekly and fortnightly clinics the other 3 or 1 clinic day(s) are for late comers, for patients who have problems, for those who need care for disabilities and for health education activities in the communities.

Clinical assessment of patients at the end of the treatment period was done only by supervisors, who also decided about release from treatment or discontinuation of the treatment in cases of irregularity of attendance.

Patients who developed complications which required hospital admission were seen by a supervisor, either at the clinic or at the area headquarters, before they were referred to the ALERT Hospital.

Prior to the start of MDT extensive health education was given to the patients concerning the new treatment. Furthermore, health education campaigns were organized in villages, during meetings with the Farmers' Associations and during political meetings.

Results

An analysis of the completion of the treatment of the 1684 patients who started their course of MDT during the period 1 January–30 June 1983 is given in Table 2. The 1501 patients who completed their course of MDT within a period of 9 months include 86 of the 95 patients who did not receive dapsone monotherapy prior to MDT. Information about the percentages of patients who, after different periods of dapsone monotherapy, completed their course of MDT was not collected.

An analysis of the percentages of the patients who completed their course of MDT in the 65 clinics is given in Table 3. As we were interested to know whether accessibility of the clinic, type of clinic, frequency of leprosy clinic days and the number of patients on treatment, related to the percentages of patients who completed their course of MDT, further analyses were made (Tables 4, 5, 6 and 7). With the use of the variance analysis test no statistically significant relation could be found between these factors and the percentage of successful completion of treatment.

In the field 4 BT patients were diagnosed with a reversal reaction involving the nerves. None of them had received dapsone monotherapy prior to MDT. Two patients developed the reversal reaction while on MDT, and 2 patients after release from MDT. In none of the patients who had received dapsone monotherapy prior to MDT was a reversal reaction diagnosed. Severe side-effects of the drugs were not reported in the group of 1684 paucibacillary patients.

We expect that because more than 90% of these patients reported themselves with leprosy in the past, they will also do so in the case of renewed activity of the disease. So far about 9% of the patients who were expected for follow-up examination have come once or twice after their release from MDT. One BT patient who did not receive dapsone prior to MDT and who developed a reversal reaction $2\frac{1}{2}$ months after release from treatment, was diagnosed as a relapse patient in the hospital. Our experienced clinical staff however, are of the opinion that this patient did not have a relapse. The severe drought situation, which has affected main parts of the Debre Berhan area, definitely contributes to the low attendance after release from treatment. Accessibility of the clinic, types of clinic, frequency of leprosy clinic days and the number of patients on treatment did not show a statistically significant relation with the percentages of patients who completed their course of MDT. At the same time that the backlog of multibacillary patients are released from MDT, the number of patients under leprosy treatment will be reduced by about 80%. However, regular follow-up examinations of patients after their release from treatment and the care for patients with disabilities of whom all but a few will not be under leprosy treatment any more, will continue to keep the workload high during the coming years.

The picture of long lines of patients waiting for their treatment belongs to the past, some years after the introduction of MDT. It seems logical that more

Table 2. Analysis of the completion of MDT

	Tegulet & Bulga		Yifat & Timuga		Total	
	No. patients	(%)	No. patients	(%)	No. patients	(%)
Patients who started MDT	814	100	870	100	1684	100
Patients who completed MDT	733	90·0	768	88·3	1501	89·1
Patients whose treatment was stopped, due to irregularity of attendance	64	7·9	93	10·7	157	9·3
Patients who died	7	0·9	5	0·6	12	0·7
Patients who were transferred to a non-MDT clinic	10	1·2	4	0·4	14	0·8

Table 3. Percentage completion of MDT in the 65 clinics

Completion of treatment (%)	No. of clinics
100	18
91–99	14
81–90	22
71–80	10
61–70	1

Table 4. Percentage completion of treatment and accessibility

Completion of treatment	No. of clinics accessible whole year	No. of clinics accessible in dry season	No. of clinics not accessible
100	9	2	7
91–99	5	6	3
81–90	10	7	5
71–80	6	2	2
61–70	—	1	—

Table 5. Percentage completion of treatment and type of clinic

Completion of treatment	Hospitals Health Centres	Health Stations	Leprosy Clinics
100	2	7	9
91–99	2	5	7
81–90	1	11	10
71–80	—	4	6
61–70	—	—	1

Table 6. Percentage completion of treatment and frequency of leprosy clinic days

Completion of treatment (%)	Weekly	Fortnightly	Monthly
100	5	10	3
91–99	8	6	—
81–90	12	9	1
71–80	3	6	1
61–70	—	—	1

Table 7. Percentage completion of treatment and number of patients on MDT

Completion of treatment	No. clinics 0–9 patients	No. clinics 10–19 patients	No. clinics 20–29 patients	No. clinics 30–39 patients	No. clinics ⩾40 patients
100	9	7	1	1	—
91–99	—	2	3	5	4
81–90	1	2	5	8	6
71–80	4	2	2	—	2
61–70	—	1	—	—	—

attention is paid to an active approach towards prevention of severe disabilities in patients who have a slight or moderate disability at the time of release from treatment; while continuing to give high priority to controlling the disease in the communities. Furthermore, for reasons of cost, consideration should be given to decreasing the frequency of leprosy clinic days. The results that the frequency

with which leprosy clinics are conducted did not show a statistically significant relation with the percentage of patients who completed their course of MDT deserve careful consideration.

In the group of 74 BT patients who did not receive dapsone monotherapy prior to MDT 4 patients were diagnosed with a reversal reaction which involved the nerves. In the group of patients who received dapsone prior to MDT no reversal reactions were reported. It should be kept in mind that in some patients a reversal reaction could have been missed, especially in those patients who did not complete their course of MDT. It is too early yet to draw conclusions about the occurrence of reversal reactions during and after MDT. More patients should be followed up in a carefully designed and regularly supervised study.

We plan to start soon a study on the occurrence of reactions in patients who receive MDT only. It has been our experience that the preparation of detailed guidelines about the different aspects of MDT, before MDT is implemented, is of extreme importance in order to guarantee smooth running of the programme. In our situation such guidelines were prepared 9 months after the introduction of MDT. However at that time most of the operational weaknesses could be corrected.

Incomplete recording of clinical signs and classification in the past, together with the fact that during the dapsone era skin smears were not routinely examined from all patients at the start of their treatment, made it impossible to get the right classification of all patients at the time of assessment for MDT.

It cannot be overstressed that with the introduction of MDT correct classification of patients is essential. For this, skilled and experienced staff are a must, as are sufficient laboratory facilities for examination of skin smears, including a built-in system of quality control.

Discussion

The results show that implementation of MDT for paucibacillary patients has been successful in the Debre Berhan area; 89·1% of the patients who started MDT during the period 1 January–30 June 1983 completed their 6 months' course within a period of 9 months. No difference was found between the percentages of patients who did not receive dapsone monotherapy prior to MDT as compared to patients who received dapsone. Despite communication problems in the area, implementation of MDT with a monthly supervised component has proved to be feasible; in only 1 out of the 65 clinics did less than 70% of the patients complete their course of MDT.

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References

[1] WHO Technical Report Series No. 675, 1982.
[2] WHO Technical Report Series No. 459, 1970.
[3] Manual for Multiple Drug Therapy (MDT) in Ethiopia, National Leprosy Control Programme, 1983.

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Monitoring dapsone self-administration in a multidrug therapy programme

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Summary In the ALERT Leprosy Control Programme implementation of multidrug therapy (MDT) started in January 1983. The majority of the patients had received dapsone monotherapy prior to MDT. To assess the intake of dapsone in the MDT programme the urine spot test is done in all the paucibacillary patients during the 4th and 6th supervised treatment day; with the multibacillary patients during the 4th, 6th, 12th, 18th and 24th supervised treatment. Results of the 4th and 6th treatment round are presented and discussed.

Of the 721 patients tested the overall percentage of patients with a positive test was 90·9%. Patients with a previous duration of treatment of more than 3 years were found to be significantly less compliant than others. Determinants like age, sex, disability grade or having a leprosy contact in the family did not influence compliance in a significant way.

Introduction

In leprosy control programmes patients on dapsone monotherapy are regarded as regular attenders if they have collected 75% or more of the tablets they were expected to collect during a year. The collection of drugs for self-administration (attendance) is generally used as a measure for drug intake (compliance) by the patients. However compliance studies by way of urine testing for the presence of dapsone in several countries showed that only 40–70% of the patients had taken the drug before attending the clinic.[1–14] One of the reasons for treatment failure with dapsone has been the irregularity of drug intake.

In the ALERT MDT programme the WHO recommended regimens have been introduced.[15] These are:

Paucibacillary leprosy—rifampicin 600 mg once a month, supervised, for 6

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months; and dapsone 100 mg daily for 6 months, self-administered.
Multibacillary leprosy—rifampicin 600 mg once a month, supervised; dapsone 100 mg daily, self-administered; and clofazimine 300 mg once monthly, supervised, and 50 mg daily, self-administered.

For paucibacillary patients the attendance for supervised treatment is the most important factor to determine whether a patient should be regarded as cured. They can be released from chemotherapy after having collected 6 doses of supervised treatment and the 6 months of dapsone for daily self-administration within a period of 9 months.[16] Multibacillary patients have to continue MDT for at least 2 years and until their skin smears are negative.[15] They have to collect the 24 doses of supervised treatment and the daily dapsone and clofazimine for self-administration within a period of 36 months.[16]

For the group of patients who received monotherapy prior to MDT, the regularity of attendance is the important criterium for release, as the majority of them will have had negative skin smears already at the start of MDT. Compliance in MDT is even more critical than in dapsone monotherapy because irregularity of drug intake may result in unmanageable situations, i.e. multiple resistance. The WHO Studygroup stresses that 'to maintain regular drug intake has now become a managerial task par excellence and needs priority attention'.[15] The International Federation of Anti-Leprosy Associations (ILEP) asks, in its publication *The introduction of multidrug therapy in leprosy*[17] for special evaluation studies, among which is the testing of compliance to monitor the intake of the drugs prescribed.

Objectives of this study

The objectives of this study are: to get information on whether or not patients take the unsupervised component (dapsone) of MDT; and to obtain determinants of patients' compliance behaviour.

At ALERT the spot test has been introduced to detect dapsone in urine. It was described in 1965 by de Castro and recommended by WHO in 1966 but has, despite its simplicity, not been used widely in the field, apart from India.[12,13,21–25] The test was found insensitive by some[20] but more recently a good correlation with the dapsone/creatinine method was reported.[13,24,25]

For clofazimine, the second unsupervised drug in multibacillary leprosy, no satisfactory test has been developed yet. However, we may probably assume that in most cases dapsone intake means clofazimine intake as well, especially because many leprosy patients have lost faith in dapsone and show a tendency to consume capsules.[18] Therefore it is likely that clofazimine has been taken when the urine test is positive for dapsone.[19] Furthermore our impression was that the vast majority of patients showed a distinct clofazimine discoloration of the skin, of

which only a few have complained so far. In the MDT programme the spot test is done during the 4th, 6th, 12th, 18th and 24th supervised treatment round. This publication gives the results of the 4th and 6th treatment round and is the first to report on compliance testing by way of the urine spot test in an MDT programme.

Patients and methods

All patients who started MDT in the 13 Addis Ababa town clinics during the period May–July 1984 and in the 11 clinics of Yerer & Kereyu area during June and July 1984 were included. Surprise home visits were not done as they are not feasible in the field and moreover were not found to render significantly different results as compared to routine clinic visits.[11]

The urine of 721 patients was tested on the 4th and 6th supervised treatment round. Patients who did not attend during the scheduled clinic days were not included. However, most patients who did not attend during the scheduled day, came one or more days later. Also excluded were patients who were absent in the treatment round prior to the test (18), and patients who had a dapsone allergy (2) or could not pass urine (3). The spot test is done by pipetting a drop of fresh urine on filter paper impregnated with modified Ehrlich's reagent. When dapsone is present, an inner spot of orange to yellow colour appears; a yellow ring in the periphery is due to urea. A very faint orange spot was recorded as $\pm$ but considered as positive. In the case of a negative test a drop of 1N HCl was added to the urine specimen and the test was repeated to exclude false negatives. Because of instability of the solution a positive control could not always be included. However, we did not experience any problem in reading the results. Recently a stable positive control solution was developed.[19] We may reasonably assume that our + and $\pm$ group is identical with the positive category as indicated by the positive control solution mentioned.

A positive test means that on average dapsone was taken 4 days ago but probably no more during the last 3 days before testing. A negative test indicates that dapsone was not taken according to schedule and possibly so long ago that the blood level has fallen below the MIC.[19]

Information was collected from each patient about sex, age, classification, leprosy contact in the family, disability grade and duration of previous treatment.

Table 1. Attendance rates and urine test results in 13 Addis Ababa town clinics.

Treatment round	Patients expected	Patients attended	%	Urine tested	Urine pos.	%	Urine ±	%	Urine neg.	%
4th	568	500	88·0	494	415	84·0	44	8·9	35	7·1
6th	582	481	82·6	473	396	83·7	22	4·7	55	11·6

Results and discussion

Tables 1 and 2 show the test results. On average, 85·0% of the patients who were expected during the supervised treatment day attended. The percentage of attenders with a positive test ranged from 88·4 to 93. When nonattenders are included in the denominator the minimal range of positive tests still varies

Table 2. Attendance rates and urine test results in 11 clinics in Yerer & Kereyu area.

Treatment round	Patients expected	Patients attended	%	Urine tested	Urine pos.	%	Urine ±	%	Urine neg.	%
4th	148	121	81·8	114	98	86·0	8	7·0	8	7·0
6th	165	142	86	142	126	88·7	3	2·1	13	9·2

Table 3. Data of patients with a positive and negative urine test

	Addis Ababa				Yerer/Kereyu			
	Positive		Negative		Positive		Negative	
	n	(%)	n	(%)	n	(%)	n	(%)
Classification								
Multibacillary	286	(60·3)	60	(73·2)	94	(64·8)	12	(60)
Paucibacillary	188	(39·7)	22	(26·8)	51	(35·2)	8	(40)
Total	474	(100)	82	(100)	145	(100)	20	(100)
Sex								
Female	247	(52·1)	41	(50)	44	(30·3)	8	(40)
Male	227	(47·9)	41	(50)	101	(69·7)	12	(60)
Total	474	(100)	82	(100)	145	(100)	20	(100)
Age								
<15	21	(4·4)	5	(6·1)	5	(3·4)	0	
15–45	361	(76·2)	62	(75·6)	100	(69·0)	16	(80)
45+	92	(19·4)	15	(18·3)	40	(27·6)	4	(20)
Total	474	(100)	82	(100)	145	(100)	20	(100)
Disability grade								
0–1	339	(71·5)	55	(67·1)	100	(69·0)	14	(70)
2–3	135	(28·5)	27	(32·9)	45	(31·0)	6	(30)
Total	474	(100)	82	(100)	145	(100)	20	(100)
Contact in family	47	(9·9)	10	(12·2)	19	(13·1)	1	(5)

Table 4. Duration of treatment in relation to compliance (Addis Ababa and Yerer & Kereyu combined).

Duration of treatment	Positive test n	%	Negative test n	%
less than 1 year	46	(7·5)	3	(2·9)
1–3 yr	188	(30·6)	16	(15·7)
3–5 yr	115	(18·7)	29	(28·4)
5+ yr	265	(43·2)	54	(52·9)
Total	614	(100)	102	(100)

between 72 and 81%. Tables 3 and 4 contain general data on compliant patients, as well as data for the patients who were negative once (92) or twice (10). A statistically significant relationship was found between noncompliance and duration of treatment prior to MDT longer than 3 years ($p < 0{\cdot}01$ in χ^2 test). Paucibacillary patients were more compliant than multibacillary patients ($p = 0{\cdot}10$). A significantly reduced compliance in patients under the age of 15 or above 45 was not observed, nor did we find a correlation between compliance and sex, disabilities or having a leprosy contact in the family.

A number of studies have dealt with the relationship between patients' variables and compliance.[3,9,11–13,24,26] The picture emerging from it is not uniform, but most authors have agreed on the following conclusions, of which the first was confirmed also in this study:

1 Patients with a long duration of treatment are less compliant. Associated with this is the observation that patients on the lepromatous side of the spectrum (who tend to have been treated longer) are less compliant than those on the tuberculoid side.
2 Patients younger than 15 years and older than about 45 are less compliant.

Some authors found a negative relationship between compliance and having a leprosy contact, having disabilities and being a female, while others could not confirm this.

Conclusions and recommendations

The intake of dapsone in the ALERT MDT programme as measured by way of the urine spot test appears to be very encouraging, especially when compared to

the 60% compliance in the monotherapy era.[10] Among others it indicates the enthusiasm of both patients and staff for the new programme.

The relationship between noncompliance and a long history of treatment has been confirmed in this study. Sex, age, disability grade and a contact in the family were not found to be important determinants. It is recommended that feedback of the test results is given to the patients afterwards. In the ALERT programme this was done by the supervisors in the health education talk and this was very satisfactory. Individual feedback was occasionally given, mostly to the patients who had been negative twice.

The urine spot test will be incorporated in the routine work of the field staff during the next treatment rounds. This is highly recommended also for other control programmes. The spot test is sufficiently sensitive, it is cheap ($0·2/100 tests), but above all it is simple enough to perform on the spot in the field.

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We would like to thank the staff of the ALERT Leprosy Control Department and the laboratory for their kind cooperation; Hubert van Dijk, Dutch medical student, for initiating the testing; Hans A Valkenburg, Professor of Epidemiology in Rotterdam and Han Huikeshoven, Royal Tropical Institute, Amsterdam for their valuable comments. Financial aid was received from the QM Gastmann-Wichers stichting.

References

[1] Low SJM, Pearson JMH. Do leprosy patients take dapsone regularly? *Lepr Rev*, 1974; **45:** 218–23.

[2] Ellard GA, Gammon PT, Harris JM. The application of urine tests to monitor the regularity of dapsone self-administration. *Lepr Rev*, 1974; **45:** 224–34.

[3] Jesudasan K, George B, Chacko CJG, Taylor PM, Kurian PV, Job CK. An evaluation of the self-administration of DDS in Gudiyatham Taluk. *Lepr India*, 1976; **48:** 668–76.

[4] Huikeshoven HCJ, Honhoff C, Van Eys GJJM, Anten JGF, Mayer JMA, Van Helden HPT. Weekly self-medication of leprosy patients monitored by DDS/creatinine ratios in urine. *Lepr Rev*, 1976; **4;** 201–9.

[5] Balakrishnan S. Monitoring self-administration of dapsone by patients. *Lepr India*, 1977; **49:** 364–71.

[6] Gyi KM, Lwin MM, Myaing YY, Oo KM, Shwe T. Reliability of dapsone self-administration in the Rangoon area. *Lepr Rev*, 1978; **49:** 283–6.

[7] Naik SS. Irregularity of dapsone intake in infectious leprosy patients attending an urban treatment centre. Its magnitude and causes. *Lepr India*, 1978; **50:** 45–53.

[8] Nigam P, Siddique MIA, Pandey NR, Awasthi KN, Sriwastava RN. Irregularity of treatment in leprosy patients. Its magnitude and causes. *Lepr India*, 1979; **51:** 521–32.

[9] Hagan KJ, Smith SE, Gyi KM, Lwin MM, Myaing YY, Oo KM, Shwe T, Tin KM, Than KN, Hla T, Kywe WW. The reliability of self-administration of dapsone by leprosy patients in Burma. *Lepr Rev* 1979; **50:** 201–11.

[10] Ellard GA, Pearson JMH, Hale GS. The self-administration of dapsone by leprosy patients in Ethiopia. *Lepr Rev*, 1981; **52:** 237–243.

[11] Cates CJ. An assessment of dapsone self-administration in Gudiyatham Taluk. How should urinary dapsone/creatinine ratios be used? *Lepr Rev*, 1981; **52:** 55–64.

[12] Kumar A, Balakrishnan S. Monitoring the regularity of self-administration of dapsone by leprosy patients. *Lepr India*, 1982; **54:** 664–70.

[13] Kumar A. Treatment compliance by leprosy out-patients and its monitoring under field condition. *Ind J Lepr*, 1984; **56:** 313–18.

[14] Huikeshoven HCJ. Editorial. *Int J Lepr*, 1981; **49:** 228–58.

[15] *Chemotherapy of leprosy for control programmes*; WHO Technical Report nr. 675; 1982.

[16] Manual for implementation of multidrug therapy in ALERT; first revised version; 1984.

[17] *The introduction of multidrug therapy for leprosy*; ILEP 1983.

[18] Naik SS, Revankar CR, Ganapati R, quoted in 19 as personal communication.

[19] Huikeshoven HCJ. A simple urine spot test to monitor dapsone self-administration. Its potential value in leprosy control programmes. *Dissertation*, London School of Hygiene and Tropical Medicine, 1984.

[20] Ellard GA, Gammon PT, Helmy HS, Rees RJW. Urine tests to monitor the self-administration of dapsone by leprosy patients. *Am J Trop Med Hyg*, 1974; **23:** 464–70.

[21] Balakrishnan S. Application of a spot test for detection of DDS in urine. *Lepr India*, 1968; **40:** 1–5.

[22] Balakrishnan S. A note on the screening for DDS in urine by spot test. *Lepr India*, 1969; **41:** 77–8.

[23] Noordeen SK, Balakrishnan S. Spot test for DDS in urine under field conditions. *Ind J Med Res*, 1972; **60:** 367–71.

[24] Kumar A, Balakrishnan S. Operational study to monitor the regularity of dapsone intake by leprosy out-patients. *Lepr India*, 1983; **55:** 521–7.

[25] Irudaya Raj PP, Lourdumary S, Aschoff M, Balakrishnan S. A comparison of screening tests for dapsone in urine. *Lepr India*, 1983; **55:** 528–38.

[26] Hertroijs AR. A study of some factors affecting the attendance of patients in a leprosy control scheme. *Int J Lepr*, 1974; **42:** 419–27.

