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# Editorial

## VOLUNTARY AGENCIES AND LEPROSY CONTROL IN INDIA

### Introduction

Health is essentially a matter for the individual. No health service, however wide and efficient, can keep a country healthy unless its people are conscious about their health needs. This underlines the basis for community participation in health programmes, particularly in the eradication of leprosy.

The past decade has witnessed a great expansion in the facilities for leprosy control in India, but in spite of a more than 14-fold increase in expenditure on leprosy eradication, since the inception of the National Leprosy Control Programme (NLCP), it has not been possible to make an impact on disease incidence.[1] The rapid increase in infrastructural facilities has not been commensurate with the utilization of services by the large masses of suffering people. Lately, the importance of initiating a qualitative change in the NLCP, by generating mass participation of the professional people as well as the rural population, through involvement of voluntary organizations (VOs), has been recognized as a national policy.[2] The present paper briefly traces the growth of voluntary leprosy control agencies in India, delineates their contribution to its control and outlines their expected role in its eradication.

### Development of voluntary organizations in leprosy

Voluntary organizations have been playing a pioneering role throughout the history of leprosy control in the country. The first known leper asylum was established in Calcutta early in the nineteenth century followed by another in Varanasi. Mission to Lepers, started in 1875 at Chamba, had been by far the biggest single agency engaged in any leprosy work. The establishment of Indian Council of the British Empire Leprosy Relief Association in 1925, renamed as 'Hind Kust Nivaran Sangh' in 1947, laid down the foundations of organized leprosy work in India.

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The first organized efforts for leprosy control in the non-governmental sector were initiated in 1951 in the form of services through outpatient clinics in villages by the Gandhi Memorial Leprosy Foundation, Sevagram, funded by the Gandhi Memorial Trust. This was also the period when dapsone was introduced, for the first time, in the control of leprosy. Thus, the strategies of leprosy control in the country were laid down, with the focus changing from the patient in the control area to the entire population. Intensive health education campaigns and house visits, to firstly identify leprosy patients and secondly bring them under treatment, characterized the strategy of the Gandhi Memorial Leprosy Foundation.

After 1951, there occurred an extensive expansion in voluntary services for leprosy patients all over the country. Presently about 100 VOs are actively engaged in leprosy relief.

International agencies have also contributed significantly to strengthen voluntary efforts for leprosy control in India. From a small beginning in 1894 in Ambala, the Leprosy Mission has developed into a widespread organization. It operates 32 centres of its own besides providing aid to 42 hospitals devoted to leprosy care programmes.[3]

The German Leprosy Relief Association joined India's fight against leprosy in 1957 by starting Chettipatty Leprosy Relief Rural Centre in Tamil Nadu. The Damien Foundation, Brussels, was the first purely voluntary agency to enter into an agreement with the Government of India to function in co-ordination with the national control programme. The International Federation of Anti-Leprosy Associations (ILEP), undertakes to support field as well as research projects of a wide international network of member associations. In India alone, it was financing 172 projects, in 1984, through the agency of 14 member associations.

With a view to providing a common platform for voluntary institutions to discuss their problems, share experience and mobilize public participation for promoting voluntary effort, a federating body, in the form of the National Leprosy Organization (NLO) India, formed in 1965.

## Role

Significant as the services of VOs are in leprosy relief, their capacity to organize social measures to alleviate human suffering, and their sensitivity and responsiveness to the needs of the people, render them just as suitable for supplementing governmental effort towards leprosy control in the fields of rehabilitation, health education and enlisting community support.

Rehabilitation in leprosy must be total. In addition to measures designed for restoring the physically handicapped, it should aim at relieving financial distress caused by the incapacitating effects of the disease and establishing programmes for economic self-reliance. Many social workers have experienced that the

formation of a nucleus for cooperative development with active involvement of patients as beneficiaries, can ensure a higher degree of economic success than bureaucratic governmental schemes. In the light of this, a cooperative sector with community resources can be visualized as a self-sustaining leprosy care system.

An inescapable necessity for promoting economic well-being will be to restore disrupted social relationships of leprosy patients. The social distance expressed as exclusion from community gatherings, both religious and ceremonial, can be effectively eradicated only through the creation of a suitable environment divested of ignorance, superstition and prejudice against the disease. Experience in providing services under the NLEP has revealed that baseless fear acts as a great deterrent in organizing rehabilitative services. The situation is further aggravated by a close relationship of the disease to poverty, overcrowding and insanitary conditions.

