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Editorial

THE FIRST CHINA INTERNATIONAL LEPROSY SYMPOSIUM: BASIC ERADICATION BY THE YEAR 2000

A Symposium of very great importance has just taken place in the People's Republic of China. The First International Leprosy Symposium took place in Guangzhou in the Province of Guangdong from 26–29 November 1985 and was attended by 220 Chinese and 140 overseas delegates. Doctors and scientists came from all parts of China and the overseas guests represented virtually all parts of the leprosy-endemic world and many countries in Europe and the Americas. Perhaps the most important point of this event centred on the stated intention of the Chinese health authorities to basically eradicate leprosy from the entire country before the year 2000. But there were other important developments to report at the same time, namely the inauguration of the China Leprosy Association and the opening of the China Leprosy Control and Research Centre in the town of Pingzhou about 15 kilometers south of Guangdong. We were also delighted to receive a first, inauguration copy of the *China Leprosy Journal**.

The first day was devoted to opening ceremonies, with speeches from the Minister of Public Health, the Governor of Guangdong Province and representatives of various national and international organizations. Shortly before lunch, Dr Ma Haide (George Hatem) gave a keynote speech of unforgettable quality in which he described the historical development of public health services in China from the 1930s to the present time. He drew attention to the fact that 30 years of effort had reduced the number of cases from about half a million at the time of the founding of the People's Republic to less than 100,000 in 1983. But he had a word of warning: 'In spite of the fact that we have made changes in our methods of control, replacing institutional care and treatment by out-patient department and home treatment, and changing monotherapy to a more effective multidrug therapy, and in spite of having trained more than 10,000 medical leprosy personnel, we still must deal with a deep-rooted fear among the population and strong social discriminaton, even though over the years we have managed to decrease this through education and publicity. However we still have a

* For further details see p. 3.

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tremendous amount of work to do to reach our goal of eradication of leprosy by the end of the century.'

In the afternoon all delegates attended the official opening of the China Leprosy Control and Research Centre in Pingzhou, followed by conducted tours of the extensive buildings and grounds. Within the framework of eradication, the aim of this Centre is 'To promote leprosy control and research work and strengthen international scientific exchanges in leprosy'. The total area is 28 acres and the buildings cover over 16,000 square metres, with ample space for patient accommodation, research laboratories, rooms for clinical examination, physiotherapy and surgery. The specific tasks which this centre intends to address include the following

1 To guide and co-ordinate the national leprosy control and research work;
2 To work out nationwide plans for leprosy control and organize their implementation;
3 To train scientific and technical personnel for the cities and province;
4 To monitor and prepare bulletins on the trends of leprosy epidemiology in each city and province;
5 To carry out clinical and basic scientific research on leprosy;
6 To study and standardize the techniques, methods and standards in leprosy control;
7 To collect and exchange scientific and technical information, popularize scientific public health education relating to leprosy and issue various publications;
8 To convene regularly nationwide and regional leprosy scientific meetings;
9 To participate in mutual international exchanges and scientific meetings;
10 To advise the Ministry of Public Health on policies of leprosy control.

The second and third days were devoted to national and international contributions, beginning with 'Current Global Strategy for Leprosy Control' by S K Noordeen, Chief Medical Officer, Leprosy Unit, World Health Organization, then proceeding to chemotherapy, epidemiology, leprosy in South East Asia, the role of voluntary agencies, training, surgery/physiotherapy, leprosy in Africa, rehabilitation/social aspects, immunology and vaccine, animal use in leprosy, leprosy in India and future strategies. All these important papers, presented by experts in their own subject, will soon be published in the proceedings of this symposium. Contributions from our Chinese colleagues were of particular interest and these included: 1, 'Thirty-five Years of Leprosy Control in China and the Future Prospects' (Dr Yang Lihe); 2, 'The Feasibility and Effect of Treatment with Dapsone, Rifampicin and Clofazimine for Multibacillary Leprosy in Field Work; the Results of the First Year'; 3, 'A Long-term Follow-up in the Surgical Treatment of Deformities in Leprosy' (Dr Zhen Tishen); 4, 'Investigation of 1080 Cases of Leprosy Eye Disease in Guangdong' (Professor Zhang and Dr Lu

Binxin); and 5, 'The Use of Hidden Nylon Thread Operation for Lagophthalmos Paralyticum' (Dr Lu Bingxin and Professor Zhang).

On the day following the Symposium proper, our Chinese hosts organized a field trip to Shunde Chronic Disease Station, about 2 hours' journey from Guandong, and we had the pleasure of meeting doctors and supporting staff on their home-ground and of hearing at first-hand about the truly extraordinary changes which have taken place in the incidence and prevalence of leprosy in recent years. In many parts of China which were previously heavily affected, no new cases are now occurring; in many others the yearly incidence is already at extremely low levels and declining.

Can it be done? Can this enormous country, with somewhat limited financial resources, really eradicate a disease which has taken such a toll of the Chinese people over so many centuries? Most of those who had the honour to attend this remarkable occasion came away with the impression that Dr Ma Haide's optimism and enthusiasm are soundly based. No fewer than 10,000 people have been trained for the task of controlling leprosy; many special centres and institutions are available; the necessary drugs (including, incidentally, thalidomide) are available in China—and above all, there is no shortage of experience, clinical and scientific ability and determination. If anyone can do it, the Chinese will.

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A C McDOUGALL, EDITOR

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No doubt the *China Leprosy Journal* will soon be in circulation to many leprosy-endemic countries, but we take this opportunity to list the *Contents* of the first issue and to wish it every possible success in the future. It is published jointly by the China Leprosy Association and the China Leprosy Control and Research Centre. Equiries about subscription should be addressed to No 2, Huifuxi Road, Guangzhou, People's Republic of China.

Articles

Studies on Prevention and Treatment

Short Reports

Lepr Rev (1986) **57,** 5–8

Secondary dapsone-resistant leprosy in Brazil: a preliminary report

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Summary In this first report of laboratory confirmation of the presence of dapsone-resistant *Mycobacterium leprae* in Brazil, the susceptibility to dapson was studied in 12 patients clinically suspected of being resistant to dapsone.

The results showed that 8/12 strains were fully resistant to dapsone (66%), and 3/12 strains were partially resistant (25%). In 1/12 case the organisms failed to grow in all groups of mice. Important indicators for dapsone resistance include irregular treatment, lepromata of the histoid variety, bacterioscopy with solid bacilli and lack of response to dapsone therapy during 6 months.

Introduction

Due to its efficacy, good safety margin, good acceptance by the patients and low cost, leprosy chemotherapy in Brazil has been based on dapsone monotherapy since 1943. However, this fact is creating a dangerous epidemic situation owing to the emergence of drug-resistant strains. Patients become subject to relapses and disseminate strains of dapsone-resistant *M. leprae* to their contacts.

The first clinical evidence of dapsone resistance was reported in 1953.[1] But because of the difficulty of finding a suitable test animal, laboratory confirmation was only obtained in 1964[2] when Shepard's food-pad technique was used for demonstrating drug resistance.

In 1977[3] primary dapsone resistance was confirmed for the first time.

Dapsone resistance, which can be partial or total, appears late; never before 5 years, generally from 10 to 15 years, and sometimes after 20 years of regular treatment.

When resistance is partial, the multiplication of *M. leprae* can only be observed when minimal doses of 1–2 mg/kg of the body weight of the drug are

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used. When bacterial multiplication occurs with this dosage we can consider dapsone resistance as total.

The World Health Organization[4] suggested that efforts should be made to provide leprosy-endemic countries with well-equipped laboratories for Shepard's foot-pad technique.

Cases where there is clinical suspicion of dapsone resistance should be confirmed by the foot-pad technique, in order to facilitate better planning of therapeutic schemes and better supervision of the treatment of individual patients.

Research in 25 countries has indicated dapsone-resistant coefficients of prevalence in the order of 1–19, and of incidence in the order of 0·1–0·8% per year.[4]

In view of such variable data, a survey of dapsone-resistant cases is justifiable in Brazil as multidrug therapy is more expensive and more toxic and requires monitoring programmes which increase the costs to the health services.

To carry out such a survey the Oswaldo Cruz Foundation set up a laboratory for Shepard's foot-pad technique and the first results of our experience are presented here.

Materials and methods

Biopsy specimens were obtained from patients with multibacillary leprosy attending the Centro de Dermatologia Tropical Alfredo da Mata in Manaus (Brazil), and suspected of secondary resistance to dapsone. Employing the technique described by Shepard,[5] *M. leprae* were recovered from each specimen and diluted so as to provide an inoculum of 5×10^3 *M. leprae* per foot-pad. Forty BALB/c mice were inoculated in the right-hind foot-pad. Beginning on the day of inoculation a group of 10 mice were fed ordinary mouse diet (Control group), whereas the other 3 groups were fed a diet which incorporated dapsone in a concentration of 0·0001, 0·001, 0·01 g/100 g diet. The dapsone concentration in the mouse diet was analysed by Ellard's Standard Method.[6]

Three months later, one mouse from the untreated group was sacrificed and *M. leprae* were harvested from the right foot-pad. When the average number of organisms reached 5×10^5 in the control group, one mouse of each treated group was sacrificed. If fewer than 5×10^5 organisms per foot-pad were harvested from the untreated mice, the experiment was continued until a concentration of 5×10^5 was reached. At this time all mice of the other groups were sacrificed and the results compared.

Results

The susceptibility to dapsone of 12 *M. leprae* strains was tested in the mouse foot-pad and the results are summarized in Table 1.

Table 1. Average number of *Mycobacterium leprae* per foot-pad ($\times 5\ 10^5$)

Patient	Sex	Age	Class	BI	Date mice inoculated	Time of harvest (days)	Dapsone concentration (g%)			
							0	0·0001	0·001	0·01
MCV	F	46	MHD	3+	07/07/82	214	4·6	50	1·6	0·7
JBM	M	50	MHD	3+	08/07/82	274	8·9	6·9	7·9	9·9
VC	M	44	MHV	3+	08/07/82	214	1·0	0·9	0·7	0·7
FPC	M	53	MHV	ND	09/07/82	277	6·9	9·9	10	9·9
MLS	M	47	MHV	2+	13/07/82	244	11	7·9	10	7·9
JWSL	M	33	MHV	4+	07/10/82	212	5·2	1·4	1·3	1·2
MGCS	F	38	MHV	ND	13/12/82	242	NM	NM	NM	NM
WPA	M	33	MHV	3+	21/01/83	224	10	19	25	10
MDM	F	33	MHV	3+	22/02/83	223	16	10	10	85
SFC	M	34	MHV	2+	22/02/83	223	24	6·6	39	10
APL	M	30	MHV	3+	18/04/83	213	5·0	10	20	80
LBS	M	32	MHV	3+	09/05/83	201	22	7·8	47	46

NM = No multiplication.
ND = Not done.

As the table shows the *M. leprae* strains from 8 patients were fully resistant to dapsone, since *M. leprae* multiplied as well in the treated mice as in the untreated mice.

M. leprae strains from 3 patients showed partial resistance to dapsone, that is the organisms did not grow so well in the group of treated mice as in the group of untreated mice.

The organisms obtained from patient MGCS failed to multiply either in the mice of the treated or in those of the untreated (control) group.

Discussion

This was the first attempt to demonstrate dapsone-resistant strains of *M. leprae*, in Brazil, by Shepard's mouse foot-pad technique.

As has been shown in other countries, our results, demonstrating that 8/12 strains were fully resistant to DDS (66%), and that 3/12 strains were partially resistant (25%), indicate the existence of mixed populations of dapsone-resistant and dapsone-susceptible strains. In 1/12 strains the organisms failed to grow in either treated or untreated mice indicating that they were already dead when inoculated. Possible explanations for this could be that the organisms had lost their viability during packing and transportation or during the preparation of the inoculum; or the organisms might have been killed in the patient[7] in the course of treatment and might therefore be considered as susceptible to dapsone.

Some indicators are very suggestive of dapsone resistance—irregular treatment, lepromata of the histoid variety, bacterioscopy with solid bacilli and no response to dapsone treatment during 6 months.

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Lepr Rev (1986) **57,** 9–18

Ethionamide, prothionamide and thiacetazone self-administration. Studies of patient compliance using isoniazid-marked formulations

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Summary The acceptability of ethionamide, prothionamide and thiacetazone as potential companion drugs for the treatment of lepromatous leprosy was assessed in two small scale studies carried out among out-patients in Hyderabad. Specially formulated tablets or capsules containing 6 mg isoniazid as an innocuous marker were prescribed and their ingestion demonstrated by collecting urine samples at surprise home visits and testing for the presence of isoniazid metabolites by a simple colorimetric procedure. About three-quarters of the prescribed thioamide doses were ingested and daily doses of 125 mg ethionamide, and 125 or 250 mg prothionamide were of similar acceptability to the patients. Furthermore, prothionamide and dapsone could be given together in a single daily capsule without compromising the dapsone compliance of the patients. However more extensive studies of thioamide compliance are required before these drugs can be confidently recommended for the treatment of lepromatous patients unable to tolerate clofazimine. Thiacetazone compliance was poorer supporting the conclusion that thiacetazone should not be recommended for the treatment of leprosy.

Introduction

The thioamide drugs ethionamide and prothionamide are recommended for the treatment of patients with lepromatous leprosy who are unable to tolerate clofazimine. The suggested regimen is 250–375 mg thioamide self-administered daily for at least 2 years with daily self-administered dapsone and monthly supervised rifampicin.[1] The success of this treatment may well be determined by the regularity with which patients take thioamides; thus information is required

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on their acceptability before they can be unreservedly advised for use in leprosy control programmes.

Experimental studies in the mouse foot-pad[2–4] and investigations of their pharmacokinetics in man[5–7] indicate that ethionamide and prothionamide have similar clinical potencies. Experimental studies have also demonstrated that when ethionamide was administered once a week its bactericidal activity was abolished and leprosy bacilli multiplied between doses.[8] Under typical out-patient conditions many leprosy patients take dapsone very irregularly and intermissions in treatment of 4 days or more are common;[9] the therapeutic activity of the thioamides would probably be compromised were they taken with this degree of irregularity.

The thioamides have been widely used in the past for the treatment of pulmonary tuberculosis but nowadays are little used. Gastro-intestinal side-effects were common, though prothionamide appeared to be somewhat better tolerated.[10] However, the dosage used (500–1000 mg daily) was higher than is advised for the treatment of leprosy. Little is known of the acceptability and side-effects of the thioamides in lower dosages, although recent reports of their hepatotoxicity when combined with rifampicin are causing concern.[11]

Thiacetazone is not recommended for use in the treatment of leprosy[1] primarily because it is a rather weak bacteriostatic drug[12] whose efficacy is likely to be seriously compromised by poor compliance. Recent studies indicate that thiacetazone concentrations capable of inhibiting the multiplication of *Mycobacterium leprae* would only be maintained for about 3 days in the event of patients discontinuing to take their thiacetazone treatment.[13] Nevertheless in view of its cheapness, there are still those who advocate its use especially in those parts of the world where previous experience in the mass treatment of tuberculosis has suggested thiacetazone is reasonably well tolerated.

In previous studies we have established the feasibility of using special formulations of antileprosy drugs containing 6 mg of isoniazid as an innocuous marker in investigations of patient compliance.[14,15] Ingestion of the marker is revealed by a simple colorimetric urine test for the isoniazid metabolites isonicotinic acid and isonicotinylglycine. This paper describes the use of these isoniazid-marked formulations to investigate the regularity with which out-patients in Hyderabad ingested ethionamide, prothionamide and thiacetazone when prescribed with dapsone for daily self-administration.

Methods

TREATMENT OF PATIENTS AND COLLECTION OF URINE SAMPLES

The general procedures followed were as employed in the previous investigation of dapsone compliance by patients in Hyderabad.[15] Twenty-one male and 9 female patients participated in the 2 studies, including 22 who had taken part in the former dapsone investigation. Their ages ranged from 15 to 74 years (mean 40

years), they weighed from 27 to 68 kg (mean 48 kg); and had previously been treated for up to 17 years (mean 5 years). Monthly supplies of their allocated medication were issued when the patients attended the clinic for their regular monthly medical check-up and they were encouraged to swallow their prescribed daily treatment first thing each morning. Urine samples were collected by means of surprise home visits approximately once every fortnight. A randomized home visiting schedule was devised for this purpose so that the paramedical worker usually came on a different day of the week in order to ensure that the patients would not be able to guess when the next visit might be due. Ninety-five per cent of the samples were collected between 9 am and 12 noon that is some 3–6 hours after the daily doses of drugs should have been ingested.

THIACETAZONE STUDY

The objective of this study was to assess the regularity of thiacetazone and dapsone self-administration when they were prescribed either as a combined capsule or as separate thiacetazone capsules and dapsone tablets for daily treatment. There was an initial 'run-in' period of 6 weeks on standard dapsone tablets (100 mg daily). During this period 18 patients were treated on 3 consecutive days with a capsule containing dapsone 100 mg plus isoniazid 6 mg in place of the standard dapsone tablets. Urine samples were collected during this period by daily home visits, and each patient's 'compliant dapsone/creatinine (D/C) ratio' determined in order to increase the precision with which their subsequent dapsone compliance could be interpreted.[15]

After the run-in period, patients were assigned to two consecutive 12 week daily treatment schedules:

(a) One capsule: thiacetazone 150 mg + isoniazid 6 mg and one standard 100 mg dapsone tablet.
(b) One capsule: thiacetazone 150 mg + isoniazid 6 mg + dapsone 100 mg.

Nine patients were assigned by random allocation to receive treatment (a) followed by treatment (b), the rest were given these treatments in the reverse order.

THIOAMIDE STUDY

The objective of this study was to compare the regularity of ethionamide and prothionamide self-administration when they were prescribed at doses of 125 mg or 250 mg for daily treatment with dapsone. During the first 36 weeks of the 48 week study, 12 patients were assigned to 3 consecutive 12-week daily thioamide plus dapsone treatment schedules:

(a) One tablet: ethionamide 125 mg + isoniazid 6 mg and one standard 100 mg dapsone tablet.
(b) One tablet: prothionamide 125 mg + isoniazid 6 mg and one standard 100 mg dapsone tablet.
(c) One capsule: prothionamide 250 mg + isoniazid 6 mg + dapsone 100 mg.

Two patients were assigned by random allocation to each of the 6 possible sequences in which the regimens could be administered (abc, acb, bac, bca, cab and cba). At the end of the 36 weeks, the 4 patients on capsules continued with the same treatment for the remaining 12 weeks while the other patients who were receiving ethionamide or prothionamide tablets were treated with 2 thioamide tablets (250 mg ethionamide or prothionamide plus 12 mg isoniazid) plus 100 mg dapsone each day.

ANALYTICAL PROCEDURES

Aliquots of urine were preserved with a crystal of thymol at 0–4°C until shipment by air (without refrigeration) to London for subsequent analysis. D/C ratios were estimated by determining the urinary concentrations of dapsone plus its diazotisable metabolites (as dapsone equivalents) and creatinine by modifications of the Bratton and Marshall and alkaline picrate procedures, respectively.[16] Urine samples were tested for the presence of isonicotinic acid and isonicotinyl glycine as described previously.[15] Among urine samples from smokers, a positive result was indicated by the formation of grey or brown colours 30 min after reaction; negative samples gave orange or pink colours.[17] Among non-smokers, positive samples gave blue or green colours, while a negative result was indicated by a straw or yellow colour or by no apparent colour formation. Negative results implied that a 6 mg marker dose of isoniazid had not been ingested during the previous 18 h.[14] In order to supplement the qualitative results, concentrations of isonicotinic acid plus isonicotinylglycine (as 'apparent' isonicotinic acid) were estimated by measuring the optical density of the reacted samples at 600 nm and apparent isonicotinic acid/creatinine (I/C) ratios calculated.[14]

Results

COMPARISON OF QUALITATIVE AND QUANTITATIVE METHODS

Among the 463 urine samples with creatinine concentrations greater than 0·1 mg/ml, there was an excellent agreement between the qualitative and quantitative assessments of the presence of isonicotinic acid and isonicotinylglycine in the urine. Thus the I/C ratios of the 185 samples read as negative by eye (40% of the total) averaged 0·41 μg/mg in contrast with a mean ratio of 2·35 for the 278 samples that were judged by eye to be positive. Similarly only 7 of the 185 samples read as negative had I/C ratios of greater than 0·75, while only 8 of the 278 positive samples had ratios of less than this value. The concordance between the qualitative and quantitative findings among the 73 samples with creatinine concentrations of 0·1 mg/ml or less was however much poorer. Thus 64 of the 66 samples that were judged by eye to be negative had I/C ratios of greater than 0·75 (mean 2·77). It was therefore concluded that the simple qualitative procedure was unreliable under conditions of extreme diuresis. The results presented in this

Table 1. Thiacetazone study. Proportions of negative isonicotinic acid urine tests.

Prescribed treatment	Proportion negative	Percentage negative
Separate thiacetazone capsules and dapsone tablets	33/77	*43*
Combined thiacetazone and dapsone capsules	23/64	*36*
All	56/141	*40*

paper are therefore restricted to the findings obtained on urine samples with creatinine concentrations greater than 0·1 mg/ml.

THIACETAZONE STUDY

The results are presented of the analyses of the urine samples collected from 16 of the 18 patients originally admitted to the study. One patient was withdrawn from the study after developing ischaemic heart disease during the run-in phase prior to starting thiacetazone treatment and another left the city to find work elsewhere.

Thiacetazone compliance

Overall compliance was unsatisfactory. Whether thiacetazone was administered as combined capsules with dapsone, or separately plus dapsone tablets, about 40% of the urine samples collected gave negative isonicotinic acid urine tests, indicating the omission of at least 1 thiacetazone dose (Table 1). There were marked differences in individual compliance among the 16 patients, the compliance of 3 was excellent (not a single negative isonicotinic acid urine test), while the drug taking of 5 was poor and accounted for about 60% of all the missed doses in the study.

Actual drug ingestion often failed to correspond with the apparent acceptability of the prescribed thiacetazone treatment. Thus 2 of 3 patients who complained of side-effects attributable to thiacetazone (giddiness, nausea, loss of appetite, weakness, abdominal pain or paraesthesia) continued to take their treatment regularly, while the compliance of 4 patients without a single complaint was poor.

Dapsone compliance during thiacetazone administration

The regularity with which the dapsone doses were taken was estimated by comparing the D/C ratios of the samples with the patients' 'mean compliant' D/C ratios. The latter were calculated from the D/C ratios of samples giving positive isonicotinic acid urine tests when they were prescribed isoniazid-marked dapsone-containing capsules.[15]

The results obtained indicated the number of dapsone doses that were likely to have been ingested during the 4 days prior to the collection of each urine sample. The cumulative percentages of missed dapsone doses for each patient during the

Table 2. Thiacetazone study. Estimated percentages of missed dapsone doses.

Prescribed treatment	Percentages of missed dapsone doses None	<20	>20
Dapsone monotherapy (run-in period)	6	3	5
Separate thiacetazone capsules and dapsone tablets	2	4	8
Combined thiacetazone/dapsone capsules	5	6	3

three treatment periods were then calculated (Table 2). The results presented are for only 14 patients, since urine samples were not obtained from 2 of the patients during the dapsone monotherapy run-in phase. Although there was a suggestion that the inclusion of thiacetazone might have discouraged the self-administration of dapsone, the percentages of missed dapsone doses during the three treatment periods did not differ significantly ($P > 0{\cdot}1$).

THIOAMIDE STUDY

The results are presented of the analysis of urine samples collected from 11 patients; the twelfth patient died of burns sustained in a domestic fire early in the study.

Thioamide compliance

During the initial 36 weeks of the study about a quarter of the patients had failed to take their prescribed thioamide dose earlier in the morning of the surprise home visit (Table 3). Very similar proportions of 125 mg tablets of ethionamide or prothionamide were ingested by the patients. Although there was a suggestion that the combined prothionamide (250 mg)/dapsone capsules might have been taken more regularly than either the 125 mg ethionamide or the 125 mg prothionamide tablets, the differences between the proportions of negative urine test were not significant ($P > 0{\cdot}25$ and $> 0{\cdot}1$ respectively). Prescribing a final 12 weeks daily treatment with two 125 mg tablets of ethionamide (to 4 patients) or prothionamide (to 3 patients) did not change the percentages of negative

Table 3. Thioamide study. Proportions of negative isonicotinic acid urine tests.

