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CONTENTS

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Editorial

OPERATIONAL PROBLEMS IN LEPROSY PROGRAMMES WHEN THE ENDEMICITY DECLINES

In many leprosy endemic countries, the large scale application of dapsone monotherapy has been followed by a marked reduction in prevalence, but by a less marked and only gradual reduction in the case detection rate, which is the only measure of incidence available to us. It is probable that factors other than control by chemotherapy have played a part in this decline. Be that as it may, there is no doubt that the correct application of multidrug therapy (MDT) will, either directly or indirectly, have a rapid and dramatic effect in reducing the caseload in many leprosy control programmes. A very large number of cases will be assessed and discharged before MDT is introduced and this will be followed by the discharge from treatment of a high proportion of the cases of paucibacillary leprosy within the first year. There are likely to be many other changes of a varying nature and these can perhaps be divided into two groups, administrative and epidemiological.

Administrative changes

Based on long experience of the management of leprosy control projects, a Leprosy Mission International study group[1] has made the following realistic assessment of the probable effects of MDT programmes of average to low efficiency:

The case load will be reduced by 50% in 5 years.

2 Thereafter the intake of new cases will remain fairly stable and maintain the level of the case load for several years, falling only gradually—provided that similar measures are being applied in adjacent areas and that the number of new cases is not inflated by immigrants.

In programmes where the level of efficiency may be higher, the caseload reduction may be considerably greater: for instance, in Malawi,[7] in the 5-year period 1980–1984 there has been a reduction from nearly 19,000 in 1980 to just over 5000 in 1984.

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Epidemiological changes

Pointing out that there is, for several reasons, likely to be a decline in incidence rates in many leprosy endemic countries, Irgens[2] has analysed data from Norway and from several other countries where such a decline has already occurred. He draws attention to two changes in the general pattern associated with the long incubation period of many leprosy cases:

There is a shift towards the older age groups among the newly detected cases.
In most countries (India being the exception) there is an increase in the lepromatous proportion among newly detected cases.
Other workers have reported important differences, having practical implications for the organization of a control programme:
In India, in areas of low endemicity, the proportion of household infections is higher than in areas of high endemicity.[3]
In the Philippines, although there has been a decline in prevalence, the numbers of new cases have not declined to the same extent. There has, however, been a gradual regular reduction in the case detection rate.[4]
In many South American countries, on the other hand, with the exception of Venezuela, the decline in prevalence has not been accompanied by any reduction in incidence.[5]

With this background of data and expert opinion, we can now proceed to discuss the operational problems likely to beset leprosy control programmes in the future. These may be considered under the following headings:

1 The need to maintain a high standard of early diagnosis.
2 This is largely dependent on the maintenance of a degree of priority at national (and local) levels for the provision of adequate leprosy treatment, training and health education.
3 The need for periodic review of referral facilities and the care and treatment of complications.
4 The proper employment of staff with specialized training in leprosy, who will be underutilized as their caseload is reduced.

The relative importance of these four considerations is likely to vary depending in particular on whether the programme is organized vertically or is integrated with the general health service but it is probable that all will apply to some degree to all programmes.

THE NEED TO MAINTAIN A HIGH STANDARD OF EARLY DIAGNOSIS

There is a general impression—though, as far as we know, no firm evidence—that the 'Index of Suspicion' both among the public and among the staff of the basic health services is lower in areas of low prevalence. This is certainly well known in

the case of tuberculosis.[6] The less leprosy there is in the community, the less likely are members of the family and other close associates to suspect leprosy in one of their number, and similarly, the staff of the basic health unit are less likely to think of the possibility of this diagnosis. In addition, it is only to be expected that the less one encounters leprosy, the less practice one has in the clinical skills required to make the diagnosis. Although not invariable and universal, there is often a relative increase in the proportion of new cases with multibacillary leprosy, the early forms of which are often more difficult to diagnose clinically and require confirmation by skin smear, so that delay in the diagnosis of new cases is a very real danger. Continuing medical education for health staff and health education for the public are vital.

THE NEED TO MAINTAIN A DEGREE OF PRIORITY AT NATIONAL (AND LOCAL) LEVELS FOR PROVISION OF ADEQUATE LEPROSY TREATMENT, TRAINING AND FOR HEALTH EDUCATION

It will be a great temptation to assume that a decline in the overall caseload, the registered prevalence, indicates a decline in incidence and a decline in the public health importance of leprosy. As we have seen this is not so, and it requires many years of patient, painstaking work for control by chemotherapy to have an effect on the transmission of the disease. It is essential, therefore, to emphasize the importance of maintaining: (a) adequate resources in terms of personnel, drugs and other equipment in order to treat all existing and new leprosy cases; (b) an appropriate level of orientation in leprosy in the training of health personnel of all cadres and continuing refresher training for specialist staff, especially those responsible for supervision and laboratory services; (c) programmes for health education about leprosy for the general public; and (d) ensuring national policy on the above aspects is implemented at local level.

THE NEED FOR PERIODIC REVIEW OF REFERRAL FACILITIES AND THE CARE AND TREATMENT OF COMPLICATIONS

It can be deduced from the data quoted above that the numbers of patients with complications will not fall to the same extent as the total numbers under treatment. Because of delay in diagnosis it is likely that the proportion with established disability at the time of initiation of treatment will increase. The discharge from treatment of a high proportion of patients with paucibacillary leprosy will result in the accumulation of multibacillary leprosy cases on the treatment registers and possibly these may be augmented by a disproportionate number of new cases. Consequently one can expect, firstly, that the numbers of cases requiring monitoring of nerve function deficit and the preventive care of disabilities will not decrease to the same extent as the total caseload and,

secondly, that the numbers requiring specialized treatment for reaction, both reversal reaction and ENL, will remain fairly stable. In addition, the patients who are no longer under chemotherapy but who have disability will continue to need care and regular follow up, including replacement footwear, surgery and physiotherapy.

THE PROPER EMPLOYMENT OF STAFF WITH SPECIALIZED TRAINING IN LEPROSY WHO WILL BE UNDERUTILIZED AS THEIR CASELOAD IS REDUCED

Vertical programmes employing staff trained only for the diagnosis and treatment of leprosy will have to arrange for their gradual retraining and redeployment and for the integration of their duties into the general health service. This may not always be easy. There will, however, continue to be a need for specialized supervision for the reasons already cited. No doubt the quality of the service could be improved by the supervisors spending some of the time available on more informal teaching of the staff of the basic health units visited, more attention to the taking and recording of skin smears, to the monitoring of nerve function deficit and the preventive care of disabilities, and on the compilation of case records and statistics. It is probable, however, that many programmes will face strong arguments questioning whether this specialized kind of supervision is economically justifiable, and in these cases it may only be feasible if combined with other duties. In some circumstances this can be done by basing the supervisor at a Health Centre; elsewhere it may be possible to make use of his special skills in fields such as the following:

In the field of Chronic Communicable Disease Control: pulmonary tuberculosis (experience in combined TB/Leprosy Control Programmes is encouraging); trachoma; general health surveys; health education duties; and in the future, in diseases for which 'pulse' therapy may become available, e.g. onchocerciases.

2 In the care and referral of disabilities, as in leprosy cases: orthopaedic problems, such as post poliomyelitis paralysis, amputations etc., requiring firstly, referral for surgery and/or orthopaedic appliances and secondly, regular follow up; ophthalmic problems, in which all leprosy staff should have had both training and experience, firstly in the first aid field treatment of minor conditions and secondly in referral to the ophthalmic specialist.

3 In the treatment of other chronic medical conditions requiring long term regular medication and periodic supervision, which basic health services often have difficulty in supplying at village level, for example: diabetes; and certain psychiatric disorders.

We should, therefore, look to the future with optimism. Our leprosy control programmes will almost certainly cater for fewer numbers, but there must be no lowering of the standards or input from the donor agencies and, where feasible,

the staff and the facilities until now available only for leprosy sufferers, can be used to meet other needs also.

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References

[1] Askew AD. Managerial implications of Multidrug Therapy. *Lepr Rev*, 1985; **56:** 89–97.
[2] Irgens LM. Secular trends in leprosy: increase in age at onset associated with declining rates and long incubation periods. *Int J Lepr*, 1985; **53:** 610–17.
[3] Christian M. The epidemiological situation of leprosy in India. *Lepr Rev* 1981; **52:** Supplement I, 35–41.
[4] Ito T. The epidemiological situation in South East Asia. Ibid. 43–51.
[5] Motta CP. The epidemiological situation in the Americas. Ibid. 61–8.
[6] Horne NW. Problems of tuberculosis in decline. Editorial, *Brit Med J* 1984; **288:** 1249–50.
[7] Lepra in Malawi. Annual Report 1984. Lepra (British Leprosy Relief Association), Fairfax House, Causton Road, Colchester CO1 1PU, England.

Lepr Rev (1987) **58,** 7–16

Characteristics of patients in the THELEP trials of chemotherapy of leprosy at Bamako and Chingleput

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

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Summary The characteristics evident before beginning treatment of 215 lepromatous patients admitted to the THELEP clinical trials of combined chemotherapy at Bamako and Chingleput, including age, sex, BI, LIB, $\log_{10}$ of the number of acid-fast bacilli per gramme tissue, clinical classification, and histopathological classification, have, in general, been found to be uniformly distributed between treatment centres, and among the regimens within each centre. Thus, there appears little likelihood that the results of treatment by the trial regimens will have been influenced by any of these characteristics. Except for the clinical and histopathological classifications, which did not agree more frequently than predicted by chance, the expected interrelationships among these characteristics were demonstrated.

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This report was prepared by L. Levy and M. Anker.

Introduction

During the latter half of 1978, admission of patients was begun into controlled clinical trials of combined chemotherapy among previously untreated patients with lepromatous leprosy at Bamako, Mali, and Chingleput, South India. The last patients were recruited during the latter half of 1983, by which time 99 patients had been admitted to the trial in Bamako and 116 into that at Chingleput. The patients were randomized among 5 regimens,* which were to be

* Patients were allocated among 6 treatment groups, 3 in each centre; however, 1 of the 5 regimens (regimen C) was employed in both centres.

Bamako regimens:

A_2, rifampicin, protionamide and dapsone, each in a daily dose of 600, 500, and 100 mg, respectively, for 2 years;

C, rifampicin, in a single initial dose of 1500 mg, and dapsone, 100 mg daily for 2 years;

E_2, rifampicin, 900 mg once weekly, and protionamide, 500 mg daily for the first 3 months, together with dapsone, 100 mg daily for 2 years.

Chingleput regimens:

A_1, rifampicin, clofazimine and dapsone, each in a daily dose of 600, 100, and 100 mg, respectively, for 2 years;

C, as for Bamako;

D_1, rifampicin, in a single initial dose of 1500 mg, clofazimine, in a daily dose of 100 mg for the first 3 months, and dapsone, 100 mg daily for 2 years.[1]

compared in terms of effectiveness in reducing the numbers of detectable persisting *Mycobacterium leprae* in skin-biopsy specimens obtained from the patients at intervals during the trials.[1] Intensive study of the 215 patients with previously untreated lepromatous leprosy has yielded considerable information with respect to the characteristics of the patients observed before treatment was instituted. The purpose of this paper is to analyse the distributions of these characteristics among the trial regimens, and to study interrelationships among the pretreatment characteristics.

Materials and methods

The patients recruited into the two trials and the methods employed in the trials are those already described.[1] In brief, patients with LL, LI or BL* leprosy were recruited who denied prior treatment, and in whose urine dapsone and its metabolites were not detectable. At each trial centre, before treatment was begun, the patients' disease was classified clinically, multiple smears of slit skin-scrapings were examined for measurement of the bacteriological index (BI), and skin-biopsy specimens were obtained and air-shipped to the UK. The fresh specimens were weighed, the numbers of *M. leprae* counted, and the susceptibility of the organisms to dapsone measured in the Department of Medical Microbiology, St George's Hospital Medical School, London. Histopathological examination, including Ridley–Jopling classification[2] and measurement of the logarithmic biopsy index (LIB),[3] were performed on the fixed specimen in the Department of Dermatology, The Slade Hospital, Oxford.

Data were analysed by means of a number of statistical techniques, including: 1, the X^2 and Fisher exact probability techniques for comparison of frequencies among two or more categories, e.g. the various clinical classes; 2, the Mann–Whitney *U* test and the Kruskal–Wallis one-way analysis of variance, for comparison of two or more groups of data, e.g. the distribution of patient-age between centres and among regimens; 3, the product–moment correlation coefficient, for analysis of the relationships between two continuous variables, e.g. BI and LIB; and 4, Kappa, for analysis of the degree of correspondence between 2 systems of classification, e.g. CLINCLAS and HISTCLAS.[4–7]

Results

Age and sex

The distribution by age and sex of the patients admitted into the two trials is

* The Ridley–Jopling system of classification of leprosy, a system based on clinical, histopathological and other criteria, employs the following terminology: BL, borderline-lepromatous; LI (or LL_s), sub-polar lepromatous leprosy; LL (or LL_p), polar lepromatous leprosy.[2]

Table 1. Distribution of patients by age and sex.

	Bamako regimen				Chingleput regimen			
	A_2	C	E_2	All	A_1	C	D_1	All
Number of patients	12	44	43	99	39	39	38	116
Median age	26	26	25	25	29	30	25·5	29
Number of males	12	44	43	99	36	36	33	105

Patient-age did not differ significantly between centres ($P=0·08$) or among regimens within centres (for Bamako, $P=0·65$; for Chingleput, $P=0·70$). The proportions of male and female patients did not differ significantly among Chingleput regimens ($P>0·10$).

shown in Table 1. The median age may be seen to be 30 or less for all regimens in both treatment centres. No significant difference of age was found between the two centres, nor among the regimens within each centre. It is evident from the data of Table 1 that only male patients were recruited in Bamako, and only a few female patients were recruited in Chingleput; in the latter centre, the proportion of female patients did not differ significantly among the 3 regimens.

Pretreatment BI, LIB and logarithm$_{10}$ of the number of acid-fast bacilli (AFB) per gramme

Median initial values of the BI, LIB and logarithm$_{10}$ of the number of AFB per g of biopsy specimen (LAFBPG) are shown for each regimen and each centre in Table 2. The median BI lay between 4 and 5 on Ridley's logarithmic scale,[8] the median LIB between 5 and 6, and the median value of the LAFBPG between 8·3 and 8·5 (the median numbers of AFB in the pretreatment biopsy specimen lay in the range 200–300 million) for all regimens in both centres. The BI was significantly larger among Bamako than among Chingleput patients, and the LIB was significantly larger among the latter. No significant difference of the LAFBPG was found between the centres, nor of the pretreatment values for BI, LIB and LAFBPG among regimens within the centres. As expected, the individual initial values for BI, LIB, and LAFBPG were closely interrelated (see Table 3).

Clinical and histopathological classifications

The distribution of patients between treatment centres and among regimens according to clinical classification (CLINCLAS) is shown in Table 4. In both centres, the majority of patients (75% in Bamako; 69% in Chingleput) were

Table 2. Distribution of patients by initial BI, LIB and LAFBPG.

	Bamako regimen				Chingleput regimen			
	A_2	C	E_2	All	A_1	C	D_1	All
Number of patients	12	41	38	91	39	39	38	116
Median BI	4·75	4·50	4·50	4·67	4·33	4·17	4·42	4·33
Number of patients	12	44	43	99	39	39	38	116
Median LIB	5·5	5·3	5·0	5·3	5·6	5·5	5·5	5·5
Number of patients	12	42	41	95	39	37	35	111
Median LAFBPG	8·3	8·5	8·4	8·4	8·5	8·3	8·4	8·4

The BIs of Bamako patients were significantly larger than those of Chingleput patients ($P=0·003$), but no significant differences of the BI among regimens within centres were discerned (for Bamako, $P=0·23$; for Chingleput, $P=0·16$). The LIB is significantly larger among Chingleput than among Bamako patients ($P=0·01$), but no significant differences were observed among regimens within centres ($P=0·09$). No significant differences of LAFBPG were found between centres ($P=0·96$) or among regimens within centres ($P=0·54$).

Table 3. Interrelationships among the pretreatment values for BI, LIB and LAFBPG.

Interaction	(Product-moment correlation coefficient) (Probability)		
BI × LIB	0·58 / 0·0001	0·32 / 0·0005	0·44 / 0·0001
BI × LAFBPG	0·49 / 0·0001	0·49 / 0·0001	0·49 / 0·0001
LIB × LAFBPG	0·65 / 0·0001	0·38 / 0·0001	0·53 / 0·0001

Table 4. Distribution of patients by initial CLINCLAS.

	Number of patients							
	Bamako regimen				Chingleput regimen			
CLINCLAS	A_2	C	E_2	All	A_1	C	D_1	All
LL	0	7	7	14	11	8	8	27
LI	12	32	30	74	25	26	29	80
BL	0	5	6	11	3	5	1	9

The proportion of patients classified LL did not differ significantly between centres nor among regimens (for Bamako, $X^2 = 2{\cdot}26$, $P > 0{\cdot}10$; for Chingleput, $X^2 = 0{\cdot}79$, $P > 0{\cdot}90$).

Table 5. Distribution of patients by initial HISTCLAS.

	Number of patients							
	Bamako regimen				Chingleput regimen			
HISTCLAS	A_2	C	E_2	All	A_1	C	D_1	All
LL	1	1	0	2	0	1	0	1
LI	11	37	31	79	38	37	36	111
BL	0	5	9	14	0	1	2	3
Other	0	1	3	4	1	0	0	1

The proportion of patients classified BL or 'other' is significantly higher among Bamako than among Chingleput patients ($X^2 = 10{\cdot}1$; $P < 0{\cdot}01$). No significant difference of the proportion classified BL or 'other' was found among regimens within centres (for Bamako, $P = 0{\cdot}07$; for Chingleput, $P = 0{\cdot}77$).

classified LI, and the proportions of patients classified LL, LI or BL did not differ significantly between centres or among regimens within each centre. The majority of patients in both centres (80% in Bamako; 96% in Chingleput) were LI by histopathological classification (HISTCLAS), as shown in Table 5. Although the proportion of patients classified BL or 'other' did not vary significantly among regimens within each centre, the proportion of patients with HISTCLAS BL or other was significantly greater in Bamako (14%) than in Chingleput (3%). It must

Table 6. Agreement of CLINCLAS with HISTCLAS.

	Number of patients					
	Bamako: CLINCLAS			Chingleput: CLINCLAS		
HISTCLAS	LL	LI	BL	LL	LI	BL
LL	0	2	0	0	1	0
LI	13	60	6	26	76	9
BL	1	10	3	1	2	0
Other	0	2	2	0	1	0

The agreement of CLINCLAS with HISTCLAS is not much different from that expected by chance (Kappa for Bamako = −0·05; for Chingleput = 0·30).

be noted, however, that statistical analysis of the data on HISTCLAS in Tables 5 and 6 are complicated by the presence of many categories including fewer than 5 patients.

The correlation between CLINCLAS and HISTCLAS, described in Table 6, shows agreement of 64% in Bamako and 66% in Chingleput. Table 6 also reveals that LI leprosy was clinically under-diagnosed in both centres. Fourteen per cent of Bamako patients and 22% of Chingleput patients were LL by CLINCLAS, but LI or BL by HISTCLAS; and 6% of Bamako patients and 8% of Chingleput patients were BL by CLINCLAS, but LI by HISTCLAS. Because both classifications include very large proportions of LI patients, i.e. 190 of 215 (88%) LI by HISTCLAS, and 154 of 215 (72%) LI by CLINCLAS, one expects that, by chance, 63% ($0{\cdot}88 \times 0{\cdot}72$) of the patients would be considered LI by both CLINCLAS and HISTCLAS. In fact, this is what was found. That the value of Kappa is smaller than 0·4 for both centres appears to confirm the poor agreement between the two methods of classification. Kappa, the statistic employed to examine the degree of agreement between two classifications,[7] measures the excess of agreement over that resulting from chance; however, this statistic is sensitive to skewed distributions, such as those encountered here, so that this result must be interpreted cautiously.

Neither the LIB nor the LAFBPG was found to vary significantly with CLINCLAS in either centre, whereas, for Bamako patients, the mean BI was significantly smaller for patients with CLINCLAS BL than for patients with CLINCLAS LL or LI (see Table 7). The relationships between BI, LIB and LAFBPG, and HISTCLAS could not be analysed in the same way, because so many of the categories included fewer than 5 patients.

Table 7. Relationships among the pretreatment values for BI, LIB and LAFBPG, and CLINCLAS.

	Bamako: CLINCLAS			Chingleput: CLINCLAS		
	LL	LI	BL	LL	LI	BL
Median BI	4·7	4·7	3·7	4·3	4·3	4·3
Median LIB	5·6	5·3	5·0	5·5	5·6	5·6
Median LAFBPG	8·6	8·4	8·3	8·3	8·4	8·2

No significant differences among values of the BI, LIB or LAFBPG were found for the several clinical classes.

Discussion

Before embarking upon an analysis of the results of a clinical trial of treatment regimens to which patients were assigned by random allocation, it is necessary to ensure that the trial has not been biased by the assignment to one regimen of a disproportionately large number of patients possessing a characteristic that might have influenced the results of treatment. In fact, analysis of two clinical trials among previously untreated patients with lepromatous leprosy conducted in Cebu (one a comparison of several regimens of clofazimine, and the other a comparison of rifampicin with dapsone, both as monotherapy) suggested an influence upon the rate of response, as measured in mice, of the $\log_{10}$ number of AFB (LAFB) in the patients' pretreatment biopsy-specimens,[9] however, as a result of the random allocation of patients to regimen, a disproportionately large number of patients with large or small values of the LAFB was not assigned to one of the regimens. Of course, one can examine the distribution across regimens of only those characteristics of patients that were identified before the trial was begun, and for which the patients were specifically examined and the results of the examinations recorded. There remains the possibility that the trial might be biased because of the maldistribution of some important patient characteristic that had not been identified.

It is, therefore, reassuring to note that, in the THELEP trials, the patient-characteristics that had been identified were not maldistributed. As reported elsewhere,[10] patients found to harbour dapsone-resistant *M. leprae* before treatment, and those whose organisms, recovered from pretreatment biopsy specimens, could not be tested for susceptibility to dapsone, were not maldistributed between centres nor among regimens within centre. And as shown here, random allocation of patients to regimen resulted in a distribution of patients according to age, pretreatment BI, LIB and LAFBPG, CLINCLAS and

HISTCLAS that, with only three exceptions, did not differ significantly between treatment centres nor among regimens within centre. These exceptions were the pretreatment BI, which was larger among Bamako than among Chingleput patients, the pretreatment LIB, which was larger among Chingleput than among Bamako patients, and a greater proportion of patients with HISTCLAS BL or 'other' among Bamako than among Chingleput patients. Because both of the latter two measurements were performed in Oxford on specimens from both centres,[1] these differences between the two centres. On the other hand, measurements of the BI were performed at each centre.[1] Although smear-reading at both centres was evaluated on a continuing basis at the Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia, USA, it is possible that the technique of the measurement differed between Bamako and Chingleput. In no case, however, was the characteristic maldistributed among regimens within centre. Therefore, in analysing the results of these trials, one may confidently compare the regimens within each centre, and the results may be compared between centres with almost equal confidence.

A second purpose for an analysis of the pretreatment characteristics of the patients is to exploit the opportunity provided by the careful study of a relatively large number of patients, all at the same stage of treatment, to examine interrelationships among these characteristics. As expected, the measures of bacterial load—BI, LIB and LAFBPG—were all significantly intercorrelated. On the other hand, as indicated by the product-moment correlation coefficients, which range between 0·32 and 0·65, the correlations were by no means perfect.

One might also have expected close correspondence between CLINCLAS and HISTCLAS. However, this was not found in these trials, the agreement between these two measures being only 64 and 66% in Bamako and Chingleput, respectively. One possible explanation for this less-than-complete agreement is a systematic difference between the interpretation of clinical criteria at the two treatment centres and that of the histopathological criteria in Oxford. In neither centre had classification previously employed the LI class, nor had there been an earlier opportunity for the clinicians to adjust their diagnostic criteria to the results of histopathological examination. There are no data upon which to judge the degree of correspondence in clinical diagnosis between centres. On the other hand, because these problems were foreseen in the design of the trials, attempts were made, by the efforts of a coordinator experienced in clinical trials, by a workshop held at one of the centres before beginning the trials, in which responsible clinicians from both centres participated, and by the participation of the coordinator and clinicians from both centres in meetings of the THELEP Subcommittee on Clinical Trials, to achieve a common set of diagnostic criteria. An alternative explanation for the lack of agreement between CLINCLAS and HISTCLAS is that clinical classification is based upon examination of many lesions, whereas histopathological classification, as carried out in these trials, was

based upon examination of only one lesion; the lesion selected for repeated biopsy may not have been the most representative of the patient's lesions.

References

[1] Subcommittee on clinical trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. THELEP controlled clinical trials in lepromatous leprosy. *Lepr Rev*, 1983; **54:** 167–76.

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

[3] Ridley, DS, Hilson GRF. A logarithmic index of bacilli in biopsies. *Int J Lepr*, 1967; **35:** 184–6.

[4] Gibbons JD. Non-parametric statistical inference. New York: McGraw-Hill Book Co., 1971.

[5] SAS User's Guide: Statistics. SAS Institute, Inc., Cary, N.C., USA; 1982.

[6] Siegel S. Non-parametric statistics for the behavioral sciences. New York: McGraw-Hill Book Co., 1956.

[7] Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley & Sons, 1981; pp. 212–36.

[8] Collaborative effort of the U.S. Leprosy Panel (U.S.-Japan Cooperative Medical Science Program) and the Leonard Wood Memorial. A statistical analysis of two chemotherapy trials in lepromatous leprosy. I. The response to therapy as measured by inoculation of mice. *Am J Trop Med Hyg*, 1978; **27:** 1005–14.

[9] Ridley DS. Bacterial indices. In: *Leprosy in theory and practice*. Cochrane RG, Davey TF, (eds), 1964. Baltimore: Williams & Wilkins, pp. 620–2.

[10] Subcommittee on clinical trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Primary dapsone-resistance in Bamako and Chingleput—final report. Submitted to *Lepr Rev*.

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Factors influencing clinic attendance during the multidrug therapy of leprosy

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Summary Factors influencing clinic attendance during multidrug therapy (MDT) of leprosy were studied in a population of paucibacillary patients at Schieffelin Leprosy Research and Training Centre (SLR & TC) Karigiri in Southern India. Information was gathered from patient records (293 patients) and by questionnaires (143 patients). Patients were grouped according to their long-term clinic attendance record. Factors associated with poor clinic attendance were detection by survey, poor attendance during dapsone monotherapy and longer periods of treatment with dapsone monotherapy prior to MDT, and absence from first or second clinics after registration for MDT. Factors associated with good clinic attendance were presence of deformity and voluntary presentation. Factors unrelated to clinic attendance were age, sex, clinic size, site or number of skin lesions and type of paucibacillary leprosy. The commonest reason given for clinic absences were work and family commitments. Various schemes for predicting poor clinic attendance behaviour were devised.

Introduction

Patient compliance with recommended treatment regimes is an important aspect of leprosy management. The successful mass treatment of leprosy is largely dependent on the regularity with which outpatients receive their drug therapy.[9] Furthermore, irregularity of dapsone (DDS) treatment was probably a major factor in the emergence of DDS-resistant strains of *Mycobacterium leprae*.[5,6,11]

Factors affecting the attendance regularity of leprosy patients have been studied during DDS monotherapy in Ethiopia,[3] Tanzania[4] and India.[1,2,8,10,12] Studies of patient records have identified several factors, e.g. degree of deformity, distance from clinic, season; which appear to influence attendance regularity, while questionnaire studies have indicated a wide range of reasons for poor attendance, e.g. ignorance, social stigma, distance from clinic.

