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Editorial

MANAGERIAL IMPLICATIONS OF MULTIDRUG THERAPY

Summary The managerial effects of multidrug therapy (MDT) are discussed, using three possible models of leprosy control programmes, and tentative conclusions recorded. The three models may be modified according to local circumstances and local experience in particular control programmes.

Introduction

The widespread use of dapsone monotherapy revolutionized leprosy treatment. Activities focused on the outpatient clinic, and the long-stay leprosy 'home' became a base for the out-patient 'control' work. The base hospital today admits mostly short-term patients from a few days to a few months. Its work includes, or should include: (a) treatment of complications, e.g. reactions, eye problems, plantar ulcers, etc; (b) health education, e.g. orientation and motivation of patients towards regular treatment, the early detection of reactions, and in prevention and care of disability; (c) surgical and vocational rehabilitation, although not at all base hospitals.

In some limited geographical areas, efficient dapsone monotherapy has brought the control of leprosy nearer, as indicated by a change in the local picture of leprosy—fewer new multibacillary cases, and a significant reduction in the number of patients developing nerve damage and resultant disabilities.

In most areas though, dapsone-resistant leprosy has appeared. The aim of multidrug therapy is to prevent and/or overcome dapsone resistance, whether secondary or primary, to prevent the emergence of other drug resistances, and to provide quicker, more effective, and shorter-term treatment than is possible with dapsone alone.

As part of its long-term planning, The Leprosy Mission appointed a study group to assess the possible managerial effects of MDT, using regimens recommended by the World Health Organisation,[1] for the following durations:

(a) *Multibacillary patients* (MB)—at least 2 years treatment, and preferably until skin smears are Bacillary Index (BI) negative.

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(b) *Paucibacillary patients* (PB)—at least 6 months treatment (although there are growing signs that field workers in some areas are reluctant to stop treatment at this point, e.g. some wish to give 12 months continuous treatment).

It is still too early to assess the effectiveness of MDT, particularly in terms of relapse rates, and it will take several years to form a balanced view. The most optimistic forecasts suggest a rapid decrease in total case load where MDT is introduced, particularly through a rapid reduction in the number of PB cases needing treatment.

PB cases form a large majority of all leprosy cases worldwide, although the ratio of PB:MB varies in different areas from 85:15 to 70:30. (For discussion later in this paper an arbitrary ratio of 75:25 will be used.)

Methods

Taking a theoretical population of 100,000 with 1000 known patients, i.e. a prevalence of 10 per 1000, the effects of the introduction and use of MDT over a five-year period were examined. Three different models were used:

A. An 'ideal' programme, assuming 100% regularity of attendance, MDT being administered for the minimum recommended times,[1] no complications, and no new patients.
B. A 'realistic' programme, assuming less than 100% regularity, some patients requiring more than the minimum length of treatment, and new patients continuing to register for treatment during the 5-year time scale.
C. A 'pessimistic' programme based on experiences of average-to-low efficiency control schemes.

(NB—Most of the experience used to identify B and C is based on Asian conditions. Other parts of the world, may require different local modifications.)

CONTROL PROGRAMME A (100,000 population; 1000 registered patients)

This 'ideal' programme is not seriously considered to be a practical proposition. It assumes 100% regularity of attendance, bringing down the caseload to nil in 5 years, and also assumes no new patients join the programme, although it is realized that the prolonged period of incubation of leprosy precludes the last possibility. It is included for comparison with other programmes. A ratio of PB:MB of 75:25 is used throughout. (See Table 1.)

CONTROL PROGRAMME B (100,000 population; 1000 registered patients)

In this programme, the case load drops to approximately 50% within 12 months, but then the number drops only gradually over the next 5 years. (See Table 2.)

Table 1

Time	PB	MB	Total	Comments
Beginning of MDT	750	250	1000	
At 12 months	Nil	250	250	Assumed: all PB treatment concluded : all MB continue treatment
At 24 months	Nil	200	200	50/250 MB patients have concluded treatment without incident
At 60 months	Nil	Nil	Nil	250/250 MB cases have concluded treatment

Table 2

Time	PB	MB	Total	Comments
Beginning of MDT	750	250	1000	
At 12 months	Nil	250		Assumed: 750/750 PB treatment concluded
	+75	+25		
	+75	+25		250/250 MB continue treatment
	150	300	450	
				Add: *100 new patients from project area: 75 PB, 25 MB *100 new patients from outside area: 75 PB, 25 MB
At 24 months	Nil	200		Assumed: 150/150 PB's treatment concluded
	+60	+50		
	+75	+20		200/250 MB's still need treatment
	135	+25		
		295	430	50/50 second batch MB's still need treatment
				Add: †80 new patients from project area: 60 PB, 20 MB *100 new patients from outside area: 75 PB, 25 MB
At 36 months	120	235	355	By similar reasoning
At 60 months	90	195	285	By similar reasoning

* The figure of 100 new patients from inside the project area, and a similar figure from outside the project area, are arbitrary assumptions. In some highly-populated areas of Asia, e.g. a figure of even 200 might reasonably be argued. Conversely, in some areas where treatment for leprosy is widely available, there may be less or even no new patients from outside joining the project.

† The figure of 80 assumes that project area patients will slowly diminish, although in fact this may not happen for 5 years or more. Indeed, initially the number may rise because of early reporting by patients desirous of the new treatment.

Other factors should be remembered though, to obtain a full picture: (i) The number of new patients from inside the project area may not diminish as predicted. The *incidence* may show little change for some years because of the long incubation period for leprosy. (ii) Most patients will need regular check ups for several years. (iii) At the start of MDT, many patients will already have had leprosy for years and a significant number will continue to need help for residual disability and/or social problems. (iv) A number of apparently uncomplicated cases can still develop disability through nerve damage during and after treatment is concluded and, again, will need continuing help, although this number should eventually diminish.

As Wheate[2] says: '. . . discharge from chemotherapy is not to be equated with discharge from care . . .'.

Both A and B programmes assume that MDT will work just as predicted, with all patients 100% regular in attendance and responding according to plan. A rather less favourable picture, based on assumptions which are more pessimistic, but which could reasonably be argued from experience, is shown in Programme C.

CONTROL PROGRAMME C (100,000 population; 1000 registered patients)

From the 24-month point onwards, and assuming a continuation of these trends, the total case load would reduce by only 20–30 per annum, and could *even increase* somewhat if 100 patients per annum continue to come from outside the project area.

At 60 months there would be a fairly stable case load of about 500 with PB and MB's about equal in number. This would continue for some years, reducing only slowly, or until a thorough MDT programme were extended into adjacent areas (with the *added* costs of another, newer programme).

To this should be added annual check ups, help for the disabled, and the socially dislocated.

In theory, non-area patients could be refused. In practice, and in many Third World situations, this is very difficult on humanitarian grounds. We are left then with a picture in which MDT, in Programme C, would reduce the case load in 5 years to 50% but perhaps no less. (See Table 3.)

Discussion

1 COSTS

MDT will certainly increase the cost of individual treatment and, therefore, increase budget demands short term. Costs of medicine vary somewhat, and the comparison of costs of the 3 programmes is based on the following:

Table 3

Time	PB	MB	Total	Comments
Beginning of MDT	750	250	1000	
12 months	250	250		Assumed: 250/750 PB have been irregular, or need further treatment
	+75	+25		250/250 MB still under treatment
	+75	+25		
	400	300	700	
				Add: 100 new patients from project area: 75 PB, 25 MB
				100 new patients from outside project area: 75 PB, 25 MB
				(Collier's[3] statistical analysis suggests equal numbers of patients may come from within or outside project area)
24 months	100	200		Assumed: 100/750 original PB still need care
	+50	+50		50/150 of later PB still need care
	+60	+20		
	+75	+25		
	285	295	580	
				200/250 original MB still need care, because BI still positive and 50/50 later MB still need care
				Add: 80 new patients from project area: 60 PB, 20 MB
				100 new patients from outside: 75 PB, 25 MB
				(The reservoir of new patients in project area begins to decrease, but not that outside the project area)

(i) Dapsone monotherapy, per patient, per annum: US $2.25
(ii) MDT per paucibacillary patient for 6 months treatment, i.e. the minimum recommended by WHO: US $6.00
(iii) MDT per multibacillary patient, per annum: US $26.00

The costs are for medicines only, and do not include the other necessary costs of a control programme, e.g. salaries, transport etc.

It may be argued that although the initial cost is higher, the effective cost in curing one patient, and the effective cost of achieving local control of leprosy, will be lower long term, because of the speed and effectiveness of MDT. Even before

control, medium term costs will also be lowered by a rapid reduction in total case load. (For a modified view see below under 'Case Load'.)

It is noted that costs for medicine may amount only to between 10–20% of the total running costs of a leprosy control programme.

Table 4. Comparative costs in US of Programmes A, B and C. (Medical costs only)

	Dapsone monotherapy	Programme A	Programme B	Cost increase* (%)	Programme C	Cost increase* (%)
1st year	2500	11,000	11,000	(448)	11.000	(448)
2nd year	2500	6500	8700	(386)	10,200	(435)
3rd year	2500	2600	8480	(376)	9380	(416)
After 5th year	±2500	Nil	5610	(249)	8000	(355)

* Percentage cost increase as compared with dapsone monotherapy

2 CASE LOAD

The introduction of MDT should reduce significantly the total case load because: (i) before the local introduction of MDT, all patients will be screened, and many inactive PB cases released from control immediately without further treatment; and (ii) within 6–12 months of introducing MDT many PB cases (PB's being approximately 75% of the total caseload) will require no further treatment other than regular annual check ups. The reduction in the number of MB patients (25% of total) will not begin before 24 months and would be spread over a period of 24–60 months, or longer, because of the longer period of treatment recommended.

However, this 'ideal' view of MDT may be modified, particularly in some countries, by any of the following: (i) A percentage of PB's will need continuing care for complications arising from nerve damage. There will be fewer of these as time goes on, particularly from among new patients treated from the beginning with MDT, but every programme inherits a significant number of patients from earlier, less-effective, treatment. (ii) Few MB patients will be BI negative within 24 months. Most will need 60 months at least, many will need more. (It is understood that, while MDT may speed up changes in the morphological index, MI, it does not alter the rate of change in BI.) (iii) The number of patients requiring MDT in a particular programme will continue to increase for some time, for three reasons: (a) because there will still be undiagnosed and unregistered cases within the area, who will slowly report for treatment; (b) there will be cases already infected but who will only gradually show clinical signs of leprosy over the next ±10 years; and (c) patients may enter the area from outside, attracted by better treatment.

3 WORK LOAD

Case load and work load are not synonymous. The reduction in case load (the number of patients under active treatment) may not reduce proportionately the work load (the amount of work needed to run the treatment programme successfully). The introduction of MDT demands the highest standards of regularity of treatment, recording of treatment, laboratory services, treatment of complications, and staff training, and therefore increases the work load. A diagrammatic interpretation is given below.

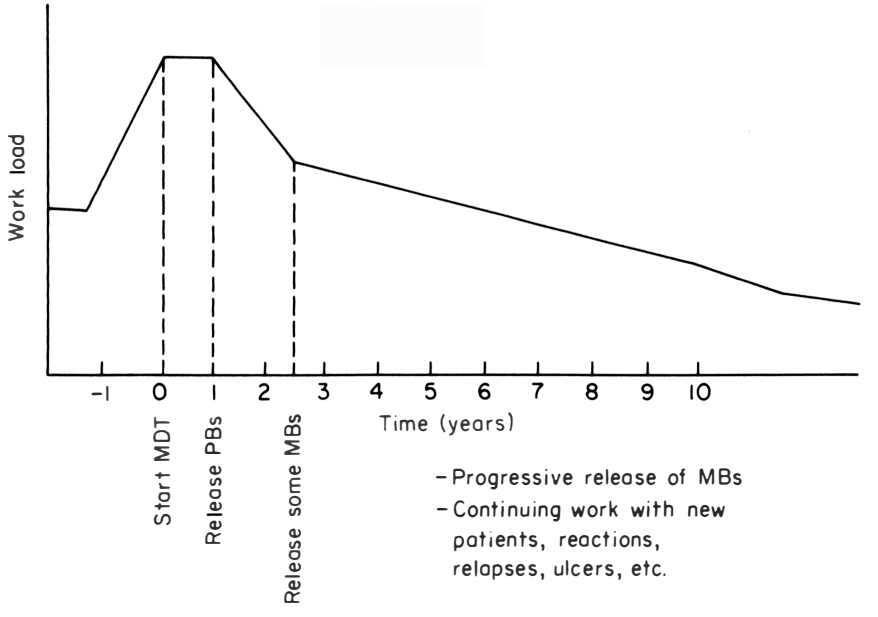

Figure 1. The effect on staff work load of introducing MDT.

4 IMPLICATIONS

Programme A. Cannot be expected to happen.

Programme B. In the Study Group's view, this is the most likely picture. After the initial release from control of old PB cases, and the discharge of many other PB's after 6–12 months MDT, the further reduction in case load will be gradual. Over the first 5 years therefore, clinics will still have to provide a regular service, although it may be possible to cut down the frequency, e.g. from weekly to monthly. A reduction in staff could then take place. Possibly up to 40–50% of paramedical workers (PMW) would no longer do intensive survey work, and the time spent at clinics would be less. In theory, skills could be 'doubled up,' e.g. a PMW could also acquire and use physiotherapy skills, or a physio-technician could take charge of shoe fitting or health education, etc. In practice, cultural

problems and/or trade union objections could slow this down. Travel would, however, be reduced somewhat.

If significant staff reductions are foreseen there are several alternatives: (i) redundancies and natural wastage. The first is unpleasant, the second slow; and (ii) redeployment in other geographical areas. Problems of language, culture and humanity may be involved. Redeployment of some categories *within* a language area is possible if control activities are extended to adjacent areas.

Rather than lose staff, it may be better to use the available time in more effective contact and absentee-tracing, health education, disability prevention, and care for patients' individual social and community needs.

The number of patients needing hospital admission would be reduced, although medical, surgical and physiotherapy services would continue to be needed by many patients for continuing disability. Reducing hospital admissions by, e.g. 50%, would not allow a similar reduction in staff or costs. For example, a ward of 20 beds may need 4 nurses to cover a 24-h day (2 on duty together during the busy day, the others singly in shifts). A 10-bed ward will still need 3 nurses to cover a 24-h day, singly in shifts.

5 GENERAL COMMENTS

(a) *Integration*. The desirability and practical outcome of integrating leprosy care into general medical services is a continuing, and separate debate. The effects of MDT on integrated services is difficult to assess. The hope that leprosy treatment would be limited, over a 24–60 months period, would help; but the need for absolute regularity of treatment with MDT is probably harder to achieve in a general health clinic than within a vertical leprosy programme.

(b) *Mobility*. If Programme A is practical then staff mobility and flexibility are important, either in moving to begin new and similar programmes in adjacent areas where their cultural background, language and experience could immediately be used, or in moving further away to areas of need. Modified movement could also be organized under Programme B although probably only to adjacent areas, rather than wider afield.

(c) *Social Care and Rehabilitation*. Whatever savings of money, time, and staff may be possible, they could well be redirected towards vocational and social rehabilitation for the handicapped.

(d) *Primary Health Care*. If case loads decrease, a widening of activities into other health problems, e.g. water supply, nutrition, immunization, could be considered.

Conclusions

This is an investigatory paper, and conclusions can only be tentative, being based on insufficient evidence of the practical effects of MDT.

(a) MDT is the most effective form of treatment now available, and is likely to be much more effective than dapsone monotherapy, although evidence of relapse rates will only become available in about 10 years time. It is very unlikely that any new, more effective drugs will become available during this time, and it will be at least that long before candidate vaccines, now under test, can be assessed.

(b) MDT will certainly increase medical costs for 5–10 years, with no corresponding reductions in other costs. This may not be dramatic, because the cost of all medicines in a control programme is usually between 10 and 20% of the total running costs.

(c) MDT will not reduce long-term costs generally, partly because of the continuing need to care for complications, and also to give social and vocational help. Also because MDT should be extended progressively to patients in adjacent areas. Budget demands, therefore, will remain high, as well as increasing by inflation.

(d) Laboratory facilities and services need to be improved, because of the importance of accurate diagnosis of MB and PB cases, in order to establish the appropriate treatment regime.

(e) Staffing levels will not be reduced significantly, although there may be significant retraining and redeployment of skilled workers.

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Lepr Rev (1985) **56,** 99–108

Rapid, radiometric *in vitro* assay for the evaluation of the anti-leprosy activity of clofazimine and its analogues

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Summary The effect of clofazimine and 6 analogues (B 3691, B 3713, B 3640, B 3648, B 720 and B 749) on the viability of *Mycobacterium leprae* was tested in a rapid, radiometric, *in vitro* assay. Thirteen human and 1 armadillo-derived freshly-extracted *M. leprae*, maintained in peritoneal macrophages, incorporated ^{3}H-thymidine to significant levels as compared to parallel cultures with heat-killed bacilli. Exposure of such cultures to clofazimine for 48 h showed significant inhibition of the radiolabel uptake without any adverse effects on the host macrophages. A sharp linear increase in inhibition was observable at concentrations from 1 to 10 ng/ml, with a plateau up to 40 ng/ml. Further increases of drug concentration up to 100 ng/ml showed marginal increase in the percentage inhibition of ^{3}H-thymidine incorporation. The analogues tested showed levels of inhibition similar to that of clofazimine when left for 72 h and 15 days in *M. leprae* macrophage cultures. However, they were less effective than clofazimine when tested for the shorter duration of 48 h at the lower concentration of 5 ng/ml.

Introduction

In recent years a rapid, radiometric, *in vitro* assay has been developed in the All India Institute of Medical Sciences for the evaluation of *Mycobacterium leprae* viability. Over a 2- to 3-week period, human and armadillo-derived *M. leprae* strains maintained in mouse peritoneal macrophages showed uptake of ^{3}H-thymidine to a significant degree as compared to parallel cultures with heat-killed bacilli.[1] That the incorporation of the radiolabel was in the bacilli and not in the host cell was shown by DNase experiments[2] and autoradiography.[4]

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This assay was used effectively: (i) to study the effect of dapsone (DDS, 4,4′-diaminodiphenylsulphone); (ii) to identify dapsone-resistant strains,[3] and (iii) to evaluate the antileprosy activity of rifampicin.[4] Moreover, immunologically-mediated inhibition of ^{3}H-thymidine incorporation was observed in *M. leprae* in macrophage cultures treated with antigen-induced lymphokines derived from tuberculoid leprosy patients.[5] Recently, we have been able to miniaturize this technique in microtitre plates (each having 96 flat-bottomed wells) thereby reducing the numbers of bacilli, radiolabel and macrophages required per assay.[6] This rapid *in vitro* assay compared well with the commonly-used mouse foot-pad model.[3] In the present study the inhibitory effect of clofazimine and its analogues has been investigated for 14 human and 1 armadillo-derived *M. leprae* strains maintained in murine macrophage cultures.

Materials and methods

ISOLATION OF *M. LEPRAE*

Skin biopsies from 14 bacilliferous, lepromatous patients, clinically suspected of dapsone resistance, were air freighted on ice from the Central Leprosy Training and Research Institute, Chingleput, India. Briefly, the bacilli were isolated in glass homogenizers with RPMI 1640 (Gibco Bio-Cult, Irvine, Scotland) and were counted by the method of Shepard & McRae.[7] The yield ranged from 3×10^7 to 4×10^8 bacilli per biopsy. The absence of contaminating bacteria and culturable mycobacteria was checked by plating on nutrient agar for 24 h and on Lowenstein–Jensen medium for 8 weeks. A sample from each batch of bacilli was autoclaved at 120°C at a pressure of 15 psi for 15 min.

MACROPHAGE CULTURES

Macrophage cultures were set up as described earlier.[2] In brief, non-stimulated peritoneal resident cells from Balb/c mice were collected by washing out the peritoneal cavity with 2–3 ml of cold RPMI 1640 containing 10 units per ml of preservative-free heparin (Upjohn Co., Kalamazoo, USA). The cells from individual mice were diluted with an equal amount of RPMI 1640 supplemented with 20% foetal-calf serum (Gibco, Bio-Cult, Irvine, Scotland). One millilitre of cell suspension (containing approximately $0{\cdot}5$–$0{\cdot}75 \times 10^6$ macrophages) was delivered into each Leighton tube incubated at 37°C. Subsequently, nonadherent cells were gently removed and the medium was replaced. The macrophages were maintained at 37°C for 24–48 h, after which 10^6 bacilli were introduced into each Leighton tube.

After the removal of unphagocytosed bacilli at 18 h, the medium was replaced with 1 ml of medium containing 1 μCi of methyl ^{3}H-thymidine (Amersham Corp.,

Arlington Heights, Illinois; specific activity; 42 Ci/mmol and respective concentration of clofazimine (B 663) and its analogues (B 3691, B 3713, B 3648, B3640, B 720 and B 749).

It was not possible to assay all the drug concentrations on each of human-derived *M. leprae* strains. Thus experiments were designed to test low (5 ng/ml); middle (10 ng/ml) and high (100 ng/ml) concentrations of clofazimine on individual *M. leprae* strains exposed for 48 and 72 h and 15 days maintained under similar culture conditions. On 1 armadillo derived *M. leprae* strain full dose response (1, 2·5, 5, 10, 20, 40, 50 and 100 ng/ml) and time kinetics (2, 6, 18, 24, 48, 72 h and 15 days) were done.

In addition 3 human derived *M. leprae* strains were exposed to 5, 10 and 100 ng/ml of clofazimine analogues (B 3691, B 3713, B 3648 and B 3640) along with clofazimine (B 663) for 48 and 72 h and 15 days.

Analogues B 720 and B 749 were tested on 2 human derived *M. leprae* strains at 5, 10 and 100 ng/ml and 15 days exposure.

The drugged medium was then removed and replaced with drug-free medium containing labelled thymidine. This medium was routinely renewed every 4–5 days. Macrophages were harvested by stripping with a rubber policeman after treatment with 100 μl of 2% Xylocaine (Astra, India). Then they were serially washed with saline containing cold thymidine 1 mg/ml, and twice with 5% trichloracetic acid and methanol. The dried discs were counted in a scintillation counter (LKB, 1215 Rackbeta II).

Using the same batch of macrophages, 5 replicates of each of the following were set up: (I) macrophage cultures alone, (II) macrophages with freshly-isolated 'live' *M. leprae,* (III) macrophages and heat-killed *M. leprae* of the same strain, (IV) II plus test concentrations (ng) of clofazimine and its analogues, (V) II plus diluent equivalent, and (VI) III + test concentrations of drug.

Mean counts per minute (cpm) $\pm$ standard error of 3 to 5 cultures were calculated. The percentage inhibition in the presence of clofazimine or its analogues was calculated as follows:

$$\text{Percentage incorporation} = \left[\frac{\text{Mean cpm of IV} - \text{Mean cpm of III}}{\text{Mean cpm of II} - \text{Mean cpm of III}}\right] \times 100$$

Percentage inhibition = 100 − percentage incorporation.

STATISTICAL ANALYSIS

For the assessment of significant values the non-parametric Mann–Whitney *U* test was used.