Prescribed treatment	Proportion negative	Percentage negative
Ethionamide tablets (125 mg)	15/52	*29*
Prothionamide tablets (125 mg)	19/57	*33*
Prothionamide capsules (250 mg)	9/51	*18*
All	43/160	*27*

isonicotinic acid urine tests significantly compared with the previous 12-week period when they had been given a single tablet a day (48% vs 47% for ethionamide, 17% vs 23% for prothionamide). However the calculated I/C ratios, which should have doubled if 2 isoniazid-marked tablets were ingested each day, revealed that among the 5 supposedly compliant patients, only 3 were regularly taking 2 thioamide tablets each day.

The compliance of the 11 patients varied enormously. Thus over 90% of the urine samples collected from 3 of the patients gave positive isonicotinic acid tests. By contrast half of the urine samples from 3 other patients were negative and accounted for about 70% of all the missed thioamide doses in the study. Compliance approximately paralleled acceptability; of the 6 patients who had no complaints about taking the thioamides, 5 took their medication reasonably regularly.

Thioamide toxicity

One patient developed a facial itch and another diarrhoea which they attributed to prothionamide and as a consequence refused to continue thioamide treatment. The symptoms however subsequently responded to treatment for *tinea barbae* and taeniasis plus amoebiasis, respectively.

Two patients developed nausea, vomiting, salivation and indigestion almost certainly due to thioamides. Both were given symptomatic treatment and encouraged to continue to take their thioamide. Both claimed to be continuing treatment, but one stopped ingesting prothionamide while continuing to take her dapsone regularly.

Two of the patients developed jaundice (after 30 and 34 weeks of thioamide treatment, respectively). Both were chronic alcoholics. Drugs were stopped immediately and the patients made uneventful recoveries. Thioamides were not restarted.

Dapsone compliance during thioamide administration

The estimated percentages of dapsone doses missed by the 11 patients during the first 36 weeks of the study are shown in Table 4. Although there was a suggestion that combining dapsone with prothionamide in a single capsule might actually have encouraged the ingestion of dapsone, the percentages of missed dapsone doses in the two treatment schedules did not differ significantly ($0{\cdot}05 < P < 0{\cdot}1$).

Table 4. Thioamide study. Estimated percentages of missed dapsone doses.

Prescribed treatment	Percentages of missed dapsone doses		
	None	< 20	> 20
Separate thioamide and dapsone tablets	2	6	3
Combined prothionamide/dapsone capsules	7	2	2

There was considerable variation between individuals in their compliance; 3 were excellent, 6 average and 2 poor by the criteria used in the previous study.[15] The last 2 patients accounted for two-thirds of all the missed dapsone doses in the entire study and also ingested their prescribed thioamides very irregularly. When the remaining 9 patients were prescribed combined prothionamide plus dapsone capsules, the 40 urine samples tested revealed only 3 single lapses in compliance, suggesting that they would have responded very favourably to thioamide-containing treatment regimens.

Discussion

Thiacetazone compliance

Throughout much of Africa and the Indian subcontinent thiacetazone rarely appears to give rise to important adverse side-effects.[18] In these areas it has been widely used in the treatment of pulmonary tuberculosis and is generally regarded as a well tolerated drug. However the absence of complaints on obvious side-effects does not necessarily imply that compliance is good. Thus urine samples were tested from lepromatous patients in Ethiopia whose daily dapsone treatment had been supplemented with daily thiacetazone (as 'Thiazina' tablets containing 150 mg thiacetazone plus 300 mg isoniazid) in an attempt to prevent the emergence of dapsone-resistant leprosy. Some two-thirds of the samples gave negative isonicotinic acid results indicating that the patient had failed to swallow a dose of thiacetazone within the previous 48 h.[19] Not surprisingly the thiacetazone supplement failed to reduce the rate at which the patients relapsed with dapsone-resistant leprosy.[20]

Although the thiacetazone compliance of the patients in Hyderabad was much better than in Ethiopia, with about 60% of the prescribed doses being ingested, it was still probably inadequate. Thus when thiacetazone was given in a combined capsule with dapsone, the estimates of numbers of missed dapsone doses indicated that in 3 of the 16 patients intermissions of at least 3 days had occurred.

In the current study, as in the previous Ethiopian one, there was frequent contact and apparently good rapport between the staff and patients. Nevertheless, in both investigations thiacetazone was shown to be irregularly ingested despite the avowed absence of side-effects in many of the patients. It would seem that the ill-effects of thiacetazone are subtle enough to defy easy description yet sufficient to discourage self-medication. Whatever the reason, both studies indicate that thiacetazone compliance is unlikely to reach the levels required for it to be a therapeutically effective component for the treatment of lepromatous leprosy.

Thioamide compliance

In view of the small number of patients studied and the marked variations in individual patient compliance, great caution must be exercised in the interpreta-

tion of the findings. However, the cross-over design employed allows us to conclude with reasonable confidence that 125 mg doses of ethionamide and 125 mg and 250 mg doses of prothionamide were of similar acceptability to the patients and that a combined formulation of dapsone plus prothionamide could be prescribed without prejudicing dapsone compliance. Overall about three-quarters of the prescribed thioamide doses appeared to have been ingested and in only 3 patients was compliance unsatisfactory. This may be regarded as an initially encouraging finding.

A major factor influencing the potential contribution of the thioamides to the treatment of lepromatous leprosy is their propensity to cause hepatic damage, especially when given in combination with rifampicin.[11] Two of the 12 patients treated with thioamides in the current study developed jaundice. Although the liver damage was predominantly attributed to alcohol, thioamide treatment was immediately terminated and will not be restarted.

Thus among the 12 patients prescribed thioamides in the current study, thioamide treatment was discontinued in 2 patients because of potential hepatic toxicity and the compliance of 2 others was inadequate. We therefore conclude that it will only be possible to recommend ethionamide or prothionamide for the general treatment of lepromatous patients unable to tolerate clofazimine after more extensive investigations of their compliance and hepatic toxicity have been undertaken.

Acknowledgments

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Lepr Rev (1986) **57,** 19–26

The effect of dapsone in high and normal dosage on the clinical and cell-mediated immune status of patients with borderline (BT–BL) leprosy

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Summary Twenty-six patients with untreated borderline leprosy, 16 of whom (R group) had red raised lesions indicating incipient reversal reaction, were allotted randomly to dapsone 1 mg or 4 mg/kg body weight/day for the initial 2 months of treatment. The R group patients on high dosage dapsone did not show significantly greater clinical improvement during the trial period. Before treatment, their immune response (leucocyte migration inhibition test) to sonicated (but not whole) *M. leprae* was higher than that of the 10 patients with macular lesions (Q group). The response of Q group patients was unaffected by dapsone treatment, but in R group patients the response was reduced to Q group level after 1 month of dapsone treatment (both dosages). This suppression persisted for a week when dapsone was temporarily discontinued.

Introduction

In patients with untreated borderline leprosy, nerve damage develops as a result of intraneural delayed hypersensitivity reactions to antigens of *Mycobacterium leprae*.[2, 5] Acute episodes are commonly accompanied by the development of red raised skin lesions, and the symptom complex is known as Type 1 lepra reaction (reversal reaction). It is unusual for this reaction to develop with catastrophic suddenness; much more commonly aches and pains and gradually developing erythema and oedema of skin lesions give warning that something is going wrong, and may cause the patient to present himself for treatment. At this stage nerves have usually not been irreversibly damaged, and may still be clinically intact.

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There is controversy as to how these patients with incipient reaction should be treated. The use of non-sulphone drugs, or of dapsone in low dosage, has been advocated, but the latter may be harmful, for one study[3] shows that patients with borderline leprosy receiving initial treatment with dapsone 5 mg daily developed significantly more reaction than did patients starting on 50 mg daily. Certainly there is a need for a simple and safe treatment that will usually prevent incipient reaction progressing to the 'full blown' stage.

The results of the same study[3] suggest that simply initiating treatment with dapsone at full dosage is good enough management. However, in another study[6] it has been reported that when Ethiopian patients were treated with dapsone 200 mg daily for 1–2 months there appeared to be exceptionally rapid clinical improvement; aches and pains and red raised skin lesions usually subsided within a few weeks and steroid treatment was very seldom required. Similar results have been seen in Indian patients (Pearson; unpublished observations). The aim of this study was therefore to determine whether any clearcut advantage was obtained by initiating treatment with dapsone at higher than average dosage in patients with borderline leprosy. In addition, because the rapid benefit of dapsone in causing skin lesions to become less inflamed, suggests that it possesses immunological activity, changes in cell-mediated immune responses which could be attributed to the action of dapsone *per se* were measured, and could be compared with the clinical progress of the patients.

Patients, materials and methods

CLINICAL STUDIES

The clinical trial was carried out at Dhoolpet Leprosy Research Centre, Hyderabad. The patients all had clinical borderline (BT or BL)[12] leprosy. None had received scientific antileprosy treatment during the previous 2 years and none required corticosteroids at the start of the trial.

Initial assessments included clinical examination with body outline charts and palpation for nerve enlargement. Slit skin smears (from 1 or both ear lobes and 2–4 active looking skin lesions) were performed, as was skin biopsy for histopathological classification.[12] Tests for nerve function included muscle power tests (VMT) of muscles supplied by the ulnar, median, and lateral popliteal nerves, and tests for protective sensation of the palms and soles. The urine was tested for dapsone (dapsone/creatinine (D/C) ratio).

The patients could be divided into 2 groups, those with quiescent looking hypopigmented macules (Q group) and those in whom some or all of the lesions were raised and erythematous (R group). Patients in both groups were randomly allocated to treatment with high (about 4 mg/kg bodyweight/day) or normal (about 1 mg/kg/day) dosage of dapsone.

The trial covered a period of $2\frac{1}{4}$ months. All patients were treated as out-patients, and were seen at 1, 2 and $2\frac{1}{4}$ months (more frequently if necessary). On each visit the assessments (which could not be done blindly) were repeated, and the patients' clinical progress (particularly changes in the erythema and oedema of skin lesions) graded as improved (mild, moderate, or marked), no change, or worse (mild, moderate or marked). Enquiries were made about possible adverse effects of the treatment noticed by the patient. The urine was tested for dapsone (D/C ratio) at each visit and the skin biopsy repeated at 2 months. Patients were withdrawn from the trial at any time, if it was judged that they required treatment with corticosteroids.

Dapsone was then withheld for a week, and the patients then reassessed. Those on high dosage were transferred to normal dosage, and those with BL leprosy received appropriate multidrug therapy.

IMMUNOLOGICAL STUDIES

Leucocyte migration inhibition tests (LMIT) were undertaken in the Department of Zoology, Osmania University, Hyderabad, and performed at the times of clinical assessments, that is pre-treatment, 1 month, 2 months, and $2\frac{1}{4}$ months. The original method of one study[15] as modified by another[10] was used. After incubation at 37°C for 18 h, the areas of migration were measured with a planimeter. All the tests were run in triplicate and the average value was used to calculate the migratory index (MI) as follows:

$$\text{MI} = \frac{\text{Average area of migration in the test chamber}}{\text{Average area of migration in the control chamber}}.$$

The *M. leprae* antigens were preservative-free armadillo derived preparations (Batch AB51) kindly supplied by Dr R J W Rees (National Institute for Medical Research, London, England). Suspensions of whole bacilli (MLW) or sonicated bacilli (MLS) were used at the concentration (or equivalent concentration) of $2{\cdot}5 \times 10^7$ bacilli/ml, which was previously shown to be optimal for this batch and this system in our laboratory.[10] Phytohaemagglutinin (PHA-P) was a 'Difco' product which was found to give optimal responses (without signs of agglutination of leucocytes) at 10 μg/ml concentration in a preliminary dose-response study (at 20 μg/ml agglutination of leucocytes was observed in the migration chambers). All reagents were stored aliquotted at -20°C until used.

Student's *t*-test was used for statistical analysis.

Results

CLINICAL

Fifty-one patients were entered for the study. However 2 (both R group, 1 high dose, 1 normal dose) had to be withdrawn because they required corticosteroid

treatment before the end of the study. A further 21 patients either defaulted from the study or attended too irregularly for their immunological results to be analysed. (These drop-outs were somewhat more frequent among the Q group patients, but were not influenced by the dapsone dosage.) The immunological results of 2 patients were incomplete due to technical problems. The results of 26 patients are available for analysis; the clinical classification, grouping, and treatment are shown in Table 1.

The clinical progress of the 26 patients is shown in Table 2. The Q group patients showed very little clinical change; R group patients did better, and there was a tendency for the high dose treated patients to show a greater degree of improvement. This trend applied to both BL and BT cases. However, when initial and final biopsies were compared, no consistent differences could be detected between the high and normal dose treated patients, even in R group cases. There was little change in the results of nerve function tests during the trial period. Urine tests indicated that most patients were taking their treatment as prescribed.

Table 1. Classification,* clinical features and dapsone dosage of 26 patients with borderline leprosy

Clinical classification	Number of patients			
	Q group		R group	
	1 mg/kg/day	4 mg/kg/day	1 mg/kg/day	4 mg/kg/day
BL	1	1	2	5
BT	4	4	6	3
Total	5	5	8	8

* The histological classification agreed with the clinical classification except that 3 BL patients were classified histologically as LLs.

Table 2. Clinical progress of 26 trial patients

Patient group	Dapsone dosage	Result of final clinical assessment				
				Improved		
		Worse	No change	Mild	Moderate	Marked
Q	Normal	0	3	2	0	0
	High	1	1	3	0	0
R	Normal	0	0	5	1	2
	High	0	0	2	3	3

IMMUNOLOGICAL

During dapsone treatment immunological tests were performed at 1 and 2 months. However, there was no consistent pattern of differences between month 1 and month 2 readings; all 'during treatment' results therefore employ the average values of the 2 readings for each patient. Similarly there were few differences between the effects of the two dapsone dosages; the results therefore compare Q and R group patients regardless of their dapsone dosage.

The pre-treatment migratory indices to PHA, MLW, and MLS are shown in Table 3; the Q and R groups of patients responded equally to PHA and MLW, but R patients responded more strongly ($0{\cdot}83 \pm 0{\cdot}02$) than Q patients ($1{\cdot}02 \pm 0{\cdot}04$) to MLS ($P < 0{\cdot}001$). Dapsone treatment had no effect on PHA or MLW responses in either group of patients. However, there was marked suppression of the response to MLS in R group patients but not in Q group (Table 3). The suppression had developed fully within a month of starting dapsone treatment, and was unchanged when dapsone had been discontinued for a week.

Figure 1 shows the percentage increase in migratory index (i.e. the degree of suppression of the immune response to MLS) for each patient in relation to his clinical progress. The suppression was not related either to the dosage of dapsone or to the clinical response of the patient.

Discussion

CLINICAL FINDINGS

The results of this study confirm those of Barnetson *et al.*[3] that the use of

Table 3. Effect of treatment with dapsone on cell-mediated immune responses of 2 groups of borderline leprosy patients (values given are mean migratory index-±standard error)

	Quiescent lesion group (Q) (10 cases)		Incipient reaction group (R) (16 cases)	
Mitogen/antigen	Before treatment	During treatment	Before treatment	During treatment
PHA-P	$0{\cdot}58 \pm 0{\cdot}08$	$0{\cdot}64 \pm 0{\cdot}04$	$0{\cdot}54 \pm 0{\cdot}05$	$0{\cdot}60 \pm 0{\cdot}04$
M. leprae (whole bacilli)	$0{\cdot}90 \pm 0{\cdot}04$	$0{\cdot}94 \pm 0{\cdot}03$	$0{\cdot}93 \pm 0{\cdot}04$	$0{\cdot}92 \pm 0{\cdot}03$
M. leprae (sonicated)	$1{\cdot}20 \pm 0{\cdot}04$	$0{\cdot}97 \pm 0{\cdot}03$	$0{\cdot}83 \pm 0{\cdot}02$ ($P < 0{\cdot}001$)	$0{\cdot}99 \pm 0{\cdot}02$

Statistical significance, if any, is given in parenthesis between the mean values.

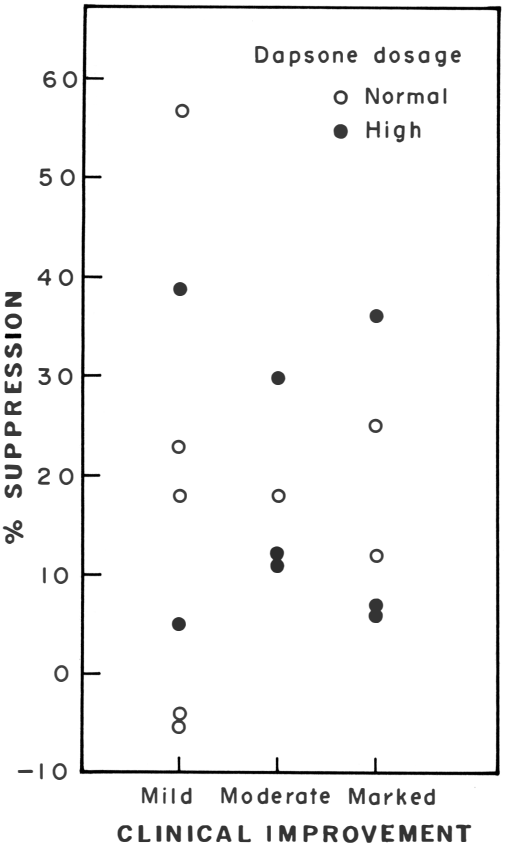

Figure 1. Percentage suppression of leucocyte migration inhibition to MLS of 16 R group patients according to their clinical improvement during the trial period.

orthodox dosage of dapsone *ab initio* will usually prevent patients with incipient reaction from developing full blown reaction. We failed to show any clear advantage in using dapsone in high dosage in these patients. Although this was not a very large scale study, this result was quite clear, even though preliminary uncontrolled studies had suggested to us that high dosage might well be much better.

The trial was too short for anti-bacterial action of dapsone to become apparent or for histological regression of the skin lesions to occur. Subsidence of inflammation of the skin lesions was therefore due to altered immune responses. That dapsone has such immunological activity has been suggested by Barnetson[3] and is supported by studies[4, 13] which showed impaired responses to PHA induced by dapsone *in vitro* and *in vivo* respectively. Moreover, in one study[17] it is reported that there is a reduction in the number of circulating T lymphocytes in dapsone treated guinea-pigs.

IMMUNOLOGICAL FINDINGS

An unexpected dissociation of responses to 'whole bacillary' and 'crude sonicate' *M. leprae* antigens has been demonstrated in the LTT system in patients with borderline (BT-BL) leprosy who developed reactions:[2] lymphocytes of patients with 'skin reactions' responded strongly to whole *M. leprae* and less strongly to the sonicate, whereas patients with 'nerve reactions' but little skin involvement responded relatively much more strongly to sonicated *M. leprae*. We have also previously reported such a dissociation of responses; MLW responses were more markedly suppressed than MLS responses following lepromin injection in healthy contacts of leprosy patients.[11] The same system and batches of antigens were employed as in the present study, in which one of the two main findings was also a 'whole/ sonicate' dissociation. MLS but not MLW inhibited leucocyte migration in R group patients. This suggests that incipient reversal reaction could possibly be a manifestation of delayed hypersensitivity response to antigens that are exposed when *M. leprae* are broken up *in vivo*. Dissociations of this sort deserve further study using better characterized antigens and systems that can identify specific lymphokines (such as gamma interferon).

Our second main finding was that this inhibition disappeared during dapsone treatment at both high and normal dosage levels. The effect was established within a month and persisted for at least a week after stopping dapsone. Suppressor T lymphocyte percentages (as estimated by rosetting)[8, 14] were unchanged throughout the study. The way in which dapsone brought about this effect is unclear, but its absence in Q group patients suggests that dapsone affects some component of the hypersensitivity process present in R group cases. This, and the absence of suppression of MLW responses in all our patients indicates that the effect is highly specific.

The lack of relationship between clinical improvement and suppression of MLS responses (Figure 1) indicates that additional mechanisms are likely to be involved in the processes which caused the skin lesions of our R group patients to subside. Indeed, dapsone has a number of activities which could suppress inflammation in skin lesions. It has been shown, for instance, to affect polymorph function,[1] macrophage activity, [7, 9] and immune complex formation.[16] The benefits of dapsone for patients with borderline leprosy are evidently not limited to its chemotherapeutic effects, and broader based studies of the immunological activities of dapsone in leprosy patients appear warranted.

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Lepr Rev (1986) **57,** 27–31

The number of *Mycobacterium leprae* in the pretreatment biopsy-specimen does not determine the rate of response of patients with lepromatous leprosy to chemotherapy with acedapsone

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Summary In an attempt to explain wide patient-to-patient variation of the rate at which patients respond to chemotherapy with acedapsone, the relationship between the logarithm$_{10}$ of the number of *Mycobacterium leprae* in the patient's pretreatment skin-biopsy specimen, and the rapidity with which the organisms became non-infective for mice, was examined for a number of patients with previously untreated lepromatous leprosy, treated in the course of a clinical trial in Cebu, Philippines. Analysis of the data failed to reveal such a relationship.

Introduction

Acedapsone [4,4′-diacetamidodiphenylsulphone (DADDS)], which produces a prolonged, low plasma level of dapsone after intramuscular administration,[1] has been shown to be an effective chemotherapeutic agent in clinical trials among patients with lepromatous leprosy. [2, 3] In the course of these trials, some patients responded as rapidly as patients treated with dapsone in full dosage, as measured by inoculation of mice with organisms recovered from skin-biopsy specimens obtained at intervals during treatment, whereas others responded much more slowly. Work was subsequently undertaken to identify the factors that determine the rate of response to treatment with acedapsone. To date, studies have shown that neither the susceptibility of the individual patient-strains of *Mycobacterium leprae*, all susceptible to dapsone administered to mice in a concentration of 0·0001 g/100 g diet or less,[4] nor the ratio of monoacetyldapsone to dapsone in the plasma of the patient[5] determines the rate at which the patients respond to

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treatment with acedapsone as monotherapy. Because analysis of the results of an earlier controlled clinical trial of clofazimine in several dosages[6,7] had suggested that the rate at which patients responded to chemotherapy was determined in part by the logarithm$_{10}$ of the total number of *M. leprae* (LAFB) recovered from the patient's pretreatment skin biopsy specimen, we wondered if the same phenomenon could explain the observed differences of the rate of response to therapy with acedapsone.

Materials and methods

In a controlled clinical trial (the 'Rifampin II' trial), conducted among patients with previously untreated lepromatous and near-lepromatous leprosy at the Leonard Wood Memorial Leprosy Research Laboratory, Eversley Childs Sanitarium, Cebu, Philippines [Collaborative effort of the US Leprosy Panel (US–Japan Cooperative Medical Science Program) and the Leonard Wood Memorial, manuscript in preparation], 27 patients were randomly assigned to treatment by acedapsone, administered intramuscularly in a dosage of 225 mg every 11 weeks. The same skin lesion was biopsied before, and at intervals of 4, 12 and 24 weeks after the start of treatment. *M. leprae* were recovered from the skin-biopsy specimens, enumerated, and inoculated into the hind foot-pads of mice, single mice were sacrificed monthly for histopathologic examination of the inoculated foot-pads, and harvests of *M. leprae* were performed from pools, usually of 4 foot-pads, all as previously described.[8,9] The values for LAFB were calculated from the number of organisms recovered from the pretreatment skin-biopsy specimens, all of which had been obtained with a biopsy-punch, and which varied in weight from 50 to 100 mg. SCORE, a measure of the rate of response to therapy, was calculated as described earlier;[7] values of 1, 2 or 3 were assigned to negative, weakly positive, and positive mouse inoculations, respectively, and SCORE was defined as the sum of the results of the inoculations performed after 4, 12 and 24 weeks of treatment. The smaller the value for SCORE, the more rapid the response to chemotherapy, as measured by inoculation of mice. The relationship between LAFB and SCORE was analysed by means of the Kendall rank correlation coefficient, *tau*.[10]

Results

The results of this study of 27 patients are presented in Table 1, in which the values of LAFB and SCORE are presented for each patient, the patients arranged in descending order of their LAFB values. These results show that there was considerable patient-to-patient variation of SCORE. However, the values for LAFB of the patients' pretreatment skin-biopsy specimens do not appear to be correlated with the values for SCORE.