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Since 1982, many leprosy treatment programmes have introduced multidrug therapy (MDT) in an attempt to reduce treatment times and counter the problems of DDS resistance.[14] There is concern[9] that poor patient compliance will seriously restrict the effectiveness of MDT.

The present investigation consisted of two parts; 1, a retrospective survey of factors related to poor clinic attendance and; 2, a questionnaire study to ascertain if patients exhibiting poor compliance behaviour have more difficulties to overcome than good attenders. Paucibacillary (PB) patients were studied since they form the great majority of leprosy patients[7] and are subject to less rigorous 'patient retrieval' procedures than multibacillary (MB) patients.[14]

Materials and methods

The Schieffelin Leprosy Research and Training Centre is responsible for leprosy control in the Gudiyatham Taluk, North Arcot District, South India. This rural Taluk has a population of 426,000, a leprosy prevalence rate of 13/1000 and an incidence rate of about 1/1000. The SLR and TC has been running a leprosy control programme since 1962, and began implementing MDT in 1982.

The Gudiyatham Taluk is divided into four blocks for the purposes of leprosy control programmes. Within each block are several village clinics (arranged to reduce patient travel to less than 3 miles) which are operated on a monthly basis. A register recording all patients who have commenced on MDT course for leprosy was used to identify all paucibacillary (PB) patients on MDT between 1982 and September 1985. Data were then taken from the identified patient's records.

Record survey

Block 1 of the Gudiyatham was chosen because it contained an accessible, representative sample (27% of PB cases on MDT) of the whole Taluk. The PB patient register recorded 403 patients who had commenced MDT. Eighty-nine were excluded from the record survey study since they had not yet had the opportunity to attend 6 monthly clinics, i.e. treatment commenced after March 1985. A further 18 patients had left the area, or died, before completion of MDT. The records of 3 patients were not traced. This produced a study population of 293 PB patients which formed the basis of the record survey study. The investigation into early prediction of attendance behaviour included some data obtained from clinics outside Block 1 (see Results).

Questionnaire study

The study population consisted of patients within Block 1, and without any deformity,[13] who had commenced MDT more than 5 months before the

interview, and who were either still under treatment or follow-up, i.e. within a few months of the completion of MDT.

Patients were interviewed at the monthly clinics and clinic absentees visited at home. One domiciliary visit only was possible within each clinic area and priority was given to patients currently under treatment. Patients who could not be contacted during that visit had to be excluded from the study.

The questionnaire was designed to detect difficulties experienced by patients in attending clinics (regardless of actual attendance rates), and to assess their attitude towards the diagnosis and treatment. Most questions required a 'Yes' or 'No' answer. Patients were interviewed with the help of a translator using a standard Tamil version of the questionnaire. The interviews lasted less than 5 minutes each. The same translator was used at all clinic interviews, but several were involved in the domiciliary visits. Wherever possible, children were interviewed with their parent or guardian.

Data analysis

The majority of analyses used the non-parametric χ-square test, with the Yates' correction for small numbers where appropriate. The correlation of attendance rates on DDS and MDT was carried out using a microcomputer.

Results

The study population was divided into two non-defaulter groups on the basis of recommended attendance rates for paucibacillary (PB) patients.[14]

Non-defaulters: a, excellent attenders (EA), 100% attendance over 6 months; b, acceptable attenders (AA), 67–99%; i.e. compatible with the completion of 6 month MDT course within 9 months.

Defaulters: a, unacceptable attenders (UA), less than 67% attendance, i.e. incompatible with the successful completion of the drug regime.

The numbers of patients in each attendance group were as follows: EA, 129 patients (44% of the study population); AA, 107 patients (37%); UA, 57 patients (19%).

Thus the total default rate was 19% of patients.

Factors related to clinic attendance

These were investigated by observing variations between the three attendance groups (EA, AA, UA).

1 Age and sex. Attendance behaviour was unrelated ($P > 0{\cdot}5$) to the age or sex of the patient (Table 1).
2 Occupation. A large number of patient records were inadequate in this aspect. Among the completed records, there was no significant relationship ($P > 0{\cdot}5$) between the six occupation groups. (Housewife, professional/student, clerk/office worker, craftsman, farmer/coolie/labourer, beggar/unemployed) and clinic attendance.
3 Clinic size. When considered within three groups (less than 100 patients, 100–150 patients, 151–200 patients), clinic size was unrelated to attendance rates ($0{\cdot}5 > P > 0{\cdot}1$).
4 Disease classification. There was no statistically significant relationship ($P > 0{\cdot}5$) between disease classification and attendance groups (Table 2).
5 Skin lesions. The site of skin lesions (i.e. face, right arm, left arm, right leg, left leg, trunk) was unrelated to clinic attendance ($P > 0{\cdot}5$). This conclusion was not altered when the presence or absence of anaesthesia in skin lesions was taken into account. The number of sites containing skin lesions was unrelated to attendance ($0{\cdot}5 > P > 0{\cdot}1$) once the patients with deformities were removed from the analysis (see below).
6 Nerve lesions. The site of nerve involvement (facial, great auricular, ulnar, median, radial, lateral popliteal, posterior tibial), and the number of nerves enlarged, had no significant relationship with clinic attendance groups ($P > 0{\cdot}5$ and $0{\cdot}5 > P > 0{\cdot}1$ respectively).
7 Deformity. This was recorded using the WHO scale.[13] Data were insufficient to study the influence of deformity grade or the site of deformity, on clinic

Table 1. Age and sex distribution (%).

Age (years)	EA		AA		UA	
	M	F	M	F	M	F
< 15	24	28	20	28	27	29
15–34	40	39	53	42	51	37
35–54	28	24	19	32	16	21
> 54	8	9	8	8	6	13
Total (%)	100	100	100	100	100	100
Total No.	75	54	54	53	33	34
χ-square	$P > 0{\cdot}5$ NS*					

* NS denotes a non-significant result.
EA, excellent attenders; AA, acceptable attenders; UA, unacceptable attenders.

Table 2. Disease classification (%).

Classification	EA	AA	UA
TT	42	47	51
BT	47	45	40
I	11	8	9
Total (%)	100	100	100
Total No.	129	107	57
χ-square	$P > 0{\cdot}5$ NS		

Leprosy classification: TT, tuberculoid; BT, borderline tuberculoid; I, indeterminate.

Table 3. Presence of deformity (%).

Deformity	EA	AA	UA
Yes	17	7	4
No	83	93	96
Total (%)	100	100	100
Total No.	129	107	57
χ-square	$P < 0{\cdot}01$		

attendance. When the presence or absence of any deformity was considered (Table 3), the presence of deformity was significantly related ($P < 0{\cdot}01$) to good attendance.

8 Foot injury. In the whole study population there were only 5 cases of severe foot injury. They were all in the EA and AA groups.

9 Mode of detection. This was found to have a significant relationship ($P < 0{\cdot}01$) with clinic attendance (Table 4). The three different categories within the survey group (general survey, contact survey, school survey) did not differ ($P > 0{\cdot}5$) with respect to clinic attendance.

10 Presence of leprosy contacts. There was no relationship ($P > 0{\cdot}5$) with clinic attendance.

11 Duration of disease prior to registration. This was unrelated to clinic attendance ($0{\cdot}5 > P > 0{\cdot}1$; Table 5).

12 Length of treatment. Longer treatment times prior to MDT (i.e. on DDS)

Table 4. Mode of detection (%).

Detection	EA	AA	UA
Survey	52	61	78
Voluntary	48	39	22
Total (%)	100	100	100
Total No.	123	99	55
χ-square	$P<0{\cdot}01$		

Table 5. Duration of disease prior to registration (%).

Duration	EA	AA	UA
< 3 months	24	16	24
3 months–1 year	47	40	43
1 year–3 years	17	25	13
> 3 years	12	19	20
Total (%)	100	100	100
Total No.	112	85	46
χ-square	$0{\cdot}5>P>0{\cdot}1$ NS		

Table 6. Length of treatment prior to MDT (%).

Treatment time	EA	AA	UA
0–10 months	58	45	39
11–20 months	24	16	14
21–40 months	9	18	23
> 40 months	9	21	24
Total (%)	100	100	100
Total No.	129	107	57
χ-square	$P<0{\cdot}001$		

Table 7. Attendance rates during previous DDS monotherapy.

MDT group	*n*	Attendance on DDS (% of possible attendance)
EA	72	94·3 ± 1·1
AA	64	86·5 ± 1·8
UA	42	74·9 ± 2·8

Data are presented as the Mean ± SEM of 'n' cases.

All groups differ from each other ($P < 0{\cdot}01$) by the Student's *t*-test.

were associated with poorer attendance (Table 6, $P < 0{\cdot}001$). The possible effect of attendance behaviour on treatment time, which when poor might be expected to lengthen the time on DDS monotherapy, is not known (see Discussion).

13 Previous compliance behaviour. The clinic attendance rates of patients on DDS monotherapy were compared with their subsequent attendance on MDT. This analysis used only cases with at least 6 months of DDS therapy prior to MDT. Attendance rates on DDS monotherapy reflected attendance during MDT (Table 7) indicating that poor compliance was evident before MDT. Linear regression analysis of individual DDS and MDT attendance rates revealed a significant correlation ($r = 0{\cdot}48$, $P < 0{\cdot}001$; $n = 178$ patients) between the two.

14 Clinic of first absence. The first clinic to be missed (after one initial attendance) was recorded and a comparison made between AA and UA groups

Table 8. Clinic of first absence (%).

Clinic number	AA	UA
2	21	68
3	26	16
4	28	11
5	15	5
6	10	0
Total (%)	100	100
Total No.	107	57
χ-square	$P < 0{\cdot}001$	

(Table 8). The two groups differed markedly ($P < 0{\cdot}001$). This appears to be due to the much higher probability of the UA patients missing any one clinic. Thus unacceptable attendance behaviour is usually evident early during MDT.

15 Seasonal variation in clinic attendance. The seasonality of clinic attendance was investigated for both MDT and DDS (where the patient had previously been on DDS monotherapy). All attendance results were expressed as a percentage of the number of patients under treatment during 1 calendar month and data accumulated over several years.

When all data were included (i.e. EA, AA, and UA groups) a marked seasonality was evident. When on MDT, attendances were lowest in June and July, and highest in October and November (numbers of patients under treatment each month ranged from 95 to 203). The pattern was similar on DDS monotherapy; attendance was low in January, May and June and high in August and October (572 patients were under treatment each month). Both MDT and DDS seasonal patterns were significant ($P < 0{\cdot}001$ and $P < 0{\cdot}05$ respectively) by the χ-square test.

A comparison of defaulters (UA) and non-defaulters (EA and AA) on MDT revealed similar patterns (Figure 1). Peak attendance among non-defaulters was in October, compared with November for defaulters. Poorest attendance was in May for non-defaulters and June–July for defaulters. Monthly totals of patients under treatment ranged between 78 and 155 in the non-defaulter group, and from 17 to 57 in the defaulter group. In both groups the seasonal pattern was significant ($P < 0{\cdot}001$ and $P < 0{\cdot}01$ respectively).

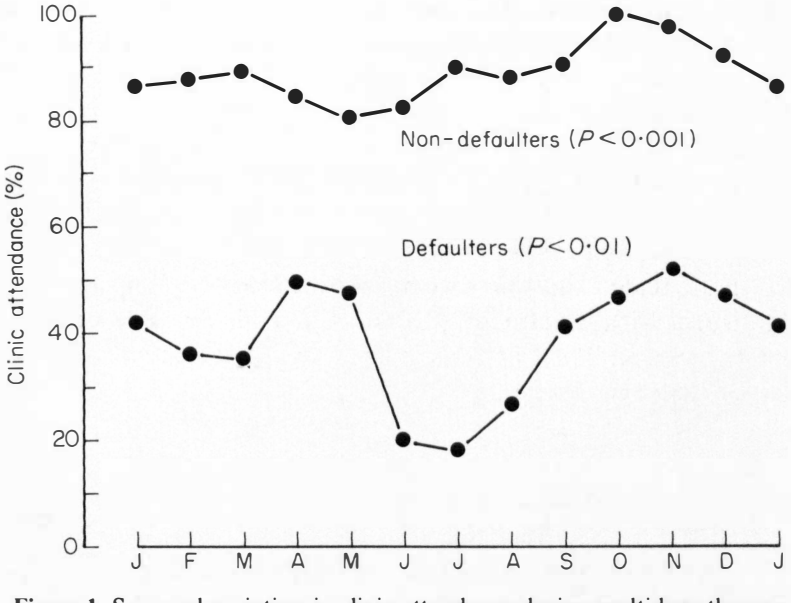

Figure 1. Seasonal variation in clinic attendance during multidrug therapy.

Table 9. Reasons for having difficulty attending clinics. Numbers and % of patients in each 'clinic attendance behaviour' group with each 'difficulty'.

	EA (Total 47)		AA (Total 48)		UA (Total 48)		Overall (Total 143)	
	No.	(% of total EA)	No.	(% of total AA)	No.	(% of total UA)	No.	(% of overall total)
Work commitments	1	(2)	10	(21)	19	(40)	30	(21)
Family commitments	1	(2)	14	(29)	22	(46)	37	(26)
Religious commitments	0	(0)	2	(4)	0	(0)	2	(1)
Distance to clinics	4	(9)	2	(4)	4	(8)	10	(7)
Stigma	2	(4)	3	(6)	4	(8)	9	(6)
Other	0	(0)	9	(19)	12	(25)	21	(15)

Questionnaire studies

The three attendance groups (EA, AA and UA) were used in this investigation.

The commonest reasons for having difficulty attending clinics were those of family (26%) and work (21%) commitments, both of which increased in frequency as attendance rate declined (Table 9). These commitments interfered with the monthly clinics, or with the paramedical worker's visits to remind patients about the clinics. The 'other reasons' group was also an important reason (15%) for attendance difficulties. Religious commitments, stigma and travel distance presented difficulties in 14% of the patients but were present equally in all attendance groups (Table 9). Patients frequently claimed to have no difficulty in attending clinics despite poor attendance rates and would admit to problems only on direct challenge.

Most patients when asked if they accepted the diagnosis of leprosy responded by pointing to the skin lesion(s), and 43% accepted that this was due to leprosy. Acceptance of the diagnosis was unrelated to clinic attendance rate (Table 10). Only 4% of patients felt that their treatment was unnecessary, and 6% admitted being unsatisfied with treatment (Table 10). This did not appear to affect attendance behaviour. The patient's knowledge of treatment duration did not affect clinic attendance (Table 11).

Early prediction of attendance behaviour

The results obtained in the records survey indicated several possible indices of attendance behaviour. These indices (i.e. presence of deformity, mode of

Table 10. Attitudes towards treatment and diagnosis.

	EA (Total 47)		AA (Total 48)		UA (Total 48)		Overall (Total 143)	
	No.	(% of total EA)	No.	(% of total AA)	No.	(% of total UA)	No.	(% of overall total)
Diagnosis not accepted	28	(60)	25	(52)	29	(60)	82	(57)
Treatment not believed to be necessary	0	(0)	2	(4)	4	(8)	6	(4)
Not satisfied with treatment	2	(4)	3	(6)	3	(6)	8	(6)
Treatment does not seem to be working	1	(2)	3	(6)	1	(2)	5	(3)
Side-effects	3	(6)	2	(4)	4	(8)	9	(6)

Table 11. Knowledge of treatment duration. (Answers in reply to the question 'How long do you have to take treatment to be cured of leprosy?')

	EA (Total 47)		AA (Total 48)		UA (Total 48)		Overall (Total 143)	
	No.	(% of total EA)	No.	(% of total AA)	No.	(% of total UA)	No.	(% of overall total)
Don't know	17	(36)	20	(42)	23	(48)	60	(42)
Six months	15	(32)	18	(37)	13	(27)	46	(32)
More than 6 months	15	(32)	10	(21)	12	(25)	37	(26)

detection and timing of absences) were investigated using patient data obtained from clinics within, and outside of block 1, Gudiyatham Taluk. As the results were very similar between clinics, data were combined into a patient population of 360, of which 68 (18·9%) were unacceptable attenders.

The observed 'sensitivity' and 'specificity' (for definitions see Table 12) of three simple 'predictive schemes' in predicting poor clinic attendance are displayed in Table 12.

Table 12. The use of 'predictive schemes' in the early prediction of poor clinic attendance.

Scheme No.	Features of the predictive schemes	Sensitivity (Proportion of the defaulter population correctly identified)	Specificity (Proportion of the non-defaulter population correctly identified)
1	Absent from both 2nd and 3rd clinics	56%	98%
2	Absent from 2nd and/or 3rd clinics	79%	86%
3	Absent from 2nd clinic and/or 3rd clinic and/or survey detection	99%	7%

Discussion

The design of the present study, and the facilities available to carry it out, differ considerably from those of earlier investigations. Earlier workers[1,3,4,8,10] have studied whole leprosy patient populations during dapsone (DDS) monotherapy, in contrast to the present population of paucibacillary (PB) patients on MDT. The low overall default rate reported here could be due to the short-treatment time, improved case-holding, or more frequent supervision present in MDT.[14] However it is to be noted that the unacceptable attender rate in the paucibacillary group is 19% despite the high level of supervision in Gudiyatham Taluk. In addition, improvements in domiciliary programmes suggested by earlier studies have influenced the planning of current programmes, e.g. travelling distances. Thus, some of the discrepancies between this study and its predecessors reflect differences in the organization of DDS monotherapy in the past, and MDT at present.

The survey of patient records identified several features among attendance defaulters (lack of deformities, detection by survey, lengthy treatment before MDT, previous bad compliance, early first absence, marked seasonality), which are in agreement with previous studies,[3,4,8] although Giel and van Luijk[3] found no relationship with deformity. Seasonal variations, which were evident among both acceptable attenders (AA) and unacceptable attenders (UA) are discussed below.

The most important negative findings of the present study involved the failure to relate patient age, sex, occupation, clinic size, disease classification or duration of disease with clinic attendance. Hertroijs[4] reported that in Tanzania attendance varied with age and sex, but this has not been confirmed by Indian studies.[1,10] Patient occupation, which Nigam[10] indicated may influence clinic attendance,

was difficult to examine in the present study because of incomplete records. The clinics in this investigation were larger and more uniform in size than those of Hertroijs,[4] thus a significant influence of clinic size was less likely to be found. Earlier studies incorporating disease classification[4,8] have encompassed all leprosy types, in contrast to the PB population reported here. This has reduced the range of disease types and may account for the discrepancy. The difference between the present study and that of Hertroijs,[4] regarding disease duration eludes simple explanation. The great cultural differences between Tanzania and India cannot be excluded.

Seasonality in attendance rate was evident regardless of the attendance groups or drug regimens, i.e. poor attendance May–July, good attendance October–November. Previous studies[1,4] have implicated seasonal migrations, climatic features (especially monsoons) and agricultural activity. None of these reasons easily account for the present findings. Seasonal migrations are not a major feature of South Indian life although some movement occurs to find work. The very hot weather of May–June may be reducing attendance, but the monsoons (September–January) appear to have no influence. The period of peak agricultural activity, the groundnut harvests of September and January–February are associated with good attendance. One speculative explanation is that the groundnut harvest keeps patients within the local area, i.e. close to the clinic. When agricultural activity is low, many people may have to travel to find temporary work outside the clinic area. An additional consideration is the influence of family/social commitments, since May–June is a common time for weddings in Tamil Nadu. The questionnaire studies are interesting in this context.

The two main reported reasons for difficulty in attending clinics were family and work commitments. Poor clinic attenders admitted to more of these problems than good attenders. However, within the UA group, reasons given for absenteeism were not always adequate to explain all the absences, e.g. weddings or funerals given as the sole reason. It is likely that other important factors such as personality and motivation were responsible. John *et al.*[6] demonstrated that personality is important during self-administration of dapsone, and the same may also be true of attendance compliance. Improved 'motivation' may be provided by intensive patient retrieval procedures, such as are applied to multibacillary (MB) patients on MDT,[14] and this may explain the generally good clinic attendance in this group.

Travelling distance was not a problem, presumably because clinics have been arranged to minimize this problem. It would appear that acceptance of the seriousness of the disease and of the importance of regular treatment, are more significant determinants of good compliance behaviour than a specific knowledge of leprosy or its treatment. The low number of respondents stating that treatment was unnecessary or unsatisfactory indicates that patient education has been effective in this aspect.

The picture of a poor clinic attender which arises from this study is that of a

patient with little awareness or motivation regarding his disease (hence survey detection), and no serious complications to change his attitudes. The attendance, which is poor on DDS, evidently worsens with the length of treatment. Patient motivation appears to be a key feature and the continued use and improvement of health education may alleviate this problem. It is possible that the shorter treatment time of MDT has improved compliance and that this will become apparent in the near future as more patients are treated with MDT alone.

Previous investigations[1,4] have outlined features which help predict poor attendance but without quantitative assessment. The reasoning behind the present use of quantitative 'predictive schemes' was that the early identification of future defaulters would allow an efficient use of resources in patient retrieval efforts. In general there is a compromise between 'sensitivity' (i.e. proportion of defaulters identified) and 'specificity' (i.e. proportion of nondefaulters excluded from the group predicted to be defaulters). The most specific scheme (number 1) should provide for efficient patient retrieval programmes contacting about half of all defaulters and could be useful where resources are limited. The other two schemes would require a greater input with respect to paramedical workload, but they would predict the majority of defaulters.

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References

[1] Bhagoliwal A, Chandra J, Mishra RS. Some observations on default among leprosy patients. *Lepr India*, 1979; **51,** 96–102.

[2] Ekambaram V. Absentism for treatment, their causes and suggested remedial measures. *Lepr India*, 1974; **46:** 46–8.

[3] Giel R, Van Luijk JN. Leprosy in Ethiopian Society. *Int J Lepr*, 1970; **38:** 187–98.

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

[5] Jacobson RR. Sulphone-resistant leprosy: Etiology, incidence and treatment in the United States. *Int J Lepr*, 1973; **41:** 684.

[6] John JK, Pannikar VK, Verghesi A, Christian M. Social and personality factors in Dapsone resistance. *Lepr India*, 1983; **55:** 100–6.

[7] Jopling WH. Handbook of Leprosy (3rd edition). London: William Heinemann Medical Books Ltd, 1984.

[8] Karat ABA, Job CK, Karat S, Sadananda Rao G, Rao PSS. Domiciliary treatment programme absentee survey. *Lepr India*, 1967; **39:** 180–9.

[9] Lancet Editorial. Chemotherapy of Leprosy. *Lancet*, 1982; **ii**: 77–8.
[10] 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.
[11] Rees RJW. Drug resistance of *Mycobacterium Leprae*, particularly to DDS. *Int J Lepr*, 1967; **35:** 625.
[12] Vellut C, Alex L, Ethirajan T. Study of the reasons for absenteeism. *Lepr India*, 1979; **51:** 568.
[13] WHO. WHO classification of disabilities resulting from leprosy, for the use in control projects. *Lepr Rev*, 1970; 41: 53–6.
[14] WHO. Chemotherapy of leprosy for control programmes. Geneva: Technical Report Series No. 657, 1982.

Lepr Rev (1987) **58**, 31–37

Plasma levels of ethionamide and prothionamide in a volunteer following intravenous and oral dosages

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Summary Available evidence which may aid a decision concerning which of the thioamides, ethionamide or prothionamide should be recommended for use in the treatment of lepromatous leprosy is inconclusive. The drugs possess similar antimycobacterial activities, but earlier work has suggested that after oral dosage ethionamide may give rise to higher blood levels than prothionamide. We report on investigations designed to examine whether this finding is as a result of different systemic availabilities, by comparing blood levels following intravenous and oral administrations. We conclude that the drugs' pharmacokinetics are very similar, each having high bioavailabilities, and that other factors such as cost may be more important determinants as to which thioamide should be used.

Introduction

The antituberculosis drugs ethionamide (2-ethyl-thioisonicotinamide, ETH, Trescatyl) and prothionamide (2-propyl-thioisonicotinamide, PTH, Trevintix) have been in clinical use for some 20 years, mainly as components of retreatment regimens for patients relapsing with drug-resistant *Mycobacterium tuberculosis*. Experimental evidence has shown that both ETH and PTH possess similar powerful antileprosy activity when tested in the mouse footpad model.[1–3] These findings, together with the results from some small scale clinical trials of monotherapy with ethionamide or prothionamide suggested a future role for the two thioamides in the combined chemotherapy of lepromatous leprosy.[4–6] The World Health Organization advises that all lepromatous leprosy patients should be treated with a combination of three bactericidal drugs,[7] and currently recommends rifampicin, dapsone and clofazimine be used. However, many light skinned patients are unable to tolerate the skin pigmentation caused by clofazimine. For these patients it is suggested that clofazimine be replaced by

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250–375 mg/day of either ETH or PTH, but no guidance was given as to which of the two thioamides was to be preferred. The available evidence which may aid an informed decision concerning which thioamide should be recommended is inconclusive. Experimental studies have failed to demonstrate any differences in the inhibitory and bactericidal activities of ETH and PTH against *M. leprae*,[2,8] or between their sulphoxide metabolites which also possesses substantial antimycobacterial activities.[9,10] Prothionamide was originally introduced in an attempt to reduce the incidences of dose-dependant gastric side-effects associated with ETH. Although there is evidence that at larger doses ETH is less well tolerated than PTH,[11] recent findings suggest that at daily doses of 125–250 mg the regularity with which the two drugs are self-administered by leprosy patients is similar.[12]

In previous investigations we have attempted to determine if there were any pharmacokinetic differences between the two thioamides of potential clinical significance. In order to compare the rates of elimination of ETH and PTH, and the extent of their conversion to the antimycobacterial sulphoxide metabolites, we devised sensitive high performance liquid chromatographic (HPLC) methods to specifically measure the two thioamides and the sulphoxides in plasma and urine.[13,14] Single dose studies showed that the half-lives for the elimination of both ETH and PTH following oral dosage were about 2 h, but that the plasma concentrations of PTH from 1 h onwards were only about half those of ETH.[13] Later investigations indicated that the observed differences were not due to greater conversion of PTH to its sulphoxide metabolite; indeed the plasma levels of PTH sulphoxide were also less than those of the corresponding ETH metabolite.[14] Nor was there evidence of significant faecal elimination of unmetabolized drugs, suggesting that the absorption of both thioamides from the gut was probably good. We postulated that the differences in the plasma concentrations of ETH and PTH may have been due to differences in tissue distribution and/or protein binding. An alternative possibility is that PTH may have been cleared more extensively on the first pass through the liver. Estimates of distribution volumes and of pre-systemic clearance can only be made by comparing intravenous and oral administration. Since there are no reported studies of the intravenous dosage of either of the thioamides we describe the results of a study to compare the systemic bioavailabilities of ETH and PTH, in the same volunteer who took part in the earlier investigations.

Materials and methods

CHEMICAL

Ethionamide and prothionamide were donated by May and Baker (Dagenham, UK) for use as analytical standards. 2-Methyl-thioisonicotinamide was a gift from Dr N Rist. Ethionamide and prothionamide sulphoxides were prepared by

oxidation of the parent thioamides as described previously.[14] Stock solutions (1 mg ml^{-1}) of the thioamides in ethanol, and of the sulphoxides in chloroform were prepared and stored at 4°C.

DRUG DOSAGES AND COLLECTION OF PLASMA SAMPLES

The study was divided in two parts. In the first part an oral dose of 500 mg PTH (Trevintix, May and Baker) was swallowed as crushed tablets with a glass of milk. Sixty minutes later 25 mg ETH (Trecator Perfusion, Theraplix, Paris, France) (2·5 mg ml^{-1}) was given by intravenous infusion over 10 min. In the second part of the study, conducted 1 week later, the formulations of the drugs were reversed; 500 mg ETH (Trecator, May and Baker) was administered orally, followed 1 h later by an intravenous infusion of 25 mg PTH (Trevintix Perfusion, Theraplix). Heparinized blood (7 ml) was collected at 30, 60, 70, 80, 90, 105, 120, 150, 240, 300 and 360 min after ingestion of the oral doses, the plasma spun down and the samples immediately frozen and stored at −20°C until analysis. On both occasions the volunteer (GAE) was administered the drugs supine, after an overnight fast.