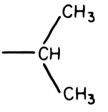
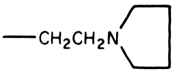
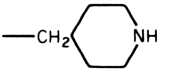
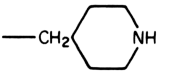
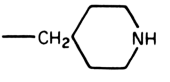
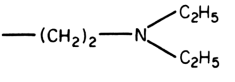
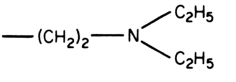
DRUGS

Clofazimine and its analogues B 3691, B 3713, B 3640, B 3648, B 720 and B 749

were prepared in the Laboratories of the Medical Research Council of Ireland. The structures and details of the analogues are given in Table 1.

Of these compounds (B 3691, B 3713, B 3640 and B 3648) were designed as part of a WHO project to develop new analogues of clofazimine which would be active against clofazimine-resistant strains of *M. leprae*. Assessment of activity was carried out *in vitro* using *M. smegmatis strain 607* (sensitive to 1·5 μg/ml) and its clofazimine-resistant variant (resistant to 30 μg/ml). These new analogues have been shown in the Johns Hopkins University, Baltimore, USA, to inhibit the clofazimine-sensitive strain at 0·2–0·4 μg/ml and the clofazimine-resistant variant at 0·4–2·0 μg/ml (N E Morrison, personal communication).

Table 1. Formulae of clofazimine and analogues

Code No.	Structure R′	Structure R	Melting point
B 663	Cl		211° decomp.
B 3691	H		161° decomp.
B 3713	CH_3		168° decomp.
B 3640	Cl		186° decomp.
B 3648	H		156° decomp.
B 720	H		—
B 749	Cl		—

All compounds were chromatographically pure and all analysed satisfactorily.

The compounds were dissolved in ethyl alcohol (1 mg/ml) and further diluted to 1 μg/ml in RPMI 1640, sterilized through 0·22 μm filters (Millipore Corporation, Mass., USA) and kept at 4°C. Working solutions were freshly made in RPMI 1640 just prior to use.

Results

M. leprae strains derived from 14 bacilliferous, lepromatous patients suspected of dapsone resistance, and from 1 infected armadillo liver, were tested in murine macrophage cultures. Of the 14 patients, 12 were proved to have full resistance for DDS in the macrophage culture assay (data not provided). None of these patients was known to have received clofazimine. Thirteen of the 14 human-derived and the 1 armadillo-derived *M. leprae* strains incorporated significant levels of ^{3}H-thymidine in cultures with freshly-isolated 'live' bacilli as compared with control cultures with heat-killed bacilli from the same biopsy ($P < 0{\cdot}005$ to $0{\cdot}001$, Figure 1).

Adherence properties of macrophages were similar in cultures with resident *M. leprae* maintained over a 2 to 3-week period with and without clofazimine or its analogues. After 72-h exposure to drugs many macrophages showed golden

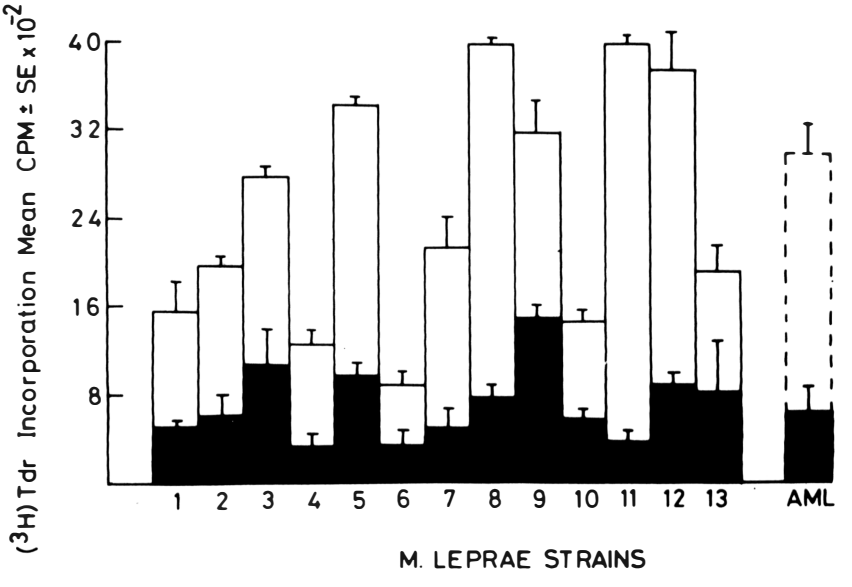


Figure 1. Incorporation of ^{3}H-thymidine by 13 human-derived *M. leprae* strains and 1 armadillo-derived *M. leprae* strain (AML) maintained in murine macrophages (mean cpm ± se of 5 replicate cultures). Numbers along the abscissa refer to *M. leprae* strains. All the strains showed significant incorporation of ^{3}H-thymidine ($P < 0{\cdot}05$) in cultures of live bacilli (□) as compared with heat-killed bacilli of the same strain (■).

brown inclusions in the cytoplasm. The effect of various concentrations of clofazimine and its analogues on individual *M. leprae* strains is expressed as the percentage inhibition of ^{3}H-thymidine uptake in cultures containing *M. leprae* and drug as compared with parallel cultures without drug. In general, it was observed that $\geqslant 50\%$ inhibition gave a P value of $<0{\cdot}05$ to $0{\cdot}01$ by the Mann–Whitney U test.

Table 2 shows representative control experiments where no significant differences in ^{3}H-thymidine incorporation were observed between (a) cultures of live bacilli exposed to ethyl alcohol diluent in concentrations equivalent to those used for dissolving clofazimine analogues, and (b) cultures of heat-killed bacilli in the presence and absence of the drug.

Table 2. Representative experiment showing negligible effects of diluent and drug on control macrophage cultures

(a)

	^{3}H-thymidine incorporation (mean cpm ± se)* Killed = 406 ± 106 Live = 4234 ± 296			
Cultures 'live'	5 ng drug	Equivalent diluent	100 ng drug	Equivalent diluent
+ B 663	1234 ± 236	4011 ± 168	1114 ± 126	4198 ± 185
+ B 3691	1186 ± 265	4210 ± 289	1268 ± 191	4111 ± 273
+ B 3648	1150 ± 256	4027 ± 135	1086 ± 160	4139 ± 225
+ B 3640	1864 ± 315	4269 ± 333	1279 ± 340	4222 ± 373
+ B 3713	1986 ± 230	4085 ± 216	1645 ± 235	4115 ± 207

(b)

Cultures	Drug conc. (ng/ml)	^{3}H-thymidine incorporation (mean cpm ± se)*
Killed + B 663	0	406 ± 106
	1	410 ± 17
	2·5	417 ± 29
	5	331 ± 36
	10	342 ± 122
	20	336 ± 29
	40	398 ± 125
	50	350 ± 20
	100	316 ± 33

* Five replicate cultures

EFFECT OF CLOFAZIMINE (B 663)

(a) *Time kinetics*

Figure 2 shows that at 10 and 100 ng/ml of B 663, inhibition of the ^{3}H-thymidine uptake was discernible at 24 h and reached significant and maximal levels at 48 h. Further incubation of cultures with the drug for 72 and 360 h (15 days) did not increase the inhibitory effects to a significant degree.

(b) *Dose response*

Results obtained on 1 armadillo-derived *M. leprae* strain maintained in macrophage cultures in the presence of 1 to 100 ng/ml of clofazimine are shown in Figure 3. A sharp, linear increase in percentage inhibition of ^{3}H-thymidine incorporation was observed from 1 to 10 ng/ml, followed by a plateau from 20 to 40 ng/ml. Increasing the concentration of B 663 from 50 to 100 ng/ml showed a marginal increment in inhibition of the radiolabel uptake.

EFFECT OF CLOFAZIMINE ANALOGUES

B 3691, B 3713, B 3640 and B 3648 were tested in parallel with clofazimine on human-derived *M. leprae* strains. Representative results obtained on 3 strains tested with 5, 10 and 100 ng/ml of drugs for 48 and 72 h and 15 days are given in Figure 4. These analogues showed significantly less inhibition than the parent compound at 48 h exposure at the lower concentration of 5 ng/ml ($P < 0{\cdot}005$ to

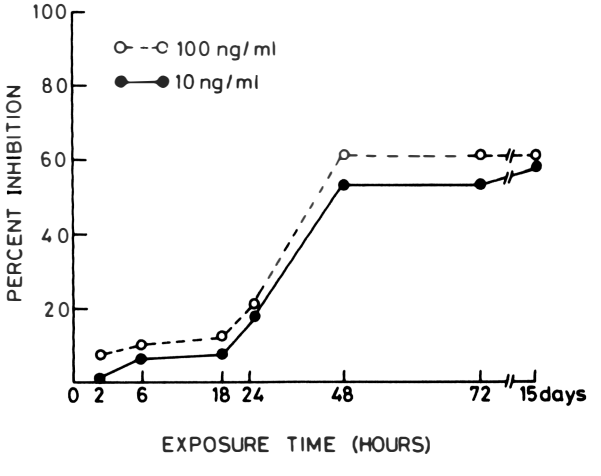


Figure 2. The response of an armadillo-derived *M. leprae* strain to a different exposure time (2 h to 360 h) of B 663 at 10 ng (●——●) and 100 ng/ml (○——○) on ^{3}H-thymidine incorporation expressed as percent inhibition.

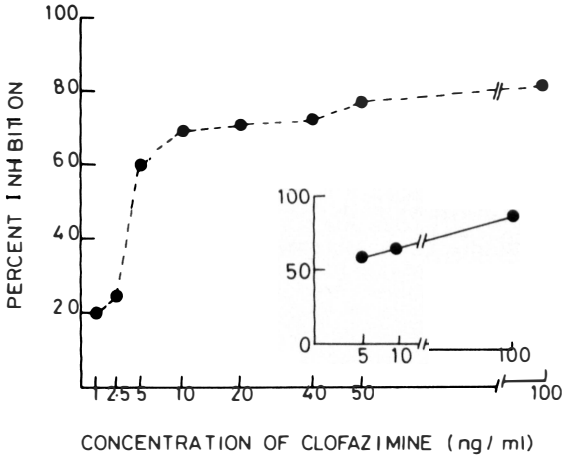


Figure 3. The effect of 1 to 100 ng of clofazimine (B 663) per ml on ^{3}H-thymidine incorporation in 1 armadillo-derived *M. leprae* strain (●– – –●) expressed as percent inhibition. The inset shows mean percent inhibition obtained with 3 human-derived *M. leprae* strains (●——●) each of which were tested at 5 ng, 10 ng and 100 ng/ml of B 663.

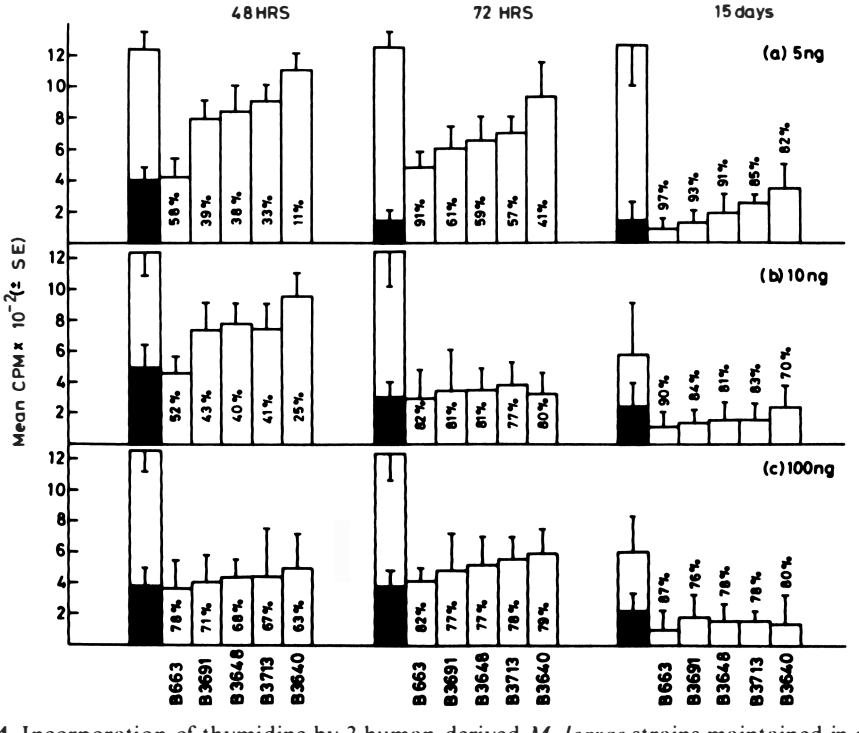


Figure 4. Incorporation of thymidine by 3 human-derived *M. leprae* strains maintained in murine macrophage (mean cpm ± se) in the presence of clofazimine (B 663) and clofazimine analogues (B 3691, B 3648, B 3713, B 3640) at different concentrations of drug: (a) 5 ng/ml, (b) 10 ng/ml, and (c) 100 ng/ml exposed for 48 h, 72 h and 15 days. The values in the bar indicate the percent inhibition of the uptake of the radiolabel in the presence of drug. □, mean cpm ± se with live bacilli ■, mean cpm ± se with heat-killed bacilli.

Table 3. Effect of clofazimine analogues (B 720 and B 749) on ^{3}H-thymidine incorporation in 2 human-derived *M. leprae* strains maintained within macrophages

		Mean cpm of 'live' *M. leprae*			
			Drug ng/ml		
Strain No.	Drugs	Without drug	5	10	100
I	B 720	872	384 (56)*	346 (60)	280 (67)
	B 749	872	427 (51)	261 (70)	273 (71)
II	B 720	5108	1700 (67)	1440 (72)	764 (85)
	B 749	5108	1381 (73)	1205 (77)	784 (82)

* Percent inhibition of ^{3}H-thymidine is shown within parenthesis.

Mean cpm $\pm$ se of cultures with killed *M. leprae* of strain I and II was respectively 338 ± 34 and 944 ± 18.

P value $< 0{\cdot}05$ to $0{\cdot}01$ by the Mann–Whitney *U* test.

0·001). However, they showed similar levels of inhibition as clofazimine when left for 72 h and 15 days.

Analogues B 720 and B749 were also tested on 2 human *M. leprae* strains in a 15-day assay. Significant inhibition of ^{3}H-thymidine incorporation was observed at 5, 10, 100 ng/ml (Table 3).

Discussion

In general, it may be observed that the clofazimine analogues exerted levels of inhibition similar to those of the parent compound. In experiments with lower concentrations of drugs and a short exposure of 48 h, clofazimine was more effective than the analogues. However, at higher concentrations of 10 ng/ml and 100 ng/ml similar levels of inhibition were observed with all drugs. As expected, percentage inhibition for each strain varied for the same analogue. Amongst the analogues B 3691 appeared to be the most inhibitory.

It is of interest that of the 4 analogues examined B 3691 is the one most closely related structurally to 2 others of our compounds, B 720 and B 749, which have been shown[8] to be active in the mouse foot-pad assay although they were of only very moderate activity in experimental tuberculosis of mice.[9] Not all clofazimine analogues are well absorbed from the mouse gut on oral administration. Of the above 6 analogues, only B 720, B 749 and, to a lesser extent, B 3691 are satisfactory in this respect.

Acknowledgments

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The effect of *Mycobacterium leprae* on PHA- and PPD-induced inhibition of leucocyte migration in leprosy patients

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Summary The effect of *Mycobacterium leprae* was studied on mitogen, PHA and antigen, PPD-induced leucocyte migration inhibition in 44 leprosy patients and 13 healthy controls using the leucocyte migration inhibition test. While *M. leprae* decreased the PHA-generated inhibition of migration of leucocytes in tuberculoid patients and healthy individuals, it enhanced the inhibitory effect on the leucocyte migration in lepromatous patients. However, a uniform decrease by *M. leprae* was observed on PPD-induced leucocyte migration inhibition in both groups of leprosy patients and healthy controls.

Introduction

The nature of resistance in tuberculoid (TT) leprosy and lack of it in lepromatous leprosy (LL) remains unknown. Bacillary load in the former is absent or minimal while in the latter it is high. The anergy obtained in LL may be attributed to this. The effect of *Mycobacterium leprae* on the blastogenic responses of peripheral blood mononuclear cells of leprosy patients induced by mitogens, Phytohaemagglutinin (PHA) and Concanavalin-A (Con-A) and a cross-reacting antigen, purified protein derivative (PPD) of tuberculin has been reported by some investigators.[1,7,13] Suppression or enhancement of the blastogenic responses not only varied with the type of leprosy but also was dependent on the *M. leprae* preparation, whole or sonicated. Two studies,[5,7] came to opposite conclusions using Dharmendra antigen and whole autoclaved *M. leprae* respectively on the inducibility of *M. leprae* specific suppression in leprosy polar groups. We report here observations on the effect of *M. leprae* on PHA- and PPD-induced release of lymphokine effecting leucocyte migration in the leucocyte migration inhibition test (LMIT).

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Materials and methods

TEST SUBJECTS

Forty-four leprosy patients, 18 LL and 26 TT attending out-patient departments of Gandhi Hospital, Sivananda Rehabilitation Home and Dhoolpet Leprosy Research Centre, all in Hyderabad City, South India, were included in the study. The lepromatous group here, includes 15 polar lepromatous type (LL) and 3 borderline lepromatous (BL) patients and the tuberculoid group includes 10 polar tuberculoid (TT) and 16 borderline tuberculoid (BT) patients. All of them were untreated. They were classified on the Ridley–Jopling scale.[11] The control group comprised of 13 healthy contacts who have been working in the field of leprosy for 3 to 5 years.

MITOGEN AND ANTIGEN

Phytohaemagglutinin-P (PHA) was a Difco product and purified protein derivative (PPD) of tuberculin (Mammalian) was obtained from Staten Serum Institut, Copenhagen. 1 μl/ml of PHA and 25 μg/ml of PPD were found to be optimal in our LMIT system (data not shown), and were used as optimal dose in this study. Armadillo-derived whole *M. leprae*, Batch No. AB 51, supplied by National Institute of Medical Research, London, was used at a concentration of $2{\cdot}5 \times 10^7$ bacilli/ml which was shown as optimal dose in LMIT in an earlier study from our laboratory.[4]

LEUCOCYTE MIGRATION INHIBITION TEST

The original method[12] was used with some modifications. Briefly to 15 ml of acid citrate dextrose (ACD) anti-coagulated blood, 7·5 ml of 3% gelatin (Sigma Chemical Co., USA) in saline was added in a culture tube. After thorough mixing, it was incubated for 45 min at a slanting position at 37°C to sediment erythrocytes and leucocyte-rich plasma was aspirated. After centrifugation, pelleted leucocytes were washed with Minimum Essential Medium (MEM), Bios, Bombay and finally resuspended in MEM to give a concentration of 30×10^6 cells/ml. Viability was checked with 0·2% Trypan Blue. The cell suspension was loaded into capillaries (Arthur Thomas Co., USA), sealed with modelling clay at one end and centrifuged at 1000 rpm for 5 min. The capillaries were then cut at the cells-medium interface and were kept in polystyrene chambers (Laxbro, Pune). Immediately, chambers were filled with MEM containing 20% foetal calf serum (FCS), Microlab, Bombay with or without antigen or mitogen and then sealed with cover-slips and incubated at 37°C for 18 h. Each test was run in triplicate. The areas of migration were measured with a planimeter. The migratory index (MI) was calculated as follows:

$$MI = \frac{\text{Average area of migration with antigen or mitogen}}{\text{Average area of migration with medium alone}}.$$

$$\text{Migratory Inhibition} = 1 - MI$$

Effect of *M. leprae* on PHA- and PPD-induced effect on leucocyte migration was observed with addition of *M. leprae* simultaneously with PHA or PPD by noting the percentage change in average area of migration with the following formula.

% *M. leprae* effect on PHA or PPD:

$$100 - \frac{(\%\text{ Migratory inhibition of } M.\ leprae + \text{PHA or PPD})}{\left(\begin{matrix}\%\text{ Migratory inhibition} \\ \text{of } M.\ leprae \text{ alone}\end{matrix}\right) + \left(\begin{matrix}\%\text{ Migratory inhibition} \\ \text{of PHA or PPD alone}\end{matrix}\right)} \times 100.$$

The increased/decreased area of migration of leucocytes in *M. leprae*- PHA or PPD combination tests, compared to the area of migration in PHA or PPD alone tests, were shown as *M. leprae* induced inhibition (−) enhancement (+) response to PHA or PPD respectively.

Two sampled Students 't' test and Median test were used for statistical analysis.[2]

Results

No significant differences were observed in the mean Migratory Index (MI) values of PHA and PPD among the 2 leprosy patient groups and healthy control group. The mean MI value of *M. leprae* of the LL group (0·97) showed a highly-significant difference ($P < 0{\cdot}001$) when compared to that of the TT patient group (0·81) and healthy control group (0·85) (Table 1 and Table 2). There was no correlation between the responses of *M. leprae* and PPD in all the 3 groups of subjects studied (lepromatous group r = 0·0102; tuberculoid group r = 0·1560; healthy control group r = 0·3826).

EFFECT OF *M. LEPRAE* ON PHA

Table 1 and Figure 1 give the details of statistics and pattern of effect of *M. leprae* on PHA responses respectively. Thirteen out of 18 LL group patients showed enhanced PHA responses on addition of *M. leprae* whereas 5 showed inhibition, with an overall median percent of enhancement of +6·0. Out of the 26 TT group patients, 19 showed inhibitory responses whereas 7 showed enhanced responses with an overall median percent of inhibition of −40·0. Eleven out of 13 healthy contacts showed inhibitory responses and only 2 showed enhanced responses with an overall median percent of inhibition of −39·0. Inhibition of PHA

Table 1. Effect of whole *M. leprae* on PHA-induced inhibition of leucocyte migration in the comparing groups

	Migratory index Mean ± SE (median)		
	Lepromatous group	Tuberculoid group	Healthy control group
Whole *M. leprae*	0·97 ± 0·01 (0·99)	0·81 ± 0·02* (0·81)	0·85 ± 0·02* (0·84)
PHA	0·57 ± 0·05 (0·55)	0·51 ± 0·03 (0·52)	0·59 ± 0·03 (0·62)
Whole *M. leprae* + PHA	0·50 ± 0·05 (0·43)	0·58 ± 0·03 (0·61)	0·65 ± 0·06 (0·69)
Median % effect of *M. leprae* on PHA	+6·0	−40·0†	−39·0†
Number of subjects	18	26	13

−, Indicates Inhibition; +, indicates Enhancement.

* Indicates $P < 0·001$ significance by Students 't' test compared to Lepromatous group.

† Indicates $P < 0·01$ significance by Median test compared to lepromatous group.

Table 2. Effect of whole *M. leprae* on PPD-induced inhibition of leucocyte migration in the comparing groups

	Migratory index Mean ± SE (median)		
	Lepromatous group	Tuberculoid group	Healthy control group
Whole *M. leprae*	0·97 ± 0·01 (0·99)	0·81 ± 0·02* (0·81)	0·85 ± 0·02* (0·84)
PPD	0·76 ± 0·06 (0·68)	0·74 ± 0·05 (0·75)	0·63 ± 0·06 (0·65)
Whole *M. leprae* + PPD	0·79 ± 0·05 (0·71)	0·74 ± 0·05 (0·77)	0·66 ± 0·05 (0·68)
Median % effect of *M. leprae* on PPD	−25·0	−41·0	−43·0
Number of subjects	18	21	13

− Indicates Inhibition.