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A preliminary study on serological activity of a phenolic glycolipid from *Mycobacterium leprae* in sera from patients with leprosy, tuberculosis and normal controls

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Summary In this article, we conducted: 1 Study on comparisons of serological activity between phenolic glycolipid (PG1) and its terminal sugar which was a synthetic antigen conjugated to bovine gamma globulin. The sera for comparison were collected from leprosy patients (182 cases), tuberculosis patients (20 cases), and normal persons (108 cases, in non endemic area of leprosy). The results indicated that there was highly significant positive correlation (correlation coefficient, $r=0.72$ $p<0.0005$) between PGl and M–BGG (monosaccharide conjugated to bovine gamma globulin) antigens and their OD values in sera from normal persons similar to those of sera from tuberculosis patients. These suggested that PGl–ELISA and M–BGG–ELISA were highly specific for detection of infection with *Mycobacterium leprae*. When comparison tests of PGl–ELISA with ML–ELISA were performed, similar sensitivity of the two tests to sera from leprosy patients was found. These tests suggested that PGl–ELISA and M–BGG–ELISA were as highly sensitive as ML–ELISA to sera from leprosy patients. For these reasons, PGl– and M–BGG–ELISA, were both considered highly sensitive and specific for detection of infection with *M. leprae*. 2 Study on correlation of PGl–ELISA with ML–ELISA and FLA–ABS.T. The results indicated that they were also highly significant in positive correlation (correlation coefficient, rFLA–ABS.T $=0.945$ $p<0.01$; rML–ELISA $=0.972$ $p<0.005$). 3 Study on blocking nonspecific binding. Preliminary studies indicated that conventional BSA and GS could be replaced with EA. The efficiency of EA was not only equal to BSA and GS, but also easier to use, much cheaper and easier to get. Therefore, authors suggested popularizing application of EA for blocking nonspecific binding to ML–ELISA and PGl–ELISA or M–BGG–ELISA.

Introduction

The important problem in study of epidemiology in leprosy is the lack of reliable

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technology for detecting subclinical infection with *Mycobacterium leprae* (ML) and early serodiagnosis of leprosy. It has been well known that FLA–ABS test (FLA–ABS.T) first established by Abe[1] was demonstrated as a tool for the above-mentioned purposes.[2] Recently, however, a new simple rapid sensitive and quantitative technology enzyme-linked immunosorbent assay (ELISA) has been developed and widely used in the determination of human humoral antibodies. On the other hand, it has shown that phenolic glycolipid (PGl), a major component of capsule surrounding ML in infected cells,[3,4] represents the only ML-specific antigen currently available in amounts sufficient for use in large-scale serological screening[5] and its terminal sugar (M–BGG) has been synthesized.[6] At the base of these, the studies on immunodiagnostic of leprosy are increasing rapidly. The present paper describes the relevant results of PG and its terminal sugar, including the blocking agents, with ELISA, and the comparison of PG–ELISA with FLA–ABS.T in our laboratory.

Materials and Methods

Antigen preparation. The antigen for FLA–ABS.T is prepared with Wu's technology;[7] PGl and M–BGG are conveyed to us by Dr Douglas.

Sera (first antibody). Sera from 182 cases of leprosy patients, 20 cases of active tuberculosis patients and 108 cases of healthy persons (nonendemic area of leprosy), and sera for positive and negative control.

Enzyme and fluorescein conjugates (secondary antibody). FITC–IgG was provided by Dr Abe; HPO–IgGMA was provided by Dr Douglas.

Detection of antibodies. It was conducted with Abe's FLA–ABS.T[8] and Douglas' ELISA[9] which can be stated briefly as follows: 0·05 ml suspension of antigen was dried onto 'U' bottom microtitre plates. Antigen-coated wells were blocked to prevent nonspecific binding by adding 0·075 ml of 5% goat serum (GS) in phosphate buffer saline (PBS), pH 7·2 and incubated overnight at 4°C. After aspirating the blocking agents, 0·075 ml of serum diluted 1 : 200 in PBS containing 1% GS was added to duplicate wells and incubated for 1 hr at 37°C. After three times washed with PBS, HPO–IgGAM (0·075 ml of 1 : 2000, diluted with PBS containing 1% GS) was added and incubated 30 min at 37°C. Plates were washed three times with PBS and 0·075 ml of substrate (0·003% hydrogen peroxide) and colour reagent (0·01% o-phenylenediamine) in citrate buffer (pH 5·0) were added and incubated in the dark for 30 min at 37°C. The reaction was stopped by the addition of 25 μl of 4N H_2SO_4 and read at 490 nm. The test results are reported as the average of duplicate wells. If the difference in OD values of the duplicate wells exceeded 10% of the mean, the test was repeated.

In the tests for comparison of agents blocking, 5% GS, 5% bovine serumalbumin (BSA), 20% egg-white albumin (EA) and 1% GS, 1% BSA, 5% EA were used in the same plates, and preliminary studies indicated that egg-white

albumin was at least as efficient as a blocking agent as either goat serum or BSA. Because it is cheaper and more widely available we subsequently used 20% EA as a blocking agent in the ELISA system. The normal values were calculated with Douglas' formula[9] as follows:

Negative upper limit (NUL) = OD value of negative control + 0·08D
D = OD value of positive control − OD value of negative control.

On the other hand, we have done Chi-square (X^2) test, correlation analysis and regression analysis, including significance test of correlation coefficient.

Results

The results of our tests are shown in Figures 1, 2, 3 and 4 and Table 1. Figures 1 and 3 were used to show individual OD values for ELISA tests against the various classification groups (LL, BL, BB, BT, TT, TB controls, normal controls). Each point represents one individual and the antibody level is expressed as OD value at 490 nm. The short bar in column of each group represents the mean OD value (M_{OD}) of each group.

Figure 1(a) shows the results of ML–ELISA. The positivity rates of various groups are: LL 100% (M_{OD} 0·47), BL 90% (M_{OD} 0·44), BB 100% (M_{OD} 0·46), BT 95.80% (M_{OD} 0·48), TT 75% (M_{OD} 0·36) and Normal controls 1% (M_{OD} 0·23); Figure 1(b) shows the results of PGl–ELISA. The positivity rates of various groups are: LL 86·6% (M_{OD} 0·47), BL 93·5% (M_{OD} 0·44), BB 93·3% (M_{OD} 0·35), BT 75% (M_{OD} 0·34), TT 33·3% (M_{OD} 0·20) and Normal controls 2% (M_{OD} 0·17).

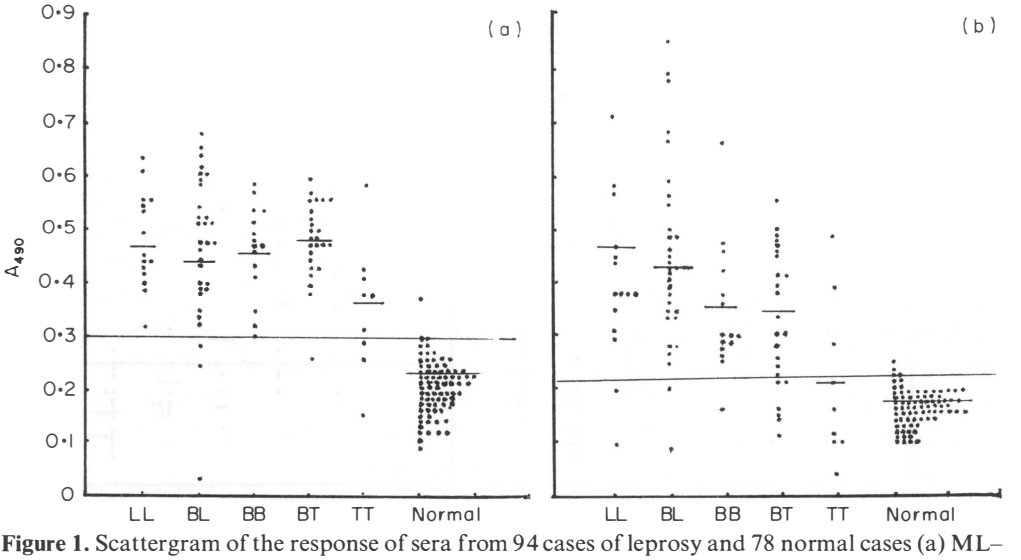

Figure 1. Scattergram of the response of sera from 94 cases of leprosy and 78 normal cases (a) ML–ELISA, (b) PGl–ELISA.

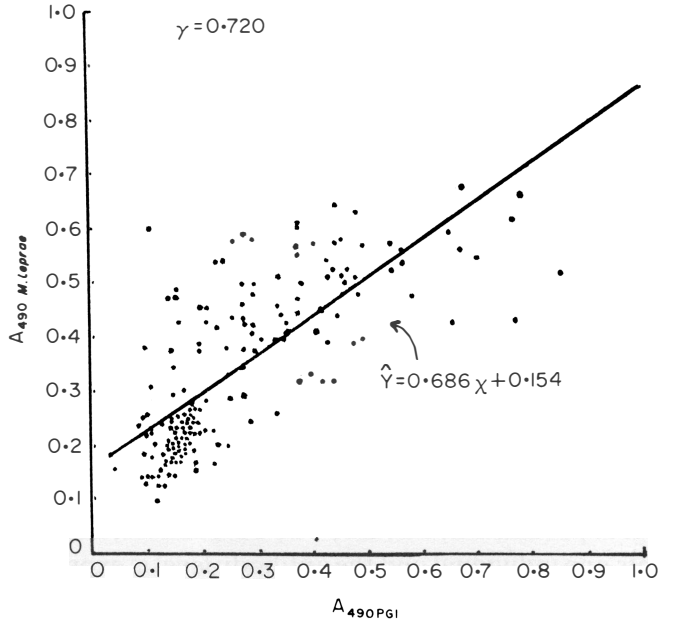

Figure 2. Correlation between ELISA values to the *M. leprae* and PGl in sera from leprosy patients (94) and normal controls (78).

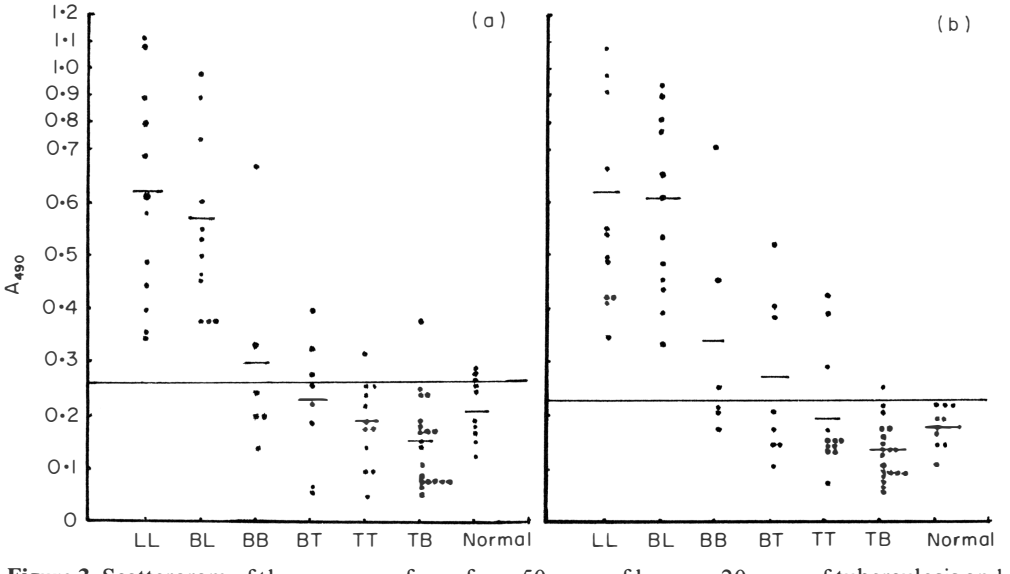

Figure 3. Scattergram of the response of sera from 50 cases of leprosy, 20 cases of tuberculosis and 10 cases of normal control. (a) M–BGG–ELISA, (b) PGl–ELISA.

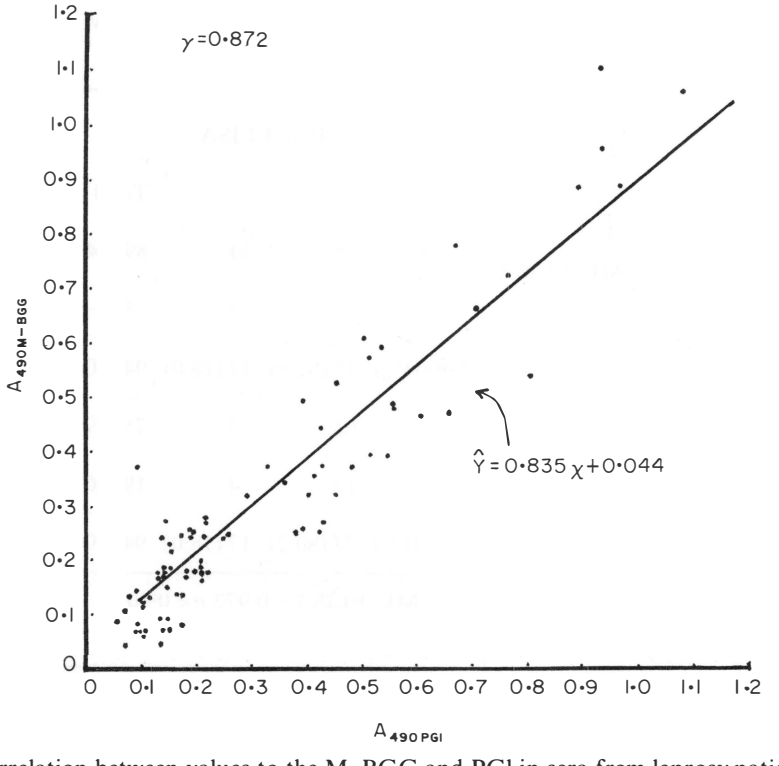

Figure 4. Correlation between values to the M–BGG and PGl in sera from leprosy patients (50), tuberculosis patients (20) and normal controls (10).

From these data: 1 from TT to LL, the content of antibody increased gradually is more regular in PGl–ELISA than in ML–ELISA; 2 from BB to LL, there was essentially the same sensitivity to both antigens, but from TT to BT, the sensitivity is higher in ML–ELISA than in PG–ELISA; and 3 in LL/BL, M_{OD} values are essentially equal in both ELISA, but in BB, BT/TT, the M_{OD} values are higher in ML–ELISA than those in PGl–ELISA. The reason will be further studied.

When ELISA values from a total of 94 leprosy patients and 78 normal controls were analysed (Figure 2), there was a significant correlation between the ML and PG antigens (correlation coefficient, $r = 0{\cdot}72$, $p < 0{\cdot}0005$). Figure 3 shows the results of (a) M–BGG–ELISA and (b) PGl–ELISA. These data indicate that: 1 from BT to LL, the positivity rates of each group are essentially equal in both of ELISA, and in BL/LL and TB are fairly the same; 2 from TT to LL, the increase of M_{OD} values to both antigens are regular; and 3 normal value is higher in M–BGG–ELISA than in PGl–ELISA, but in TB, the OD values of both ELISA are all lower than those in normal controls.

The correlation analysis (Figure 4) of both ELISA indicated that there was a significant correlation between the PGl and M–BGG antigens (correlation coefficient, $r = 0{\cdot}872$, $p < 0{\cdot}0005$).

Table 1. Results of comparisons of PGl–ELISA with ML–ELISA and FLA–ABS. (Sera from leprosy patients).

		PGl–ELISA		
		+	−	Total (%)
ML–ELISA	+	75	14	89 (94·7)
	−	2	3	5 (5·30)
	Total (%)	77 (82·0)	17 (18·0)	94 (100)
FLA–ABS.T	+	62	13	75 (79·8)
	−	15	4	19 (20·2)
	Total (%)	77 (80·2)	17 (18·0)	94 (100)
Correlation analysis:		γML–ELISA = 0·972 $p < 0·005$		
		γFLA–ABS·T = 0·945 $p < 0·01$		

Table 1 shows the results of comparisons of PGl–ELISA with ML–ELISA and FLA–ABS.T, which are obtained from leprosy sera. The positivity percentages are: 94·7% in ML–ELISA, 82·0% in PGl–ELISA, 75·8% in FLA–ABS.T. Correlation analysis shows that they have highly significant correlation (correlation coefficient, $r_{\text{ML–ELISA}} = 0·972$ $p < 0·005$; $r_{\text{FLA–ABS.T}} = 0·945$ $p < 0·01$).

Discussion

The comparison of ML–ELISA with PGl–ELISA in sera. From the data in Figures 1 and 3, the reactivity of both antigens to sera at BB, BL/LL patients and Normal controls is the same, but at BT/TT patients, the sensitivity of *M. leprae* is higher than that of PGl. However, the PGl–ELISA is more specific for infection with *M. leprae* than ML–ELISA,[12,13] so it may be practical to combine PGl–ELISA with ML–ELISA for detecting subclinical infection with *M. leprae*, and PGl–ELISA may be more useful for serodiagnosis of multibacillary leprosy.

The comparison of M–BGG and PGl with sera (Figures 2 and 4). Although the negative value was higher in M–BGG–ELISA than in PGl–ELISA, this does not influence the finding in BL/LL patients, and the use of M–BGG has several advantages: approximately six-fold less antigen is required to coat ELISA plates for the same reactivity,[11] and Tween 20, a nonanion detergent, may be used in the ELISA. However, PGl and its derivatives are easily removed from ELISA antigen

plates with Tween 20. M–BGG is more easily prepared for use in antigen-coating buffers since a sonication step is not required. These results suggest that PGl–ELISA may be replaced with M–BGG–ELISA, which is more applicable to leprosy endemic areas where the armadillo does not reside. Indeed, the outlook for a synthetic antigen for worldwide application to the serodiagnosis of leprosy looks promising.

Comparison of PGl–ELISA with ML–ELISA and FLA–ABS.T. From the data in Table 4, the ML–ELISA is the most sensitive one, and PGl-ELISA is more sensitive than FLA–ABS.T, the correlation analysis indicated that three methods are highly significant correlation. In fact, we have found FLA–ABS.T with sera from untreated leprosy patients are very sensitive. Moreover, M_{OD} values of ELISA are also lower than before. These may be relative to the sera from patients who have received chemotherapy with combinations of three drugs (DDS, RFMP, CLF) for a long period.

In addition, the conventional BSA and GS can be replaced with EA for blocking nonspecific binding. The efficiency is not only equal to BSA and GS, but also facile, much cheaper and easier to get.

In conclusion, although the ML–ELISA and PGl–ELISA methods still cannot find all the paucibacillary patients and the subclinical leprosy infections they are much more sensitive than FLA–ABS.T and excellent for determining multibacillary patients, and PGl–ELISA is more specific for *M. leprae* than ML–ELISA and FLA–ABS.T. Additionally, as they are simple, rapid, require little antigen, and provide at least a semiquantitative measurement, it can be said that combinations of ML–ELISA with PGl–ELISA or PGl–ELISA alone may be useful as an epidemiological tool to detect subclinical leprosy infection and in evaluating contacts. Because the test can reflect antibody content, it is possible that it may be useful for following the response of patients to treatment, evaluating the status of disease among patients, and even estimating the degree of infectivity of leprosy patients. As for M–BGG–ELISA, although the normal value presumed in our test is higher, it is still valuable for mentioned purposes, especially in places where there is a shortage of PGl antigen.

Acknowledgments

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References

[1] Abe M, Saito T, Mathur SK. Early Serodiagnosis of Leprosy by Indirect Immunofluorescence. *Lepr India*, 1976; **48:** 272–6.

[2] *Report of the Sixth Meeting of the Scientific Working Group on the Immunology of Leprosy*, Geneva, 1982: 15.

[3] Brennan PJ, Barrow WW. Evidence for species-specific lipid antigens in *Mycobacterium leprae*. *Int J Lepr*, 1980; **48:** 382.

[4] Hunter SW, Brennan PJ. A novel phenolic glycolipid from *Mycobacterium leprae* possibly involved in immunogenicity and pathogenicity. *J Bacteriol*, 1981; **147:** 728–35.

[5] Young DB, Buchanan TM. The Phenolic Glycolipid from *Mycobacterium leprae*: Use in serological tests. *Proceedings of the Workshop on Serological Test for Detecting Subclinical Infection in Leprosy*, Tokyo; 1983; 19.

[6] Fujiwara T, Hunter SW, Cho SN, Aspinall GO, Brennan PJ. Chemical synthesis and serology of the di- and trisaccharides of the phenolic glycolipid antigens from the leprosy bacillus and preparation of a disaccharide protein conjugate for serodiagnosis of leprosy. *Infect Immun*, 1984; **43:** 245–52.

[7] Wu Qinxue *et al.* Preliminary application of fluorescent leprosy antibody absorption test. *Acta Acad Med Sin* (in Chinese), 1982; **4,** 392–4.

[8] Abe M *et al.* Fluorescent leprosy antibody absorption (FLA–ABS) test for detecting subclinical infection with *Mycobacterium leprae*. *Int J Lepr*, 1980; **48:** 109–19.

[9] Douglas JT *et al.* Development of an ELISA for Detection of Antibody in Leprosy. *Int J Lepr*, 1984; **52:** 19–25.

[10] Young DB, Buchanan TM. Detection of Antibodies to the *M. leprae* Phenolic Glycolipid by Enzyme-Linked Immunosorbent Assay (ELISA). A Personal communication, 1984.

[11] Douglas DB *et al.* Comparison of natural and synthetic antigens for the early detection of leprosy. *Joint US–Japan Tuberculosis and Leprosy Symposium*, Tokyo: 1984: 143–9.

[12] Cho SN *et al.* Serological specificity of phenolic glycolipid I from *M. leprae* and use in serodiagnosis of leprosy. *Infect Immun*, 1983; **41,** 1077–83.

[13] Hunter SW *et al.* Further specific phenolic glycolipid antigens and a related diacyphthiocerol from *M. leprae*. *J. Biol Chem*, 1983; **258:** 7556–62.

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Serological study of leprosy employing ELISA with arabinogalactan of *Mycobacterium smegmatis* as antigen

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Summary An ELISA has been developed for detecting circulating antibodies in leprosy sera using arabinogalactan, a cell-wall polysaccharide of *Mycobacterium smegmatis* as the antigen. In normal sera, arabinogalactan specific IgM is higher than IgG, whereas in untreated leprosy sera anti-arabinogalactan (AG) IgG is more than the corresponding IgM. With long-term treatment of the disease, IgM level goes up compared to IgG.