ANALYTICAL METHODS

As anticipated, the plasma levels of the intravenously and orally administered thioamides differed greatly because of the different size of the dose employed. Thawed plasma samples were therefore divided into two aliquots, the larger one (2·5 ml) for measurement of the intravenously administered thioamide and the smaller (between 0·2 and 0·7 ml) for determining the higher levels of the ingested thioamide. Both aliquots were diluted to 3 ml with distilled water and extracted and analysed by HPLC using the method previously reported for the simultaneous determination of the thioamides and their sulphoxide metabolites in plasma.[14] In brief, the samples were extracted with 7 ml of chloroform after the addition of an appropriate amount of 2-methyl-thioisonicotinamide as the internal standard. After extracting the organic phase with 1 ml 0·1 M HCl and neutralizing, the compounds were back extracted into chloroform, and this extract dried down. HPLC analyses were performed with a Waters Associates Model M6000A pump, a Model 440 absorbance detector (set at 340 nm) and a U6K valve injector. The normal phase silica column (Hypersil, Shandon Southern) was eluted with chloroform/propan-2-ol/water (916:80:4) at a flow rate of 2·5 ml min^{-1}. Estimates of the concentrations of thioamides in plasma samples were made by reference to a series of calibration curves prepared as described previously.[13,14]

STATISTICAL METHODS

The kinetics of the plasma concentrations were analysed by the ESTRIP curve

stripping procedure[15] and by iterative computer fitting of a biexponential equation of the form

$$C_t = Ae^{-\alpha t} + Be^{-\beta t},$$

using MLAB,[16] a programme for evaluating mathematical models and functions. Values for the half-lives for the absorption and elimination of the drugs were calculated from the rate constants obtained by these procedures. The ESTRIP programme also calculated the areas under the plasma time curve using the trapezoidal rule. Total areas under the plasma time curves (AUC) were obtained by extrapolation to time infinity.[17]

Results

The kinetics of the elimination of ETH and PTH from the plasma after oral and intravenous administration is illustrated in Figure 1. The absorption of PTH following oral dosage appears to be very rapid. Thus, the peak plasma concentration occurred within 30 min of ingestion with the consequence that an accurate estimation of the half-life for the absorption could not be calculated. By contrast ETH peak plasma levels occurred after about 90 min. At this time the PTH concentration had fallen to about half the level reached at 30 min. This elimination pattern is very similar to that encountered in the same volunteer 5 years previously.[13] The rate of decline in plasma levels, calculated using the rate constants obtained by the ESTRIP procedure, was equivalent to half lives of $1{\cdot}85 \pm 0{\cdot}08$ h for ETH and $1{\cdot}78 \pm 0{\cdot}17$ h for PTH ($p > 0{\cdot}05$). The data for ETH was best fitted by the ESTRIP procedure assuming a lag period of 17·9 min and gave a calculated half-life for the absorption of ETH of $18{\cdot}5 \pm 2{\cdot}7$ min. Alternative estimates, calculated by the MLAB programme, gave values for the terminal half lives of ETH and PTH of $1{\cdot}60 \pm 0{\cdot}31$ h, and $1{\cdot}49 \pm 0{\cdot}13$ h, respectively, similar to those obtained with the ESTRIP procedure.

Following intravenous dosage, plasma levels of the thioamides declined biexponentially (Figure 1), with half-lives for the distribution phases (as calculated using ESTRIP) of 7·2 and 5·8 min for ETH and PTH, respectively. The terminal rates of elimination were equivalent to half-lives of $1{\cdot}77 \pm 0{\cdot}07$ h for ETH and $2{\cdot}06 \pm 0{\cdot}12$ h for PTH. These values for the terminal half-lives are not significantly different from the corresponding half-lives following oral administration. The corresponding estimates using the MLAB programme were 7·0 and 6·4 min for the distribution half-lives of ETH and PTH, respectively; and $2{\cdot}06 \pm 0{\cdot}34$ h for ETH, and $2{\cdot}18 \pm 0{\cdot}11$ for PTH, for the terminal half-lives.

The total areas under the plasma time curves (AUC), were 55 and 1215 μg ml^{-1} min after intravenous and oral dosage with ETH, respectively. Those for PTH were 48 and 870 μg ml^{-1} min^{-1}. Using these values, the systemic availabilities[17] of oral ETH and PTH were calculated to be 1·1 and 0·9,

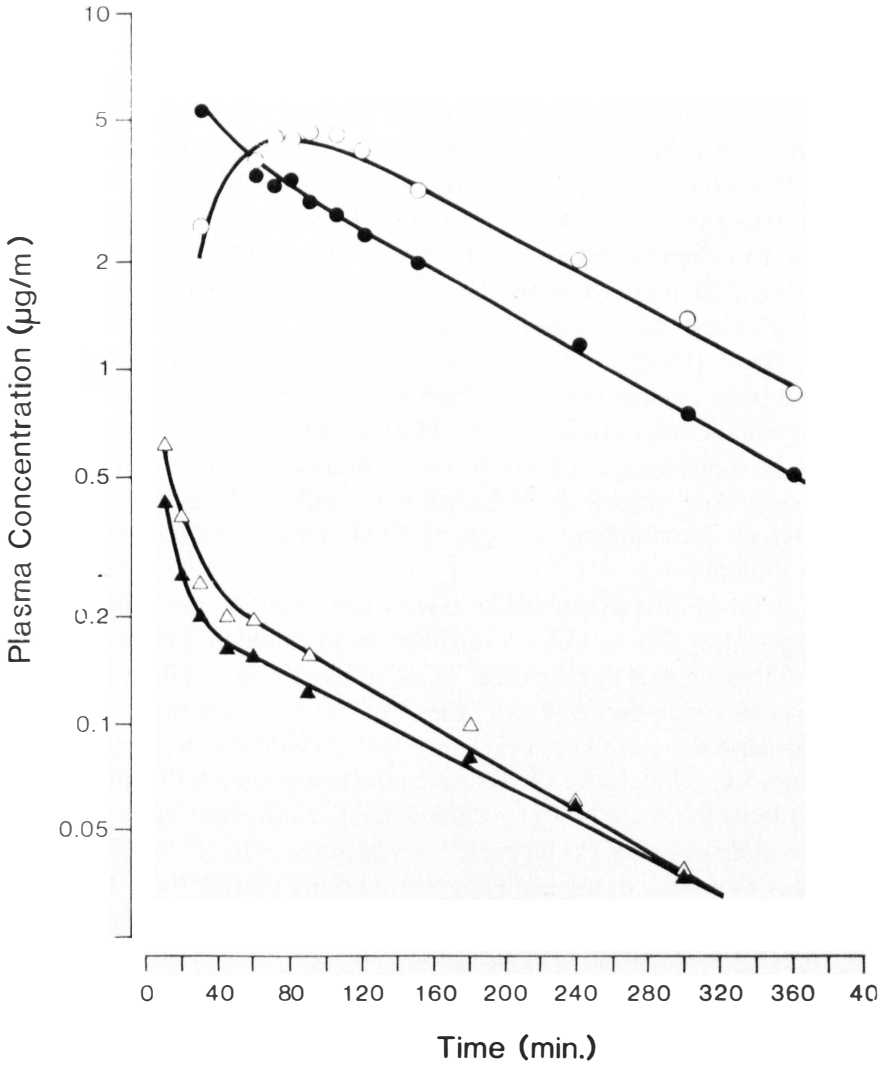

Figure 1. Plasma concentrations following oral dosage with 500 mg ethionamide (○) or prothionamide (●), and after intravenous administration of 25 mg ethionamide (△) or prothionamide (▲).

respectively. Thus it appears that both thioamides are essentially completely absorbed and are not subjected to any appreciable first pass metabolism. Volumes of distribution following intravenous administration, calculated from the formula $V = \text{dose}/B \times \text{AUC}$, where B is the terminal rate constant, were 79 and 93 l for ETH and PTH, respectively.

Discussion

The HPLC method for ETH and PTH devised by us previously is ideally suited to

measure plasma levels after combined dosage with both drugs. By using this approach it was hoped that some of the variation normally encountered when drugs are given separately, as in a cross-over study, would be reduced. Nevertheless, the pattern of elimination of ETH and PTH following oral dosage was very similar to that found in the same subject some 5 years previously.[13] In that study, however, plasma samples were obtained at hourly intervals from 1 h onwards, and as a consequence failed to reveal the more rapid absorption of PTH demonstrated in the current study (Figure 1). Thus the lower plasma levels of PTH from about 2 h onwards would appear to be due to faster absorption. Such a conclusion is supported by the initial lag period of about 18 min calculated for ETH by the ESTRIP programme. By contrast, the rate of absorption of PTH was so rapid that peak plasma levels occurred within 30 min of administration of the dose. The systemic availabilities of ETH and PTH were high and neither drug appeared to be cleared significantly during its first passage through the liver or gut wall. The only appreciable pharmacokinetic difference encountered was the higher apparent distribution volume of PTH, which could well be due to its greater lipophilicity.

Although the results presented here were obtained in only a single volunteer, they do suggest that pharmacokinetic differences between ETH and PTH are very slight and not of clinical significance. Thus, in assessing which of the thioamides might be best recommended for the use in the combined treatment of lepromatous leprosy, it is likely that other factors will play a far more important part. Information concerning the relative effectiveness of ETH and PTH should soon be available from a short-term clinical trial in lepromatous leprosy currently being undertaken in Cebu, Phillipines,[18] in which the rate of loss of viability of *M. leprae* in skin biopsies among patients treated daily with 250 or 500 mg doses of ETH or PTH is being compared. In view of reports of relatively high incidences of hepatic toxicity associated with treatment of lepromatous patients with daily ETH or PTH combined with daily or monthly rifampicin,[19–21] it is clearly important that liver function be monitored in future clinical trials of the thioamides in the combined chemotherapy of lepromatous leprosy. For the present moment, the major determinants as to which thioamide should be used should be relative cost and availability.

Acknowledgments

We should like to thank Theraplix and May and Baker for their kind donation of the ethionamide and prothionamide formulations used in this study.

References

[1] Shepard CC. Combinations involving dapsone, rifampin, clofazimine, and ethionamide in the treatment of *M. leprae* infections in mice. *Int J Lepr*, 1976; **44:** 135–9.

[2] Colston MJ, Ellard GA, Gammon PT. Drugs for combined chemotherapy: experimental studies on the antileprosy activity of ethionamide and prothionamide, and a general review. *Lepr Rev*, 1978; **132:** 311–4.

[3] Colston MJ, Hilson GRF, Bannerjee DK. The 'proportional bactericidal test'. A method for assessing the bactericidal activity of drugs against *Mycobacterium leprae* in mice. *Lepr Rev*, 1978; **49:** 7–15.

[4] Committee on Experimental Chemotherapy. Experimental chemotherapy of leprosy. *Bull Wld Hlth Org*, 1976; **53:** 425–33.

[5] Flock H, Rist N, Jacobi J. Intérêt de l'éthionamide en thérapeutique antilèpreuse. *Bull Soc Path exot*, 1966; **59:** 715–24.

[6] Rollier R, Rollier M. Traitement de la lèpre lépromateuse par l'éthionamide. *Maroc Med*, 1972; **52:** 148–66.

[7] World Health Organization Study Group. Chemotherapy of leprosy for control programmes. *World Health Organization Technical Report Series*, No. 675, 1982.

[8] Shepard CC, Jenner PJ, Ellard GA, Lancaster RD. An experimental study of the antileprosy activities of a series of thioamides in the mouse. *Int J Lepr*, 1985; **53:** 587–94.

[9] Libermann D, Rist N, Grumbach F. Le S-oxyde de l'α-éthylthioamide isonicotinique. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences*, 1963; **257:** 307–8.

[10] Matsuo Y, Tatsukawa H, Murray JF, Peters JH. Prothionamide and prothionamide-S-oxide in experimental leprosy. *Int J Lepr*, 1981; **49:** 302–6.

[11] Fox W, Robinson DK, Tall R, Mitchison DA, Kent PW, Macfadyen DM. A study of acute intolerance to ethionamide, including a comparison with prothionamide, and of the influence of a vitamin B-complex additive in prophylaxis. *Tubercle*, 1969; **50:** 125–43.

[12] Stanley JNA, Pearson JMH, Ellard GA. Ethionamide, prothionamide and thiacetazone self-administration. Studies of patient compliance using isoniazid-marked formulations. *Lepr Rev*, 1986; **57:** 9–18.

[13] Jenner PJ, Ellard GA. High performance liquid chromatographic determination of ethionamide and prothionamide in body fluids. *J Chromatog*, 1981; **222:** 245–51.

[14] Jenner PJ, Ellard GA, Gruer PJK, Aber VR. A comparison of the blood levels and urinary excretion of ethionamide and prothonamide in man. *J Antimicrob Chemother*, 1984; **13:** 267–77.

[15] Brown RD, Munro JE. ESTRIP, a BASIC computer program for obtaining initial polyexponential parameter estimates. *J Pharm Sci*, 1978; **67:** 1687–91.

[16] MLAB (On-line Modelling Laboratory). Laboratory of Statistical and Mathematical Methodology. Division of Computer Research and Technology. N.I.H., Bethesda, Maryland, USA, 1978.

[17] Gibaldi M, Perrier D. Pharmacokinetics. 2nd Ed. New York: Marcel Dekker, 1982.

[18] WHO publication TDR/THELEP-SC (9)/81.3. Report of the ninth meeting of the Steering Committee of the Scientific Working Group on Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Geneva, 8–10 April 1981.

[19] Cartel JL, Millan J, Guelpa-Lauras CC, Grosset JH. Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampin and a thioamide. *Int J Lepr*, 1983; **51:** 461–5.

[20] Pattyn SR, Janssens L, Bourland J, Saylan T, Davies EM, Grillone S, Feracci C, The Collaborative Study Group for the Treatment of Leprosy. Hepatotoxicity of the combination of rifampin-ethionamide in the treatment of multibacillary leprosy. *Int J Lepr*, 1984: **52:** 1–6.

[21] Ji Baohong, Chen Jiakun, Wang Chenmin, Xia Guang. Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev*, 1984; **55:** 283–9.

Lepr Rev (1987) **58,** 39–51

Affinity of *Mycobacterium leprae* with Lewis rat Schwannoma cell line (Lewis TC 98)

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Summary The possible affinity of *Mycobacterium leprae* with Lewis TC 98 cell line established from Lewis rat spinal Schwannoma tissue was investigated. Lewis TC 98 cells phagocytosed *M. leprae* well, showing a phagocytic index of over 60% after 5-hr exposure at MC ratio = 25 (explained in the Introduction), higher than C6 cells from rat Glioma and still more higher than cells from human Neuroblastoma. In a comparative study with three kinds of inocula, i.e. live *M. leprae*, heat damaged *M. leprae*, and *M. lepraemurium*, only live *M. leprae* revealed a high affinity with Lewis TC 98 cells. Also, the phagocytic activity to *M. leprae* of Lewis TC 98 cells was not affected by changing the condition of the cell growth with low doses of foetal bovine serum (FBS) in a culture medium. These results may suggest the special affinity of *M. leprae* with Schwann cells and the possible presence of a receptor with reactivity to live *M. leprae*, presumably existing on cell surfaces of Lewis TC 98 cells. However, two rabbit antisera against Lewis TC 98 cell surface antigens could not block the interaction between Lewis TC 98 cells and *M. leprae*.

Introduction

A characteristic feature of *M. leprae* which causes leprosy is their neurotropism. Thus, the possible affinity between *M. leprae* and the Schwann cells as one of the main targets has given one of the basic explanations for the cause of the involvement of the peripheral nervous system in leprosy.[1,2] During the last two decades, therefore, many attempts to clarify this affinity have been made *in vitro*. Primary cultures derived from human acoustic Schwannoma have been used as cell material on account of their vigorous phagocytic activity and their high affinity with *M. leprae*.[3,4] Further studies elucidated the poor affinity of heat damaged *M. leprae* compared with that of live *M. leprae* with Schwann cells from the dorsal root ganglia of newborn mice.[5] *M. lepraemurium* also revealed a poor

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affinity with organized nerve tissue cultures.[6] Moreover, it has been shown that Schwann cells are capable of engulfing any particulate matter, such as hemosiderin, myelin debris and India ink particles.[7] These findings would become a basis for our investigation of the close relationship between *M. leprae* and Schwann cells. However, conventional cell materials always need more complicated techniques and chances of success in the preparation of nerve tissue cultures. In this study, we used Lewis rat Schwannoma cell line (Lewis TC 98) established from Lewis rat spinal Schwannoma tissue. This was thought to be a more adequate cell material for the target of *M. leprae* because of easier maintenance and propagation of the cells for the experimental use. This article reports the characteristics of the affinity of *M. leprae* with Lewis TC 98 cells quantitatively *in vitro*. In this report, the proportion of total number of exposed Mycobacteria to total number of cells in a plate is simply expressed as MC ratio and the term phagocytic index is used as the meaning of a proportion (%) of the number of cells containing ingested bacilli to the number of cells to be inoculated. The series of experiments were conducted in this study on: 1, how changing MC ratio when *M. leprae* are infected influences the phagocytic activity of Lewis TC 98 cells and how low doses of FBS in a medium affects their phagocytic activity; 2, a comparison of the phagocytic activity of Lewis TC 98 cell line on *M. leprae* with two other neural cell line, i.e. rat Glioma cell line (C6) and human Neuroblastoma cell line; 3, the relative affinity of three inocula, i.e. live *M. leprae*, heat damaged *M. leprae* and *M. lepraemurium* that does not infect the nervous tissues,[6] with Lewis TC 98 cells; 4, a detection of a receptor, if any, on Lewis TC 98 cells, based on the presumption that the receptor masked cells by antiserum would show a lower phagocytic index than unmasked cells.

Materials and methods

CELL LINES AND MYCOBACTERIA

Lewis rat Schwannoma cell line (Lewis TC 98) was kindly furnished by Dr B H Liwnicz, University of Cincinnati College of Medicine; human Neuroblastoma cell line by Dr T Ito and Dr H Nomaguchi, Osaka University; and rat Glioma cell line (C6) was purchased from Flow Laboratories Inc., Virginia.

Mycobacteria used in this study were *M. leprae* serially passaged in nude mice, and *M. lepraemurium* (Hawaiian strain) developed in BALB/C mice. These mycobacteria were kindly supplied by Dr M Matsuoka, National Institute for Leprosy Research, Tokyo. After storage of the footpad of nude mouse and BALB/C mouse spleen at $-80°C$ for 3 weeks, the respective suspensions were prepared in Hank's balanced salt solutions containing 0·1% bovine albumin and stored at 0°C (wet ice) until use. All inoculations described in this report were completed within 48 hr after preparation of mycobacterial suspensions.[8,9] Counts

of mycobacteria were taken by the method of Shepard[10] and the bacterial suspensions with appropriate MC ratio for the experiments were prepared by making a suitable dilution with the medium. The heat damage of *M. leprae* was done by autoclaving.

PREPARATION OF HOST CELLS AND PROCEDURES OF INOCULATION AND OBSERVATION

Three cell lines were propagated in RPMI-1640 medium supplemented with 10% heat inactivated FBS with 100 IU of penicillin. First, 5 ml of 1×10^5 cells in 10% FBS medium were cultured on 60-mm diameter Falcon plastic plates with 6 glass slips in a 5% CO^2 chamber at 37°C for 24 hr. After washing with FBS free medium, cells on glass slips were infected with mycobacteria supplemented in 5 ml of 10% FBS medium and cultured under the same conditions. In the series of experiments, low percentages of FBS in the medium, i.e. 5% and 2·5% were used in the only experiment to elucidate how changing the conditions of cell growth influenced the phagocytic activity, during all stages of experiment. The cultures were terminated at desired intervals of cultivation, specifically at 1, 3 and 5 hr, respectively. The terminated one pair of cultures on each glass slip were washed with 1/100 M phosphate buffered saline, pH 7·2 (PBS), fixed in 10% buffered formalin for 24 hr, and stained with Ziehl–Neelsen for acid-fast bacilli. More than 200 cells were randomly examined microscopically and the phagocytic indexes were scored.

PREPARATION OF ANTISERA TO LEWIS TC 98 CELL MEMBRANE ANTIGENS

Antisera were prepared as follows: Lewis TC 98 cells in vigorous condition were harvested by rubber policemen, washed twice with cold physiologic saline and prepared in 2×10^6 cells ml^{-1}. Then inoculations of 0·5 ml each of cell suspension were respectively made into 2 rabbits intravenously. Two weeks later, bloods were collected and separated sera were stored at −20°C until use. The titres of these two antisera against antigenic determinants on the surface of Lewis TC 98 cells were titrated as 1:640 (antiserum-1) and 1:40 (antiserum-2), respectively by the indirect membrane immunofluorescence test. Two sera before inoculations (serum-1 and serum-2) did not contain any detectable antibodies. Before experiment, antisera and sera before inoculations as controls were inactivated by heat at 56°C for 30 min and filtered through a membrane filter (0·45 μ pore size).

IMMUNOFLUORESCENCE

The indirect membrane immunofluorescence test[11] was used. The living cells on glass slips were washed twice with PBS, allowed to stand to react with diluted antiserum at 37°C for 30 min and washed with PBS. The cells were then reacted

with fluorescein isothiocyanate (FITC)-conjugated anti-rabbit IgG (Cappel Laboratories, West Chester, PA) for 30 min at 37°C. After washing with PBS, glass slips were placed on a slide. Fluorescent cells were examined under a fluorescence microscope, Chiyoda-Fluorophoto.

BLOCKING TEST OF A RECEPTOR ON LEWIS TC 98 CELLS BY ANTISERA

Lewis TC 98 cells were cultured on glass slips in four plates and each plate was used for the cell treatments by four different sera, i.e. antiserum-1, antiserum-2, serum-1 and serum-2, respectively. Cells on glass slips were washed with FBS free medium and then treated with 10-fold diluted antiserum for 30 min in the same chamber. After washing with FBS free medium, antibody treated cells were immediately infected with fresh medium supplemented with *M. leprae* prepared

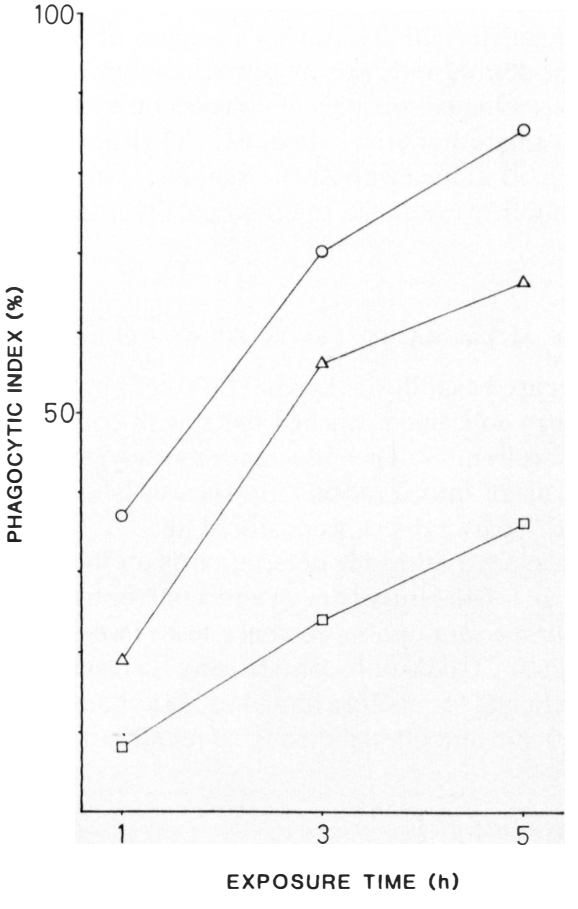

Figure 1. Relationship between MC ratio and phagocytosis by Lewis TC 98 cell line of *M. leprae*. (○——○) MC ratio = 50, (△——△) MC ratio = 25, (□——□) MC ratio = 12·5.

at MC ratio = 25. The terminated one pair of glass slip cultures were fixed, stained and then the phagocytic indexes were scored as described above. The presence of antibodies reacted with cell surface antigens were also examined by the indirect membrane immunofluorescence test, at 0, 1 and 3 hr after infection.

Results

INFLUENCES ON THE PHAGOCYTIC ACTIVITY OF CHANGING MC RATIO AND THE CELL GROWTH

The influence of MC ratio on the phagocytic index is shown in Figure 1. The phagocytic indexes at MC ratio = 50 and MC ratio = 25 after only 1 hr inoculation were already 37 and 19%, respectively, which continued to rise sharply to reach over 80 and 60% within 5 hr. In the case of MC ratio = 12·5, 8% shown on the phagocytic index after 1 hr went up gradually and reached 36% after 5 hr.

It is worth considering that the phagocytic activity would be activated in vigorous cells. Proceeding from this observation, the growth of Lewis TC 98 cells

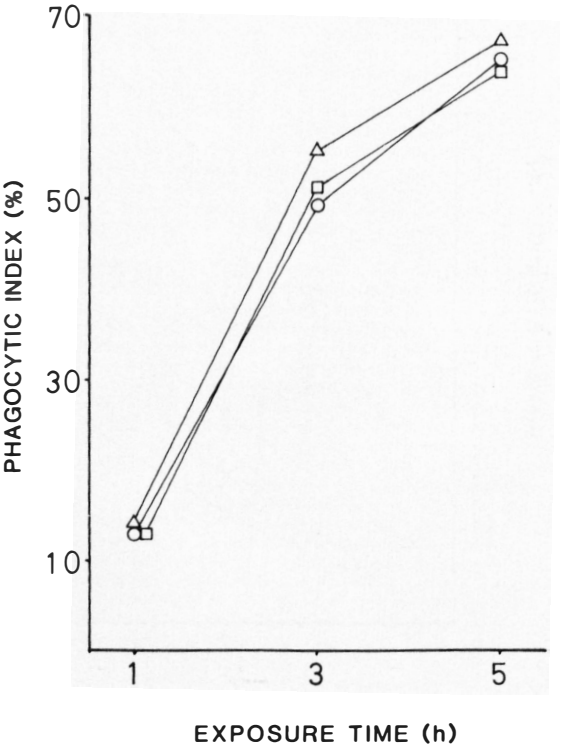

Figure 2. No reduction of phagocytosis by Lewis TC 98 cell line cultured in the medium with low percentages of FBS. (○——○) 10% FBS, (△——△) 5% FBS, (□——□) 2·5% FBS.

was controlled by low doses, i.e. 5 and 2·5%, of FBS in the medium, and its influences on the phagocytic index was investigated at MC ratio = 25 (Figure 2).

Contrary to expectation, there was no definite relationship between the percentage of FBS and the phagocytic index. This result indicates that Lewis TC 98 cells under controlled growth conditions are capable of engulfing *M. leprae* as many as cells in the growth medium, and might be an evidence of some special affinity between *M. leprae* and Schwann cells.