* Indicates $P < 0·001$ significance by Students 't' test compared to lepromatous group.

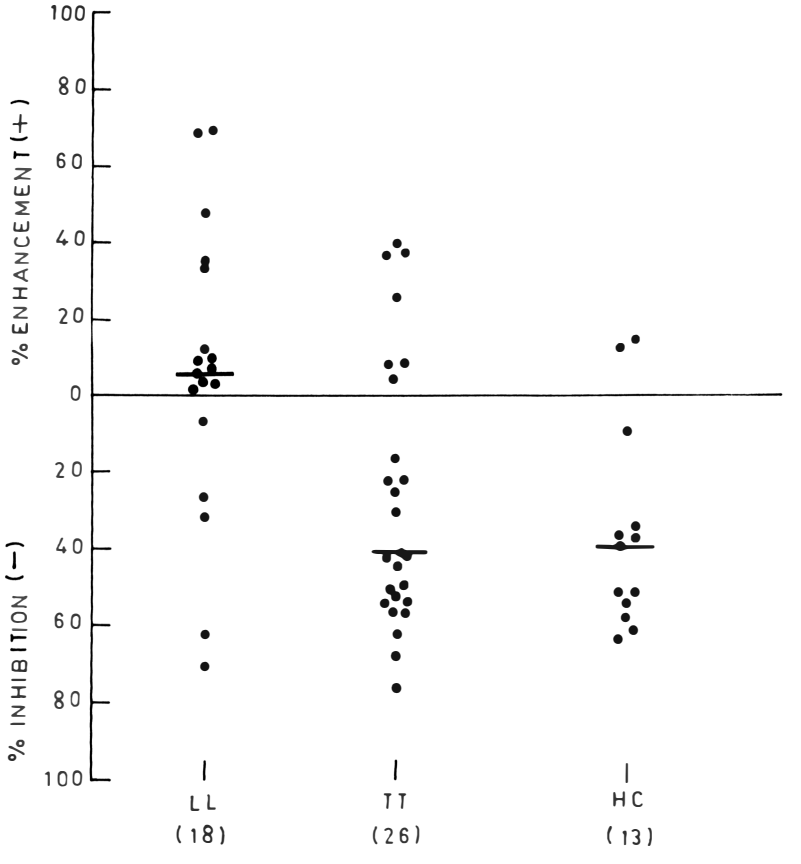

Figure 1. Effect of *M. leprae* on individual PHA responses in lepromatous (LL), tuberculoid (TT) and healthy contact (HC) groups (− denotes median).

responses in the TT and healthy contact groups was very significant ($P<0{\cdot}01$) when compared to the LL group.

EFFECT OF *M. LEPRAE* ON PPD RESPONSES

The effect of *M. leprae* on PPD responses are given in Table 2 and pattern in Figure 2, for the comparing categories respectively. Thirteen out of the 18 LL group patients showed inhibitory responses to PPD on addition of *M. leprae* and the remaining showed enhanced responses with an overall median percent inhibition of −25·0. Out of the 21 TT group, 16 showed inhibitory responses whereas 5 showed enhanced responses, with an overall median percent inhibition of −41·0. Among the healthy contacts, 10 showed inhibitory responses whereas 3 showed enhanced responses, with an overall median percent inhibition of −43·0. There is no significant difference between the 3 groups compared.

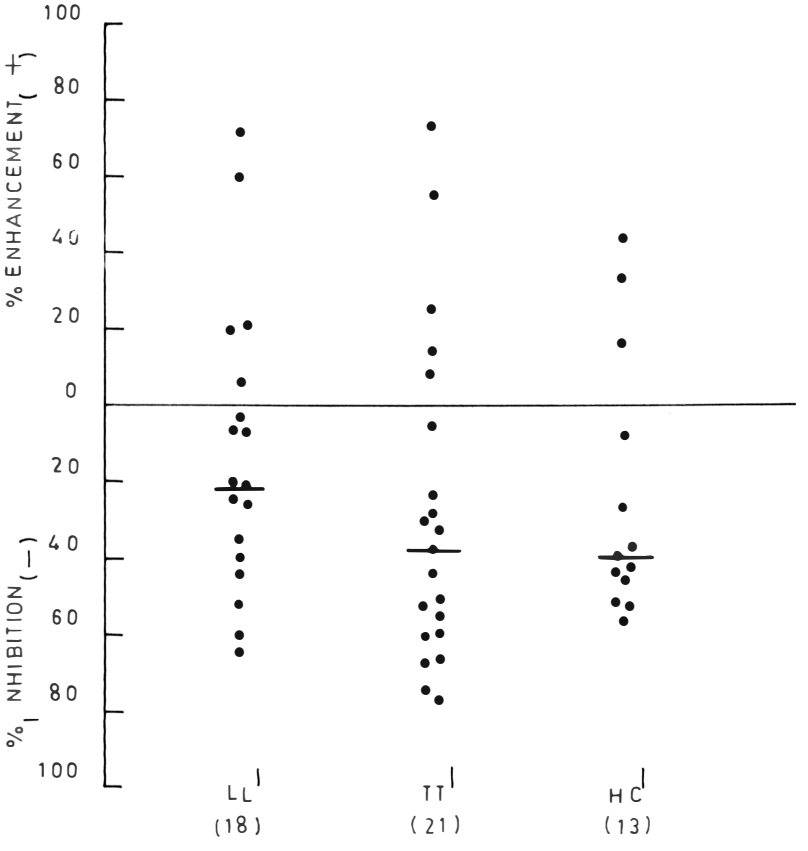

Figure 2. Effect of *M. leprae* on individual PPD responses in lepromatous (LL), tuberculoid (TT) and healthy contact (HC) groups (− denotes median).

Discussion

It has been reported[1] that sonicated *M. leprae* suppressed PHA-induced blastogenic responses of peripheral blood mononuclear cells of all leprosy patients and contact individuals. Under similar conditions, whole *M. leprae* showed stimulatory proliferative responses to BT patients but had no effect on BL and LL patients. Similarly, it has been reported[13] that the *in vitro* blastogenic response of PHA stimulated peripheral blood mononuclear cells can be suppressed by the addition of *M. leprae* among LL, TT patients and healthy volunteers. No significant suppressive effect was observed with PPD. However, one study[7] has reported uniform suppression with PPD in all leprosy patients.

Some elegant studies on the antigen specific suppressive effects of *M. leprae* utilized Con-A as a mitogen and inducer of suppressor cells for blastogenic responses of the peripheral blood mononuclear cells *in vitro* from leprosy patients. One study[5, 6] has reported inhibition of blastogenic responses by

Dharmendra lepromin in the LL and BL patients and further showed that TH_2^+/OKT8$^+$ cells associated with suppressor activity are involved. On the other hand, another study[7] using whole, autoclaved *M. leprae* showed suppression of Con-A induced lymphocyte proliferation in TT patients, whereas there was enhancement in LL patients. It was also shown that there is an absence of hyperactive clones of suppressor cells in LL patients.[8]

Recent studies, however, have shown that LL patients have defective lymphocytes and that the lack of response is not due to absence of *M. leprae* reactive T cells. One study[3] has shown that addition of Interleukin-2 (IL-2) to peripheral blood mononuclear cells from LL patients makes them respond to proliferative stimulus of *M. leprae*. Further, another study[9] shows that peripheral blood mononuclear cells from LL patients are defective in the production of gamma Interferon essential for activation of macrophages and this defect was partially restored by the addition of purified IL-2 and *M. leprae* antigen to the culture medium and not with IL-2 alone.

We have measured the effect of *M. leprae* on a different parameter, the migration of leucocytes which is inhibited by a lymphokine, leucocyte inhibitory factor (LIF) released by peripheral blood mononuclear cells when they are stimulated with a mitogen or an antigen. PHA, a mitogen, inhibited the migration of leucocytes in normal individuals and leprosy patients to the same extent (Table 1). *M. leprae* antigen also slows down the migration of leucocytes in TT patients which is of the same magnitude as in normal contacts. However, LL patients do not give this response. When *M. leprae* was added along with PHA in this study, the inhibitory response was more than additive in LL patients whereas it was reduced in TT patients. The less than additive effect in TT patients is as expected when 2 simultaneous stimuli are applied. However, the enhanced response in LL patients is interesting. PHA is a potent inducer of IL-2 secretion and preferentially stimulates OKT4$^+$, a helper subset of T lymphocytes.[10] The synergic effect observed when PHA and *M. leprae* are added together, is due to the release of IL-2 by PHA which in the presence of *M. leprae* brings out the enhanced response in LL cells and which *M. leprae* alone cannot elicit. These results are identical to the observations[3] which demonstrated proliferative responses of peripheral blood mononuclear cells after addition of IL-2 along with *M. leprae* and indicate that *M. leprae* reactive T cells are present in the LL patients and IL-2 makes them respond to *M. leprae* stimulus. It would be interesting to observe if IL-2 replaces PHA in its effect on leucocyte migration of LL patients.

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Radioimmunoassay of serum cortisol levels in leprosy patients with special reference to type I and type II reaction

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Summary In the present paper, an attempt has been made to assess the adrenal cortical functions in leprosy patients, especially in LL cases and also in patients with type I and type II lepra reaction by estimating serum cortisol levels in them and comparing these results with those in healthy adults. Both the patient and control population belonged to a copper mining district in an eastern state of India.

Eighty leprosy patients including 23 LL, 17 BL, 3 BB, 7 BT and 30 patients with type I (10 cases) and type II (20 cases) lepra reactions formed the basis of this study. Forty-one age-matched normal adults from similar socio-economic status served as controls. The mean basal serum cortisol levels in 23 LL cases and 41 controls were 18·21 and 12·98 μg/dl, respectively. Diurnal variation of serum cortisol level was studied in 4 LL cases who showed normal circadian rhythm. Intramuscular injection of ACTH in another 4 patients (2 LL and 2 BL) showed an increase of mean serum cortisol level from 14·75 μg/dl to 21·75 μg/dl after 30 min of challenge. Most interestingly, it was found that at the onset of type II lepra reaction the mean serum cortisol level increased to 17·35 μg/dl and after remission of ENL its level decreased to 11·41 μg/dl. The difference was statistically significant ($P < 0{\cdot}01$). On the contrary, no such variation was found in patients with type I reaction.

Introduction

Leprosy is a chronic infective disease which not only involves skin and mucous membrane but also endocrine organs.[1] The adrenal gland is not usually affected. Small nodules have been reported in zona faciculata and reticularis and also

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around the medullary veins.[2, 3] Some studies have[4-6] determined urinary 17 ketosteroids and 17 corticoids while another study[7] evaluated the functional state of adrenals in leprosy by estimating serum cortisol levels. Lately reduced suppressor T-cells in ENL patients have been described.[8, 9] Also it is suggested[10] that during stress there is raised cortisol level with increased percentage of helper-inducer-T-cells. It is therefore interesting to assess the adrenal function by estimating serum cortisol levels, for very little information is available in literature on this aspect, especially during lepra reaction. The present study focuses attention on multibacillary lepromatous and borderline lepromatous cases and also in patients during reaction and following clinical remission of reaction. It seems likely that it may throw some light on the role of the adrenal gland on the course of lepra reaction.

Materials and methods

Fifty multibacillary patients including 23 polar lepromatous (LL), 17 borderline lepromatous (BL), 3 borderline borderline (BB), and 7 borderline tuberculoid (BT) cases took part in this study, 37 were males and 13 females. The diagnosis of these patients was made on the basis of 5 group classification.[11] Their age ranged from 12 to 65 years; and the duration of their illness varied from 1·5 to 25 years. None had any endocrine disorder. Dapsone was being administered to all of these patients. In addition 15 of them were receiving multiple drug therapy comprising clofazimine and rifampicin.[12] Of these patients, 4 LL male cases were subjected to excess diurnal rhythm of serum cortisol levels. Another 4 male cases (2 LL and 2 BL) were subjected to test endogenous cortisol production after adrenocorticotrophic hormone (ACTH) challenge. No patient was on corticosteroid therapy at the start of the test. To study the adrenal function during lepra reaction, 30 patients including 4 females were taken (Table 1). The diagnosis of the type of reaction was made on recognition of their well-formed clinical features.[13] Their ages ranged from 15 to 70 years; and their duration of illness from 1 to 11 years. All these patients received corticosteroids to control their reaction. In addition 7 cases of LL and BL leprosy with type II reaction also received rifampicin. Remaining patients were on dapsone. Two samples of blood were collected from these patients, one at the onset of reaction and before administration of steroids; and the other at the clinical remission of reaction only after they were totally weaned of steroids. Forty-one healthy male volunteers of similar age range and socio-economic background and from the same area served as controls.

For estimating the basal serum cortisol level 5 ml of blood was collected from each subject at 9 am. To study the circadian cortisol rhythm, paired blood samples were taken at 9 am and 6 pm. The adrenal cortical sufficiency during stress was assessed by the collection of paired samples before, and 30 min after, intramuscular injection of 40 units ACTH.

Table 1. Histological types of the patients of type I and II lepra reactions

	Lepra reaction (no. of cases)	
Histological type	Type I	Type II
BT	4	—
BB	5	—
BL	—	10
LL	1*	10
Total	10	20

* Histoid leprosy.

SERUM CORTISOL DETERMINATIONS

Serum cortisol levels were determined by radioimmunoassay using reagents purchased from Cambridge Medical Diagnostics Inc, USA.[14] Briefly, 25 μl of test serum samples were mixed with 100 μl of ^{125}I cortisol containing about 4 mci of ^{125}I in phosphate buffer (pH 5·0), bovine serum albumin and goat anti-rabbit gammaglobulin. Thereafter, 1 ml of rabbit anti-cortisol serum in phosphate buffer, pH 5·0 containing bovine serum albumin, rabbit gammaglobulin and a displacing agent were added to the mixture, incubated for 90 min at 37°C, centrifuged, supernatant drained and the radioactivity in the precipitates was counted in a gammacounter (IC4702, Electronic Corporation of India).. The counts of the test samples were compared with those obtained with reference cortisol standards: 1, 2, 5, 6, 15, 35 and 75 μg/dl.

Results

Table 2 shows the basal serum cortisol levels in normal subjects and leprosy patients. Although the mean serum cortisol level in patients with lepromatous leprosy (18·21 $\pm$ 16·82 μg/dl) was higher than that in the normal (12·98 $\pm$ 6·43), the difference was not statistically significant. Table 3 shows the diurnal variations of serum cortisol levels in leprosy patients. It was found that the levels of the hormone in the morning samples were higher than that in the evening samples. Table 4 shows that ACTH injection could induce the steroidogenesis in lepromatous cases about 46% above their basal level after 30 min of the challenge.

The mean serum cortisol level in 10 patients at the onset of type I lepra

Table 2. Basal serum cortisol levels in normal volunteers and leprosy patients

Group	Number	Basal serum cortisol level μg/dl Mean ± SD (range)
A Normal subjects	41	12·98 ± 6·43 (2·3–30)
B Leprosy patients		
(i) LL	23	18·21 ± 16·82 (5·8–75)
(ii) BL	17	12·30 ± 6·65 (2·9–30)
(iii) BB	3	16·00 ± 3·56 (13–21)
(iv) BT	7	10·21 ± 3·07 (6–16·5)

Statistical evaluation.
t test between A and B (i): > 1·43 (not significant).

Table 3. Circadian rhythm of serum cortisol levels in lepromatous patients

Leprosy patient	Type	Duration of illness	Serum cortisol level μg/dl 9 am	6 pm
TS	BL	5	18	7·4
RL	BL	7	13	8
SM	LL	2	23	17
SD	BL	8	16	10

Table 4. Serum cortisol level in lepromatous patients before and after ACTH challenge

Leprosy patient	Type	Duration of illness	Serum cortisol level μg/dl Before ACTH injection	0·5 hr after ACTH injection
LG	LL	1½	12	18
DM	LL	3	10	15
KB	BL	3	18	27
KM	BL	1	19	27
	Mean		14·75	21·75

Table 5. Serum cortisol level in leprosy patients with type I and type II reactions

Group	Number of patients	Serum cortisol level μg/dl Mean ± SD (range) (A) At onset	(B) At remission	Statistical evaluation (A) and (B) 't' value	'P' value
(a) Patients with type I reaction	10	11·04 ± 4·91 (2·3–18·0)	10·1 ± 3·92 (6·2–18·0)	Not done	Not done
(b) Patients with type II reaction	20	17·32 ± 15·30 (1·6–60)	11·41 ± 5·90 (1·6–30)	3·27	< 0·01 (S)
Statistical evaluation: (a) and (b) 't' value between a and b		3·14	Not done		
'P'		< 0·01 (S)			

No increase of serum cortisol level was seen in type I reaction at onset; in contrast a significant elevation of the hormone level was found in type II reaction during attack.

S = Significant.

reaction (11·04 ± 4·91 μg/dl) was not statistically different from that at remission (10·1 ± 3·92 μg/dl). On the contrary the mean serum cortisol level in 20 patients at the onset of type II reaction (17·32 ± 15·30 μg/dl) was significantly higher (*P* value < 0·01) than that at remission (11·41 ± 5·90 μg/dl (*P* < 0·01) (Table 5). However after remission the levels are comparable in both types of reaction. On further analysis of the individual hormone levels, it was found that 7 out of 10 patients at the onset of type I reaction showed serum cortisol level within the normal mean basal level (12·98 μg/dl), while 10 out of 20 patients at the onset of type II reaction showed higher than the mean normal levels. Statistical analysis was performed to evaluate the diagnostic efficacy of serum cortisol level to differentiate type I and type II reactions, taking normal mean serum cortisol level at 13 μg/dl. The values above this level were taken as raised levels.

Chi square analysis

Serum cortisol level	Type I reaction (% patients)	Type II reaction (% patients)
Raised	30	50
Normal or below normal	70	50

Chi square was found to be 8·33 (*P* < 0·01).

Discussion

The clinical manifestations of chronic adrenal insufficiency, regardless of cause, are attributable to deficiencies of cortisol (glucocorticoid) and aldosterone (mineralocorticoid) which are the principal secretions of the adrenal cortex. One common form of adrenal insufficiency deserves special comment. Large doses of cortisone and related glucocorticoids are often used in asthma, various autoimmune diseases and lepra reaction. When such treatment is extended beyond 4 or 5 weeks, suppression of cortisol releasing factor and ACTH secretion ensues. If the steroid is then abruptly discontinued, the hypothalamic pituitary axis is unable to respond normally to the low circulatory cortisol level.[15]

Conflicting data regarding the adrenal cortical function in patients of lepromatous leprosy are found in other studies. One[16] reported normal circulating serum cortisol levels in 11 LL patients (7–12 μg/dl) and indicated that further study on the subject would not be worthwhile. However, recently another report[7] studied hydrocortisone production by 36 lepromatous patients after insulin load and found a paradoxical type of hormone production in 23 cases. Their data indicated markedly exhausted hydrocortisone producing function of the adrenal cortex, especially in active lepromatous diseases.

We found the radioimmunoassay of serum cortisol level by double antibody technique to be very accurate and specific. The basal level of serum cortisol (at 9 am) in our patients of all histological types was never below that observed in the normal controls (Table 2). This observation is parallel to that of another study.[16] Also Table 3 provided evidence of normal circadian rhythm in the patients. Further, ACTH injections in these patients could induce increased steroidogenesis in them (Table 4). A normal cortisol response to ACTH injection causes a rise of at least 7 μg/dl above basal cortisol levels at 30 min.[17] These data, therefore, lend support to the functioning adrenal cortex in our patients. The mean serum basal cortisol level in the LL patients of Balybin & Nazarov[7] was also higher ($32{\cdot}63 \pm 1{\cdot}53$ μg/dl) than that in their normal subjects ($25{\cdot}12 \pm 2{\cdot}36$) μg/dl). It is noteworthy that the serum cortisol level in normal Russian subjects (25·12 μg/dl (mean) with a range of 7·45 to 37·24 μg/dl) is higher than that in normal Indian individuals ($12{\cdot}98 \pm 6{\cdot}43$ μg/dl) (Table 2) as well as in North Americans (with a mean of 12·4 (5–25 μg/dl).[17] This difference might be due to climatic and/or nutritional variations between these two groups of populations. Balybin & Nazarov[7] studied cortisol production under insulin load in LL patients and observed a paradoxical type of response. In contrast we studied the adrenal cortical function in our cases by ACTH load and found stimulation of the adrenals. Thus, the results of the 2 studies might not be comparable. As far as we know this is the first study of serum cortisol level in the reactional state of leprosy patients. Curiously, no change of the serum cortisol level was observed in type I lepra reaction, while at the onset of type II lepra reaction, the mean serum cortisol level increased and following remission, it touched normal levels (Table 5). Out of

20 lepromatous cases with type II reaction, serum cortisol level decreased in 13 patients, while it increased in 6 and remained stationary in 1 (Fig. 1). The histoid case most probably represented relapse during a period of non-treatment or dapsone resistance. His nodules became red, swollen and reactivated, which was diagnosed as reversal reaction. Earlier Ridley described exacerbation of histoid nodules which were characterized by the presence of epitheloid cells.[18]

Thus, observed decrease of serum cortisol level after clinical remission may be partially due to the withdrawal of prednisolone therapy given to all with type II reaction. It is known that radioimmunoassay of cortisol cross reacts with prednisolone by 17% (manufacturer's literature).[14] However this explanation is unable to explain no change of serum cortisol level in patients with type I reaction

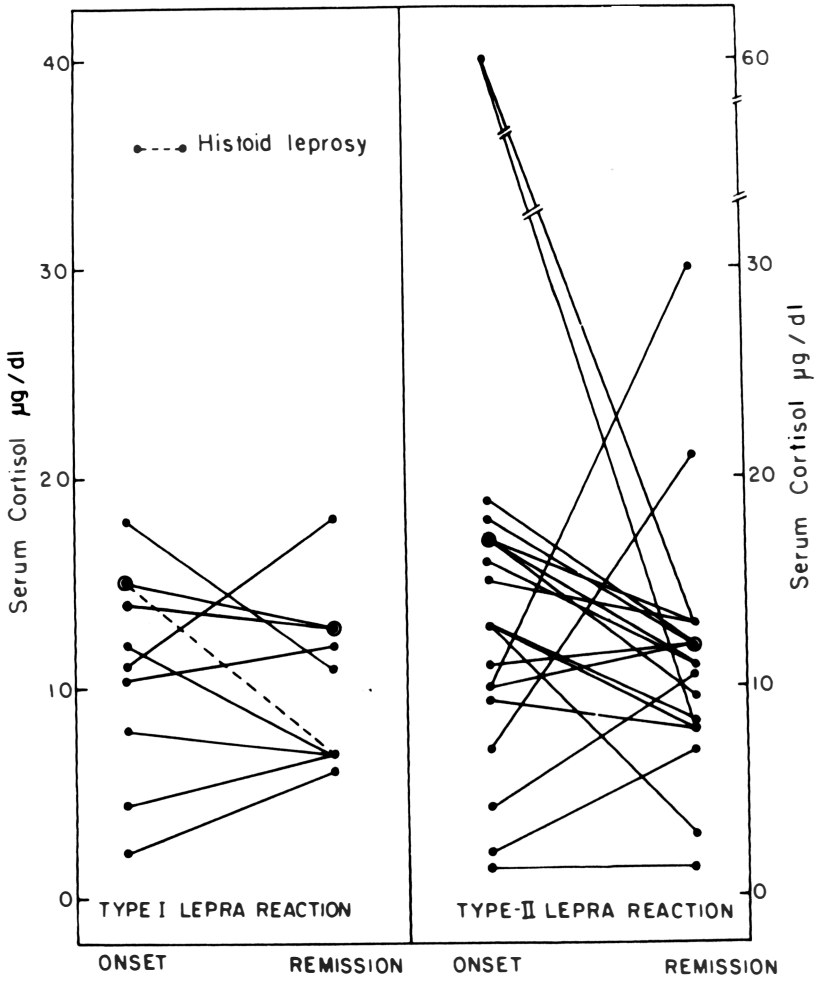

Figure 1. Serum cortisol levels in patients with type I and type II lepra reactions are shown at onset and after remission.