Introduction

Infection with mycobacteria is usually associated with the induction of a non-protective humoral immune response against its various antigens. The search for a specific antigen, which might be useful for early detection of leprosy or for screening of at-risk populations, has been intensive. *Mycobacterium leprae* contain antigenic components which are specific as well as highly cross-reactive with other mycobacteria. In the latter class, belong 2 immunogenic polysaccharides, arabinomannan (AM) and arabinogalactan (AG).[1, 2] One study observes[3] that pretreatment antibody level of arabinomannan was directly proportional to the quantity of *M. leprae* present, and patients with low antibody titres represent a paucibacillary state. Moreover in paucibacillary states the titre against AM goes down with treatment, but in multibacillary states such a correspondence cannot be established. A further study[4] thoroughly investigated the AM, developed an ELISA and showed high specific antibody in untreated cases, low antibody response in the treated cases and almost negligible antibody to the control. This antigen, although very specific for LL cases, fails to discriminate TT/BT and household contacts from normal populations. One study[5] showed that *M. smegmatis* was most reactive against lepromatous sera using the ELISA technique. The other polysaccharide component, arabinogalactan (AG), has

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been shown to be more seropositive than AM.[6] We, therefore, decided to investigate the feasibility of AG as a screening antigen.

We have isolated arabinogalactan from cell-wall surface of *M. smegmatis* and have tested it for reactivity with serum antibodies in individual patients. A specific ELISA has been developed for the demonstration and quantification of specific IgG and IgM antibodies against arabinogalactan. Antibodies against this component occur frequently in leprosy patients as well as in normal individuals. With a highly-purified preparation of AG we have observed that in normal individuals antigen specific IgM level in sera is higher than that of IgG. In untreated leprosy patients specific IgG level is higher than that of IgM level, while with treatment of the disease the specific IgM level goes up. These findings, though surprising, might be due to the fact that our population is exposed to a plethora of atypical mycobacteria and are mostly BCG vaccinated, and hence maintain a high level of antibody against this cross-reactive antigen. We show here that a comparison of IgG and IgM levels against this antigen, in other words the ratio, IgM:IgG, provides us with an interesting discriminatory point to confirm the disease status. Our objective in the present study was to investigate whether AG specific IgM, IgG antibody levels in normal and infected individuals have any significant correlation with the development of the disease.

Materials and methods

Arabinogalactan was obtained from *M. smegmatis* by the published procedure[2, 6] of fractional precipitation with ethanol, 80% alcoholic precipitated fraction was utilized as the major source of antigen. The fraction was dissolved in a minimum quantity of distilled water and reprecipitated 3 times with absolute ethanol, then it was triturated with ether and acetone. It was finally purified by passing through Sephacryl 1200 (Pharm. Fine. Chem., Sweden) giving a single fraction, which was used for ELISA.

CHEMICAL PROPERTIES OF PURIFIED POLYSACCHARIDE

Purified polysaccharide fraction was positive for the phenolsulphuric acid reaction.[8] Galactose and arabinose were detected and estimated by paper chromatography and also by gas liquid chromatography (Hewlette Packard, column SE-30). Arabinogalactan peptidoglycan comprised 24% carbohydrate, 3% protein[9] and approximately 65% of fatty acid.[10]

ENZYME-LINKED IMMUNOSORBENT ASSAY

Linbro plates were coated with arabinogalactan solution (100 μl/well) in bicarbonate buffers (pH 9·6). Wells were then washed with phosphate buffered

saline (PBS), incubated with 100 μl of PBS containing 5% BSA at 37°C for 2 h. The contents were aspirated and 100 μl of human serum, diluted with PBS containing 20% normal bovine serum was added and incubated overnight in a moist chamber. After 3 washes with PBS, rabbit antihuman IgM, IgG-HRPO conjugate (Dakopatts, Denmark, diluted in 1:4000, PBS-1% BSA) was added, incubated and washed with PBS. One hundred microlitres of H_2O_2-O-phenylene-diamine substrate dye reagent in citrate phosphate buffer was then added and kept for 15 min. Reactions were terminated with 50 μl of 5N H_2SO_4 and the absorption was read at 492 nm in titre Tek Multiskan (Flow Laboratories, Inc. USA) ELISA reader.

HUMAN SERA

Sera from 15 normal healthy laboratory workers (without any known mycobacterial diseases), from All India Institute of Medical Sciences, New Delhi, and also sera from 30 apparently healthy Indians (with a record of BCG vaccination), comprised our normal control population.

The second test group of sera was from 44 untreated LL leprosy patients, whose ages ranged from 15 to 60 years, with a wide spectrum of leprosy, and was donated by Dr S N Choudhury, School of Tropical Medicine, Calcutta.

The third group of sera was from treated leprosy patients, and was donated by Dr Narayanan, TRC, Madras, India. Except for 6 BT cases the rest of the sera were from LL patients; the bacillary index in the group ranged from 0 to 5. All the patients were on therapy at the time serum was obtained. The duration of therapy ranged from 2 to 25 years. Sera were preserved by the addition of 0·1% sodium azide and were stored at -70°C until used.

Serum was assayed in triplicate and the arithmetic mean of the OD_{492} readings was used in all further analysis. The mean and standard deviations for each of the 3 study populations were calculated.

Results

Results from Figure 1 illustrate a standard serum dilution curve for 5 untreated LL pooled sera, with different antigen concentrations. From this curve, the optimum level of 50 μg/well of antigen and sera dilution of (1:100) was chosen and used in all subsequent ELISA experiments.

Figure 2 shows the ELISA results for 44 individual cases each of normal, treated and untreated leprosy sera using Dakopatts Rab antihuman IgM, IgG, IgA—HRPO conjugate. The mean value ($0{\cdot}625 \pm 0{\cdot}164$) for normal cases was significantly higher than that observed in untreated patients ($0{\cdot}332 \pm 0{\cdot}125$). Interestingly, the treatment of lepromatous leprosy patients for 2 or more years resulted in an elevation of the level ($0{\cdot}516 \pm 0{\cdot}210$.

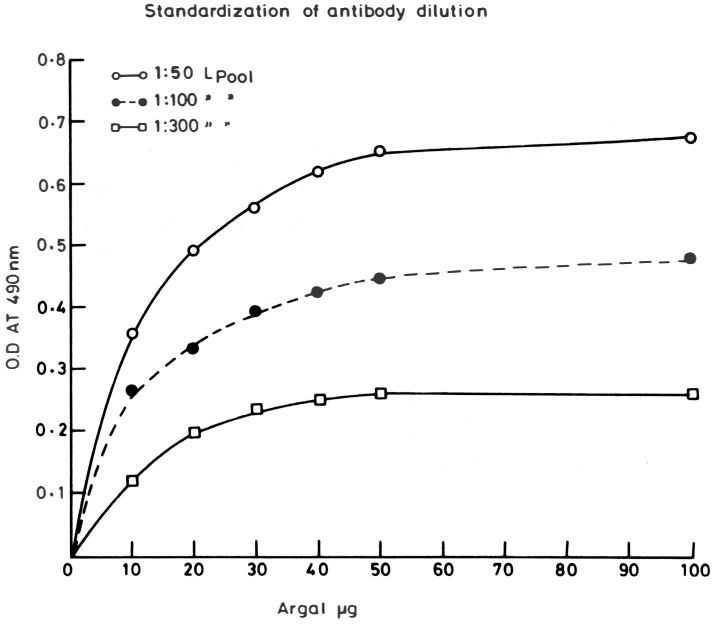

Figure 1. Standardization of arabinogalactan by ELISA technique. An antigen concentration range of 10–100 μg was used and titrated against 3 different dilutions of sera pooled from 5 individual untreated lepromatous leprosy patients.

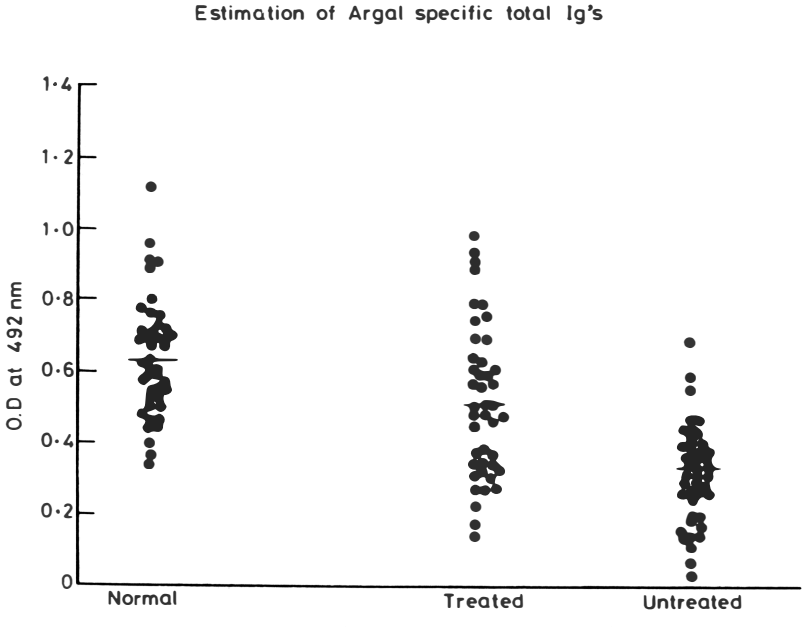

Figure 2. ELISA with Argal antigen. Each dot represents total antibody level against arabinogalactan, 44 individual cases each of normal, treated LL and untreated LL sera were used.

To determine whether the observed differences involved a class specific antibody response to AG, we estimated specific IgG and IgM levels in individual normal, LL and TT as well as in normal and leprosy-pooled sera using rabbit-antihuman-HRPO conjugates. The results are given in Figure 3. While there is no dramatic difference in total immunoglobulin level against AG among these categories, specific IgG response is considerably more compared to IgM response in pooled and individual leprosy sera than in normal controls. The same trend is confirmed in the results given in Figure 4, where groups of individual normal, treated and untreated LL patients are compared. The picture as presented is significantly different in untreated LL patients from that of normal controls, while interestingly the treated patients show a mixed picture. In Figure 5, we compared anti-AG, -IgG and-IgM levels in a number of short-term treated LL and BT patients' sera; again IgG, IgM levels in these cases and consequently the ratio, IgM:IgG is less than unity.

Discussion

Results presented above indicate an interesting phenomenon that basal anti-arabinogalactan IgM levels in normal healthy individuals are found to be greater than specific IgG levels. With *M. leprae* infection, however, the relative levels are modulated, and in LL cases IgG titres are higher than IgM titres. We do not know if this trend is universal or specific to the Indian population we tested. Because the population in tropical countries, like India, is continually exposed to many

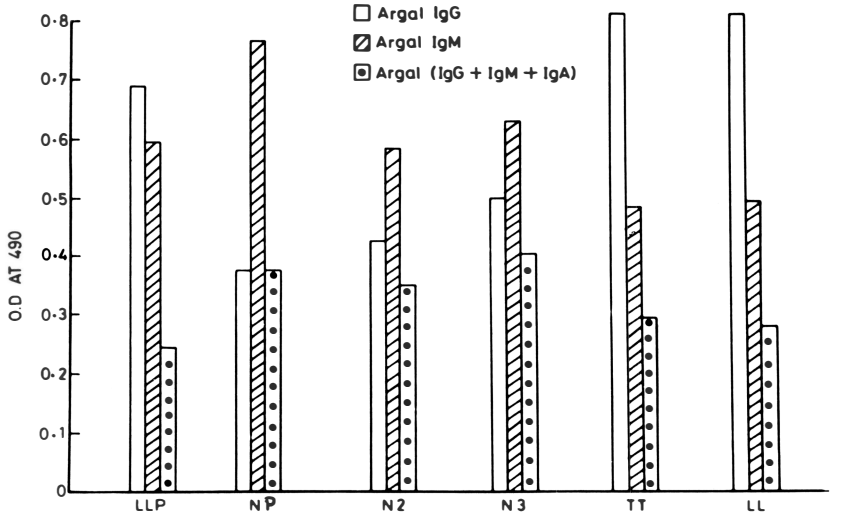

Figure 3. Comparison of antibody levels against arabinogalactan (AG) in normal pooled, leprosy pooled and individual control as well as individual untreated TT and LL patients.

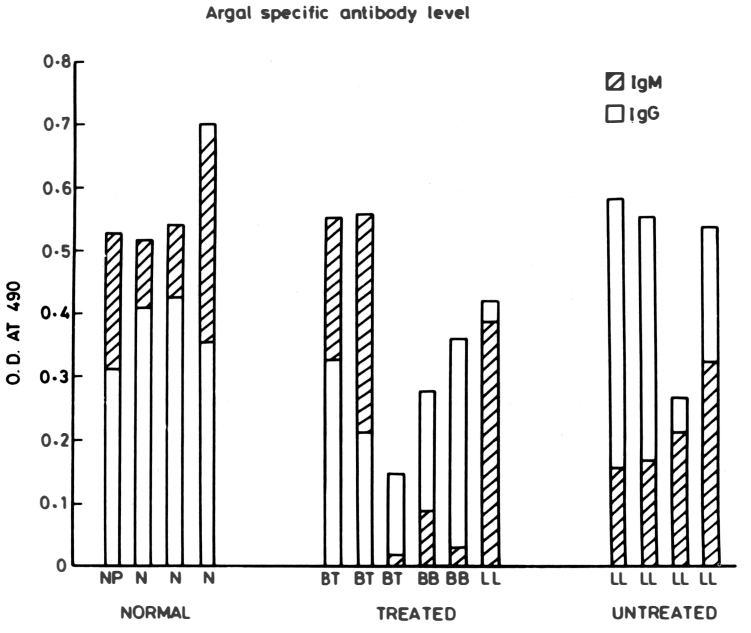

Figure 4. Comparison of specific antibody levels against Argal. The level of IgM is more in normal than in untreated patients' sera.

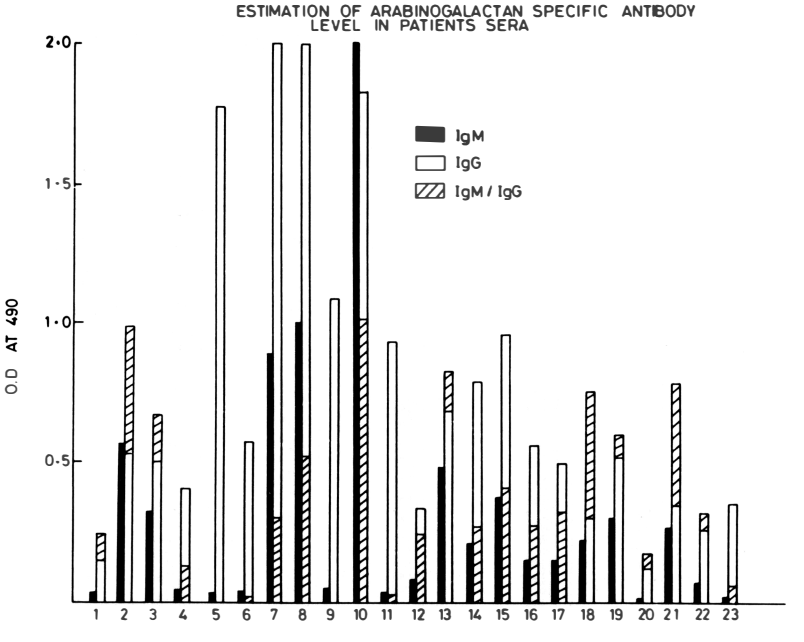

Figure 5. Profile of anti-AG-IgG, IgM and IgM : IgG ratio in 23 treated LL patients' sera. IgM is low compared to IgG, IgM : IgG ratio is below unity.

atypical and soil mycobacteria it is possible that normal individuals already maintain a sustained IgM response against very common, AG-antigen. Also, a vast number of the population in India have already been BCG vaccinated.[13] It has been demonstrated in lepromatous leprosy that anti-*M. leprae* IgG is about twice as high as IgM[14,15] and that the IgM response is mostly against specific phenolic glycolipids, which somehow lack an IgM to IgG switch.[16] More common polysaccharide antigens (AG and AM), after *M. leprae* infection, normally switch over to IgG response, so that the IgG level goes up, at the expense of IgM, giving rise to an inverse relationship with corresponding levels in the normal population.

The observed trend, however, is contrary to what has been observed with other antigens.[17, 18, 19] Usually increasing antibody activity is observed throughout the leprosy spectrum, lowest activity in household contacts, higher median-activity in sera from indeterminate leprosy patients (only of IgM response) and highest median activity in sera from untreated leprosy patients. Here with AG, the total specific immunoglobulin level shows a slightly reversed trend. The reason for this trend is not clear to us, and we feel from the wide range of scatter (Figure 3), that the difference in total immunoglobulin may not be as much if it is averaged over a very large number of samples. Instead of total immunoglobulin, if one compares specific IgG and IgM levels, the ratio of IgM:IgG $> 1{\cdot}0$ in the case of normal and $< 1{\cdot}0$ for persistent infection, and possibly increased again with treatment. This is a significant and consistent finding and provided us with an interesting point in terms of a cut-off value (1·0) to determine the status of the disease. In Figure 5, results are shown with sera from a number of individual lepromatous leprosy patients with a wide spectrum of severity of the disease, in all cases, except nos. 2 and 10, the ratio is much less than unity.

Chemotherapy of leprosy has been associated with decreasing antibody titres, whereas relapsed tuberculoid patients generate a higher antibody level.[10] Monitoring therapeutic improvement remains a difficult task as no clear correlation of antibody level including antiphenolic glycolipid-1 antibodies, with bacillary index has been established. IgM assay with specific phenolic glycolipid has been promising but is not foolproof, anti-AG, -IgM:IgG ratio offers an alternative method, and in combination with phenolic glycolipid-1 assay may be of better predictive value.

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References

[1] Azuma I, Kimura H, Niinaka T, Aoki T, Yamamura Y. Chemical and immunological studies on mycobacterial polysaccharides. I. Purification and properties of polysaccharides from human tubercle bacilli. *J. Bacteriol*, 1968; **95:** 263–71.

[2] Misaki A, Seto N, Azuma I. Structure and immunologic properties of D-arabino-D-galactans isolated from cell walls of Mycobacterium species. *J Biochem* 1974; **76:** 15–27.

[3] Miller RA, Dissanayake S, Buchanan TM. Development of an enzyme linked immunosorbent assay using arabinomannan from *Myocobacterium smegmatis*: a potentially useful screening test for the diagnosis of incubating leprosy. *Am J Trop Med Hyg*, 1983; **32:** 555–64.

[4] Miller RA, Harnisch JP, Buchanan TM. Antibodies to *Mycobacterial* arabinomannan in leprosy: correlation with reactional states and variation during treatment. *Int J Lepr*, 1984; **52:** 19–25.

[5] Douglas JT, Naka SO, Lee JW. Development of an ELISA for detection of antibody in leprosy. *Int J Lepr*, 1982; **52:** 19–25.

[6] Kanetsuna F, San Blas G., Chemical analysis of a mycolic acid-arabinogalactan mucopeptide complex of mycobacterial cell wall. *Biochem Biophys Acta*, 1970; **208:** 434–43.

[7] Fujiwara T, Hunter SW, Cho SN, Aspinall GO, Brenan PJ. Chemical synthesis and serology of disaccharides and trisaccharides of phenolic glycolipid antigens from the leprosy bacillus and preparation of a disaccharide protein conjugate for sero-diagnosis of leprosy. *Infect Immun*, 1984; **43:** 245–52.

[8] Dubbois M, Gill, KA, Hamilton JK, Rebers PA, Smith F. Estimation of carbohydrate by phenol-sulphuric acid method. *Anal Chem*, 1956; **28:** 350.

[9] Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. *J Biol Chem*, 1951; **193:** 265.

[10] Bligh EG, Dyer WJ. A rapid method of total lipid extraction and purification. *Can J Biochem & Physiology*, 1959; **37:** 911–17.

[11] Stanford JL, Nye PM, Rook GAW, Samuel N, Fairbank A. A preliminary investigation of the responsiveness or otherwise of patients and the staff of a leprosy hospital to groups of shared or species-specific antigens of mycobacteria. *Lepr Rev*, 1981; **52:** 321–7.

[12] Stanford JL, Aguas T, Ganapati R, Pevankar CR, Rees RJW. Pilot studies of immunoprophylaxis and immunotherapy in man with *M. vaccae*, *M. leprae* and BCG. XII-International leprosy conference, Abstract No. 11, Feb. 20–25, p. 104, New Delhi.

[13] Tuberculosis prevention trial, Madras–Indian Council of Medical Research, New Delhi. *Ind J Med Res*, 1980; 72: Suppl. 1–74.

[14] Melsom R, Duncan ME. Demonstration of antibodies against *Mycobacterium leprae* both in immunoglobulin G and M in sera from pregnant and non-pregnant lepromatous leprosy patients. *Lepr Rev*, 1980; **51:** 125–35.

[15] Touw J, Langendijk MJ, Stoner GL, Belehu A. Humoral immunity in leprosy: immunoglobulin G and M antibody response to *Mycobacterium leprae* in relation to various disease patterns. *Infect Immun*, 1982; **36:** 885–92.

[16] Cho SN, Yanagihara DL, Hunter SW, Gelber RH, Brennan RP. Serological specificity of phenolic glycolipid-1 from *Mycobacterium leprae* and use in serodiagnosis of leprosy. *Infect. Immun*, 1983; **41**(3): 1077–83.

[17] Young BD, Buchanan TM. Development of an enzyme-linked immunosorbent assay to measure antibodies to the phenolic glycolipid. XII Intl. Lepr. Congress, New Delhi, 1984; 11/98(P) Feb. 20–25.

[18] Brett SJ, Payne SN, Draper P, Grigg R. Analysis of the major antigenic determinants of the characteristic phenolic Glycolipid from *Mycobacterium leprae*. *Clin exp Imm*, 1984; **56:** 89–96.

[19] Douglas JT, Worth RM. Field evaluation of an ELISA to detect antibody in leprosy patients and their contact. *Int. J Lepr*, 1984; **52:** 26–33.