Table 1. SCORE as a function of LAFB among lepromatous patients treated with acedapsone as monotherapy in the Rifampin II trial

Patient	LAFB*	SCORE	Patient	LAFB*	SCORE
MAHU	7·98	7	COND	7·48	5
DIWA	7·97	5	MAGL	7·43	3
PEND	7·91	3	DOMI	7·42	7
ALIM	7·88	7	SUMO	7·42	3
PAGA	7·85	7	SALA	7·39	5
ORTE	7·84	6	BAGU	7·32	7
MARC	7·76	4	GARN	7·23	9
ORDO	7·75	7	PENA	7·23	5
DICD	7·71	3	FLOR	7·12	5
BACU	7·64	7	PATD	7·03	9
RICA	7·61	5	ILLU	6·76	9
ELLE	7·58	3	SUAR	6·52	6
LAPI	7·53	7	ALIN	6·36	6
MERC	7·50	9			

* LAFB *vs.* SCORE: $tau = -0{\cdot}142$; $P = 0{\cdot}335$.

Discussion

The rate at which patients with lepromatous leprosy respond to chemotherapy is usually measured by inoculation of mice in the hind foot-pad with a standard number of *M. leprae* recovered from serial skin biopsy specimens; organisms recovered from untreated patients almost always multiply in the mice, whereas the decreasing proportion of viable organisms recovered from patients during effective treatment is detected, after a shorter or longer period of treatment, as failure of bacterial multiplication. The duration of therapy before the patient's *M. leprae* become unable to multiply in mice has been shown to vary from regimen to regimen.[11]

In the analysis of the results of a trial of intermittently administered clofazimine,[6] it was noted that patients whose pretreatment biopsy-specimens contained smaller numbers of organisms responded more rapidly than did those whose specimens contained larger numbers.[7] It was suggested that the difference in the rates at which patients responded to clofazimine had resulted from an artefact. Because a standard number of *M. leprae* is inoculated into mice, those bacterial suspensions containing larger numbers of organisms undergo greater dilution than do those containing fewer organisms; the human tissue components included in the suspensions are diluted to the same degree as the organisms. Thus, it appeared likely that the contaminating human tissue components, present in

the less diluted bacterial suspensions (those yielding a smaller value for LAFB) in greater concentration, inhibited multiplication of *M. leprae* in mice, thus giving the appearance of a more rapid response to treatment.

Although this hypothesis had not been tested, some corroborating evidence was found. In the course of the first demonstration of 'persisting' *M. leprae* in patients treated with dapsone for at least 10 years,[12] organisms from the same suspensions multiplied more frequently in thymectomized-irradiated than in normal mice, although the inocula were small, and in many cases no organisms could be counted. Because of the small numbers of organisms available from the biopsy-specimens, dilution of the bacterial suspensions had been minimized. It appeared likely that the poorer growth of *M. leprae* in normal mice reflected the greater ability of the normal mouse to respond immunologically to the foreign tissue components inoculated together with the organisms.

Additional evidence for such a phenomenon was the demonstration, in the course of a study of the effect of mouse interferon injected locally into the *M. leprae*-infected foot-pad,[13] that multiplication of the organisms was inhibited by both the 'interferon control' (a filtrate of an L-cell culture that had not been infected with Newcastle disease virus, and had not produced interferon) and foetal calf serum, a component of the cell-culture medium. Finally, in the course of a study of the survival of *M. leprae* after freezing in various media (L Levy, unpublished data), organisms that had been suspended in either 90 or 100% rabbit serum but had not been frozen were inhibited from multiplying in the mouse foot-pad.

It is clear, however, that the outcome of this analysis of the results of a clinical trial of monotherapy with acedapsone, is not consistent with the hypothesis that contamination with human tissue is one of the factors that determine the rate at which lepromatous patients respond to chemotherapy, as measured by inoculation of mice. Thus, another explanation must be sought for the patient-to-patient variation of the rate of response to acedapsone. That 17 of the 27 patients, the results of whose study are presented here, were those shown earlier[4] to harbour *M. leprae* susceptible to dapsone administered in a concentration no larger (and frequently smaller) than 0·0001 g/100 g mouse diet, and that, some years after these patients had been recruited, primary resistance to dapsone was demonstrated to be rare in the population from which these patients had been drawn,[14] should exclude primary resistance to dapsone as a factor determining the rate of response to acedapsone in this study.

Acknowledgments

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with the Leonard Wood Memorial, who made available the data analysed in this paper.

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Lepr Rev (1986) **57**, 33–37

A study of drug interactions in leprosy—1. Effect of simultaneous administration of prothionamide on metabolic disposition of rifampicin and dapsone

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Summary A study has been undertaken to examine the potential effects of prothionamide (PTH) on the pharmacokinetics of rifampicin (RMP) and dapsone (DDS) in 15 untreated leprosy patients. A daily administration of RMP and DDS for 7 continuous days followed by that of RMP, DDS and PTH for 7 more days formed the drug schedule. RMP and DDS levels were estimated in timed blood samples collected on days 7 and 14. Twenty-four hour urinary excretions of the 2 drugs were also determined on day 7 and 14 of drug administration. The results showed a lack of any significant effect of PTH on pharmacokinetics of RMP and DDS.

Introduction

Drug interaction is one of several important factors that modify drug responses in man. A number of clinically important interactions have been documented.[1] Multidrug therapy is currently recommended for all highly bacillated (BL/LL) leprosy patients with a view to prevent or reduce the problems of bacterial resistance and bacterial persistence as have been found with use of DDS alone.[2, 3] Such a treatment might mean that leprosy patients will run a risk of drug interactions whether these are pharmacokinetic or pharmacodynamic in nature. While there are a few reports pertaining to pharmacodynamic interactions resulting in increased occurrence of hepatitis in patients treated with rifampicin (RMP), ethionamide (ETH), dapsone (DDS) and clofazimine (CLF) in combinations of any 2 or 3 drugs for a long period,[4–6] there is no reference to pharmacokinetic interactions between these drugs. It has been reported that addition of RMP to DDS results in an increased clearance of the latter. The present investigation was undertaken to see if a third drug like prothionamide (PTH) would result in any effect on blood levels and excretion of RMP and DDS.

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Materials and methods

Fifteen uncomplicated lepromatous (BL/LL) leprosy patients were included in this study. None of the patients had had any drugs during the past 4 weeks. All of them were admitted to the ward for supervised drug administration. They were given RMP 600 mg and DDS 100 mg daily for 7 consecutive days on empty stomachs. Venous blood was collected in oxalate vials, 3 h, 5 h, 7 h, 12 h and 24 h after patients had taken the seventh dose.

Plasma was separated immediately. Drug assays were made either immediately or the plasma aliquots were frozen at $-80°C$ till assay was done. Twenty-four hour urine specimens were collected on day 7. From day 8 onwards these patients were administered PTH 500 mg daily in addition to combined administration of RMP and DDS as before. On day 14, timed blood and urine specimens were collected as on day 7.

The protocol of 14 days comprising two equal halves of 7 days was chosen so that the findings of this study will have a better practical application, since the patients on multidrug therapy are given RMP daily for the initial 14 days along with DDS and PTH. Moreover, the self-induction of RMP gets to a steady state in 7 days and any significant change in pharmacokinetics of RMP on completion of 14 days can be attributed to PTH.

Plasma RMP levels were determined by microbiological assay[7] using *Staphylococcus aureus*. Urinary RMP was determined by amyl alcohol extraction method.[8] Urinary excretion of creatinine was evaluated by alkaline picrate method.[9] Plasma DDS levels were determined after 3 h, 5 h and 24 h, by a micro adaptation of the spectrophotometric method of Simpson[10] cited by Shepard *et al.*[11] Urinary DDS was measured by the colourimetric method of Ellard *et al.*[12]

The plasma $t^{\frac{1}{2}}$ for DDS was calculated from regression lines representing the logarithmic decay of the concentration of DDS with time.

Plasma half-life ($t^{\frac{1}{2}}$) for RMP was calculated in a similar way. Area under concentration-time linear gradient curve (AUC) for RMP was calculated for the period 0–12 h and expressed as $\mu g\ ml^{-1}$ h. Urinary excretion of the drugs was expressed as the ratio of microgram of DDS or RMP to milligram of creatinine. Statistical significance of the findings was evaluated by paired t test.

Results

It was found that the values for plasma DDS did not show any statistically significant alteration with additional administration of PTH, although mean 3 h DDS levels were slightly higher following PTH intake. Twenty-four hour urinary excretion of DDS also did not show any significant variation. The plasma half-life ($t^{\frac{1}{2}}$) for DDS was $18 \pm 2{\cdot}1$ h before and $19 \pm 2{\cdot}1$ h with PTH (Table 1).

The plasma RMP values too, did not present any significant variation with addition of PTH (Table 2). A marginal increase in plasma $t^{\frac{1}{2}}$ for RMP was found

Table 1

Regimen	Plasma DDS level mg/dl			Plasma $t^{\frac{1}{2}}$ h	24 h urinary DDS	
	3 h	5 h	24 h		mg	D:C
RMP+DDS (15)	0·170±0·020* (0·141–0·204)†	0·150±0·010 (0·128–0·168)	0·086±0·010 (0·063–0·096)	18±2·1 (13·2–20·5)	67·9±13·6	73·1±12·9
RMP+DDS+PTH (15)	0·186±0·020 (0·151–0·206)	0·160±0·020 (0·130–0·185)	0·089±0·015 (0·071–0·110)	19±2·1 (15·6–21·5)	70·4±11·5	72·9±11·8

Paired t test: not significant.
* ±SD
† Range.
‡ DDS: creatinine ratio, μg/mg.

Table 2

Regimen	Plasma RMP μg ml^{-1}					Plasma $t^{\frac{1}{2}}$ h	AUC 0–12 h μg ml^{-1} h	RMP in urine	
	3 h	5 h	7 h	12 h	24 h			mg	R:C
RMP+DDS (15)	9·42±0·59*	6·08±0·73	4·09±0·85	2·84±0·70	0·40±0·10	3·2±0·31	58·6±6·3	92·6±21·5	84·7±21·7
RMP+DDS+PTH (15)	8·98±0·63	6·4±0·58	4·5±0·74	3·1±0·7	0·42±0·15	3·7±0·38	60·3±5·2	106·4±24·4	94·1±16·6

paired t test: not significant.
*±SD
** RMP: creatinine ratio, μg/mg.

subsequent to the addition of PTH. There was no change in values for AUC 0–12 h when PTH was added. Urinary excretion pattern for RMP too remained the same subsequent to PTH administration.

Discussion

Most of the drugs used in multidrug therapy of leprosy are antituberculosis drugs. There are a number of reports on interactions between these drugs. Para-amino salicylic acid (PAS) is found to cause decreased RMP levels in plasma after simultaneous oral administration of the two.[13] This has been attributed to PAS' impeding gastrointestinal absorption of RMP, due to an alteration of the physico-chemical properties of RMP by PAS granules or by a decrease in the gastric emptying rate combined with more rapid intestinal transit. No significant effect on serum concentration or half-life of RMP or Isoniazid was found after simultaneous administration of the 2 drugs.[13]

The microbiological assay employed in this study was sensitive enough to detect RMP levels down to 0·05 μg ml^{-1}. Although the microbiological assay for RMP suffers from interference from its metabolite desacetyl RMP, it was felt adequate to measure total RMP as this metabolite is also biologically active.

Rifampicin is known to induce its own metabolism in addition to that of a number of drugs. This fact was kept in mind while drawing the protocol for the present study. During continuous administration of rifampicin, the half-life gradually decreases as a result of enzyme induction until a steady state is reached.[14] The maximum induction of rifampicin metabolism is probably attained by day 7 on daily treatment.[15] In the present study a slight increase in the plasma $t^{\frac{1}{2}}$ for RMP was found subsequent to the addition of PTH during the second half of the study. This insignificant rise could then be attributed to self-induction of RMP rather than PTH.

A decrease in blood and tissue levels of DDS during concurrent RMP administration has been reported.[16] The increased plasma DDS clearance in patients receiving RMP concurrently was suggested to be due to an enzymic induction.[17] It has been observed[18] that RMP had a transient mobilizing effect on DDS depot in the body, resulting in an increased excretion of DDS in urine. In another study[19] it has been observed that this DDS clearing phenomenon did not vary significantly in between acetylator phenotypes. Low plasma DDS levels comparable to values reported elsewhere have been found in the present study.

The findings of the present study suggest that PTH does not have any effect on pharmacokinetics of either RMP or DDS. Further studies are being planned to examine the possible effects of DDS and RMP on pharmacokinetics of PTH.

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Lepr Rev (1986) **57,** 39–43

A method to determine pressure distribution of the hand

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Summary A simple method to determine pressure distribution, and to identify areas of localized high pressure of the deformed and often insensitive hand is presented. The method will also be useful to evaluate tool adaptations and the effect of surgery on the contact bearing area of the hand.

Introduction

There are 3 methods to measure the distribution of pressure on hands and feet. The identification of areas of localized high pressure is especially important in the management of deformed hands and feet which very often are also insensitive. Once areas of high pressure have been identified, tool adaptations and modified footwear will help to prevent recurrence of ulcers.

In one method force transducers are used. This method requires expensive electronic instrumentation and therefore is not practical to use in leprosy hospitals when we are dealing with large numbers of patients. Time, money and expertise are also usually not available. In another method the so-called slipper socks* or gloves are used. The gloves and socks are lined with pressure sensitive capsules that contain different coloured dyes that burst at specific pressures and thus will stain the glove or sock.

The third method which is the most practical uses the Harris mat.† This rubber mat contains ridges of graduated heights which form squares of varying size. Light pressure will be revealed in the print as large squares. With heavier

* Slipper socks available from: National Hansen's Disease Center, USPHS Hospital, Vocational Rehabilitation Department, Carville, LA 70721, USA.

† Harris mats available from: Downs Surgery, Inc. 2500 Park Central Blvd. Decatur, GA 30035 and Apex Foot Products, 330 Philips Avenue, South Hackensack, NJ 07601.

0305-7518/86/057039+05 $01.00

pressure the deeper ridges of the smaller squares will also be printed on the paper and the print will be darker. For the foot we can make a static print where the patient is just asked to step on the mat. We can obtain a dynamic print when we ask the patient to step on the mat when he takes a few steps in the room, or we can put a piece of Harris mat the size of his shoe within the shoe and ask him to take a few steps.

As far as we know the Harris mat has only been used to assess pressure distribution of the foot. We feel that these mats can also be used to assess pressure distribution of the hands. It is especially suitable to assess the contact bearing area of the hand in a cylindrical grip. Most of the farming tools will require such a grip. The different types of pinch cannot be evaluated with this method.

Method

A piece of Harris mat, the size of the circumference of the cylinder, is cut from a larger mat. The mat is then glued onto the cylinder. In our case the diameter of the cylinder was 2 inches. Wooden cylinders with different diameters and also Harris mats of different thicknesses can be used. The best would be to use a cylinder which is the size of the common farming tools used in your area. You could also have samples of the common tools in your department with a piece of Harris mat wrapped around them. 'Velcro' or rubber band can be used at the edges of the mat if you do not want to fix it permanently to the cylinder or tool.

The mat is inked using black printers ink (Figure 1), then a piece of absorbent paper is placed around the mat. The surface is rubbed gently with cotton wool to spread the ink evenly and remove any excess of ink (Figure 2). A piece of paper the size of the cylinder is then carefully wrapped around the cylinder. Only the edges

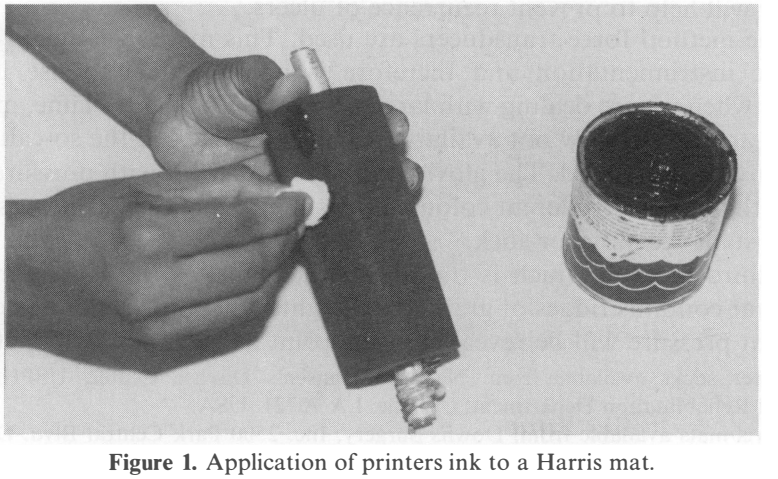

Figure 1. Application of printers ink to a Harris mat.

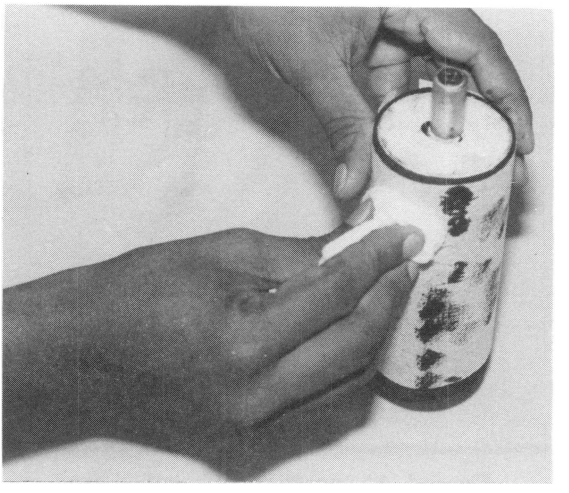

Figure 2. Even distribution of ink and removal of excess ink.

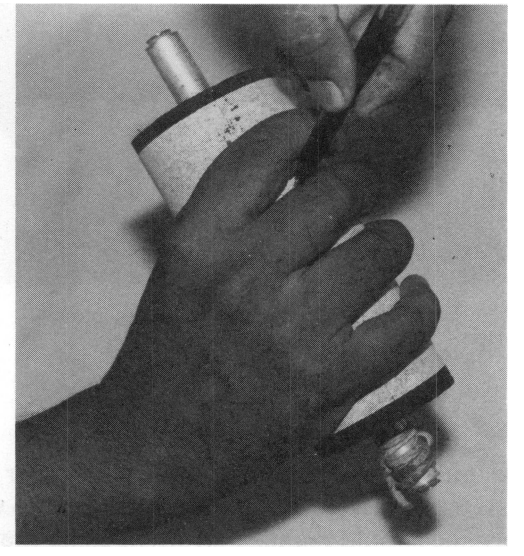

Figure 3. Tracing the outline of a hand.

should be touched in order not to leave prints on the paper. The patient is then asked to grasp the cylinder firmly. The outline of the hand is then traced with a pen so that after removal of the paper it will be easy to accurately localize the areas of high pressure (Figure 3). Prints of a normal hand and a claw hand are shown in Figures 4 and 5.

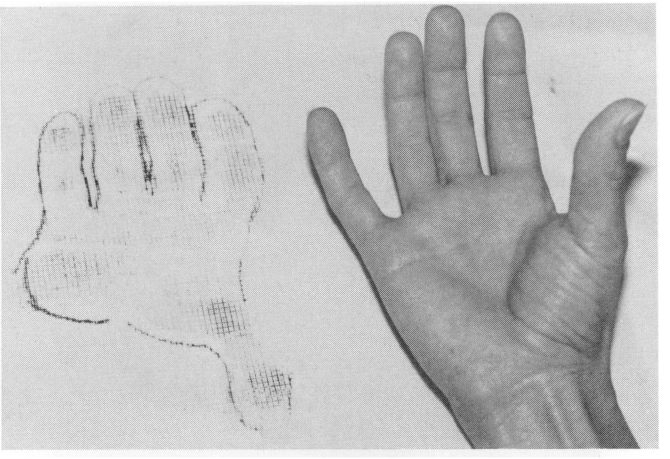

Figure 4. An impression of a normal hand.

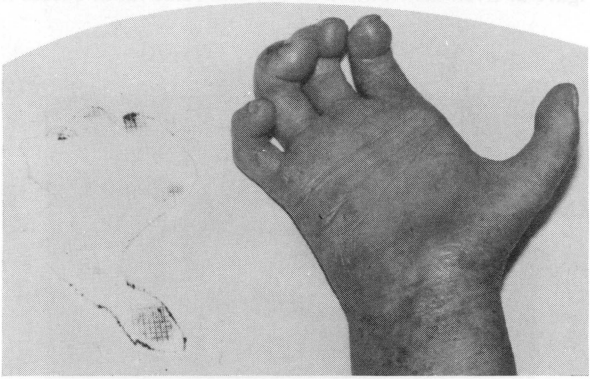

Figure 5. An impression of a claw hand.

Discussion

It is difficult with this method to measure the effect of shear forces on the hand. The glove method that uses pressure sensitive micro capsules would be superior in this regard. However, one should realize that when using the gloves there should be a glove that fits well for every hand. This would make this method expensive to use in developing countries. The glove could also to some extent already correct certain deformities.

The Harris mat method is easier to use and will identify areas of localized high pressure, though in a static grip. The areas of high pressure may increase and change when the hand is at work. It is not wise to wait and see when and where injuries may occur, when it is possible to determine what the potential danger areas are. The patient can then be advised about working habits and tool adaptations can be made.

This method can also be very useful to evaluate the contact bearing area of the hand pre- and postoperatively in conjunction with tendon transfer surgery. The method does not quantitate the pressure but gives a good clinical impression of the area of the hand that is in contact with the tool and will clearly show areas with increased pressure.

A cylindrical object of glass or plastic from the laboratory is also a good tool to assess the contact bearing area of the hand. The patient is asked to grasp this object and the examiner will be able to see through the cylinder the areas of the hand that are in contact with the cylinder. These areas will show more white as blood will be pressed from them.

One of us has also used a grip index to evaluate grip contact pre- and postoperatively in conjunction with tendon transfer surgery. The fingers were given a maximum grade of 3, one for each phalanx, and the thumb a maximum grade of 2 (two phalanges). The number of phalanges that were in contact with the cylinder were written down. A normal hand would, therefore, have a grip index of 2-3-3-3-3. A claw hand could have a grip index of 2-3-3-1-0. This would indicate that the thumb, index, and middle finger were in full contact with the cylinder, that only the distal phalanx of the ring finger was in contact and that the little finger was without any contact. Using this method we were able to show that there was an increased grip contact postoperatively. With these 2 methods, however, we will only be able to record the area of the hand that is in contact with the cylindrical object. Localized areas of high pressure can only be identified with the Harris mat method.

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We wish to thank Dr P W Brand who suggested this method of pressure assessment to us.

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Adhesive zinc tape treatment of uncomplicated ulcers amongst leprosy outpatients

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Summary The operational feasibility of ordinary adhesive zinc tape treatment of ulcers under field conditions, was studied on 89 uncomplicated superficial ulcers amongst 50 leprosy outpatients. Deep ulcers with or without sinus and purulent discharge were not considered fit for tape treatment. All the 13 hand ulcers and 62 (82%) of the 76 plantar ulcers healed in $3{\cdot}8 \pm 2{\cdot}1$ and $9{\cdot}5 \pm 7{\cdot}6$ weeks of tape treatment, while patients were ambulatory. The tape treatment was found to be effective, economical, acceptable and convenient to patients, and operationally feasible. The available adhesive leucoblast may be used for ulcer treatment in field and hospital situations.

Introduction

The timely and regular management of ulcers on anaesthetic hands and feet of leprosy patients is necessary to prevent the deformities of limbs. Since our mobile leprosy clinics function only once a month, ulcer patients find it very difficult to get their ulcers dressed regularly. It is not feasible either to provide gauze and bandage to patients or hospitalize them for treating their simple plantar ulcers. This makes it necessary to find some simple, effective, economical, and operationally feasible method(s) of ulcer treatment, by patients themselves with little training and supervision.