(Table 4), who also received prednisolone. One study[10] has suggested that during any psychological stress there was an increase in the percentage of OKT4 (helper-inducer T lymphocytes) along with increased serum cortisol concentration. Other studies[8, 9] have found reduced suppressor T cells in ENL patients compared to normal controls and there was no significant effect on T-lymphocyte subpopulation during chemotherapy of BT patients. However the fact that the T_H level rises does not necessarily mean that $T_{S/C}$ fall. Nevertheless the 3 following separate observations are valid: (a) $T_{S/C}$ falls in ENL patients; (b) T_H rises with raised cortisol level; and (c) cortisol level rises in ENL patients.

It is thus postulated that those patients who showed increase of serum cortisol levels, even after clinical remission of type II lepra reaction, might go into relapse because they were still in stress and might have a decreased percentage of suppressor T-lymphocytes. One study[7] has also suggested that lepromatous patients with a history of relapse should be further studied because they are vulnerable to glucocorticoid deficiency during stress. Leprologists often encounter sudden onset of lepra reaction in lepromatous cases during stress such as cold climate, infections, etc. At present, it is difficult to differentiate type I and type II reactions either clinically or by laboratory tests. Only histological examination of biopsy of the reaction nodule can distinguish the 2 lesions. Hopefully, serum cortisol levels of the patients at the onset of reaction may be helpful to differentiate type I and type II reactions. However, a wide variation of the serum cortisol levels among individual patients with reaction, warrants further study in more cases to firmly establish the role of serum cortisol as a diagnostic aid of types of lepra reaction.

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The outpatient treatment of nerve damage in patients with borderline leprosy using a semi-standardized steroid regimen

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Summary Thirty-three patients with borderline leprosy who had developed recent (less than 6 months duration) loss of nerve function were treated with a semi-standardized course of corticosteroids, the average initial dose was 25 mg prednisolone daily, and the average duration was 5 months. Treatment was unsupervised and no patient was admitted to hospital. The results were assessed by tests of voluntary muscle power and of sensory function, of the 57 nerves studied, 38 showed marked improvement and none got worse. There were no serious side-effects. Patients were taught exercises to prevent deformity, and residual muscle weakness did not progress to contractures. Corticosteroid treatment is safe enough, and confers sufficient benefit to be used in standard dosage under field conditions.

It is common experience that a patient will present himself for treatment because of recent nerve damage (motor or sensory) or signs of incipient nerve damage ('aches and pains' or paraesthesiae), commonly of only a few months duration. In such cases there is a good prospect of improvement if effective treatment for neuritis is instituted promptly. This is even more true of those patients who develop nerve damage during the first years of chemotherapy.

In patients with borderline leprosy the nerve damage is caused by the cell mediated immune response to antigens of *Mycobacterium leprae*, and many patients with recent nerve damage show signs of actual or incipient Type 1 lepra reaction (reversal reaction) in their skin lesions. The natural history of this reaction (rapid onset, gradual subsidence over a period of months) suggests a logical pattern of steroid treatment.[1] But no 'standard course' has yet won general acceptance.

It is often difficult to treat patients with nerve damage under field conditions, indeed, there is a tendency to insist on hospitalization for steroid treatment. But patients will probably refuse unless they have severe painful neuritis. Moreover

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there are often few beds available and no effective referral system. If the beds are in a general medical unit, hospital staff will usually have little knowledge or interest in the management of leprosy neuritis.

It is not surprising that field staff, unauthorized to give effective treatment for neuritis and often unable to refer patients for such treatment, may consider it unimportant to look for signs of nerve damage. In this situation it would be helpful if there was known to be a standard course of corticosteroids, which was effective in improving most patients, and was seldom harmful when used under field conditions. This paper reports the results of an out-patient study using a semi-standardized course of prednisolone to treat patients with recent nerve damage. We hope it will contribute towards defining a standard course for field use.

Patients and methods

The study included all borderline leprosy patients registered during 1982 for treatment in Dhoolpet Leprosy Research Centre, Hyderabad, who had, by their history, developed signs of nerve damage within the previous 6 months. About half of them had received some previous treatment for leprosy, the rest were untreated.

INITIAL ASSESSMENT

This included clinical examination of the skin lesions and palpation of nerves. Slit skin smears for acid fast bacilli were taken in all cases, and skin biopsy to confirm the clinical classification in about half the patients.

Nerve damage was assessed by tests of voluntary muscle power (VMT) of muscles supplied by the facial, ulnar, median and lateral popliteal nerves.[2] Sensory tests (ST) in areas supplied by affected nerves were performed using graded nylon bristles;[3] tests for protective sensation (indentation of the skin by a ball-point pen tip) were also undertaken.

The VMT results for the ulnar nerve were scored by adding the figures (0–5 scale) for the 2 muscles tested, which were abductor digiti minimi and 1st dorsal interosseous. Other nerves, where only one muscle or group was tested, were scored by doubling the VMT figure. Thus the scores for all nerves could be directly compared.

TREATMENT

All patients received dapsone 50–100 mg daily as anti-leprosy chemotherapy. Treatment for neuritis was with prednisolone. The average initial dose was 25 mg daily; this was normally reduced by 5 mg daily per month. However, dosage was

adjusted for body weight, and also for severity of neuritis (the more severe the neuritis the higher the initial steroid dosage). Patients were advised to take the full daily dosage of both dapsone and prednisolone as a single morning dose. All treatment was unsupervised, on an out-patient basis.

HEALTH EDUCATION

This was undertaken by the doctor who saw the patient, and occupied 30 per cent or more of an average consultation. Points covered included:

Appropriate active and passive exercises for affected muscles. It was emphasised that treatment might prevent permanent weakness and sensory loss, but exercises were needed to strengthen muscles and prevent stiffness and contractures.

2 Education on the risks of anaesthesia (if it was present) and the principles of hand and foot care.

3 Encouragement to take tablets regularly, and warning that prednisolone was dangerous if not taken according to instructions.

ASSESSMENTS DURING TREATMENT

Most patients were seen every 1–2 months during the period of steroid treatment, and every 2–6 months thereafter. Routine examination included palpation for nerve tenderness, and VMT and ST to assess the degree of improvement. Patients were asked to demonstrate how they did their exercises at home. Note was made of any symptoms that might be due to drug toxicity. Health education was continued according to the patients needs.

In most patients the steroid dosage was reduced month by month. However, if there was persistent or recurrent nerve pain or tenderness, or if function deteriorated, the steroid dosage was prolonged and/or temporarily increased.

Results

Forty-five patients were included in the trial, of whom 33 (classified clinically as BT-24, BB-2, BL-7) completed their steroid treatment and were available for follow up. Some had more than one affected nerve; the number of damaged nerves was 57 (BT-37, BB-5, BL-15). In about 80% of cases the final follow up assessment was more than 6 months after steroid treatment had been discontinued (Table 1).

A 'good' end result was defined as VMT power of 4 or 5 (i.e., a nerve score of 8–10). Table 2 shows the initial steroid dosage, number of patients, and results of treatment. About three-quarters of the nerves showed a good result. The degree

Table 1. Duration of follow-up period from start of treatment; 33 trial patients

Duration of follow-up (months)	Number of patients
6–9	3 (9%)
10–12	4 (12%)
13 or more	26 (79%)

Table 2. Initial dosage of prednisolone and end result of treatment of 33 patients (57 nerves)

Initial dosage of prednisolone (mg per day)	Number of patients	Number of nerves	
		Good result	Bad result
30	13	16	8
25	7	10	2
20	11	13	5
15	2	3	0
Total	33	42 (74%)	15 (26%)

of improvement (difference between initial and final scores) was 6 or more in two-thirds of the nerves (Table 3); none of them got worse. BB and BL nerves did as well as BT nerves.

The sensory status at follow up is shown in Table 4. It was normal or near normal in half the patients; only a quarter of them had lost protective sensation.

There were few toxic effects which could be attributed to the treatment. A few patients complained of epigastric pain which responded to antacids and reduced spice in the diet. A few developed infections of the hands or feet which were controlled by antibiotics. None developed signs of progressive tuberculosis, severe intestinal parasite infestation, diabetes or hypertension. The course was too short for osteoporosis to be a problem, and no patients complained of symptoms of adrenal insufficiency on stopping steroid treatment.

Table 3. Initial dosage of prednisolone and degree of improvement of 57 nerves

Initial prednisolone dosage (mg per day)	Number of nerves showing improvement in nerve score of			
	0–2	3–5	6–9	Total
30	7	1	16	24
25	2	2	8	12
20	4	3	11	18
15	0	0	3	3
Total	13 (23%)	6 (10%)	38 (67%)	57

Table 4. Results of sensory testing of 57 nerves

Sensory status	Number of nerves
Anaesthesia	15 (27%)
Protective sensation present	13 (23%)
Light touch absent	
Light touch felt (sensation normal or mildly impaired)	29 (50%)

Discussion

Nerve damage is not the only cause of deformity. Failure to do simple exercises leads to unnecessary stiffness and contracture formation; failure of reasonable hand and foot care will allow injuries and infections to cause further tissue loss and scarring. But the deformities which are commonly seen in patients who have been diagnosed reasonably early and treated (but without steroids) reasonably regularly indicate the need for more intensive measures to recognize and treat recent nerve damage as quickly as possible.

Not all improvement of function is attributable to recovery of nerve function. Motor units of a partially denervated muscle can hypertrophy, and sensory damage can to some extent recover by filling in from neighbouring nerve territories. Thus the management of a patient with nerve damage is not just a matter of prescribing corticosteroids; health education, centred round the need for regular exercises and hand and foot care is of comparable importance.

Nevertheless, steroids offer an increased prospect of reversing nerve damage and so obviating the need for a lifetime of burdensome exercises and precautions.

However, steroids are dangerous if misused, and in any case are only part of the overall management of neuritis (albeit the part which makes the rest really worthwhile). There is scope for discussion of what grades of worker could be authorized to use steroids. But effective treatment of nerve damage depends on steroids being available to use in defined courses by workers who have regular patient contact.

The present study was based on a 'city centre' clinic, and patients, though managed as out-patients, were always seen by a doctor. We did not aim to demonstrate the field use of steroids. But the study has shown 3 important preliminary points:

In the dosage we employed, steroids were safe for out-patient use. We took no special steps, for instance, to exclude tuberculosis in patients who looked well and had no cough. We did not advise patients to avoid work, even if it was manual and involved the risk of injuries and infections. Patients were warned that the tablets were dangerous in high dosage; we seldom found them taking too many, and were not pestered to continue prescribing them after the end of the course of treatment. On the other hand, the few patients who developed recurrent painful neuritis knew that they would be prescribed additional dosage to control their symptoms, and would not have to try to buy extra tablets for themselves elsewhere.

2 In the dosage we employed, steroids were effective. Most patients showed improvement, and most ended up with useful hands and feet. Even those with persistent weakness usually did not develop contracture deformities, and so avoided the stigma of being obvious 'lepers'. Although much of the benefit must be attributed to the steroid treatment, the health education, which was an integral part of the management, played an important role in its success.

3 Our patients were not angels. They were sometimes late for appointments, and no doubt sometimes forgot to take their tablets. Results such as ours can reasonably be expected in out-patients with unsupervised treatment.

The results of a similar study[4] have been reported.

This used a longer course of prednisolone, starting at higher dosage (40 mg daily for 2 weeks, 30 mg daily for 2 weeks, then 25–20–15–10–5 mg daily, reducing the dosage monthly. The whole course lasted for 6 months, and patients were admitted to hospital for months 1 and 2. The results of their study were much the same as ours (see Table 5, where the two studies are compared using the scoring system[4] for VMT's). This suggests that the results of both studies are about the best that can be obtained, and that lower dosage than we used, which would be more suitable for the field use of steroids, might still give worthwhile benefits.

We did not use a rigid dosage schedule in this study, and more work will be needed to define a standard course. The patients attending Dhoolpet Leprosy Research Centre are self-selected, and probably have more severe disease, and so

Table 5. Number of treated nerves and VMT results of nerves that improved, comparing results of Touw *et al.*[4] with those of the present study

	Touw *et al.*[4]	Kiran *et al.*
Ulnar nerves		
Number	53	34
Number improved	32 (60%)	23 (68%)
Average initial VMT score*	18	26
Average final VMT score*	42	46
Median nerves		
Number	40	10
Number improved	27 (67%)	10 (100%)
Average initial VMT score*	36	26
Average final VMT score*	48	48

* Only nerves which showed improvement are included in these groups. VMT score is as in Touw *et al.*[4]

probably risk more severe and prolonged neuritis, than patients in a normal field programme. It is therefore probable that a standard dosage schedule will start at a lower dosage than we usually used. But if the treatment is to do more good than harm the dosage must be high enough, and the course long enough, to relieve the symptoms of neuritis in most cases. A course which commonly fails to do this is unlikely to do any good at all.

Further studies are needed to define a course of steroids for field use which adequately balances benefits and toxicity. But in the meantime consideration should be given to the training needs of those who use steroids to treat neuritis. We suggest the following. The doctor or field worker using steroids to treat neuritis must know:

1 How to diagnose borderline leprosy (BT to BL on the Ridley–Jopling scale) and distinguish it from lepromatous.
2 How to palpate nerves and recognize when they are enlarged and/or tender.
3 How to test for protective sensation of the hands and feet.
4 How to do VMT's of the abductor digiti minimi, abductor pollicis brevis, and dorsiflexors of the foot.
5 How to teach hand and foot care, particularly the treatment of minor injuries and recognition of infection at an early stage.
6 How to teach maintenance exercises for the hands, particularly to prevent finger and thumb web contractures and strengthen the extensor muscles of the fingers.
7 The symptoms and signs of damage to nerves commonly damaged in leprosy,

including sensory loss, and how to obtain accurate information about them from the patient.

8 The standard treatment regimen used to treat patients with evidence of recent nerve damage.

9 The signs of steroid toxicity and how to treat patients who develop them.

10 How to recognize inadequate response to treatment.

11 How and where to refer patients in whom treatment appears to be ineffective.

Acknowledgment

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Lepr Rev (1985) **56,** 135–141

Ocular complications in patients with leprosy in Karigiri, South India

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Summary The examination of 143 leprosy patients revealed that 91 had ocular lesions attributable to leprosy and of these 13 were blind. The commonest lesion was madarosis and the commonest cause of blindness was chronic iritis (31% of all blind patients). Lagophthalmos remains an important condition and found in 25% of patients while corneal lesions account for a large number of ocular problems in leprosy (exposure keratitis 31%, interstitial keratitis 8%). Most affected is the 40–60 year, age group and most of the affected patients had long-term disease. Lepromatous patients were also encountered more frequently (70%) among the involved patients. A large number of patients also suffered from gross deformities (53%) and even more so amongst the blind (77%). This study does point out the importance of careful and regular examination of the eyes of leprosy patients by all involved with the care of these unfortunate people.

Introduction

As early as 1873, Hansen and Bull drew attention to the high incidence of ocular complications in leprosy in their book *The leprous disease of the eye* where they commented that there is no disease which so frequently gives rise to disorders of the eye as leprosy does.[1] In spite of this early awareness there is still considerable ignorance of many aspects of the problem. Good studies of the subject are few and far between. Several prevalence surveys have been carried out but there is still no standard method of classifying the lesions and this makes their comparison difficult.

The incidence of ocular leprosy is known to vary according to climate, sex, race, type of leprosy and skin pigmentation. One study[2] has demonstrated a prevalence in Malaysia of 16·3% while another has shown that 96% had ocular manifestations in Panama,[3] both studies being amongst institutionalized patients.

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Studies in India where leprosy is so common are surprisingly few in number. The following list is an exhaustive survey of the literature available on the prevalence of ocular complications in different parts of India:

Author	State	% with eye lesions	Type of study
Neve (1900)[4]	Kashmir	25	Institutional
Kirwan (1928)[5]	Bengal	20	Institutional
Balakrishnan (1966)[6]	Tamil Nadu	46	Institutional
Ebenezer (1968)[7]	Tamil Nadu	11	Retrospective
Saxena (1971)[8]	Madhya Pradesh	70	Institutional
Dutta (1972)[9]	Assam	80	Institutional
Sehgal (1976)[10]	Goa	25	Out-patients
Acharya (1978)[11]	Various	11·3	Hospital
Reddy (1981)[12]	Andhra Pradesh	5·1	Field

Many of the above studies are based on clinical data collected in practice rather than planned organized surveys. Hence they vary considerably in quality. Almost all the studies are on institutionalized patients and do not reflect the leprosy patient population as a whole. The only field study was done by Reddy *et al.* Some of the studies list as few as 4 types of ocular lesions while others list more than 20. There is also marked variation in the classification of lesions and there is no general agreement as to whether certain lesions (e.g. cataracts) are secondary to leprotic involvement or not. The numbers of each study are also very variable. Some are based on surprisingly few patients (e.g. Dutta, 45; Saxena, 43) while others are more substantial (e.g. Acharya, 309).

Methods and subjects

The Schieffelin Leprosy Research and Training Centre in Karigiri, Tamil Nadu consists of a referral hospital of 180 beds. The leprosy control area of Gudiathum Taluk is an area of 1822 square kilometres with a population of 530,000.

The prevalence of leprosy was 26 per 1000 in 1965 but came down to 19 per 1000 in 1981. The total number of patients in this area was 9950 (1981) of which 6099 were registered in the control area. Because of population movements and the common practice of patients to seek help away from home for social reasons, many of the patients at the hospital, both in-patients and out-patients, come from neighbouring districts.

Patients attending the out-patient clinic at the Eye Department, over a period of 8 weeks, were examined for ocular complications. Their name, age, sex, hospital number, classification of disease and duration of disease were systematically documented. The Ridley–Jopling 5-group system of classification based on immunological studies was used in this survey.[13] Classification was done clinically, except where histological examination of skin or nerve biopsies were indicated. Each patient was examined in the following way. Vision was tested

using Snellen charts with conventional or Tamil letters and the E-chart for those unable to read. Patients were tested for digital discrimination, hand movement or light perception if their vision was poorer than 6/60. Vision was recorded in the conventional way after refractive error was corrected, since refractive error is unrelated to leprosy. Presence of brow and eyelid lesions were also noted and facial palsy with lagophthalmos was tested for. In all cases, the eye was examined with a focussing torch and pupillary reflexes noted. The cornea, anterior chamber and iris were examined with a binocular loupe. Corneal sensitivity was tested with a wisp of cotton. The majority of patients were examined biomicroscopically with a binocular slit lamp. Fluorescein strips were used to detect active ulcers, tonometry performed with a Schiötz tonometer and fundoscopy by an ophthalmoscope after instilling a midriatic.

Physical deformities (disabilities) were also noted and classified according to the WHO international classification: grade I, anaesthesia alone; grade II, correctable deformity; and grade III, uncorrectable deformity.

Eye lesions not related to leprosy were excluded from the study and they include senile cataracts, primary glaucoma, pterygiums, Bitot's spots and refractive errors.

Results

A total of 143 patients were examined as detailed above and of this number, 91 patients had ocular complications attributable to leprosy. Senile cataracts, foreign bodies and other eye conditions not related to leprosy made up the 52 patients not included in this study.

Of the 91 patients with ocular lesions 75 were males while 16 were females (82% males, 18% females). This gives a 5:1 male to female ratio, which is spuriously high because of the 143 random patients examined: 104 were males compared to 39 females. Furthermore, there is a male predominance over female in the prevalence of leprosy in this area being 1·5 × greater and this predominance is even greater amongst sufferers of lepromatous leprosy (2·6 ×). Sex specific prevalence however does give a higher male involvement of 72% compared to 41% amongst females.

There was a wide range of age groups affected from the age of 9 years to over 60. Those of the fifth decade were most affected (31 patients). The type of leprosy according to the Ridley–Jopling classification of the 91 patients showed the following distribution: 64 were lepromatous (LL), 11 were borderline lepromatous (BL), 13 were borderline tuberculoid (BT), 1 tuberculoid (TT), and 2 Indeterminate (I).

Of the patients with eye involvement, 28 had grade I deformity, 15 had grade II deformity and 48 had grade III deformity. If the definition of blindness is taken to mean a vision of less than 3/60 in the better eye, there are 13 blind patients in the

series. The cause of their blindness may be multiple. The main lesion in the 13 patients responsible for the blindness are: 4 with chronic plastic iridocyclitis; 1 with bilateral facial paralysis; 2 with interstitial keratitis; 1 from healed corneal ulcers; 2 bilateral cataracts and 3 with old corneal opacities of unknown cause (forgotten). Of this number, 10 had grade III deformities. A summary of the distribution of individual lesions of the eye caused by leprosy is listed in Table 1.

Discussion

It must be emphasized that this study suffers from the same failures as the clinical observations of other authors based on hospital populations. It thus gives no indication of the actual prevalence of ocular lesions in this district. The only extensive field study is by Reddy[12] et al., who in Andhra Pradesh shows (4·72%) of LL and (1·15%) of non-LL patients had ocular lesions. However, their study is largely dependent on paramedical workers for the detection of ocular lesions. One study[14] had noted that paramedical workers are quite incompetent in this respect in a field test. While most could identify lagophthalmos, they were unable to detect cataracts, scleritis, episcleritis, iridocyclitis and ectropion. This, together with the fact that many lesions are silent, may mean that the figure derived by Reddy is far too conservative. A more realistic figure is likely to be 10–20%. However, prevalence of ocular leprosy does vary from place to place and clearly there is a need to make further studies along standardized lines.

Most authors have demonstrated a male predominance of ocular leprosy over females. Das[15] found 85% males to 15% females, Acharya[11] 70% males to 30% females. This is partly due to the higher prevalence of leprosy amongst males as noted earlier. Males were also noted to be 1·8 × more likely to develop ocular lesions in this series.

There have been no previous studies on the disabilities or deformities that patients with ocular lesions had. This study shows a high incidence (53%) of grade III deformities, i.e. incorrectable deformities which include loss of fingers, amputations and gross deformities of the hands. This does illustrate how tragic loss of vision, on top of these deformities can be. Even in the 31% with anaesthesia alone, many have glove and stocking anaesthesia which means loss of a great deal of the sense of touch and pain.