[20] Yoder L, Naafs B, Harboe M, Bjune G. Antibody activity against *Mycobacterium leprae* antigen 7 in leprosy: studies on variation in antibody content throughout the spectrum and on the effect of DDS treatment and relapse in BT leprosy. *Lepr Rev*, 1979; **50:** 113–21.

[21] Zeiger AR, Tanzon CU, Sheagren JN. Antibody levels to bacterial peptidoglycan in human sera during the time course of endocardities and bacteremic infection caused by staphylococums ourens. *Infect Immun* 1981; **83:** 785–800.

[22] Heymer B, Schleifer KH, Read S, Zabriskie JB, Krause RM. Detection of antibodies to bacterial cell wall peptidoglycan in human sera. *J Immunol*, 1976; **117:** 23–6.

Lepr Rev (1986) **57,** 147–157

Suppressor determinants of mycobacteria and their potential relevance to leprosy

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Summary This paper extends our studies of the local and distant suppressions of skin-test responses to mixed mycobacterial reagents previously demonstrated in Nepal and Bombay. Several new mixtures were prepared, which included DEAE separated fractions of a sonicate of *Mycobacterium vaccae* (Vaccin). Local suppression was a major feature of the results in all the centres except Kopri in Bombay. All of the Vaccin fractions were capable of inducing local suppression. Distant suppression associated with all the fractions was observed at one of the Bombay centres, but not the other ($p < 0{\cdot}00001$). In Kenya distant suppression also occurred at only one of the centres ($p < 0{\cdot}00003$), but at this centre it was associated significantly with only 2 of the 5 fractions tested ($p < 0{\cdot}001$ in each case).

Our results may well depend on geographical differences probably associated with the quantity and quality of sensitization by fast-growing environmental mycobacteria. The possibly essential part played by suppressor determinants within the fractions described in the initial infection with *M. leprae* and in the pathogenesis of multibacillary disease is discussed.

Introduction

The purposes of this paper and the three preceding it,[1–3] have been to investigate the ability of mycobacteria to suppress cell-mediated responses to themselves or to other mycobacterial products injected at a distant site. This is relevant to

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leprosy since it may be the way in which the initial infection gets established, and in lepromatous leprosy it may be the fundamental mechanism underlying the so-called immune defects invariably present in that disease. Other aspects of suppression of immune mechanisms may prove to be of considerable use in immunotherapy. We have employed sonicates of cultivable species of mycobacteria in studies designed to determine how many different suppressor functions mycobacteria may exert and who is susceptible to them.

In our previous investigations of skin test responsiveness to mixed mycobacterial reagents, 2 distinct types of suppressor phenomena have been observed. The first involves local suppression of responses at the site of injection to a reagent prepared from 12 slow-growing mycobacterial species by the addition of a mixture of 12 fast-growing species. This type of local suppression was demonstrated in Nepal[1] and in Bombay,[2] and may be the mechanism by which a tiny infective inoculum of leprosy bacilli becomes established in the tissue.

The second type of suppression, which had been observed in Kopri Colony (Bombay) alone, involves distant suppression of response to the mixed slow grower reagent (SG) on one arm by injection of the same SG reagent mixed with a reagent prepared from a single fast grower on the other arm. The fast grower reagents associated with the second type of suppression included Chitin, Diernhoferin, Vaccin and Rhodesin (called group A)[2]. It was postulated that this type of suppression might be due to species specific determinants of these organisms. Its occurrence, therefore, would seem to depend on prior sensitization by the species concerned. If *Mycobacterium leprae* has determinants producing suppression of this type it could explain the development of lepromatous disease and the species specific aspects of the immune defect.

For the present study a sonicate of *M. vaccae* has been fractionated on a DEAE column and the individual fractions added to the SG mixture in order to determine which of them might be associated with suppressor activities. The system has been tested in 6 centres; Kopri Colony, and Vimala Dermatology Centre in Bombay, Alupe Leprosy Research Centre and Tumu Tumu Hospital in Kenya, Fontilles Sanatorium in Spain and AHRI/ALERT, Addis Ababa, Ethiopia.

Materials and methods

Persons tested included leprosy patients and staff in Bombay and Addis Ababa, and staff alone at the other centres. Each individual received 4 simultaneous intradermal tests, 2 on each forearm. All reagents used were at a concentration of 2 μg/ml, and the dose injected was 0·1 ml. The mean of 2 diameters of induration was recorded after 72 hr and reactions of 2 mm or more were taken as positive.

Some of the reagents employed were the same batches as those used in our previous studies. These were the first 3 listed below and the first two of number 4.

1 SG: a mixed reagent prepared from 12 slow-growing species.
2 FG: a mixed reagent prepared from 12 fast-growing species.
3 F/S: an equal mixture of the 2 above.
4 An equal mixture of SG + Vaccin, SG + Chitin, SG + Leprosin A or one of 5 reagents consisting of equal volumes of SG together with DEAE column separated fractions of Vaccin.

Each person received the first 3 reagents and one of the group 4 reagents.

Preparation of Vaccin fractions

A 2·5-cm column was packed to a height of 35 cm with DEAE cellulose equilibrated in 0·01 M tris HCl buffer at pH 7·8. Elution was effected using a continuous tris molarity gradient to a final concentration of 1·0 M tris. The eluent was collected in approximately 5-ml volumes, and absorption was measured at a wavelength of 280 nm. Tubes containing the peaks were pooled and passed through a 0·22-μm filter into presterilized dialysis tubing. The fractions were then concentrated and dialysed for 4 days at 4°C against normal saline. Five of the fractions were obtained in sufficient quantities to allow the preparation of skin test reagents, these were F2, F4, F5, F6 and F7. The numbers indicate the order of elution from the column and correspond to the increasingly negative charge of the constituents. The protein strengths of the preparations were assessed and their concentrations adjusted to 2·0 μg/ml with borate buffer, pH 8·0.

The skin test reagents for the 4th site were prepared by mixing equal volumes of SG together with one of these fractions.

We have slightly changed our definitions of suppression. Local suppression was previously described only in Category 3 reactors but has now been expanded to include those in Category 1. Distant suppression of the SG reagent *was* defined as a response which is half or less of that to the F/S, but since the F/S reagent itself may be suppressed, it is now compared with response to the F/S *or* 4th reagents.

The Fisher Exact Test has been employed for statistical analyses.

Results

A total of 528 individuals received skin tests of which 144 had BCG scars, which did not appear to influence the results. However this may need further evaluation.

Previous data has been examined in relation to the 3 categories of skin test responders.[1] Category 1 contains individuals who produce positive reactions to all mycobacterial reagents. Category 2 respond to none of them at routine test concentration, while category 3 responders react to some reagents and not to others. However, categorization using reagents of the type presently under

investigation may differ somewhat from those achieved using reagents prepared from single species. The numbers found in each category in the 6 centres are shown in Table 1.

There is a marked expansion of category 2 nonreactors at Vimala, Addis Ababa and Fontilles. In the first 2 cases this is at the expense of category 3 reactors but at Fontilles it results in total loss of category 1. Conversely Alupe has no category 2 nonresponders.

Table 2 gives the number, percentage positive and mean positive reaction sizes, together with their standard deviations in persons in categories 1 and 3. As an example of the individual results obtained, those for the Kenyan centres of Alupe and Tumu Tumu are shown in Table 3. The figures in brackets are the results from a small investigation of the duration of SG suppression in individuals some 12 months after the first tests. Of the 15 people retested with SG alone, the 8 who previously had total SG suppression all gave positive responses at 72 hr with an average area of induration of $6{\cdot}9 \pm 2{\cdot}8$ mm.

When comparing the total percentages positive at the different centres, suppression of responses is associated with many of the reagents. Vimala, Tumu Tumu, AHRI/ALERT and particularly Fontilles show decreased responses to F/S as compared with SG ($p < 0{\cdot}002$). The reverse was true at Kopri and Alupe ($p < 0{\cdot}001$). Similarly when responses to the 4th reagents are compared with those to SG alone the reduction of responses is highly significant ($p < 0{\cdot}00005$) in Alupe, Fontilles, Tumu Tumu and AHRI/ALERT. The difference is not significant at Vimala and the trend is reversed in Kopri ($p < 5{\cdot}0 \times 10^{-15}$).

The figures for the FG reagent indicate that the degree of sensitization varies considerably at the different centres, from 37% positivity at Vimala to 98% at Alupe. This high level of sensitization by fast growers may explain the lack of category 2 individuals at Alupe.

Table 1. The distribution of the 3 categories of skin test responders in the 6 centres.

	Categories of responders					
	I		II		III	
Centres	all +ve		all −ve		mixed	
Kopri	12/83	14%	8/83	10%	63/83	76%
Vimala	4/46	9%	19/46	41%	23/46	50%
Alupe	11/55	20%	0/55	0%	44/55	80%
Fontilles	0/40	0%	16/40	40%	24/40	60%
Tumu Tumu	4/38	11%	6/38	16%	28/38	74%
Addis Ababa	24/266	9%	112/266	42%	130/266	49%

Table 2. Number and percentage of positive reactors together with mean reaction sizes and standard deviations of individuals in skin test responder categories 1 and 3 at the 6 centres.

Centre	Reagents tested in all persons			Variable fourth reagents
	SG	FG	F/S	
Kopri	24/75 32% 7·7±5·2	30/75 40% 7·0±3·8	44/75 59% 10·7±6·5	69/75 92% 10·8±4·2
Vimala	23/27 85% 10·8±3·7	10/27 37% 7·2±3·9	6/27 22% 7·3±4·5	20/27 74% 10·6±3·2
Alupe	33/55 60% 9·0±3·0	54/55 98% 9·0±2·8	53/55 96% 10·6±2·8	12/55 22% 8·3±3·9
Fontilles	24/24 100% 9·9±3·8	16/24 67% 7·8±2·8	0/24 0% 0	5/24 21% 8·7±1·9
Tumu Tumu	29/32 91% 11·1±4·5	12/32 38% 6·0±2·6	10/32 31% 9·6±4·9	10/32 31% 8·2±5·6
AHRI/ALERT	133/154 86% 9·1±4·0	58/154 38% 7·2±3·2	98/154 64% 8·6±3·2	80/154 52% 10·2±4·5

Note that the percentages positive to F/S are significantly lower than those to SG in Vimala, Fontilles, Tumu Tumu and AHRI/ALERT ($p<0·002$) and that the reverse is the case in Kopri and Alupe ($p<0·001$).

Of the 528 individuals tested, 266 produced positive skin test responses to the SG reagent. Thirty of these had received fractions of *M. vaccae* alone as the fourth reagent, to which a single positive response was recorded to F6 (1/9) with no reaction to F2 (0/11) or F5 (0/10). The local suppressions associated with the F/S combination and with the mixed fourth reagents can be assessed in 232 persons (see Table 4), 111 of these showed local suppression to F/S (48%) although there was a significant variation between places. Suppression at the fourth reagent sites was found in 7/39 who received the half dose of SG alone; 2/27 who received SG + Vaccin; 6/19 who received SG and Leprosin A; 3/21 who received SG + Chitin. These differences are not significant statistically. Suppression at the sites of the fourth reagents incorporating Vaccin fractions was found in 29/36 who received SG + F2, 11/17 who received SG + F4, 16/20 who received SG + F5, 23/28 who received SG + F6 and 20/25 who received SG + F7. Although not significantly different from each other all the fractions produced significantly more suppression than did the half dose of SG alone ($p<0·001$) or any of the fourth reagents containing whole tuberculins. With regard to suppression associated with reagents including the fractions, there was a highly significant

Table 3. Mean responses in millimetres to the 4 skin test reagents tested on individuals at Alupe and Tumu Tumu in Kenya.

4th Reagent constituents	ALUPE				TUMU TUMU			
	SG	FG	F/S	4th	SG	FG	F/S	4th
SG + Saline	0	0	7	0	21	0	0	15·5
	13·5	10	15	8	17	7·5	16·5	19
	12	5	13	11	0	0	0	3
	5·5	8·5	7·5	10	13	0	0	4·5
	15	10	12	11	17	0	14·5	12
	10	10	10	7	14	4·5	9·5	6
	8	7	9	8	8	6	8·5	8·5
	9·5	10	12	10	13·5	5	4·5	6·5
SG + F2	12	12	12	10	15·5	0	0	0
	9·5 (8)	10	12	0	2	0	0	0
	7·5	10	10	0	0	0	0	2
	0	6	6	0	7·5	8·5	10·5	0
	10 (6·5)	12	10	0	15	10·5	15	0
	11 (10)	10	12	0				
	7	6	12	3				
	14 (7·5)	10	12	0				
	10 (6)	7·5	11	0				
	10	10	15	4				
SG + F4	10 (14·5)	12	11	0	12·5	0	0	0
	7	5	10	0	14·5	0	0	0
	10	5	12	0	8·5	3	0	5
	8 (10)	12	11·5	0	12·5	0	0	0
	5	13	14	0				
	7	10	11	0				
	12	12·5	13	16				
	0	7	7	0				
SG + F5	0	12	12	0	13·5	0	0	0
	3	11	10	0	6	5·5	0	0
	0 (9)	6	12·5	0	10·5	0	0	0
	0 (4)	10·5	10	0	12·5	0	0	0
	0	9·5	10	0				
	0	12	12	0				
	0	10	11	0				
	0 (6·5)	5	9·5	0				
SG + F6	0	5·5	13	0	2	0	0	0
	0 (3·5)	12	13	0	9	0	0	0
	4	10	10·5	0	14·5	0	0	0
	0 (10)	7	14	0	0	2	0	0
	0 (8)	8	8·5	0	12	0	0	0
	0 (4)	10	10	0				
	0	9	7	2				

Table 3. (*cont.*)

4th Reagent constituents	ALUPE				TUMU TUMU			
	SG	FG	F/S	4th	SG	FG	F/S	4th
	3	12	11	0				
	0 (10)	10	11	0				
	0	10	11	0				
SG+F7	0	12	13	0	9·5	0	0	0
	0	5	13·5	0	11	0	0	0
	0	3	8·5	0	6	6	2	0
	0	3	15	0	9	0	11	0
	5	13	0	0	12	4	0	0
	7	12	0	0	12·5	10	4	0
	10·5	3	3	0				
	12	11	9·5	0				
	9·5	11	4	0				
	10	10	8·5	0				
	9·5	5	3	0				

Figures in parentheses are the results of tests with SG alone carried out several months later.

difference ($p < 0{\cdot}0001$) between the 2 Bombay centres and the 4 other centres. See bottom of Table 4.

Distant suppression of the SG reagent was observed in 110 (33%) of the 37 category 1 and 3 individuals as shown in Table 5. (Not included in the results are those persons at AHRI/ALERT who were tested at the fourth site with the fractions of *M. vaccae* alone.) SG suppression occurred in 5/43 of those who received a half dose of SG (taken as a control value): 20/44 who received SG+Vaccin ($p < 0{\cdot}001$); 5/22 who received SG+Leprosin A (ns); 14/37 who received SG+Chitin ($p < 0{\cdot}007$); 11/46 who received SG+F2 ($p < 0{\cdot}005$); 11/26 who received SG+F4 ($p < 0{\cdot}005$); 13/35 who received SG+F5 ($p < 0{\cdot}01$); 19/46 who received SG+F6 ($p < 0{\cdot}002$) and 12/38 who received SG+F7 ($p < 0{\cdot}03$).

All fourth reagents tested in Kopri showed significant distant suppression although unfortunately the control reagent SG+saline was not tested in this place. These results are in sharp contrast with those for Vimala, this difference being very highly significant ($p < 0{\cdot}00001$). With the exception of SG+Vaccin no significant distant suppression occurred in AHRI/ALERT, however reagents containing F4 and F7 were not tested there. As in India the two Kenyan centres show striking differences in that none of the fractions produce distant suppression in Tumu Tumu, whereas suppression is significant with fractions 5 and 6 in Alupe

Table 4 Numbers of individuals with a positive response to SG who exhibit local suppression of F/S and 4th reagent mixtures by area and composition of 4th reagents.

	India		Ethiopia	Kenya		Spain	Totals of suppression		
	Kopri	Vimala	AHRI/ ALERT	Alupe	Tumu Tumu	Fontilles			
F/S suppression	7/21 33%	19/22 86%	35/104 34%	5/33 15%	21/28 75%	24/24 100%	111/232 48%		
	$p<0{\cdot}002$			$p<0{\cdot}001$					
SG+saline	NT	NT	4/19	0/7	2/7	1/6	7/39 18%		
SG+Vaccin	1/10	NT	1/17	NT	NT	NT	2/27 7%		
SG+Leprosin A	NT	NT	6/19	NT	NT	NT	6/19 32%	ns	
SG+Chitin	0/2	NT	3/19	NT	NT	NT	3/21 14%		
SG+F2	1/3	2/6	8/8	8/9	4/4	6/6	29/36 81%		0·0001
SG+F4	0/1	2/5	NT	6/7	3/4	NT	11/17 65%		
SG+F5	0/2	0/2	11/11	1/1	4/4	NT	16/20 80%	ns	
SG+F6	0/2	2/5	11/11	2/2	3/3	5/5	23/28 82%		
SG+F7	0/1	0/4	NT	7/7	6/6	7/7	20/25 80%		
Totals of suppression when the 4th reagents contain fractions of vaccin	1/9 11%	6/22 27%	30/30 100%	24/26 92%	20/21 95%	18/18 100%	117/232 50%		
	ns (not significant)				ns				
	$p<0{\cdot}001$								

NT = Not tested

($p<0{\cdot}001$). There was no evidence of distant suppression with the 3 fractions tested in Spain.

Discussion

There are many ways of analysing the very complicated data obtained. The results confirm the principles of our previous investigations and demonstrate both local and distant suppression associated with mycobacterial extracts. These suppressor functions appear to be associated with different determinants and

Table 5. Number and percentage of individuals in skin test responder categories 1 and 3 showing distant suppression of the response to the SG reagent grouped according to location and the constitutents of the 4th reagent.

	India		Ethiopia	Kenya		Spain	
	Kopri	Vimala	AHRI/ ALERT	Alupe	Tumu Tumu	Fontilles	Total
SG + Saline	NT	NT	2/21	1/8	1/8	1/6	5/43* 12%
SG + Vaccin	9/18	NT	11/26 $p<0{\cdot}005$	NT	NT	NT	20/44 45% $p<0{\cdot}001$
SG + Leprosin A	NT	NT	5/22 ns	NT	NT	NT	5/22 23% ns
SG + Chitin	11/15	NT	3/22 ns	NT	NT	NT	14/37 38% $p<0{\cdot}007$
SG + F2	9/10 $p<0{\cdot}001$	0/6	0/9 ns	1/10 ns	1/5	0/6	11/46 24% $p<0{\cdot}005$
SG + F4	8/8 $p<0{\cdot}001$	1/6	NT	2/8 ns	0/4	NT	11/26 42% $p<0{\cdot}005$
SG + F5	5/8 $p<0{\cdot}005$	0/3	0/12 ns	8/8 $p<0{\cdot}001$	0/4	NT	13/35 37% $p<0{\cdot}01$
SG + F6	8/9 $p<0{\cdot}001$	0/5	1/12 ns	10/10 $p<0{\cdot}001$	0/5	0/5	19/46 41% $p<0{\cdot}002$
SG + F7	6/7 $p<0{\cdot}001$	2/7	NT	4/11 ns	0/6	0/7	12/38 38% $p<0{\cdot}03$
	36/42 86%	3/27 11%		25/47 53%	1/24 4%		110/337 33%
	$p<0{\cdot}00001$			$p<0{\cdot}00003$			

* Control value for statistical analyses.

individuals vary in their responses to them. This variation depends on geographical location and the degree of sensitization to mycobacteria. BCG status and whether or not the individual is being treated for leprosy do not affect the results significantly, but a true appraisal of this requires further study. Racial effects that could not be ruled out in our previous studies, appear not to have

influenced the present data since quite different results have been obtained from different centres within the same racial areas (see Table 3).

Taken as a whole, both local and distant suppression can be associated with each of the fractions, although the effects vary geographically. Local suppression occurred with all fractions at the African and Spanish centres, but not at all at the Indian centres (Table 4). On the other hand local suppression by the complete F/S reagent occurred in one Indian centre, Vimala, but not the other, and in one Kenyan centre, Tumu Tumu, but not the other. Distant suppression associated with all the fractions was found at Kopri, but not Vimala; the reverse of local suppression by F/S. Distant suppression was also found at Alupe, but only associated with fractions 5 and 6, and not at Tumu Tumu; again the reverse of local suppression by F/S.

Purely local suppression is seen most clearly amongst the staff members of Sanatorio de Fontilles (see Tables 2 and 4) where the F/S mixture never produced a positive reaction and all 3 fractions tested also induced local suppression.

Our data shows very little relationship between the 2 types of suppression, strongly suggesting that different determinants are involved.

Leprosy patients were included in our study groups in Bombay and Ethiopia. Those tested in Alupe and Fontilles, were leprosarium staff members and thus can be considered as contacts of the disease. Tumu Tumu is a general hospital in an area of low leprosy endemicity, thus those tested were unlikely to have had more than occasional contact with leprosy. In view of this it remains possible that distant suppression may be associated with clinical leprosy or contact with it, but the results from Tumu Tumu make it unlikely that local suppression is leprosy associated.

The importance of the results obtained, although they are complicated and difficult to assimilate, is straightforward. Mycobacteria have been shown to possess immune suppressor activities of 2 types varying in their effects from place to place. If the leprosy bacillus itself possesses these functions then they may well be the essential mechanisms for immunosuppression required for successful infection local suppression and for the pathogenesis of multibacillary leprosy distant suppression. Our first attempts to demonstrate these functions in *M. leprae* with the combination of SG + Leprosin A failed, but more extensive studies and the preparation of fraction of Leprosin A are obviously essential.

Acknowledgements

We should like to thank the patients and staff of the centres where our studies were carried out for their willing participation. We are also grateful to Dr R J W Rees for providing the Leprosin A. Our thanks are also due to Lepra for extensive support and to the British Council and the Medical Research Council for additional financial assistance.

References

[1] Stanford JL, Nye PM, Rook GAW, Samuel NM, Fairbank A. A preliminary investigation of the responsiveness or otherwise of patients and staff of a leprosy hospital to groups of shared or species specific antigens of mycobacteria. *Lepr Rev*, 1981; **52:** 321.