COMPARATIVE EXPERIMENT WITH OTHER NEURAL CELL LINES

Lewis TC 98 cells were compared with two other neural cell lines, i.e. human Neuroblastoma cells and rat Glioma cells (C6), to clarify any differences between their affinities with *M. leprae* at MC ratio = 25. As shown in Figure 3, Lewis TC 98 cells showed an affinity significantly higher than those of C6 and Neuroblastoma cells. It is of interest to note that the phagocytic index of C6 cells was lower than that of Lewis TC 98 cells but higher than that of Neuroblastoma cells. It seems

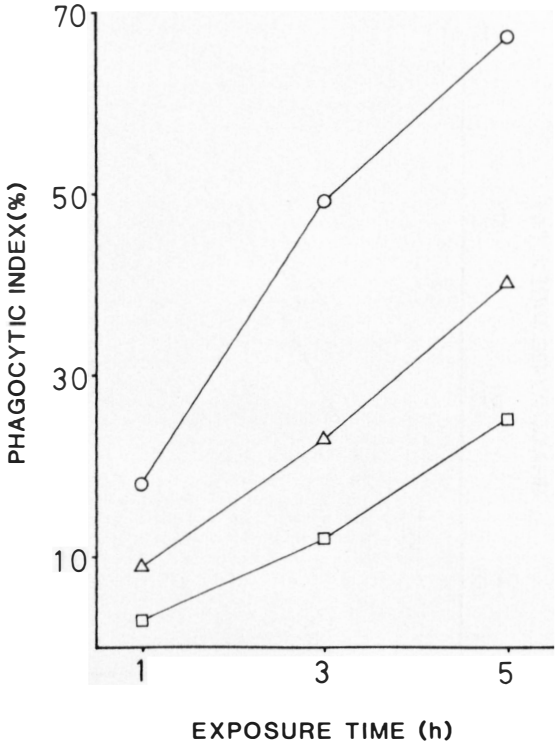

Figure 3. Comparison of phagocytosis by three neural cell lines of *M. leprae*. (○——○) Lewis rat Schwannoma cell line (Lewis TC 98), (△——△) rat Glioma cell line (C6), (□——□) human Neuroblastoma cell line.

this phenomenon should be discussed in relation to the styles of the nerve damage in leprosy.

COMPARATIVE EXPERIMENT WITH HEAT DAMAGED *M. LEPRAE* AND *M. LEPRAEMURIUM*

The poor affinities of *M. lepraemurium* with organized nerve tissue cultures and heat damaged *M. leprae* with Schwann cells from dorsal root ganglia *in vitro* were respectively described by Fildes[6] and Mukherjee *et al.*[5] In order to find out whether Lewis TC 98 cells show the same property, live *M. leprae*, heat damaged *M. leprae* and *M. lepraemurium* were inoculated to Lewis TC 98 cells at MC ratio = 25. The results in Figure 4 show that the uptake of heat damaged *M. leprae* was very poor, reduced to almost the same level as *M. lepraemurium* which did not show any affinity. Overall, the lack of affinities that heat damaged *M. leprae* and *M. lepraemurium* had with Lewis TC 98 cells coincided with the data described by the above two investigators.

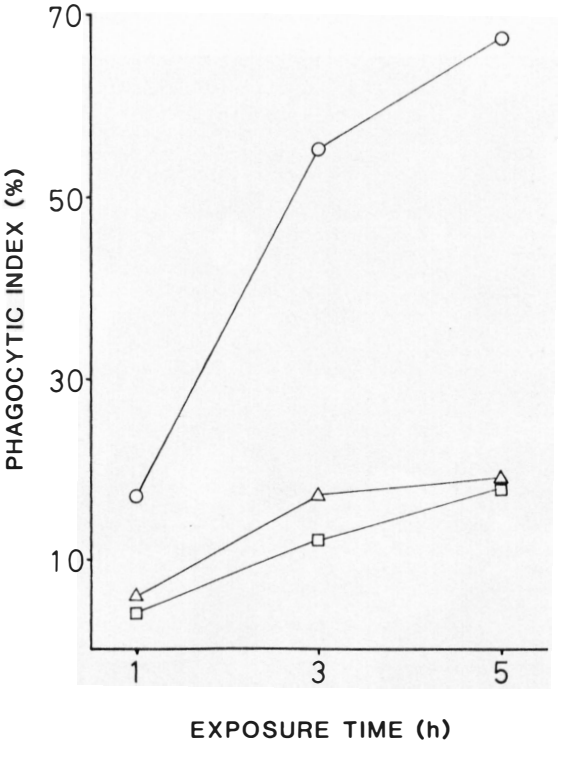

Figure 4. High affinity of live *M. leprae* different from other inocula with Lewis TC 98 cell line. (○——○) live *M. leprae*, (△——△) heat damaged *M. leprae*, (□——□) *M. lepraemurium*.

BLOCKING TEST OF A RECEPTOR ON LEWIS TC 98 CELLS BY ANTISERA

The indirect membrane immunofluorescence was concomitantly carried out to know if both antibodies reacted were sufficiently kept on cell surfaces, i.e. at 0 hr, namely immediately after treatment with antibodies, 1 and 3 hr after infection respectively. Lewis TC 98 cell surfaces at 0 hr were intensely stained with 100% of positive cells. Even cells after 3-hr exposure, 100% of cell surfaces were positively stained with a great intensity as well (Figure 5).

The result of phagocytic indexes was shown in Figure 6. The data represent that phagocytic indexes of antibody treated Lewis TC 98 cells were not inhibited and they paralleled with those of control cells treated with sera before inoculations.

Discussion

For an experimental attempt to cultivate *M. leprae in vitro*, primary cultures derived from human acoustic Schwannoma were used by Lumsden.[3] In his experiments with Schwannoma cells and *M. leprae*, he demonstrated the vigorous

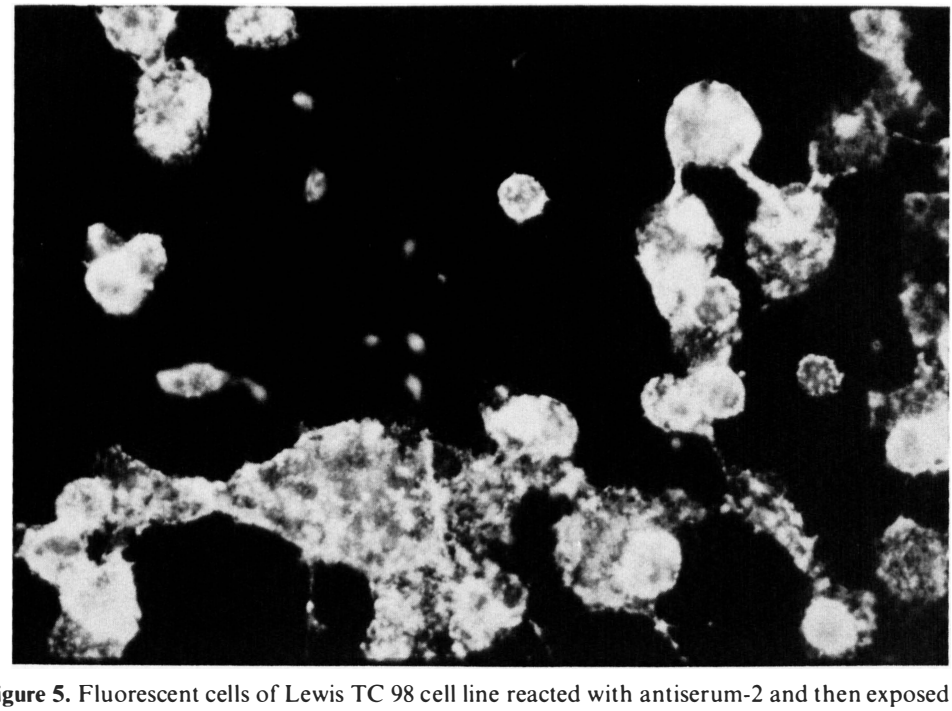

Figure 5. Fluorescent cells of Lewis TC 98 cell line reacted with antiserum-2 and then exposed *M. leprae* for 3 hr in an indirect membrane immunofluorescence. Photograph was taken after keeping the stained cells at 4°C overnight.

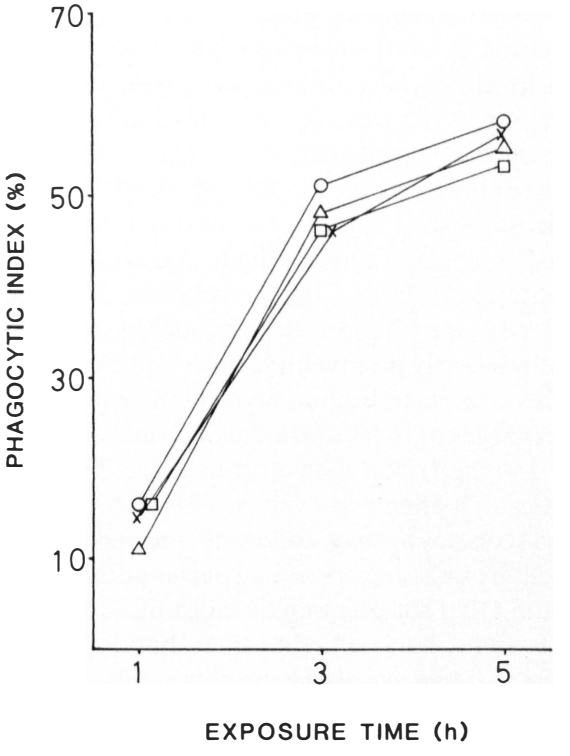

Figure 6. No reduction of phagocytosis by antisera treated Lewis TC 98 cell line. (○——○) antiserum-1, (△——△) serum-1, (□——□) antiserum-2, (X——X) serum-2.

phagocytic activity of Schwannoma cells. Lalitha *et al.*[4] reported that the phagocytic index of Schwannoma cells *in vitro* was over 90% 2 hr after the inoculation of *M. leprae*, although MC ratio was unknown. As shown in Figure 1, the phagocytic index was largely influenced by MC ratio when Schwannoma cells were used as a host. This discrepancy might be due to the difference in the multiplicity of contacts between *M. leprae* and Schwannoma cells on plates. They might have exposed more highly concentrated *M. leprae* suspensions to Schwannoma cells than we did with our materials. However, our data on the phagocytic index seem to be similar to the findings of Lalitha *et al.* While on the other hand, normal Schwann cells from dorsal root ganglia of newborn mice *in vitro* phagocytosed *M. leprae* from 15·9% for the phagocytic index at 24 hr to 67·2% at 72 hr after inoculation and that failed to sufficiently phagocytose heat damaged *M. leprae*, suggesting the importance of the viability of the bacilli infected.[5] In our cultures, although our results coincided with their data on the unsusceptibility of heat damaged *M. leprae*, the uptake of live *M. leprae* by Schwannoma cells was greater; in other words, the phagocytic index was about 20% within only 1 hr and over 60% after 5 hr exposure at MC ratio = 25. The difference in the phagocytic index between newborn Schwann cells and Schwan-

noma cells would be ascribable to the different cell situations, i.e. nontransformed and transformed cells. The vigorous phagocytic activity of human Schwannoma cells reported by Lumsden[3] and Lalitha *et al.*[4] could just explain these different phenomena. In fact, it was reported that normal Schwann cells from dorsal root ganglia of newborn mice, after phagocyting *M. leprae*, failed to incorporate DNA precursor, indicative of the blockage of DNA synthesis.[12] Meanwhile, since Lewis TC 98 cells, though established from Lewis rat spinal Schwannoma tissue, which is generally regarded as a benign tumor, divide and grow by doubling about every 24 hr, and propagate regardless of the presence of *M. leprae* in cells just like malignant tumor cells, they might be considered to be in more activated conditions than both the early premyelin secretory phase of normal Schwann cells and primary cultures of benign human acoustic Schwannoma.

In the second experiment, which was carried out with low doses of FBS, the data shown in Fig. 2 suggests that the vigorous Lewis TC 98 cell growth does not necessarily lead to the high phagocytic index. This also indicates that *M. leprae*, in the first stage of phagocytosis, may adhere to the surface of Lewis TC 98 cells regardless of the cell growth, suggesting a special affinity between them.

The data indicating that the phagocytic index of Lewis TC 98 cells was higher than that of C6 cells and still more higher than that of Neuroblastoma cells may be explained by the differences of the original cells of these tumors and the involvement of the peripheral nervous system, extending to and ceasing abruptly at the dorsal root ganglion, in leprosy (Fig. 3).[3] 1, Lewis TC 98 cell line originated in Schwann cell, the myelin forming cell of the peripheral nervous system; 2, C6 cell line originated in Glia cell of central nervous system, though undistinguishable whether it is oligodendroglia that is myelin forming cell of central nervous system or not;[13] 3, Neuroblastoma cell line originated in Sympathoblast. The fact that Lewis TC 98 cells were the most phagocytically active, especially compared to C6 cells, would suggest that leprosy was a disease of the peripheral nervous tissue.

The comparative experiment with three kinds of inocula, as shown in Figure 4, showed that only live *M. leprae* was highly phagocytosed. The other two inocula, i.e. heat damaged *M. leprae* and *M. lepraemurium*, were slightly phagocytosed at about the same level. At first, corresponding to the data described by Mukherjee *et al*,[5] heat damaged *M. leprae* were not engulfed well, probably suggestive of the destruction or the loss of some component on *M. leprae* that adheres to the host cell surfaces by autoclaving. The apparently poor affinity of *M. lepraemurium* tends to confirm the data reported by Fildes.[6] She observed large numbers of *M. leprae* and isolated *M. lepraemurium* predominantly in macrophages and fibroblasts in tissues of foetal rat and mouse dorsal root ganglia and whole cross-sections of mice containing somite, cord and ganglia, but unfortunately failed to detect an obvious affinity between *M. leprae* and Schwann cells. In fact, corresponding with her data, our cultures inoculated with *M. leprae* also showed high phagocytic indexes and large numbers of bacilli in the cells

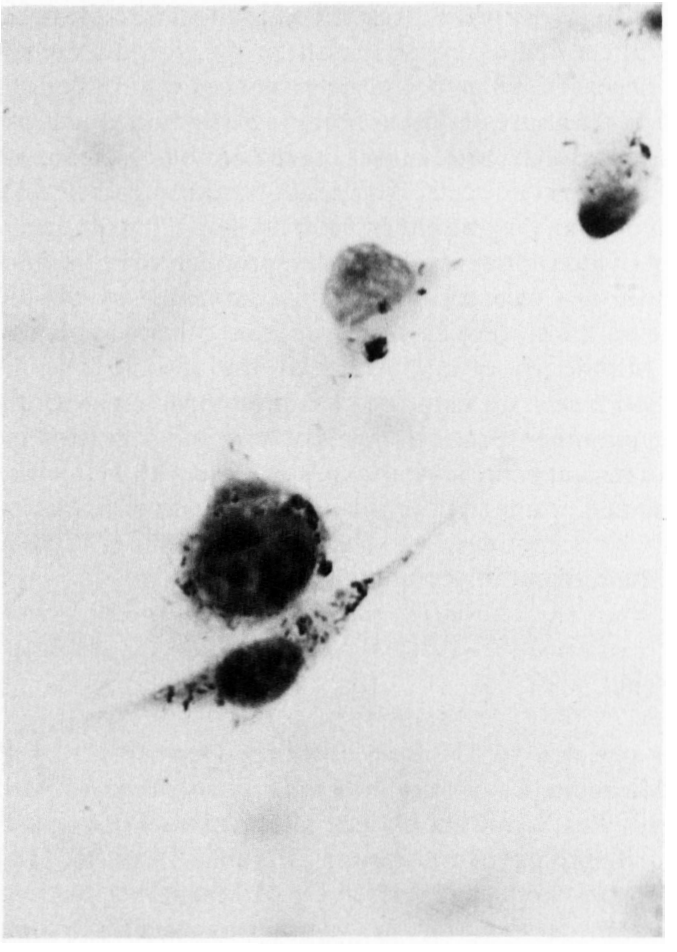

Figure 7. Lewis TC 98 cells engulfing large numbers of *M. leprae*, stained with Ziehl–Neelsen's method.

(Figure 7), whereas those inoculated with *M. lepraemurium* showed low phagocytic indexes and only isolated bacilli in the cells, indicating a poor affinity of *M. lepraemurium* with Schwann cells.

In conclusion, from the joint findings presented here, the following hypothesis could be accepted: that is, Lewis TC 98 cells and nontransformed Schwann cells as well may have two functional features that help to phagocytose live *M. leprae*. One is their general phagocytic activity, low levels of which may be explained by the poor affinities of heat damaged *M. leprae* and *M. lepraemurium*. The other is the specific adherence of live *M. leprae* to the surface of cell membranes in the first stages of phagocytosis, presumably explained by the presence of receptors on the cell surfaces specifically reactive to live *M. leprae*. From this hypothesis, the blocking test by two rabbit antisera against Lewis TC 98 cell surface antigens,

titrated as 1:640 and 1:40 respectively by the indirect membrane immunofluorescence test, was attempted, assuming that the phagocytic index would be reduced if receptors on Lewis TC 98 cells had been masked by antibodies. As shown in Figure 6, however, cells treated by antisera revealed no reductions on phagocytic index. This indicates that these antisera could not block the interaction between *M. leprae* and Schwannoma cells. This result further suggests two possibilities on this phenomenon: one may be either the weakness of the antigenicity or the too scanty amount of a receptor, resulting in no production of the antibody; another may be the lack of a receptor, presumably explained by the difference of the electric charge on the surface of *M. leprae* from other mycobacteria.

Recently Mukherjee *et al.*[14] reported the specific phenomenon of the adherence of *M. leprae* to Schwann cells in comparison with the insignificant adherence of eight other species of mycobacteria and suggested the possibility of the existence of receptors on Schwann cells reactive with *M. leprae*. Their and our observations would be one step for further investigations of the special affinity of live *M. leprae* with Schwann cells to clarify the mechanism of *M. leprae* infection and also the involvement of peripheral nervous system.

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References

[1] Antia NH. Leprosy—a disease of the Schwann cell. *Lepr India*, 1982; **54:** 599–604.

[2] Weddell AGM, Jamison DG, Palmer E. Recent investigations into the sensory and neurohistological changes in leprosy. In: *Leprosy in Theory and Practice*. Bristol: John Wright, 1964, 205–20.

[3] Lumsden CE. Leprosy and the Schwann cell *in vivo* and *in vitro*. In: *Leprosy in Theory and Practice*. Bristol: John Wright, 1964, 221–50.

[4] Lalitha VS, Bapat CV, Dastur DK. Culture and phagocytic characteristics of Schwann cells *in vitro*. A possible model substrate for cultivation of *M. leprae*. *Int J Lepr*, 1977; **45:** 266–72.

[5] Mukherjee R, Mahadevan PR, Antia NH. Organized nerve culture. 1. A technique to study the effect of *M. leprae* infection. *Int J Lepr*, 1980; **48:** 183–8.

[6] Fildes C. Organized nerve tissue cultures infected with *Mycobacterium leprae* and *Mycobacterium lepraemurium*. *Int J Lepr*, 1974; **42:** 154–61.

[7] Palmer E, Rees RJW, Weddell G. The phagocytic activity of Schwann cells. In: *Cytology of Nervous Tissue*. Rep Ann Mtg Anatomical Soc, 1961, 49.

[8] Dhople AM. Effect of freezing *Mycobacterium leprae* in tissues. *Lepr India*, 1982; **54:** 461–70.

[9] Shepard CC, MacRae DH. *Mycobacterium leprae*: Viability at 0°C, 31°C, and during freezing. *Int J Lepr*, 1965; **33:** 316–23.

[10] Shepard CC, MacRae DH. A method for counting acid-fast bacteria. *Int J Lepr*, 1968; **36:** 78–82.

[11] Klein G, Clifford P, Klein E, Stjernswärd J. Search for tumor specific immune reactions in Burkitt lymphoma patients by the membrane immunofluorescence reactions. *Proc Natl Acad Sci USA*, 1966; **55:** 1628–35.

[12] Mukherjee R, Mahadevan PR, Antia NH. Organized nerve culture. II. DNA synthesis in Schwann cells in the presence of *M. leprae*. *Int J Lepr*, 1980; **48:** 189–92.

[13] Benda P, Lightbody J, Sato G, Levine L, Sweet W. Differentiated Rat Glial Cell Strain in Tissue Culture. *Science*, 1968; **161:** 370–1.

[14] Mukherjee R, Antia NH. Adherence of *M. leprae* to Schwann cells *in vitro*: a specific phenomenon. *IRCS Med Sci*, 1985; **13:** 853–4.

Lepr Rev (1987) **58**, 53–60

The 'Ellis' and 'Ryrie' tests

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Summary Two simple non-time consuming tests for the detection of reaction and guidance of reactional therapy in leprosy patients are described and analysed. The tests showed to be useful both in hospital and in the field.

Introduction

Leprosy would be a rather innocuous disease if it were not for the permanent disability which may follow neural damage. Such damage usually results from episodes of so called reactions, reversal reaction (RR), a cell-mediated immune reaction, occurring in borderline patients[1,2] and erythema nodosum leprosum (ENL), an immune complex reaction[3,4] occurring in lepromatous patients.

When reactions are detected early and treated properly, patients will not suffer from major nerve damage.

For an experienced leprologist, it is usually not too difficult to discern that a patient is in reaction, but for less experienced field workers it is often more difficult.

When a reaction is diagnosed it is important to give the antireaction treatment in an adequate dosage for an adequate time.[5] Treatment of RR is now more or less standardized[6] with effective results.[7,8] However for ENL, being an episodic occurrence, guidelines in therapy are more difficult to establish, especially concerning dosage and duration, as individual patients respond differently.

This paper describes and analyses results obtained using two simple tests which may help in the detection and treatment of reaction.

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Material and methods

Data from patients on the National Leprosy Register of Zimbabwe are analysed. Patients are classified clinically and bacteriologically according to the Ridley–Jopling classification.[9]

From computerized data of the initial assessment of 2356 patients data were extracted from those who were diagnosed as being in 'reaction', either RR or ENL, or who had a positive 'Ryrie' or 'Ellis' test.

Patients were considered to be in RR when there were active inflamed skin lesions, tender nerves or signs of recent nerve damage as detected by voluntary muscle testing (VMT)[10] or graded sensory testing (GST).[11] Lepromatous patients were considered to suffer from ENL, when they developed painful erythematous nodules, tender nerves, lymphadenopathy or arthritis with or without fever. The 'Ryrie' test was first described by Ryrie over 40 years ago (B P B Ellis; personal communication). This test is based on the observation that patients in ENL have a tendency to walk as if on hot coals, due to the pain experienced in physical contact between ground and plantar surface of the foot.

The 'Ryrie' test is performed by passing a blunt instrument (the handle of a reflex hammer) over the plantar surface of the foot with light pressure (as in the Babinski reflex test), whilst observing the patient's face. The test is considered positive when the patient shows to experience pain by wincing.

Figure 1. 'Ellis' test.

The 'Ellis' test has been used for many years by B P B Ellis investigating leprosy patients in Zimbabwe and elsewhere. In this test the arm of the patient just above the wrist is squeezed gently with both hands as shown in Figure 1. The test is considered positive when the patient's face indicates pain.

To evaluate the efficacy of these tests a number of patients admitted for reactional treatment at the Tropical Disease Unit of the Harare Hospital were carefully followed in a longitudinal study.

The results of the 'Ellis' test were analysed to determine why it became positive, by comparing it with pinching of the skin, palpation of nerves and pressure on the periosteum.

Table 1. Number of patients in reaction, patients with positive 'Ellis' and 'Ryrie' tests grouped according to experience of the examiners.

Reaction (73)		'Ellis' test positive (%)	'Ryrie' test positive (%)	Detected by either tests (%)
Hospital	13	77	70	77
Rural exp	32	63	41	69
Rural inexp	28	36	43	54
		In reaction	(%)	
'Ellis' test positive (103)				
Hospital	11	10	91	
Rural exp	32	20	63	
Rural inexp	60	11	17	
'Ryrie' positive (164)				
Hospital	9	9	100	
Rural exp	61	13	21	
Rural inexp	94	12	13	

Table 2. Results of the 'Ellis' test in relation to tender lower arm structures.

Ellis' test	Tender nerves	Tender periost	Tender skin	Nothing
Positive				
16	9 (56%)	4 (25%)	10 (62%)	4 (25%)
Negative				
5	2	0	0	0

Table 3. A and B follow-up of 2 patients in RR. C and D follow-up of 2 patients in ENL.

Patient A															
RR	24/8		31/8	18/9	9/10		10/11								
Clinically	Neuritis raised lesions							after 5 months tapering off prednisolone is stopped							
'Ellis'	+ +		− −	− −	− −		− −	no positive 'Ryrie' or 'Ellis' tests							
'Ryrie'	− −		− −	− −	− −		− −								
Prednisolone (mg)	40		30	25	20		20								
VMT and ST	much down ↑ reaction				ST improving			improvement of both ST and VMT							
Patient B															
RR	7/8	21/8	31/8	4/9	7/9	14/9	18/9	25/9	2/10	5/10	9/10	16/10	30/10	27/11	
Clinically	Neuritis			Neuritis											
'Ellis'	+ +	− −	+ +	+ + + +	+ +	+ +	+ +	± ±	+ +	± ±	− −	− −	− −	− −	discharged
'Ryrie'	+ +	− −	− −	− −	+ +	+ +	− −	− −	± ±	± ±	− −	− −	− −	− −	
Prednisolone	60	45	60	80	80	80	60	65	50	50	45	40	30	25	
VMT and ST	severely ↑ reaction	down													both improving
		20/12			8/2	15/2	22/2	29/2							
Clinical			prednisolone												
'Ellis'		− −	stopped by		+ +	± ±	+ +	− −	prednisolone slowly reduced over a						
'Ryrie'		− −	mistake in		− −	− −	− −	− −	6-month period 'Ryrie' and 'Ellis'						
Prednisolone		20	January		60	60	45	40	stayed negative.						
VMT and ST					both down ↑ reaction				both marked improvement						

Table 3 (*continued*)

Patient C														
ENL	21/12		24/12	27/12	7/1	11/1	13/1	15/1	20/1	25/1	1/2	8/2	15/2	22/2
	ENL Nodules					ENL Nodules								
Clinical	Neuritis		Neuritis		ENL Nodules	Neuritis	Neuritis				Neuritis			
'Ellis'	++ ++		+ +	+ +	+ +	++ ++	+ +	± +	± ±	− −	− +	− ++	− −	− −
'Ryrie'	+ +		+ +	+ +	+ +	++ ++	− −	+ +	± ±	− −	− −	− −	− −	− −
Prednisolone (mg)	120		80	70	60	100	80	80	60	50	45	100–90–60	50	45
Colchicine (mg)											1,5	1,5–1–0·5		
	↑ reaction					↑ reaction						↑ reaction		
No major changes in VMT and ST														
Patient D														
ENL	30/3	2/6	9/6	13/6	16/6	20/6	27/6	30/6	4/7	11/7	14/7	18/7		
Clinical						ENL Nodules								
'Ellis'	+ +	+ +	+ −	− −	+ +	+ +	− −	− −	− −	− −	− −			
'Ryrie'	+ +	− ±	− −	− ±	− −	− −	± ±	− −	− −	− −	− −	discharged		
Prednisolone (mg)	50–40	30–20	10	10	30	30	20	15	10	5				
Colchicine (mg)		1,5	1	1	1	2	2	2	2	2	1			
	VMT ST deteriorated		VMT improving								ST improving			
	↑ reaction					↑ reaction								

Results

Analysis of the initial assessment of 2356 patients indicated that 73 were in reaction. In 103 patients the 'Ellis' test was positive in one or both wrists and in 164 the 'Ryrie' test was positive.

Of the patients with a positive 'Ellis' test 40 (39%) were in reaction as were 34 (21%) with a positive 'Ryrie' test.

In order to assess the influence of experience in performing these tests, the available data were analysed according to where they were performed. Comparison is made of results obtained from a hospital, provinces with experienced staff and provinces with less experienced staff (Table 1).

Table 2 analyses the 'Ellis' test performed on 11 patients admitted to hospital with a reaction. Three were suffering from a RR and 8 had ENL. In 1 patient only one wrist was assessed as an infection of a finger on the other hand could have influenced the results.

When the 'Ellis' test was positive in a patient with RR, the radiocutaneous or median nerve was found to be tender in nearly all cases. In patients with ENL more structures were found to be tender with the skin most frequently involved. In 4 wrists the 'Ellis' test was found positive, without either tender skin, periostia or nerves.