Madarosis remains the commonest lesion, 59% of the present series is a shade higher than Acharya's study but almost twice the other two. Ectropion, found in 9% of the patients is of similar magnitude as in the other figures. It was almost always associated with lagophthalmos, although senility may be a contributory factor. Entropion was found in a higher number of patients than previously documented and was usually associated with trichiasis.

Chronic conjunctivitis covers a rather loose group of conditions which include mainly exposure conjunctivitis from the loss of blink reflex. It is usually

Table 1. Ocular lesions in leprosy

Lesion Site	Type	No. of patients		%
Eyebrows	Madarosis: mild	15		
	moderate	20	54	59
	severe	19		
Lids	Madarosis	27		30
	Nodules	1		1
	Lagophthalmos: mild	7		
	moderate	11	23	25
	severe	5		
	Ectropion	8		9
	Entropion/trichiasis	8		9
Conjunctiva	Exposure conjunctivitis	10		11
Corneal	Corneal anaesthesia	22		24
	Corneal ulcer: mild	4		
	moderate	6	10	11
	severe	0		
	Exposure keratitis: mild	9		
	moderate	8	28	31
	severe	11		
	Pannus	7		8
	Superficial punctuate keratitis	5		5
	Interstitial keratitis	7		8
	Nodules	1		1
Episclera	Episcleritis	5		5
Sclera	Scleritis	2		2
	Scleral nodules	1		1
Uveal tract	Acute iridocyclitis: mild	5		
	moderate	2	10	11
	severe	3		
	Chronic iritis	14		15
	Irregular pupils	32		35
	Pupillary reflex: sluggish	17	30	33
	absent	13		
	Anisocoria	22		24
	Iris atrophy	17		19
	Polycoria	1		1
	Iris prolapse	7		8
	Anterior synechiae	4		4
	Posterior synechiae	17		19
	Iris pearls	1		1
Secondary glaucoma		3		3

associated with facial palsy and seen in 11% of cases and a similar figure is quoted by Reddy.

Corneal anaesthesia was seen in 24% of patients. However, it must be noted that not all cases of anaesthesia are a direct complication of bacillary invasion but may be secondary to healed corneal ulceration with the formation of a dense leucoma. Acharya found 59% with such a defect and Reddy 32%. Krassai had reported few cases of anaesthesia in his study.[16] The reason for this discrepancy is not immediately clear.

Superficial punctuate keratitis, found in 5% of the cases compares with similar figures (5%, 4%, 3%) by other authors. This does show that it is a relatively unusual condition although pathognomonic of leprosy and also transient and often asymptomatic.

Exposure keratitis was found in a large number of patients, 31% compared with only 3% reported by Reddy, although Acharya reported 24%. It is always associated with lagophthalmos or corneal anaesthesia with loss of blink reflex. Of the 23 cases of lagophthalmos, 10 also had corneal anaesthesia out of a total of 22 with corneal anaesthesia.

Thus, out of 22 patients with corneal anaesthesia, 10 had lagophthalmos (45·5%) while out of the 69 patients without corneal anaesthesia, 13 had lagophthalmos (18·8%). This demonstrated that lagophthalmos was significantly more frequent among patients with corneal anaesthesia. ($P < 0{\cdot}05$, χ^2 test). This finding is consistent with Anita's theory of the pathogenesis of facial palsy.[17]

Scleritis and episcleritis remain as relatively rare conditions, found in 2% and 5% respectively. Only 1 case of episcleral nodule was noted. Acute iridocyclitis was found in a larger proportion (11%) of patients than previously reported (3%, 3%, 1%) but half of the cases were very mild.

Chronic iritis (chronic plastic iridocyclitis) was found in 15% of patients. Similar figures have been reported by Das and Reddy. This study also confirmed Choyce's observation that chronic iritis was the most common cause of blindness in leprosy. In this study it accounted for 31% of the blind patients. Much work has been done by ffytche[18] in an attempt to unravel the pathogenesis of this condition. He concluded that chronic iritis, unlike acute iritis, is not due to immune complex deposition but due to paralytic atrophy of the iris caused by lepromatous involvement of nerve supply to the iris manifesting clinically as iris pearls.

No case of posterior segment involvement was diagnosed. Reddy also found no involvement, while Acharya found only 2 patients with choroidal lesions in his large series of 309 patients. This does demonstrate the rarity of posterior segment involvement and possibly early effective treatment of multibacillary disease may well arrest its appearance.

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Lepr Rev (1985) **56,** 143–152

*SPECIAL ARTICLE—LEPRA PRIZE ESSAY 1983**

'Naaman's dilemma'—factors influencing the compliance of patients to prescribed drugs in chronic diseases, with particular reference to leprosy

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'And Elisha sent a messenger unto him, saying "Go and wash in Jordan seven times, and thy flesh shall come again to thee, and thou shalt be clean". But Naaman was wroth, and went away, and said "Behold, I thought, he will surely come out to me, and stand, and call on the name of the Lord his God, and strike his hand over the place, and recover the leper. Are not Abana and Pharpar, rivers of Damascus, better than all the waters of Israel? May I not wash in them and be clean?" So he turned and went away in a rage.'[1]

The history of therapeutics is that of an accelerating change from the management of tradition to the management of fashion. Historical investigation of traditional attitudes to treatment[2,3] helps explain patient expectations and rejection of modern powerful drugs. Some themes common to most cultures include:

All treatment modes are useful, including diet, hygiene, quarantine, and psychotherapy. Today this is more successfully exploited by traditional medical systems, such as the Indian Ayurvedic which advises leprosy patients on physical activity and sexual indulgence.[4] A patient given only a bottle of pills may justly feel dissatisfied.

2 A religious element has always been emphasized, in which diagnosis, prognosis and treatment are not distinguished. Modern dispensing may not leave room for the community priest, or even consistent personal care.

3 Participation is the rule, with treatment procedures, of the individual, his family and friends and of local community leaders. The advantages of this involvement for promoting compliance are only slowly being rediscovered.

4 The basis for treatment does not require scientific justification, but rather tradition and intuition. This conservative outlook contrasts sharply with the modern turnover of proposed therapies.

5 Drugs have never been free. If, in theory, free treatment would seem to encourage open access to services, often in practice the bought medicine is better respected and used correctly.

6 Drugs are not necessarily simple in formula nor free of unpleasant side-effects. These are 2 priority problems according to modern therapeutics, but in good hands such drugs may be more trusted and accepted for their potency.

* This essay is an abridged version of one of the prize-winning entries for 1983 in a yearly essay competition, organized by LEPRA and offered to undergraduates in all the medical schools of the UK. Prize-winning essays for previous years have been published in this Journal and in the *International Journal of Leprosy*. EDITOR

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As the problems of efficacy and availability have been eroded, the problem of compliance has been increasingly exposed.[5] The early momentum of steadily reducing incidence of leprosy now appears to be lost,[6] while pharmacological barriers have been superseded by social and economical ones.

A Definition of the problem

The difficulties in making an effective response to the compliance problem begin with an uncertainty about the aims of treatment and a confusion between population and individual aims.

(i) POPULATION AIMS

To effectively and rapidly diminish the infectivity of the host.[7] This places priority in case-finding for the more infectious, but less prevalent lepromatous form,[8] and in regimen for the rapidly bactericidal agents such as rifampicin.[9]

2 To rehabilitate the patient into his former home and employment. This implies making drugs available at workplaces and communal domestic facilities, and increasing cost-effective orthopaedic and occupational therapy facilities.

(ii) INDIVIDUAL AIMS

To achieve a satisfactory symptomatic outcome. This requires a drug treatment with minimal side-effects and a rapid response to reversal reactions. Results ought not to be based solely on negative smears, but on systematic evaluation of outcome using, for example, the Brook indices:[10]

(a) Symptom status—related to the major reason for referral.
(b) Activity status—related to the tasks demanded at work.
(c) Ambulatory status—based on the ability to walk an arbitrary distance.

2 To maintain a good doctor–patient relationship and a positive attitude to maintaining health. This becomes the priority after the initial recovery period, and requires a holistic concern for the patient, and very different compliance motivators. The particular challenge for leprosy treatment is aptly summed up by Graham Greene:
'a patient can always detect whether he is loved or whether it is only his leprosy which is loved'.[11]

B Extent of the problem

Patients have rejected treatments for as long as they have been proposed, though modern doctors have forgotten Hippocrates' warning that the physician 'should keep aware of the fact that patients often lie when they state that they have taken certain medicines'.[12] Non-compliance with self-administration of dapsone in leprosy was also long appreciated. Ross-Innes observed that outpatient treatment could rarely be relied upon, and saw the need for a depot injectable form of dapsone for supervised treatment.[13]

Objective surveys of outpatient compliance in leprosy were delayed by the peculiar difficulties of direct urine testing for dapsone as a measure of drug ingestion; specifically, the long half-life and diuresis-dependent excretion of the drug. This was partially solved by Ellard *et al.*[14] using the dapsone:creatinine ratio. This still requires consecutive samples, or a suitably supervised control population, to interpret the results, but has been used by many workers in subsequent surveys (see Table 1).

C Definition of compliance

Compliance is 'action in accordance with a request, command, etc.' (Shorter Oxford Dictionary), and summarizes a complex behaviour pattern which may be usefully divided into three to appreciate different requirements in different situations: (i) unawareness—the mistaken action due to the failure of communication of the necessary instructions—a lack of instruction; (ii) error—the mistaken action due to misinformation, misinterpretation or memory failure—a lack of reinforcement; and (iii) Non-conformance—the mistaken action due to the voluntary conscious response of the individual to behavioural advice—a lack of faith.

Compliance is not an entity, but a chain of events, and problems can arise at any stage within it (Figure 1).

The initial hypothesis for a compliance study must identify one such factor. There may be no close correlation between patient attendance at clinics and regular consumption of drugs,[13]—this is only the case if treatment is administered there and then.[20]

Table 1. Typical figures for non-compliance in dapsone treatment

Study	Location	Sample	Test	Non compliance rate
Hertroijs (1974)[15]	Tanzania	5734 O/P'S	Records & Interviews	32% (attendance)
Low & Pearson (1974)[16]	Ethiopia	89 O/P'S	Urine D:C ratio	44%
Ellard et al (1974)[17]	Malawi	206 O/P'S	D:C ratio	49%
Hagan et al (1979)[18]	Burma	585 O/P'S, 138 I/P'S	D:C ratio	58%, 8%
Ellard et al (1981)[19]	Ethiopia	295 D/P'S	D:C ratio	

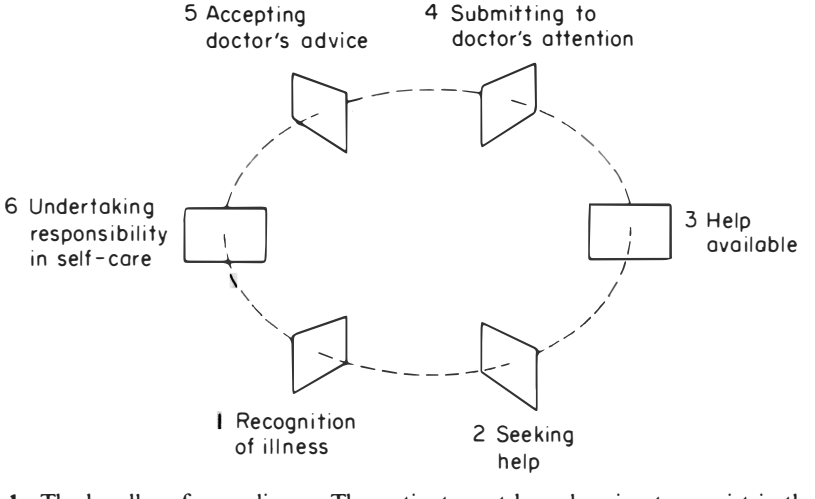

Figure 1. The hurdles of compliance. The patient must keep lapping to persist in therapy.

D Design of compliance surveys

For results to be interpretable to other clinicians and applicable to clinical conditions, it is essential to be specific and explicit about our interpretation of 'compliance', defining the patients and treatments involved.[21]

(i) Defining patients—The sample must be representative (e.g. referral hospital vs peripheral clinic) and followed through[22] (i.e. using an inception cohort of patients, following up defaulters at home, etc.).
(ii) Defining treatment—The disease criteria ought to be defined from the start, and the means of dispensing described, as well-planned organizational methods may be more significant than the variables tested.[20]
(iii) Criterion used for compliance—A measurable index for patient compliance is by definition an oversimplification of behaviour, dependent on complex social, medical and personal problems,[23] and must be interpreted in that context:

The 'ideal' index for compliance rapidly performed and interpreted, quantifiable for comparisons, related to 'therapeutic threshold', closely linked to perceived compliance problems, suitable for mass-testing and longitudinal studies, comparable with other studies, cost-effective within treatment programmes, acceptable to the patient.

Just as the measure used must be related to the appropriate 'hurdle of compliance' so the test result must be related to a pre-determined therapeutic goal, depending on treatment effectiveness and public health strategy. '100% treatment compliance' is neither desirable nor necessary. The costs of tests may be prohibitive in some circumstances, but must be compared with the potential cost of wasted drugs and retreatment. Common methods are shown in Table 2.

Combinations of these methods are often used. Important questions that must be asked of any proposed method are: (i) who does the test? (doctor, health worker, patient, independent investigator); (ii) with whom are you involved? (patient, relative, local figure, doctor); (iii) where do you perform the test? (clinic, home, workplace); and (iv) is the patient aware of the purpose of the test? (before, after performed).

E Factors influencing compliance

The great thrust of early compliance research was the attempt to find demographical variables which would predict the non-compliant patient. The failure of such indicators to identify problem patients[31] suggests that the search for the 'non-compliant personality' should be abandoned, to concentrate more on specific patient-treatment problems and the patients' perceived difficulties.

An important factor in interpreting any results is the 'surveillance effect', the fact that experimental conditions themselves influence compliance greatly, by patient selection, doctor motivation, stricter follow-up efforts etc.

(i) MEDICAL FACTORS

Chronic diseases are protracted, usually non-lethal, intermittently severe in natural history, and require chronic treatment. The patient may respond to this in two ways, depending on treatment effectiveness. If palliative, it might make him bored and disillusioned; if relieving, it might make him complacent and irregular. In leprosy, the apparent mildness of its benign onset as a small macule, and the incidence of spontaneous healing in children, may discourage presentation to a doctor.[9, 33] Though polypharmacy of any kind makes compliance difficult,[34] combination therapy is essential in

Table 2. Criteria used for compliance

Variable	Measure	Advantages	Disadvantages
Clinical judgement	'Intuition'	Nearest the goal Part of clinical practice	Proven inaccurate.[24, 25]
Outcome	e.g. smear activity	Nearest the goal	Misses spontaneous recovery.
		Part of clinical practice	Drug resistance.
Pill count	e.g. discrepancy estimate[28]	Simple Useful adjunct	Ignores drugs returned, given away, discarded and hoarded.
Urine testing	e.g. urine dapsone: creatinine ratio[17] INH label[26]	Cheap	Pharmacokinetics-dependent.
		Practical for any drug objective	Cross-reactions. Fraudulent samples.
Blood testing	e.g. ELISA assay[27]	Closer to drug use	Kinetics-dependent still. Poor patient acceptability.
Interview		Essential for behavioural study and planning interventions	Grossly underestimating. Time consuming.
Monitors	e.g. Moulding's medication monitor[29]	Objective Records behaviour pattern	Not = ingestion. Supervision bias costly ? too frightening[30]

the age of antibiotic resistance (Table 3) and must be well-designed to avoid 'drug-drug interactions'.[34]

Side-effects, such as leprous reversal reactions,[35] drug sensitivities and neuropathy, are generally well-tolerated. On the other hand, a subjectively obvious effect of treatment is important to avoid Volpone's attitude 'No, no, no, I'm very well, you need prescribe no more'.[36] The addition of simple topical preparations, such as the obsolete erisul ointment[37] rubbed into the affected skin, would increase patient satisfaction in a disease treatment sadly lacking this element.

(ii) PERSONAL FACTORS

Although personality types do not correlate with non-conformance, analyses of patients' attitudes, such as the 'health belief model',[38] provide clues towards explaining health behaviour. Examination of the doctor-patient relationship, such as by recording and analysing clinical interviews,[39] suggest defects of technique which can be modified by the clinician. Cost of drugs may not be a major obstacle,[40] but use of expensive alternative traditional remedies must be taken into account. Educative measures are an important, but not exclusive, priority in the prescribing interaction.[41]

(iii) SOCIAL FACTORS

An analysis of cultural and economic factors, which profoundly influence the patient's (and doctor's) behaviour, explain the process of turning vague symptoms into a significant illness.[42] This defines the illness in terms of 'how disabling is it?' and even 'who is to blame?', which varies for leprosy in different cultures.[37] Non-conformance may depend more on the extent of disability (i.e.

Table 3. WHO-recommended treatment protocols (1982)[9]

	Paucibacillary (TT, BT)	Multibacillary (BB, BL, LL)
Daily self-administered	Dapsone 100 mg/d po	Dapsone 100 mg/d po + Clofazimine 50 mg/d po
Intermittent supervised	Rifampicin 600 mg/4 wk im	Rifampicin 600 mg/4 wk im + Clofazimine 300 mg/4 wk im
Duration	For 6 months	For indefinite period

social circumstances) than the severity of disease (i.e. personal experience).[43] The patient's 'sick role' is also defined: 'is the patient expected to continue work?, to socialize?'.

F Design of intervention trials

Before trying manoeuvres to improve the situation, reliable treatment trials should establish efficacy of the regime and the endpoint or therapeutic goal for compliance, and surveys should identify the main source of difficulty and suggest relevant intervention methods. The manoeuvre should be isolated from other variables, especially the amount of time doctor spends with patient (a most effective placebo), with appropriate control groups. A representative sample of the treatment population should be randomized into trial and control groups, and stratified according to known factors affecting compliance[22] or described demographically after randomization (for a good example, see refs[44, 45]). Both benefits and 'side-effects' should be reported—health education may make some patients more reliable, while increasing the demand for treatment and terrifying the rest of the population (see Figure 2).

The question must be asked if the result is just 'striving officiously', doing more harm than good to the patient,[56] or violating Mill's dictum as applied to public health: 'the only purpose for which power can rightfully be exercised over any member of a civilized community against his will is to prevent harm to others'.[57]

Since Kinnear Brown's work in Uganda in the 1930's, and T F Davey's in East Nigeria in the 1940's, the value of peripheral treatment centres for leprosy has been recognized.[37] With dispensing devolved onto semi-skilled workers (and former patients) and attractive clinics, the emphasis was placed on community involvement and morale. The use made of modern treatment outposts is often disappointing;[15] perhaps permanent, established, well-run clinics, requiring time and effort to

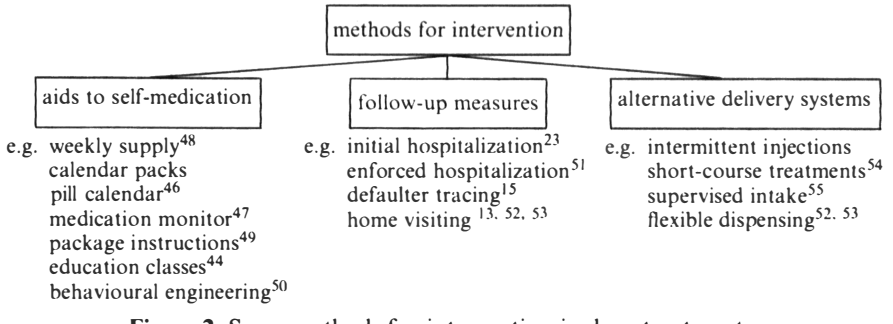

Figure 2. Some methods for intervention in drug treatments.

obtain treatment, seen to regard the disease seriously, and impressing prognosis on the patient from the outset, would be psychologically more effective.

G Proposals for improving compliance

(i) TEACHING

Doctors are teachers (Lat. 'docere'), but before they teach others, they need to be taught. As Samuel Butler would say, 'He that complies against his will, is of his own opinion still'.[58]

Doctors must listen to their patients, and treatment systems require feedback of patient concerns.[59] Individually, the patient in hospital can be instructed on the regime and allowed to practise self-administration under observation before discharge.[41] With family and friends present, a 'therapeutic contract' can be negotiated and participation encouraged.[60] In the community, advertising such as Ryrie used in Malaysia,[61] and re-establishment of traditional community leaders' and healers' involvement in treatment, can encourage trust and social acceptance.

(ii) CO-OPERATION

The continued devolution of responsibility for dispensing to field workers must continue,[62] concentrating on: strategic location of dispensing points such as at workplaces;[63] emphasizing continuous care and encouraging feedback; and closer communication between doctors and drug suppliers.[64] Compliance is not just the patient's problem—doctor compliance to matters of policy[65] and drug availability through rural distribution systems[18] are at least as important challenges.

(iii) SUSPICION

Few doctors overestimate compliance.[25] A high index of suspicion of non-compliance, within sensible ethical limits, must be held to a patient not getting better on a proven drug treatment. Simple manoeuvres such as pill-counting or regular questioning, or even subtle urine tests, must be considered within economic limits.

(iv) TREATMENT

'When a lot of remedies are suggested for a disease, that means it can't be cured'.[66] The WHO-recommended regimens (Table 3) should be uniformly applied. Combination tablets should be produced to simplify the regimen—compliance advantages[34] outweigh difficulties or contraindications and side-effects.[67] More drastic measures, such as compulsory detention,[51] use of psychotropic drugs,[68] and abandonment of the hard-core unco-operative,[69] illustrate the seriousness of the problem, but are of historical interest only.

H Conclusions

We have seen how a historical perspective, a definition of problems and possible solutions, and an analysis of past research can direct and guide efforts to regain the momentum of reducing the incidence and morbidity of chronic diseases such as leprosy. Perhaps the largest discovered need is for better quality research, to understand and logically tackle individual situations. A sound protocol for studies of dapsone compliance has been recently described.[17]

The future must be seen with hard economic spectacles. The WHO aims—for chemotherapy, to interrupt the chain of transmission and avoid permanent disabilities[8]—are economically sound. The waste of non-compliance was the motivating force for original compliance research. The medical costs, in terms of retreatment and rehabilitation, as well as the social costs of manpower and exile, should be made plain to all.

As well as politicians and administrators, practitioners in the front-line must recognize the need and consider imaginatively alternative strategies.[65] Edmund Burke wrote, after the French Revolution, 'Every politician ought to sacrifice to the graces, and to join compliance with reason'.[70] After the therapeutics revolution, physicians will doubtless need to also—to effect Naaman's cure tomorrow.

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SPECIAL ARTICLE

Leprosy and procreation—a historical review of social and clinical aspects

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The clinical and immunological aspects of interactions of leprosy and pregnancy in terms of relapse, reactivation, exacerbation of the disease and leprosy reactions have recently received considerable attention.[1] Furthermore, the development of techniques to demonstrate IgA and IgM anti-*Mycobacterium leprae* antibody activity in cord sera, presumptive evidence for the transmission of live *M. leprae* bacilli across the placenta[2] and the development of leprosy in very young children[3] have suggested that the incubation period of *M. leprae* may be very much shorter than hitherto acknowledged.