While recently new drugs have radically altered attitudes of many people towards leprosy, these must be reinforced through persistent and sustained health education campaigns. Since the government have the exclusive use of mass publicity and educational agencies such as the radio and the TV, the non-governmental organizations can supplement this effort by judicious use of press, group and individual education. The ultimate aim would be to explain to the people the true nature of leprosy in order to create confidence and build a rational attitude towards its sufferers.

## Contributions

The VOs engaged in leprosy have their own specific objectives functioning mainly at the community level. In recognition of the great potential of these institutions, the Directorate General of Health Services, Government of India, has evolved a mechanism for annual meetings with them with a view to establishing communication and an exchanging of information, and also to understand the nature of their work.

Information supplied by 88 VOs operating in leprosy control in India revealed that they provided services to a population of 590·00 lakhs spread over areas with great variation in the leprosy prevalence rate (1·1–32·0 per 1000). They were all geared to control activities through survey, education and treatment. Up to March 1986 a total of 8·40 lakh patients had been detected; of which 6·88 lakh were under treatment by 82 participating VOs in SET activities.[4]

Most of the VOs are multifunctional in nature, rendering curative as well as rehabilitative services, besides organizing the training of medical and health auxilliaries. With a bed strength of 19,000 in 1985 in 70 VOs, these institutions had rehabilitated about 36,000 physically handicapped patients in addition to providing vocational training to another 21,782.[5]

An idea of the contribution made by voluntary organizations can be obtained

**Table 1.** Leprosy services being provided by government and voluntary sectors as on 1.9.1986.

| Activity | Voluntary sector | Government sector | Total |
|---|---|---|---|
| 1 Population covered | 59·00 | 400·00 | 459·00 |
| (in millions) | (11) | (89) | (100) |
| 2 Leprosy cases on record | | | |
| (in millions) | 0·84 | 2·50 | 3·34 |
| 3 Leprosy cases under treatment | | | |
| (in millions) | 0·68 | 2·38 | 3·06 |
| 4 Leprosy cases discharged | 0·18 | 2·22 | 2·40 |
| after cure | (4) | (96) | (100) |
| 5 Rehabilitation of leprosy cases | | | |
| Medical | 36,000 | 8,000 | 44,000 |
| Vocational | 21,782 | 7,000 | 28,782 |
| 6 Training | | | |
| (a) No. of training centres | 12 | 32 | 44 |
| (b) Annual training capacity | | | |
| Medical Officers | 121 | 119 | 240 |
| | (50) | (50) | (100) |
| Paramedical staff | 575 | 1765 | 2340 |
| | (25) | (75) | (100) |
| (c) No. trained so far | | | |
| Medical officers | 1978 | 2529 | 4507 |
| | (50) | (50) | (100) |
| Paramedical staff | 7225 | 22,326 | 29,551 |
| | (20) | (80) | (100) |
| 7 Annual budget (Rs. in | 180·00 | 420·00 | 600·00 |
| millions) | (26) | (74) | (100) |

Figures in parenthesis represent percentages.

from Table 1 which compares their services with those provided by the National Leprosy Eradication Programme.

Recognizing the wealth of expertise in the voluntary organizations and their contributions towards leprosy control, the Government of India introduced a scheme of financial assistance to these agencies in the form of grants-in-aid. The scheme envisages that the interested voluntary organizations would approach the Ministry of Health for grants as governed by conditions laid down. The number of voluntary organizations availing the grants-in-aid during the past 5 years is shown in Table 2.[6]

Starting as a scheme of financial assistance, the government's partnership with VOs has steadily grown over the years. Voluntary activities now converge,

**Table 2.**

| Year | No. of VOs | Amount (Rs. in millions) |
|---|---|---|
| 1980–81 | 32 | 3·1 |
| 1981–82 | 39 | 3·5 |
| 1982–83 | 44 | 3·1 |
| 1983–84 | 44 | 3·5 |
| 1984–85 | 49 | 5·1 |
| 1985–86 | 56 | 5·5 |

by and large, on NLEP goals. As requested by them, their performance was subjected to an independent evaluation along with that of the National Leprosy Eradication Programme in 1986 and their expertise was also made use of during this evaluation. The quality of work carried out at these institutions was found to be very satisfactory, as assessed by the members of the Evaluation Team visiting eleven of the VOs in randomly selected districts.[7]

Some of the voluntary organizations have developed material to aid in training medical and paramedical staff working for leprosy eradication, while others have developed prototypes of educational material for public and leprosy patients.