The role of zinc in wound healing, especially amongst zinc deficient persons like those suffering with burns and leprosy, is now well established. The ordinary adhesive zinc tape has been used for healing local wounds, over many years.[1, 7, 9] The zinc tape treated wounds have been demonstrated to heal in shorter periods than gauze and bandage/sponge treated ones.[2, 4] One study[8] has reported the ordinary adhesive zinc tape treatment of ulcers amongst leprosy patients to be very successful. Later another study[6] compared the adhesive zinc tape treatment, with gauze and bandage treatment, of simple plantar ulcers amongst their hospitalized leprosy patients, and found the tape treatment healed ulcers in a shorter period.

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Since it is not feasible to admit patients to treat their simple plantar ulcers, the present project was specifically undertaken to study the operational feasibility of adhesive zinc tape treatment of uncomplicated ulcers under our field conditions. The comparison of tape treatment with other methods of ulcer treatment as well as the pathogenesis of ulceration and its recurrence, were not envisaged in this operational study.

Materials and methods

The study was carried out amongst outpatients attending a mobile treatment unit, operating in Rural Field Operation Area (Sriperumbudur Taluk of Chingleput District) of Central Leprosy Teaching and Research Institute, Chingleput, Tamil Nadu. Fifty adult leprosy patients (32 males and 18 females) with 93 uncomplicated superficial ulcers with or without serous discharge were included in the trial. Complicated ulcers (deep ulcers with or without sinus and purulent discharge) were not considered fit for adhesive zinc tape treatment. More than 91% of the selected patients were agricultural labourers, belonging to the low income group. All patients had grade 1 or 2 (WHO classification) disabilities.

Of the 44 patients with 76 plantar ulcers, only 27 patients with 45 plantar ulcers wore locally available plastic chappals/shoes for an average period of $2{\cdot}34 \pm 2{\cdot}99$ (SD) years before getting ulcer(s), and most of them continued to do so during the tape treatment. In order to study the effect of tape treatment under ordinary circumstances of non-availability of proper footwear to large numbers of patients, the efforts were not made to equip the trial patients with microcellular rubber footwear; on average each patient walked for $4{\cdot}5 \pm 2{\cdot}2$ (SD) km/day.

Of the 93 ulcers, 4 plantar ulcers amongst 2 male patients were not dressed regularly by them, hence these were excluded from the trial. The distribution of the remaining 89 ulcers (76 plantar and 13 hand) treated with adhesive tape is shown in Figure 1. All the 89 ulcers were classified into 3 groups according to their area, namely: (1) *Small* with $\leqslant$ 2 sq cm area (73%), (2) *Medium* with 2·1–4 sq cm area (10·1%), and (3) *Big* with >4 sq cm area (16·9%). All the ulcers on hands were small in size. About 64% of ulcers were of recent duration up to 3 months, while about 15% were more than one year old. The mean duration of each hand and plantar ulcer was $0{\cdot}10 \pm 0{\cdot}16$ and $0{\cdot}84 \pm 2{\cdot}0$ years, respectively. Most of these ulcers followed a blister (70%) or injury (16%) at the site, whereas in 14% of ulcers the reason was not specified. Only 69 ulcers (65 plantar and 4 hand) showed minimal-moderate serous discharge.

The adhesive zinc tape used in this trial was made of a plastic web coated with an adhesive substance composed of gum, resin and approximately 30% zinc oxide. The tape was fixed on a readily removable siliconized kraft paper, thereby making it easy for distribution and application on ulcers, even by patients with anaesthetic finger stumps. Each roll of tape measured $2{\cdot}5$ cm $\times$ 5 m.

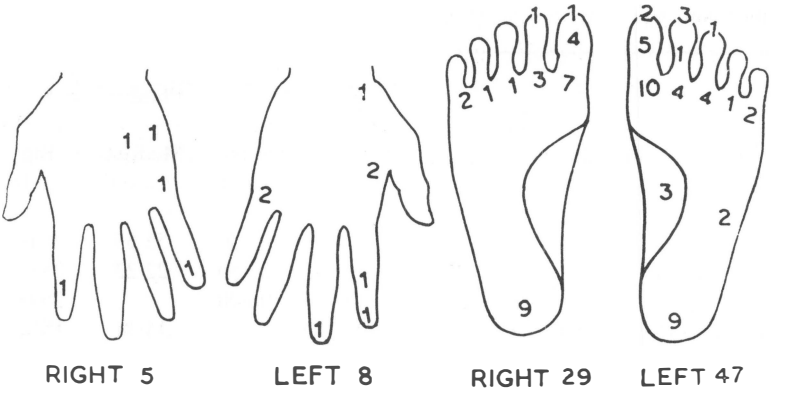

Figure 1. Distribution of 89 ulcers.

The tape was applied directly on the ulcer, after cleaning the ulcer with plain water and air drying in the field. All patients were taught how to apply the tape and were made to practise in the presence of a doctor. Proper education about care of feet and hands was given to them. Patients were advised not to soak their feet daily since this would reduce the adhesive quality of the tape and necessitate daily changing of the dressing. A sufficient quantity of tape was supplied to the patients for reapplication once the previous tape started coming off. The effect of tape treatment was evaluated every week, until the ulcers healed. Patients were ambulatory for their work during the tape treatment. All the relevant information were recorded on predesigned proforma.

Results

HEALING OF ULCERS WITH ADHESIVE ZINC TAPE TREATMENT

The tape treatment stopped discharge from all four ulcers on the hand and 97% plantar ulcers in $3{\cdot}5 \pm 1{\cdot}6$ and $5{\cdot}1 \pm 4{\cdot}3$ weeks, respectively (Table 1). Likewise, all the hand ulcers, and 82% plantar ulcers healed in $3{\cdot}8 \pm 2{\cdot}1$ and $9{\cdot}5 \pm 7{\cdot}6$ weeks of tape treatment, respectively (Table 2), while patients were ambulatory for their work.

All 14 (18·4%) non-healed plantar ulcers, mostly on bony pressure points (Figure 2), became complicated while on tape treatment; of which 8 ulcers on heels and base of big toes developed sinus.

MATERIAL COST AND OPERATIONAL FEASIBILITY OF TAPE TREATMENT OF ULCERS

The average amount of adhesive zinc tape issued (and utilized), number of tape dressings applied, and estimated cost of tape to heal an ulcer, are given in Table 3.

Table 1. Time taken to stop discharge from plantar ulcers

Time taken (weeks)	Plantar ulcers (%)			
	Small $n=40$	Medium $n=09$	Big $n=16$	Total $n=65$
1–4	67·50	55·55	25·00	55·38
5–8	27·50	22·22	25·00	26·16
9–12	05·00	—	25·00	09·24
13–25	—	11·11	18·75	06·15
Did not stop after 25 wk	—	11·11	06·25	03·08
Total	100·00	99·99	100·00	100·00
Average time (wk) to stop discharge	3·6±2·4	5·7±5·2	8·7±5·5	5·1±4·3

Table 2. Time taken to heal ulcer (%)

Time taken (weeks)	Plantar ulcers				Hand ulcers (all small)	Grand total
	Small $n=62$	Medium $n=09$	Big $n=15$	Total $n=76$	$n=13$	$n=89$
1–4	32·69	11·11	13·33	26·32	69·20	32·58
5–8	30·77	33·33	13·33	27·63	30·80	28·09
9–12	09·62	—	06·67	07·89	—	06·74
13–25	15·38	22·22	33·33	17·73	—	16·86
Not healed even after 25 weeks treatment*	11·54	33·33	33·33	18·42	—	15·73
Total	100·0	100·0	100·0	100·0	100·0	100·0
Average weeks to heal ulcer	8·1±6·6	11·0±9·3	14·8±8·9	9·5±7·6	3·8±2·1	8·5±7·3

* All these 14 recurrent plantar ulcers for an average duration of 1·4±1 year were amongst 13 males (46±7 years age) who walked about 4–5 km/day while working as agricultural labourers/weavers (Figure 2).

Presuming that an ulcer will take the same time to heal with gauze and bandage treatment as with adhesive zinc tape; even then the gauze and bandage treatment at the rate of one dressing (minimum of Rs 1) per day may cost about 40 times more than tape treatment.

The adhesive zinc tape treatment of ulcers was found to be acceptable and convenient to patients and operationally feasible under field conditions. On average it took 4 minutes to completely dress an ulcer with tape, that is about 3 minutes for cleaning the ulcer with plain water and its air drying, and a further 1

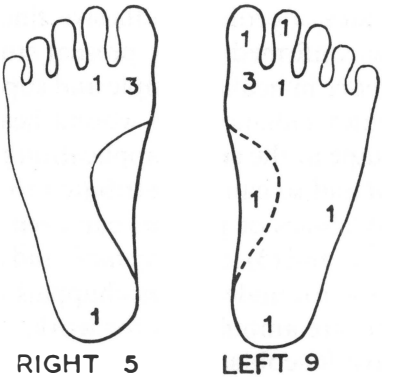

Figure 2. Distribution of ulcers not healed.

Table 3. Adhesive zinc tape issued, dressings applied and cost to heal ulcer

Average		Ulcers			
		Small	Medium	Big	Total
Tape issued (cm)*		196·1 ± 171·6	246·4 ± 277·8	509·4 ± 201·3	200·7 ± 284·3
Tape dressings applied (number)	Total	16·0 ± 18·5	30·0 ± 37·7	45·7 ± 36·3	21·5 ± 25·7
	Per week	2·1 ± 2·6	2·9 ± 3·6	3·7 ± 3·3	2·4 ± 2·9
Tape cost (Rs) to heal ulcer**		1·6 ± 1·4	1·9 ± 2·2	4·1 ± 1·6	1·6 ± 2·3

* More than 95% of issued tape was utilized by patients for dressing their ulcers.

** Cost worked out on market price (1984) of ordinary adhesive leucoplast (tape) at rate of Rs 4/- per roll of 2·5 cm × 5 m.

minute to apply the tape to the ulcer. No local allergic reaction due to tape was noticed.

Discussion

The dressing of ulcers with medicament, gauze and bandage is not only much costlier but also creates obvious problems to medical teams as well as patients.[8] Application of below-knee plaster of Paris also takes about 6–8 weeks to heal an uncomplicated superficial and discharge-free plantar ulcer. Besides the cost and expertise needed to apply the plaster, it makes the patients associate the healing of ulcers with plaster rather than with foot care, thus it is more likely to reulcerate. Moreover, at times POP predisposes the bones for disuse osteoporosis and fractures of bones.[5]

However, the advantages of ordinary adhesive zinc tape treatment of ulcers, as reported earlier,[6, 8] are confirmed by the present study and also that the tape treatment is (1) *quite effective* in healing simple and superficial ulcers, on account of its (a) zinc content which enhances the wound healing process, and (b) the longer stay (sticking) of tape at the site of application prevents ulcer contamination, (2) more *economical* and so can be distributed to all ulcer patients through outpatient mobile leprosy clinics or patients can even purchase the tape from a market whenever necessary, and (3) it is *acceptable* and *convenient* to patients as it can be easily applied and worn under shoes/chappals without any problem and stigma, and while patients are ambulatory for work.

The available adhesive leucoblast may be used in treating uncomplicated superficial ulcers in field and hospital situations, and is better if fixed on thin polythene sheets for easy distribution and application by patients.

In the present study, the non-healing of about 18% of plantar ulcers in spite of 25 weeks of tape treatment (Table 2) could be for a variety of reasons: (1) site of the ulcer was on the constant pressure point (Figure 2), (2) an underlying primary cause of ulcer(s) which needed to be rectified, and (3) carelessness on the part of the patient in the care of his limbs and ulcer; and not necessarily due to failure of tape treatment. Likewise, the regular use of MCR-footwear by the patients with anaesthetic feet could certainly help in reducing the duration of tape treatment to heal, and to prevent the recurrence of plantar ulcer(s).

In conclusion it is necessary to emphasize that there is no better treatment to cure and prevent ulceration and deformities, than continuous health education and motivation of patients for regular treatment and proper care of limbs.

Acknowledgments

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Lepr Rev (1986) **57,** 53–56

Treatment of plantar ulcers in leprosy patients in the community with adhesive zinc tape

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Summary The prevalence of plantar ulcers in 1483 leprosy patients attending village clinics in South India was 4·3%. Patients with 'simple' ulcers, i.e. involving only skin and subcutaneous tissue containing no necrotic bone or fibrous tissue and not obviously infected, were randomly allocated to treatment with zinc oxide impregnated adhesive plaster (zinc tape) or conventional antiseptic soaked gauze dressings. The 2 groups were comparable in age, sex, type of leprosy, the length of time the ulcer had been present and the distance walked each day.

The area of the ulcer was estimated before treatment and after one month. Four ulcers treated with zinc tape healed completely compared with 2 in the control group and mean ulcer area fell from 91·9 ± 11·3 mm² (mean ± SEM) to 42·4 ± 15·5 mm² in the zinc tape group, and from 89·8 ± 13·9 mm² to 56·7 ± 17·4 mm² in the control group.

It is concluded that zinc tape is at least as effective as ordinary dressings in healing ulcers. It is more acceptable to patients than untidy, dirty bandages and so deserves more widespread use.

Introduction

Neuropathic foot ulcers are a significant cause of morbidity in patients suffering from leprosy, and the correct treatment of the ulcers is an important part of patient care. The ulcers arise as a result of loss of sensation over the skin of the foot.

In patients with normal gait, weight is transferred first from the heel then along the lateral border of the foot to the 5th metatarsal, from there across the metatarsal heads to the first metatarsal and thence to the pad of the great toe. Ulcers invariably lie along this line, most occurring over the 1st and 2nd metatarsal heads, and to a lesser extent the heels and part of the great toe.[1]

Ulcers are usually debrided if necessary and treated with antiseptics then

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covered with thick gauze pads, and the foot extensively bandaged. Ulcers less than 2 cm in diameter treated in this way will heal in approximately 30 days[2] under hospital supervision. The white bandages are unsightly and quickly become filthy. The antiseptic soaks through staining the bandages yellow and inevitably with continued use they become ragged and malodourous.

The use of below-knee (BK) plaster of Paris results in rapid healing (3–4 weeks) and has been used for many years[3] although these are again unsightly, inconvenient and generally disliked by patients. More recently the smaller, cheaper plaster shoe has proved an effective alternative to the BK plaster[4, 5] and since the ankle is not immobilized may cause less problems with disuse osteoporosis. Plaster shoes are also more acceptable to patients. Once healed the recurrence of the ulcer may be prevented by regular foot care and the wearing of footwear with microcellular rubber soles.[6]

Direct application of zinc oxide impregnated adhesive plaster (zinc tape) first suggested by Dr Stenstrom in 1976 has proved successful in healing ulcers in hospital patients and may heal them more quickly than gauze dressings.[2] The tape acts as an occlusive dressing and small amounts of zinc diffuse into the granulation tissue raising serum zinc levels.[7] Zinc deficiency is common in leprosy patients,[8] and leads to slow healing. Zinc supplements are advocated for zinc deficient patients with leg ulcers,[9] and local application seems a convenient way of raising tissue concentrations while avoiding systemic side effects. The tape has the advantage over bandages of being undetectable to the casual observer.

The results of a randomized controlled trial of zinc tape in the treatment of plantar ulcers under field conditions are presented.

Patients and methods

Patients were selected from those attending peripatetic village clinics, based around the Schieffelin Leprosy Research and Training Centre, Karigiri, South India. The area is predominantly rural, patients spending many hours of the day working in the fields and sugar plantations.

Each village in the area is visited once a month by the clinic. All patients attending the clinics in a two-week period were screened for plantar ulcers and from these those with 'simple' plantar ulcers were selected. Simple ulcers were defined as those involving only skin and subcutaneous tissue, not infected, and containing no necrotic bone or fibrous tissue. Consecutive cases were randomly allocated to zinc tape or control groups. All ulcers in the study were cleaned with an antiseptic solution of cetrimide followed by ethanol which ensures thorough drying, necessary for adhesion of the plaster. Routine debridement of the edges was carried out, and the ulcers probed if necessary, to ensure that there were no deep sinuses.

Ulcers in the control group were dressed with gauze soaked in MGSA (a paste of magnesium sulphate and glycerin with proflavin and benzalkonium choride).

The foot was bandaged with plain linen bandages. To the ulcers in the zinc tape group 2 cm wide strips were applied covering the ulcer and approximately 2 cm of healthy skin around it.

In each case the patient was supplied with sufficient materials to change the dressing once, before the clinic was visited again the next month. Each patient was supplied with sandals made with micro-cellular rubber soles, with an individually tailored arch support. The size of the ulcer was measured before and after one month of treatment. The response was assessed by a change in area.

Demographic data were collected together with information about the wearing of shoes, duration and position of the ulcer, the type of leprosy (lepromatous or non-lepromatous) and the estimated distance walked each day.

Results

Of the 2328 patients due to attend 12 clinics in the two-week study period for routine prescription of drugs and assessment of response to treatment, 1483 (63%) actually attended: of these, 63 (4·3%) had plantar ulcers and 43 of these fulfilled the criteria for simple plantar ulcers.

The distribution of the ulcers over the foot (Table 1) was in accordance with that found by other workers,[2] being predominantly over the 1st and 2nd metatarsal heads. One patient developed an ulcer over the cuboid bone. Some patients were seen with ulcers over the lateral malleolus caused by sitting cross-legged. These were not entered into the study.

Random allocation resulted in 22 ulcers in the new treatment group and 21 in the control group. Fourteen patients from each group returned to the clinic after one month (65%).

Four ulcers treated with zinc tape healed completely compared to 2 in the control group. The mean ulcer area in the control group was $89{\cdot}9 \pm 13{\cdot}9$ mm^2 (mean $\pm$ SEM) this fell to $56{\cdot}7 \pm 17{\cdot}4$ mm^2 after one month of treatment. In the zinc tape group the mean ulcer area fell from $91{\cdot}9 \pm 11{\cdot}3$ mm^2 to $42{\cdot}4 \pm 15{\cdot}5$ mm^2 after one month.

Table 1

Site of ulcer	Number of ulcers found at that site
Pad of great toe	4
1st metatarsal head	8
2nd metatarsal head	6
3rd metatarsal head	2
4th metatarsal head	2
5th metatarsal head	3
Cuboid	1
Calcaneum	2

The difference between the means is 14·3 mm^2. Because of the wide variance of the sample the difference in favour of zinc tape is not significant (Students t = test: $t = 0{\cdot}83$ $P = 0{\cdot}4$).

The 2 groups were comparable in terms of distance walked each day, duration of the ulcer, sex and classification of leprosy. The zinc tape group was rather younger (mean $41{\cdot}9 \pm 16{\cdot}8$ years) than the control group (mean $50 \pm 8{\cdot}2$ years) but this difference is not significant ($t = 1{\cdot}63$ $P = 0{\cdot}2$).

Discussion

The results show a prevalence of plantar ulcers among leprosy patients of 4·3%, which indicates the magnitude of the problem. Even if the disease is successfully treated, nerve damage may be permanent in many cases. A simple, quick and cheap method of treating plantar ulcers is needed; zinc oxide adhesive tape may well fulfil these criteria. It has the advantage over bandaging in that it is invisible with the patient's foot inside the sandal, and is therefore less stigmatizing. Zinc tape may also be more effective than conventional dressing, although the advantage shown in this small study did not reach statistical significance.

Acknowledgments

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Dapsone syndrome occurring in two brothers

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Summary Two cases of dapsone syndrome occurring in brothers under treatment for multibacillary leprosy in Papua New Guinea are described. Both patients had rash, fever and jaundice, together with signs suggestive of chest infection. One patient died after developing a haemorrhagic diathesis, but the other improved rapidly after therapy with corticosteroids was commenced. Previous case reports of dapsone syndrome are reviewed.

Introduction

Dapsone (diamino-diphenyl sulphone) was first synthesized in 1908, but its antibacterial properties remained undiscovered until 1937.[1] Since the early 1940s it has been used in the treatment of a very wide variety of conditions,[2–4] but its chief importance has been in the treatment of leprosy. In 1949, it was reported that dapsone therapy precipitated an infectious-mononucleosis-like syndrome in 12% of a series of 305 Nigerian leprosy patients within 2–5 weeks of commencement of the drug.[5] A further 3 cases of 'dapsone syndrome'[6] were described in 1951,[7] but it should be noted that very large doses of dapsone were being prescribed in those early years, in the region of 300 mg/day. The fact that few additional cases have been reported since then, despite the millions of leprosy sufferers receiving the drug, is probably related to the lower dosages used, and justifies the conclusion that the syndrome is a rare complication of dapsone therapy. I describe the occurrence of this syndrome in two brothers prescribed dapsone for the treatment of leprosy.

Case 1

A 20-year-old Melanesian man was referred to Port Moresby General Hospital, Papua New Guinea, from a rural health centre in August 1983 with a suspected

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dapsone reaction. Dapsone 100 mg/day plus clofazimine 100 mg/day had been commenced for multibacillary leprosy approximately 6 weeks previously, but the dapsone had been stopped 2 days prior to admission after he had developed a rash.

On admission, on 18 August, he was a well-built young man who had a morbilliform rash over the trunk and limbs, and looked unwell. He had a fever, his sclera were jaundiced, and there was tender hepatomegaly but no splenomegaly. His lips were cracked and dry, but there was no evidence of submucosal or subcutaneous haemorrhage. He had a dry cough.

Investigations showed serum bilirubin (SBR) 96 μmol/l, (normal <17) with direct bilirubin 63 μmol/l, SGOT 83 and SGPT 100 (normal for both <40IU/l), serum creatinine 141 μmol/l (normal <125 μmol/l) and blood urea 5·5 mmol/l (normal 3–8 mmol/l). A chest X-ray was normal, and a blood culture grew a micrococcus regarded as a contaminant. A working diagnosis of severe dapsone reaction was made and all drugs were stopped.

Repeat biochemistry one week later showed normal serum electrolyte levels with urea 14·8 mmol/l, creatinine 159 μmol/l, SBR 180 μmol/l (direct bilirubin 154) and SGPT 170 IU/l. Haematological findings were Hb 109 g/l, total WCC $5{\cdot}3 \times 10^9$/l (N 64%, L 25%, E 1%, M 10%) and normal platelets.

Over the next 2 weeks fever and chest signs prompted treatment with intravenous ampicillin and an orciprenaline inhaler, and his general condition improved. Reassessment on 13 September (day 26) showed Hb 107 g/l, WCC $6{\cdot}5 \times 10^9$/l (N 66, L 29, E 4, M 1) and normal platelets; urea 6·0 mmol/l, creatinine 97 μmol/l, SBR 70 μmol/l, SGOT 170, alkaline phosphatase 160 (normal <100 IU/l).

Six days later he complained of nose bleeds, mouth ulcers and joint pains. Examination showed a temperature of 36·5°C, signs of shock, and a respiratory rate of 40. The sclera were still jaundiced, there was frank epistaxis, plus mouth ulcers and cracks in the skin of both elbows. Haemoglobin was now 92 g/l, WCC $13{\cdot}3 \times 10^9$/l (N 73, L 16, E 1, M 10) and platelets were 'markedly decreased'. The picture was thought to represent septicaemic shock secondary to chest infection. Blood pressure rose to 110/70 mmHg after a rapid infusion of Haemaccel. Supplemental oxygen was given. Ampicillin was continued, and gentamicin commenced. Supportive care included Gastrogel tablets, thymol mouth washes and nystatin drops, and antiseptic cream and lotion to the skin cracks.

Blood pressure fell overnight to 70/50 mmHg but again responded to a rapid infusion of fluid. The next day epistaxis continued and was now accompanied by frank haemoptysis. The respiratory rate had fallen to 22, Hb to 63 g/l, with WCC $15{\cdot}0 \times 10^9$/l (N 80) and platelets $10{\cdot}0 \times 10^9$/l. Biochemistry showed Na^+ 128 mEq/l, urea 18·5 mmol/l, creatinine 97 μmol/l, SBR 185 μmol/l, SGOT 215, alkaline phosphatase 174. He was transfused with 2 units of packed red cells, but his general condition remained unchanged.

The following day (day 34) he was transfused with 2 units of fresh frozen

plasma, and ampicillin was discontinued in favour of intravenous crystalline penicillin, as the respiratory rate had risen to 44, and it was felt that the picture was one of a life-threatening pneumonia, possibly pneumococcal. Blood culture, reported later, grew a bacillus species, regarded as a contaminant. That evening, he was observed to be restless, and again found to be shocked. He then had a respiratory arrest and could not be resuscitated.