Further detailed but limited studies will be necessary to investigate further some of the findings.[4–6] Nevertheless it has been shown that due to maternal immunosuppression occurring during pregnancy, the mother's leprosy may become overt, relapse if cured, or deteriorate during pregnancy and puerperium, with increased likelihood of her developing erythema nodosum leprosum (ENL), especially during pregnancy and lactation, and reversal reaction during lactation, with the development in addition of progressive nerve damage with sensory and motor loss.

At the same time the child born to the mother with leprosy has a lower birth weight, a slower growth rate, an increased susceptibility to infection and a higher death rate under the age of 1 year than the child of a healthy mother. These are all most marked in the children of mothers with lepromatous leprosy.

The mother with leprosy, particularly lepromatous leprosy, living in a developing country without any form of social security, knows that she will be ultimately dependent upon her children to care for her, either in sickness or in her old age, and therefore has to produce and rear sufficient healthy children for this purpose. Because of increased infant mortality, in particular neonatal loss, she has to undergo more pregnancies than her healthy counterpart, to ensure live children and thus, although she realizes the risk of pregnancy, she has to undergo the risk of pregnancy time and again. Moreover, in time as she develops dapsone resistance, there is the ever present risk of her transmitting dapsone-resistant leprosy to her child—a further complicating factor in the battle to control leprosy.

In the light of new knowledge and understanding of leprosy, and advances in reproductive immunology, it is of great interest to review historical records and theories of causation and transmission of disease, and in particular the role of procreation.

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Earliest historical records

The earliest indubitable references to leprosy come from India and go back to the sixth century BC.[7] Earliest descriptions of the disease from India and China are surprisingly accurate, and clearly describe the disease which is known today as leprosy which is caused by *Mycobacterium leprae*. Both skin and nerve signs of the disease were recognized and chaulmoogra oil was mentioned as a treatment.[8] It was likely that leprosy was brought to Europe and the Mediterranean basin by the armies of Alexander the Great after his Indian campaign, 327–326 BC. Thus leprosy referred to in the Bible in the days of Jesus Christ may well have been 'modern' leprosy.

The Hebrew word translated as leprosy comes from the same root as 'stricken by God'. Thus leprosy came to be regarded as a curse or judgement by God, as seen in the story of Miriam, Moses' sister[9] and Gehazi, Elisha's servant.[10] Furthermore, while 'leprosy' referred to in the Old Testament is unlikely to have been what we understand as leprosy, but rather a collection of infectious diseases and conditions affecting the skin, clothing of wool, linen and leather, and the walls of dwellings,[11] Biblical references to leprosy[12] have done much to instil the idea of uncleanliness, incurability and communicability of the disease.

That leprosy was regarded as an infectious disease and was treated as such is clear from events of history. The spread of leprosy along the routes of invading, and retreating armies, and along trade routes by land and sea; the epidemic of leprosy coinciding with the return of the Crusaders; the establishment of leper hospitals outside the towns, the laws forbidding lepers entry to towns, are all evidence. Guy de Chauliac, practising in the fourteenth century not only provided an unequivocal description of leprosy but gave, in great detail, instructions regarding the examination of one suspected of having leprosy—as he observed:

'. . . in the examination and judgement of lepers there must be much circumspection, because the injury is very great, whether we thus submit to confinement those that ought not to be confined, or allow lepers to mix with people, seeing the disease is contagious and infectious.'[13]

Cullen (1772) in his 'Nosology' described the disease as contagious,[14] while Schillingii (1778) stated that leprosy could be transmitted by the pus from abscesses, also by respiration and from a leprous wet nurse to a suckling infant.[15]

Causation and transmission of leprosy

From earliest records 2 themes run side-by-side: leprosy was highly infectious and leprosy could result from incurring the anger of supernatural powers as has been referred to earlier and as is seen in the story of Troylus and Cresseid.[16] Cresseid attributed her misfortunes in love to the fickleness and pranks of the gods and, thus, incurred their wrath:

'Thy cristall ene minglit with blude I mak,
Thy voice sae clear, unpleasand hoar and hace,
Thy lustie lyre owerspred with spottis blak,
And lumpis haw appearand in thy face.
Where thou cumis, ilk man sall flee the place.
Thus sall thou go begging frae hous to hous
With cup and clapper like ane Lazarous.'
. . .
'Therefore in secreit wyse ye let me gang
Into yone hospitall at the tounis end.'
. . .
'Then in ane mantill and ane baver hat,
With cup and clapper wonder privily,

He opnit ane secreit yett, and out thereat
Convoyit her, that nae man suld espy,
Into ane village half ane mile thereby,
Deliverit her in at the spitail hous,
And daylie sent her part of his almous.'

(Henrysoun, c. 1420–1490)

In Judaio–Christian circles it was generally understood that leprosy was God's judgement for sin[17] and that this judgement could be extended to the third and fourth generation.[18] However, this thinking was not confined to the centres of Judaio–Christian teaching, as in Chinese tradition leprosy was regarded as punishment for sexual misdemeanour and was transmissible within the family to the third and fourth generations:[19–22] the children born of the fourth generation were considered healthy and could return to society.[23]

Sexual transmission of leprosy

The idea that leprosy was transmitted as a venereal disease was prevalent in England in the Middle Ages, and prompted some of the rules of the leper houses[24]. As Donne recorded:

'By thee the silly amorous sucks his death [sic: seely]
By drawing in a leprous harlot's breath.'

(Donne, 1573–1631)[25]

Richter[26] maintained that leprosy was transmitted by sexual contact. In China, women with leprosy believed they could be cured of their disease if they had sexual contact with a healthy male, thus transferring the disease to him. Thus, the practice of 'selling leprosy' was developed. The dread of this scourge exerted a great influence on promiscuous intercourse in China and on the general moral conduct of the people.[19, 21] In Mysore, India, it was also a common belief that leprosy was a form of venereal disease.[27]

After the advent of syphilis to Europe in the sixteenth century there was undoubtedly some confusion between the clinical features of syphilis and leprosy caused in part by the similarity of the clinical picture of ulcers, sores, lymphadenopathy and destruction of nasal bones: thus the term 'syphilitic leprosy' came into use. The observation that syphilis is transmitted by sexual contact may have given additional support to the theory of sexual transmission of leprosy.

Hereditary transmission of leprosy versus spread by contagion

The Greek and Arabian physicians had a universal belief in hereditary transmission of leprosy as they maintained 'all body fluids (including semen) were affected'.[28] It is likely that such a belief influenced laws regarding marriage and divorce in Europe dating from the seventh century, and the practice in Europe, of the castration of lepers and the burial alive of the leprous mother and child. The theory of hereditary transmission of leprosy was held by many physicians until the end of the nineteenth century.

The strongest case for hereditary transmission of leprosy seems to be that of the leprosy victims in the Shetland Islands, who in the eighteenth century were all from a few families.[29] However, if hereditary transmission was so important, one is faced with the question as to why leprosy in the Shetlands died out when the victims of the disease were effectively isolated on the island of Papastour.

Amongst the Punjabees generally, the belief in hereditary transmission of leprosy was so deeply grounded that they were in the habit of burying alive not only the leper himself, but also his relations and friends lest in multiplying their kind, the disease would be communicated to distant generations.[30]

In Iceland leprosy was considered to be both an inheritable and a very infectious disease.[31] The Lolos, natives of Szechuan province of China, the Siamese and Javanese all believed in hereditary transmission of leprosy.[32] The Annamites (amongst whom leprosy was very prevalent) declared 'leper parents always gave birth to leper children although, on the other hand, the malady does not declare itself before the tenth, eleventh or twentieth year.'[33]

The theory of hereditary transmission was not universally held—even Danielssen and Boeck who were the chief protagonists of this theory virtually denying the possibility of leprosy being contagious, stated that a few cases of leprosy could occur spontaneously.[34]

Schillingii in 1778 had observed that leprous parents could give birth to healthy babies but such babies could not remain free of leprosy unless they were separated from their parents at the time of birth and brought up in a healthy environment, with wholesome feeding.[35] This was supported nearly a hundred years later by Leloir who maintained that children separated from leprous parents early had a very good chance of escaping leprosy, especially if they were sent to a non-infected district, but if they remained with their parents there was very slight chance of escape.[36] Adams had maintained that as the reproductive capacity of both men and women was impaired, leprosy should be a self-limiting disease if hereditary transmission was so important.[37]

The dispute regarding hereditary transmission and contagion in the spread of leprosy raged throughout the nineteenth century.

The case for hereditary predisposition to the disease rather than hereditary transmission of leprosy was put forward by Hjaltelin[38] and supported by Kierulf who noted that the spontaneous development of the disease was always in endemic areas and never where it was unknown.[39] The observation that 11 parents of children with leprosy developed the disease *after* the birth of the children was made by Holmsen[40] who, along with Kierulf, believed in the existence of a specific virus for leprosy.

Drognat-Landré (1868) however was the first to seriously analyse the problem, prompted by seeing, in Holland, 10 Dutch patients with leprosy contracted in the colonies. After making observations on leprosy in the native and ex-patriot communities, and noting the appearance of leprosy in children of leprous parents, in a critical review of the history of the disease in Surinam, Drognat-Landré concluded that contagion was the sole means of propagation of leprosy.[41] His monograph, published at a time when leprologists in many countries were in hot pursuit of the 'virus of leprosy', was eclipsed by Hansen's discovery of the bacillus of leprosy and fell into obscurity for 70 years.[42]

Further support for hereditary predisposition to leprosy was given by Tache and Roose. Roose, who had observed the occurrence of leprosy in 4 children aged 4 to 6 years felt that these children, who possibly had inherited a predisposition to leprosy, had been infected by their leprous parents after birth by contagion.[43] However, Impey considered that there was no proof of hereditary transmission of leprosy and that hereditary predisposition occurred only in a small number of cases,[44] and Choksy in Bombay, observed that only 5% of leprosy was due to hereditary transmission, although 11% had a family trait.[45]

Hansen and Looft, who argued against the hereditary transmission theory on the grounds that the bacillus is a parasite and not a heredity factor with anatomical and physiological peculiarities, suggested that the term 'hereditary transmission' be replaced by 'hypothesis of latent infection'.[46]

It is of interest that the question 'Is the contagion of leprosy transferable by way of intra uterine infection?' was asked nearly 100 years ago[47] and that this question is only now being answered.

Social attitudes and laws in relation to leprosy, marriage, divorce and procreation

In the seventh century, Rothan, King of Lombards, made laws to prevent marriage of lepers.[48] A hundred years later, in 757 the parliament of Pepin, King of France, passed a law in which leprosy

was regarded as a cause of separation, thus the healthy partner of the marriage was allowed to remarry.[49] In 789 Charlemagne proclaimed laws forbidding the marriage of lepers.[50] A similar edict was made about 950 by the Welsh King Hoel Dha; however, at this time the term 'leprosy' covered various skin diseases.[49] In 1186, Pope Urban III allowed that subsequent leprosy was a sufficient reason why a betrothed couple should not be compelled to marry.[51]

Scots law, prior to the days of King Malcolm Canmore, in its practice of hygienic measures to control disease, ordered castration of epileptics, the insane or carriers of diseases transmissable from father to son; at the same time, to prevent the spread of leprosy, it banished any woman sufferer from the company of men, with the penalty of burial alive with her child, should she give birth whilst suffering from leprosy.[52] The practice of castration of lepers was apparently widely practised in the Middle Ages.[53]

Segregation of lepers from healthy persons in the Middle Ages was followed by separation of the sexes as evidenced by the rules of leper houses. Rules for St Julien's Hospital, thirteenth century, stated that those admitted were to be single: if they were married they were to part by consent and vow chastity.[24] Sometimes the lepers' wives lived with them, as was the case at the Edinburgh Greenside Hospital in 1591, where to enforce complete segregation of the lepers, one of the wives was allowed to go out to the market while the lepers took it in turns to sit and beg alms at the hospital door.[54]

In France in 1757, leprosy was a valid cause for divorce. In Britain at the same time there were regional laws which forbade cohabitation if either husband or wife were a leper: a leper in these circumstances being considered as dead.[50, 55] Icelandic law in 1776 forbade the marriage of lepers,[56] while Norwegian law in 1781 allowed divorce of lepers and remarriage of the healthy partner.[57] In 1790 in Norway, a second law was passed allowing husbands whose wives were placed in the leper hospital at Bergen, to remarry, the woman declared to be civilly dead.[50] In Crete, in 1874, the Bishop found it necessary to recommend to the priests not to sanction marriages with or among lepers.[50]

In China leprosy was regarded as legal grounds for annulment of promise of marriage contract[58] or divorce.[59] In the Kwantung province in China, in the nineteenth century, in arranging child betrothals, great care was taken in ascertaining the absence of leper trait in the other party: despite this the Chinese were willing to hire lepers to care for their children! In Cochin China, where leprosy was very prevalent, the Annamite leper did not remarry: if leprosy declared itself after marriage, the husband avoided his wife's bed for fear of giving her the disease.[60] In the Canton Province of China, marriage between lepers was only permitted with those having the same type or grade of the disease.[61]

In the nineteenth century, regulations regarding marriage within leper asylums varied considerably. On the one hand in South Africa, where leprosy was considered to be spread by contagion rather than hereditary transmission, conjugal intercourse was discouraged between lepers until they were past child-bearing age, and was not permitted at all between lepers and healthy persons.[44] On the other hand, in India, where marriages amongst lepers were not prolific[45] we find that marriage was permitted for mutual care rather than enjoyment of sexual relations.[62] It was observed that of 1600 inmates of Matunga leper asylum, Bombay, in 9 years only 7 children were born. A similar observation was made in Hawaii where in a colony of 2864 lepers, only 26 children were born,[62] and in the Maracaibo Island leper colony where marriage was permitted, only 2 children were born in 15 years.[45]

Reduced fertility amongst lepers, however, was not always the rule. In Indo-China, where the birth rate amongst lepers was high and hereditary transmission of leprosy was considered most important, a strong case was made for sterilization of leprosy patients of both sexes.[53] In Panama, at the Palo Seco asylum, marriages of lepers were allowed only after sterilization of the male on his written request.[63]

In Korea, the segregation of sexes practised in leper hospitals resulted not only in sexual perversion, but also in patients leaving the leper hospital. Such patients formed, in some cases, transient attachments with those of the opposite sex and joined leper camps—children born in such

circumstances not only had a precarious home life, but if they remained with their parents, half of them became infected with leprosy. A system of arranged marriages and arranged adoptions (in accordance with local customs) together with voluntary sterilization was found to be effective in providing for the needs of segregated lepers.[64]

Leprosy in relation to childbearing

In the pre-sulphone era leprosy was associated with subfertility, if not frank infertility.[62, 65, 66] This was attributed to frigidity,[67] and to 'decreasing sexual instinct' with progression of the disease.[68] Testicular atrophy had been observed[37, 65] and also azoospermia due to destruction of the testicle by scarring with connective tissue.[69]

Leprosy occurring prior to puberty resulted in primary amenorrhoea,[70] while leprosy occurring after puberty was observed to cause menstrual irregularity progressing to secondary amenorrhoea.[65, 70, 71] Secondary amenorrhoea was attributed to infection of the fallopian tubes, ovaries or uterus, based on observations of 2 autopsies out of 17 in which tubercles were seen on these organs.[72] However, as a number of those patients also had tuberculosis, one wonders whether the tubercles seen were lesions of tuberculosis rather than leprosy.

In 1897, Zambaco recorded a large number of abortions in women with leprosy. These he attributed to septicaemia with *M. leprae* resulting in placental infection leading to foetal infection and subsequently, abortion. He suggested that these abortions had not been diagnosed as due to foetal leprosy because as happens in many cases of abortion, both foetus and placenta had been discarded without being properly examined,[67] an observation repeated 30 years later by Montero.[73]

It was generally thought, and taught, that the few full-term pregnancies which *did* occur were observed to be normal, with most babies appearing healthy at birth and with no gross abnormality of the placenta.[66] It is therefore of particular interest that Zambaco observed that many of the children born to women with leprosy were remarkably small for the period of gestation.[74]

The adverse effect of pregnancy on leprosy appears to have been first observed by Zambaco.[75] He described 4 women who developed overt leprosy in association with pregnancy, 3 immediately postpartum and 1 during the third trimestre. He observed reaction in the skin occurring in 2 cases postpartum until 3 months of lactation, and in 1 patient he observed silent neuritis with the sudden development postpartum of 'main en griffe' in 2 successive pregnancies in 1 patient. His description is worth translating and runs thus:

'. . . the influence of pregnancy is disastrous for women with leprosy. The disease reveals itself for the first time and progresses rapidly. The birth of the baby in turn affects the development of the illness, in all comparable to the development of tuberculosis in the same circumstances.'[76]

Puberty was seen to affect the incidence of leprosy with a sudden increase in the number of girls in proportion to boys.[77–79] The appearance of overt leprosy in association with pregnancy or exacerbation of the existing disease was noted,[73, 80–83] and deterioration of leprosy patients was observed to be more frequent in those who were not receiving treatment (18 out of 23) than in those who were on treatment with sulphones (5 out of 23).[84]

Although exacerbation of leprosy was seen during pregnancy it was said to be much more common during the puerperium and the early months of lactation.[85] Reaction due to leprosy was observed postpartum,[80] while 1 out of 6 women with leprosy suffered from 'lepra fever' during pregnancy.[77]

Most of the observations on the association of leprosy and pregnancy and the effect of one on the other, are contained in individual case reports or relatively small retrospective surveys. No record of any clearly-defined prospective study could be traced in the available world literature prior to 1975.

The outcome of pregnancies in mothers with leprosy

While considerable research has been carried out on the children of parents with leprosy, this has been largely of an epidemiological nature to determine the susceptibility of these children to leprosy, and to investigate methods of preventing the infection, such as separation of children from parents at different ages after birth. Such studies were carried out in the Philippines, in India and in South America. More recently, massive immunization campaigns have been conducted to test the efficiency of BCG in preventing leprosy in children in leprosy endemic areas.[86, 87]

Relatively little has been recorded of the general state of health of the children of mothers with leprosy, although Zambaco recorded that many children born to mothers with lepromatous leprosy were small 'like an abortion at term', and that they died within a few months of birth of athrepsie.[67] In another context he wrote (here I translate):

'in former times children of leprous women, born like little old men, did not develop normally but died of athrepsie without showing in their body any sign of leprosy. This foetal cachexia which leads to death *in utero* or shortly after birth, without the lesions of leprosy is certainly due to leprosy and maybe described under the name of paraleprosy'.[88]

More recently, it was noted that whereas minor ailments were similar to those seen in the healthy community, among the children of lepers, skin diseases were very common and the infant mortality was very high, with 42% of the children dying of infections, debility, marasmus and athrepsie.[89] Similar observations have been made since then:

'. . . the children . . . are of a reduced vitality and frequently succumb shortly after birth',[90] and '. . . all children of leper parentage are very delicate and seem to have a predisposition to respiratory and gastric diseases which take a big toll of them'.[91]

The low birth weights, small placentae, and low placental coefficients in pregnancies of mothers with leprosy, most marked in those with lepromatous leprosy, were only recorded very recently.[92] As the majority of perinatal deaths occur in the small group of intra-uterine growth retarded infants born to non-leprous women,[93] it is tempting to assume a cause and effect regarding the low birth weight and increased mortality of children of mothers with lepromatous leprosy.

The future

While historical review and recent clinical research has indicated the nature of some of the problems of the interaction of leprosy in pregnancy, a number of investigations are still required to elucidate questions raised in recent studies.

A prospective trial of additional chemotherapeutic agents to prevent relapse in pregnancy while at the same time measuring the dapsone excretion in urine could be used to evaluate the question 'Is patient compliance more important than maternal immunosuppression during pregnancy in the causation of relapse/dapsone resistance?' A prospective clinico-pathological study of ENL in women in relation to the menstrual cycle and pregnancy/lactation could well elucidate the immunological trigger mechanisms in ENL. The high incidence of neuritis in BL patients, and the clinically puzzling mixture of ENL and reversal reaction in this group of patients also merit investigation as a prospective clinico-pathological study with frequent nerve and skin biopsy in addition to immunological tests.

Certain aspects of the effect of leprosy on pregnancy require further study in themselves. One is the hypothesis that impaired placentation in women with lepromatous leprosy is due to their impaired cell-mediated immunity. Another is the observation that patients receiving dapsone, rifampicin and clofazimine have impaired foeto-placental function in terms of oestrogen excretion. This is most marked in patients with lepromatous leprosy, and therefore could be related to the patient's lowered immune responsiveness rather than her drug therapy.

Further immunohistological studies of placentae from lepromatous women are also required using specific antisera to see whether and where *M. leprae*/*M. leprae* antigen lodge in relation to maternal and foetal circulations. Maximum information would be obtained from studying placentae from untreated lepromatous women reporting for the first time late in pregnancy.

A longitudinal study is necessary to assess the effects of the mother's leprosy on her child. Two separate issues require investigation, firstly the development of leprosy in the child, which children develop leprosy and why; and, in those who do not develop leprosy, whether hypersensitivity can be equated with protective immunity. Secondly, whether transfer of maternal cells across the placenta or through the breast milk after birth has any role in the causation of failure to thrive, and whether improving nutritional factors after birth results in improved infant growth. Also, whether immune complexes such as are found in patients with lepromatous leprosy cross the placenta from mother to child, or form in the foetus/neonate, causing intra-uterine growth retardation and failure to thrive after birth, as has been suggested in other infections.

Clearly, the study reported from Ethiopia is not 'an end' but 'a beginning'.

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Lepr Rev (1985) **56,** 163–166

Domiciliary and Field Work

Low cost printing for development

These 4 booklets (104 pp combined, A4 size) cover in a clear and concise way many aspects of printing and design showing how communities or individuals can set up their own printshops. Topics covered are: Booklet 1, background, alternatives, planning, choosing a print method, design (ideas, approaches and techniques), and finishing. Booklet 2, block printing, stencil duplicating, screen printing, Hecot jelly pads, spirit duplicating, and photocopying. Booklet 3, Dealing with the printer, colour, imposition, offset lithograpy printing, letterpress printing, and glossary. Booklet 4, Have your own printshop, Is there a need for a printshop? setting up, what you will need, running a printshop, and paper.

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OXFAM-LEPRA, Oxford, UK. A mini-pack of teaching materials on leprosy

Following the development and distribution of a larger pack of teaching–training materials on leprosy during the past 2 or 3 years, OXFAM in cooperation with LEPRA have assembled 100 packs containing only 8 items, as follows:

1 *Chemotherapy of Leprosy for Control Programmes* (1983). Technical Report Series 675, 1211 Geneva 27, Switzerland.
2 *OXFAM Memorandum on the Implementation of Multiple Drug Therapy (MDT) for Leprosy* (1984). The Health Unit, OXFAM, 274 Banbury Road, Oxford OX2 7DZ, UK.
3 *Leprosy* (1979) by Bryceson and Pfaltzgraff. Published by Churchill Livingstone, Edinburgh, UK.
4 *The Diagnosis and Management of Early Leprosy* (1983) by Browne. Published by the Leprosy Mission International, London, UK.
5 *Better Care in Leprosy* (1978). Published by the Voluntary Health Association of India, New Delhi, India.
6 *Insensitive Feet* (1981) by Paul Brand. Published by the Leprosy Mission International, London, UK.
7 *Technical Guide for Smear Examination for Leprosy by Direct Microscopy* (1983) by Leiker and McDougall. Published by the Leprosy Documentation Service (INFOLEP), Amsterdam, the Netherlands.
8 *Atlas of Leprosy* (1983). Published by the Sasakawa Memorial Health Foundation, Tokyo, Japan.