Of the 44 leprosy training centres undertaking training of medical and paramedical staff in the programme, twelve function under the VOs; their output thus far being 1978 medical workers and 7225 trained paramedical workers. Acting as referral centres some of these institutions provide services in: confirmation of diagnosis; guiding the treatment in such cases that fail to respond to prescribed treatment; managing complications and reactions; undertaking surgical correction of deformed patients; and providing vocational training to the disabled.

Fifteen highly endemic districts with a population of 44 million and an estimated caseload of 0·6 million are under varied phases of multidrug therapy (MDT). The activities in one of the above districts are under a voluntary organization. MDT guidelines developed by the government in consultation with the voluntary organizations is followed by voluntary organizations as well.

The voluntary organizations have been advised by the Leprosy Eradication Programme Headquarters to initiate multidrug therapy to the hospitalized cases who could be given regular treatment for the prescribed duration. The voluntary organizations are also identifying together with the programme personnel to detect dapsone refractory cases and putting them under multidrug treatment.

NLEP has an extensive network of services provided by the government. These inputs need to be converted into desired outputs in terms of quantitative

targets by involvement of VOs and through people's participation. While most VOs do work within the overall objectives of the NLEP, creation of specific roles with a view to supplementing each other's efforts will make the programme much more purposeful. The professional associations can mobilize a vast medical and auxiliary manpower to provide the necessary technical support. Unfortunately at the present moment, there is no standing mechanism for interaction between the government and non-governmental agencies. The two meetings of VOs organized by the Ministry of Health in October 1985 and October 1986 were steps in the right direction. But this partnership needs strengthening and put on a far more permanent basis.

Following the announcement of the Government of India to eradicate leprosy by the turn of the century, there has been widespread international interest in the National Leprosy Eradication Programme. Bilateral agencies like SIDA, DANIDA have come forward with financial support and cooperation. In addition, the already existing international organizations provide substantial financial, material and technical support. Thus, the resources of several agencies converge on the single focus of leprosy eradication. It must be ensured that these efforts become mutually supportive with a clear understanding and appreciation of each other's role. It can be facilitated by establishing a consortium or other similar mechanisms to develop linkages between various agencies at the national and state levels. Such a mechanism will ensure imaginative utilization of all existing facilities, exploitation of total professional and para-professional manpower both under the health services and the non-governmental bodies towards the goal of leprosy control.

In conclusion, it may be stated that the voluntary organizations and the NLEP are working in close cooperation with mutual trust and understanding. The government is keen in strengthening this relationship further to achieve the desired long-term goal of arresting leprosy in all cases in the country.

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## References


[1] Ramaiah TJ, Kumar S, Sharma AC. *Leprosy Control work in India*, National Institute of Health & Family Welfare. New Delhi.

[2] Government of India, Ministry of Health & Family Welfare. *Report of the Working Group on the Eradication of Leprosy, Publication & Information Directorate*. New Delhi, 1982.

[3] *The Leprosy Mission in Southern Asia, Annual Report*. The Leprosy Mission Trust—India, 1984.

[4] Government of India, Directorate General of Health Services, Personal Communications. 1985.

[5] Govt. of India, Directorate General of Health Services, Leprosy Division. *Status Report on Voluntary Organisations & NLEP*. 1986.

[6] Govt. of India, Directorate General of Health Services, Leprosy Division. *Leprosy—Status Report*. 1986.

[7] Govt. of India, Directorate General of Health Services, Leprosy Division. *Leprosy: Report of Independent Evaluation of NLEP*. 1986.

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# Studies of reactivity of some Sri Lankan population groups to antigens of *Mycobacterium leprae*. I. Reactivity to lepromin A

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*Summary* This paper reports a survey of lepromin reactivity in adult population groups in areas at three different elevations (geographical localities) in central Sri Lanka, using a lepromin A with a bacillary content of 3 or $4 \times 10^7$ bacilli/ml. The patterns of reactivity observed with both Fernandez and Mitsuda reactions were clearly bimodal and similar in all areas. The distributions of reactions were divisible into 'non-reactor' ('negative') and 'reactor' ('positive') components. For both Fernandez and Mitsuda reactivity the demarcation between non-reactor and reactor components seemed to be best made at a reaction size of 3 mm. The mode of reactors of the Fernandez reaction was at 3–6 mm, and of the Mitsuda reaction at 5–8 mm. Both types of reactivity showed no change with increase of age. Fernandez reactivity showed no evidence of any change with sex, race, BCG vaccination status or geographical area. Mitsuda reactivity did not seem to be affected by race or geographical area, but there seemed to be possible changes with sex and BCG vaccination status. Even so, there seems to be a trend for higher reaction sizes in males, and the BCG vaccinated, with both types of reactivity.