Case 2

Some 4 months later, in January 1984, the brother of Case 1 was referred from the same health centre with a suspected dapsone reaction. Dapsone and clofazimine (100 mg/day of each) had been started on 13 December 1983 for the treatment of leprosy lesions which had been present for 18 months. He had developed a rash on the 8 January, 5 days prior to admission.

On admission, he was a well-built, 20-year-old man with an erythematous maculopapular rash involving the trunk, face and limbs, together with a red nodular lesion, 4 cm in diameter, in the left prepatellar area, and a further 10 cm 'island' lesion with satellite nodules on the upper lateral thigh. There were large hypopigmented, non-anaesthetic macules on the right upper arm and posterior aspect of the left thigh. He was not jaundiced, the oral mucosa was normal, and there was lymphadenopathy in the neck and axillae. There was no weakness, but an early left ulnar claw was present, and there was anaesthesia to light touch in the left ulnar fingers, left lateral leg, and medial right foot. He gave a one-week history of epigastric discomfort made worse by food and relieved by defaecation. There was no history of cough, haemoptysis or haematemesis, no fever, and the chest and abdomen were normal on examination. A diagnosis of borderline (BB) leprosy with drug reaction was made, and all drugs were stopped. Investigations included skin smear (Bacteriological Index 4·0, Morphological Index 12% in one of the lesions), and routine laboratory tests—Hb 124 g/l, WCC $10{\cdot}0 \times 10^9$/l (N 72, L 16, E 4, M 8), alkaline phosphatase 126, SGOT 66; SBR, urea, creatinine and serum electrolytes were not estimated.

By day 3 the rash was fading, revealing large hypopigmented macules over the whole trunk. He developed a fever, and examination showed slight jaundice, 3 cm tender hepatomegaly, lymphadenopathy as previously noted, but no splenomegaly.

On day 6 the temperature had risen to 39°C, he had two episodes of vomiting and diarrhoea, and still complained of epigastric pain. The rash appeared worse, probably due to erythema associated with the fever, but the physical findings were unchanged. Investigations showed Hb 121 g/l, WCC $16{\cdot}0 \times 10^9$/l (N 35, L 28, E 24, M 2, Band cells 6, and atypical lymphocytes 5, with increased toxic changes in the neutrophils relative to those present at admission). Blood culture and hepatitis B screen were negative.

The next day the rash was unchanged, fever persisted, and he had developed a moist cough. Examination showed him to be frankly jaundiced, with 7–8 cm tender hepatomegaly, no splenomegaly and lymphadenopathy unchanged. Breath sounds were equal but bronchial with fine expiratory rhonchi in all zones. A chest X-ray was normal. His parents were requesting that he be allowed weekend leave to consult a traditional healer, but they were persuaded that he should remain in hospital. Prednisolone 40 mg/day was commenced.

Two days later (day 9) he was afebrile and feeling and looking better. The rash was beginning to resolve, as was the lymphadenopathy, but he still had a moist cough. There was 6-cm hepatomegaly, but it was only slightly tender. The breath sounds were no longer bronchial, although scattered fine rhonchi were still heard. SBR was 233 μmol/l (direct bilirubin 168), SGOT 300, alkaline phosphatase 62.

Over the next week he improved steadily. The chest became normal to clinical examination, the jaundice faded, and the lymphadenopathy and hepatomegaly gradually resolved. The rash faded completely, but desquamation began on day 11.

The prednisolone dose was reduced to 30 mg/day over the next 2 weeks and he was discharged on day 35. He was then seen weekly in out-patients and remained well, on a reducing dose of steroid. On 7 March (day 53), Hb was 130 g/l, WCC $8{\cdot}1 \times 10^9$/l with 6% monocytes and 1% atypical lymphocytes still present. Liver function tests were normal.

Comment

Although it was not possible to carry out a full screen for infectious, particularly viral, diseases, these 2 cases are typical of the 'dapsone syndrome'.[6] Each patient was taking clofazimine at the time his illness began, but this clinical picture has not been described as a complication of therapy with that drug, and the second case later resumed taking clofazimine regularly, without adverse effect.

A morbilliform rash developing approximately 5 weeks after the inception of dapsone therapy is such a common complication as to be known as 'dapsone dermatitis',[8] but the full 'dapsone syndrome' appears to have a much lower incidence.[3, 9–11] Indeed, although one study[12] has reported the development of a typical rash in 4·6% of a series of 108 new cases of leprosy treated with dapsone in Port Moresby, only 20 cases of the 'dapsone syndrome' appear to have been reported in the literature[2, 4, 6, 7, 9, 10, 13–16] in the 35 years following the original description.[5] Those authors ascribed the condition to the exacerbation of an existing but sub-clinical infection with infectious mononucleosis, on the basis of persisting lymphocytosis and high Paul-Bunnell titres. Indeed, in view of the rarity of subsequent case reports, the high incidence originally reported[5] might suggest an infectious illness. Later reports consider that the syndrome is due to an idiosyncratic hypersensitivity reaction to dapsone.[1, 4, 6, 9]

Eight of the 20 patients reported since 1949 received dapsone for conditions other than leprosy, and, including the 2 present cases, only 36% developed the complete clinical complex of rash, fever, jaundice and lymphadenopathy, which is in keeping with the observation of one study[16] that the full syndrome is rare. Where it occurred, fever was generally high and lasted for one week or more. Characteristically the jaundice and hepatomegaly took even longer to resolve. Steroids were given in 7 cases, but were associated with a rapid resolution of fever in only 3 of these.

The first case reported here is only the fourth death from the 'dapsone syndrome' recorded, but an overall case fatality rate of 19% is not inconsiderable, even though there may be a tendency for more serious cases to be reported. Two of the fatal cases had falling platelet counts accompanied by pulmonary haemorrhage in the terminal phases. In one reported case[10], the platelet count fell 'without evidence of disseminated intravascular coagulation', but the appropriate laboratory tests to rule out disseminated intravascular coagulation were not performed in the first of the present cases.

The occurrence of the syndrome in siblings has not previously been reported but, in view of the apparent rarity of the condition, supports the suggestion[15] that it occurs in individuals with a genetic predisposition.

Acknowledgments

Professor I Riley kindly drew my attention to several of the references, and he, Professor S Naraqi and Dr A Saweri were the consultants involved in the management of the 2 cases. Drs J Schneider and J Potter provided comments on the manuscript.

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Lepr Rev (1986) **57,** 63–66

Fatal dapsone agranulocytosis in a Melanesian

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Summary The death from agranulocytosis and septicaemia of a young Melanesian male receiving unsupervised treatment with 100 mg daily of dapsone for indeterminate leprosy is reported. The historical recognition and clinical management of agranulocytosis resulting from dapsone is discussed. Careful observation of leprosy patients for side-effects during the initial weeks of treatment is recommended. This may include hospital admission and regular blood counts when possible.

Introduction

Sulphones were first noted to be effective for leprosy in rats in 1941.[1] Clinical trials in humans followed soon after; however, it was not until 1958 that it was clearly recognized that agranulocytosis can result from the use of dapsone.[2] A patient was described who recovered from agranulocytosis which had occurred after the administration of 125 mg of dapsone daily for dermatitis herpetiformis. In 1970, a more alarming report was published[3] concerning 16 US soldiers in Vietnam who developed agranulocytosis after receiving 25 mg of dapsone daily as malaria prophylaxis for periods of from 3 weeks to 3 months; 8 died. At least 4 of the fatal cases had septicaemia with positive blood cultures for pseudomonas. Two had received kanamycin before their death. A further case of agranulocytosis was reported in an Australian soldier in Vietnam in 1970; he had also been taking 25 mg of dapsone daily for 4 months. This patient developed an infection in a bayonet wound caused by pseudomonas and also had pseudomonas septicaemia. He recovered following treatment with colistin. At the time these cases occurred, dapsone was being given routinely as an anti-malarial to many thousands of servicemen in Vietnam. This practice was stopped when the risks of agranulocy-

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tosis from dapsone became apparent. However, more recently agranulocytosis has been reported as a complication of weekly Malaprim (100 mg dapsone, 12·5 pyrimethamine) prophylaxis.[5]

This paper reports the death of a young Melanesian male from agranulocytosis. A clinical diagnosis of leprosy had been made at a heath centre. The patient was then immediately discharged home and took a course of dapsone without supervision.

Case history

A 23-year-old man was seen at a rural health centre with skin lesions. The diagnosis of leprosy was considered. A skin smear was negative. A biopsy was later reported to be suggestive of indeterminate leprosy. He was started on dapsone, 100 mg daily. Because he wanted to go off and build a boat, the health centre staff released him to take treatment on his own. During the treatment he noted headache, body aches, jaundice, fever and dark urine. He presented himself to Alotau Hospital 48 days after starting treatment.

FINDINGS

On admission, he had a temperature of 38[4], a pulse of 26, and his blood pressure was 100/60. A few crepitations were noted in the left chest, together with hepatosplenomegaly and tender left inguinal lymph nodes. Possible diagnoses considered by the admitting doctors were leprosy reaction, malaria, hepatitis and bacteraemia. The patient was given procaine penicillin and chloroquine. Laboratory tests were ordered. The patient deteriorated rapidly and at 17 h after admission the pulse was 100 and respirations 44. He was then given intravenous fluids, crystalline penicillin, and chloramphenicol. He began complaining of chest pain, and coughed up green liquid sputum, became increasingly tachypnoeic and hypotensive, and had green liquid diarrhoea. He died 26 h after admission.

Results of blood tests taken before death were reviewed the following day. Haemoglobin was 11 g/100 ml, white cell count 700/mm.[3] The blood smear showed many fragmented red cells and schistocytes, with very few neutrophils. The bilirubin was 1·8 mg%. A wet stool preparation showed pus cells and erythrocytes, but no amoebae. A blood smear for malaria was negative. Due to the uncertain cause of sudden death, the coroner was notified, and a post-mortem was ordered. Bilateral pneumonia with consolidation was found.

A microscopic examination of the liver showed only oedema and increased bilirubin pigment. There was no hepatitis. The spleen was reported as normal. Cultures taken from the lung at autopsy grew *Pseudomonas aeruginosa*, resistant to all antibiotics except gentamicin and carbenacillin.

Discussion

This patient died of a pseudomonas pneumonia which arose in the presence of severe agranulocytosis; septicaemia was also likely. The agranulocytosis was presumably a toxic effect of the dapsone therapy, which had been unsupervised. It is unknown whether the patient was taking the prescribed dosage of dapsone. It is possible that he was taking a greater dose than recommended, hoping to improve more rapidly. Although he felt unwell during the treatment, he did not report to the health staff until the day prior to his death.

Although agranulocytosis resulting from dapsone treatment is probably relatively rare, it would seem wise to keep new leprosy patients under close observation after initiating treatment, since other reactions to dapsone, as well as leprosy reactions, commonly occur in the first weeks to months of taking the drug. Because treatment of leprosy is sometimes toxic and can be lengthy, I also believe it is wise to take a skin biopsy when new patients are first seen to confirm the diagnosis and type of leprosy. This information will be useful to sceptical health workers later in treatment, when obvious signs of the type of leprosy involved may no longer be visible. Other side-effects attributed to dapsone commonly include haemolytic anaemia, and only rarely methaemoglobinaemia, various skin disorders, hepatotoxicity, acute psychosis, and headache. I therefore monitor haemoglobin or haematocrit levels and white cell counts weekly in leprosy patients during the first couple of months of therapy.

Early symptoms of agranulocytosis include abrupt onset of sore throat, fever, chills, malaise, fatigue and weakness. Inflammation of the throat is said to soon progress to necrosis, with formation of a membrane and subsequent ulceration. Diagnostic criteria for drug-induced agranulocytosis include a neutrophil concentration of less than $0{\cdot}2 \times 10^9$/l, and recovery in the 14 days after withdrawal of the drug.[6] If a patient does develop agranulocytosis, death, if it occurs, is due to infection, particularly with pneumonia and/or septicaemia. In managing a patient with this disorder, cultures of blood, sputum and any wounds should be taken if possible. In view of the common occurrence of pseudomonas infections, prophylactic administration of an aminoglycoside antibiotic, such as gentamicin, is advisable. Other organisms which cause sepsis in such patients include *E. coli*, *Proteus* and *Staphylococcus aureus*. Initial treatment with a broad spectrum penicillin or cephalosporin, probenecid and perhaps metronidazole is also recommended until results of cultures are known. Isolation of the patient is important,[6] and treatment of shock with fluids, and good oral hygiene are also advised.[7]

Agranulocytosis has been reported to have a mortality of about 20% or more. De Gruchy commented that this is a disturbingly high mortality, when one considers that agranulocytosis is self-limiting following withdrawal of the causative drug. Leukaemoid reactions are seen occasionally during the recovery phase.[8]

Finally, although chronic mycobacterial diseases such as leprosy and tuberculosis can often be managed successfully by non-specialists in rural hospitals and health centres, various complications do arise relatively frequently during the initial phase of treatment. It is therefore probably wise to admit such patients to hospital or a health centre during the first few weeks of treatment, if space is available. This is particularly important if the patient is unreliable or comes from a remote village. Regular observation is essential. If patients deteriorate during treatment, temporary cessation of all therapy is advisable, until drug toxicity and other reactions have been carefully excluded. Such careful and cautious management could, I believe, prevent many of the numerous deaths and complications which do occur during treatment of leprosy and tuberculosis.

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Lepr Rev (1986) **57,** 67–69

Obituary

DR ROBERT GREENHILL COCHRANE
CMG, MD, FRCP, DTM & H
1899–1985

With the passing of Dr Cochrane, the doyen of British leprologists, we come to the end of an era. He did more than anyone of his generation to 'put leprosy on the map' and to advocate that the disease should be studied scientifically. He was the first to use dapsone in the treatment of patients suffering from leprosy, and was senior author of a book that was for several years the standard text on leprosy. He had many associations with BELRA (now LEPRA), but he was bigger than any one organization—he was a world figure.

Robert Cochrane ('Bob' to his friends) was born on 11 August 1899 of missionary parents in China. When but a few months old, his life almost came to an untimely end, for the whole family was captured by the Boxers, and narrowly escaped. Nothing daunted, they returned to China after leave in Britain. His father, Dr Thomas Cochrane had visions of founding a Christian Hospital and Medical School. With money from the Chinese reparations to the Great Powers and a personal gift from the Empress Dowager herself, he embarked upon the creation of the prestigious Union Medical College in Peking.

The young Cochrane received his early education from his mother, but when he was 9 he entered the School for the Sons of Missionaries in Blackheath, later in Eltham, where he was awarded his Rugger colours and founded a Christian Union. He graduated in Medicine from Glasgow University in 1924, and took the Conjoint Diplomas and the London DTM & H. The same year, he sailed for India under the auspices of the Mission to Lepers (now the Leprosy Mission), and, after sitting at the feet of the renowned Dr Ernest Muir in Calcutta for 3 months, he was appointed to Purulia and then Bankura in West Bengal. During this time, he began his world travels, in the course of which he met several outstanding leprologists in the Far East.

He severed his connection with the Mission in 1927, the year he was admitted to MRCP. The next year, he submitted a thesis on leprosy to his old University, for which he was awarded its MD. In 1929 his long association with BELRA began, when he became its first Medical and General Secretary. This young organization (founded in 1925) needed a person of Dr Cochrane's drive and professional standing in those early critical days. In this capacity he resumed his journeys abroad, visiting the West Indies and several countries in Africa. He was invited to Manila in 1931 to a meeting of persons interested in leprosy called by the Leonard Wood Memorial Foundation. It was here that the International Leprosy Association was founded. Dr Cochrane became its first Secretary-Treasurer.

In all these travels and contacts, including a short spell in India in 1932, he was building up his acquaintance with leprosy as a world problem, but he felt that he ought to resume clinical work to supplement his growing knowledge. He therefore (in 1935) applied for appointment, successfully, as Chief Medical Officer of the Chingleput Leprosy Sanatorium (known then under the name of Lady Willingdon), and while there was asked to become Director of the Leprosy Campaign for the whole of Madras State. He continued to discharge these functions when, in 1942, he began his long association with the Bellore Christian Medical College and Hospital. For 3 years (1948–51), he was

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back at Chingleput again, before he left India, having been awarded the Kaiser-i-Hind Medal in Gold, First Class, for his outstanding public services.

For the next 3 years, he resumed his connection with BELRA, as its Medical Secretary, but he had other irons in the fire. He founded the Leprosy Research Fund in 1951, which was renamed the Leprosy Study Centre in 1965—a teaching, co-ordinating and histopathological reference Centre. Part of the funds necessary for this initiative came from Dr Cochrane's appointment as Technical Leprosy Adviser to the American Leprosy Missions Inc, and part from the Wellcome Trust. Based in London, Dr Cochrane was being called upon increasingly by governments and missions to advise on their leprosy programmes and to conduct seminars. He was a most stimulating—not to say provocative—lecturer. He kept himself up to date, and encouraged clinicians and others to interest themselves in the disease that he himself found so fascinating. It was he who saw the possibilities of a rimino-phenazine derivative known under its code number of B 663, and prevailed upon me to conduct clinical trials in Nigeria. Now known as Lamprene (or clofazimine), this drug is generally recognized as an excellent anti-leprotic, with anti-inflammatory activity.

Dr Cochrane was unashamedly a Christian. It was his faith that motivated him and inspired him in his varied and long life. It kept him going during the years when he was campaigning for the inclusion of leprosy in medical curricula, and for the abolition of the stigmatizing epithet 'leper'. Some people might have felt that at times he was a little too aggressive and self-opinionated, but they forgave him because of his undoubted qualities and his pertinacity.

His memory is perpetuated in the 'Robert Cochrane fund for Leprosy', which is administered by the Royal Society of Tropical Medicine and Hygiene, and in the incomparable collection of some 16,000 series of stained histopathological sections housed in the Hospital for Tropical Diseases in London.

Dr Cochrane leaves, to mourn his loss, a widow (his second wife), and 3 children from his first marriage.

Many people in many lands will honour the memory of a great and a good man.

STANLEY G BROWNE

The following is reprinted from *The Times*, 6 August 1985.

Dr Robert Cochrane, one of the world's leading leprologists, who played a noteworthy part in the introduction of modern sulphone therapy died on August 3 at the age of 85.

Robert Greenhill Cochrane, son of Dr Thomas Cochrane, the famous missionary founder of the Union Medical College, Peking, was born in North China on August 11, 1899. He was educated at the School for the Sons of Missionaries (now Eltham College) Blackheath and did his medical training at Glasgow University and St Bartholomew's Hospital, London. He had already decided to devote his life to leprosy and, in the mid-1920's under the auspices of the Mission to Lepers, sailed for India to work at Purulia in Bihar after a period of special training in Calcutta. He rapidly earned a high reputation as a worker in the field of leprosy.

In 1929 Cochrane was appointed general and medical secretary of the British Empire Leprosy Relief Association (BELRA), but in 1933 he returned to India and began his great work as chief medical officer of the Lady Willingdon Leprosy Sanatorium at Chingleput, Madras, which soon attracted the best leprosy research workers in India, and which was chosen, after independence, to become the All India Institute of Leprosy Research and Training.

In 1944 he was appointed director and principal of the Christian Medical College at Vellore. He converted the institution from a women's college to a co-educational one and played a leading role in making it the outstanding medical college in India.

In 1948 Cochrane returned to England and rejoined the service of BELRA for a period before leaving to become technical medical adviser to American Leprosy Missions Inc working from London. With help from the Wellcome Medical Foundation Cochrane founded the Leprosy

Research Fund and financed the leprosy centre in Wimpole Street to aid leprosy research and training. From 1961 to 1965 Cochrane was adviser on leprosy to the Ministry of Health and consultant leprologist to the Tropical Diseases Hospital. In 1966 he returned again to India to work in Madras State. Then in 1968 he transferred his activities to Tanzania under the Africa Inland Mission.

Cochrane performed notable service in getting leprosy recognised as a "respectable" disease worthy of integration into general medicine, in pioneering early diagnosis, and in introducing sulphone into treatment. He also helped persuade surgeons to take an interest in the prevention and correction of deformities. The textbooks which he wrote became standard works on the subject.

A sincere practising christian, Cochrane was equally at home in the pulpit and at the bedside.

From his first marriage in 1927 to Ivy Nunn he had three children, two of whom have served in the mission field. After the death of his first wife in 1966 he married in 1968 Dr Martha Jeane Shaw, a missionary in Tanzania, who survives him. While at the Vellore Medical college, Cochrane was awarded the Kaisar-i-Hind medal, first class in gold, for public service in India. In 1969 he was appointed CMG.

DR STANLEY GEORGE BROWNE CMG, OBE

It is with the greatest of regret that we announce the death of Dr Stanley Browne on 29 January 1986. A full obituary will be published in the June issue of this Journal.

Editor

Lepr Rev (1986) **57,** 70–79

Letters to the Editor

OILY INJECTIONS OF DAPSONE; AN ACCEPTABLE FORM OF TREATMENT?

Sir,

Oily injections of DDS, comprising a 25% suspension of DDS in ethylchaulmograte, were in the sixties prepared by Roussel Laboratories, Paris. Many leprosy-endemic countries still have a stock of this preparation, which was provided by UNICEF, and is therefore usually called UNICEF injections.

At the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Addis Ababa, UNICEF injections have been used from the early seventies for over a hundred patients who did not respond satisfactorily to oral DDS therapy and were therefore either not taking the prescribed therapy or harbouring DDS resistant *M. leprae*. The injections were given once weekly intramuscularly in a dosage of 1·5 ml containing 375 mg DDS. The patients attended regularly and asked for a supply of tablets in case they had to travel for longer than a week. Patients who responded to DDS injections and became clinically inactive were advised to continue tablets but, almost without exception, preferred to have the injections.

These injections thus appeared a convenient way of administering DDS supervised, without occupying hospital beds. Our only worry was whether or not the dosage given was sufficient, for in some countries 1·5 ml was administered twice weekly.

We therefore welcomed the opportunity in 1981 of a collaborative study with the Biopharmaceutical Department of the University of Amsterdam. One of the projects was a study[1] of serum levels in 20 patients on UNICEF injections. The serum level curves were found to be very regular over the week and were about equivalent to that found in patients taking 1 mg dapsone orally per kilogramme bodyweight, which is acceptable. At that time, 8 patients were also questioned about possible unwanted effects of the injections and, to our surprise, 6 patients considered them painful. Other complaints were swelling at the injection site and difficulty in walking or sleeping for some days after the injections.

This unexpected finding prompted us to plan an interview of all patients on UNICEF injections, with a view to assessing side-effects and acceptability. A nurse of Ethiopian nationality, assisting in the clinic held for assessment of suspected dapsone-resistant patients, and therefore known to the patients on DDS injections, was instructed on the general purpose of the study and on the questions to be asked. The patients were first asked whether or not they liked the injections and then whether they had complaints which they thought were related to the injections. We were also interested in the opinion of the patient on the status of his disease and his desire or willingness to discontinue the injections and to change to either DDS tablets or other antileprosy treatment.

Of the 70 patients treated with injections, 67 were interviewed, of whom 35 were male patients. All except 1 were started on injections to exclude non-compliance with the DDS tablets as the cause for their relapse or unsatisfactory clinical improvement. Most of the patients were classified lepromatous (BL or LL); 4 patients had borderline tuberculoid (BT) leprosy and 1 patient, who initially had been lepromatous, presented with a BT relapse. The mean age of the females was 34·5 years and of the males 38·6 years. The duration of DDS injections in females was found on the average to be 2 years longer; 4·6 years against 2·3 years in the men. Three women were on injections

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for more than 10 years. Ten female and 12 male patients were on injections for less than 1 year but all patients had injections for a minimum of 2 months.

Six (9%) of the 67 interviewed patients did not like the injections. Particulars of these patients are presented in Table 1.

The 5 patients who preferred to discontinue DDS injections had a good reason for it, except patient 4: they were not satisfied with the effect of the therapy or had serious complaints which they attributed to the injections.