[2] Nye PM, Price JE, Revankar CR, Rook GAW, Stanford JL. The demonstration of two types of suppressor mechanism in leprosy patients and their contacts by quadruple skin testing with mycobacterial reagent mixtures. *Lepr Rev*, 1983; **54:** 9.

[3] Morton A, Nye PM, Rook GAW, Samuel N, Stanford JL. A further investigation of skin test responsiveness and suppression in leprosy patients and healthy school children in Nepal. *Lepr Rev*, 1984; **55;** 273.

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Ciprofloxacin (4-quinolone) and *Mycobacterium leprae*

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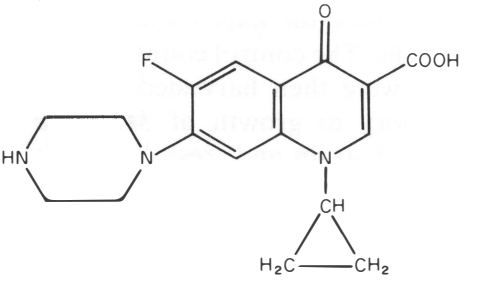
Summary A new synthetic antimicrobial agent, ciprofloxacin (4-quinolone compound), active against a wide variety of bacteria including *Mycobacterium tuberculosis* was tested in the mouse footpad system against *M. leprae*. At doses tested, ciprofloxacin was found to be ineffective in suppressing the growth of *M. leprae*.

Introduction

Dapsone has been the mainstay of treatment of leprosy for over 40 years especially in areas where the disease occurs most commonly. Other more active bactericidal drugs have been introduced during the last 15 years but these are much more expensive for use in national programmes and some like clofazimine cause unsightly skin pigmentation problems. Dapsone resistance, both secondary and primary, is now posing a real threat to the control programmes and a search for new, safe and cheap compounds including development of new bactericidal drugs has been strongly emphasized.[1] A new group of synthetic quinolone compounds related to nalidixic acid has recently been developed, some of which have been found to be actively bactericidal against a wide variety of Gram-negative and Gram-positive organisms.[2] Most active amongst these, so far, is ciprofloxacin (see below).



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This, in common with other 4-quinolone compounds, acts by interfering with DNA gyrase (topoisomerase) enzymes which are needed to supercoil strands of DNA in order to fit these long filaments in the bacterial cell.[3] Ciprofloxacin also affects RNA synthesis at higher concentrations. In *in vitro* studies ciprofloxacin has been found to be inhibitory to the growth of *M. tuberculosis*.[4] A further quinolone, ofloxacin was found to have similar antimycobacterial activity *in vivo*[5] but was markedly less active in treatment-failure cases of cavitary tuberculosis with a high incidence of resistance development during treatment.[6] In preliminary *in vitro* studies in our laboratory, ciprofloxacin has also been found to have bactericidal activity against *M. tuberculosis* (unpublished data) and the present work describes experiments to determine activity of this compound against *M. leprae* in the mouse footpad.

Materials and methods

Two strains of *M. leprae* were used in this study, 1 (Experiment 1) isolated from an untreated lepromatous leprosy patient and subsequently found to be dapsone sensitive and the other (Experiment 2) a mouse passage dapsone-sensitive strain. The detailed methods of mouse inoculation, assessment of bacillary growth in footpad homogenates, and drug–diet preparation have been previously described.[7–9] In brief, 5000 acid-fast bacilli were inoculated in 20 μl volume into the hind footpads of groups of mice. The drug was administered in dosages of 0·01%, 0·001% and 0·0001% (wt/wt) mixed with powdered mouse food from day 30 to day 90 in Exp. 1 and from day 45 to day 105 in Exp. 2 following the kinetic method.[10] When the bacillary numbers had reached about 5×10^5 in the control animals, groups of three mice were harvested from the drug-treated groups, the footpads from these mice were homogenized, slides prepared, stained and counted by an established technique.

Results

Bacterial count in the untreated control mice in Exp. 1 reached $3{\cdot}5 \times 10^5$ after 6 months but only $1{\cdot}5 \times 10^5$ in Exp. 2 (mouse passage strain). Treated animals were therefore harvested at this time for Exp. 1 while a further control harvest was made for Exp. 2 at 9 months. The control count in Exp. 2 at this time was 8×10^5 and the treated animals were then harvested also. Neither concentration of ciprofloxacin was inhibitory to growth of *M. leprae* in the mouse footpad (Figure 1). Mouse-passaged strain and fresh human isolate behaved similarly. There was a slight reduction in the numbers of acid-fast bacilli at the highest concentration in Exp. 1, but was not considered significant. No acute or chronic toxic manifestations were observed at any drug concentrations.

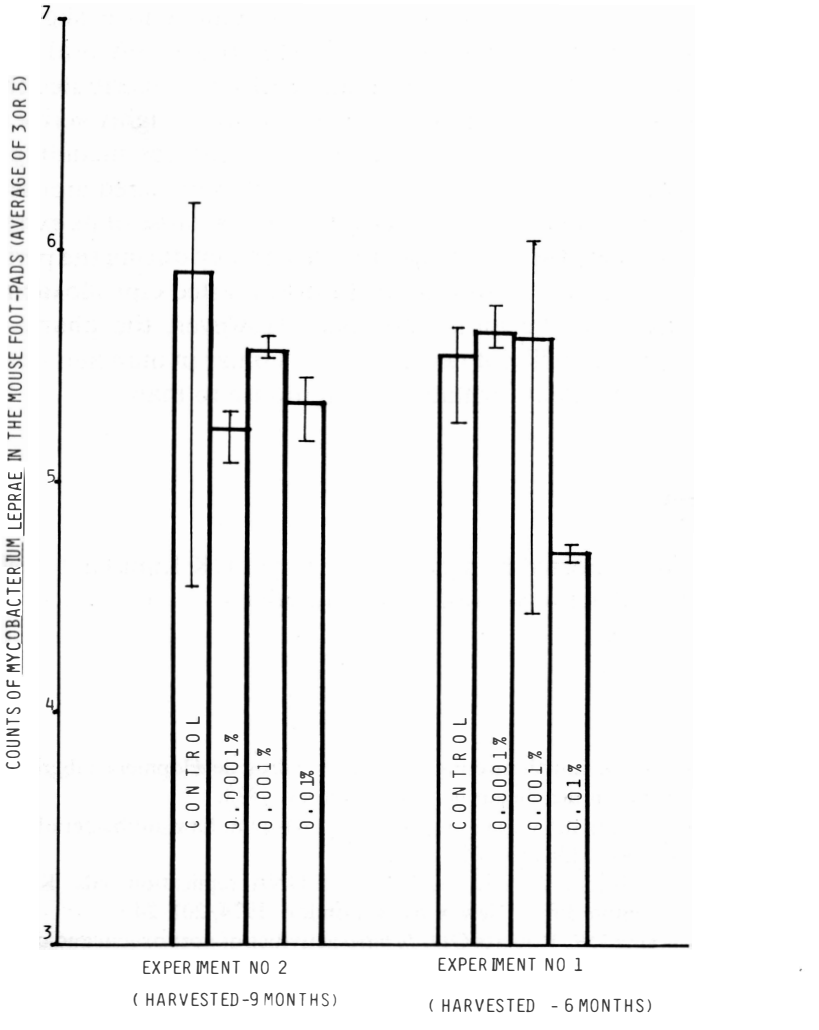

Figure 1. Effect of graded dosages of ciprofloxacin on *Mycobacterium leprae* infection in the mouse footpad. Ciprofloxacin was given for a limited period of 60 days starting 30 days after infection in Exp. 1 and 45 days after infection in Exp. 2.

Discussion

Despite its antibacterial activity against *M. tuberculosis* in *in vitro* studies, ciprofloxacin failed to inhibit growth of *M. leprae* in the mouse footpad. This is not entirely unexpected as antitubercular drugs are known to produce variable effects on *M. leprae*. Antileprosy drugs like dapsone and clofazimine, have no effect on the growth of *M. tuberculosis* while rifampicin is equally active against both organisms. The highest level of the drug, i.e. 0·01% used in this study was

equivalent to 1·5 g of the drug for a 60-kg human. This is slightly in excess of manufacturer's recommended dose, i.e. 500 mg twice daily orally in tablet form. The drug is well absorbed from the gut and uniformly distributed throughout the body (manufacturer's information). Ciprofloxacin is highly stable in acid and in aqueous solution it is stable at different temperatures including 37°C. In the present experiment ciprofloxacin was mixed with powdered mouse food, enough for about 2 weeks, and left at room temperature. Because of its extreme stability it seems highly unlikely that the drug will lose potency during the period of storage. It can therefore be concluded that at the doses tested ciprofloxacin is ineffective against *M. leprae* in the mouse footpad. However, the pharmacokinetics of ciprofloxacin in mice will not necessarily be similar in man and it is therefore not possible to extrapolate information from mouse to man.

Acknowledgment

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References

[1] WHO: Report of the fourth meeting of the *ad hoc* drug development subgroup of the Scientific Working group on the chemotherapy of leprosy. 1983.

[2] Smith JT. Awakening the slumbering potential of 4-quinolone antibacterials. *The Pharmaceutical Journal,* 1984; **233:** 299–305.

[3] Worcel A. In: Mechanism and regulation of DNA replication. eds. Kolberg AR and M Kohiyama. Plenum Press. New York & London. 1974; 201–24.

[4] Gay JD, DeYoung DR, Roberts GD. *In vitro* activities of norfloxacin and ciprofloxacin against *Mycobacterium tuberculosis*, *M. avium* complex, *M. chelonei*, *M. fortuitum* and *M. kansasii*. *Antimicrobial Agents and Chemotherap*, 1985; **26:** 94–6.

[5] Tsukamura M. *In vitro* activity of a new antibacterial substance ofloxacin. *Am Rev Resp Dis,* 1985; **131:** 348–51.

[6] Tsukamura M, Nakamura E, Yoshi S, Amano H. Therapeutic effect of a new antibacterial substance ofloxacin (DL 8280) on pulmonary tuberculosis. *Am Rev Resp Dis*, 1985; **131:** 352–56.

[7] Hilson GRF, Banerjee DK, Holmes IB. The activity of various antituberculous drugs in suppressing experimental *Mycobacterium leprae* infections in mice. *Int J Lepr*, 1971; **39:** 349–53.

[8] Holmes IB, Hilson GRF. The effect of rifampicin and dapsone in experimental *Mycobacterium leprae* infections: minimum inhibitory concentrations and bactericidal action. *J Med Microbiol*, 1972; **5:** 251–61.

[9] Holmes IB, Banerjee DK, Hilson GRF. Effect of rifampicin, clofazimine and B1912 on the viability of *Mycobacterium leprae* in established mouse footpad infection. *Proc Soc Exp Biol Med*, 1976; **151:** 637–41.

[10] Shepard CC. Studies in mice of the action of DDS against *Mycobacterium leprae*. *Int J Lepr*, 1967; **35:** 616–24.

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Immunopathogenesis of acute lepromatous uveitis: a case report

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Summary Various immunological parameters were examined in a patient with acute anterior uveitis who was also suffering from lepromatous leprosy. The most significant abnormality detected was a reduction in a subpopulation of T-lymphocytes known as suppressor cells, which occurred only during the acute attack and returned to normal once the attack subsided.

This finding leads to the speculation that acute anterior uveitis in lepromatous leprosy may be regarded as an intraocular component of erythema nodosum leprosum, precipitated by an imbalance of T-lymphocytes and probably mediated through immune-complex deposition in the uveal vasculature.

Introduction

Leprosy has the highest incidence of ocular complications of any systemic infection, and it is responsible for blindness in about 5% of those afflicted.[1]

Uveitis may occur in any form of leprosy but is commoner in the lepromatous form. It may be of 2 types: (a) *chronic anterior uveitis* in which there is a low grade bilateral uveitis associated with patchy or diffuse iris atrophy and progressive miosis. This is thought to have a neuroparalytic origin,[2] and (b) *acute anterior uveitis* (*AAU*), which is less common than the chronic type, usually bilateral, and the aetiology is thought to be due to deposition of immune complexes within the iris.[3]

One of the many systemic complications of lepromatous leprosy (LL) is a peculiar reactional state known as erythema nodosum leprosum (ENL). This is a form of vasculitis which can occur spontaneously but more often follows the introduction of chemotherapy. Histologically the lesions are characterized by an intense perivascular infiltration with polymorphonuclear leucocytes. The vessels in the centre of the lesion may show fibrinoid necrosis and endothelial swelling.

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These histological appearances in conjunction with the demonstration of immunoglobulin, complement and mycobacterial antigen deposits around blood vessels in some ENL lesions have formed the concept that ENL is an immune-complex mediated disease, similar to a type III Arthus reaction.[4] Patients with ENL may develop an acute anterior uveitis and many of the other manifestations found in chronic serum sickness including fever, lymphadenopathy, albuminuria, arthralgia, orchitis and neuritis.

Mshana[5] states that AAU as a complication of leprosy occurs only during ENL, and proposes that ENL is initiated by a decrease, absolute or relative, of suppressor T-cells. It was decided, therefore, to study various immunological parameters including T-lymphocyte subsets in the peripheral blood of a patient with AAU also suffering from LL. Any abnormalities detected might shed more light on the immunopathogenesis of acute anterior uveitis in lepromatous leprosy.

Case report

The patient, a 60-year-old man, had his lepromatous leprosy confirmed 24 years previously, 2 years after emigrating from India. At that time he had symmetrical peripheral nerve involvement of all limbs, marked nasal and palatal infiltration and stridor as a result of unilateral laryngeal leprosy. No ocular features were reported. He has had continuous treatment with daily dapsone 25 mg and clofazimine 100 mg.

His ocular symptoms began 12 years ago with intermittent discomfort of both eyes, attributable to upper and lower lid trichiasis due to atrophy of the tarsal plates and overlying muscles. He became aware of a gradual deterioration of vision from his left eye. This was due to marked miosis that was resistant to mydriatic agents. Seven years ago he had an optical iridectomy which improved the vision from 6/24 to 6/18. His present attack developed with a 1-week history of a painful, red right eye with blurred vision.

The corrected visual acuities were right 6/12, left 6/24. There was marked bilateral atrophy of the lids which resulted in upper and lower lid trichiasis that induced a fine superficial punctate keratopathy. There were small discrete opacities in the anterior 1/3 of the stroma in the supero-temporal quadrant of both corneae. Band keratopathy was more marked in the left eye. Both corneae had impaired sensation. The right eye had mild limbal injection but a dense fibrinous exudate and cellular reaction in the anterior chamber. The pupil was 2·0 mm in diameter. The left anterior chamber had a flare and no cells, a 1·5-mm pupil that could not be dilated and an iridectomy in the infero-temporal quadrant. There was diffuse atrophy of both irides. Intraocular pressures were 7 mmHg in each eye. The acute anterior uveitis responded to hourly dexamethasone 0·1%, atropine 1% qds over 1 month but a residual flare remained.

Laboratory investigations

Venous blood was examined during the acute attack of anterior uveitis and during remission, 5 months later.

LYMPHOCYTE PARAMETERS

The following techniques have previously been described in detail.[6] Briefly, lymphocytes were isolated by a standard density gradient technique using Ficoll–Paque. Total number of T-cells were estimated by an E-rosetting technique using neuraminidase-treated sheep red blood cells. The number of helper and suppressor T-cells was measured by an indirect immunofluorescence technique after incubation with the monoclonal antibodies OKT4 and OKT8 (Ortho Diagnostics) respectively.

Table 1. Immunological parameters measured during the acute attack of anterior uveitis and in remission in a patient with lepromatous leprosy.

Parameter	Acute attack	Remission	Normal values
Total lymphocyte count (10^9/l)	2·52	2·48	1·5–4·0
% E-rosetting T-cells	58	55	65–75
% Helper T-cells (OKT4 + ve)	37	37	36–43
Suppressor T-cells (OKT8 + ve)	16	22	22–26
Helper/suppressor (OKT4/OKT8) T-cell ratio	2·31	1·68	1·54–1·99
Serum immunoglobulins (g/l)			
IgG	18·4	20·9	6·0–15·0
IgA	6·34	6·97	0·95–4·0
IgM	0·925	1·12	0·6–3·0
Antinuclear antibody	+ ve 1:10 dilution	+ ve 1:10 dilution	15% + ve
Antismooth muscle antibody	− ve	+ ve 1:10 dilution	16% + ve
Antigastric parietal cell antibody	− ve	− ve	3% + ve
Circulating immune complexes (% IgG)	0·25	0·55	0·08–0·82

The values obtained were compared to those of a large group of healthy controls. All measurements (patient and controls) were performed by one of the authors (PIM).

The measurement of lymphocyte subpopulations was carried out the same day the blood was taken, because blood stored at 4°C is known to produce a low yield of E-rosetting and helper T-cells.[7]

CIRCULATING IMMUNE COMPLEXES (CIC)

CIC were precipitated by a standard polyethylene glycol (PEG) technique.[6]

SERUM ANTIBODIES

Circulating antibodies to nuclear material, smooth muscle and gastric parietal cells were detected by a standard indirect immunofluorescence technique.

SERUM IMMUNOGLOBULINS

Serum IgG, A and M were measured using a standard rate nephelometric technique.

Discussion

Various immunological abnormalities have been reported[8] in patients with lepromatous leprosy, including polyclonal hypergamma globulinaemia and autoantibodies against a wide range of antigens. It was not surprising, therefore, that raised IgG, IgA, antinuclear and antismooth muscle antibodies were found in this patient's serum.

The most important finding in this patient, however, was the abnormality in T-lymphocyte parameters. Although the total lymphocyte count was within normal limits, the total T-cell values during the acute attack and in remission (as measured by the number of E-rosettes) were decreased. During the acute attack of anterior uveitis the number of suppressor T-cells (TS) was found to be decreased but the number of helper T-cells (TH) was within normal limits, thus causing an increase in the helper:suppressor (TH:TS) T-cell ratio. During remission, however, the number of TS returned to normal as did the TH:TS ratio. Although only two samples were taken (during the acute attack and remission) the blood was drawn at the same time of the day on both occasions and the lymphocytes analysed immediately by PIM. Diurnal variation[9] of lymphocyte subpopulations and the effect of temperature and storage[7] were, therefore, eliminated. The reproducibility of the technique has been confirmed in a previous study[10] which measured lymphocyte subpopulations repeatedly over a six-month period.

Various T-lymphocyte abnormalities have already been described in leprosy. E-rosetting T-cell values have been found to be decreased in 2 studies,[11,12] 1 of which also showed an increase in B-lymphocytes. Tuberculoid leprosy appears to show no abnormalities in T-cell subsets, but lepromatous patients exhibit striking variations.[13–15] Treated LL patients show normal numbers of TH and TS but untreated LL patients have raised numbers of TS and slightly reduced numbers of TH causing a decrease in the TH : TS ratio. It is interesting to note, however, that LL patients with ENL show decreased numbers of TS, thereby causing an increase in the TH : TS ratio. This abnormality is not permanent and in patients who remain free of ENL for a few weeks the TH : TS ratio returns to normal. The latter findings were also a feature in our patient.

Reduced numbers of TS (which have also been found in other ophthalmological conditions including Graves' ophthalmopathy,[16] recurrent herpes simplex keratitis[17] and Mooren's ulcer[6]) may lead to unchecked helper T-cell activity resulting in the overproduction of serum autoantibodies, raised serum immunoglobulins and immune-complex mediated inflammation.

In a histopathological study of iris biopsies obtained during cataract extraction in patients with lepromatous leprosy, 13 out of 27 cases had histological evidence of active inflammation and the tissue was infiltrated by lymphocytes, plasma cells and mast cells. Five of these also showed evidence of vasculitis and perivasculitis suggesting that the disease may have started as an acute anterior uveitis. The vasculitis probably represents an immune-complex mediated reaction, although a type II or type IV allergic reaction following deposition of bacteria-derived antigens on the vascular endothelium cannot be excluded.

Although acute anterior uveitis in lepromatous leprosy occurs as a manifestation of ENL, raised circulating immune complexes (using a PEG precipitation technique) were not found in this patient. This finding is not unusual as many patients with nonleprous AAU also have normal levels of circulating immune complexes (CIC). The reason for this may be that immune complexes are either formed locally or appear only intermittently during the disease process and therefore may not be present in the circulation all the time. Recent studies[18] have shown specific receptors for the Fc portion of the antibody molecule and for certain components of complement in the capillaries and along the basement membrane of the ciliary body. It is possible, therefore, that the uveal tract acting as an 'affinity column' could become a repository for phlogistic antigen–antibody aggregates irrespective of the level of CIC. Alternatively immune complexes may be generated within the uveal vessels by sequential binding of antibody, complement and circulating antigen leading to acute inflammation.

One can speculate from the findings in this case report that the immunopathogenesis of AAU in LL may be regarded as an intraocular component of ENL, precipitated by a reduction in TS and probably mediated through immune-complex deposition in the uveal vasculature.

Acknowledgments

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References

[1] ffytche TJ. Iritis in leprosy. *Trans ophthal Soc UK*, 1981; **101:** 325–7.

[2] ffytche TJ. Role of iris changes as a cause of blindness in lepromatous leprosy. *Br J Ophthalmol*, 1981 **65:** 231–9.

[3] Hobbs HE, Harman DJ, Rees RJW, McDougall AC. Ocular histopathology in animals experimentally infected with *Mycobacterium leprae* and *M. lepraemurium*. *Br J Ophthalmol*, 1978; **62:** 516–24.

[4] Wemambu SNC, Turk JL, Waters MFR, Rees RJW. Erythema nodosum leprosum: a clinical manifestation of the Arthus phenomenon. *Lancet*, 1969; **ii:** 933–5.

[5] Mshana RN. Hypothesis: erythema nodosum leprosum is precipitated by an imbalance of T-lymphocytes. *Lepr Rev*, 1982; **53:** 1–7.

[6] Murray PI, Rahi AHS. Pathogenesis of Mooren's ulcer: some new concepts. *Br J Ophthalmol*, 1984; **68:** 182–7.