Intended mainly for: Medical students, medical officers (with or without experience of leprosy), leprosy control officers, nurses, tutors and other potential teachers.

In view of the high cost of postage by air or surface mail, OXFAM strongly recommends 'personal' delivery. Copies may be obtained by calling at OXFAM in Oxford during normal working hours or by writing to The Health Unit, OXFAM, 274 Banbury Road, Oxford OX2 7DZ, UK. Delivery, especially for bulk orders, may also be possible through embassies and consulates in London and by liaison with ILEP, the International Federation of Anti-Leprosy Associations, 234 Blythe Road, London W14 (Tel. 01–602 6925) which holds twice-yearly meetings, often abroad. Cost £10 (USA $15).

Penlight for testing thermal sensitivity in leprosy

Dr H Sansarricq, formerly Chief Medical Officer, Leprosy, WHO, Geneva, has kindly supplied the following information about a device which may be of value in the early diagnosis of leprosy.

"Testing of thermal sensitivity during clinical examination for leprosy has usually been done by the use of 2 test tubes; one with warm water and the other with cold water. The limitations of the method were the varying temperatures of the warm water and also the difficulty of obtaining hot water during village work.

A new invention may solve the above problems. The device consists of an electronic head which fits into the body of a SONCA PENLIGHT. It is powered by 2 penlight batteries and the tip heats up to a factory preset temperature. Present prototypes have some set at 40°C and others at 45°C. The other end of the body serves as the cool probe and testing is easily done by alternating the warm and cool ends as the examiner desires. The penlight body is insulated against the body-heat of the operator."

The device, developed by Mr M O'Regan who was a Technical Officer with the Leprosy Unit, World Health Organization (WHO), Geneva and Mr Bent Stumpe, an electronics engineer with the European Centre for Nuclear Research (CERN),

(continued on p. 166)

Schieffelin Leprosy Research and Training Centre, Karigiri—Courses 1985–1986

Courses	Qualification	Duration	Commencing date 1985	Commencing date 1986
Medical officers				
a Condensed course in leprosy	Doctors and senior medical personnel	1 week	14–19 Jan. 8–13 April 2–7 Sept.	6–11 Jan. 7–12 April 8–13 Sept.
b Medical students course	Undergraduates	1 week	(Dates fixed acc. to college holidays)	
c Medical officers course	Medical personnel engaged in leprosy work	6 weeks	4–16 Feb.–Mar. 1–9 July–Aug.	3–14 Feb.–Mar. 7–15 July–Aug.
d Special course for ophthalmology teachers		3 days	(Proposed)	
e Ophthalmic aspect in leprosy	Qualified medical personnel (included in 6 weeks course)	3 days	(Proposed)	
Other categories				
a Non-medical supervisors' course	Fully qualified paramedical workers with a minimum of 3 years experience	4 months	3 June	9 June
b Orientation course in leprosy	For paramedical personnel (nurses, physios, OT & administrators) 1 week CONDENSED COURSE +3 weeks in-service training	1 month	14–19 Jan. 8–13 April 2–7 Sept.	6–11 Jan. 7–12 April 8–13 Sept.
c Paramedical workers course	+2 passed, graduates preferred	6 months	11 Sept.	10 Sept.
d Advanced course in leprosy control	Selected, experienced non-med. supervisors	12 months	By arrangement	
e PMW refresher course	Qualified PMWs	1 month	3 June	9 June
f Physiotherapy technicians course	+2 passed or PUC preferred	9 months	12 June	11 June
g Laboratory tech. course	+2 passed, Science graduates preferred	12 months	8 July	7 July
Inservice training				
a Prosthetic tech.	+2 passed or PUC preferred	18 months	21 Jan. 10 July	20 Jan. 16 July
b Shoemakers' course	V standard with knowledge of English preferred	6 months	Jan. and July	Jan. and July

c	Smear technicians course	+2 passed (reg. qualified lab. techns refresher)	3 months	7 Jan. 3 June 2 Sept.	20 Jan. 11 June 15 Sept.
d	Medical record keepers	+2 passed with proficiency in typing and good English	2 months	By arrangement	
e	Inservice training in Medicine, surgery, pathology, lab. technology and lep. control	For qualified medical personnel	9 months	By arrangement	

Schedule of fees

S. No.	Course	Tuition (Rs.)	Registration (Rs.)	Medical (Rs.)	Library (Rs.)	Establishment (p.m.) (Rs.)
Medical						
1.	Condensed course in leprosy	100	15			
2.	Medical officers' course	300	15			
3.	Medical students' course	free	free			
4.	Orientation course	200				
5.	In-service training	150/pm				
6.	Electives	300/fs	(full session)			
Non-medical						
7.	Non-medical supervisors	300	10	25	5	30
8.	Paramedical workers	300	10	25	5	30
9.	PMW refresher course	100	10	25	5	30
10.	Physiotherapy tech. course	450	10	25	5	30
11.	Laboratory tech. course	500	10	25	5	30
12.	Prosthetic tech. course	300	10	25	5	30
13.	Orthopaedic shoemakers'	100	10	25		30
14.	Smear technicians course	200	10	25	5	30
15.	Medical record keepers	100	10	25		30
16.	In-service training	100/pm				

Note: '+2' signifies 12 years of schooling equivalent to 'A' levels.
Note: NOT APPLICABLE to INDIAN Government Candidates. 50% concession (Tuition) to all TLM and ALM candidates.

All correspondence to the Training Officer, SLR and TC, SLRS PO, via Katpadi 632 106, North Arcot District, S. India.

Geneva, was funded by the Appropriate Technology Unit and the Leprosy Unit of the WHO. Twenty prototypes have been manufactured by Speyside Electronics of Scotland. Field tests of the device are planned following a protocol prepared by Dr Srinivasan, Central Leprosy Teaching and Research Institute, Chingleput, India.

Primary eye care

Primary eye care comprises a simple but comprehensive set of preventive and curative actions, which can be carried out by primary health workers, by specialized auxiliary personnel or by other interested persons.

The clinical activities involved in primary eye care consist of basic ways of dealing with the 3 major eye symptoms presented by patients: inflamed ('red') eyes, loss of vision, and pain in the eye. At the primary level the health worker can manage these problems either by definitive treatment, by referral after immediate treatment or by referral alone. General guidelines for this action have been developed, but they must be adapted to conditions in the communities served.

In addition, the primary health care worker should carry out promotive and preventive activities, focusing on essential education and community participation with regard to the prevention of visual loss.

Only a few medicaments and other materials are necessary for primary eye care. At the very least, an antibiotic eye ointment (usually a tetracycline) is needed, but other drugs that may be useful are vitamin A capsules, a second antibiotic ointment and zinc sulphate drops (for mild irritations). Bandages, sticking plaster (tape) and eye shields are very useful for primary workers, and optional equipment may include a simple chart to measure visual acuity and a hand torch.

The most important factor necessary to initiate primary eye care is the training of primary health workers to recognize eye conditions and to take appropriate action to deal with the problem. Training manuals for primary health workers should therefore include material on primary eye care. Primary eye care must be supported by reinforcing training and by adequate referral services at the secondary level.

From: *Strategies for the prevention of blindness. A primary health care approach.* Geneva, World Health Organization, 1984, pp. 14–15.

Correspondence course for leprosy technicians, Marie Adelaide Leprosy Centre, Karachi

Dr Ruth Pfau, Adviser on Leprosy to the Ministry of Health in Pakistan, has recently started a correspondence course for leprosy technicians in Pakistan. The course consists of six lectures spread over a period of one year. The first subject is the treatment of leprosy. The object is to keep paramedical staff abreast of new developments and to reinforce and broaden knowledge gained at annual workshops. The information issued on Multiple Drug Therapy covers the selection of patients, classification, precautions before starting drug treatment, health education, side-effects, procedure after stopping MDT, referral to hospital, and record keeping. There is also a questionnaire.

[Although carried out within one country, this approach amounts to 'distance learning'. David Morley and Felicity Savage-King have recently drawn attention to the enormous (untapped) potential of this approach. ('Appropriate teaching aids'; *Brit Med J*, **289,** 20 October 1984, pp 1057–8.) To quote from their closing paragraph, such an approach '. . . could train the whole health team and provide a continuing training programme for health workers who have had practical experience of the problems that they are expected to deal with and need some feedback. Above all, distance learning is a way to get ideas about how to improve health outside academic institutions and in the community.' Editor].

OXFAM, Oxford; *Questions and answers on the implementation of multidrug therapy (MDT) for leprosy*

This is a 32-page booklet, A5 size, in question and answer form, produced by OXFAM as Number 3 in its 'Practical Guide' series. Starting with 'What is MDT?' and ending with 'Will the implementation of MDT lead to the control, and perhaps even to the eradication of leprosy?', 15 questions, all of a practical nature, are posed, and an attempt made to answer them in the light of existing knowledge about a fast-expanding subject. Price: £1.50 per copy, with a 25% discount on orders of more than 10, plus postage charges on bulk orders. Enquiries: OXFAM, Health Unit, 274 Banbury Road, Oxford OX2 7DZ.

Technical Guide for Smear Examination for Leprosy by Direct Microscopy

Published by the Leprosy Documentation Service (INFOLEP) at the Royal Tropical Institute, Mauritskade 61a, 1092 AD Amsterdam, the Netherlands, this 34-page paperback booklet covers ll main aspects of smear examination. It was produced with the support of the Netherlands Leprosy Relief Association and the Ordre Militaire et Hospitalier de Saint Lazare de Jerusalem in the Netherlands.

The main headings include—introduction; technique of smear-taking; technique of staining; examination by microscopy. Five thousand copies have been printed in English and arrangements are being made for its translation and printing in French, Spanish and Portuguese.

Lepr Rev (1985) **56**, 167–170

Reports, News and Notes

Retirement of Dr H Sansarricq

Dr Hubert Sansarricq retired from the World Health Organization on 31 July 1984, after more than 12 years of service as Chief Medical Officer of the Leprosy Unit.

Dr Sansarricq brought to his post in WHO a wealth of experience in leprosy control and tropical medicine, acquired in the course of his career in the French army, during which he worked primarily in Francophone Africa. After taking his medical degree in Bordeaux, France, in 1954, he served in Algeria, Mali and Upper Volta. Interspersed with his tours of duty in Africa, he attended courses in microbiology in Marseilles and the Institut Pasteur in Paris. At the time of his recruitment to fill the WHO post, he was serving as Chief of the Microbiology Laboratory of the Central Army Teaching Hospital in Algiers, and as Assistant Professor of Hygiene in the Faculty of Medicine of Algiers.

Dr Sansarricq's tenure of the WHO post coincided with a period of great progress in leprosy research, particularly that related to the control of leprosy. Just prior to his assuming the post, unlimited multiplication of *Mycobacterium leprae* in the armadillo had been announced, and the first report of the extraordinary efficacy of rifampicin therapy of lepromatous leprosy had appeared. Dr Sansarricq was an active participant in the establishment of the IMMLEP programme, and the prime mover in the organization of the THELEP programme; these WHO research programmes in leprosy had been made possible by the advent of the armadillo and rifampicin. In addition to his active support at the birth of these 2 research programmes, he continued to participate and to promote their activities, and served as liaison between IMMLEP and THELEP and several voluntary agencies. Moreover, he foresaw the importance of molecular biology to leprosy research, and played a crucial part in the recruitment into leprosy research of an outstanding microbial geneticist.

In the course of his involvement in IMMLEP and THELEP, Dr Sansarricq became convinced of the seriousness of the threat of dapsone resistance to programmes of leprosy control, and of the need to develop practical regimens of combinations of effective drugs. Perhaps his most important contribution to enhancing the effectiveness of leprosy control activities, therefore, was his convening a WHO Study Group on Chemotherapy of Leprosy for Control Programmes. Numerous regimens, all different from one another, had been recommended, and Dr Sansarricq recognized the need to create order. Then, having succeeded in stimulating recommendations for practical multi-drug regimens for the control of leprosy, he devoted all of his efforts and resources to seeing to the implementation of these regimens, mobilizing support from WHO Regional Offices, voluntary agencies, and national governments.

That we have advanced so gratifyingly in our effort to control leprosy is largely the result of Dr Sansarricq's contributions. Those who were privileged to work closely with him during his tenure as Chief Medical Officer of the WHO Leprosy Unit have been encouraged by his more recent activities to hope that he will continue to lend his broad expertise and enormous dedication to this most important cause.

0305-7518/85/00167+04 $01.00

Sasakawa Memorial Health Foundation: English publications

A. PROCEEDINGS OF THE INTERNATIONAL WORKSHOPS:

SP-1. *The 1st International Workshop on Training of Leprosy Workers in Asia—Bangkok and Pattaya, 1976*, 228 pp.
SP-2. *The 1st International Workshop on Chemotherapy of Leprosy In Asia—Manila, 1977*, 213 pp.
SP-3. *The 1st International Workshop on Leprosy Control in Asia—Jakarta, 1977*, 249 pp.
SP-4. *The 2nd International Workshop on Training of Leprosy Workers in Asia—Bangkok, 1979*, 242 pp.
SP-5. *The 2nd International Workshop on Leprosy Control in Asia—Kathmandu, 1979*, 163 pp.
SP-6. *The 3rd International Workshop on Leprosy Control in Asia—Taipei, 1980*, 188 pp.
SP-7. *The 3rd International Workshop on Training of Leprosy Workers in Asia—Bangkok, 1982*, 140 pp.
SP-8. *The 4th International Workshop on Leprosy Control in Asia—Kuala-Lumpur, 1982*, 197 pp.
SP-9. *The 5th International Workshop on Leprosy Control in Asia—Singapore, 1983*

B. PROCEEDINGS AND TEXTS OF OTHER MEETINGS (NATIONAL AND INTERNATIONAL):

SPO-1. *The 1st Seminar on Leprosy Control Cooperation in Asia—Tokyo, 1974*, 118 pp.
SPO-2. *The 2nd Seminar on Leprosy Control Cooperation in Asia—Tokyo, 1975*, 153 pp.
SPO-3. *International Symposium on Leprosy and Joint Chemotherapy Trial Meeting—Seoul and Anyang, 1978*, 137 pp.
SPO-4. *The 1st National Workshop on Leprosy Control—Nepal, 1979*, 96 pp.
SPO-5. *International Symposium on the Epidemiology of Leprosy—Geilo, Norway, 1981*, published by British Leprosy Relief Association as Supplement to Leprosy Review, Vol **52,** 1 Dec. 1981, 304 pp.
SPO-6. *The 2nd National Workshop on Leprosy Control—Nepal, 1981*, 103 pp.
SPO-7. *Symposium on Immunotherapy and Immunoprophylaxis of Leprosy (Texts) 1982*, 55 pp.
SPO-8. *Proceedings of the Workshop on Serological Tests for Detecting Subclinical Infection in Leprosy, 1983*, 99 pp.

C. OTHERS:

SO-1. *Sasakawa Foundation Fellowship, 1978*, 99 pp.
SO-2. *Sasakawa Foundation Fellowship, No. 2, 1981*, 102 pp.
SO-3. *Sasakawa Memorial Health Foundation, 1982*, 18 pp.
SO-4. *Leprosy in Japan* by Dr F Ohtani, Ministry of Health and Welfare, Japan, 1982, 35 pp.
SO-5. *Health for All by the Year 2000*, by Dr H T Mahler, Director-General, WHO, 1981, 12 pp.
SO-6. *The Way toward Eradication of Hansen's Disease*, by Prof M F Lechat, President, International Leprosy Association, 1981, 14 pp.
SO-7. *Leprosy in China*, by Dr Stanley G Browne, Secretary, International Leprosy Association, 1982, 25 pp.
SO-8. *An Atlas of Leprosy (Philippines)*, by Dr R Guinto *et al.*, 1981.
SO-9. *An Atlas of Leprosy (Philippines)*, by Dr R Guinto *et al.*, 1983 (revised).
SO-10. *A Self-Instruction Module on Self-Instruction* by Dr Charles R. Auscherman & Dr W Felton Ross, 1983, 98 pp. (Offprint of SP-7.)
SO-11. *Basic Epidemiological Indicators for Monitoring Leprosy Control* by Prof M F Lechat & Dr M Vanderverken, 1983, 24 pp. (Offprint of SP-8.)
SO-12. *Leprosy in Global Context* by Prof Michel F Lechat, 1983, 8 pp. (Offprint of SP-9.)

(It is our understanding that these publications are intended mainly for those working in the leprosy-endemic areas in which the Sasakawa Memorial Health Foundation is particularly active, but that certain items may be available to others on application to the Sasakawa Memorial Health Foundation, the Sasakawa Hall, 6F, 3-12-12 Mita, Minato-ku, Tokyo 108, Japan. *Editor.*)

Medical Laboratory Manual for Tropical Countries; Volume 2; Microbiology; ELBS edition

This manual, written and published by Monica Cheesbrough, Tropical Health Technology Ltd, 14 Bevills Close, Doddington, Cambridgeshire, England, PE15 OTT, is now available as an ELBS edition at a cost of only £2.95, plus approximately £1.60 for surface mailing. The laboratory examination of slit-skin smears in leprosy is dealt with in detail. Details of the ELBS system were given in this Journal on page 433 of Volume **55** (Number 4, 1984).

Slide-set: Leprosy in the light-skinned

This is a colour transparency teaching set with printed text, comprising 50 slides illustrating the main aspects of leprosy in the light-skinned patient. This valuable and long-needed material has been produced by Dr D L Leiker of the Royal Tropical Institute, Amsterdam, the Netherlands and the set is available on application to the Regional Officer for Communicable Diseases, the World Health Organization, 8 Scherfigsvej, DK 2100, Copenhagen ø, Denmark. The main headings are: bacteriology, distribution, diagnosis, classification (includes reactions), and chemotherapy. Especially for those working in Europe or North America, this set should be of great practical value. See also *Leprosy in the light skin* an illustrated manual by D L Leiker and E Nunzi, published by Associazone Italiana 'Amici di Raoul Follereau' Via Borselli 4, 40135 Bologna, Italy (price: USA $30.00).

Leprosy at the basic health service level

This is a manual of 76 pp in A4 format, inexpensively produced. The text in French is by Dr Guido Groenan and Dr Kayembe Tshilumba and the line drawings by an American Peace Corps Volunteer, Maria Madison. The title is descriptive and the book has been written essentially for workers at the level of 'health promoters', 'community health agents' or health 'animateurs'. However, the introduction concludes that it should be of practical value to anyone who is responsible for the distribution of medicines to leprosy patients. Part 1 covers the ten main aspects of leprosy control. Part 2 covers basic knowledge of leprosy and

includes information for the teachers of primary health care workers. Part 3 deals mainly with health education. This is a most valuable document written for leprosy workers at a level which has so far received all too little attention. It could profitably be studied and adapted for English, Spanish and Portugese-speaking countries and for translation into local languages. Enquiries to Les Amis du Père Damien, 16 rue Stevin, 1040, Brussels, Belgium.

Behçet's Disease; International Conference in London, September, 1985

This international, multidisciplinary conference on Behçet's Disease, to be held in London, aims to discuss recent advances in the aetiology, immunology, diagnosis and treatment of this intractable disease. As the disease affects a number of tissues and organs, the object of the meeting is to bring together physicians, opthalmologists, dermatologists, stomatologists, rheumatologists, neurologists and gastroenterologists, who have special interest in this disease.

Apply to Miss M Mitchell, Conference Office, 1 Wimpole Street, London W1M 8AE. (We print details of this conference on a disease which may not at first sight have much to do with leprosy because of the remarkable results of thalidomide in the treatment of Behçet's disease and oro-genital ulceration, confirmed from many parts of the world. The programme will also cover virology and epidemiology, and under treatment it is to be hoped that the matter of non-teratogenic analogues will be included. *Editor*.)

Robert Cochrane Fund for Leprosy

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

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

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

XIII International Leprosy Congress, The Hague, Netherlands, 1988

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

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

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

II Congress of Hansenology of the Endemic Countries, December 1985

This congress is scheduled for 3–5 December 1985 at the Baton Rouge Hilton Hotel and the National Hansen's Disease Center in Carville, Louisiana. The College of Hansenology of the Endemic Countries is an international organization of health professionals, physicians, social and paramedical workers concerned with the microbiology, immunology, experimental animal models, pathology, clinical aspects, therapy, physical and psychosocial rehabilitation, and the epidemiology of Hansen's diesease. Panels, working groups, and free communications are planned, addressing these themes. One-half day will be devoted to a visit and tour of the National Hansen's Disease Center in Carville.

For further information contact: Dr R Azulay, President, College of Hansenology of the Endemic Countries, Rua Nascimento Silva, 16/201, CEI-22.421-PANEMA, Rio de Janeiro-R.J., Brasil; or Dr R Hastings, President, II Congress of Hansenology of the Endemic Countries, National Hansen's Disease Center, Carville, LA, 70721, USA.

International Symposium on Mycobacteria of Clinical Interest

Date: 27–28th September, 1985. Themes—immunopathology of leprosy and tuberculosis; modern methods for the rapid diagnosis of tuberculosis; human mycobacteriosis; therapy of leprosy and tuberculosis; experimental chemotherapy, etc.

Apply to Secretariat, International Symposium on Mycobacteria of Clinical Interest, Department of Microbiology, School of Medicine, University of Cordoba, CORDOBA-4, Spain.

XIII World Conference on Health Education, 1985

Trinity College in Dublin will be the venue for the XIIth World Conference on Health Education which will be held 1–6 September 1985. The theme chosen is 'Health for All—Meeting the Challenge'. Five sub-themes will focus on a particular aspect of meeting the challenge of health for all: 'Have we all a choice? What are the constraints? What progress so far? Who first? Is it the same everywhere?' For information please write to Mary D'Ardis, Conference Coordinator, Health Education Bureau, 34 Upper Mount Street, Dublin 2. Tel.; 76 11 16.

University of Dundee; Centre for Medical Education

For over 8 years this teaching centre has run courses for medical teachers on a variety of topics, including assessment teaching methods and curriculum planning. Those in 1984 include 'Effective Teaching in Medical Education', 'Assessment in Medical Education' and 'Curriculum Planning in Medical Education'. The duration of each is for a few days only and accommodation

can be arranged; fees are moderate. Apply (for 1985) to The Centre for Medical Education, The University, Dundee DD1 4HN (Tel: 0382-23181).

International Conference on Biomechanics and Clinical Kinesiology of Hand and Foot, Madras, 16–18 December 1985

The aims of this conference are: 1 To acquaint anatomists, biomechanical engineers, physiotherapists and surgeons, especially those involved in the care and rehabilitation of hand and foot following leprosy and trauma, with the current developments in the field of functional morphology and biomechanics of hand and foot, so that a better understanding is obtained in the management of the deformities of these organs; and 2 To identify specific areas of further research in these problems.