The remaining 61 patients considered their disease to have improved, except 2: 1 patient took the injections irregularly and was clinically active and the second was a BT patient who experienced a reversal reaction. All 61 patients preferred, without exception, to continue on weekly injections. In spite of this positive attitude to injections, quite a number of these 61 patients experienced unwanted effects: 9 patients considered the injections to be painful, the pain usually lasting for some days. Four patients experienced a local swelling and 6 patients experienced both pain and swelling. One patient reported local swelling with difficulty in walking.

Of the 67 patients that were interviewed, a total of 39% had complaints and there was, in this respect, no difference between males and females. However, complaints were reported in a relatively higher proportion of the patients treated for a relatively short time: 58% and 50% in the female and male patients respectively, treated for a maximum of 1 year.

This study indicated that an alarmingly high proportion of patients treated at ALERT with weekly oily DDS injections of the above composition experienced adverse effects which they attribute to the injections. However in some cases the relation between the injection and their complaints was very doubtful, e.g. pain on the third day after the injection, a hungry feeling for 7 days. But in most cases the complaints were almost certainly caused by the injections, e.g. pain and/or swelling at the site of injection for varying periods of time but in some cases as long as 7 days.

Table 1. Particulars of patients who disliked DDS injections

	Sex	Age	Duration of injections	Complaint related to injection	Opinion on disease status	Therapy preferred
1	M	34	1 year	Pain (at injection site)	Worse, due to rheumatic pains	Other drugs
2	M	45	9 months	Hungry, dry skin and weakness for a week	No change	DDS tablets
3	F	21	1 year	Local pain and swelling for a week	No change	DDS tablets
4	F	30	6 months	Pain for a few minutes	Improved	DDS tablets
5	F	13	8 months	Local pain, shivery for a week	No change	DDS injections
6	M	60	2 years	Local pain and difficulty in walking	Numbness in limbs	DDS tablets

Gluteal abscesses were not seen in this group and over 7 years, I remember only 1 abscess due to DDS injections.

At the time of the interview, the WHO recommended form of multiple drug therapy (MDT) had already been introduced at ALERT and our patients in this study must have heard about the new leprosy therapy. Nevertheless, 93% of the group preferred to continue on DDS injections and proved to be, at a later stage, very difficult to convince of the merits of the new therapy. The alleged seriousness of the unwanted effects of the injections in about 40% of the patients, has to be balanced against the fact that over 90% of them preferred to continue injections, even when they were offered a potent alternative therapy. It should be noted that in general Ethiopians seem to be less obsessed by the supposedly beneficial effects of injectable drugs, as is the case in many African countries where any form of oral therapy is considered inferior. Of the 6 patients who expressed their dislike of the injections, 4 were possibly more dissatisfied with their clinical condition, than with the inconvenience of the injections.

Under the circumstances described for this group of patients in Addis Ababa, it seems that weekly oily DDS injections are an acceptable form of DDS therapy, especially for cases where supervised DDS therapy is indicated. Intramuscular dapsone has been used for many years in Venezuela for all lepromatous and Mitsuda-negative indeterminate cases[2] and it was used in Malaysia by the British Medical Research Council group in their early controlled clinical drug trials and studies on dapsone resistance.[3–5] It was also used quite extensively (as a 25% suspension of dapsone in chaulmoograte d'ethyle in the 1950s and 1960s in several French-speaking countries of Africa (Dr Arthur Cap, personal communication). Published reports give the impression that few problems have arisen but it would be of interest to have more specific information, particularly from those who have used such preparations extensively.

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RESPONSE TO LEPROMIN UNALTERED BY APPLICATION OF ZINC TO THE SKIN IN LEPROMATOUS LEPROSY PATIENTS

Sir,

Writing in the Lancet in 1979, Golden *et al.* [1] drew attention to the fact that thymic atrophy in malnourished children can be reversed by zinc supplementation. To see if their defect in cell-

mediated immunity was also associated with zinc deficiency, they skin-tested 10 children with *Candida* antigen on both forearms, 1 test site being covered with locally applied zinc sulphate and the other with placebo ointment. There was a highly significant increase in the typical delayed hypersensitivity reaction at the site covered with zinc and the authors concluded that zinc deficiency is a cause of the immune defect in malnutrition. They also commented that the local application of zinc might enhance the reliability of skin tests, in, for instance, the diagnosis of tuberculosis. A year later, Fernandez *et al.*[2] published further evidence of the importance of dietary zinc deficiency in causing impairment of cell-mediated immune responses. Oral zinc has been used beneficially as an adjunct to antileprosy drugs in various situations.[3–5]

We decided to investigate the possibility of altering skin test responsiveness of lepromatous leprosy patients to lepromin, by zinc topical application. Fifteen inmates of Hansen's Disease Rehabilitation Centre (Janla, Orissa), categorized as lepromatous leprosy based only on clinical features, were chosen for the study. Age of the patients ranged from 10 to 60 years; duration of the disease was from 6 months to 30 years; all were currently under treatment with dapsone 50–100 mg daily, though for varied periods. Slit-skin smears were positive for acid-fast bacilli in all but 5 patients.

Zinc was applied (1% $ZnSO_4$ in white petroleum jelly) to the middle one-third of the flexor aspect of the right forearm (test), twice a day with an interval of about 8 h between the applications. Plain petroleum jelly, applied over a corresponding area of the left forearm served as untreated control. Patients were instructed not to remove the applied jelly for at least 3 h after each application. This was done for 15 days.

On the sixth day of applying jelly, 4 patients developed mild urticaria at the site of application (in 2 patients urticaria was present in both the left and right forearms; in the other 2, urticaria was confined to the right forearm). This disappeared completely by the next day. A single patient developed erythema (right forearm > left forearm) on day 10 of the study which persisted for 3 days. The significance, if any, of these observations is not known.

On day 16, lepromin (Dharmendra antigen, courtesy of U Sengupta, CJIL, Agra) was injected intradermally in both the forearms of all 15 patients. All the patients remained lepromin negative.

It is possible that the period of application of zinc (15 days) was insufficient and we fully appreciate that no firm conclusions can be drawn from an isolated study of this kind on a limited number of patients. However, it is our intention to continue this work and to extend our studies to include patients with the non-polar forms of leprosy. Meanwhile, we submit these preliminary observations in the hope that others will report similar studies on the effect of locally applied zinc in leprosy, tuberculosis or related diseases.

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TRANSMISSION OF LEPROSY BY ANIMAL BITE
REPLY TO: 'TUBERCULOID LEPROSY AT THE SITE OF A DOG BITE'

Sir,

We are writing this letter with reference to Garg's Letter to the Editor,[1] one of us (CMG), along with others, have reported a case of indeterminate leprosy developing 2 years following a dog bite.[2] The case has been followed and has now developed a classical tuberculoid lesion at the same site. Although there are several reports of the development of a leprosy lesion at the site of injury, (tattooing and vaccination), ours is probably the first case reported from a dog bite.

Is this just a coincidence? Or has the injury acted as a portal of entry for pre-existing lepra bacilli on the surface of skin, or was the animal perhaps harbouring the organism at the time of bite? In addition, the possibility of a preexisting leprosy lesion at the site of bite has to be considered.

The concept of man being the only reserver for *Mycobacterium leprae* is now changing. There are reports of occurrence of naturally acquired leprosy in chimpanzees,[3] Mangabey monkeys,[4] and armadillos.[5] Successful transmission of human leprosy to animals has been reported in chimpanzees, golden and chinese hamsters, cotton rats, mystromys, mice and armadillos.[6] There is no scientific reason to think that dogs may harbour *M. leprae*, but if more reports are made of leprosy lesions in human beings following dog bites, perhaps this possibility should be kept in mind.

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LEPROSY FOLLOWING MECHANICAL TRAUMA
REPLY TO: 'TUBERCULOID LEPROSY AT THE SITE OF A DOG BITE'

Sir,

The letter by Garg[1] was enlightening but somewhat unspecific with regard to the cardinal clinical, bacteriological, histopathological and immunological features which are so important to the diagnosis of leprosy.

Furthermore it should be recognized that several well documented and illustrated reports have found a place in literature, since the first description by Lowe & Chatterjee,[2] the details of which are included in Table 1.

It is apparent that tuberculoid/indeterminate leprosy may result from mechanical injury

Table 1

S. No.	Author(s)	Age & Sex	Mode of injury	Site	Incubation period	Diagnosis			
						Clinical	Bacterio-logical	Histopatho-logical	Lepromin test
1	Lowe & Chatterjee[2]	26 M 27 M	Tattooing	Lower leg Thigh	6 months 5 years	T	—	T	—
2	Porrit & Oslen[3]	25 M 26 M	Tattooing	Forearm Thigh	$2\frac{1}{2}$ years	MA	Scanty	T	—
3	Sehgal *et al.*[4]	25 F	Smallpox vaccination	Lt upper arm	6 months	T	Negative	T	++++
4	Sehgal[5]	25 F	Tattooing	Both forearms	7 years	T	Negative	T	++++
5	Mittal *et al.*[6]	30 M	Abrasion	Lt medial malleolus	6 months	T	Negative	T	−
6	Kapoor & Bhale Rao[7]	19 M	Abrasion	Lt thumb	15 days	T	Negative	T	−
7	Gupta *et al.*[8]	21 M	Dog bite	Lt forearm	2 years	I	Negative	I	++
8	Garg[1]	45 M	Dog bite	Rt forearm	$3\frac{1}{2}$ years	T	Negative	T	−

MA: Maculo-anaesthetic; T: Tuberculoid; I: Indeterminate.

comprising trauma, inoculation, vaccination, and tattooing in predominantly young males. The time lapsing between injury and the manifest clinical entity is variable and ranges from 15 days to as long as 7 years. The exposed areas are more susceptible to such injury.

The characteristic—saucer, the right way up—morphology was seen only in a case by Sehgal *et al*,[4] whereas its variants were seen by others.[1–3, 5–8] The latter were apparent in the form of hypopigmented, mildly scaly erythematous, macules conforming to the scar mark(s). Impairment/loss of sensation was, however, a common feature. Thickening and/or tenderness of the nerves was determined only by Sehgal *et al.* [4] and Sehgal.[5]

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SUPPLIES OF THALIDOMIDE FOR USE IN LEPROSY

Sir,

It is our understanding that Chemie Grunenthal in Germany recently stopped production of thalidomide and handed over remaining stocks to WHO for distribution. However, in a letter dated 15.7.85, Dr Noordeen has explained that WHO cannot accept responsibility for distributing the limited stocks offered by Chemie Grunenthal, mainly due to concern that WHO would not be able to exercise sufficient control over the safe use of this drug, particularly in the light of the increasing use of thalidomide in several other conditions, where severe side-effects have been reported.

We fully recognize the hazard of teratogenicity which accompanies the use of this drug, but we wish to record that in our 7-year experience with thalidomide in the treatment of type 2 reactions in lepromatous leprosy, we have found it to be extremely valuable and well tolerated. Our strong impression is that for this purpose in leprosy, it is not in fact associated with an unacceptable incidence of toxic or side-effects, a point which has recently been made in the medical press.[1] If used

[1] Thalidomide in dermatology and leprosy, Editorial, *The Lancet*, June 22, 1985.

under strictly controlled conditions, essentially in a hospital or special centre and by authorized staff, we believe this drug offers exceptional benefit to the patient with ENL.

We are currently being asked to implement multiple drug therapy for all patients with leprosy, including multibacillary cases and a steady proportion of the latter, in virtually all parts of the world, develop ENL. It is our experience that thalidomide is superior to steroids for the management of such cases and we therefore write to ask what is happening with regard to the supply of this drug to those who have to treat leprosy patients with this type of reaction? Is the matter being discussed by national or voluntary agencies, with a view to a solution?

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REPLY TO: 'QUALITY CONTROL OF SKIN SMEAR SERVICES IN LEPROSY PROGRAMMES; PRELIMINARY EXPERIENCE WITH INTER-OBSERVER COMPARISON IN ROUTINE SERVICES'

Sir,

We were interested to read this article (de Rijk *et al.*, *Lepr Rev* 1985, **56,** 177–191) and agree that quality control is an important element in attempting to improve the standard of work in leprosy control programmes. However, we venture to suggest that the approach described in the above article may be too complicated for most situations and that very few 'routine' laboratories will be able to follow the recommendations given.

The basic need in this context is to establish criteria for 'Good', 'Fair' and 'Poor' work which can be applied not only by a reference laboratory technician, but also by others who may be responsible for the running of the control programme.

In studying the procedures outlined in Dr de Rijk's article, we think it is very unlikely that laboratory personnel of adequate ability will in fact be available in most situations. Before such procedures are considered further we believe it is important to recognize, in all laboratories where slit-skin smears are examined for leprosy, that staff should be properly trained, systematically supervised and adequately paid. Furthermore, they should never be overburdened with excessive amounts of work; the examination of 15 different smear slides per day each carrying 3–4 smears on each slide, together with their careful reporting, is probably about as much as the average technician can cope with per day. It is also important to make sure that technicians are not asked to examine vast numbers of negative, or virtually negative slides for long periods of time. Our experience has indicated that sincerity, conscientiousness and real interest are essential ingredients to the achievement of good quality work. To achieve this and maintain it, day in day out, calls for proper guidance and encouragement by senior staff.

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FAILURE OF SPECIFIC ANTIGEN PRESENTATION IN LEPROMATOUS LEPROSY

Sir,

Recently Narayanan *et al.* (*Lepr Rev* 1984, **55,** 301–308), using monoclonal antibody OKT-6, have reported a normal number of Langerhans cells in the epidermis of lepromatous leprosy cases and a slightly higher count in cases of tuberculoid leprosy. In the infiltrate they have noted T-6 positive cells lacking dendritic processes reminiscent of LCs in the lymphocyte mantle of TT/BT, whereas in the infiltrate of lepromatous leprosy T-6 positive cells were conspicuously absent. The Ia positivity was seen with the lymphocytes surrounding the epitheloid cells in TT and with foamy macrophages in lepromatous leprosy. Based on these observations authors have concluded that in leprosy there may not be significant defect in the antigen presentation.

In our earlier studies, using histochemical staining for ATPase activity, we have observed in the epidermis a significant reduction in LCs population in LL and an adequate number in TT. Combining the observations with OKT-6[1] and ATPase[2], it can be interpreted that in LL most of the LCs were inactive. This was further confirmed by our electron microscopic study[3] of LC in leprosy, where we observed a decreased number of lysosomes and rough endoplasmic reticulum; dense matrix and indistinct cristae of mitochondria; numerous vacuoles in cytoplasm, and a normal nucleus, suggesting that cells were inactive.

OKT-6 is more of an anatomical marker and does not indicate the functional state of LC, whereas ATPase activity reflects functional activity of a cell. The difference in LC count in two studies could be, as also suggested by Narayanan *et al.*, due to a difference in staining methods. Narayanan *et al.*, have also observed less numbers of Ia positive LCs in epidermis as compared to T-6 positive in LL patients. In sarcoidosis, an example of anergy, Fox *et al.*, reported a decrease in both Ia & T-6 positive LCs in the epidermis.[4] It is the Ia of LCs which plays the key role in antigen presentation. LCs when treated with anti-Ia antibodies fail to present antigen to lymphocytes.[5] Another important factor in eliciting sensitization is the presence of an adequate number of LCs in the epidermis.[6] In lepromatous leprosy the decrease in the number of active LCs and low count of Ia positive LCs in the epidermis can explain their poor sensitizing capacity to various chemical sensitizers.

In the recent past, in multibacillary leprosy, researchers have shown defects in lymphocyte[7] and macrophage functions,[8] low IL-2[9] and γ-interferon activity[10] and recently we have also shown defects in antigen presenting cells (LCs)[3]. It is interesting to note that all these defects in afferent and efferent limbs of the immune system have developed after the entry of bacilli. Once the specific unresponsiveness sets in, the APCs subsequently fail to present the specific antigen to the local lymphoid system and thus it becomes difficult to induce sensitization. This inability of APCs to present antigen could be due to the presence of specific T-suppressor factor (TsF) as shown by Ptak and Gershon in their model of contact hypersensitivity in animals.[11]

In the past we have put forth a hypothesis, based on the work of Ptak *et al.* in the field of contact dermatitis,[12] that it is the initial mode of entry of bacilli which decides the type of leprosy one will develop. If the organism enters the body through the epidermis and is presented to skin-associated lymphoid tissue by LCs it will generate specific sensitization, but when it bypasses LC or finds entry through oral or nasal routes it generates specific unresponsive state. We feel that work in the field of mode of entry and identification of specific antigen might be helpful in understanding this disease.

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FAILURE OF PASSIVLEY TRANSFERRED LEPROSY LYMPHOCYTES TO DEMYELINATE PERIPHERAL NERVE

The above 'Letter to the Editor' by S S Pandya and S S Naik appeared in *Lepr Rev* (1985) **56,** 365–66. We apologize for omitting to include the authors' address, which is as follows:

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Lepr Rev (1986) **57,** 80–82

Leprosy Control and Field Work

***A practical guide to the diagnosis and treatment of leprosy in the basic health unit;* Wheate and Pearson, Third edition 1985**

It is a pleasure to see that the third edition of this extremely popular booklet by Dr Harold Wheate and Dr John Pearson has now been published by the German Leprosy Relief Association in Würzburg. The previous editions, developed from the combined experience of the 2 authors in Malaysia, Africa and Ethiopia over a period of many years, had an enormous distribution to most parts of the world. It is in fact probably not an exaggeration to say that if one had to consider a single item of teaching-learning material from all that is now available, this little booklet of 28 pages may have been the most successful for its intended purpose. In his foreword, Dr Felton Ross draws attention to the skilful way in which the authors have achieved the presentation of knowlege about a difficult subject whilst at the same time avoiding complicated detail. The text has been translated into Portuguese, Arabic, Marathi and Indonesian, but we understand that it is not available in either French or Spanish (if this is confirmed, it is surely a matter which should be given priority consideration by ILEP or some similar body). There are 2 tiny misprints; on page 6, under 2, the word 'Severe' should read 'Several'. On page 10, in the flow chart, there should be a vertical bar underneath 'No loss of sensation to cottonwool touch'. To those who are involved in the application of MDT, particularly to large numbers of paucibacillary patients, the note at the top of page 25 is of considerable interest:

'Explain that weak muscles may well become stronger and loss of sensation improve even after the disease is cured and treatment has been stopped. Continued treatment of cured cases does not encourage recovery of nerve damage. This is particularly important for paucibacillary patients who have received treatment for only six months; their nerve function will often continue to improve, for a year or more after anti-leprosy treatment has been stopped.'

We would appreciate correspondence to this Journal, from those with experience of 6/12 MDT for paucibacillary leprosy, especially in India, on the matter of continued improvement of nerve function *after* stopping treatment. *Editor.*

PILLSAFE; plastic containers for daily administration of tablets or capsules

Our attention has been drawn to the availability of a plastic container, designed for blind or partially sighted people, carrying Braille to indicate the days of the week. It consists of a row of 7 compartments, each with a 'snap' lid, one for each day of the week. Each compartment is big enough to admit a finger and to contain a tablet or capsule, (or indeed several if these are prescribed). They are produced at low cost in 2 colours (yellow and blue) by PILLSAFE, PO Box 54, Banbury, Oxon, UK. To our knowledge they have had no application (or trial) outside this country in third world situations, but in certain situations it would not be unreasonable to consider the use of 4 such units, carrying 28 tablets or capsules, for the self-administration of drugs for the treatment of leprosy or tuberculosis. As with all such devices, this would of course not assure the actual ingestion of medication by the patients, but it would at least preserve the drugs efficiently and could serve as a valuable 'calendar' and a means of checking the regular extraction of tablets or capsules by the patient.

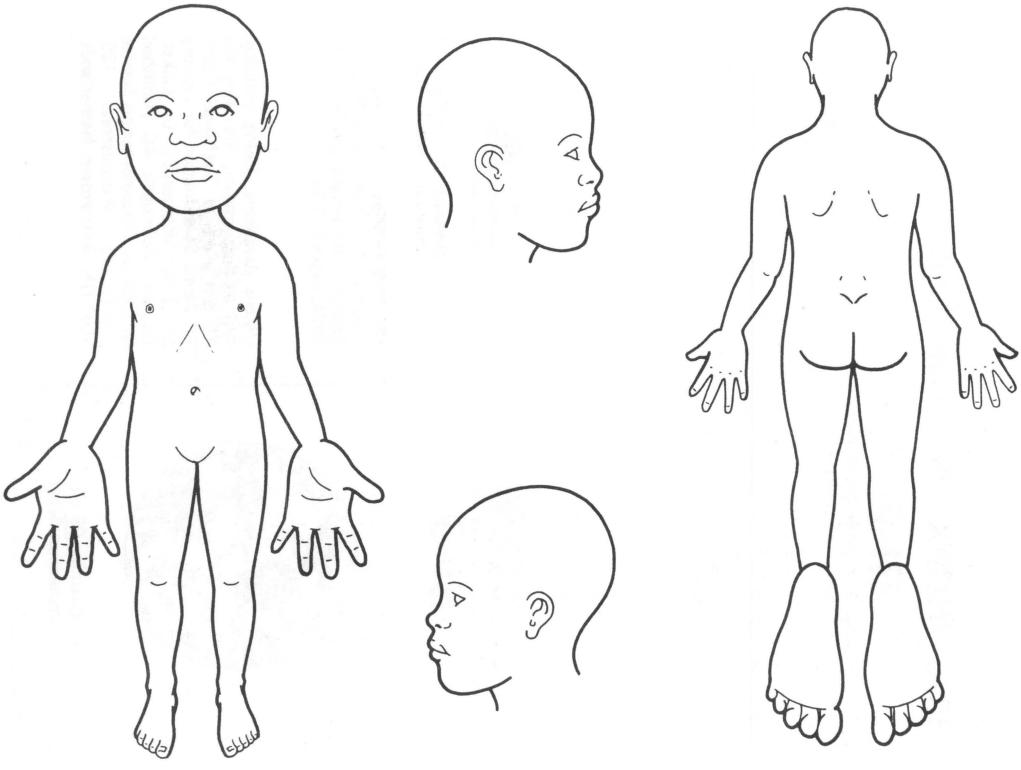
***Multidrug therapy; a working guide.* The Leprosy Mission, Southern Asia, 1983**

This is a strongly-bound book of 88pp, 18 × 24 cm, written by Dr E S Thangaraj of the Leprosy Mission, Southern Asia, 4th Floor, Sheetla House, 73–74 Nehru Place, New Delhi 110 019, India. It is sub-titled 'Working guide; guidelines for adaptation' and was developed specifically for the training and re-training of workers in leprosy for the new approaches needed in the implementation of multiple drug therapy. There are 35 subject headings covering every aspect of the subject for this purpose. This is an outstandingly useful and practical book which should be of the greatest value, not only in India but in many other parts of South East Asia, and it could, with some modification, serve as a basis for similar guides in other parts of the world.

Outline body diagrams for the charting of lesions and deformities

Although every control programme has its own diagram for this purpose, often well adapted to local facial type and body configuration, we take this opportunity to publish one which has been in use with LEPRA in Malaŵi

0305-7518/86/057080+03 $01.00



Body diagram for lesions, slit-skin smears or biopsies.

for a number of years and which was recently re-drawn by a professional artist in Oxford. It has been revised and modified on several occasions and we now publish it in the hope that it may be of value to others who have not yet developed a compact and satisfactory format for this purpose.

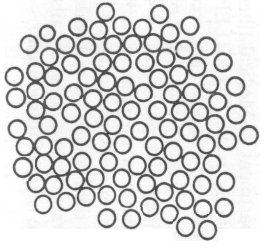
Mini-leprosy guide, 1986, National Leprosy Organisation, India
We are grateful to Mr Tare, Director of the Gandhi Memorial Leprosy Foundation in Wardha, Maharashtra, India, for sending a copy of the NLO Diary for 1986, which combines a diary with many pages of information about leprosy and the NLO itself. As in past years, the first 30 pages contain a great deal of information on the clinical signs and classification of leprosy and the closing pages cover many aspects of the work of the Indian National Leprosy Eradication Programme, NLO, GMLF and WHO. There is also a valuable list of health education material on leprosy available from GMLF (P.O. Hindinagar, Wardha 442 103, Maharashtra, India).