[7] Murray PI, Rahi AHS. Effect of temperature and storage on lymphocyte subpopulations. *Lancet*, 1983, **ii:** 1373–4.

[8] Wager O. Immunological aspects of leprosy with special reference to autoimmune diseases. *Bull Wld Hlth Org*, 1969; **41:** 793–804.

[9] Ritchie AWS, Oswald A, Micklem HS, Boyd JE, Elton RA, Jazwinska E, James K. Circadian Variation of Lymphocyte subpopulations: a study with monoclonal antibodies. *Br Med J*, 1983; **286:** 1773–5.

[10] Murray PI, Dinning WJ, Rahi AHS. T-lymphocyte subpopulations in uveitis. *Br J Ophthalmol*, 1984; **68:** 746–9.

[11] Dwyer JM, Bullock WE, Fields JP. Disturbance of the blood T:B lymphocyte ratio in lepromatous leprosy. *New Engl J Med*, 1973; **288:** 1036–9.

[12] Nath I, Curtis J, Bhutani LK, Talwar GP. Reduction of a subpopulation of T lymphocytes in lepromatous leprosy. *Clin exp Immunol*, 1974; **18:** 81–7.

[13] Bach M-A, Chatenoud L, Wallach D, Phan Dinh Tuy F, Cottenot F. Studies on T-cell subsets and functions in leprosy. *Clin exp Immunol*, 1981: **44:** 491–500.

[14] Wallach D, Cottenot F, Bach M-A. Imbalances in T cell subpopulations in lepromatous leprosy. *Int J Lepr*, 1982; **50:** 282–90.

[15] Mshana RN, Haregewoin A, Harboe M, Belehu A. Thymus dependent lymphocytes in leprosy. 1. T lymphocyte subpopulations defined by monoclonal antibodies. *Int J Lepr*, 1982; **50:** 291–6.

[16] Felberg N, Sergott R, Savino P, Blizzard J, Schatz N. Lymphocyte subpopulations in Graves' ophthalmopathy. *Arvo Abstracts.* Supplement to *Invest Ophthalmol visual Sci.* St. Louis: Mosby, 1983; 192.

[17] Stelzer GT, Eiferman RA, Watson S. Alterations in T-cell subsets in patients with recurrent herpes simplex keratitis. *Arvo Abstracts.* Supplement to *Invest Ophthalmol Visual Sci.* St Louis: Mosby, 1983; 192.

[18] Lowder CY, Lyon H, Char DH. C3b receptors in the human uveal tract. *Arvo Abstracts.* Supplement to *Invest Ophthalmol Visual Sci.* St. Louis: Mosby, 1983; 38.

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SPECIAL ARTICLE

Flow charts for use in leprosy control programmes

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Introduction

These charts were developed as a personal exercise during a visit to Green Pastures Leprosy Hospital, Pokhara, Nepal. They are an attempt to summarize in a readily accessible format the clinical and administrative 'standing orders' which govern the work of leprosy control project paramedical workers in remote clinics. They could be modified and translated for use in other settings.

Purpose of flow charts

The charts do not cover the diagnosis and classification of leprosy. They are intended to be used in the follow-up of patients once appropriate therapy has been initiated. Such patients constitute the majority of attenders at leprosy clinics.

CHARTS 1 AND 2

These cover the routine assessment of patients on multidrug therapy (MDT) and the decision to discharge those who have completed treatment. The charts select those patients who may have potentially serious problems and divert them to charts 3 and 4 for fuller assessment. All patients must progress to one of the end points on chart 2.

CHARTS 3 AND 4

These deal with selected 'problem patients' currently receiving MDT and discharged patients returning with immunological reactivation or bacteriological relapse. The chart does not differentiate types of reaction but directs attention to the symptoms and severity of the reaction and its initial management.

Policy in Western Nepal is to refer to hospital all patients with reactions and other significant problems. LCP paramedics have Aspirin, chloroquine, atropine and steroids to initiate treatment.

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Use of flow charts

The major use of these charts would be in the education of new staff. Conventional teaching methods pass on large quantities of confusing and seemingly unrelated detail. These charts integrate and organize this material and direct attention to the only important question, 'What should I do now for this patient?'

Students could use the charts under supervision at an early stage in their training. They would rapidly assimilate the content and logic of the charts. 'Learning by doing' increases confidence, teaches decision making and reinforces classroom teaching.

The charts could also be a useful 'aide-memoire' for health workers who only see an occasional leprosy patient.

Acknowledgments

I would like to thank H Bedenbender, Leprosy Control project Staffworker of Pokhara, Nepal and Dr F Ross of the American Leprosy Mission for helpful advice.

Chart 1(a). Compliance–adherence to prescribed medication.

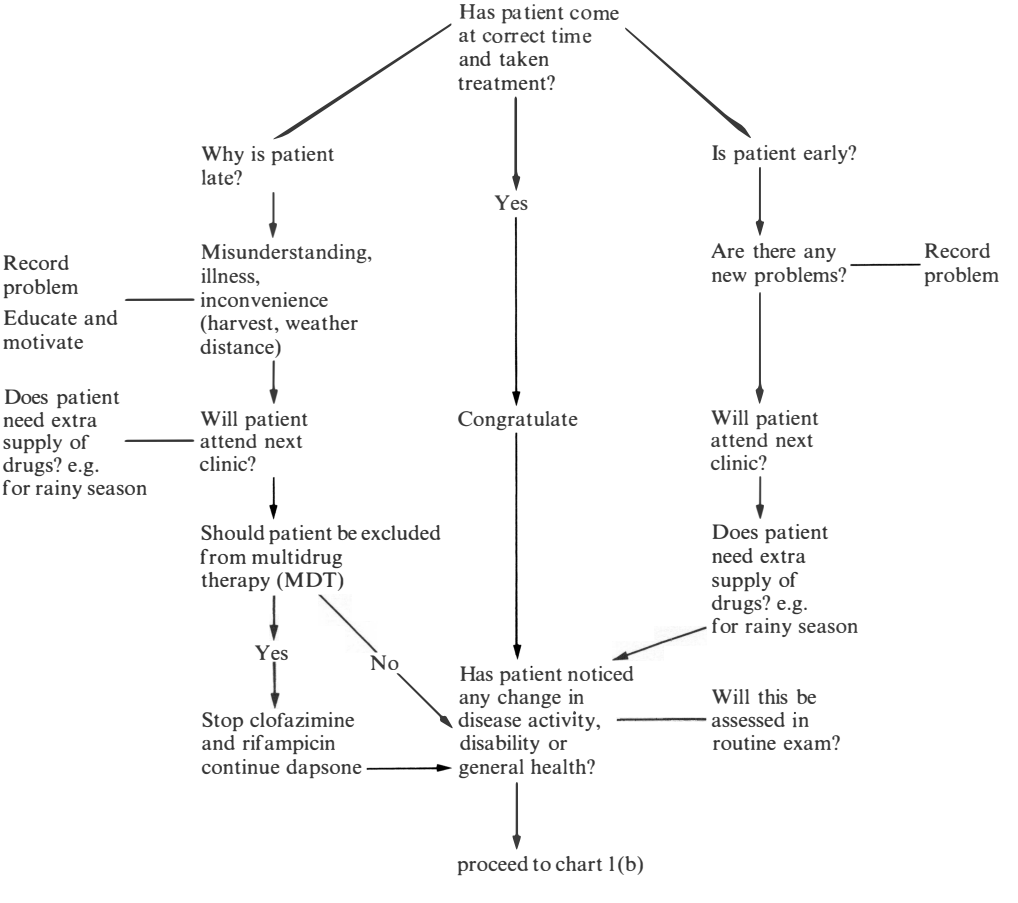


Chart 1(b). Clinical examination and assessment.

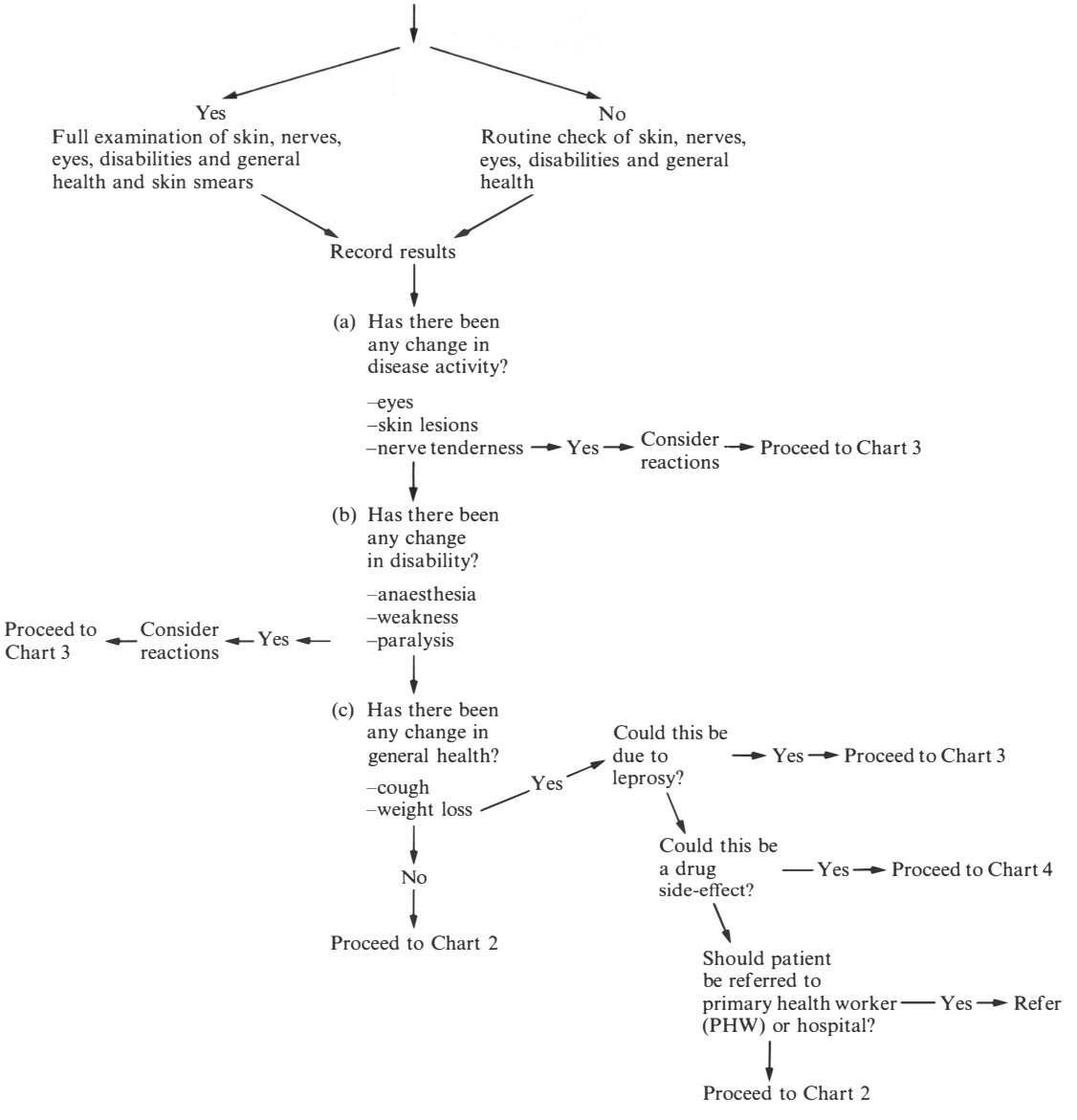


Chart 2(a) Supervision of multidrug therapy.

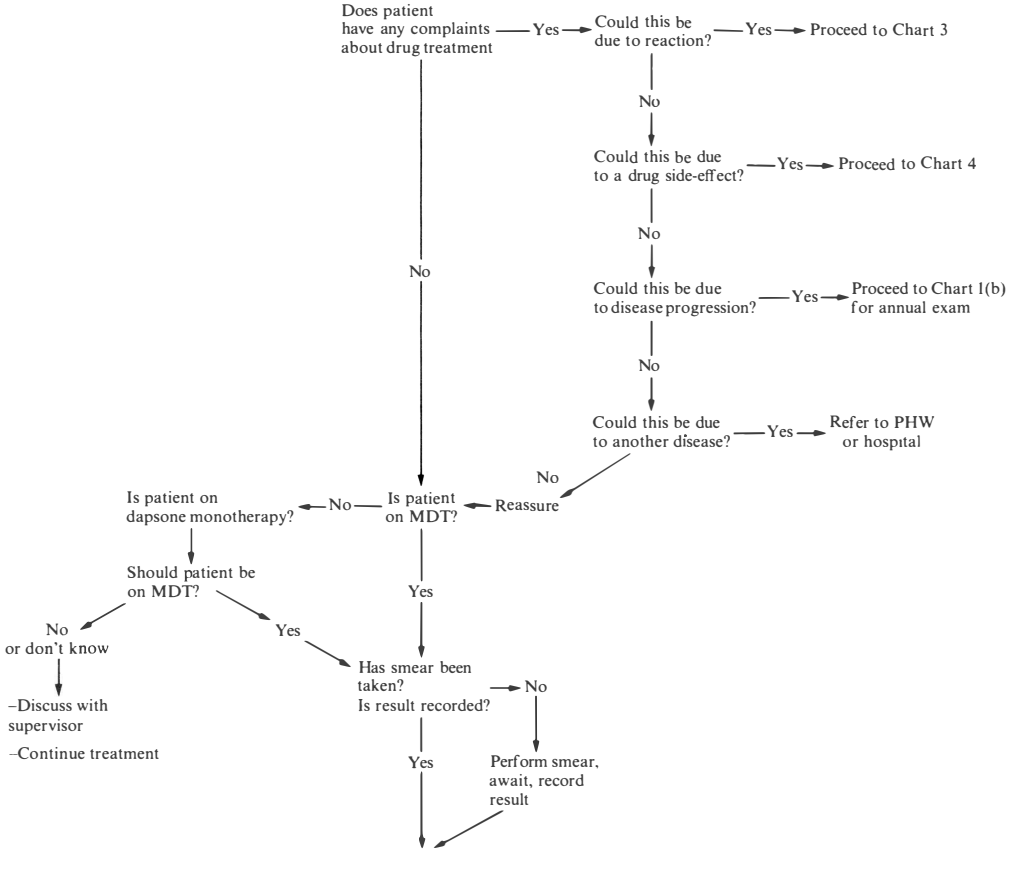


Chart 2(b). Duration of multidrug therapy.

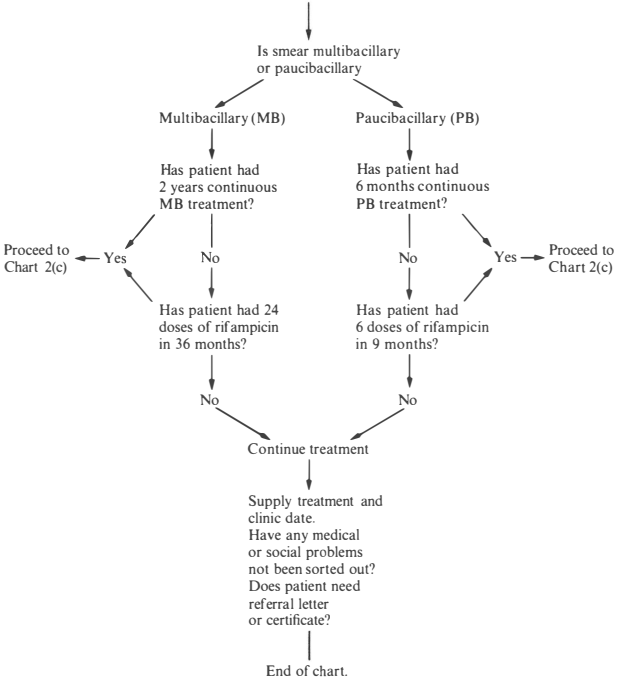


Chart 2(c). Progress and termination of multidrug therapy.

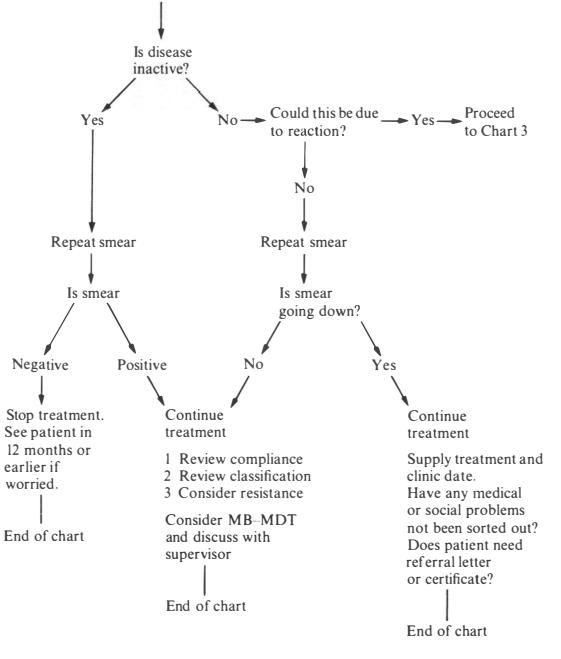


Chart 3. Problems, reactions and relapse.

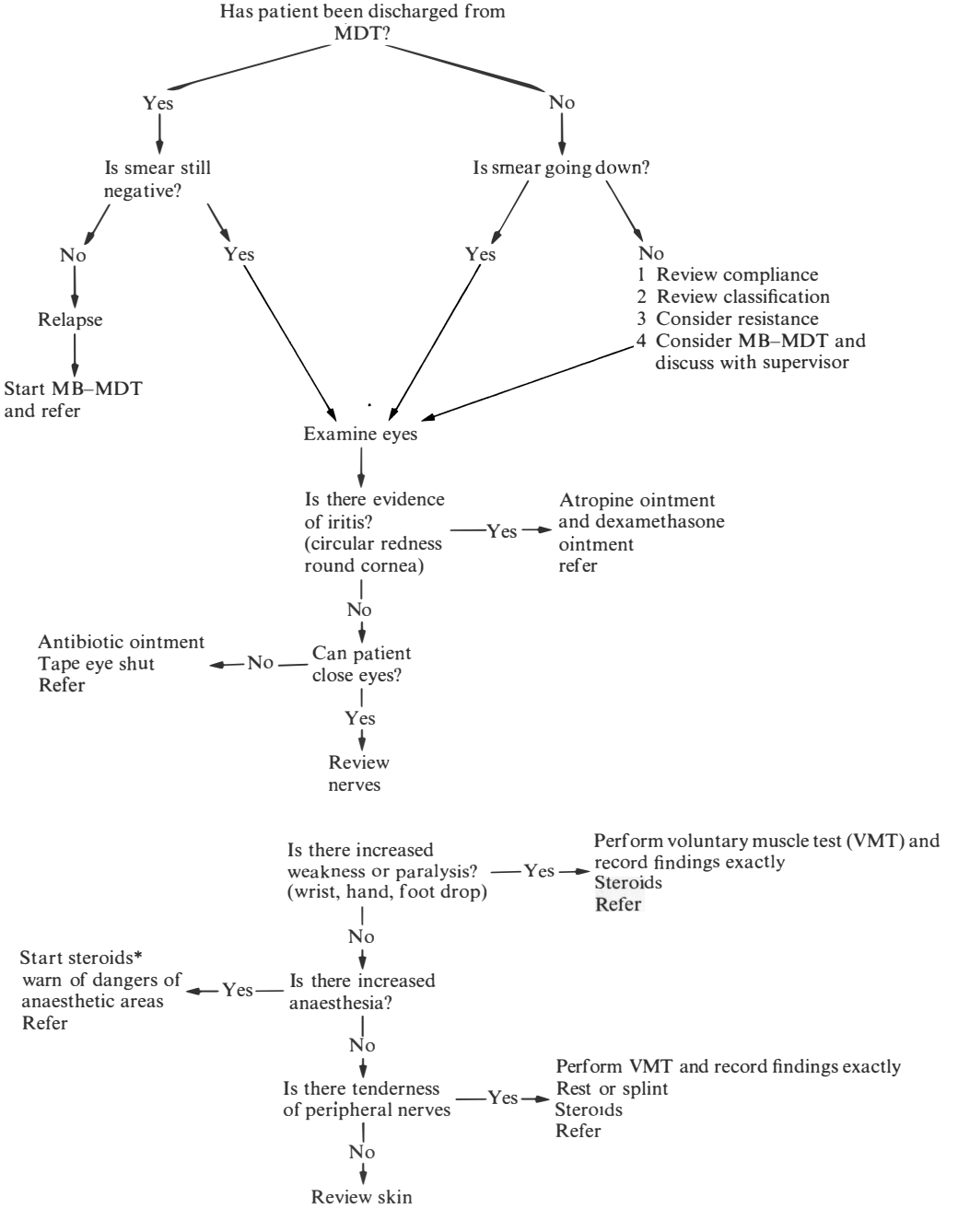
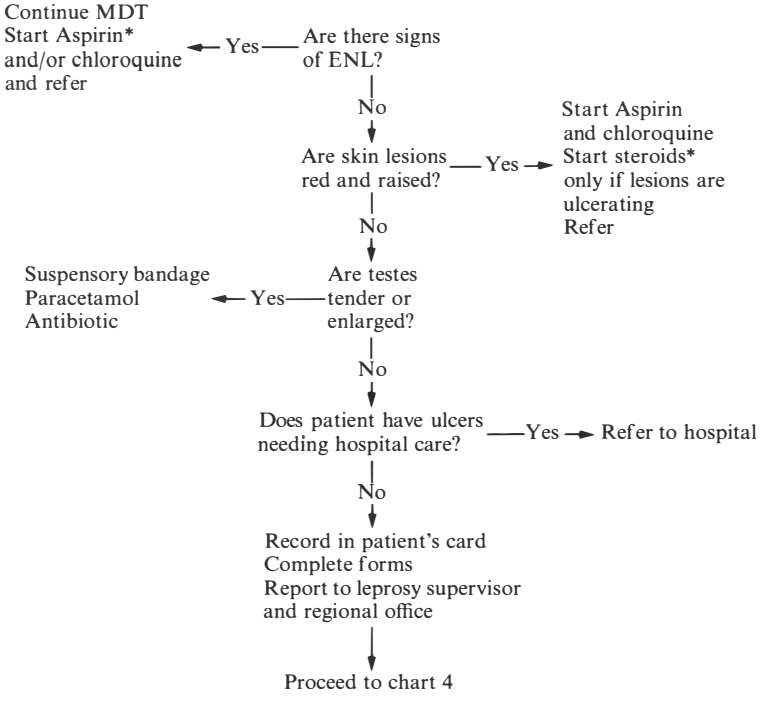