For further details of themes and accommodation etc. write to Dr K Mothiram Patil, Organizing Secretary, ICBACKHAF, Biomedical Engineering Division, Department of Applied Mechanics, Indian Institute of Technology, Madras-600 036, India.

XXVIth IUAT World Conference on Tuberculosis and Respiratory Diseases, Singapore, 4–7 November 1986

The Conference is open to members and non-members of the IUAT. The programme will cover the fields of *tuberculosis* and *non-tuberculous respiratory diseases*, including smoking-related issues, from the clinical, immunological, physiological, diagnostic, therapeutic, preventive and epidemiological points of view, as well as aspects related to *action programmes* and their assessment, training of personnel, related diseases such as those due to non-tuberculous mycobacteria and problems of *delivery of services* (such as primary health care, compliance, community mobilization).

There will be 6 morning plenary sessions, afternoon parallel sessions, poster sessions, sunrise seminars and several workshops. Official languages will be English and French. Spanish interpretation is being considered.

Abstracts for proposed presentations should be sent to: IUAT Secretariat, 3, rue Georges Ville, 75116 Paris, France. Abstract forms will be distributed by the end of March 1985 to all IUAT members. Non-members may obtain copies by writing to us in Paris. *Proposals must concern original work in progress.*

The IUAT world conferences are the only international forum for tuberculosis, and in respiratory disease the IUAT is working out a programme of research, training and action for the promotion of respiratory health.

For practical information, kindly write to: Secretariat of the XXVIth IUAT World Conference on Tuberculosis and Respiratory Diseases, c/o SATA, 267 Cantonment Road, Singapore 0208, Republic of Singapore.

Back numbers of *Leprosy Review* required

The Honorary Editor, Dr Dharmendra of the *Indian Journal of Leprosy* would very much like to hear from anyone who has the following issues of *Leprosy Review* available. This is to enable a complete library of *Leprosy Review* to be established for the use of people in India.

The issues required are: Volume 21 (1950) all issues; Volume 28 (1957) No. 2, April; Volume 29 (1958) No. 4, October.

Should you have any of these issues available it would be greatly apreciated if you would contact Dr Dharmendra at the Editorial Office of the *Indian Journal of Leprosy*, A-2/50 Safdarjang Enclave, New Delhi 110 029, India.

Video-tape: 'Chemotherapy of Leprosy for Control Programmes', Oxford

The Department of Medical Illustration in Oxford has produced a 14-minute video-tape (VHS PAL 625 system) describing recent regimens of drug treatment for leprosy, based on the Report of a WHO Study Group entitled '*Chemotherapy of Leprosy for Control Programmes*', published by WHO in Geneva in 1982 in the Technical Report Series, Number 675.

The intended audience includes—medical students, medically qualified doctors, senior personnel in ministries of health in leprosy-endemic countries, tutors and teachers in medical and para-medical schools, programme planners, leprosy control officers and supervisors, senior staff in pharmacies, drug supply and distribution.

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

Cost: £12 sterling ($16 US dollars), plus Value Added Tax (VAT), but inclusive of postage. Apply directly to: Department of Medical Illustration, the John Radcliffe Hospital, Headington, Oxford OX3 9DU, England.

Lepr Rev (1985) **56,** 171–175

Letters to the Editor

ADVERSE REACTIONS TO RIFAMPICIN AND DAPSONE

Sir,

The WHO short-term multiple drug regimen[1] was adopted in Guyana in December 1981 and during the subsequent 3 years the following adverse reactions to drugs have been observed:

Rifampicin. Two patients (one multibacillary and one paucibacillary) experienced a typical cutaneous syndrome in response to rifampicin as described by Aquinas.[2] The multibacillary patient was successfully desensitized but as the paucibacillary patient had previously received dapsone monotherapy and was inactive at the start of MDT desensitization was not considered worthwhile. This syndrome is quite different from any other drug reaction I have previously seen and exactly follows the pattern described by Aquinas. Proof of the causality of rifampicin was obtained by challenge with rifampicin alone.

Dapsone. Two paucibacillary patients developed adverse reactions to dapsone. The first developed an irritating, papular rash that cleared on withholding treatment. Challenge with rifampicin alone was uneventful but challenge with dapsone alone produced a florid rash and severe facial oedema. This patient completed treatment on supervised rifampicin and clofazimine only. A second paucibacillary patient developed a very insignificant, papular rash and as challenge with dapsone did not provoke any acute symptoms treatment was completed using a reduced dose of 50 mg daily. The rash healed leaving large, irregular, slate-grey blotches, rather than the typical, oval splashes of fixed drug eruption. However, as investigations did not reveal any alternative cause for the rash or the pigmentation I felt that the dapsone was probably responsible. This has recently been confirmed by the return of the patient with rash and facial oedema following self-treatment with sulphonamides for an incidental infection. Her leprosy remains inactive and the hyperpigmentation has completely cleared. Both responses to dapsone occurred within the first 6 weeks of treatment and may be considered hypersensitivity reactions.

The actual incidence of side-effects to rifampicin amounted to approximately 1 in 4500 doses given in the domiciliary programme. In the same period over a quarter of a million dapsone tablets were consumed without producing other than 1 mild and 1 moderately severe reaction. All 4 patients involved were women.

It is interesting to speculate why we should see 2 reactions to dapsone in 3 years compared with only 1 during the entire 11 years preceding MDT. Is this just a chance happening or are we becoming more alert to our patients' problems? One of the beneficial effects of MDT has been the fostering of improved staff/patient relationships. Could it be that patients who previously threw away their tablets in disgust and defaulted on encountering unpleasant side-effects are now returning to clinic in search of help? I look forward to hearing what is happening elsewhere.

PATRICIA ROSE

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Georgetown Hospital
Georgetown
Guyana

0305-7518/85/00171+05 $01.00

References

[1] Report of a WHO Study Group on Chemotherapy of Leprosy for Control Programmes. Oct. 1981; pp 24–5.

[2] Aquinas M, Allan WGL, Horsfall PAL, Jenkins PK, Hung-Yan W, Girling D, Tall R, Fox W. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *Br Med J*, 1972; **1:** 765–71.

WHO DISABILITY GRADING

Sir,

I have some questions and suggestions regarding WHO disability grading, and would be interested to hear the views of other readers as to its use and usefulness.

I am using the term 'deformity' to mean change of form, and thus to cover deformity due to paralysis (lagophthalmus, clawing, dropfoot) and deformity due to absorption. I am using the term 'disability' to cover *also* loss of sensation.

WHO purposes for disability grading

In its booklet *OMSLEP Recording and Reporting Systems for Leprosy Patients, second edition* (1983), WHO states that 'an information system should be seen in a decision-making context' and gives two purposes for its disability grading.

The first stated purpose is as an index 'which can be *used to assess the delay in case-detection*. This index should be close to zero when case-finding is early and when screening coverage is high'.

WHO ask in their suggested Individual Patient Form and Detection Form, for the number of newly registering patients having 'WHO grade < 2 disability (bone absorption, claw hands and dropfoot)—omit anaesthesia'.

Thus they require only two categories: with and without deformity or ulceration; and only the highest grading for any one patient: eye, hand or foot.

Comment. For this purpose the grading could be greatly simplified. WHO need ask for only two grades in newly registering patients: deformity and/or ulceration in either eye, hand *or* foot; or no deformity or ulceration.

A second overall purpose for records described by WHO is that of 'evaluation of the efficiency of programmes'. WHO's main purposes in regard to leprosy are a reduction in the number of patients with active disease and eventual disease eradication. However, under a heading 'Cohort Analysis' WHO give as one index that can be observed any *increase* in disability grading *from* 0·1 or 2 to 2 or 3 '*so that occurrence of new disability can be observed*'.

Comment. Those working towards disability control in leprosy patients would like to know: (a) the number of patients suffering decreasing nerve function; and (b) the number of patients suffering worsening secondary deformity.

However, I think it important to recognize that WHO grading in its present form is *not appropriate* for this purpose, despite the fact that attempts are sometimes made to use it in this way. I myself have tried to do so but one cannot determine either of the above properly. For example: the hand with slight sensory loss and clawing of the little finger will be graded as 2. If subsequently the hand shows complete ulnar and median nerve lesions, plus several wounds and open cracks, the grading will remain at 2. Yet if the *only* added problem is little stiffening then the grading will change to 3. If the area of sensory loss of a foot increases from one toe to the whole sole, the WHO grading will remain unchanged at 1.

I have followed up some Ethiopian and Tanzanian patients whose WHO disability grades had changed from 0 to 1 or from 1 to 0. I found that almost all changes were due not to real ones but either to differences in testing *method* (some used cotton wool, others pressed hard with a ballpoint pen) or in test *area* (some tested the hand and foot dorsum, others did not). Neither area nor method are specified in WHO grading keys.

ILEP purposes for disability grading

In their form B, ILEP ask for numbers of *registered* patients having WHO grade < 2 disability. The purpose of collating this information *only* for patients registered for chemotherapy is not clear to me.

Comment. In patients having nerve lesions affecting eyes, hands and/or feet deformity may well increase over the years. Apart from paralysis, WHO grades 2 and 3 disability problems are those *secondary* to nerve damage. They do not cease when the patients are released from chemotherapy control and their names are removed from the register. Patients having sensory and/or strength loss may need continuing care, education and supply of protective devices. It would be useful to include patients needing such continuing support in any national disability statistics.

Under the present ILEP recording system many patients with an increasing disability problem are *never* included in disability statistics. For example: A patient's foot may lose sensation before he is released from control—this grade 1 disability will not appear on ILEP statistics. During the years that *follow* his release from control the patient may suffer increasing grades 2 and 3 ulceration and absorption but because his name has been removed from the register these will not appear in statistics.

Under the present ILEP system the shorter the treatment course becomes on multidrug therapy the better the disability statistics will appear!—whether or not they have in fact changed. There will be no purpose in comparing statistics from year to year if treatment durations have changed.

If ILEP, WHO or national authorities wish to know the extent of the continuing disability problem amongst patients released from chemotherapy control, then it will presumably be necessary for them: (a) to have patients who attend for support listed in a 'disability problems' section of the attendance register; or (b) to define criteria for removing patients' names from this register—for 'release from disability control'. Such criteria might for example be: either 'has not attended for support for the whole year' or 'has attended but has had no increase in disability for two years and needs no continuing supply of protective devices'.

Disability records needed by those responsible for disability prevention activities

Those planning and evaluating disability prevention activities would like to know:

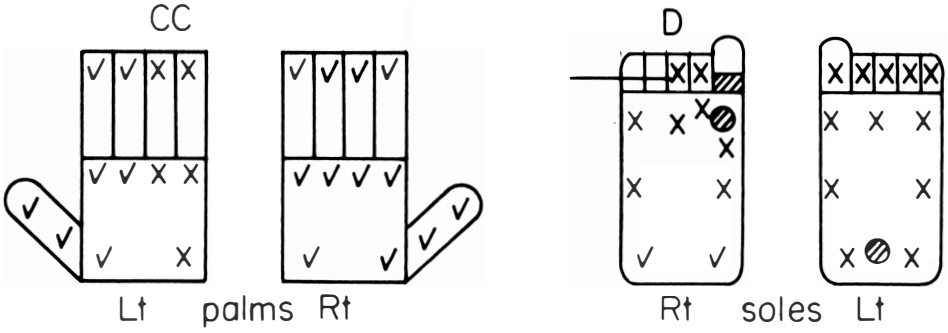
(a) Number of patients, registered either for chemotherapy or for disability control, having nerve lesions (WHO grade < 1): (i) affecting eyes; (ii) affecting hands; and (iii) affecting feet. These numbers will be useful for assessing needs for teaching and for protective devices.

(b) Numbers of patients having decreased sensation or strength during the year. This information is important in patients with active leprosy and in multidrug therapy programmes. However, it can only be determined where strength loss and area of sensory loss are given in some detail (see Figures 1 and 2) and *reliably*.

(c) Numbers of patients having wounds or open cracks during the year or increased absorption/reduced vision where records give such detail.

(b) and (c) can be used for the purposes of identifying patients needing action to halt increasing disability, and of evaluating effectiveness of this action.

Examples of records usable for these purposes are given in Figures 1 and 2. In my opinion hand and foot maps showing areas of sensory loss and other information illustrated, and having a key, are a vital part of useful disability records. Any changes can be recorded on new, hand-drawn diagrams. Many national leprosy casesheets already incorporate outline maps of hands and feet. At present these are often ill-used because they lack keys and because staff lack training in proper use of them but they could *become* useful.



Blink problems. Rt: yes/(no) Lt: yes/(no) (If yes: comment below) Decrease in sensation/strength within past 6/12: (yes)/no. (If yes: comment) Rt hand 3/12.

Sensory test = light skin dinting: √, pt feels within 3cm; X, does not feel; C, clawed; D, dropfoot; ▨, wound or open crack; ——, absorption level.

Figure 1. Suggested use of sensory hand and foot maps with blink comment.

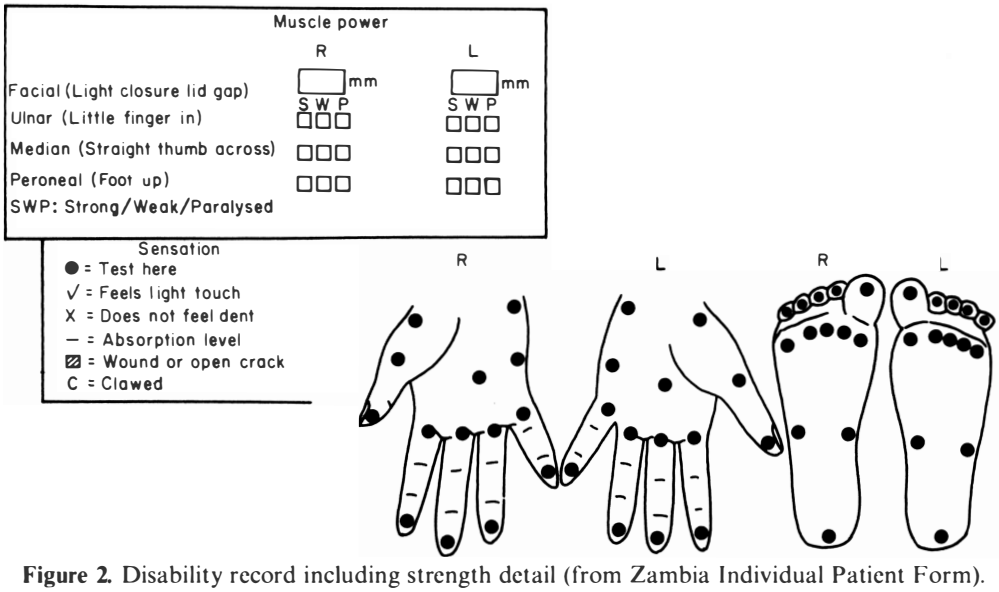


Figure 2. Disability record including strength detail (from Zambia Individual Patient Form).

Conclusions

I suggest:

(a) That a system of WHO +/− deformity grading is substituted for the present 0–3 grading and that only one grade per patient is recorded on the Individual Patient Form if this is all that WHO and ILEP use.

(b) That WHO encourages the use of disability records similar to those shown above, and usable for purposes of identifying patients in need and evaluating their progress. I would like to see use of the WHO expanded 'form for recording disabilities from leprosy', which appears in their 'A Guide to Leprosy Control' discouraged. I see its use, in several African countries that I visit, as effectively blocking the introduction of a disability record useful for the purposes as stated.

(c) That WHO sanction the use of disability records from selected areas in which testing and recording are reasonably *reliable* for national returns made to them. This seems to me more helpful than the present method of including information from a large number of largely inaccurate returns.

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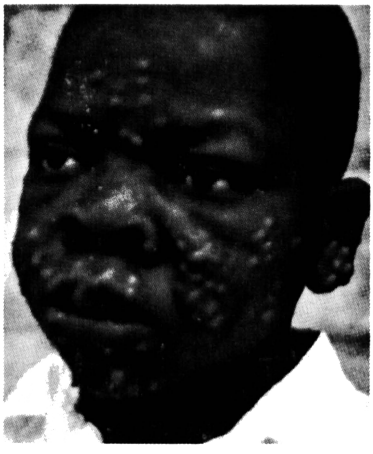
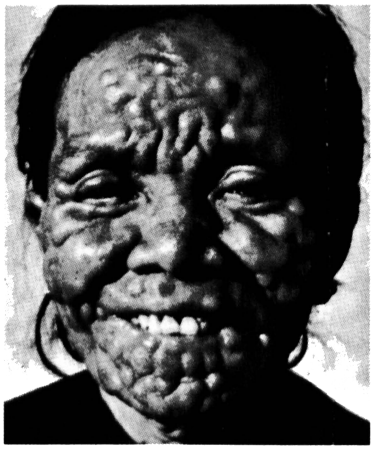
++ A CIBA-GEIGY CONTRIBUTION + TO THE FIGHT AGAINST LEPROSY ++

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





Two highly effective drugs for use in the treatment of leprosy

Lamprene
Capsules of 50 mg and 100 mg

Composition: Clofazimine. *Capsules* of 50 mg and 100 mg. Indications: *Leprosy:* prevention of secondary resistance to sulphones, as well as of lepra reactions in patients with lepromatous (LL) and borderline (BL, BB) leprosy. Treatment for lepromatous (LL) and borderline (BL, BB) forms of leprosy resistant to sulphones. Suppression of lepra reactions, e.g. erythema nodosum leprosum (ENL). Administration and **dosage:** For the treatment of leprosy, Lamprene should be employed in combination with other suitable antileprosy drugs. The dosage of Lamprene must be adapted to the patient's body weight and to the state of activity of the disease. The capsules should preferably be taken during meals or together with milk. *For the prevention of resistance to sulphones and of lepra reactions in cases of lepromatous (LL) and borderline (BL, BB) leprosy:* 50–100 mg Lamprene daily, or 100 mg 3 times weekly, during the first 4–6 months of long-term treatment with dapsone (50–100 mg daily). *In cases resistant to sulphones:* long-term treatment with Lamprene in a dosage of 100 mg daily, combined during the first 2–3 months with rifampicin (®Rimactane, 600 mg daily). *In lepra reactions:* if lepra reactions (e.g. ENL) occur, the basic therapy given hitherto should be continued. To suppress the lepra reactions, Lamprene should be administered under surveillance in relatively large, individually determined doses. The dosage generally recommended is one of 300 mg daily for 3 months. As soon as the lepra reaction has been brought under control, the dosage should be gradually lowered to a level at which its suppressant effect is still just sufficient. Note: Treatment with Lamprene should be given under medical supervision. Daily doses of 300 mg or more should not be administered for longer than 3 months. If gastro-intestinal symptoms develop during treatment with Lamprene, the dosage should be reduced or the interval between doses prolonged. In the event of persistent diarrhoea or vomiting, the patient should be hospitalised. During long-term medication with Lamprene, as well as in patients with a history of liver or kidney disease, it is advisable to perform clinical examinations and tests of hepatic and renal function every 3 months. The use of Lamprene in patients complaining of recurrent abdominal pain, or suffering from damage to the liver or kidneys, should wherever possible be avoided. Unwanted effects: Lamprene is generally well tolerated. The following side effects have been observed: red to brownish-black discolorations. Dryness of the skin, ichthyosis, pruritus, photosensitivity, acneform eruptions, and non-specific skin rashes. Nausea, vomiting, abdominal pain, diarrhoea, anorexia, and loss of weight are encountered chiefly in the presence of accompanying gastro-intestinal diseases or in cases where large doses (> 300 mg) have been used for a prolonged period (> 3 months). Packages: *Lamprene 50:* 100 and 1,000 capsules of 50 mg. *Lamprene 100:* 100 and 1,000 capsules of 100 mg. Further information is available on request.

Rimactane
Capsules of 150 mg and 300 mg

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

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CONTENTS

EDITORIAL
Managerial implications of multidrug therapy. A. D. ASKEW 89

ORIGINAL ARTICLES
Rapid, radiometric *in vitro* assay for the evaluation of the anti-leprosy activity of clofazimine and its analogues. A. MITTAL, P. S. SESHADRI, M. L. CONALTY, J. F. O'SULLIVAN and INDIRA NATH . 99
The effect of *Mycobacterium leprae* on PHA- and PPD-induced inhibition of leucocyte migration in leprosy patients. T. DHARMA RAO, S. S. LAKSHMANA RAO, ROOPA RAJAN and P. R. RAO . . 109
Radioimmunoassay of serum cortisol levels in leprosy patients with special reference to type I and type II reaction. K. SAHA, K. N. RAO, V. N. SEHGAL, S. GADI, V. K. JAIN and A. K. CHAKRABARTY . 117
The outpatients treatment of nerve damage in patients with borderline leprosy using a semi-standardized steroid regimen. K. U. KIRAN, J. N. A. STANLEY and J. M. H. PEARSON 127
Ocular complications in patients with leprosy in Karigiri, South India. HER HSIN TSAI and N. SURYAWANSHI 135

SPECIAL ARTICLES
'Naaman's dilemma'—factors influencing the compliance of patients to prescribed drugs in chronic diseases, with particular reference to leprosy. R. MACRORIE 143
Leprosy and procreation—a historical review of social and clinical aspects. M. ELIZABETH DUNCAN . 153

DOMICILIARY AND FIELD WORK 163
Low cost printing for development—OXFAM–LEPRA, Oxford, UK. A mini-pack of teaching materials on leprosy—Penlight for testing thermal sensitivity in leprosy—Primary eye care—Correspondence course for Leprosy technicians, Marie Adelaide Leprosy Centre, Karachi—OXFAM, Oxford; Questions and answers on the implementation of multidrug therapy (MDT) for leprosy—Technical Guide for Smear Examination for Leprosy by Direct Microscopy—Schieffelin Leprosy Research and Training Centre, Karigiri, Courses 1985–86

REPORTS, NEWS AND NOTES 167
Retirement of Dr H. Sansarricq—Sasakawa Memorial Health Foundation: English publications—Medical Laboratory Manual for Tropical Countries Vol. 2: ELBS Edition—Slide-set: Leprosy in the light-skinned—Leprosy at the basic health service level—Behçet's Disease; International Conference in London, September 1985—Robert Cochrane Fund for Leprosy—XIII International Leprosy Congress, The Hague, Netherlands, 1988—II Congress of Hansenology of the Endemic Countries, December 1985—International Symposium on Mycobacteria of Clinical Interest—XII World Conference on Health Education, 1985—University of Dundee; Centre for Medical Education—International Conference on Biomechanics and Clinical Kinesiology of Hand and Foot, Madras, 16–18 December 1985—XXVIth IUAT World Conference on Tuberculosis and Respiratory Diseases, Singapore, 4–7 November 1986—Back numbers of *Leprosy Review* required—Video-tape: 'Chemotherapy of Leprosy for Control Programmes', Oxford

LETTERS TO THE EDITOR
Adverse reactions to rifampicin and dapsone. PATRICIA ROSE 171
WHO disability grading. JEAN M. WATSON 172

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