Leprosy smears; bacteriological index (BI) chart
The chart illustrated opposite has been developed by the Department of Medical Illustration in Oxford and revised on the basis of advice kindly offered by colleagues, notably in the TALMILEP section of ILEP. It is intended for laboratory workers who have to examine slit-skin smears in leprosy and record the bacteriological index, which is critically important to the proper classification of patients into either pauci- or multibacillary groups for MDT. The classic BI figure, as originally described and published, is stated in the top line. Underneath each diagram, an indication is given of the number of oil immersion fields which should be examined before arriving at a figure for the BI. This chart can of course be photocopied onto paper, but it is our strong recommendation that it should be copied onto card and then laminated and sealed in plastic. This gives the chart a much greater chance of survival under tropical laboratory conditions. Details of the availability and possible distribution of this chart may be published in a future issue of this journal.

LEPROSY SMEARS : BACTERIOLOGICAL INDEX - 'BI' (Ziehl-Neelsen stain)

BI=0

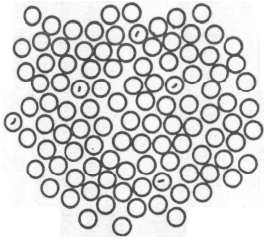
No bacilli in 100 oil immersion fields



Examine 100 oil immersion fields

BI=1

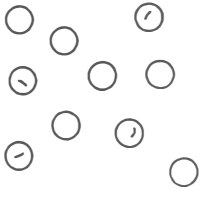
1-10 bacilli, on average, in 100 oil immersion fields



Examine 100 oil immersion fields

BI=2

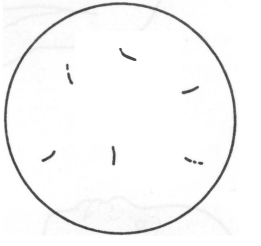
1-10 bacilli, on average, in 10 oil immersion fields



Examine 100 oil immersion fields

BI=3

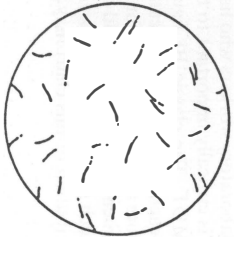
1-10 bacilli in an average oil immersion field



Examine 25 oil immersion fields

BI=4

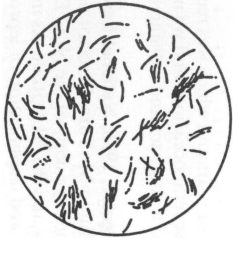
10-100 bacilli in an average oil immersion field



Examine 25 oil immersion fields

BI=5

100-1000 bacilli in an average oil immersion field



Examine 25 oil immersion fields

BI=6

1000 or more bacilli in an average oil immersion field

Examine 25 oil immersion fields

Original reference to the Bacterial (or Bacteriological) Index: Ridley DS, Bacterial Indices. In Cochrane, RG and Davey, TF (Editors), 'Leprosy in Theory and Practice' Bristol; John Wright and Sons Ltd, 1964, pages 620-22.

Details of taking, fixing, staining, and reading smears, including the BI, are given in 'Technical Guide for Smear Examination for Leprosy by Direct Microscopy' by Leiker, DL, and McDougall, AC. Published by Leprosy Documentation Service (INFOLEP), Wibautstraat 135, 1097 DN, Amsterdam, Netherlands.

Lepr Rev (1986) **57,** 83–90

Teaching Materials and Services

The Wellcome Tropical Institute; inventory of resource materials to support overseas education in tropical medicine
Dr Katherine Elliott, Resources Consultant to this unit, has written to a large number of people in the United Kingdom with an interest in tropical medicine, concerning an exciting new project which is being developed at the Wellcome Tropical Institute in London. Although intended essentially for UK participants at this stage, the material developed will obviously be directed mainly to those abroad and since leprosy is in the list of priorities, we take this opportunity to print the following information from her letter of July 1985:

'In September, Professor Eldryd Parry takes up his appointment as Director of this Institute, recently opened by the Wellcome Trust. One proposed major purpose of the Institute is to respond to the educational resource needs of overseas institutions involved in postgraduate teaching of tropical medicine, beginning with the six major tropical diseases: malaria, leprosy, trypanosomiasis, leishmaniasis, onchocerciasis and schistosomiasis. To do this effectively, the Institute wishes to enlist the interest of all who may be in any way involved with information dissemination to doctors, medical students and other health professionals.

Professor Parry has asked me, as a matter of urgency, to make as comprehensive an inventory as possible of all educational resources (other than textbooks) concerned with the six diseases listed. This inventory should enable us to promote the wider use of existing resources and, at the same time, to discover any important gaps which need to be filled by the preparation of additional materials. It will also be helpful to have on record, for the purpose of encouraging future collaborative action, the spectrum of UK interests in tropical medicine education.

As well as listing materials you have produced, are producing—or even plan to produce, we would appreciate it if you could include comments about materials from other sources that you find useful. We would also particularly welcome your views on important areas that are, in your experience, *not* covered in relation to the six tropical diseases—(for example, do existing materials adequately cover the immunological aspects of leprosy?).'

Dr Katherine Elliott,
Resources Consultant

***Questions and answers on the implementation of multiple drug therapy (MDT) for leprosy.* OXFAM, Oxford**
This booklet on MDT sold out its first edition half-way through this year and has now been slightly revised for the printing of a second edition. It is aimed at senior personnel in leprosy control with a good knowledge of written English and it is intended to cover some of the practical difficulties which have already been encountered by those in the field. Price £1.50 per copy, with a reduction of 25% for orders of 10 or more copies. Apply to OXFAM 274 Banbury Road, Oxford OX2 7DZ, England.

Teaching materials and services. Gandhi Memorial Leprosy Foundation
On the occasion of a recent visit to Oxford, the director, Mr Tare, kindly drew our attention to the very considerable number of items of educational material now available from the Gandhi Memorial Leprosy Foundation, PO Hindinager, Wardha 442 103, Maharashtra, India. Those in English include the following:

Publications: 1 Window on Leprosy, Rs 75; 2 Society and Leprosy, Rs 30; 3 Hints on Diagnosis and Treatment of Leprosy, Rs 7; 4 Gandhi Looks At leprosy, Rs 5; 5 Leprosy Everyone's Concern, Rs 2.

Folders and Pamphlets: 1 Leprosy—Know the facts Rs 10 (per 100); 2 Leprosy—A misleading disease Rs10 (per 100); 3 This lies in your power Rs 10 (per 100); 4 Ten points to remember Rs 10 (per 100); 5 Leprosy—Questions and Answers Rs 30 (per 100).

Films:
1 Controlling leprosy, a colour documentary, 2000 ft, 20 min, 16 mm prints available in English and Hindi, Rs 4100 (per print). Language versions can be made available if order for 30 prints assured, Rs 4600 (per print). Video cassette (English and Hindi), Rs 800.
2 Diagnosis of leprosy. A black and white film, 1850 ft, 20 min, for medical and paramedical groups, nursing schools, public health training centres. (In preparation).

0305-7518/86/057083+08 $01.00

Flashcards: A set of 10 flashcards printed in 4 colours on ivory card, laminated. Size 10″ × 7″ spiral bound. Protected in a plastic jacket. Useful for any health educational programme, Rs 30 (per set).

Album: Contains 20 enlarged photographs of 5″ × 4″ size, Rs 45.

TALC; new colour slide-text: ***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 All 4AX. (The cost of the set with script is between £2.00 and £5·50, depending on presentation).

Courses in tropical medicine at the University of Barcelona, Spain
It is perhaps not generally known that courses in tropical medicine are held regularly in this University. The overall direction is from the Chair of Microbiology and Parasitology, in collaboration with Medicus Mundi and the Infectious Diseases Section of the Hospital Clinic of Barcelona. The co-ordinators are Drs Manuel Corachan and Jordi Mas. The duration is 3–4 months. All the usual subjects under the heading of tropical medicine are in the syllabus, but an important feature of this course is that it gives considerable emphasis to community and public health in the tropics and to tropical paediatrics. We do not have information about costs, accommodation, etc, but these may be obtained from Dr Corachan, Hospital Clinic i Provincial de Barcelona, Villarroel, 170 Barcelona 36, Spain.

***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.

Glaxomed slide lectures; Bombay, India
Two sets on leprosy are available from The Medical Education Department, Glaxo Laboratories (India) Ltd, Worli, Bombay 400 025, India. They have been assembled by experts in the field and are of high quality. They are divided into 2 sets, each of 24 slides, with full text. Further details of costs and postage can be obtained from Dr Pritam Phatnani, Head of Medical Education at the above address. These slides and the accompanying information are produced in India by Indian leprologists and are probably the best currently available for the teaching of clinical leprosy in that country.

***Skin biopsy in leprosy* by D S Ridley, Second Edition**
A second edition of this booklet by Dr Dennis Ridley, Bland–Sutton Institute of Pathology, The Middlesex Hospital, London W1P 7PN, has just been published. The first edition had a circulation of several thousand copies all over the world and was very greatly appreciated. It is published in the Documenta Geigy 'series' by CIBA–GEIGY Ltd, Medical Department, CH 4002, Basle, Switzerland and it is our understanding that there will normally be no charge for the booklet or postage, but this should be confirmed by those who apply. The sub-title is 'Histological Interpretation and Clinical Application' and the main chapter headings cover: the Biopsy and its Preparation; The Pathogenesis of a Skin Lesion; the Examination and Interpretation of a Skin Section; Diagnosis and Differential Diagnosis; Relapse—Histology and Bacteriology; Classification and the Spectrum; Reactions; Numerical Indices. In his Preface, Dr Ridley draws attention to the upsurge or interest in the immunocytochemistry of leprosy in recent years, which has called for a slight change of emphasis in the new text. As previously, all sections of this beautifully produced booklet are illustrated in colour.

ILEP catalogue on training; 1986

We are grateful to the International Federation of Anti-leprosy Associations (ILEP) in London for permission to reprint information in full from their Catalogue. We wish to emphasize however that further information (and indeed all enquiries concerning these centres) is *not* available from ILEP in London. Those interested should write directly to the training centres concerned, and *not* to ILEP. Furthermore, ILEP does not sponsor people wishing to undergo training in leprosy; this is normally achieved by application to governments, voluntary agencies working in leprosy, or (using the correct forms of application) to organizations such as WHO or the British Council. The total list is as follows:

ALERT: (All Africa Leprosy and Rehabilitation Training Centre) (WHO Collaborating Centre for Training in Leprosy). PO Box 165, Addis Ababa, Ethiopia.

Contact, Director of Training. Telephone, 201200-201201-201524. Telegrams/Telex, ALERT ADDISABABA/ 21312 GLRA ET. Nearest airport, Addis Ababa. Accommodation, Hostel: maximum 28 people. (Cost: US$ 10 per day). Language, English. Recognition of courses, by WHO and Government.

INTERNATIONAL COURSES

DOCTORS COURSE ON CLINICAL LEPROSY AND LEPROSY CONTROL: 6 January–8 February 1986 and 5 May–7 June (5 weeks) for Medical Officers involved or going to be involved in clinical management of leprosy patients, leprosy control work or training in leprosy of health personnel.

Requirements: It is generally required that participants who will undertake leprosy control work should, prior to the course, visit and study their future project. It is also recommended that they prolong their stay by not less than 2 weeks for further in-service training in leprosy control.

TUBERCULOSIS COURSE ON TB AND TB CONTROL: 14 April–1 May 1986 (3 weeks) for Medical Officers and paramedical health staff involved in tuberculosis control.

RURAL AREA SUPERVISORS COURSE ON CLINICAL LEPROSY, LEPROSY CONTROL, SUPERVISION AND TEACHING METHODOLOGY: 15 September–15 November 1986 (9 weeks) for Senior Rural Area Supervisors.

Requirements: Senior Rural Area Supervisors should be in charge of leprosy control activities on provincial or national level.

JUNIOR RURAL AREA SUPERVISORS

Requirements: Junior Rural Area Supervisors should have not less than 5 years experience in leprosy and on their return expect to be upgraded to a senior position.

PHYSIOTHERAPY COURSE ON ASSESSMENT AND MANAGEMENT OF DISABILITIES IN LEPROSY AND PRE- AND POST-OPERATIVE CARE; 5 May–14 June 1986 (6 weeks) in conjunction with the second Doctors course for physiotherapists, occupational therapists, other paramedical health staff with experience in leprosy physiotherapy.

NATIONAL COURSES (dates still to be fixed)

Medical Undergraduates 9–12 weeks; Student Nurses 8–10 weeks; and Health Assistants 4–6 weeks.

Other Ethiopian and non-Ethiopian health personnel with limited responsibilities in leprosy work may be attached to these courses when places are available.

IN-SERVICE TRAINING

Programme	*Qualifications required*	*Recommended duration*
Clinical leprosy	Medical Officers, qualified nurses, medical assistants	minimum of 2 months
Clinical leprosy and leprosy control	as above	minimum of 4 months
Septic surgery and amputation surgery	Qualified general surgeon, surgical residents, medical officers with good experience in surgery	3 months
Reconstructive surgery	Qualified plastic, orthopaedic or general surgeons, surgical residents, medical officers with good experience in leprosy.	3 months dependent on extent training required and basic qualifications

Physiotherapy	Physiotherapists, occupational therapists, other paramedical health personnel.**	4–6 months
Laboratory techniques in leprosy	Laboratory technicians*** Laboratory assistants**	1 month 2 months
Dermato-histopathology techniques (in Armauer Hansen Research Institute)	Laboratory technicians**	3 months
Orthopaedic Workshop Techniques, making of protective footwear (Sandals Standard and Plastazote)**		6 months
Prosthetics	Orthopaedic Workshop Technicians**	12 months

** = good command of English

BAMAKO: Institut Marchoux, BP 251, Djikoroni, Bamako, Mali.

Telephone, 22.51.31. Contact, Dr M Nebout, Directeur. Aeroport, Bamako. Logement, Internat. Bourses d'Etudes, Octroyées soit par les gouvernements des stagiaires soit par les différents organismes comme l'OMS et les Associations-membres de l'ILEP dont l'Association Française Raoul Follereau. Les demandes de bourse auprès de ces organismes doivent être présentées au Secrétaire général de l'OCCGE (Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies, B.P. 153, Bobo-Dioulasso, Haute-Volta). Langue, Français.

L'enseignement est ouvert en priorité au personnel médical et paramédical ressortissant des huits Etats-membres de l'OCCGE (Bénin, Côte d'Ivoire, Haute-Volta, Mali, Mauritanie, Niger, Sénégal, Togo) et aux candidats étrangers qui en font la demande à l'OCCGE, sur titres.

1 INFIRMIER SPECIALISTE: Description: Bactériologie, immunologie, classification de la lépre, clinique, thérapeutique, épidémiologie, santé publique, etc. A la fin de l'enseignement, l'infirmier spécialiste dermatologie-léprologie doit être capable de remplir les fonctions d'adjoint du médecin-chef du secteur dans la lutte contre l'endémie lépreuse.

Participants: Infirmier d'Etat, Agent technique de santé, infirmier ordinaire certifié contrôleur-lèpre depuis 2 ans.

Durée: 2 ans. Octobre 1985–juillet 1987.

2 INFIRMIER CONTROLEUR-LEPRE: Description: L'enseignement comporte 30 heures de cours théoriques plus des travaux dirigés et des stages pratiques. A la fin de l'enseignement, l'infirmier contrôleur-lèpre doit pouvoir diriger un district composé de 4 à 5 circuits-lèpre.

Participants: Infirmier ordinaire ou équivalent.

Durée: 3 mois. ler octobre-30 décembre de l'année et éventuellement 2ème

3 UN CERTIFICAT D'ETUDES SPECIALES DE DERMATOLOGIE-LEPROLOGIE a été créé en décembre 1983 et mis en application à la rentrée scolaire 1984–1985.

La durée est de 3 ans à l'Institut plus 1 an dans une faculté française. L'Institut a ainsi 2 médecins maliens en C.E.S. 1.

Le decret ouvrant ce C.E.S. aux médecins des 8 pays de l'OCCGE va sortir prochainement.

Les médecins intéressés devront faire la demande au Secrétaire général de l'OCCGE.

DES STAGES sont offerts à des médecins, des chirurgiens et des étudiants de médecine *de toute origine* désireux de parfaire à leurs frais leur formation en léprologie.

L'Institut peut également recevoir des chercheurs qui voudraient s'instruire à leurs frais auprès de son animalerie expérimentale, de son unité épidémiologie ou chirurgie.

Renseignements plus detaillés disponibles sur demande au Bureau de coordination de l'ILEP.

BAURU: Hôpital Lauro de Souza Lima, Rodovia Cte. Joao Ribeiro de Barros, Km. 115, Caixa Postal 62, CEP 17.100, Bauru, Sao Paolo, Brésil.

Téléphone, (0142) 23.59.22. Contact, Dr Diltor V A Opromolla. Langue, Portugais.

COURS LEPROLOGIE: 17 au 22 février; 16 au 21 juin; 01 au 06 septembre; 08 au 13 décembre.

COURS PREVENTION DES INVALIDITES DE LA LEPRE:
20 janvier au 01 février; 07 au 19 avril; 15 au 27 septembre; 10 au 22 novembre.

COURS READAPTATION (CHIRURGIE REPARATRICE POUR LA LEPRE):
03 au 15 mars; 12 au 24 mai; 04 au 16 août; 06 au 18 octobre.

Stages. Les stages avec un maximum de 2 stagiaires sont organisés sur demande avec un délai minimum de 2 mois.

Frais d'inscription: 15 dollars US. Frais d'hébergement: 8 dollars US par jour.

NOTE: Des bourses d'étude peuvent être octroyées par la direction de l'unité.

CARVILLE: National Hansen's Disease Center, United States Public Health Service Hospital, Carville, LA 70721, USA.
Telephone, (504) 642.77.71. Contact, Dr R J O'Connor, Director of Education and Training. Nearest airport, New Orleans International. Accommodation, available. Language, English. Recognition of courses, by Government, American Medical Association and Academy of Family Practice.

MEDICAL SEMINAR IN HANSEN'S DISEASE: 25–26 February, 20–21 May, 4–5 November.

Purpose: To promote an increased level of understanding among members of the medical profession regarding current concepts in the diagnosis and treatment of Hansen's Disease.

Eligibility: Dermatologists, General Practitioners, Public Health Physicians and other medical specialists, particularly those residing in endemic areas.

INTERNATIONAL SEMINAR ON HANSEN'S DISEASE: 6–12 April, 7–13 September.

Purpose: To provide medical and allied health personnel planning to work with Hansen's Disease abroad, with latest information concerning diagnosis, treatment, management and control of Hansen's Disease.

Eligibility: Medical and allied personnel.

SEMINAR ON HANSEN'S DISEASE FOR PATHOLOGISTS: 7–8 October

Purpose: To present up-to-date, practical information on the histopathology of Hansen's Disease and the role of the pathologist in its diagnosis and treatment.

Eligibility: Pathologists and practising dermatologists.

MANAGEMENT OF INSENSITIVE FEET: MEDICAL AND THERAPEUTIC APPROACHES: 28–30 January, 21–23 October.

Purpose: To promote an increased level of understanding among members of the medical, nursing and allied health professions regarding current concepts in the management of insensitive feet.

Eligibility: Physicians, therapists, podiatrists, nurses and other health personnel.

MANAGEMENT OF THE INSENSITIVE HAND: BIOMECHANICS OF DEFORMITY AND CORRECTION: 29 April–1 May

Purpose: To provide education and training in the treatment of the insensitive hand.

Eligibility: Physicians, therapists and allied health personnel.

INDIVIDUALIZED TRAINING PROGRAMMES

Purpose: To provide an opportunity for persons now working, or planning to work, as professional Hansen's Disease personnel to learn current concepts in the management of this disease. Generally, a person accepted for such individualized training will already be a practising professional in a medical or scientific discipline; therefore the major purpose of this learning experience is to provide highly specialized training in one or more aspects of Hansen's Disease, such as laboratory research techniques, rehabilitation methods, educational media design and production, clinical laboratory training etc.

Dates and Duration: Individualized training opportunities are offered throughout the year. If possible, it is recommended that the training commences with attendance at a seven-day International Seminar (April or September) or a two-day Medical Seminar (February, May, November). The actual length of the training will be determined for each individual; generally, it will be from several days to several months in length.

Additional information is available on request from the ILEP co-ordinating bureau.

CEBU: Leonard Wood Memorial Center for Leprosy Research, PO Box 727, Cebu, Philippines.

Telephone, (32) 827.46. Telegrams, WOODMEM CEBU. Contact, Dr Steenbergen, Director. Nearest airport, Cebu. Language, English. Recognition of courses, WHO, Government.

August (10 days): 8th International workshop on MDT in Leprosy Control using the Primary Health Care concept.

July/August (6 weeks): Epidemiological Aspects of the Operational Management of MDT

October: Courses for Medical Technologists in Skin Smear Methodology.

IN-SERVICE TRAINING

Requests should be sent to the Director through the employer of the applicant. The training can be tailored to the specific needs of the applicant in the following areas of interest: 1 Clinical research (drug trials and design);

2 Epidemiological research (population basis studies, prevalence surveys); and 3 advanced laboratory techniques—immunology (ELISA), FDA-EB staining, mouse foot-pad inoculation technique, and histopathology of leprosy.

DAKAR: Institut de Léprologie Appliquée de Dakar (ILAD), BP 11023 CD Annexe, Dakar, Sénégal.

Telephone 22.36.16. Contacts Dr J Millan, Directeur ILAD and Dr J C Naudin, DAHW. Aeroport Dakar-Yoff. Logement à l'ILAD: 8 chambres individuelles (pas de repas; en ville: logément en hôtel aux frais des intéressés.
Frais d'inscription, Pour le Certificat de Léprologie de la Faculté de Médicine 50,000 francs CFA. Les autres cours et stages sont gratuits (soutien financier de Amici di Raoul Follereau, Deutsches Aussätzigen-Hilfswerk et l'ordre de Malte). Bourses d'Etude, L'Institut ne prenant en charge ni le voyage ni les frais de séjour des stagiaires, ceux-ci peuvent solliciter des bourses d'étude soit auprès de leur gouvernement, soit auprès d'organismes tels que l'OMS ou les Associations- membres de l'ILEP. Langue, Français. Reconnaissance des cours, Le Certificat de Léprologie est reconnu par l'Université de Dakar. Responsables, Directeur de l'ILAD, Médecin Chef de projet DAHW, and Médecin Chef du Service National des Grandes endémies. Enseignants, Médecins et Physiothérapeute de l'ILAD, Médecin Chef de projet DAHW, Médecin chef du SNGE, et, pour le Certificat de léprologie, plusieurs Professeurs de Faculté.

Le programme de 1986 n'étant pas encore disponsible, nous donnons ci-dessous, à titre d'information, le schéma du programme. Pour des renseignements exacts, veuillez vous adresser directement à l'ILAD.

COURS COLLECTIFS

MEDECINS: Durée: 4 jours, Dates: décembre, nature: perfectionnement, Observations: responsables des Grandes-Endémies.

MEDECINS/GESTIONNAIRES: Durée: 1 jour. Nature: gestion (DAHW). Observations: personnel des Grandes-Endémies.

INFIRMIERS-SPECIALISTES: Durée: 5 jours. Dates: février. Nature: perfectionnement. Observations: personnel des Grandes-Endémies.

INFIRMIERS: Durée: 1 jour. Nature: perfectionnement. Observations: personnel des postes de santé.

RESPONSABLES SOCIAUX: Durée: 6 jours. Nature: formation. Observations: personnel des villages de lépreux.

MEDECINS ET ETUDIANTS EN 7e ANNEE: Durée: 50 heures réparties en 3 mois. Dates: mars–juin. Nature: formation. Observations: Certificat de Léprologie de l'Université.

STAGES INDIVIDUELS

INFIRMIERS: Durée: 3 jours. Dates: février. Nature: microscopie. Observations: personnel des Grandes-Endémies.

Des stages individuels peuvent être organisés sur demande et en fonction des possibilités de l'Institut, dans les disciplines suivantes: clinique, chirurgie, microscopie, physiothérapie et cordonnerie. De tels stages ne sont profitables que pour des personnes possédant déjà une bonne formation générale dans le domaine de la lèpre.

Pour une formation approfondie des médecins, la formule recommandée est un stage à l'ILAD de 4 mois, coïncidant avec les cours pour le Certificat de Léprologie.