Table 3 shows the follow-up of 4 patients, 2 with ENL and 2 with RR in whom the 'Ellis' and 'Ryrie' tests were used to guide treatment.

Discussion

The low number of reactions (73) found in the initial assessment of 2356 patients, may be explained by the fact, that the majority of these patients had previously received dapsone monotherapy, before they were assessed and transferred to multiple drug therapy (MDT).

Of the 300 previously untreated patients 26 were reported to be in reaction (12 ENL, 9 RR and 5 unknown, but most likely also RR). This is the same percentage ($\pm$ 10%) as found among new patients attending the out-patients department of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Addis Ababa, Ethiopia (9 out of 70 new borderline patients and 2 out of 16 new lepromatous patients) (Naafs 1975; unpublished observation).

In many of the patients in reaction both 'Ellis' and 'Ryrie' tests were positive. With these relatively simple tests 64% of these patients could be detected, although experience played an important role (Table 1). In a number of patients, the fact that one or both of these tests were positive made the examiner look more carefully for other signs which could show that the patient was in reaction; tender nerves, erythematous or infiltrated lesions or symptoms of recent nerve damage.

Although the specificity of these tests is high, 0·972 for the 'Ellis' test and 0·943

for the 'Ryrie' test, the sensitivity is less, 0·54 for the 'Ellis' test only 0·46 for the 'Ryrie' test, but 0·64 for the both combined (Table 2).

In patients in reaction whose tests were negative extensive 'glove and stocking' anesthesia was often present. It is remarkable that the 'Ryrie' test was often falsely positive in patients with extensive plantar anesthesia. It is possible that in these patients the deep sensation is still intact and that its stimulation is not inhibited by 'lateral inhibition' evoked by plantar skin stimulation.

Another frequent reason for a false positive 'Ryrie' test was the observation; that inexperienced examiners frequently mistook the reaction of the patient on 'tickling' for a reaction to pain.

What actually is 'measured' in a true positive 'Ryrie' test is not clear. It is possible that during a reaction the threshold for pain stimuli is lowered, as is shown for touch stimuli[11] in patients with acroedema in RR.

A positive 'Ellis' test in patients in RR is usually due to the local tenderness of the radiocutaneous and/or median nerve. However, in a few patients not included in Table 2 it was found that the 'Ellis' test could be positive even in the absence of nerve tenderness.

A positive 'Ellis' test in patients in ENL could also be related to tenderness of other structures (Table 2). Although most of the patients the skin was tender, the number of patients that responded with tenderness of the periostia was unexpectedly high. This could indicate that the periosteum is more often involved in ENL than generally assumed.

In 4 wrists the 'Ellis' test was positive despite non-tenderness of nerves, skin or periostia. This could be due to a general lower threshold for pain stimuli, or the involvement of other structures; myositis, tendovaginitis, with involvement of the synovia of the tendon sheats.[12]

False positive 'Ellis' tests were often found to be due to excessive pressure on squeezing of the wrist by inexperienced examiners.

In Table 3 it can be seen that in RR 'Ellis' and 'Ryrie' tests rapidly become and stay negative after instigation of antireactional therapy. Provided this treatment follows the recommendations of Naafs *et al.*[5] and the suppression of cell-mediated immunity lasts long enough to prevent a recrudescence of the reaction. This was not the case in patient B in whom the prednisolone was stopped too early. In the same patient there were some problems in determining the right start dose of prednisolone.

In ENL, the tests showed to be of great value, often being positive before other clinical signs, including ENL nodules or nerve tenderness appeared.

In our opinion these simple, non-time consuming tests showed to be a valuable addition to the common routine investigations in detecting patients in reaction, especially for the less experienced examiners in the field.

Both tests showed to be of value in determining the dosage of antireactional treatment especially in patients with ENL, experiencing episodic reactional periods.

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We thank Mr B P B Ellis for introducing us to the 'Ryrie' and 'wrist' test.

References

[1] Godal T, Myrvang B, Samuel DR, Ross WF, Løfgren M. Mechanisms of 'reaction' in borderline tuberculoid (BT) leprosy. *Acta Path. Microbiol. Sc. Sect A Suppl* 1973; **236:** 45–53.

[2] Bjune G, Barnetson R StC, Ridley DS, Kronvall G. Lymphocyte transformation test in leprosy: correlation of the response with inflammation of lesions. *Clin exp Imm*, 1976; **25:** 85–90.

[3] Bjørvatn B, Barnetson R StC, Kronvall G, Zubler RH, Lambert PH. Immune complexes and complement hypercatabolism in patients with leprosy. *Clin exp Imm*, 1976; **26:** 388–96.

[4] Ridley MJ, Ridley DS. The immunopathology of erythema nodosum leprosum: the role of extravacular complexes. *Lepr Rev*, 1983; **54:** 95–108.

[5] Naafs B, Pearson JMH, Wheate HW. Reversal reaction: prevention of permanent nerve damage. Comparison of short- and long-term steroid treatment. *Int J Lepr*, 1979; **47:** 7–12.

[6] Naafs B. Therapy of neuritis during reaction in leprosy. Quaderni di cooperazione sanitaria—Health cooperation papers. 1981; 65–70.

[7] Touw-Langendijk EMJ, Brandsma JW, Andersen JG. Treatment of ulnar and median nerve function loss in borderline leprosy. *Lepr Rev*, 1984; **55:** 41–6.

[8] Kiran KU, Stanley JNA, Pearson JMH. The outpatients treatment of nerve damage in patients with borderline leprosy using a semi-standardised steroid regimen. *Lepr Rev*, 1985; **56:** 127–34.

[9] Ridley DS, Jopling WH. Classification of leprosy according to immunity. *Int J Lepr*, 1966; **34:** 255–70.

[10] Brandsma JW. Basic nerve function assessment in leprosy patients. *Lepr Rev*, 1981; **52:** 161–71.

[11] Naafs B, Dagne T. Sensory Testing: A sensitive method in the follow-up of nerve involvement. *Int J Lepr*, 1977; **45:** 364–8.

[12] Malaviya GN, Ramu G, Mukherjee A, Hussain S, Ramanathan VD. Synovial swellings over wrist in leprosy. *Ind J Lepr*, 1985; **57:** 350–3.

Lepr Rev (1987) **58,** 61–67

An unusual bullous reaction in borderline leprosy

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Summary A 45-year-old male patient suffering from borderline lepromatous leprosy with reaction, developed round or irregular, well defined, large tense bullae on existing leprosy lesions. There was deposition of IgG, IgM, IgA and fibrin along the basement membrane. It was not a bullous drug eruption due to either rifampicin, dapsone or clofazimine, but a component of leprosy reaction. Difficulties in classifying as either Type I or Type II reaction are discussed.

Introduction

Bullous eruptions are rarely observed in leprosy patients. Generalized bullous drug eruptions due to rifampicin[1] and DDS[2] have been reported. Vesicles and bullae have been observed in purpuric, tender erythematous plaques of Lucio phenomenon and in the evanascent, tender erythematous skin nodules called erythema nodosum leprosum (ENL) lesions which may occur as a part of Type II leprosy reactions.[3]

Type I leprosy reactions occur in borderline leprosy. Existing lesions become more red and oedematous. Systemic disturbances are rare, though the patients may develop oedema of hands, feet or face. On the other hand in Type II reactions, seen in borderline lepromatous (BL) and lepromatous leprosy (LL), systemic disturbances are usual and ENL lesions may occur, but there is no change whatsoever in the appearance of leprosy lesions.[3]

Case report

A 45-year-old, male, gave a 4-year history of a progressively enlarging hypopigmented hypo-aesthetic patch over the left side of the chest and a

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stationary patch over the left thigh. Two months earlier, he had suddenly developed multiple erythematous plaques over the body, paraesthesia over hands, forearms, shins and face, oedema of hands and feet and pain in wrist and ankle joints. This was not associated with fever, malaise or drug intake.

On examination, there were numerous, asymmetrically, distributed, raised erythematous, plaques with smooth stretched surface and gradually sloping borders. The margins were indistinct in places. Two of these plaques were large, being 12 cm in diameter, whereas most others were small, varying between 1 and 3 cm in diameter. Hair loss and hypo-aesthesia were noted only in the larger lesions. There was glove and stocking type of anesthesia. Ulnar, lateral popliteal and radial nerves on both sides were thickened and tender. Axillary and inguinal lymph nodes were enlarged, discrete, mobile and non-tender. Oedema of hands and feet was gross. Systemic examination was unremarkable.

Investigations revealed Hb 13·2 gm dl^{-1}, total leukocyte count 5200 cu mm^{-1}, neutrophils 60%, lymphocytes 32%, eosinophils 4%, monocytes 4% and erythrocyte sedimentation rate by Westergrens method was 23 mm in one hour. No abnormality was detected in urine and stool examination. Blood chemistry revealed random glucose 60 g dl^{-1}, urea 16 mg dl^{-1}, creatinine 1·4 mg dl^{-1}, sodium 140 mEq L^{-1}, potassium 3·4 mEq L^{-1}, albumin 3·6 g dl^{-1}, globulin 4·3 g dl^{-1}, total bilirubin 1·6 mg dl^{-1}, alkaline phosphatase 3·3 IU dl^{-1}, glutamic oxaloacetic transaminase 60 units ml^{-1} and glutamic pyruvic transaminase 45 units ml^{-1}. Chest X-ray examination was normal. Histopathology of lesions revealed normal epidermis, a Grenz zone and loose foamy macrophage granulomas scattered throughout the oedematous dermis. There were numerous lymphocytes and occasional foreign body giant cells. Nerves had onion-skin perineurium. Ziehl-Neelsen staining showed numerous (5+) granular acid-fast bacilli (AFB).

At this stage the patient was thought to have BL leprosy in Type I reaction. He was put on multidrug regimen with rifampicin 600 mg, clofazimine 300 mg, DDS 100 mg and prednisolone 30 mg daily. The reaction subsided mildly over the first few days, but worsened between the 12th to 14th day. At this time numerous, round to irregular, well defined, tense bullae measuring 5–20 mm in diameter appeared over all the leprosy lesions (Figures 1 and 2). Most of them contained clear fluid though some were haemorrhagic. A few small lesions occurred over soft palate.

The patient was hospitalized and repeat haemogram and blood chemistry done at this time were essentially similar to that at presentation. However improvement of liver function tests was observed. The bulla fluid contained polymorphs and occasional eosinophils. Acantholytic cells and AFB were not seen. Histopathology of the bulla (Figures 3–6) showed a location in the subepidermis. It contained fibrin, neutrophils, red blood cells (RBC) and occasionally plasma cells and eosinophils but no acantholytic cells. At the base of bulla and in the dermis, there were foamy macrophage granulomas, with a few

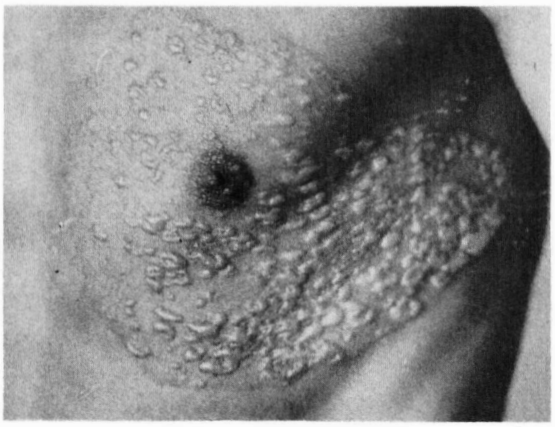

Figure 1. Irregular, large and tense bullae confined strictly to the plaque on left side of chest.

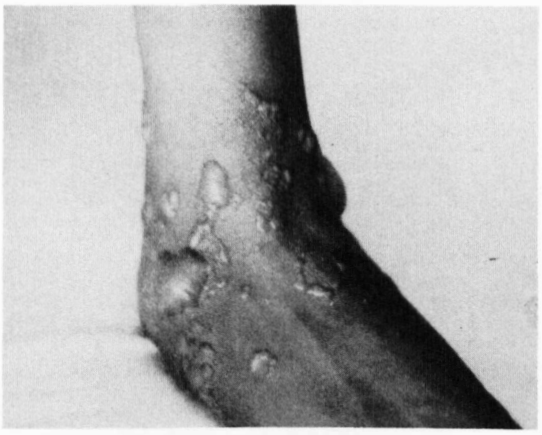

Figure 2. Bullae confined to leprosy lesion on left forearm.

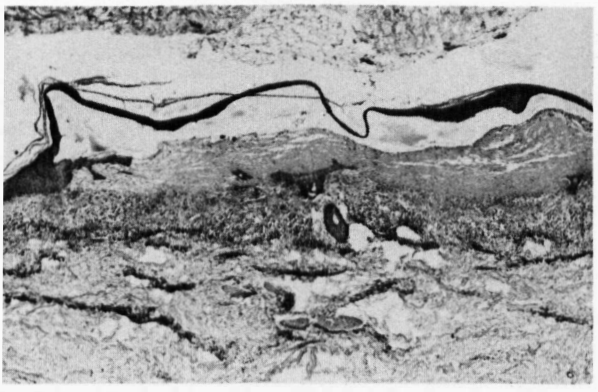

Figure 3. Large subepidermal bulla with slight regeneration of epidermis. Diffuse and loose granuloma at the base. Infiltrate along neurovascular bundles and around adnexa in deeper dermis (H & E × 25).

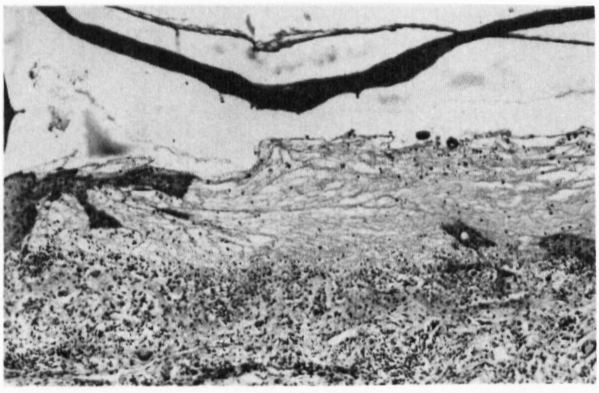

Figure 4. Marked oedema of upper dermis and fibrin deposition. Dilated vascular spaces. Dense infiltrate with few langhan giant cells (H & E × 72·5).

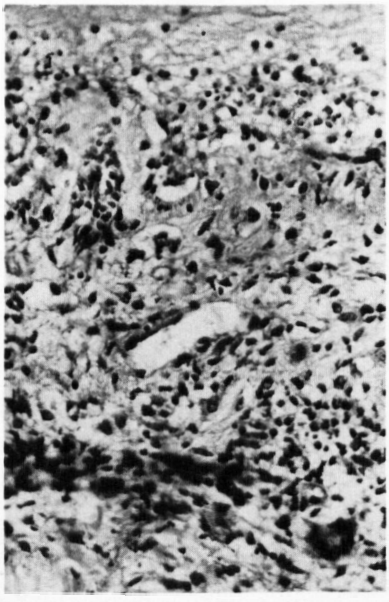

Figure 5. Dilated vessels, extravasation of RBC, neutrophiles, nuclear dust, lymphocytes, langhan giant cells, vacuolated macrophages and oedema of dermis at the base of bulla (H&E × 250).

epithelioid cells and lymphocytes, occasional Langhans and foreign body giant cells. Significantly the granuloma was heavily infiltrated by neutrophils, some showing karyorrhexis, with a few eosinophils and plasma cells. There was mild extravasation of RBCs. AFB were 2+ and fragmented. At the edge of bulla, indirect immunofluorescence of cryostat sections showed positive staining for IgM, IgG, IgA and fibrin but no C_3 along the basement membrane.

At this time, antileprosy drugs were stopped, while prednisolone was

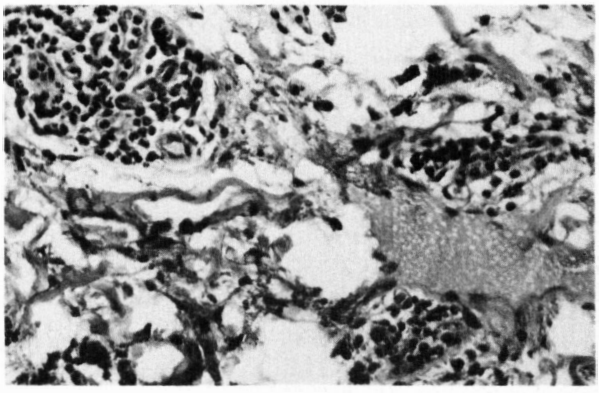

Figure 6. Infiltrate of vacuolated macrophages, lymphocytes, neutrophils along neurovascular bundles in lower dermis (H&E × 250).

increased to 60 mg per day. Within 3 days the bullous eruption was controlled and the patient improved gradually. By 4 weeks prednisolone could be reduced to 10 mg/day. In the 3rd and 5th week the patient developed occasional small bullae along with mild exacerbation of reaction. They subsided spontaneously without any further treatment. Histopathology of bullae were identical to that examined at the time of hospitalization.

During the 6th week provocation tests were conducted. Rifampicin 600 mg/day was introduced followed 3 days later by DDS 100 mg/day. Though there were no drug eruptions, including bullous eruption, the patient developed arthralgia and swelling of vestibule and inferior turbinate leading to difficulty in breathing. Investigations including histopathology were essentially similar to that observed at time of presentation. However, the foam cell granulomas had scant lymphocytes, mild fibrosis and 2+ AFB.

Rifampicin was withdrawn and prednisolone was increased to 60 mg/day, whereupon there was improvement. On reintroduction of rifampicin the patient developed similar symptoms within 24 hours, and thereafter rifampicin was avoided. Introduction of clofazimine 300 mg/day led to moderate improvement. Chloroquine phosphate 250 mg twice daily was introduced in the 12th week. Over the succeeding 3 weeks there was rapid improvement and the steroids were withdrawn without further deterioration in the clinical state.

Discussion

Large, tense, histologically subepidermal bullae with deposition of IgM, IgG, IgA and fibrin but no complement along the basement membrane, were confined almost exclusively to leprosy lesions. It was not a drug eruption as provocative tests with rifampicin, clofazimine and DDS did not reproduce bullae.

Clinically similar bullae occur in bullous pemphigoid (BP), occasionally in dermatitis herpetiformis (DH) and bullous erythema multiforme (EM): None of these occurred coincidentally in this leprosy patient. These have a classical clinical picture and diagnostic immunohistological features. In DH, IgA is deposited at tip of dermal papillae and along the basement membrane.[4,5] In EM iris lesions are pathognomonic,[6] and the immunologic study may reveal deposits of IgM and C_3 in the walls of the superficial dermal vessels,[4] but none along the basement membrane.[6] In BP, IgG and C_3 are deposited along the basement membrane,[4,7] Complement (C_3) deposition occurs in virtually all BP skin lesions and at times C_3 deposit occurs in the absence of IgG.[7] Rarely, BP localized to plaques of psoriasis and characterized by deposition of IgG and C_3 along the basement membrane has been observed.[8,9] In the apparently similar present case there was, however, no deposition of C_3.

Bullae can appear in the purpuric, painful, tender, red patches of Lucio phenomenon and in the ENL lesions occurring during Type II leprosy reaction.[3] None of these two types of lesions were observed in this patient.

Occurrence of bullae during heightened phases of leprosy reaction, firstly, 11 days after start of antileprosy therapy and subsequently during 3rd and 5th week of hospitalization when patient was not on antileprosy drugs, along with its strict localization to existing leprosy lesions, suggest that it was an integral concomitant manifestation of leprosy reaction.

The patient initially presented with Type I reaction in BL leprosy which apparently had progressed from borderline tuberculoid (BT). Bullae seemingly appear to be a part of this reaction. Langhans giant cells in macrophage granuloma at the base of bulla can be explained on this basis.

Histopathologically it was not possible to decide whether the bullous reaction represented Type I or Type II. There were large numbers of neutrophils which are often regarded as the hallmark of Type II reaction. But they do occur also in Type I reaction. At times, in BL, no histological distinction between these two types of reactions is possible.[10] However, there was extravastion of red blood cells and almost near total disappearance of AFB from the granulomas. These are common findings in Type II reactions. Further, deposition of immunoglobulins along the basement membrane, at the edge of bulla indicates an activity of humoral response and Type II reaction is probably immune complex mediated. But, bullae were localized to existing leprosy lesions, and in Type II reactions lesions do not show any change.[3]

Whether this bullous reaction is a variant or a combination of Type I or Type II leprosy reaction is difficult to conclude. Interestingly, it has recently been proposed that ENL is initiated most probably by a cell-mediated response[11] and is perpetuated perhaps by immune complexes.[12]

Acknowledgment

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References

[1] Nigam P, Dayal SG, Goyal BM. Erythema multiforme bullosum due to rifampicin. *Lepr India*, 1979; **51:** 249–51.

[2] Dutta RK, Erythema multiforme bullosum due to dapsone. *Lepr India*, 1980; **52:** 306–9.

[3] Jopling WH. Leprosy reactions (Reactional states). In: *Handbook of Leprosy*. London: William Heinemann Medical Books Ltd (2nd ed.), 1978; 66–74.

[4] Lever WF, Schaumburg-Lever G. Non infectious vesicular and bullous diseases. In: *Histopathology of the skin*. Philadelphia: J B Lippincott Company, 1983; 92–135.

[5] Katz SI, Marks JM. Dermatitis herpetiformis. In: *Dermatology in General Medicine*. Fitzpatrick TB, Eiren AZ, Wolff *et al.* (eds), New York: McGraw-Hill Book Company (2nd ed.), 1979; 326–30.

[6] White JW, Jr. Hypersensitivity and miscellaneous inflammatory disorders. In: *Dermatology*. Moschella SL, Hurley HJ (eds), Philadelphia: W B Saunders Company (2nd ed.), 1985; 464–98.

[7] Jorden RE. Bullous pemphigoid, cicatricial pemphigoid and chronic bullous dermatosis of childhood. In: *Dermatology in General Medicine*. Fitzpatrick TB, Eiren AZ, Wolff K *et al.* (eds), New York: McGraw-Hill Book Company (2nd ed.), 1979; 318–23.

[8] Abel EA, Bennett A. Bullous pemphigoid. Occurrence in psoriasis treated with psoralens plus long-wave ultraviolet radiation. *Arch Dermatol*, 1979; **115:** 988–9.

[9] Person JR, Rogers III RS. Bullous pemphigoid and psoriasis: does subclinical bullous pemphigoid exist? *Brit J Derm*, 1976; **95:** 535–40.

[10] Ridley DS. Reactions, In: *Skin Biopsy in Leprosy*. Basle: Documenta Geigy, 1977; 47–52.

[11] Laal S, Bhutani LK, Nath I. The natural emergence of antigen reactive T cells in lepromatous leprosy patients during erythema nodosum leprosy. *Infec Immunity*, accepted for publication.

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

Lepr Rev (1987) **58,** 69–78

SPECIAL ARTICLE

Leprosy in Cross River State, Nigeria

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Summary This spatial study of leprosy was stimulated by reports of medical workers in the State that serious and advanced cases of the disease are appearing, and that possibly there are pockets of infection which need to be identified and taken into account by the State's Leprosy Control Programme.

A preliminary examination of the spatial pattern of leprosy in the State is presented here, and shows higher prevalence rates for the disease in the areas of sparsest population. The work is continuing, and will attempt to explain these distribution features.

An account is given of some prevailing local attitudes to leprosy and their consequences for the control of the disease. The structure of the control service (State and Federal) is outlined, and constraints limiting its effectiveness are discussed.

Introduction

Cross River State, one of the 19 states of the Federal Republic of Nigeria, is located in the south-eastern corner of the country, adjacent to the Republic of the Cameroons. It encompasses about 29,000 km^2 between latitudes 4°N and 7°N. In the last official census of the country in 1963 the recorded population was 3·5 M, and official projections estimate a current population (1986) exceeding 6 M.[1]

The state lies wholly within the tropical zone but the northern area, the Obudu Plateau, over 1200 m high, is temperate. There are two seasons: the rainy season from May to October and the dry season from November to April, but along the coast no month is completely dry. Summer rainfall totals 3500 mm in the south-east and decreases northwards, but there are no water shortage problems. During the dry season, the relatively cool and very dry dust-laden Harmattan wind blows from the north, its effect decreasing towards the coast.

The economic mainstay of the State has always been its agriculture except on the coast where fishing is important, and the population of the state is predominantly rural. The staple food crops are roots (yam and cassava), supplemented by maize and plantains. Cash crops, especially palm oil, rubber and cocoa are produced by small farmers in the south, and also by large scale plantations mainly in Odukpani and Akamkpa. Since most of the state lies within the tsetse fly belt, meat is

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expensive. Fish is available in the south and is preferred but is rare in the north. Protein and iron deficiency are common nutritional problems among all sections of the population. Malnutrition, especially seasonally, is very serious in many village communities.

Petroleum is drilled offshore near Eket but has done little to transform the economy of Cross River State. Revenues go direct to the Federal Government and the industry employs only a few personnel who form a privileged enclave in Eket, a town with poor transport links with the rest of State, and without reliable mains water or electricity. One major impact of oil has been the disruption of the traditional fishing industry of the coastal area, sending fishermen further afield to less disturbed and less polluted waters, especially eastwards to the Cameroons.

Calabar is the State capital and the main industrial and employment centre in the State. There is a limited flow of people from the rest of the state for employment and education, but it has none of the usual "shanty town" developments of other African cities, and its growth is relatively controlled. However, severe overcrowding does exist in the older parts of the city due to natural rates of population increase among the indigenous Efik people.

The State is divided into 17 Local Government Areas for administration from the State capital each with its own Headquarters (map 1). These LGA headquarters in the densely populated south are dynamic towns with industries and factories of their own. Those in the sparsely populated north of the state are hardly more than villages with only the basic administrative functions which include the Leprosy Control Units. The southern part of the State has some of the highest rural population densities in West Africa and this pressure on agricultural resources has led to regular outmigration especially of young males. Their destinations are less populated areas of their own State, notably Akamkpa and also the Cameroons and formerly Fernando Po offshore, all for the purpose of agricultural labouring. The migration is far from permanent, being seasonal or at most of only a few years' duration. Such movements are significant in leprosy control, especially in view of the movement across the international border with the Cameroons, recently re-opened (February 1986). These agricultural labourers as well as the increasingly mobile offshore fishermen are represented among the leprosy cases studied.

The leprosy problem

There are 8000 registered cases of leprosy in Cross River State and it is by no means one of the worst states of Nigeria. In 1975 it was ranked only 8th out of the 19 states of the Federation for leprosy prevalence rates,[2] and one state had a rate 10 times higher. The average prevalence rate for the state is approximately 1·3 registered cases per thousand people. This relatively low figure requires qualification on two grounds. It has been estimated that actual cases in CRS are double the number registered (whereas in some northern states in Nigeria it is believed that actual cases are half of those registered).[3] The explanation is probably related to the heavy stigmatization of leprosy in CRS (see below). The second qualification is that the 1·3 per thousand average prevalence masks great variations within the State. Prevalence rates calculated (Table 1) and mapped for each LGA (Figure 1) help to demonstrate this, but there are also known to be pockets of high prevalence within LGA's but these await further identification and study. Meanwhile, the map and table show rates by LGA varying from only 0·12 in Eket in the coastal area to 10·90 in Obudu. This reflects the popular perception of leprosy among people in the south of the State that 'it is much worse in the north'.

It is easy to recognize the association in the State of areas of highest leprosy prevalence with areas of lowest population density, and vice versa (Figures 1 and 2). A similar association has been noted elsewhere in Africa as well as in Nigeria.[4] The explanations for such an association are not obvious. Population density may be a direct or indirect variable in the situation. Indirectly it may indicate the function of better infrastructure, modernization, better housing, higher standard of living etc. which are to be expected in areas of denser settlement and which have also been associated

Table 1. Cross River State: leprosy prevalence per 1000 population by local government area, 1984.