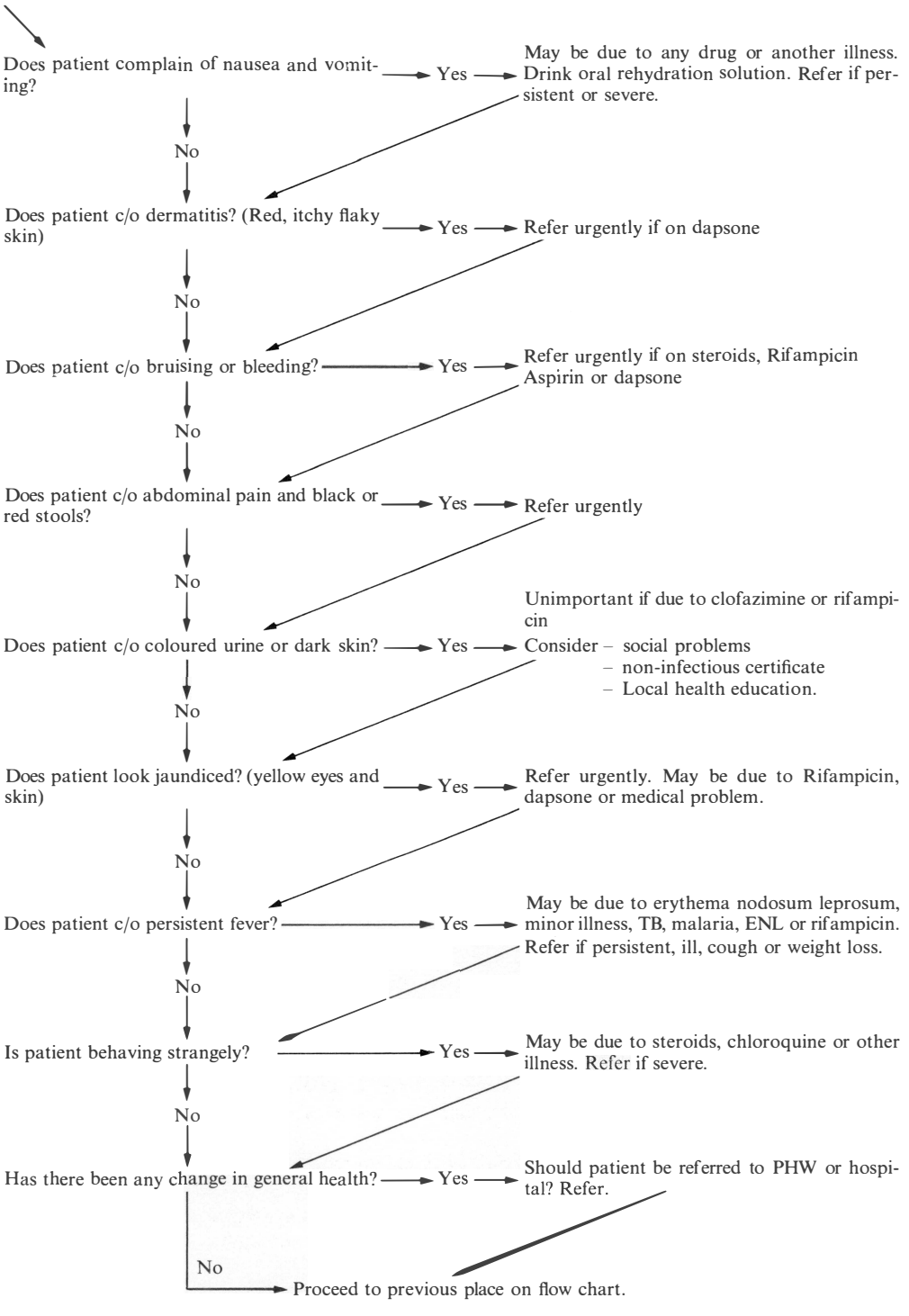
Chart 3 (*cont.*)



* Do not use Aspirin and steroids together.

Chart 4 overleaf

Chart 4. Medical problems and drug side-effects.



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Obituary

DR STANLEY G. BROWNE
CMG, OBE, MD, FRCS, FRCP, DTM
1907–1986

Dr S G Browne, a world authority on leprosy and a lifelong medical missionary, died suddenly on 29 January. He was 78.

Stanley George Browne was born in England on 8 December 1907 and studied medicine at King's College Hospital, graduating MB, BS with honours in 1933; by 1935 he had gained both the FRCS and the MRCP. He then served for 23 years with the Baptist Missionary Society at Yakusu in the Belgian Congo (now Zaire) from 1936 to 1959. He was in charge of an area of 10,000 square miles, in which he developed from scratch a programme of comprehensive community care based on 18 health centres and 36 treatment centres. This pioneering programme was an outstanding achievement and became a model in Africa for the control of endemic diseases.

By 1959, when Stanley left the Congo, his achievements in the control and treatment of tropical diseases were respected and well known, particularly because of his prolific publications and his flair for clear writing in both English and French. Already his special interest in and devotion to the detection and treatment of leprosy were apparent, and thus in 1959 he took over the directorship of the Leprosy Research Unit in Uzuakoli, eastern Nigeria, as well as becoming senior specialist leprologist to the government of Nigeria. From then until 1966 the reputation and achievements of Uzuakoli under the dynamic leadership of Stanley were further enhanced, particularly in the unit's use of chemotherapy. The highlight of this programme stemmed from Stanley's pioneering studies on B663, one of the then newly synthesized riminophenazine compounds. From Stanley's carefully conducted pilot and extended trials in lepromatous leprosy B663 proved to be a powerful antileprosy drug and was also found to have anti-inflammatory activity. Thus the work on one of the three most effective antileprosy drugs, renamed clofazimine, was originally undertaken by Stanley.

After leaving Uzuakoli in 1966 Stanley was invited by Dr Robert Cochrane to take over the Leprosy Study Centre in London. This he accepted, and he continued as director until the centre was closed in 1980, thereby having a focal point for consultation, training, and histopathological research on leprosy. During these 14 years in London Stanley's skill in leprosy was used locally by many organizations—for example, by the Department of Health and Social Security as adviser in leprosy, as medical consultant to the Leprosy Mission International, as medical secretary to LEPRA, and as editor of *Leprosy Review*. In his travels he visited nearly 80 countries, and he was leprosy consultant to many of them. There is hardly an honour or appointment within the world of leprosy that was not Stanley's at some stage. A prolific author on leprosy, he made more than 500 contributions to scientific literature and journals.

Throughout, Stanley remained a dedicated and active Christian; he was president of the Baptist Union in 1980–1. He is survived by his wife, Mali, and three sons.—RJWR.

DJ writes: One of Stanley Browne's chief contributions was the discovery of the larval stage of the vector of *Onchocerca volvulus*, which led to the control of river blindness over a wide area. He later founded a leprosarium at Yalisombo in which he tested the earliest supplies of diasone. His teaching and organizing abilities promoted Yakusu into being the second teaching hospital in the Congo. As

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a director, École Agrée d'Infirmiérs et d'Aides Accoucheurs, he trained several infirmiers and aids to serve 10,000 square miles in 18 community care units and 36 treatment centres. He received honours twice from the Queen and on four occasions from the king of the Belgians. He was one of those dynamos whose powers of concentration permit them never to waste a minute. This could be a little daunting to some. But any real inquirer or anyone in need who made contact with him at once found a warm heart and an unusual determination to help. Former colleagues and all who were privileged to know him are left with an indelible impression of complete reliability both as a Christian and as a scientific doctor.

Lepr Rev (1986) **57,** 179–180

Letters to the Editor

SIX MONTHS MDT FOR PAUCIBACILLARY LEPROSY: NERVE DAMAGE AND RELAPSE

Sir,

Although general experience to date indicates that the recommended six months period of dual therapy is satisfactory for the majority of patients with paucibacillary leprosy, it is apparent, perhaps particularly in India, that in some cases it may not be adequate. At the point of completing the six months' regimen, or on follow-up during the months or years after stopping treatment, active lesions in skin and/or nerves may be observed. The correct interpretation of such lesions calls for a combination of clinical and laboratory skills, which is not always available, in particular to distinguish reversal (up-grading) reaction from activity due to the continued presence of living bacteria and inflammation. I am aware that precise criteria for effecting this distinction, especially under field conditions, have yet to be developed—and this may prove a difficult task—but in the meanwhile there is one problem which should receive attention. A significant number of patients diagnosed and treated as having paucibacillary leprosy relapse *with a reaction*, frequently associated with deterioration in nerve function. The risk factors associated with such a serious and unfortunate occurrence are as yet very poorly understood and I should like to make a plea to all concerned with the implementation of MDT to initiate studies designed to define them, attention being paid to at least the following two categories of patients:

1 *Those presenting with evidence of recent nerve damage, either at the outset of or during the period of MDT.*

We need much more information about this group, especially as concerns their response to steroids and the need to provide continued MDT cover if steroids have to be maintained beyond the six months period.

2 *Those who relapse with reaction (reversal, upgrading) after MDT has been stopped.*

Our experience[1] in ALERT, Addis Ababa, indicated that accurate classification may be of particular relevance in this context; we found that in BT cases reaction tended to occur during the first six months of dapsone monotherapy, whereas in BB/BL cases a considerably longer interval generally elapsed. As far as I am aware there are no published reports of a similar difference in cases on MDT, but it needs to be emphasized that differentiation between multibacillary and paucibacillary leprosy is not always easy, even with reliable skin smears, and that patients who relapse with reaction substantially after the six months period of the regimen recommended for paucibacillary leprosy may, in fact, have been multibacillary from the outset. Further studies, both to investigate this possibility and to determine the optimum treatment to prevent resultant disability, would clearly be of great value.

34 Upland Road, Sutton, Surrey SM2 5JE H W WHEATE

References

[1] Naafs B, Wheate HW. Time interval between start of multileprosy treatment and development of reactions in patients with borderline leprosy. *Lepr Rev.* (1978) **49,** 00–00.

HYPERSENSITIVITY REACTION TO DAPSONE

Sir,

I would like to follow on from Dr Mary Joseph's report of four cases of hypersensitivity reaction to dapsone (*Lepr Rev* 1985; **56:** 315–320) by reporting a fatal case due to the same reaction.

The case was in an Indian patient and the diagnosis was based on the history and clinical presentation. The man presented in his early forties with widespread, symmetrical macules over his limbs, face and trunk with early infiltration of his face and some erythema. He was referred to the

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Belgaum Leprosy Hospital by a general medical practitioner who suspected the diagnosis of leprosy. The clinical presentation was of BL leprosy and his skin smears were positive. He denied previous treatment and was commenced on 100 mg of dapsone daily as an outpatient (this was prior to the introduction of multidrug therapy).

He was brought back to the hospital several days later suffering from fever, nausea, malaise and generalized exfoliative dermatitis. The clinical picture was suspicious of a hypersensitivity reaction to dapsone and at this point he admitted to previous treatment with dapsone. This had been prescribed elsewhere one year previously when he had developed a skin rash and jaundice several weeks after commencing dapsone therapy. He had been admitted to hospital on that occasion and a review of his hospital records revealed that the differential diagnosis then was either infective hepatitis or a drug reaction; however the dapsone was stopped and he made a good recovery. He had not taken any dapsone since that time.

On admission this time he was febrile, had generalized lymphadenopathy and an enlarged, tender liver. His liver function tests were abnormal. The dapsone was stopped and in view of his serious clinical condition he was commenced on corticosteroids. His condition rapidly deteriorated over the next 4–5 days when he became markedly jaundiced and showed evidence of acute liver failure and finally died in hepatatic coma despite high-dose corticosteroid therapy. A post-mortem examination was performed which failed to show any pathology other than the hepatic changes.

The man presumably suffered from the so called 'DDS syndrome' described by leprologists at the advent of the dapsone era. Dapsone hypersensitivity reaction was regarded as extremely serious and was not infrequently fatal.[1] However there have been few reports of this reaction in recent years and a review in the *Lancet* in 1981[2] commenting on two cases[3,4] noted that it had virtually disappeared in the previous 20 years. Since then there have been single case reports[5] and now Dr Joseph's recent report describes four cases.

The questions remain to be answered as to how common is this reaction and whether or not its frequency has increased over the last 5 years. It has been suggested that the practice of commencing dapsone therapy at 100 mg daily, as opposed to the lower doses used formerly, has increased the incidence of the reaction;[3] but this is in conflict with the view that the hypersensitivity reaction to dapsone is not related to the dose.[4] The lack of reports of the reaction in recent years can be explained in three ways; the reaction is occurring but is not being recognized, or it is occurring and being recognized but is not being reported, or finally the reaction is extremely rare. It is very important that we establish which of these possible explanations is the right one.

It seems very improbable that Dr Joseph would come across four cases in a short period of time if the condition was extremely rare which suggests that one of the first two explanations may be the right one. If the condition is increasing in frequency it is important that we establish this since the cause may be a preventable one such as an impurity in the dapsone manufacture or a drug interaction associated with the new multidrug therapy.

I suggest that a centralized recording system is set up for the notification of suspected cases of hypersensitivity reactions to dapsone. It would be necessary to enrol treatment centres first rather than simply recording suspected reaction so that a true estimate of the frequency can be made. Cases of suspected reactions or death within 2 months of the commencement of treatment with dapsone should be reported giving details of the dose, manufacturer and batch number of the dapsone tablets prescribed as well as the detailed clinical history of the patient.

Cardiovascular Epidemiology Unit W C S SMITH
Ninewells Hospital and Medical School, Dundee DD1 9SY

References

[1] Cochrane RG, Davey TF. Leprosy in theory and practice. John Wright and Sons Ltd, Bristol 1964: 378.

[2] Anonymous. Adverse reactions to dapsone. *Lancet* 1981; **2:** 184–185.

[3] Frey HM, Gershon AA, Borkowsky W, Bullock WE. Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; **94:** 777–779.

[4] Tomecki KJ, Catalano CJ. Dapsone hypersensitivity. *Arch Dermatol* 1981; **117:** 38–39.

[5] Kromann NP, Vilhelmsen R. The dapsone syndrome. *Arch Dermatol* 1982; **118:** 531–532.

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Leprosy Control and Field Work

Plastic containers for clofazimine (Lamprene)
Ciba-Geigy have written to inform us of the availability of small plastic containers for clofazimine, devised to take 30 capsules of 50 mg, or 15 capsules of 100 mg, for daily self-administration by patients in either paucibacillary or multibacillary leprosy. They have a strong screw cap and the contents should be airtight. The company will supply them in reasonable quantities entirely free of charge; apply to Mr Peter Friedli, Ciba-Geigy, Pharma International, CH-4002, Basle, Switzerland.

Questions and Answers on the Implementation of Multiple Drug Therapy (MDT) for Leprosy
The Health Unit in OXFAM have recently revised and reprinted this booklet in their Practical Guide series, Number 3. It is a 35-page booklet covering the basic regimens recommended by WHO for the treatment of both paucibacillary and multibacillary leprosy, proceeding to a number of questions which have been raised by those using MDT in the field, and attempting to supply some of the answers. The appendices include; 1, a description of the OXFAM–LEPRA teaching–training pack of materials on leprosy; 2, a flow chart; 'basic steps for consideration in the implementation of MDT'; 3, quality control of slit-skin smears, 4, a copy of a chart for the bacteriological index (BI) in leprosy; 5, a body diagram for slit-skin smears or biopsies; 6, a grid system/diagram for the charting of lesions, slit-skin smears or biopsies; and 7, a scheme taking one from the 'start of MDT' to 'completion of surveillance'. Price £1.50, from The Health Unit, OXFAM, 274 Banbury Road, Oxford OX2 7DZ, England.

Ganta Leprosy Center, Liberia, Africa
Particularly in view of its importance in the teaching and training of Liberian medical students in leprosy, we record the following information about this centre: The Ganta Leprosy Center was founded by the Methodist Mission in the early 1930s for victims of leprosy for which there was no cure at that time. The Methodist Mission took care of the Center up until 1976 when the National Leprosy Control Program took over. In April 1980, Sister Dr Margaret Chambers became the resident doctor with the task of revitalizing the Center as the only Referral Hospital for leprosy patients in the country. It handles severe cases of leprosy, those with complications of the disease like reaction, neuritis, ulcers, eye involvement, those needing surgery, etc. requiring hospitalization.

At the Center we now have 120 patients hospitalized, 200 patients who live at the Center for follow-up and observation, 40 patients who require custodial care as they are too crippled to manage on their own, and there is a group of 350 people who live in the town at the gate, which consists of patients, ex-patients, and the families.

One of our main goals is to help the patients help themselves, and many projects have been developed at the Center to help them achieve a degree of self-sufficiency so that they may be self-supporting when they return to their villages. Efforts are made to involve all the patients. Those who are not strong enough for farming are directed to the Arts and Crafts Project, where they learn a skill they can cope with. Full address: Ganta Leprosy Center, PO Box 1010, Monrovia, Liberia.

Bubble or calendar packs for multiple drug therapy in leprosy
Recently, in association with the Sasakawa Memorial Health Foundation, Ciba-Geigy in Switzerland have developed bubble or calendar packs for the dispensing of multiple drug therapy to patients with both paucibacillary and multibacillary leprosy. A diagram of one side of the pack for multibacillary patients is shown below; a similar but smaller pack has been made for the treatment of paucibacillary leprosy using only two drugs (dapsone and rifampicin). A few thousand of these packs have been produced in Manila and are currently in use in two different areas of the Philippines. Plans are under discussion for a controlled clinical trial, possibly in Thailand, to establish if this 'device' significantly improves patient compliance and regularity of attendance. The expense of production is of course considerable and there is unfortunately no guarantee that tablets once removed by the patient at home (during self-administration of dapsone or clofazimine) will be ingested.

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However there is preliminary evidence that the packs are highly appreciated by both patients and staff and it is to be hoped that they will contribute, at least under some circumstances, to the more effective implementation of MDT. Please note that these packs are not as yet available from either of the agencies mentioned above but that we shall print further information about them in a future issue of this Journal, together with an account of any trial which may be set up.

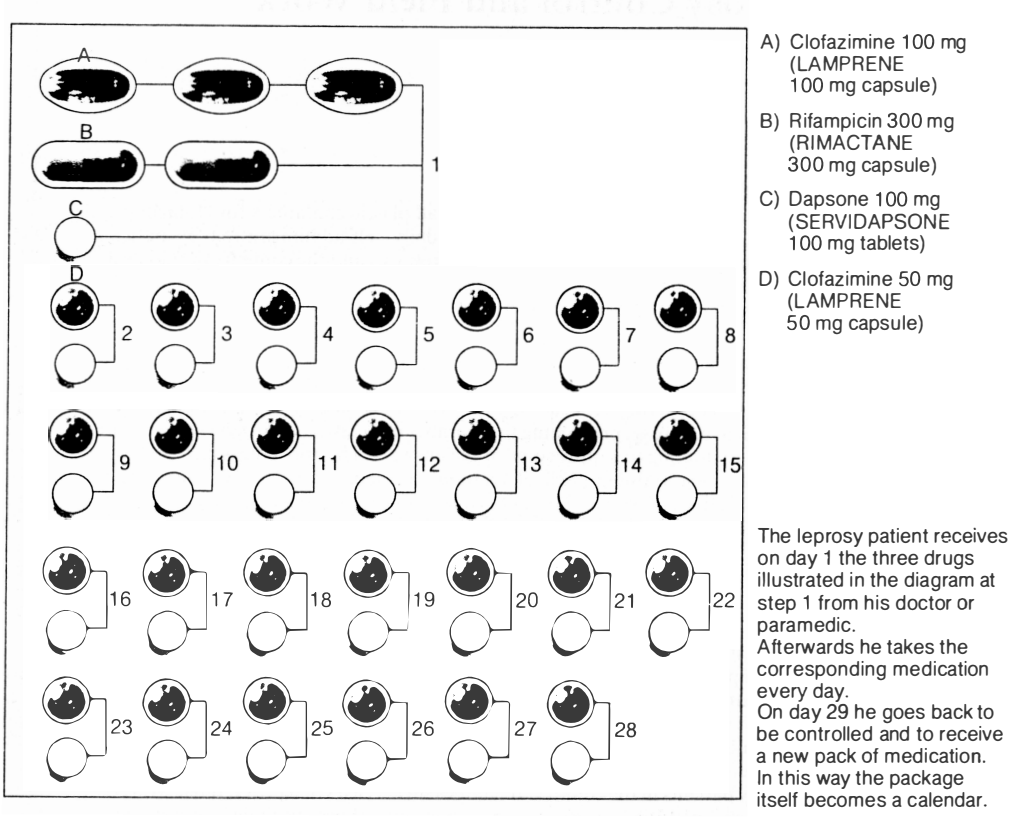

Figure 1. This diagram shows 1 side of the pack for drugs used in the treatment of multi-bacillary leprosy: those at top left are given under supervision, once monthly. Those labelled 2–28 are taken by the patient daily, at home, unsupervised. On the other side of the pack, the tablets and capsules are clearly visible in their individual 'bubbles', for pressing out at the time of administration. A similar, but smaller pack has been produced for dapsone and rifampicin in the treatment of paucibacillary leprosy.

With acknowledgements to Ciba-Geigy for permission to reproduce this diagram from their publication *Leprosy Can Be Cured*, first edition, Basle, May, 1985.

Clofazimine; a tip to prevent capsules sticking together

Many leprosy workers, particularly in hot climates, have noted with dismay that capsules of clofazimine may on occasion stick together, sometimes resulting in a more or less total loss of the content of a bottle. Dr Jon Wok Lee, WHO Medical Officer, Tomey Memorial Hospital, Suva, Fiji, has observed that this can be avoided by a simple measure. Take a tablet of dapsone and crush it into a fine powder. If this powder is then mixed or shaken up with the clofazimine capsules, it acts as a kind of separating 'talc' in the container and prevents the capsules sticking together.