ENSEIGNEMENT EN DEHORS DU CENTRE

Poursuite de la formation des agents des Services Généraux selon le programme fixé par le Médecin Chef de la DAHW.

Un Cours International de l'OMS pour le perfectionnement des responsables de la lutte contre la lèpre se déroulera à Dakar en février 1986.

FONTILLES: Sanatorio de San Francisco de Borja, Fontilles (Alicante), Espagne.

Telephone, (965) 58.33.50. Contact, Dr José Terencio de las Aguas, Médico Director. Aeroports, Valencia et Alicante. Logement, disponible dans le centre. Langues, Espagnol et français. Reconnaissance des cours, par la Direction Générale de la Santé, par l'Ecole Professionnelle de Dermatologie, et par l'Ordre de Malte. Bourses d'étude, octroyées par l'Ordre de Malte.

Septembre/octobre (1 semaine), Médecins.

Octobre/novembre (2 semaines), Auxiliaires médicaux et missionaires.

KARIGIRI: Schieffelin Leprosy Research and Training Centre, SLR Sanatorium PO, PIN 632 106, North Arcot District, South India.

Telephone, Vellore 21522 with extension to Director/Deputy Director in Administration. Deputy Director of Training—SAX Karigiri No 25. Training Unit—SAX Karigiri No 37. Telegram, LEPSEARCH VELLORE 7. Contact, Training Officer. Nearest airport, Madras. Nearest rail station, Katpadi. Accommodation, Guest House: 30 persons (limited single rooms sometimes available). Hostel: Men–60 persons. Women–16 persons. Language, English.
Recognition of courses, In-service training courses in reconstructive surgery, pathology, leprosy control, medical aspects, are recognized by WHO and Indian government. All paramedical and technical courses are fully recognized by Indian Government.

MEDICAL OFFICERS

CONDENSED COURSE IN LEPROSY for doctors and senior medical personnel 7–12 April, 8–13 September, 17–21 November (1 week).

MEDICAL STUDENTS COURSE for undergraduates 1 week (dates fixed according to college holidays).

MEDICAL OFFICERS COURSE for medical personnel engaged in leprosy work 15 January–26 February, 7 July–15 August (6 weeks).

SPECIAL COURSE FOR OPHTHALMOLOGY TEACHERS (proposed) 3 days.

OPHTHALMIC ASPECT IN LEPROSY for qualified medical personnel (proposed) 3 days, included in 6 weeks course for Medical Officers.

OTHER CATEGORIES

NON-MEDICAL SUPERVISORS COURSE for fully qualified paramedical workers with a minimum of 3 years experience. 4 months commencing 9 June.

ORIENTATION COURSE IN LEPROSY for paramedical personnel (nurses, physios, OT and administrators), consisting of 1 week CONDENSED COURSE + 3 weeks in-service training. 1 month commencing 6 January, 7 April, 8 September.

PARAMEDICAL WORKERS COURSE for +2 passed, graduates preferred. 6 months commencing 25 August.

ADVANCED COURSE IN LEPROSY CONTROL for selected, experienced, non-medical supervisors. 12 months (by arrangement).

PMW REFRESHER COURSE for qualified paramedical workers. 1 month commencing 9 June.

PHYSIOTHERAPY TECHNICIANS COURSE for +2 passed or PUC preferred. 9 months commencing 11 June.

LABORATORY TECHNICIANS COURSE for +2 passsed, science graduated preferred. 12 months commencing 7 July.

IN-SERVICE TRAINING

PROSTHETIC TECHNICIANS FOR +2 passed or PUC preferred. 18 months commencing 20 January and 16 July.

SHOEMAKERS COURSE for V standard with knowledge of English preferred. 6 months commencing January and July.

SMEAR TECHNICIANS COURSE for +2 passed (reg. qualified laboratory technicians refresher). 3 months commencing 20 January, 11 June and 15 September.

MEDICAL RECORD KEEPERS for 2 passed with proficiency in typing and good English. 2 months (by arrangement).

MEDICINE, SURGERY, PATHOLOGY, LAB TECHNOLOGY AND LEPROSY CONTROL for qualified medical personnel. 6 months (by arrangement).

Note: 1 +2 signifies 12 years of schooling, equivalent to A Levels.

YAOUNDE: Centre d'Enseignement et de Documentation de l'OCEAC (Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale), BP 288, Yaoundé, Cameroun.

Telephone, 23.22.32 (Secrétaire général). 23.00.61 (Centre d'Enseignement et de Documentation). Contacts, Dr D Kouka Bemba, Secrétaire général, Dr L Sentilhes, Secrétaire général honoraire, Dr R Josseran, Chef du Centre d'Enseignement et de Documentation, Dr P. Ambassa (Adjoint au Chef du centre d'enseignement). Aeroport, Yaoundé. Langue, Français.

STAGE NATIONAL DE FORMATION INFIRMIERS CONTROLLEURS LEPRE ET TUBERCULOSE
Durée: 8 semaines. Dates: janvier–février. Lieu de stage: OCEAC Yaoundé. Nombre de participants: 20. directeur du cours: Dr R Josseran.

Le stage s'adresse aux Infirmiers Diplômés d'Etat de la République de Guinée Equatoriale et de la République du Cameroun qui désirent se spécialiser dans la lutte contre la lèpre et la tuberculose. (Dépistage et traitement des malades, prévention des complications neurologiques et oculaires, surveillance du traitement, recueil des données épidémioloques, actions éducatives.)

2ème ANNEE DU COURS DE FORMATION DES TECHNICIENS SUPERIEURS EN SANTE PUBLIQUE, OPTION EPIDEMIOLOGIE APPLIQUEE
Durée: 7 mois. Dates: mars–septembre. Nombre de candidats: 16 infirmiers provenant des Etats Membres de l'OCEAC. Directeur du cours: Dr R Josseran.

A l'issue de leur formation, ces cadres intermédiaires seront les collaborateurs des médecins et seront responsables de l'exécution des programmes de santé en cours, dont ceux de lutte contre la lèpre.

STAGE NATIONAL DE FORMATION INFIRMIERS CONTROLEURS LEPRE ET TUBERCULOSE
Durée: 8 semaines. Dates: septembre–octobre. Lieu de stage: Libreville. Nombre de participants: 20. Directeur du cours: Dr R Josseran.

Ce stage s'adresse aux Infirmiers Diplômés d'Etat de la République Populaire du Congo et du Gabon.

COURS D'INITIATION AUX METHODES EPIDEMIOLOGIQUES SHDS/OMS/OCEAC
Durée: 6 semaines. Dates: novembre–décembre. Nombre de participants: 12. Directeur du cours: Dr R Josseran.

Ce stage s'adresse à des jeunes médecins des Etats d'Afrique Centrale: qui désirent se spécialiser en épidémiologie et en statistiques appliquées à l'epidémiologie; qui désirent se spécialiser en Santé Publique et veulent acquérir des connaissances de base en matiére de statistique et d'épidémiologie médicale.

SEMINAIRE DE RECYCLAGE DES INFIRMIERS CONTROLEURS LEPRE ET TUBERCULOSE
Durée: une semaine. Date et lieu: à la demande des Services nationaux des Etats Membres de l'OCEAC. Nombre de participants: 25 maximum. Directeur du cours: Dr R Josseran.

Trois semaines sont prévues pour l'instant en 1986. Ce stage s'adresse aux Infirmiers Diplômés d'Etat des Etats membres de l'OCEAC. Il est axé sur les techniques de dépistage bacilloscopique, rappels cliniques, la prévention et le traitement des complications, utilisation des nouveaux schémas thérapeutiques, surveillance et recueil des données épidémiologiques.

NB. Etats membres de l'OCEAC: Cameroun, Guinée Equatoriale, Congo, RCA, Gabon, Tchad.

Flannelgraphs; a medium for the exchange of ideas about health; TALC, London

From Teaching Aids at Low Cost (TALC), P.O. Box 49, St Albans, Herts, AL1 4AX, England, we have just received a set of flannelgraphs on hookworms, roundworms and tapeworms, together with information on the preparation and use of this medium of teaching. The flannel material comes on sheets about the size of a small tablecloth, printed with colourful pictures on various health-learning themes,which are to be cut out with scissors. This means of exchanging ideas on health has been used and developed by Professor David Morley at TALC over a period of many years and has been found to have the following advantages:

A field worker can easily carry the flannelgraphs without a vehicle. Electricity or expensive equipment are not needed.
We can use the pictures again and again if they are properly stored.
Flannelgraphs are simple and clear. They provide a visual framework on which to hang ideas.
We can build up the subject picture by picture. We can replace negative ideas by positive ones and move and change the scene.
We can leave the pictures up for as long as necessary for questions and discussion.
The flannelgraphs are quick to set up and use in homes, or in a group.
People can easily add to and adapt the flannelgraphs.
Most important of all, it is easy to encourage audience participation with flannelgraphs.

TALC wishes to emphasize that flannelgraphs should be used as a two-way exchange of ideas to promote questions, discussion and positive input by the audience and community. To our knowledge nothing of this kind has ever been developed for leprosy, although the advantages listed above are impressive. This approach might well be of value, notably in the hands of primary or community health care workers, for the early detection of leprosy and for health education in the context of multiple drug therapy. Enquiries on cost, postage, etc, to the above address.

Lepr Rev (1986) **57,** 91–94

News and Notes

More pages for *Leprosy Review*
This journal now has a circulation of over 1300, 4 times yearly, to more than 100 different countries, including all the main leprosy-endemic parts of the world. In recent years, the number of original articles submitted for publication has also increased and we have often found it difficult to find space for editorials, special articles, reports, news, notes, abstracts, book reviews and teaching material. We are therefore delighted to report that at a recent meeting in London the director of LEPRA authorized the use of 96 pages per issue during 1986 in order to accommodate the amount of material which is now regularly in hand. We take this opportunity to thank our contributors; the expert assessors; those who have written letters to the Editor; the editorial staff and the printers in Oxford. *Editor.*

Thesis on the Marchoux Institute from Dr Guy-Michel Nebout, France
We were delighted to receive a copy of this thesis (in French), written by Dr Guy-Michel Nebout as his thesis for the Doctorate in Medicine (Diplome d'Etat) in the Academie de Paris, Faculté de Médecine Lariboisière-Saint-Louis, Paris. After an introductory section, Dr Nebout describes the chaulmoogra era; the introduction of modern chemotherapy; research work in the Institute; surgery; current activities and future plans. The annexes contain a biography of Professor Marchoux. There are a number of excellent line drawings and illustrations. This account will surely be of the greatest interest to workers in French-speaking countries of Africa and particularly to those who are familiar with the sustained contribution of the Marchoux Institute to '. . . .la lutte contre la lèpre en Afrique Noire'.

Newsletter; International Agency for the Prevention of Blindness (IAPB)
We continue to receive copies of the IAPB news and to read with interest of the worldwide efforts which are being made to combat blindness. The current issue (July 1985) contains reports of—Vitamin A for Ethiopia; recommendations on collaboration with non-government organizations; an eye survey in Saudi Arabia; a 12-minute videotape on the activities of IAPB, available from Dr Carl Kupfer, President, National Institutes of Health, National Eye Institute, Building 31, Room 6A03, Bethesda, Maryland, 20205, USA. There is on the back page of the Newsletter a valuable list of organizations and agencies dealing with eye disease in various parts of the world.

HEARU; Handicapped Education and Aid Research Unit, London
We are indebted to the director, Kennett Westmacott, for the following information:

HEARU provides for the needs of disabled adults, whether their disability has been recent or not, suffering from a wide range of diseases.

We are simply a workshop which teaches the families, friends, and in some cases the disabled persons themselves, how to make an inexpensive range of living aids using simple domestic hand-tools, basic materials and uncomplicated methods.

In trying to help the disabled person become as independent as possible, we have developed simple designs and aids that will add to their comfort and will enable them to cope with some of the tasks they have had to depend on others for.

Each aid is also designed according to the needs of the individual. Together with the family and the therapist we find out what is needed and make a simple aid to meet that need.

The process of designing and making aids can be seen as a difficult task but at HEARU we emphasize its simplicity. Our day and evening workshops with their simple tools are aimed at those individuals with absolutely no practical skills. Those with the initial lack of confidence are provided with sympathy and patience. The aids are designed to cost no more than £10 in materials, although most of them are made for less than £2.

Most of our basic designs are flexible enough to be adapted to the needs of different people. They range from aids for washing, grooming and dressing to furniture modifications and leisure-time aids. One of the many pieces made has been the hand grip which, although very simple, has allowed over 200 people with their crippled hands to use spoons, forks, pencils, combs, toothbrushes and plugs.

0305-7518/86/057091+04 $01.00

HEARU is thought to be unique in Britain—if not the world. It works closely with ILEA (Inner London Education Authority) and several big London hospitals. Its work is recognized internationally and it has links with the British Council and UNESCO.

For further information about the HEARU workshop contact Kennett and Jean Westmacott, Handicapped Education and Aid Research Unit, City of London Polytechnic, Walburgh House, 56 Bigland Street, London E1 2NG. (We have also received from this centre details about different courses which are open to 'any keen applicant'. Kennett Westmacott is in correspondence with this office on the design of a simple loom for disabled people in African villages, which we hope to publish in a later issue in 1986. *Editor.*)

Graves Medical Audiovisual Library; Newsletter Autumn 1985

The total list of materials available from this expanding centre has to be seen to be believed and the 'New Titles' list for autumn 1985 underlines the continued collection of subject matter, covering almost every conceivable aspect of medical practice. From the letter itself, 2 items are of particular interest:

1 Concord Films Council. We recently visited Concord, another sister organization, to renew old acquaintances and to exchange views. Like us they have grown from modest beginnings in the late 50s; now they are the largest 16 mm educational film library in the UK. They supply video as well as film for all areas of education and for all sorts of special interest groups.

Concord was started by Quakers Eric Walker and Lydia Vulliamy, in 1959, in response to a need for films on peace issues. They now distribute films from over 350 other bodies covering a very wide range of topics. More than 3000 titles are listed in their catalogue including a large selection on medical subjects, particularly mental and physical handicap, child development and health education. The address: 201 Felixstowe Road, Ipswich, Suffolk, IP3 9BJ England. Telephone: (0473) 76102.

2 *National Medical Slide Bank.* We first started to think about this in 1977 and now we are pleased to announce the launch of a major project to set up a large medical slide library.

There are lots of good slides of medical subjects held in many of the main teaching hospitals, but there are many teachers, especially in the paramedical professions, who require slides but don't have ready access to good pictures. The slide bank will meet these needs and many others.

We are working in co-operation with Chadwyck-Healey Ltd, a company who have many years experience of publishing special collections, usually in microfiche. They will be producing a videodisc version of the bank once it's established.

Mr David Tredinnick is retiring early from his post of director of Medical Illustration at St Bartholomew's Hospital to join us for 2 years to work on the project as project director.

Gandhi Memorial Leprosy Foundation Centre for Social Science Research and Development in Leprosy

We are indebted to the Director, Mr S P Tare, for the following information about a new centre.:

The Centre for Social Science Research and Development in Leprosy, established by the Gandhi Memorial Leprosy Foundation at its Wardha Campus, started functioning with effect from 2 September 1985.

The Centre proposes to initiate research in social science areas with a view to promote efficient functioning of a leprosy control programme. Some of the priority research areas are: 1 Health services research in MDT; 2 Perception studies of patients, community and health workers about the leprosy problem; 3 Nature and extent of social stigma; 4 Evaluation of health education programmes; 5 Integration of leprosy control work in primary health care.

The centre would welcome suggestions and comments for research on social science issues in leprosy from individual scholars and institutions. Those interested in pursuing research in their own institution or on behalf of the Centre are welcome to contact the Research Advisor.

The Centre will also organize workshops on social science research methodology for leprosy workers at Wardha and in other institutions. It would be the responsibility of the Centre to offer guidance to researchers in other institutions to design the research projects.

Professor R K Mutatkar, Medical Anthropologist from Poona University, has joined the Centre as Research Advisor.

The GMLF has formed a Social Science Advisory Panel of 8 experts which includes 1 leprologist, 1 leprosy worker, 1 educationist, 1 communication expert, 2 anthropologists, and 2 sociologists. The Panel will give all guidance to the Centre.

For further information: contact Shri S P Tare, Director, Gandhi Memorial Leprosy Foundation, Wardha-442, 103 India.

Poland honours Dr Wanda Blenska

The Medical Academy of the University of Poznan, Poland, recently conferred on Dr Wanda Blenska of the Buluba Leprosy Centre in Uganda the newly endowed 'Karl-Marcinkowski-Medal'. Dr Blenska has worked since 1950 in this centre in Uganda, which was founded by sisters of the Irish Order of St Francis in 1934. Apart from clinical and control work, Buluba has become famous in Uganda as a centre for teaching and training,

much of it supported by the German Leprosy Relief Association. We congratulate Dr Blenska on this richly-deserved honour from her mother-country and pay tribute to the long and highly significant contribution which she has made towards the control of leprosy in Uganda.

Distinguished Service Cross with Star for Dr Ruth Pfau

The Federal President Richard von Weizsäcker has awarded the Distinguished Service Cross with Star on behalf of the Federal Republic of Germany to Dr Ruth Pfau, sister of the Congregation 'Töchter vom Herzen Mariä', working in Pakistan. Dr Pfau has been working in leprosy since 1960, beginning with the care of about 700 patients in a shanty-town area of Karachi. She is now consultant adviser to the Ministry of Health and has established a comprehensive leprosy control programme covering the whole country, with about 17,000 patients currently under treatment. We warmly congratulate Dr Pfau on this honour and wish her every possible success in the continuing fight againt leprosy in Pakistan.

***Technical Guide for Smear Examination in Leprosy*, translated into Spanish**

The original version of this Guide for smear examination in leprosy has now been translated and published in Spanish and is available from Ayuda Alemana a los Enfermos de Lepra (AYU), Partado Aereo 91049, Zona 8, Bogota, Colombia. Enquiries may also be made to the German Leprosy Relief Association, D-8700 Wurzburg 11 Dominikanerplatz 4, West Germany. The English version is being reprinted and a French translation is in hand. Plans are also under discussion for a possible printing in India.

An ethical code for animal experimentation

This article from the WHO Chronicle, **39** (2); 51–56 (1985) carries the following summary:

Early in 1985 the Council for International Organizations of Medical Sciences (CIOMS) published *International Guiding Principles for Biomedical Research Involving Animals*. This was the culmination of a three-year programme initiated in 1982 with the encouragement of the WHO Advisory Committee on Medical Research and the active collaboration of expert staff members of WHO.

Particularly in view of the increasing—and at times violent—activities of various animal welfare groups, this article should be read in full by those who are responsible for laboratories in which animal experimentation takes place. The 'International Guiding Principles for Biomedical Research Involving Animals; Basic Principles', on page 54 of this article are of such importance that we reproduce them here in full:

I. The advancement of biological knowledge and the development of improved means for the protection of the health and well-being both of man and of animals require recourse to experimentation on intact live animals of a wide variety of species.
II. Methods such as mathematical models, computer simulation and *in vitro* biological systems should be used wherever appropriate.
III. Animal experiments should be undertaken only after due consideration of their relevance for human or animal health and the advancement of biological knowledge.
IV. The animals selected for an experiment should be of an appropriate species and quality, and the minimum number required, to obtain scientifically valid results.
V. Investigators and other personnel should never fail to treat animals as sentient, and should regard their proper care and use and the avoidance or minimization of discomfort, distress, or pain as ethical imperatives.
VI. Investigators should assume that procedures that would cause pain in human beings cause pain in other vertebrate species although more needs to be known about the perception of pain in animals.
VII. Procedures with animals that may cause more than momentary or minimal pain or distress should be performed with appropriate sedation, analgesia, or anaesthesia in accordance with accepted veterinary practice. Surgical or other painful procedures should not be performed on unanaesthetized animals paralysed by chemical agents.
VIII. Where waivers are required in relation to the provisions of article VII, the decisions should not rest solely with the investigators directly concerned but should be made, with due regard to the provisions of articles IV, V, and VI, by a suitably constituted review body. Such waivers should not be made solely for the purposes of teaching or demonstration.
IX. At the end of, or when appropriate during, an experiment, animals that would otherwise suffer severe or chronic pain, distress, discomfort, or disablement that cannot be relieved should be painlessly killed.
X. The best possible living conditions should be maintained for animals kept for biomedical purposes. Normally the care of animals should be under the supervision of veterinarians having experience in laboratory animal science. In any case, veterinary care should be available as required.
XI. It is the responsibility of the director of an institute or department using animals to ensure that investigators and personnel have appropriate qualifications or experience for conducting procedures on animals. Adequate opportunities shall be provided for in-service training, including the proper and humane concern for animals under their care.

PATH: Program for Appropriate Technology for Health

The relatively new organization known as PATH—Program for Appropriate Technology in Health—is a non-profit, non-governmental group devoted exclusively to the development and application of appropriate health technologies for primary health care in developing countries. Its journal, *Directions*, is published 3 times a year. Single copies are distributed at no cost to health program managers in developing countries and others interested in primary health care programs. For more information or copies of the newsletter write to editor Viven Davis Tsu, PATH, Canal Place, 130 Nickerson Street, Seattle, Washington 98109, USA.

Volume 5, No 1 for the first quarter of 1985, is devoted to 'primary eye care' and should probably be in the possession of all those who are involved with the diagnosis and treatment of eye problems in patients with leprosy. It is well-illustrated, clearly written and brief. The back page lists teaching–learning material relevant to this theme.

Notice on leprosy; Tata Steel and UNICEF in India

The Leprosy Awareness Campaign, c/o UNICEF, Information Service, Lodi Estate, New Delhi 110 003, in association with Tata Steel, has issued a notice of half-page size for publication in the Indian newspapers entitled 'I once had leprosy' and showing a 14-year-old boy whose leprosy was detected early and successfully treated, leaving no deformities. The accompanying text has headings: Early detection; Early intervention; Sustained treatment; There is nothing to fear. The footnote records that this approach has been taken '. . . in the interest of better understanding and support for the leprosy patient.' This bold and forthright approach by 2 important agencies in India is greatly to be admired and it is to be hoped that their message will have its intended impact in a country where social attitudes are of such critical importance to leprosy.

***Revista de Leprologia;* Fontilles, Alicante, Spain**

We appreciate receiving regular copies of this journal from Fontilles Leprosarium in Spain. The latest issue carries an excellent editorial by the director, Dr Terencio de las Aguas on physical rehabilitation of the patient with leprosy, followed by an extensive study of deep sensitivity in patients with leprosy by Dr Rosa Mateos Garcia of the Medical Faculty of Valencia. There are 112 references and this article makes an important contribution to an aspect of clinical leprosy which is often far from well described in textbooks. We take this opportunity of drawing attention to the exhaustive list of reviews of published articles on leprosy which regularly appear in this journal from Fontilles; this issue has no fewer than 34 pages of reviews, covering (in Spanish) all the usual subject headings from the medical press.

Leprosy eradication in Paraguay in the near future

The following information has been taken from Press information Number 29, issued by the German Leprosy Relief Association in October 1985:

'Within the next few months all the leprosy patients of Asuncion, the capital of Paraguay, will be cured. By 1990 leprosy will be eradicated in the whole country as in Malta, where the programme was successful by the end of 1984.' This announcement was made by Professor Dr Enno Freerksen, Director of the project, on the occasion of a seminar held in the Research Institute Borstel, near Hamburg, in co-operation with the German Leprosy Relief Association.

This success has been made possible by a combination of drugs developed at the Borstel Research Institute for Experimental Biology and Medicine supported by GLRA. It was Professor Freerksen who launched this project. In Paraguay there are 4000 tuberculosis patients being treated at the same time; the components of the multidrug therapy developed by Professor Freerksen and his collaborators are Rifampicin and Isoprodian (the latter = DDS, prothionamide and isoniazid).

IV European Leprosy Symposium on Leprosy Research, Genoa, Italy 1–5 October 1986

The main topics of this Symposium organized by Associazione Italiana 'Amici di Raoul Follereau' are: Biochemistry of *M leprae*; *In vitro* cultivation of *M leprae*; Immunology; Drug development for leprosy; and Multiple drug therapy of leprosy.

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

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

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

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

CONTENTS