Rank	LEA	Prevalence
1	Obudu	10·90
2	Ogoja	10·11
3	Ikom	4·89
4	Etinan	1·29
5	Akamkpa	1·29
6	Obubra	1·04
7	Calabar Municipality	0·83
8	Ukanafun	0·43
9	Odukpani	0·43
10	Itu	0·42
11	Abak	0·34
12	Ikot Ekpene	0·33
13	Ikono	0·28
14	Ikot Abasi	0·27
15	Uyo	0·26
16	Oron	0·21
17	Eket	0·12

with improvements in the leprosy situation. So population density here may be a surrogate for economic development.

Etinan, ranked highest in population density Table 3, may be expected therefore to have the lowest prevalence rate and may seem an anomaly in having a prevalence of 1·29 per 1000. But the map (Figure 3) shows that it has the only leprosy hospital in the south of the State and so it attracts patients from all the neighbouring LGA's as well as from Rivers State, which is particularly poorly served with leprosy services. So this inflates both prevalence and also incidence rates for Etinan LGA. Similarly, the clinic in Calabar attracts patients from neighbouring LGA's due to its accessibility and also for the anonymity it offers and so its prevalence rate is inflated.

The number of new cases registering in the whole State in 1984 was in excess of 300. This gives an overall incidence rate of 0·05 new cases per 1000 population. The rate varies between LGA's and approximately matches the rank order of prevalence rates. However, there is a higher than expected incidence rate in Ikot Ekpene, which requires further investigation, especially as new cases were reporting not only to the local unit but also to the Etinan leprosy hospital right into 1986.

Of the total new cases, one quarter were diagnosed as lepromatous. Children under 15 years represented two fifths of all new cases. The numbers of male and female new cases were similar. (But a noticeable feature is the dominance of total female patients registered in the State. They make up 60% of all registered cases under 40 years, but in the 40 + age group male and female cases are equal. Conversely, male in-patients outnumber female in all age groups.)

Attitudes to leprosy

The inbred fear of leprosy combined with the traditional belief in the supernatural cause of the

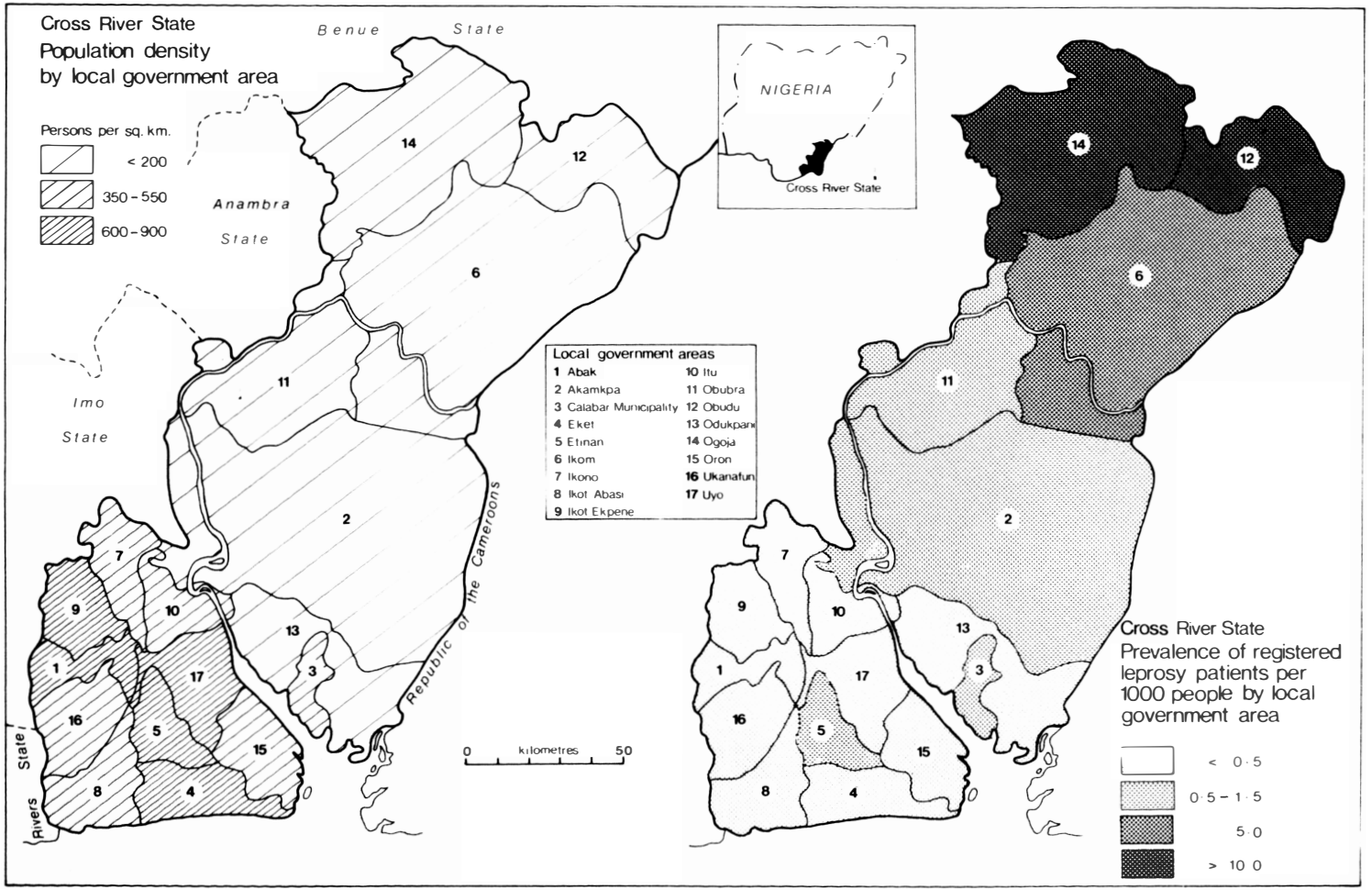


Figure 1. Note that neither population density nor leprosy prevalence rates for CRS are mapped in sequential uniform classes due to the nature of the data.

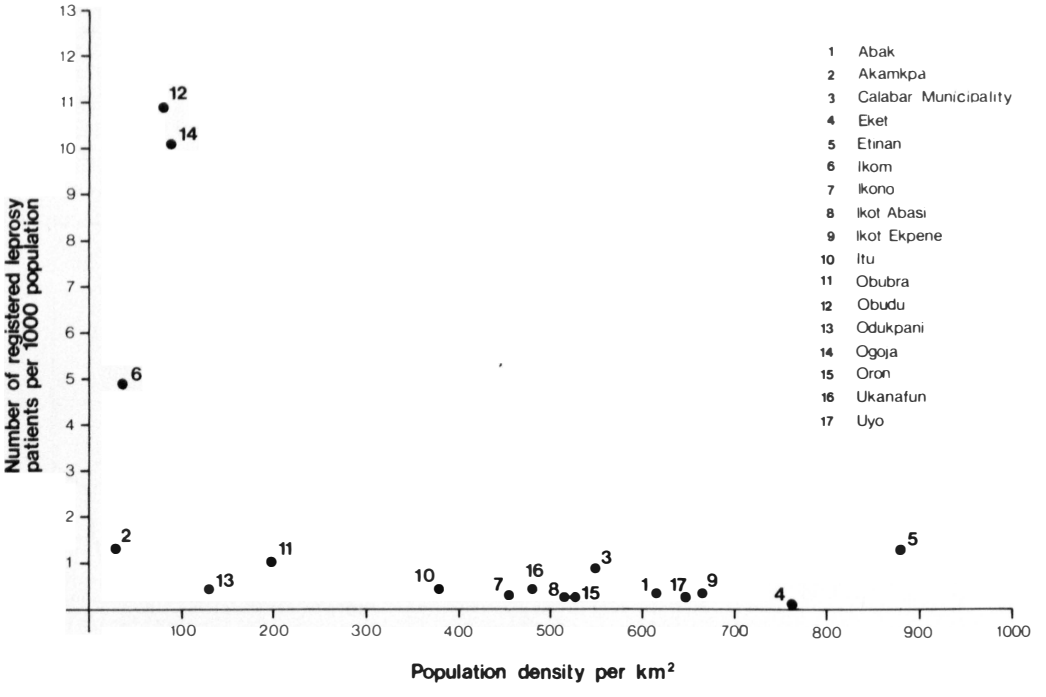


Figure 2. Prevalence of leprosy and population density by Local Government Area, 1984.

disease mean that it is severely stigmatized in CRS and this adversely affects the control programme in a number of ways. Frequently there is late reporting of new cases, the patient hiding the condition for as long as possible. By the time the case is reported many contacts may have been infected and the disease may have advanced in the patient to cause irreversable deformity. During this time the patient is likely to have been treated by native medicine which may have caused further injury, or the patient may have received treatment for skin conditions other than leprosy due to poor diagnosis. This reflects the low level of education with reference to leprosy both of paramedics and doctors, and is a cause for concern in some quarters in the State and has led to a compulsory leprosy module being recently introduced at the University of Calabar Medical School.

A second result of the prevailing attitude to leprosy is in poor patient compliance with therapy, once diagnosed. Two factors are involved here, in addition to the usual one of the long duration of treatment. For outpatients to make monthly clinic trips for drugs may be expensive in money and in time, especially during the season of intense agricultural activity. It may also lead to awkward questions being asked of a patient who wishes to hide the condition. The other factor relates to the patient's own perception of the cause of the disease which, in nearly every case interviewed, revealed a suspicion of witchcraft by a named jealous neighbour or relative. Enormous doubts can arise about the efficacy of the pills especially when you see or feel little change in your condition and when you believe someone intends you evil and has already called on the power of witchcraft to give you leprosy and sustain the condition by preventing the ulcer from healing, etc. Even when patients are shown evidence of bacilli numbers decreasing they are frequently sceptical. Doctors, nurses and leprosy control officers can become very disheartened with their patients' lack of cooperation.

The third result of the stigma attached to the disease is the effect it has on the staffing of the leprosy control service in the State, which is generally undermanned and under-resourced. Even the

monthly salary supplement of 10 Naira (approximately £5) which is paid to all workers in leprosy (and TB) as 'danger money', does little to alleviate the problem. There are 136 medical doctors in government service in the State, mostly indigenous Nigerians, but the 4 doctors involved in leprosy work are all ex-patriates. (The medical course module in leprosy at the University of Calabar may remedy this situation for the future however.) Nevertheless, there are some highly dedicated workers who are committed to their patients even though they receive little encouragement thanks to the poor career structure, which at present offers them few incentives to remain in leprosy control work. But another staffing problem arising from stigma is the opportunity it provides for blackmail.

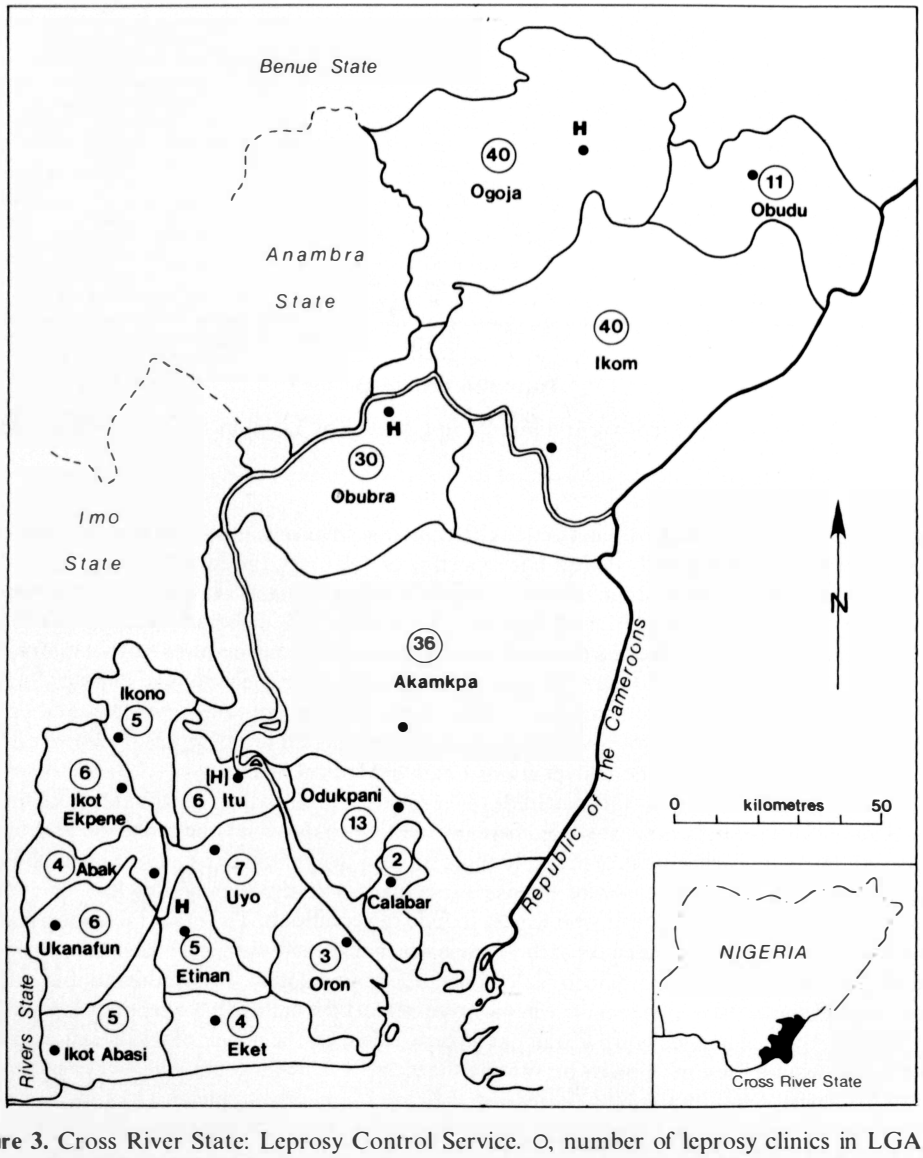


Figure 3. Cross River State: Leprosy Control Service. ○, number of leprosy clinics in LGA; H, Leprosy hospital; ●, LGA Headquarters: location of leprosy control unit; (H), former leper colony at Itu (1928–68).

Patients wishing to receive treatment but to conceal their disease may be forced to pay sums of money by unscrupulous control officers. As well as placing severe hardship on the patient, it may also prevent referral to a hospital of a case in need of special attention.

Only when the stigma against leprosy are removed by education of the public, the patients and the medical profession, will these three major constraints on the efficient operation of the leprosy control service in the State be eradicated.

CRS Leprosy Control Service

Leprosy was not recognized as a serious medical problem in CRS until 1926 when a Scottish missionary doctor at the General Hospital in Itu began to treat a few patients with hydnocarpus oil he obtained from India, the first doctor in Nigeria to do so. The famous missionary, Mary Slessor, had also cared for leprosy cases in this area earlier in the century. But after 1926 and the news of a treatment, cases appeared as if from nowhere and in the first 6 months 400 outpatients were under treatment with weekly injections. This led to the establishment in 1928 of the first African colony of leprosy patients. This was on a sandbank in the Cross River at Itu, a long established river port in the tropical forest, trading with Europe and also a centre of missionary activity. From the beginning there was a government grant supporting it, although it remained under the control of the Church of Scotland Mission, and during its existence received support from BELRA (now LEPRA), the Mission to Lepers (now the International Leprosy Mission) and Toc H. In 1928 suitable land was allocated by local chiefs and construction work began by the 800 patients. BELRA supplied the hydnocarpus oil from India and also supplied literature on leprosy and provided other help. By 1931 there were 1100 in-patients and several hundred outpatients.[5]

Hydnocarpus oil was the principal method of treatment until 1951 when every patient was put onto the sulphone treatment in addition. Some 28,000 were to receive treatment at Itu, an average 4300 patients each year before it was destroyed by bombs in Nigeria's civil war. Some former Itu patients and staff are to be found as staff in the existing 3 leprosy hospitals in the State and even further afield.

The Itu Leprosy Colony became a model for colonies elsewhere in Nigeria and Africa and also revealed the seriousness of the leprosy problem in the area. Three more hospitals were to be established by European missions within the State (Figure 3, Table 2), and from the late 1930's and into the late 1950's a large number of segregated villages were established by local communities. All

Table 2

Hospital location	Foundation	Date	Doctors	Patient beds	Facilities
Etinan	Qua Iboe Mission	1932	2	173	Lab., Theatre, Shoemaker, Limbmaker
Mbembe, Obubra	Church of Scotland Mission	1959	weekly visit	30	Lab., Shoemaker's workshop unstaffed since 1984
Ogoja	Roman Catholic Mission	1943	1 since 1985	63	Lab., Physio., Shoemaker

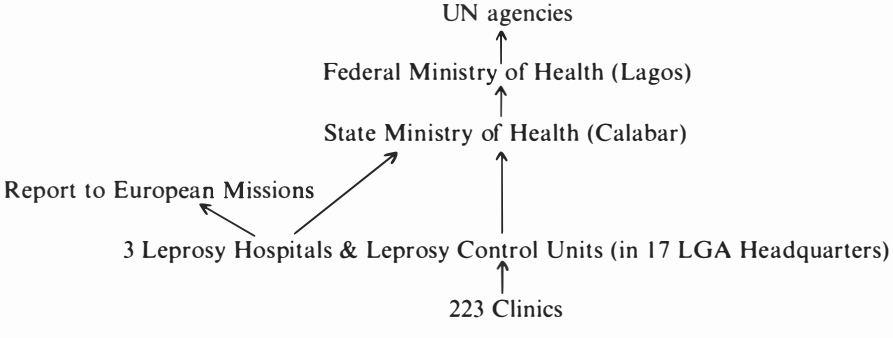
Table 3. Cross River State: population density by local government area, 1984.

Rank	LGA	Density per km^2
1.	Etinan	880
2	Eket	763
3	Ikot Ekpene	664
4	Uyo	648
5	Abak	614
6	Calabar Municipality	548
7	Oron	526
8	Ikot Abasi	517
9	Ukanafun	479
10	Ikono	451
11	Itu	379
12	Obubra	196
13	Odukpani	129
14	Ogoja	87
15	Obudu	80
16	Ikom	35
17	Akamkpa	28

of these are now officially abandoned but some became the site of a leprosy clinic and one became the Leprosy Hospital at Mbembe.

The current leprosy control service is administered by the State Ministry of Health from Calabar through the Leprosy Control Units located in the 17 LGA Headquarters (Figure 2) and in the 3 specialist leprosy hospitals. These all submit monthly and annual returns for the State and Federal Health Ministries and for UNICEF and the WHO. They also administer the leprosy clinics which are scattered throughout each LGA and which are mostly convened on a monthly basis for examination of new patients, distribution of drugs, discharges and referral to hospitals. Regular village, school and plantation surveys were also administered from these 17 Leprosy Control Units until the severe economic constraints which have damaged the whole control service especially since 1980.

Reporting structure of Leprosy Control Services



Outside the reporting structure there is also a Leprosy Advisory and Coordinating Committee, both at National level (inaugurated 1982) and 3 at regional level (the Eastern Zonal Committee dates back to 1980 and incorporates Cross River State). These Committees meet at regular intervals to plan strategies for leprosy control within their zones, and they organise training workshops. Recurrent themes in their deliberations include the issues of an inadequate supply of trained personnel, poor funding of the service and the problem of defaulters.

In each LGA headquarters there is a Leprosy Control Unit ideally staffed by one Leprosy Control Assistant and one Leprosy Control Attendant, but at the end of 1984 there were only 12 assistants and 11 attendants and since that date there have been further cutbacks in government employment which have affected the Service. The structure also provides for a State Consultant Leprologist but the post has never been filled.

The constraints on operating an effective leprosy control service at present are not a lack of administrative structure because that exists, as has been shown. The problems are lack of sufficient trained personnel and of transport for their movement from headquarters to clinics, and also frequent drug shortages. Lack of motor vehicles and spare parts, and of river boats means that in many LGA's the leprosy control personnel remain in headquarters, unable to visit regularly the monthly clinics or follow up defaulting patients or carry out surveys, and the consequences are that even when drugs are available they are not distributed. All of these have serious implications for the future of leprosy in the State.

During the colonial period and the early years of independence walking, bicycles and canoes were the main means of transport. Then came two events which changed the face of CRS: the Civil (Biafran) War 1967–70 which was centred here and in neighbouring states, then the subsequent oil boom. The Civil War seriously disrupted the smooth operation of the Leprosy Control service in the region, as well as destroying the hospital at Itu and scattering its patients. The oil boom helped Nigeria in the 1970's to recover from the economically devastating effects of the war. Roads were built, cars and motor cycles were imported, and with cheap fuel the use of bicycles declined. Therefore, resourcing a mobile unit of the medical service, which leprosy units must be in this rural state, became much more expensive. It has now become nearly impossible in the 1980's with the drop in oil prices which is ruining Nigeria's heavily oil-dependent economy. Thus, the leprosy control service of CRS is one more casualty of the world oil recession.

Transport problems explain the drugs shortage, especially the shortage of Dapsone. Medical supplies are available from Lagos, but there is no centralized distribution system. Each state in the Federation has a high degree of autonomy and is responsible for payment and collection of its own medical supplies. With a shortage of reliable vehicles, trips to Lagos (800 km) for supplies are erratic. Supplies of expensive drugs for MDT present yet another problem, and clofazimine especially was being reported to be in short supply in 1984, and subsequently.

Conclusions and recommendations

Leprosy control has a low priority in the State medical service, for many reasons. As has been shown it is short of staff and transport and a regular drug supply. The present vertical administrative structure is unlikely in the near future to receive the appropriate resources, especially transport, to enable it to function adequately in its task of finding new cases, providing the most appropriate treatment (such as multiple drug therapy) on a regular, supervised basis, and following up defaulters.

A fresh approach is required and it is suggested that this will contain at least three essential ingredients. These are, firstly, a massive education and re-education programme which will contribute to the destigmatization of the disease among all strata of society. People must also be convinced that leprosy can be cured and that early reporting is essential. Paramedics, medical

doctors and native doctors (who have official recognition and registration in Nigeria) must become familiar with the diagnosis and treatment of the disease.

Secondly, a steady and reliable flow of all necessary drugs must be assured. A means must also be found of making the new multiple drug therapy more widely available and this will require the development of techniques to make it simple to administer.

The third component of a new approach must be the involvement of people at the village level. It may be that a new control strategy will depend upon educated people implementing it in their own communities through village meetings, surveys and with reference to existing medical services.

The leprosy problem in Cross River State is not insurmountable. The control of the disease and its eventual eradication only needs some fresh thinking and commitment.

Acknowledgments

I am grateful to LEPRA, to The Nuffield Foundation and to The Britain–Nigeria Association for financial support to enable me to conduct fieldwork in Nigeria. However, the work would not have been possible without the excellent and willing co-operation and encouragement of medical workers and leprosy patients in Nigeria. I thank them all for their help.

References

[1] Population Bulletin 1980–83. Statistics Division, Ministry of Economic Planning, Calabar, 1980.
[2] Damien Foundation. *Atlas of Leprosy*. Brussels, 1979.
[3] De Plantes MZ. Informal Report of WHO visit to Cross River State, February 1983.
[4] Hunter JM, Thomas MO. Hypothesis of leprosy, Tuberculosis and Urbanisation in Africa. *Soc Sci Med*, 1984; Vol. 19, No. 1, 22–57.
[5] Macdonald AB. Can Ghosts Arise: the Answer of Itu. Edinburgh, 1957.

Lepr Rev (1987) **58,** 79–84

SPECIAL ARTICLE

The insensitive foot. Northwick Park experience

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Summary The problems of the pathogenesis and management of plantar ulceration in diabetic subjects and patients with leprosy are compared. Use of the total contact cast for treatment of an ulcer and methods for prevention of recurrence by appropriate insoles in footwear are described.

Introduction

Neuropathic foot ulceration may occur due to diverse pathological conditions; leprosy, diabetes mellitus spinal dysraphism, trauma to peripheral nerves, lesions of the cauda equina or spinal cord. Despite the variety of pathogeneses, the essential cause of the ulceration is the same. The tissues of the foot are subjected to a level of physical insult above the threshold at which tissue destruction occurs, without producing sufficient discomfort to the subject to trigger a response which will prevent further damage.

These conditions are for the most part irreversible and in the case of diabetes may be progressive. It is almost always impossible to do anything about the threshold level of insult at which tissue damage occurs, or the threshold level of stimulus at which avoidance of further exposure to the physical insult becomes mandatory. It is however quite possible to reduce the level of physical insult to the foot below the threshold level for tissue damage by education of the patient, special casting techniques and modified footwear. Applying this principle, we have had great success in healing neuropathic ulceration and preventing its recurrence. Furthermore it is open to us to prevent ulceration in the first place by identifying those at risk and applying sufficient prophylactic measures to keep the level of insult sustained by the foot below the tissue damage threshold.

At Northwick Park, the brief of our research grant is to identify and quantify risk factors in diabetic foot ulceration. As in leprosy, these patients may develop progressive neurological destruction even when under treatment. The threshold of tissue damage in diabetes may be lowered due to vascular obstruction, and tissue resistance to infection may be reduced by compromised cell-mediated immunity. Apart from these features the ulceration in leprosy and diabetes has many of the same characteristics and the same principles apply.

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Risk factors

Risk factors in the formation of diabetic ulceration are traditionally classified after Oakley *et al.*,[9] according to the system they affect. It is preferable to think functionally and consider risk factors on an aetiological basis.

What are the factors which place our patients at risk of ulceration? (a) Raised sensory threshold of avoidance reflex. (b) Reduced threshold of tissue resistance to damage. (c) Increased physical insult to the foot.

RAISED SENSORY THRESHOLD OF AVOIDANCE 'REFLEX'

Sensory neuropathy reduces the subjects awareness of impending tissue damage. This does not only apply to mechanical modalities like pressure and shear stress, but also to thermal injury. We have seen painless ulceration resulting from chilblains and frostbite in Indians with diabetic neuropathy walking in sandals in the snows of Harrow.

REDUCED THRESHOLD OF TISSUE RESISTANCE TO DAMAGE

It is an oversimplification to talk of a single threshold of tissue damage but the concept is useful. The amount of trauma the tissues will withstand before ulceration will depend not only on the direction of the force and the area over which it is applied, but also, as Brand demonstrated,[6] on the duration, frequency, and recent history of other trauma.

Major vessel obstruction is a common contributory feature reducing the tissue damage threshold in diabetes but, in leprosy it will only be as common as in the normal population. Where it does occur it may seriously affect the prognosis.

Autonomic neuropathy is thought to produce A-V shunting of blood in the foot[13] possibly at the expense of cellular nutrition. The associated loss of sweating produces a dry cracked foot offering plentiful portals for the ingress of opportunistic infection. The mildly bactericidal effect of sweat is lost.

Small vessel disease; opinion is divided as to whether microangiopathy occurs in the foot in diabetics in the same way as it does in the eyes and kidneys. All the features attributed to it can be explained by autonomic vascular shunting. There is no suggestion of microangiopathy in leprosy.

INCREASED PHYSICAL INSULT TO THE FOOT

Thermal injury has already been mentioned and is only more likely because of the sensory loss.

Mechanical injury can be resolved into two directions; perpendicular load which is at right angles to the skin surface, and shear load which is parallel to the skin surface.

It is applied force per unit area that is the important factor in both cases, 'the perpendicular and shear pressures'. In these units shear has much more damaging effect on the tissues, but the magnitude of shear is less.

Motor neuropathy produces a specific cavus deformity of the foot with initially interphalangeal flexion and later metatarso-phalangeal hyperextension and dislocation. The protective load distributing fibro-fatty pad under the metatarsal heads is dislocated distally so it can no longer help to dissipate load as low pressure over a wider area.