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Teaching Materials and Services

TALMILEP

On the occasion of the ILEP meeting in Lisbon in December 1985, TALMILEP held its first meeting as a joint project under the coordination of the German Leprosy Relief Association (DAHW). A budget was organized to cover the cost of TALMILEP's activities planned for 1986, with support from 7 member organizations within ILEP. Estimated amounts were allocated to—*Survey* of teaching and learning materials in all ILEP projects in cooperation with the ILEP Coordinating Bureau; *Assessment* of materials under the guidance of Dr Felton Ross (American Leprosy Missions, Inc.); *Production* of various items, including a French language edition of the *Technical Guide for Smear Examination for Leprosy by Direct Microscopy*, published by the Leprosy Documentation Service in Amsterdam, *Leprosy in Africans* by Jacyk in English/French, *Essentials of Leprosy* by Pearson and Ross, *The Diagnosis and Management of Leprosy Patients from ALERT*, Addis Ababa, *Chart for the Bacteriological Index* (*BI*) *in Leprosy* from Oxford; *Distribution* mainly by the Leprosy Mission International in London. Additional plans are under discussion for the translation of various items of teaching–learning material into other languages and their distribution. Contact: TALMILEP Secretariat, German Leprosy Relief Association, Postfach 348, D-8700 Wurzburg 11, W. Germany.

Principles of health education

The following is taken from a recent communication from the Centre for Medical Education, 2 Roseangle, The University, Dundee DD1 4HN, Scotland:

'Health education is an essential component of any programme to improve the health of a community, and it has a major role in promoting: (a) good health practices; (b) the use of preventive services; (c) the correct use of medications; and the pursuit of rehabilitation regimes; (d) the recognition of early symptoms of disease and promoting early referral; and (e) community support for primary health care and government control measures.

Despite the potential benefits of health education, existing schemes are often inadequate and ineffective. In this article I review a range of experiences in the developing world to identify the ingredients for effective and appropriate health education. The key decisions that form the basis for any planning are decisions over what the desired change should be, where the health education should take place, who should carry it out, and how it should be done.'

Low cost health care and manpower training

An annotated bibliography on low cost rural health care and health manpower training, with special emphasis on developing countries, has been produced by the International Development Research Office. The bibliography is published in regular volumes costing £5.00 each, and is available from I T Publications Ltd, 9 King Street, London WC2E 8HW.

The School of Medical Education, University of New South Wales, Australia

The Centre for Medical Education Research and Development was established in 1973 at the University of New South Wales through a tripartite agreement between the World Health Organization, the Commonwealth Government and the University. Its primary goal is to assist in raising the standards of health care through the advancement of education for the health professions. In September 1983 Council of the University approved a Faculty of Medicine resolution to upgrade the Centre to a School of Medical Education. The School trains teaching and administrative staff responsible for education in the health professions, assists organizations responsible for education and training programmes, and provides consultant services and conducts research.

The School operates at Faculty level within the University of New South Wales Medical School, at the national level in collaboration with various institutions within Australia, and at the regional level in collaboration with the World Health Organization as the WHO Teacher Training Centre for Health Personnel in the Western Pacific Region.

The WHO Regional Teacher Training Centre is supported by the Australian Development Assistance Bureau, the Australian Department of Health, the University of New South Wales and the World Health Organization.

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The academic programme within the University covers a Master's degree course in Health Personnel Education by course work or research, advanced study and research in the field of health personnel education leading to the degree of Doctor of Philosophy, a series of intensive courses on specific educational topics, and a seminar programme.

Enquiries to: Helen Fodor, School of Medical Education, University of New South Wales, PO Box 1, Kensington NSW 2033, Australia.

A training manual for laboratory procedure in MDT in tuberculosis and leprosy

We are grateful to Dr H C Louden, The Leprosy Mission, PO Box 447, Madang, Papua New Guinea, for sending copies of the above manual together with another on the use of the microscope. That on laboratory procedure covers all the basic steps for the examination of sputum and skin smears and is profusely illustrated with line drawings. The manual on the microscope is for staff at health centre level, emphasizing the most important practical points in the use and care of the '. . . most important machine in a laboratory'. Two courses have already been run using these manuals as the basic text, whilst collecting specimens and carrying out staining techniques in the base laboratory, under skilled supervision. Practical training is given in reading smears; results are checked and further training arranged where this is found necessary.

Videos on sale by TALC, London

Teaching Aids at Low Cost (TALC) now has a small number of videos on VHS format only for sale at £13.00 sterling, inclusive of surface mail (£2 extra for air mail). These include 'Chemotherapy of Leprosy for Control Programmes'; a 15-minute video describing multiple drug therapy for leprosy using the regimens recently recommended by WHO. Apply: TALC, PO Box 49, St Albans, Herts AL1 4AX, United Kingdom.

***Health Education Research*; a new journal**

A pilot issue of this new journal has recently appeared; it is published by IRL Press in Washington DC and Oxford UK and the policy is described in this extract from the Editorial:

'*Health Education Research* publishes original contributions across the entire spectrum of health education and health promotion. The perspective is international, and standards will be determined through conventional academic refereeing by specialists of acknowledged expertise. Its sub-title *Theory and Practice*, is quite deliberate: it publishes material both on theoretical processes and models and on their practical implementation. Contributions are thus welcome not only from academics in health education and related disciplines, but especially from practising health educators. Although the journal is to be published to academic standards, practitioners should be aware that the journal aims for a practical perspective on problems. It is the quality and relevance of *content* that matters, not whether material is structured in academic terms. Indeed, the overriding criterion of publication for any article is quite straightforward: will practising health educators gain any real understanding of the processes, rationale or philosophy underlying the health education activities in which they are currently engaged? Or, to state it more simply, "What have I learned from this that will help me in what I do?' If the answer is nothing, then the article is not for this journal.'

Executive Editor: Dr D S Leather, University of Strathclyde, Advertising Research Unit, Department of Marketing, 173 Cathedral Street, Glasgow G4 0RQ, United Kingdom.

Skin Smear Technicians' Course, Karigiri, South India

Mr George William, Training Officer at the Schieffelin Leprosy Research and Training Centre, Karigiri, PIN 632 106, North Arcot District, South India, has kindly supplied details of the syllabus used in these highly successful courses: 'Duration—3 months. Medium of Instruction: English. Course content: Introduction of leprosy—polar concept; Introduction to microbiology; Microscope—Its parts—use of a microscope; Staining of micro-organisms; Ziehl–Neelsen stain; Preparation of stain; Staining by ZN stain; Use of a chemical balance for weighing reagents; Use of volumetric flask, pipettes; % solutions; Wade's technique of slit and scrape technique; Preparation of smears from the nasal mucosa; Fixation of smears; Examination of skin smears and estimation of Ridley's Bacillary Index (BI) and Morphological Index; Technique of collection of skin scrapings for dermatophytes; Destruction of micro-organisms and various techniques used in sterilization in a laboratory; use of a hot air oven for sterilization of instruments used in the laboratory; Cleaning of glass-ware; Measures to avoid mistakes in the labelling of specimens and the writing of reports in the laboratory; Safety in the laboratory and first aid; and field trip and collection of smears under field conditions.'

A diploma in education for primary health care, Manchester, UK

A Diploma in Education for Primary Health Care is offered by the Department of Community Medicine of the Manchester Medical School and the Department of Adult and Higher Education at the University of Manchester. The three course components cover: health and the role of health education; adult education methods and skills, including an integrated intersectoral approach based on community participation; and

optional courses on literacy, adult education in developing countries, population, etc. Topics treated include the need for PHC, role of the village-level worker and of an adequate referral system, PHC in the context of integrated rural and urban development and as part of a world-wide emphasis on people's participation in development. The Diploma is an advanced award open to graduates, and to nongraduates who have relevant qualifications and experience. It may be completed in one year of full-time study, or 3 years part-time. The academic year begins in September. Inquiries about course content, fees and other administrative details, as well as requests for application forms, should be addressed to: The Administrative Assistant, Department of Adult & Higher Education, The University, Manchester M13 9PL, United Kingdom.

The African Medical and Research Foundation: AMREF

The African Medical and Research Foundation (AMREF) is an independent nonprofit organization which has been working for more than 27 years to improve the health of people in eastern Africa, mostly in Kenya, Tanzania, Southern Sudan and Uganda. AMREF runs a wide variety of innovative projects with an emphasis on appropriate low-cost health care for people in rural areas. Project funds come from government and nongovernment aid agencies in Africa, Europe and North America as well as from private donors. AMREF is in official relations with the World Health Organization. AMREF has offices in a number of countries (UK, USA, Germany, Sweden, Canada, Denmark, France and The Netherlands).

For further information please contact: *United Kingdom*: African Medical and Research Foundation, 68 Upper Richmond Road, London SW15 2RP. Tel: 01-874 0098; *Kenya*: African Medical and Research Foundation (Headquarters), P.O. Box 30125, Nairobi, Tel: 501301/2/3, 500508.

Diagnostic tests for developing country diseases; DIATECH

We recently received the following press release from PATH, Canal Place, 130 Nickerson Street, Seattle, WA 98109, USA:

The Program for Appropriate Technology (PATH), an international, nonprofit organization, is initiating a five-year project in collaboration with the United States Agency for International Development (USAID) and the Department of Immunology and Infectious Diseases, Johns Hopkins University. The DIATECH project will develop and make available diagnostic tests specifically for use in developing countries: The diseases selected for priority attention are: malaria, diarrhoeal diseases and acute respiratory diseases.

Additional diseases will be added to this list, and may include: onchocerciasis, filariasis, leishmaniasis, trypanosomiasis, acquired immune deficiency syndrome, and tuberculosis. The DIATECH project will develop diagnostic technologies through subcontracts to universities, private and public research organizations, firms, and individuals. Subcontracts will lead to the development of reagents, design of test kits, field evaluation, training, manufacturing, introduction, distribution, and impact evaluation of appropriate diagnostic systems.

Leprosy is not mentioned in this preliminary announcement, but in view of the potential role of serological tests in this disease, it may be of value to keep in mind participation by the above programme.

Posters for health education in developing countries

Although very difficult to assess in objective terms, there is a general opinion amongst health educators that carefully thought-out and designed posters, taking full account of local attitudes and traditions, may be valuable. If they are properly displayed and kept in good condition it is certainly a matter of common observation in developing (and even developed) countries, that people will indeed examine and read them, particularly in maternal and child health clinics and it seems increasingly likely that they have led to improvements in health education. The vital importance of pre-testing, revising and even testing again, has been emphasized in a recent publication on water and sanitation by Bob Linney and Ken Meharg (*Waterlines*, Volume 4, October 1985). They have also organized a number of workshops, mainly in India, for the local production of posters, and Bob Linney is keenly interested to hear from anyone who would like advice or technical help in the production of posters for leprosy. His address is: Holly Tree Farm, Walpole Lane, Walpole, Halesworth, Suffolk, UK.

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News and Notes

IV European Leprosy Symposium on Leprosy Research, Genoa, Italy, 1–5 October 1986
The main topics of this Symposium organized by Associazione Italiana 'Amici di Raoul Follereau' are: Biochemistry of *M. Leprae*; *In vitro* cultivation of *M. leprae*; Immunology; Drug development for leprosy; and Multiple drug therapy of leprosy.

The objective of the Symposium is to exchange, in the interim between two ILA Congresses, recent information and views and to promote further research.

The symposium is open to those who are already engaged in leprosy research as well as others engaged in other research projects relevant to leprosy research.

Each topic will be introduced by a position paper to be presented by an invited speaker. This will be followed by presentations of original research by other participants and discussion.

There is no registration fee but for further details of the Symposium and accommodation please write to: Organizing Secretariat, Associazione Italiana 'Amici di Raoul Follereau', Via Borselli 4, 40135, Bologna, Italy.

XXXIVth Working Session of ILEP in Lisbon, December 1985
This session included meetings of subcommittees of the Medical Commission on the monitoring of MDT programmes and research priorities; a full day for the Medical Commission proper; computer demonstrations of the latest development of the PROMIS system for project management; discussion between ILEP and the International Leprosy Association; consideration of the ALERT, Addis Ababa, budget and a final Plenary Session. Meetings also took place to make further plans for the structure of the next International Leprosy Congress, to be held in The Hague, Netherlands 1988. The Medical Commission considered: research priorities; the Karonga (Malawi) leprosy prevention study; the study of the operational effectiveness of MDT in various control programmes; alternative drug regimens, including Isoprodian; early diagnosis in leprosy; fixed combinations of antileprosy drugs; calendar or bubble packs for MDT; thalidomide and reorganization of the Medical Commission. The next meeting of ILEP will be in Edinburgh, Scotland, in the first week of July 1986.

International Federation of Anti-Leprosy Associations (ILEP)
For those who are perhaps not yet aware of the continuing activities of this organization in so many different parts of the world, we record the following information:

The International Federation of Anti-Leprosy Associations (ILEP) was founded in Berne in 1966 and groups together 25 national leprosy relief associations belonging to 20 industrialized countries. These associations are active in some 80 endemic countries where their work covers more than 800 centres/projects, caring for more than a million leprosy patients. The total annual support given is in the order of US $35 million. The main administrative bodies of the Federation are the General Assembly, which has ultimate authority and power and meets every two years, and the Standing Committee headed by the ILEP President (who is elected for a two-year period) which deals with matters referred to it by the General Assembly.

ILEP is essentially a coordinating body whose Member-Associations are members of a *working* community. It is the Member-Associations who, in their respective countries, raise the funds which allow them to undertake anti-leprosy projects in the field. Relationships between Members, whether inside or outside the Federation, are governed by one basic principle: each Member-Association is an autonomous organization in its own right, free to take its own decisions and carry out its own leprosy work.

It is the function of ILEP to set up a coordination system (Coordinating Bureau, Working Sessions, advisory bodies) which will allow the Federation to derive maximum benefit from the combined efforts of the whole community, while at the same time respecting the independence of each Member-Association. At the heart of ILEP is the Coordinating Bureau, consisting of a few staff working under the General Secretary. This office, though not operational itself, runs a computerized information network which provides operational data, i.e. data which results in some sort of action. This information is supplied by the Member-Associations and by the projects they are supporting. In return, the network produces a number of documents which have two basic functions: to let each member know what his fellow members are doing, and to allow each Association to participate as efficiently as possible in the work of the other Members, as far as they are willing and able.

0305-7518/86/057186+04 $01.00

The Medical Commission is an advisory body which regularly makes recommendations on the projects being supported by Member-Associations, especially in the area of scientific research. The Commission also draws up the ILEP Guidelines. These are a collection of broad principles which advise Member-Associations on ways in which they can apply ILEP strategy to their own projects. Each Association is free to choose in what area they wish to work and has the right to decide what projects to support. As regards the work itself, however, the Member-Associations all refer to the ILEP Guidelines for advice.

In order to facilitate the implementation of the Guidelines in the field, Working Groups have been formed—task forces which work towards promoting certain aspects of the campaign against leprosy, such as training, publicity, health education, as well as encouraging socio-economic programmes, combined leprosy/TB programmes or Primary Health Care programmes.

Address: 234 Blythe Road, London W14 0HJ.

LEPRA prize essay competition 1984

We record with pleasure the award of a first prize to Mr Michael Seckl, a medical student of University College Hospital, London, for an outstandingly good entry on the subject of 'Antibodies and Recombinant DNA Technology; Present and Future Uses in Leprosy and Tuberculosis'. His award was made at an Annual General Meeting of LEPRA in 1985 and his essay was published in the *International Journal of Leprosy*, Volume 53, Number 4, December 1985. The subjects for 1985 were either 'Leprosy will be controlled by an anti-leprosy vaccine in conjunction with chemotherapy, not by improvement in socio-economic conditions' or 'The relation between allergy and immunity in leprosy'. We would like to take this opportunity to thank the Editor of the *International Journal of Leprosy* for his continued interest in the publication of prize-winning essays from medical students in this country. Enquiries: Editorial Office, *Leprosy Review*.

Western Region Leprosy Workers Conference, Goa, India

This conference was organized by the HKNS branches of Maharashtra, Gujarat, Goa and Madhya Pradesh and National Leprosy Organisation in collaboration with the Directorate of Health Services, Goa, Rajasthan, Diu and Daman. One hundred and ninety-nine Delegates from these states attended.

In his inaugural speech Shri Baba Amte laid stress on the importance of involvement of youth in leprosy work. Dr M G Deo, Research Director, Cancer Research Institute, Bombay; Dr R Ganapati, Director, Bombay Leprosy Project and Dr M V Yellapurkar, Joint Director of Health Services (Maharashtra) in their guest lectures dealt with the 'Role of vaccine in leprosy control', 'Multidrug therapy in leprosy' and 'Strategies for eradication of leprosy' respectively.

In seven scientific sessions 29 scientific papers were presented exclusively by paramedical workers based on their field experience.

Six papers on multidrug therapy which were presented indicated in general that after two years of therapy 54% of multibacillary patients were rendered smear negative. In addition to delivery of multidrugs through paramedical staff, one of the studies also showed that therapy could be successfully practised even through student volunteers, even in difficult situations like leprosy colonies.

Though the national target is to achieve eradication of leprosy by 2000 AD, a questionnaire study conducted in Bombay indicated ignorance about the disease even amongst highly educated families. According to another study, mobile exhibitions in busy commercial points in a city like Bombay could be used to educate the public as well as to detect leprosy cases at low cost. Usefulness of transportable video equipment in medical colleges to teach leprosy was also demonstrated. Papers dealing with varied aspects like the importance of smear examination, difficulties of leprosy control programme in tribal areas, common sites of occurrence of single lesions on the body, utility of sample 'tile test' to detect DDS in urine etc., were also presented.

This conference emphasized the potential of paramedical workers and even nonsalaried volunteer force, provided proper guidance and encouragement are given.

Leprosy workers meet, Madurai, South India, 1985

Following a meeting organized by OXFAM and held in Wardha in the Gandhi Memorial Leprosy Foundation in 1982, a group of leprosy workers from various parts of Tamil Nadu met in Madurai in March 1985 to plan a follow-up meeting. With support from the Bangalore Office of OXFAM, a further meeting was indeed organized in July 1985 at the De Nobili Pastoral Centre in Madurai, attended by 136 participants, 60 of whom were from voluntary institutions, 56 from Government, 6 from community health projects; there were also 14 observers. The main group reports and discussions covered—multidrug therapy; the absentee problem; new case detection; urban problems; rehabilitation, deformity, social aspects; health education; integration with community health. Mr John Dalton summarized the likely value of this event as follows:

'For a meeting of this type it would be very hard to show concrete results; but it is hoped that some of the encouraging feedback received—to the effect that workers returned with renewed determination and new ideas—is representative. On the whole those attending gave a favourable evaluation. For many it was their first

meeting of any sort, for others it was a meeting with a difference. The mixture of workers from both Government and voluntary sectors plus the informal nature of the discussions in Tamil was much appreciated and contributed to the success of the meeting. Most of those attending got a chance to speak at the group or combined sessions and observers were generally impressed by the quality of the exchanges.'

Robert Cochrane Fund for Leprosy

The fund, in memory of the contribution of the great leprologist Robert Cochrane, is administered by the Royal Society of Tropical Medicine and Hygiene. It is to be used to finance up to 2 travel fellowships each year to a maximum value of £1000 each.

The intention is to enable leprosy workers to travel for practical training in field work, or in research, or to enable experienced leprologists to travel in order to provide practical clinical training in a developing country. There is no restriction on the country of origin or destination providing the above requirements are fulfilled.

Application forms are available from the Society and must be received by the Society at least 6 months ahead of the proposed trip. All applications must be sponsored by a suitable representative of the applicant's employer or study centre, and agreed by the host organization. A 2 page report on the travel study should be submitted to the Society within 1 month of the recipient's return. Apply: The Administrator, Royal Society of Tropical Medicine and Hygiene, Manson House, 26 Portland Place, London W1N 4EY.

XVII World Congress of Dermatology, Berlin, 1987

We have received preliminary information about this Congress which will be held in Berlin from 20 to 25 September 1987. The main headings of the programme are: special lectures; advances in dermatology; symposia; workshops; courses; free communications; case presentations; informal discussion groups; poster communications; scientific exhibitions; audio-visual communications; scientific film sessions; update educational sessions; question and answer sessions. Further information from Professor Dr C E Orfanos, General Secretary, Department of Dermatology, University Medical Centre, Steglitz, Hindenburgdamm 30, D-1000, Berlin 45, Germany.

XIII International Leprosy Congress, The Hague, Netherlands, 1988

The President and Secretary of the International Leprosy Association are happy to announce that the XIIIth International Leprosy Congress will be held at the Hague, Netherlands from 11 to 17 September 1988. The Pre-Congress Workshops will be held on 8, 9 and 10 September 1988. The Inauguration of the Congress has been tentatively fixed for the evening of 11 September 1988 and the Scientific Sessions will start on 12 September. The concluding session will be on the forenoon of 17 September 1988.

Mr H E M De Bok of the Netherlands Leprosy Association is making the arrangements for the Congress and the first Information Brochure will be sent to you by September 1985.

If you have any suggestions, please contact: Dr R H Thangaraj, Secretary ILA, No. 5 Amrita Shergill Marg, New Delhi 110003, India.

CIBA-GEIGY Leprosy Fund: 3 million Swiss francs

With the aim of contributing toward the worldwide control and eradication of leprosy, the CIBA-GEIGY Leprosy Fund was recently established in Basle, Switzerland, on the occasion of World Leprosy Day. The fund, amounting to 3 million Swiss francs, is to be administered by an executive committee comprising representatives of the International Federation of Anti-Leprosy Associations (ILEP) and CIBA-GEIGY Limited, Basle. Only ILEP-coordinated projects are eligible for support from this fund. The CIBA-GEIGY representatives are Mr E. Decosterd, Mr P. Friedli, Dr K.M. Leisinger and Professor Dr S.J. Yawalkar.

Increase of subscription to *Leprosy Review*

The price of this Journal has been well below that of other medical journals for many years and it was decided at a recent Editorial Board Meeting to increase the annual charge to £20, or £5 per copy from March 1987 onwards.

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