## Introduction

The lepromin test, like the tuberculin test has been in use for a long time, and a large body of literature has accumulated on it. However, because the availability of lepromin had been restricted in earlier years the literature on this test is not as extensive as that on the tuberculin test. Further, the earlier literature has been of reports of investigations carried out using lepromins prepared from *Mycobacterium leprae*, of human origin, often prepared by individual investigators, and therefore of variable quality. Now, under the auspices of the IMMLEP programme, lepromin of armadillo origin in a standardized preparation is

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available (lepromin A), in larger quantities for research purposes. We report here an investigation of the patterns of sensitivity to lepromin A in Sri Lanka.

## Materials and methods

The populations tested were from three geographically different areas in Sri Lanka, selected for expected differences in tuberculin sensitivity (as it has been shown earlier that the prevalence of nonspecific mycobacterial sensitization may vary with the altitude and geographic area.[1,2] The characteristics of the populations tested are summarized in Table 1.

Those tested were unselected members of the adult population (over 12 years of age) who volunteered to permit testing; only approximately one third of the whole population of a geographically defined area, who were eligible for testing, permitted testing. Some individuals who volunteered were excluded where there was a possibility that the results of the test may be interfered with, e.g. pregnancy, atophy, chronic disease states, steroid therapy. Every person who permitted testing, was administered two antigens intradermally using standard techniques,[3] on the volar aspect of the left forearm at sites 6–7 cm apart.

The antigens used for testing were; 1, lepromin A with a bacillary content of 3 or $4 \times 10^7$ bacilli/ml (kindly supplied by Dr Hastings of the National Hansen's Disease Centre, Carville, USA) through courtesy of the Chief, Leprosy Section, World Health Organization, Geneva); 2, the Soluble Protein Antigen (SPA) of *M. leprae*, prepared by ultrasonic disruption of the organism, with a protein content of 10 $\mu$g/ml (batch CD 19) (kindly supplied by Dr R J W Rees of the IMMLEP *M. leprae* Bank, Harrow, Middlesex, UK); and 3, Tuberculin PPD-RT 23, 2 TU per dose (Staten Seruminstitut, Copenhagen, Denmark).

The test results were read as the maximum transverse and vertical diameters of induration palpated, at 48 and 72 hr in the case of the Fernandez reaction (of the lepromin test); and at 72 hr in the case of the tests using SPA, or with tuberculin; with the latter the maximum transverse diameter only, was read.[3] (Erythema was ignored as it was difficult to define clearly, if not impossible to read, in dark-skinned individuals.) The Mitsuda reaction of the lepromin test was read (at 28 days) as the maximum transverse and vertical diameters of the nodule observed (palpated). However, in these studies we have used only the transverse diameters of all types of reactivity (see below).

The relationships between the transverse and vertical diameters of the Fernandez and Mitsuda reactions and SPA reactions, and reactivity and age (all continuous variables) were evaluated using regression analysis. The frequency distributions of the Fernandez and Mitsuda reactions of different groups of persons (BCG positive and negative, different sexes and racial groups—all discrete variables) were compared using chi-square tests.

The results presented in this paper are those with the lepromin test only; those with SPA will be described in a subsequent paper.