This deformity, the pedal equivalent of the intrinsic minus hand, results in the loss of the load sharing function of the toes.

In the normal individual, as the heel lifts in walking, the toes take over the load bearing function of the heel so the area of contact remains large. In the neuropathic deformity, when the heel lifts, the metatarsal heads only, divested of their protective fibro-fatty padding, transmit the body

weight at much higher pressure. In severe cavus deformity there may be so much mid-foot flexion that the patient cannot get his heels to the ground at all.

The synovial sheaths around the flexor tendons to the toes normally provide an interface for the dissipation of shear stresses under the foot. The immobility of the toes means that the flexor tendons do not move, and all shear stresses are experienced by the thin skin now lying under the metatarsal heads.

The increased loading of the metatarsal heads causes the rays to spread producing a wide forefoot. If this wide forefoot is pushed into a normal shoe ulceration of the sides of 1st and 5th metatarsals may result. Pressure between the dorsally subluxed toes and the upper of the shoe may produce ulceration of the dorsum of the toes.

It should be noted that pressure applied to a convex surface tends to act cumulatively so that the pressure beneath the surface is greater than the applied pressure. This amplification is greater the tighter the curvature of the surface.[5] Hence the sides of metatarsal heads and dorsa of the toes are particularly vulnerable.

Common orthopaedic foot deformities may afflict neuropathic patients like anyone. A bunion which may be subjected to pressure from the upper and hallux rigidus will result in tremendous pressure under the interphalangeal joint of the great toe.

Fixed flexion deformity at knee, hip or ankle may contribute to increased forefoot loading as the patient may not be able to get the heel on the ground except in very awkward postures. Bauman *et al.*[1] demonstrated the increased forefoot load in a case of 'dropped foot'.

Risk evaluation

How have we attempted to quantitatively assess the degree to which patients are affected by these risk factors?

HISTORY

An attempt has been made to estimate the amount of standing and walking each patient does and what loads are carried as magnitude duration and frequency of load are important.

CLINICAL EXAMINATION

Simple examination is valuable in assessing some of the problem features: overweight, hyperkeratosis in response to increased loading under the metatarsal heads, fissuring of the hyperkeratotic rim around the heel, pressure under the tips of clawed toes which if the nails are too long will be transmitted to the nail bed causing sub-ungual abscesses. Pressure on the sides of the metatarsal heads and the dorsa of the toes is best detected by examining the feet with the shoes. The distal medial corner of the great toe nail is a common site of bother. Dermatophyte infections may be an important portal of infection.

RAISED THRESHOLD OF AVOIDANCE 'REFLEX'—SENSORY TESTING

The biothesiometer is an electric vibrator with a controllable and calibrated amplitude of vibration. Excellent control data for age variation has been published.[4] Most of our cases of neuropathic ulceration have a vibration threshold outside two standard deviations with none less than one standard deviation from the mean. A more accurate indication is expected from this method by the completion of this study with the inclusion of greater numbers and the calculation of 'variance' for each result. Unfortunately, age related control data is available for this machine only for the medial malleolus and great toe.

The Semmes Weinstein Hairs[10] are a modification of the Von Frey horsehairs using nylon fibres mounted in acrylic handles. If the fibre tip is pressed at right angles to the skin so that the fibre is maximally bent yet only touching the skin at the tip, the force applied to the skin will be constant, independent of minor movements of the hand and is repeatable. The force is related to the diameter of the fibre. It is possible to measure the sensory threshold by determining the finest fibre that can be perceived at a point. By repeating this determination at a matrix of points (in our case every square centimetre) it is possible to build up detailed sensory threshold maps of the foot. To do this with all 20 fibres in the set would be very tedious. Workers at the National Hansen's disease centre, in Carville,[3] have shown that 1 fibre represents normal threshold of sensation and 1 represents the threshold of protective sensation. They advocated the use of a 3rd fibre, the thickest in the set that would still bend, to represent severe sensory loss. Thus four levels of sensory threshold can be determined; normal, loss of protective sensation, severe sensory loss (only feels the thickest fibre) and very severe sensory loss (cannot even feel the thickest fibre).

This mapping has been completed in 23 cases of ulceration and in 13 control cases with varying degrees of neuropathy. The results are still undergoing analysis at the time of writing. Our results with diabetics are consistent with the Carville findings in leprosy. With the exception of a grossly vascular cause, ulceration does not occur in areas having protective sensation.

REDUCED TISSUE RESISTANCE TO DAMAGE

Autonomic function in the foot can be assessed by skin galvanometry but our information is that this test is difficult to control and unreliable. Instead we are looking at autonomic function in another area by testing the autonomic cardiac reflexes.

Sepsis plays an important part in ulceration. Swabs from the throat, perianal region and toe webs of 44 patients with neuropathy have shown much lower than expected carriage rate of staphylococci and streptococci. We would suggest that lack of sweating of the neuropathic foot may protect against such carriage. We would expect then the moist conditions of a dermatophyte web infection to favour superinfection by such organisms and work is under way to look into this.

Inflammation secondary to mechanical injury or infection lowers the tissue resistance to further damage. Such inflammation is accompanied by hyperaemia detectable accurately with thermography.

An AGA 780 Infrared Thermographic System coupled to a Pericolar Image Analysis computer was used to record infrared thermograms of the skin surface. Measurements were carried out in standardized environmental conditions, in a temperature controlled room maintained at $27° \pm 0{\cdot}5°$. Ulceration in the neuropathic foot was frequently associated with increased skin temperature around the ulcer necrotic area while cold ulcers were generally found in feet with an atherosclerotic component of the disease.

INCREASED PHYSICAL INSULT TO THE FOOT

The pedobarograph is a computerized quantitative method working on an optical principle, which we are using to measure the interface pressure between the bare foot and the floor during walking,[2] at intervals of 40 ms. We hope to be able to arrive at a figure above which there is a significant risk of ulceration.

A method has been described for measuring shear during gait[11] but we have no experience of this. The Carville microsphere sock is probably the only way of objectively indicating excessive dorsal and lateral pressure. At present we rely on clinical examination.

Treatment

In the presence of adequate blood supply and with adequate control of serious infection, neuropathic ulcers will heal if the causative insult is removed or diminished.

In the case of lateral and dorsal ulcers, this usually means providing footwear to accommodate the foot without applying excessive shear and perpendicular pressure. It may mean removing a foreign body from the shoe. In the case of high plantar pressure due to neuropathic deformity of the foot, the load on the metatarsal area for instance can be distributed as low pressure over the entire plantar aspect of the foot by the application of a plaster cast which is the exact shape of the sole of the foot, a total contact cast.[7,8] We apply this as a below knee cast with padding over the pretibial border, the malleoli and the toes only. The toes are enclosed to prevent access of foreign bodies to the cast and to prevent the toes striking furniture etc. A rockered sole is fitted well back under the pretibial border to allow the cast to tilt forward with the minimum of effort, without the toes striking the ground and increasing the forefoot load.

We believe that the cast from the ankle up to the knee functions not to share in load bearing as has been suggested by some, but to minimize shear by ensuring that the sole of the foot is always approximately at right angles to ground reaction vector, and resisting fore/aft motion in the cast. This type of cast has been very effective in healing plantar ulcers, usually within 6 weeks.

Prevention of recurrence

Recurrence can be prevented by achieving the same conditions in the shoes as in the cast. Following Tovey's[12] work we made an insole accurately shaped to the sole of the foot. The supporting cradle is made of rigid compressed *high density* plastazote. Sinks are cut in the cradle under areas of high risk and these holes are filled with the closed cell foam neoprene, which will not bottom out. The whole insole is then covered with neoprene for high load conditions, or an open cell foam, poron or PPT for lighter loading. This can only be accommodated in an extradepth shoe. Some are available commercially, but many severe cases require bespoke manufacture to accommodate deformity. The shoe is usually given a rockered sole with a thirty degree toe clearance and the fulcrum of the rocker set half way between the pretibial border and the 1st metatarsal head. This is necessary to prevent toe/ground contact of the trailing foot on stepping forward. Except in those important cases with fixed flexion deformities, the shoe is given a zero pitch, as if there was no heel. This allows more toe clearance with much less height.

Patients are advised to moisten the feet daily with Boots E45 cream to prevent cracking, and to inspect the feet daily for areas of redness and increased warmth.

Prophylaxis

Besides the obvious advise to reduce risk of injury to the foot: weight reduction, walking and standing less, walking slower with shorter steps, keeping the nails in good trim and the skin moist, daily foot inspection, checking the shoes for nails and foreign bodies attention is paid to footwear. All patients should have shoes which will accommodate the foot without applying pressure. In the presence of deformity this may require prescription footwear; stock extradepth or bespoke depending on severity. Patients whom on testing are found to have significant neuropathy without high plantar pressures are given extradepth shoes with plain poron or neoprene 8-mm insoles depending on loading. Those with high plantar pressure are given these shoes with the total contact insoles described for prevention of recurrence. We have not yet found it necessary to give rockered soles to a patient at risk who has not had ulceration. This is probably because we are still arriving somewhat late on the scene and all severely at risk patients will already have had at least one ulcer.

The future

It is hoped to institute at risk screening of all our diabetics in the clinics as follows.

Those with no palpable ankle pulses will have a doppler examination of their ankle vessels. Those with poor flow will be given shoes and plain poron/neoprene insoles.

All will be screened with a biothesiometer. Those in the at risk group, at present > 2 standard deviations from the mean will have a pedobarograph measurement. Those without high pressure will have shoes as above. Those with high pressure will have sensory mapping of the pressure areas. Those with protective sensation in the at risk area would have total contact insoles without rockers, those without protective sensation would have both, plus very regular supervision. The place of EMG and autonomic testing has yet to be determined. Dermatophyte infections will be treated vigorously.

References

1 Bauman JH, Girling JP, Brand PW. Plantar Pressures and Trophic Ulceration, an Evaluation of Footwear. *J Bone Jt Surg (Br)*, 1963; 45-B: 652–73.

2 Betts RP, Franks CI, Duckworth T. Analysis of Pressure and Loads under the Foot. *Clin Phys Physiol Meas.* 1980; **1(2):** 101–24.

3 Birke JA, Chief Physical Therapy Dept, National Hansens' Disease Center, Carville, LA. Personal Communication, May 1985.

4 Bloom S, Till S, Sönksen P, Smith S. Use of a biothesiometer to measure vibration thresholds and their variation in 519 non-diabetic subjects. *Br Med J*, 1984; **288:** 1793–5.

5 Brand PW. The diabetic foot. In: *Diabetes Mellitus, Theory and Practice*, 3rd edn. Ellenberg M, Rifkin H. (eds), New Hyde Park: Medical Examination Publishing Co. Inc., 1983; 829–49.

6 Brand PW. Pathomechanics of Pressure Ulceration. In: *Symposium on the Neurological Aspects of Plastic Surgery.* Fredricks, Brock. (eds), St Louis: C V Mosby Co., 1978; 185–9.

7 Coleman WC, Brand PW, Birke JA. The Total Contact Cast. *Journal of the American Podiatry Association*, 1984; **74(11):** 548–52.

8 Helm PA, Walker SC, Pullium G. Total Contact Casting in Diabetic Patients with Neuropathic Foot Ulcerations. *Arch Phys Med Rehab*, 1984; **65:** 691–3.

9 Oakely W, Caterall RCF, Martin MM. Aetiology and management of lesions of the feet in diabetes. *Br Med J*, 1956; **2:** 953–7.

10 Semmes J, Weinstein S, Ghent L, Hans-Lukas T. Somatosensory changes after Penetrating Brain Injury in Man. Cambridge: Harvard University Press, 1960.

11 Tappin JW, Pollard J, Beckett EA. Method of measuring 'shearing' forces on the sole of the foot. *Clin Phys Physiol Meas*, 1980; **1(1):** 83–5.

12 Tovey FI. The manufacture of diabetic footwear. *Diabetic Medicine*, 1984; **1(1):** 69–71.

13 Ward JD. The Diabetic Leg. *Diabetologia*, 1982; **22:** 141–7.

Lepr Rev (1987) **58,** 85–89

Letters to the Editor

CALENDAR (BLISTER) PACKS FOR MULTIPLE DRUG THERAPY IN LEPROSY: AN INEXPENSIVE, LOCALLY-PRODUCED VERSION

Sir,

I was interested to see the report in *Lepr Rev*, (**57,** 2) June 1986, concerning the bubble package for MDT designed by Ciba-Geigy. May I draw your attention to a calendar pack developed by The Leprosy Mission for use in Southern Africa. Figure 1 (overleaf) shows the packs we have developed for use in Swaziland.

These packs were developed for two reasons:

1 When MDT, according to WHO recommendations was adopted in 1982, Lamprene was only available in capsules of 100 mg. This meant that patients receiving triple drug therapy for multibacilliary leprosy would have to remember to take Lamprene on alternate days to reach the daily recommended dosage of 50 mg. There was concern that despite careful instruction from clinic personnel, some patients would take the 100 mg capsules on a *daily* basis, as with the Dapsone tablets, leaving them with no Lamprene for the remaining 2 weeks of the month.

2 It appeared that despite full verbal and written instructions to clinic personnel, some peripheral workers had difficulty in counting out pulse doses correctly. There was also a tendency for some personnel to issue drugs in bottles as supplied by manufacturers, with the result that some patients received daily treatment sufficient for a period of 3 months, missing the intervening pulse doses.

Our calendar packs eliminated drug counting on the part of both patients and peripheral workers.

These packages are extremely cheap to make and no special equipment is required once they have been printed. Cardboard of any suitable thickness may be used. Different colours are employed to distinguish treatment for paucibacilliary and multibacilliary patients. Different colour tones could be employed to distinguish lower doses for children.

Polythene tubing manufactured for water-ice 'lollies' is used for the 'bubbles'. The exact width (normally 40 mm) and grade of tubing may vary without affecting packaging. The tubing is cut into suitable lengths (about 50 mm) with scissors or heat-sealing guillotine if available. The drugs are put into the open-ended sachets which are then doubled over and stapled to the card.

A full set of dispensing instructions are printed on the back of the card. This saves personnel the bother of consulting manuals for instructions. Experience suggests that such separate instructions are seldom read and often lost. Peripheral clinic staff frequently rotate. New personnel may be unfamiliar with leprosy treatment and instructions must therefore be readily available. Most of our patients cannot read and would therefore not benefit from written instructions.

Reply-paid postcards giving details of the patient and his place of treatment are stapled to the calendar pack. When the patient reports to the clinic, the pulse dose sachet is torn from the top of the card and the patient swallows the contents in the presence of the peripheral worker, who enters the date on the postcard and detaches it from the calendar pack.

These postcards are returned to the programme administrator. Where a postcard is not received for a patient he is presumed to have defaulted and a field worker is despatched to contact both clinic and patient.

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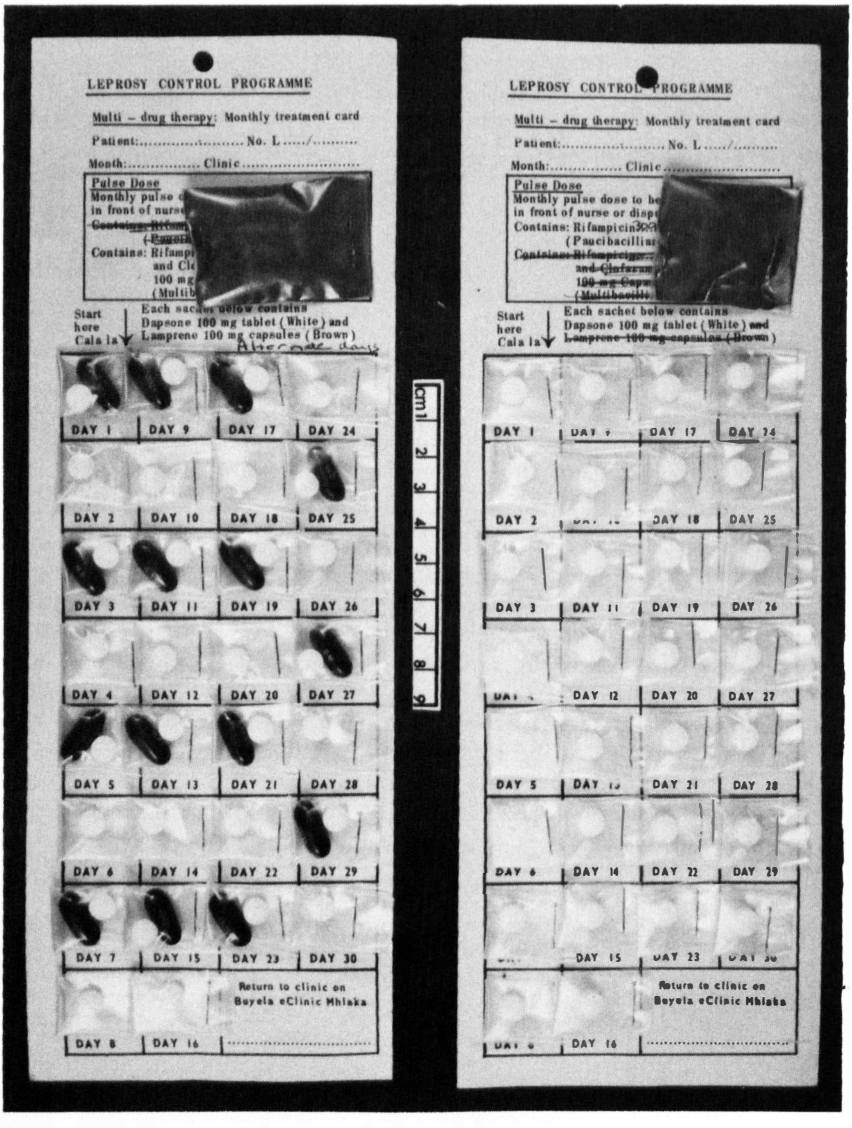

Figure 1. Calendar (blister) packs for multiple drug therapy in leprosy. *On the left* is the pack for the treatment of multibacillary leprosy, using daily (unsupervised) dapsone and clofazimine in a dose of 100 mg 3 times weekly, the days of the week going vertically downwards. The monthly (supervised) dose of clofazimine and rifampicin is in the plastic bag, upper right, alongside 'pulse dose'. (The discolouration is artificial due to damage in posting to the UK.) *On the right* is the pack, of a distinctively different colour, for the treatment of paucibacillary leprosy, using daily (unsupervised) dapsone and monthly (supervised) rifampicin.

The calendar pack is taken home by the patient who tears a sachet from it each day and (hopefully) swallows the contents.

Many of our rural patients share single rooms with relatives at night. To provide clear space during the day, belongings are packed into steel trunks which are then stacked in a corner. When

drugs were issued in bottles, it was found that patients stored these bottles in their trunks, which had a habit of being at the bottom of the stack, with consequent detrimental effects on compliance. Holes are punched in the top of the calendar packs and patients are asked to hang the packs on hooks on the wall out of the reach of children. Local rural dwellings are poorly ventilated so there is little risk of the drugs being exposed to excessive light. This simple change has had a positive effect on compliance. The patient has easy access to his drugs and it is also a simple matter for field workers to examine the pack during home visits.

Drug management is greatly facilitated by these packs, which are issued to clinics for specific patients for a few months at a time. Possibilities for incorrect dispensing and abuse are curtailed.

The packs are easily adapted to different conditions and regimes. The treatment of reactions, where for example increased doses of clofazimine are needed, is easily provided for by these packs. These packs are readily adapted for the dispensing of prednisolone, which is often available only in 5 mg tablets—a problem for patients who cannot count and who may be on daily prednisolone doses of 50 mg.

Hard data as to the efficacy of these packs versus other methods of dispensing MDT is lacking, but compliance has improved by about 15% and verified clinic attendance in excess of 80% has been maintained using these packs. The assessment of daily compliance at home is more difficult and subjective, but to date we have no evidence of patients tearing sachets from the packs to falsify compliance.

Directors of large programmes may be put off the introduction of such packs because of the amount of labour entailed. However, this is a task with which many in-patients are able to help. Teams of school children may also be organized with little difficulty to package drugs.

During the SADCC conference hosted by LEPRA in Lilongwe, Malawi, in May 1986, a few of the delegates felt that these packages might be of value in their programmes. I am therefore publicising the idea through your journal in the hope that they will be of benefit to programmes in other continents.

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'ERADICATION' OF LEPROSY FROM MALTA

Sir,

I am consultant dermatologist to the Medical and Health Department in Valletta. My patients come from all strata of society in Malta and Gozo. I was not fortunate enough to attend the Symposium on Multidrug Therapy in Leprosy which was held in Wurzburg between 24–26 April 1986. Nevertheless, I was surprised to read in the official programme that delegates at the meeting spoke in terms of successful eradication of leprosy from Malta. I would not wish your readers to take this statement too literally because at the Department of Dermatology in the past 3 years we have diagnosed 4 patients with multibacillary leprosy who had previously been seen at other sections where the true nature of their illness had gone unrecognized. Perhaps I need not mention also that some of the 200-odd patients currently on our leprosy register, though bacteriologically negative, are still struggling with the long term sequelae of the disease which unfortunately makes them prone to ostracism from the rest of the community.

We in Malta owe a debt of gratitude to Professor Enno Freerksen, his German colleagues, and their local collaborators Dr E Bonnici and Dr G Depasquale for their sterling and innovative work. In my opinion, however, their approach lacked two important aspects, namely an active case-

finding programme, and intensive education of local doctors and paramedics to facilitate early diagnosis. Waiting, as they normally do, for patients to be referred to them they can never be in a position to claim that leprosy has been eradicated in Malta.

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REPLY TO 'ERADICATION' OF LEPROSY FROM MALTA

Sir,

1 Eradication is aimed at eliminating a self-reproducing epidemic, in this case leprosy. At the start of the programme 201 cases of leprosy were registered in Malta; 44 further so far unknown cases were detected during the course of the programme (June 1972–31 December 1984).

All cases were treated with Isoprodian–RMP. After discontinuation of treatment they were closely followed up for the occurrence of relapses (by now the majority of the cases have been followed up for almost 10 years). Up to this date (30 September 1986) no relapses have occurred.

2 When the programme became effective the number of newly detected cases dropped rapidly and continually. These cases were not newly infected persons but cases having remained unknown (and mostly also untreated) so far:

Number of cases detected per year:

Until 1972	73	74	75	76	77	78	79	80	81	82	83	84	85	86
10–20 cases	10	9	6	4	0	6	2	2	1	3	1	0	2	2

3 In a report made for the government (31 December 1984) I pointed out that with the conclusion of the programme, endemic, i.e. self-reproducing leprosy, does no longer exist in Malta. One had to reckon with finding in the years to come some cases having remained unknown. But this would not mean that the endemic was reactivated. The newly found cases would receive the same treatment as those of the programme.

4 Obviously, bacterial negativity had rarely been reached during the time of DDS monotherapy, which had been administered in Malta with great consistency and accuracy. However, this treatment had not halted severe processes (blindness, mutilations, attacks of the pharynx, etc.). Of course, these irreversible damages found at the beginning of the programme could not be repaired through chemotherapy. However, they cannot be taken as evidence for the fact that leprosy has not been eradicated in Malta. These cases are the sad victims of the fact that the new therapy has come too late for them. They are bacteriologically negative and clinically stable. Some of these former leprosy patients are so bad off (for reasons of age and/or for social reasons) that they need special help. Already during the course of the programme the Maltese Government had decided to build an old people's home for former leprosy patients—a unique and exemplary measure.

5 Dr Vella Briffa believes the programme to be defective in 2 points:

Lack of an active case-finding programme

In earlier times this question was often discussed, also with representatives of the government. We arrived at the conclusion that the hitherto way of inconspicuous detection used (having exact knowledge of the most afflicted regions and families) was the lesser evil. Active case-finding would only disquiet the population without serving the cause. Nobody wanted this.

Better information of the physicians

In Malta physicians receive (at any rate used to receive; Dr Agius-Ferrante) detailed information about leprosy during their study. This was a function of the Malta Medical School and the eradication programme has at no stage been involved.

There had always been some non-registered cases having remained unknown (very seldom

today)—but not because of the lack of knowledge of the physicians, but for the typical social reasons known in all leprosy-endemic countries.

It might be an important additional task for Dr Vella Briffa to reduce the prejudices still existing among physicians with regard to leprosy. Sometimes we had great difficulty obtaining the admission of cured former leprosy patients to the hospital, because 'lepers' were not wanted. In the interest of the patients something should be done in this direction.

6 The leprosy problem has been solved in Malta. This fact is not changed by the detection of cases having remained unknown so far. I would not even be astonished if, at a later date, one or another relapse would occur. In many countries, even in the United Kingdom and in the FRG, singular cases of leprosy do exist, but no one would dare to claim that there is endemic leprosy in these countries. What is decisive is not a singular case but the putting of an end to the continuation of a self-reproducing endemic.

In summary, it can be said that Dr Vella Briffa passes judgement on a measure which he has not witnessed. His concerns are understandable, his reflections correct. However, the points in question have formerly been discussed in detail, and have been settled in practice.

So far Malta is the only state which (with the assistance of the Order of the Knights of Malta and the German Leprosy Relief Association) took the decision (against opposition) to get rid of leprosy. This is of historical merit to the Maltese Government and the physicians engaged in the project, Drs George Depasquale and Edgar Bonnici, and should not be curtailed.

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E FREERKSEN

WHY CLASSIFY LEPROSY PATIENTS INTO PAUCIBACILLARY AND MULTIBACILLARY GROUPS?

Sir,

In technical report series 675(R) WHO recommend that all leprosy patients be divided into either paucibacillary or multibacillary types and that the former should have 6 months treatment only, the latter a minimum of 2 years, but continuing wherever possible until smears are negative. In paucibacillary cases, these may be diagnosed clinically or histopathologically '. . . with a bacteriological index of less than 2 according to Ridley scale at any site.'

It is already becoming apparent that mistakes are being made in the allocation of the patients into either paucibacillary or multibacillary groups for WHO regimens and in some countries this is aggravated by the fact that routine bacteriological examination of slit-skin smears is not properly carried out. I write to record my belief based on many years experience in India and Nigeria that there is in fact an inherent technical problem regarding the selection of body sites for routine skin smears. In addition to the selection of a site there are also problems in smear taking, staining and reading. Furthermore the peripheral nerves rather than the skin lesions may be far more important from a bacillary point of view. More and more cases with discrepancies in skin and nerve are being seen and for obvious reasons, nerves cannot be examined routinely for this purpose especially in the field. There is a need for clinical parameters which can be applied in the field for assessing the real bacteriological and immunological status of leprosy patients.

In tuberculosis treatment is standardized, no matter how many bacilli are revealed. Is there perhaps a case in leprosy for abandoning our attempts to divide patients into paucibacillary and multibacillary groups especially for chemotherapy and to give all of them a minimum of 2 years' treatment with 3 drugs?

ALERT
P.O. Box 165
Addis Ababa, Ethiopia

N B B REDDY

Lepr Rev (1987) **58,** 90

Leprosy Control and Field Work

Tuberculosis and Leprosy Control Programme, Yei River District, Sudan

Dr V Erasmus, Coordinating Adviser, Primary Health Care Programme Yei, AMREF/GTZ (Juba-Sudan), c/o AMREF Headquarters, Wilson Airport, PO Box 30125, Nairobi, Kenya, Africa, has kindly supplied details of the TB and Leprosy Control Programme for South Sudan. In January 1986, he reports '. . . a District Health Planning Committee was set up in Yei River District. One of the priority areas identified was disability arising from poliomyelitis, leprosy, trauma etc. TB and leprosy themselves are serious problems, and therefore initially two programmes were developed: (i) Leprosy and disability control and rehabilitation; and (ii) tuberculosis control.

As planning proceeded, it became clear that for disease control, TB and leprosy were better dealt with together. Consequently a TB and leprosy control programme was developed and is in fact being implemented now. The Disability Control and Rehabilitation Programme remains as it is, except that the case-finding system is attached to the TB and Leprosy Control programme.

This does not imply that these are separate vertical activities, but are in fact coordinated by the District Health Planning Committee; this is an interagency (both Government and non-government) body including AMREF, MSF, ERAD, NAD, SRPY, SSCP and other health-related agencies. Clear out referral pathways have been identified.

The programmes are meanwhile proceeding well and local cooperation from the Chiefs, Headmen and general population has been surprisingly good. The first survey is being undertaken now. We greatly welcome the proposal by Professor David Morley of the Institute of Child Health in London that it may be possible to send students out here from the UK to participate in our field work.

Technical Guide for Smear Examination and BI Chart; now in Thai

We congratulate Mr Wolfgang Kampf, German Leprosy Relief Association, 257/3 Kaeonawarat Road, Main PO Box 215, Chiang Mai, Thailand, for effecting translation of both the Smear Guide and the BI Chart (see descriptions in *Lepr Rev* **57,** 81–2) into Thai. These have already been distributed to various parts of the country, where they are greatly appreciated.

International Disability Education and Awareness, UK

Christine Wilson, Disability Awareness Trainer, International Disability Education and Awareness (formerly Third World Group for Disabled People), 16 Bath Street, Frome, Somerset BA11 1DN, England, keeps us informed of 5-day courses on disability and rehabilitation in the developing world which are organized in the UK, from time to time, by this agency. She writes:

'These courses are aimed at developing the confidence and skills of people working, or about to work overseas, with people with disabilities. Practical, theoretical and interactional sessions combine to encourage participants to share their experiences, skills and ideas and to look at some of the fundamental issues behind Disability and Development.

Emphasis is on working with other people as our main resources and allies, and ways in which we can improve our communication and teaching skills in order to put this into effect.

Participants and tutors are encouraged to use English as a secondary language, throughout the course. Having contributors from many different countries enables us to explore cultural barriers to communication and to appreciate the diversity of our experiences'. For further information write to the address above.

Calendar (blister) packs for the implementation of MDT in leprosy

Following the initiative of the Sasakawa Memorial Health Foundation and Ciba-Geigy in introducing blister (calendar) packs for the multiple drug treatment of both pauci- and multi-bacillary patients, using WHO regimens, in the Philippines, a similar approach is planned for 3 areas of India in 1987. DANIDA has decided to dispense all anti-leprosy drugs in its planned programmes for India in this form. It is understood that about 1·7 million packs are currently under production and that they will be put into field use in early 1987. In Thailand, a controlled trial of packs has been planned in two 'vertical' and two 'horizontal' programmes, also due to start in early 1987.

0305-7518/87/058090+01 $01.00

Lepr Rev (1987) **58**, 91–92

Teaching Materials and Services

Orientation in leprosy for doctors, HKNS, India

This is a strongly bound paperback, 18 × 24 cm, of 28 pp, published by Hind Kusht Nivaran Sangh, 1 Red Cross Road, New Delhi 110 001, India. Its object is quite simply to '. . . give a short orientation to all medical doctors and to ensure their involvement in the National Leprosy Eradication Campaign.' It is written by Dr and Mrs Thangaraj and Dr K C Das. This excellent booklet covers all basic aspects of leprosy from diagnosis, through classification to the management of reactions and the use of multiple drug therapy. It would in fact be of great value to medical students in India and probably also to several categories of health worker; with some modification it could in fact be used in other countries, where the need for such a text on leprosy for doctors and medical students has yet to be filled.

Leprosy I and II. Colour transparency sets from Glaxo Laboratories (India) Ltd

These excellent sets have been produced by Glaxo, India; they were assembled by Dr V D Parekh (Grant Medical College, Bombay), Dr R Ganapati (Bombay Leprosy Project) and Dr Chetan Oberai (Grant Medical College, Bombay). Using 48 colour transparencies, they cover virtually all aspects of the disease and there is a full written text. Some of the recommendations on chemotherapy, such as the use of isoniazid, may not be universally acceptable, and it is possible that the sections on treatment generally will have to be revised soon in view of current WHO advice on multiple drug regimens for paucibacillary and multibacillary cases. Slide 44 and page 10 in Section II would also benefit from a clearer distinction between the two main types of adverse immunological reaction in relation to treatment. These are, however, minor comments on material which will greatly benefit leprosy work in India and elsewhere, and we congratulate the authors and the Glaxo Laboratories on this initiative.

The following lecture sets are available, post free, at the rates given below: 1 Diabetes mellitus, 3 parts (72 colour slides & text) Rs. 150/-; 2 Cerebrovascular dieases, 3 parts (72 colour slides & text) Rs. 150/-; 3 Scabies (24 colour slides and text) Rs. 50/-; 4 Ringworm (24 colour slides and text) Rs. 50/-; 5 Viral infection of the skin (24 colour slides and text) Rs. 50/-; 6 Venereal diseases (24 colour slides and text) Rs. 50/-; 7 Leprosy, 2 parts (48 colour slides & text) Rs. 100/-; 8 Ischaemic Heart Disease (24 colour slides and text) Rs. 50/-; 9 Acute myocardial infarction (24 colour slides and text) Rs. 50/-.

Payment may be sent by demand draft payable to Glaxo Laboratories (India) Ltd, Medical Education Department, Worli, Bombay 400 025, India on receipt of which the set(s) will be despatched together with an officially stamped receipt acknowledging payment.

NB. These slide–lecture sets are the copyright of Glaxo Ltd and are to be used for teaching purposes only.

Teaching and learning materials on leprosy from The Leprosy Mission (International), London

There are 20 items on the TLMI list of materials and a checklist is provided indicating their suitability for doctors, health programme planners, health educators, shoe workshop managers, junior health workers, supervisors, senior health workers, laboratory technicians, physiotherapy technicians, medical students and surgeons. Some items are free, others are to be paid for. Sea mail is used free of charge, but there is an extra charge for despatch by air mail, if this is requested. Enquiries to: Teaching and Learning Materials, The Leprosy Mission (International), 50 Portland Place, London W1N 3DG, England—*but please note that workers in India* should apply for the printed book list and prices to The Leprosy Mission, CNI Bhavan, 16 Pandit Pant Marg, New Delhi 110 001, India.

TALC: 3 colour slide–texts for leprosy

Leprosy lesions in skins of different colours. Dr Grace Warren of the Leprosy Mission International (50 Portland Place, London W1N 3DG) has produced a valuable set of 24 slides, with written text, on the above subject. As usual with material from Teaching Aids at Low Cost (TALC), the quality of the transparencies is high throughout, giving a remarkably clear impression of the appearances of leprosy in peoples of different racial origin and skin colour. The ample written material accompanying the slides begins with a page on how to use this set and then proceeds to a description of indeterminate, borderline and lepromatous leprosy lesions as seen on

the skin, using question and answer form. There are also 'Teachers Notes' interspersed throughout the text. There are 3 appendices; 1 on the examination of a patient who might have leprosy; another on classification and a third on checking for resistance to dapsone. Of the other TALC sets on leprosy, Lp *Leprosy in childhood* has sold very nearly 5000 since it was produced in 1971 and LpCn *Classification of leprosy* has sold over 2000 since 1976. This third set on leprosy will surely be of the greatest value to those working in areas where skin colour is light and it could well be studied in association with the slide set on the same subject from the Regional Office of the World Health Organization, Copenhagen, or with the illustrated manual *Leprosy in the light skin* by Dr D L Leiker and Professor E Nunzi and produced by the Associazione Italiana 'Amici di Raoul Follereau' in Bologna. For the above TALC set (LpD), apply to Teaching Aids at Low Cost, PO Box 49, St Albans, Herts A11 4AX. (The cost of the set with script is between £2.00 and £5.50, depending on presentation.)

Leprosy for Medical Practitioners and Paramedical Workers. R H Thangaraj and S J Yawalkar

This booklet of 92 pages has been written by Dr Thangaraj, Director of the Leprosy Mission in Southern Asia, New Delhi, and Professor Yawalkar, a dermatologist in the International Clinical Research department of Ciba-Geigy, Basle. Both authors have extensive experience of leprosy, mainly from India, and this is apparent throughout the pages of this informative and up-to-date publication. The chapters begin with the historical background, proceeding to prevalence, bacteriology, epidemiology, evolution of lesions, clinical features, differential diagnosis, treatment, reactions, deformities and their management, prevention, control and rehabilitation. There are 95 colour pictures of high quality, together with numerous diagrams and tables of practical value. There are 100 references and a page of recommendations for further reading. As the sub-title states, this book was written for doctors and paramedical workers, but it will also be found of great value to medical students, particularly in leprosy-endemic countries and to many other grades of health worker. A particularly valuable element in this publication is the emphasis placed on correct diagnosis, classification into pauci-bacillary or multibacillary groups (making use of the bacteriological index in slit-skin smears) and treatment with multiple drugs, according to the recommendations of the World Health Organization (*'Chemotherapy of leprosy for control programmes'; Technical Report Series 675, WHO, Geneva, 1982*). This booklet is free and it is to be hoped that it will receive a wide distribution in all leprosy-endemic countries as soon as possible. Apply to: Medical Department, Ciba-Geigy, CH 4002, Basle, Switzerland.

The Wellcome Tropical Institute—Museum and Distance Learning

The Wellcome Tropical Institute is funded by the Wellcome Trust and was established in 1984 to develop the Wellcome Museum of Medical Science and to work with governments and universities in the tropics to support their own courses in tropical medicine, and to develop continuing education for medical officers away from teaching hospitals. Thus the Institute intends to complement the work of the two British Schools of Tropical Medicine and will develop work outside the normal functions of these Schools, and to provide a focus in London where those who work in the tropics can meet each other. The Institute is pleased to collaborate with any individuals or organisations involved in the development of tropical medical education, both in the UK and abroad. Overseas we work with the institutions which need support for their teaching in tropical medicine. In the UK, we hope to generate an increased and informed interest in tropical medicine, chiefly, but not solely through our Museum and its exhibitions.

Museum—existing material is being completely revised and we are continually aware of the need to acquire fresh material which will ensure that the Museum remains topical, relevant and current as a teaching information centre to all levels of students and visitors. A new venture is to establish Museum displays in appropriate institutions in this country and abroad. Teaching and display materials are being produced on a variety of topics concerning health and disease in a form which can be exported and presented in institutions overseas. Another venture is the creation of special exhibitions on topics of current interest in tropical medicine. The first of these, on malaria, will open in March 1987.

Distance learning—a programme has been devised as a means of promoting continuing postgraduate education. This programme is targeted at district medical officers. Its aim is to strengthen rural health services by giving active and continual support to medical staff in rural areas where they work. We hope that the material provided will reinforce the medical training of doctors, and will also serve to stimulate interest in the areas of tropical health care, community development and education and research. Great care is being taken to present the programme modules in the most appropriate and sympathetic form of self-instruction. The presentations may include non-paper media such as slide-sound and video. The Programme will emphasize practical problem solving activities in the areas of clinical practice, administration and management of resources, community health care, epidemiology and education. We hope to assist medical schools to develop their own Distance Learning and Training Programmes.

There is also a Library and Archive Centre. For further details of any of these items apply to: The Wellcome Tropical Institute, 200 Euston Road, London NW1 2BQ.

Lepr Rev (1987) **58**, 93–94

News and Notes

XIIIth International Leprosy Congress, 11–17 September 1988, The Hague, The Netherlands

Scientific sessions and scope of the Congress:

Congress subjects: Twelve congress subjects are planned, namely: I Immunology, II Clinical Aspects, III Experimental Leprosy, IV Microbiology, V Epidemiology and Control, VI Treatment, VII Nerve Damage, VIII Surgery and Rehabilitation, IX Ophthalmology, X Social Aspects, XI Experimental Therapy, XII Pathology.

Poster sessions: Special attention will be given to poster presentations in order to maximize the personal discussions and explanations of your research. The organizing committee will provide a well planned schedule of poster presentations during the congress days in connection with, and completing the 12 congress themes. The organization will provide professional graphical assistance to participants for the preparation of their posters. This service is provided to present your scientific results in the most perceptive manner.

State of the art: Every morning a 1-hour session will cover all the recent progresses in the main fields of research. The 'Starters of the day' will be given by 5 experts on: A, Immunological Tools for Leprosy Control; B, Recent Developments in Molecular Biology; C, Operational Aspects of Multidrug Chemotherapy; D, Nerve Damage; and E, Social Aspects in Primary Health Care.

Workshops: The workshops will be held in the week preceding the congress. The summaries made by the chairmen will be made available by the end of the congress. Subjects to be covered are: Immunology, Epidemiology, Chemotherapy, Control, Information Systems, Diagnosis and Clinical Aspects, Training, Prevention and Management of Impairment Rehabilitation, Vaccine Trials, Social Aspects, Health Education.

Teaching and Training Sessions: During the congress continuous teaching and training sessions will be held. Video films, continuous slide presentations and films will cover the following subjects: 1, Immunology; 2, Pathology of Early Leprosy; 3, Reactive Phenomena; 4, Epidemiology; 5, Case Taking; 6, Information Systems; 7, Deformity; 8, Disability Assessment; 9, Vocational Rehabilitation; 10, Health Education. After each presentation a question and answer period is planned.

Congress Location and Hotel Accommodation: The 13th ILA Congress will be held in The Netherlands Congress Centre, The Hague, The Netherlands, from 11–17 September 1988. Hotel accommodation will be provided in several price categories ranging from ca. Dfl. 50,- to Dfl. 250,- and more. *Congress Bureau*: For all information concerning the congress, please contact the Congress Bureau: QLT Convention Services, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands. Tel. +31 (0)20-26 1372, Tlx. 31578 inter nl att qlt. This Meeting is co-sponsored by the World Health Organization.

XIIth International Congress for Tropical Medicine and Malaria, September 1988

This congress will be held in the International Congress Center RAI in Amsterdam from 18–24 September 1988, immediately after the International Leprosy Congress (above).

Information can be obtained at: Organisatie Bureau Amsterdam, Europaplein 12, 1078 GZ Amsterdam, The Netherlands. Tel. +31 (0)20-440807, Tlx. 13499.

Dermatology Meeting, Oxford, UK

A joint meeting of the International Society of Dermatology and the International Society of Dermatopathology has been provisionally agreed for 4–8 September 1988, in Oxford, UK. Further details, including confirmation of these dates, will be published in the near future, but the indications are that this meeting will indeed take place in early September 1988, making 3 for that month. *Editor*.

People's Republic of China; training of doctors for leprosy control and eradication

Dr Ma Haide (George Hatem) has written to say that 30 medical college graduates will be selected over a period of 3 years (approximately 1986–1989; 10 per year), to be trained as leprologists, capable from 1990 onwards of directing the country towards basic eradication of leprosy by the year 2000. Discussions have already been held in China on the course content and yearly training programme, including the possibility of part training outside China and we look forward to hearing further details of this important initiative.

0305-7518/87/058093+02 $01.00

Tuberculosis update: PATH; USA

PATH is published by the Program for Appropriate Technology in Health, from 4 Nickerson Street, Seattle, WA 98109–1699, USA. In Vol 6, No 1, 1986, most of the issue was devoted to tuberculosis and in No 2, some interesting comments from readers were recorded:

'Our recent issue on tuberculosis (Vol 6, No 1) brought a great deal of comment from our readers. Several pointed out that the fluorescent method of sputum slide examination is not more sensitive than the standard test (it only allows the microscopist to work more quickly) and that the bactericidal effect of ethambutol is probably better rated as 'low' while streptomycin should be rated as 'medium.'

One reader asked us to mention the drug interaction that occurs between rifampicin and oral contraceptives (OCs). Studies have shown that rifampicin speeds up the body's metabolism of oral contraceptive steroids and reduces their effectiveness. This effect is especially apparent with low-dose OCs, so women taking rifampicin and trying to prevent pregnancy should use another method of birth control.

Clarification is necessary for the purified protein derivative (PPD) doses that were mentioned for use in skin tests. For tests using PPD RT23, a 2 Tuberculin Unit (TU) dose is specified. This is roughly the equivalent of 5 TU dose of standard PPD. Finally, the most recent price data place the drug costs of a 6 month, intermittent regimen consisting of initial daily treatment with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by twice-weekly treatments with isoniazid and rifampicin at close to US $32, rather than the $18 figure given in the TB issue.'

Solar Solutions for the Cold Chain

The most recent edition of *Africa Health*, Vol 8, No 6, August/September 1986, carried an article of considerable interest to those who handle vaccines and other materials which require efficient refrigeration. John Lloyd of the WHO Expanded Programme on Immunization analyses the equipment which is currently available and draws attention to some of the problems which have been encountered. The opening paragraphs of this valuable article read as follows: 'Solar powered refrigerators made for storing vaccines and freezing the icepacks used to carry vaccines have finally emerged from some 5 years of development and trials in the field. They are now being purchased in large numbers for the WHO Expanded Programme on Immunization.

Despite a poor record of reliability with early photovoltaic powered (PV) refrigerators, the technology has steadily improved and system designs have become more efficient and less costly.

In the face of rising fuel costs, and the falling availability and poor quality of kerosene in many parts of Africa, even the best of the absorption refrigerators are unable to guarantee an effective cold chain in these areas. As funds become available, therefore many countries including Zaire, Uganda, Ghana, the Gambia, Kenya, Tanzania, Mali, Somalia and the Sudan are starting to implement large scale solar electrification of their cold chain systems.

For the manufacturers who have invested heavily in the development and improvement of this equipment over the last 5 years, this is welcome news. The promise of secure, long term storage for vaccine at no fuel cost is good news also for the EPI. But out of the euphoria of technological success are emerging logistic and management questions which, if not adequately addressed, threaten to point solar refrigeration to the same undesirable end as some other high technology transfers into the African region.' Africa Health is circulated free of charge to physicians, administrators and health professionals in government, private and charitable institutions (as stated on the reader application card) in the following countries: Botswana, the Gambia, Ghana, Kenya, Liberia, Malawi, Nigeria, Sierra Leone, the Sudan, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe. All correspondence should be addressed to Africa Health, 9 Heneage Street, London E1 5LJ, UK. Telephone: 01-377 9262.

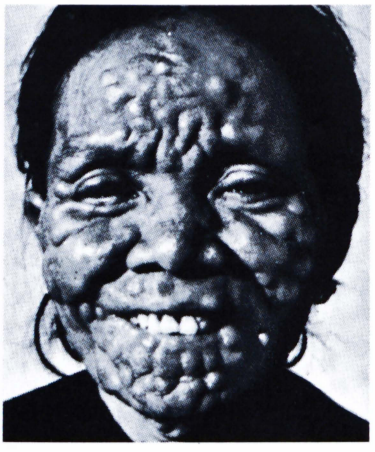
Proceedings of the Western Regional Leprosy Workers' Conference, Goa, India

The Western Regional Leprosy Workers' Conference was organized at Monte-de-Guirim, Mapusa, Goa from 8–10 November 1985. This was jointly organized by the Directorate of Health Services, Goa, branches of Hind Kusht Nivaran Sangh (Western Region-Goa, Maharashtra, Madhya Pradesh, Gujarat and Rajasthan) and the National Leprosy Organization and attended by 199 delegates from Gujarath, Goa, Madhya Pradesh and Maharashtra, Rajasthan. As the main objective of this Conference was to encourage paramedical workers to present scientific papers based on their experience, all the presentations were limited to them, apart from 3 guest lectures by eminent scientists. Twenty-nine papers were presented at different sessions including laboratory aspects of leprosy, operational and clinical aspects, physiotherapy, rehabilitation and social welfare, health education, training and treatment.

The organizers are to be congratulated on their decision to encourage the presentation of results by paramedical workers. The subjects covered were refreshingly practical and could well be taken up by others responsible for regional meetings of this kind. They included: Laboratory aspects of leprosy; Factors affecting accuracy in reporting on smears for afb; Hypopigmented lesions on the face in children; Do we need to treat single lesion cases?; Case finding programmes in tribal areas; Role of splints in the treatment of the leprotic hand; Health education and training (exhibition on wheels; a technique for detection of leprosy); Video films for education in leprosy and supervised administration of MDT in leprosy colonies through volunteers.

++ A CIBA-GEIGY CONTRIBUTION + TO THE FIGHT AGAINST LEPROSY ++

®Lamprene Geigy
and (= clofazimine)
®Rimactane Ciba
(= rifampicin)



Two highly effective drugs for use in the treatment of leprosy

Lamprene
Capsules of 50 mg and 100 mg

Composition: Clofazimine. *Capsules* of 50 mg and 100 mg. Indications: Lamprene, employed in combination with dapsone and rifampicin (Rimactane), serves as treatment for multibacillary forms of leprosy, such as lepromatous (LL), borderline lepromatous (BL), and mid-borderline (BB) leprosy, as well as erythema nodosum leprosum (ENL). Combined chemotherapy is necessary in order to prevent the emergence of resistant strains of *M. lepræ*. Dosage: *Adults* (of approx. 60 kg body weight): for the treatment of multibacillary leprosy (LL, BL, BB) the WHO (World Health Organisation) recommends the following dosage schedule: Lamprene: 300 mg once a month under surveillance + 50 mg once a day as self-medication. Rifampicin: 600 mg once a month under surveillance. Dapsone: 100 mg once a day as self-medication. This threefold combination should be administered for at least 2 years and, whenever possible, until such time as the skin smears become negative. If the patient develops ENL, the treatment with dapsone and rifampicin should be continued as before, whereas the dosage of Lamprene should be raised to at the most 300 mg per day. These high daily doses must not be given for longer than 3 months. *Children:* Children should receive lower doses adapted to their body weight. Administration: The capsules should be taken at mealtimes or together with milk. Contra-indication: Known hypersensitivity to clofazimine. Precautions: Leprosy patients suffering repeatedly from abdominal pains and diarrhoea, as well as those with liver or kidney damage, should if possible not be treated with Lamprene. Treatment with daily doses of Lamprene exceeding 100 mg should not be continued for longer than 3 months, and during this time the patient should be kept under medical supervision. If gastro-intestinal symptoms develop during the treatment, the dosage should be reduced or the interval between doses prolonged. In the event of persistent diarrhoea or vomiting, the patient should be hospitalised. Pregnancy and lactation: As in the case of any form of drug therapy, Lamprene should be employed with caution during pregnancy, especially in the first 3 months. Clofazimine crosses the placental barrier and causes temporary discoloration of newborn infants. The active substance also passes into the breast milk. Unwanted effects: The following side effects have been observed: Reddish to dark-brown discoloration of the skin and of the leprous lesions, particularly in pale-skinned patients at sites exposed to light. Discoloration of the hair, conjunctiva, cornea, and lacrimal fluid, as well as of sweat, sputum, urine, and faeces. This discoloration is reversible, although in the case of the skin it often does not disappear completely until some months after the cessation of treatment. Dryness of the skin, ichthyosis, pruritus, photosensitivity, acneform eruptions, and non-specific skin rashes. Nausea, vomiting, abdominal pains, diarrhoea, anorexia, loss of weight, and eosinophilic enteropathy. Storage: Protect from heat and moisture. Packages: 100 capsules of 50 mg or 100 mg. Further information is available on request.

Rimactane
Capsules of 150 mg and 300 mg

Composition: Rifampicin. *Capsules* of 150 mg and 300 mg. Indications: *Leprosy:* in combination with other antileprosy drugs as treatment for lepromatous and dimorphous (borderline) forms of leprosy, as well as in patients with other forms of leprosy, in whom intolerance of, or resistance to, other antileprosy drugs is encountered. Administration: At least ½ hour before a meal on an empty stomach according to WHO recommendations. Contra-indications: Hypersensitivity to rifamycins. Jaundice associated with reduced bilirubin excretion. Note: Daily treatment with Rimactane is generally better tolerated than intermittent therapy. Resumption of treatment with Rimactane after termination of a course of long-term therapy with the drug involves risks and should therefore, if possible, be avoided. In patients with *liver diseases*, as well as in *severely undernourished patients*, treatment with Rimactane entails a higher risk and its therapeutic benefits should therefore be weighed against the possibility of its causing further damage. If such treatment is necessary, the dosage must be correspondingly reduced. During pregnancy the use of Rimactane should, if possible, be avoided. Rimactane passes into the breast milk. Mothers in whom its use proves unavoidable should refrain from breast-feeding their infants. Unwanted effects: Gastro-intestinal disturbances; disorders of hepatic function, e.g. mild transient elevation of the transaminase values, may occur – chiefly at the start of treatment – but do not generally necessitate discontinuation of the medication; isolated occurrences of jaundice, leucopenia, and eosinophilia; particularly in patients taking Rimactane intermittently or in patients in whom daily treatment is resumed after a temporary interruption, side effects – possibly of immunopathological origin – may take the form of influenza-like symptoms ('flu syndrome) and, in rare instances, of cutaneous manifestations, thrombocytopenia, purpura, and fever, as well as of acute renal failure, dyspnoea, or haemolytic anaemia. If serious complications occur, such as thrombocytopenia, purpura, renal failure, or haemolytic anaemia, treatment with Rimactane should be stopped at once and not reinstituted at a later date. Packages: 8, 16, and 80 capsules of 150 mg; 8 and 40 capsules of 300 mg. Further information is available on request.

1. Chemotherapy of leprosy for control programmes, Report of a WHO Study Group, WHO Technical Report Series 675, WHO, Geneva 1982.
2. S. J. Yawalkar, J. Languillon, S. K. Hajra, A. C. McDougall, S. Gosh, D. V. A. Opromolla, C. J. S. Tonello. Once-monthly rifampicin plus daily dapsone in initial treatment of lepromatous leprosy. Lancet 1199, 29 May 1982.

HEAD OF OCCUPATIONAL THERAPY SECTION
ALERT, ADDIS ABABA, ETHIOPIA

The ALERT Occupational Therapy (OT) Section is part of the Division of Surgery and Rehabilitation. The Head of OT is responsible to the Head of this Division, at present, Dr Victor Smith.

Under the umbrella of OT, various activities take place:

1 Assessment and functional training for patients before and after hand surgery.
2 Health education for in-patients including knowledge assessment, education programme and actual teaching.
3 Safety training for patients with loss of sensation (i.e. cookery classes), protective glove production and tool training.
4 Teaching the general public about leprosy, using a large mobile puppet theatre.
5 Rehabilitation counselling at 'Wadiko Yetenessa Leprosy Patients' Association'. This organisation is concerned with income-generating activities for disabled patients.
6 Teaching, Health Education and OT as appropriate, during National and International Courses conducted by the ALERT Training Department.

The head of OT is assisted by 4 Ethiopian staff members who are fluent in English and the commonly spoken Ethiopian languages. One assistant is experienced, but the other staff are new to the job and require training and supervision.

The Head of OT takes part in ward rounds whenever necessary and contributes to hospital routine, records, statistics, reports, etc. The purchase of essential materials, repairs and maintenance of buildings and equipment has to be applied for at ALERT Administration and closely followed-up.

An applicant for this position should be fluent in spoken and written English including medical terms. Participation at the ALERT Physiotherapy Course (6 weeks) is required in order to gain sufficient knowledge about anatomy, physiology, clinical aspects of leprosy, complications, care of hands, feet and eyes, and treatment.

Apply to: **German Leprosy Relief Association (Deutsches Aussätzigen Hilfswerke, e.V., Postfach 348, 8700 Würzburg 11, West Germany, or ALERT, Executive Director, P.O. Box 165, Addis Ababa, Ethiopia.**

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It is understood that the paper is offered to *Leprosy Review* alone, that it will be subject to editorial revision, and that its copyright becomes the property of the British Leprosy Relief Association. Papers should be typewritten, in double spacing, on one side of A4 (210 × 297 mm) paper, with wide margins (4 cm left, and 2 cm right). The top copy and a carbon copy (or photostat) of all papers should be sent. Two copies of photographs, graphs, diagrams, etc., are required.

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