**Table 1.** Characteristics of populations tested

| Location | Geographic characteristics | | | Racial groups | Numbers tested and read at 48 hr or 28 days | | | Antigens used |
|---|---|---|---|---|---|---|---|---|
| | Elevation (meters) | Rainfall (mm) | Main occupations (agriculture) | | BCG − | BCG + | Total tested | |
| Pussellawa | 900 | 2230 | Tea growing<br>Rice growing | Indian Tamil and Sinhalese | 140 | 101 | 241 | (1) Lepromin A (bacillary content $3 \times 10^7$ bacilli/ml)<br>(2) Tuberculin |
| Nuwara Eliya | | | | | | | | |
| A. Pedro | 1950 | 2230 | Tea growing<br>Market gardening | Indian Tamil | 98 | 63 | 161 | As at Pussellawa |
| B. Mahagastota | 1800 | | Tea growing<br>Market gardening | Indian Tamil and Sinhalese | 105 | 79 | 184 | (1) Lepromin A (bacillary content $4 \times 10^7$ bacilli/ml)<br>(2) Tuberculin<br>(3) SPA |
| Galagedera | 150 | 2080 | Mixed cultivation (cocoa, coconut, coffee and rice growing) | Sinhalese and Indian Tamil | 134 | 104 | 238 | (1) Lepromin A (as at Mahagastota)<br>(2) SPA |
| Total tested | | | | | 477 | 347 | 824 | |

SPA, soluble protein antigen of *M. leprae*.

**Results**

The patterns of reactions observed are presented as frequency distributions as such distributions are easily compared with others. Since there are thought to be basic differences in the genesis of the two types of reactivity (Fernandez and Mitsuda) elicited by the lepromin test, initially these patterns will be considered separately.

The analysis of results showed that the transverse and vertical diameters elicited were highly correlated in both the Fernandez and Mitsuda reactions. Hence, in keeping with the recommendation for the tuberculin test,[3] we have used only the transverse diameter in frequency distributions etc. Further, both types of reactions showed no change with age (increase of age), showing that reactivity of both types had probably reached maximum levels (for the individual) by the age of 12 years. Hence age as a variable was disregarded in further analysis.

### THE MITSUDA REACTION

Presented in Figure 1 are the patterns of Mitsuda reactivity of the whole population tested, from the three areas tested. (In one geographic area, Nuwara Eliya, two population groups (Pedro and Mahagastota) located three miles apart were tested. Since both groups seemed to show differing patterns of Fernandez

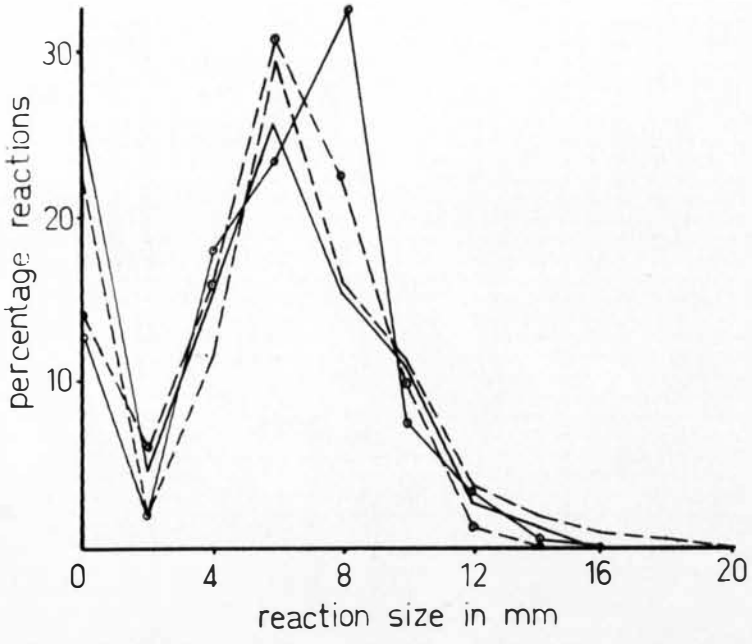


**Figure 1.** Frequency distributions of Mitsuda reactions of the whole population of the different localities (Pedro, – – – o – – –; Pussellawa, ——o——; Mahagastota, ———; Galagedera, – – – – – –).

reactions both are presented as separate population groups.) The overall similarity of the patterns observed in the four groups is marked. The distributions are clearly bimodal with the mode of 'reactors' being at 5/6 to 7/8 mm reaction sizes.

In order to attempt to differentiate between the observed reactor and non-reactor components in Figure 1, a detailed examination of the distribution of reactions in the 0–5 mm size range was made (Figure 2). This showed that in this investigation, a reaction size of 3 mm or more could be arbitrarily considered to be a satisfactory level at which to differentiate 'reactors' ('positive') from 'non-reactors' ('negative'—2 mm or less).

In Table 2 are presented the means of Mitsuda reactions in the different groups of individuals according to sex, race and BCG vaccination status. The

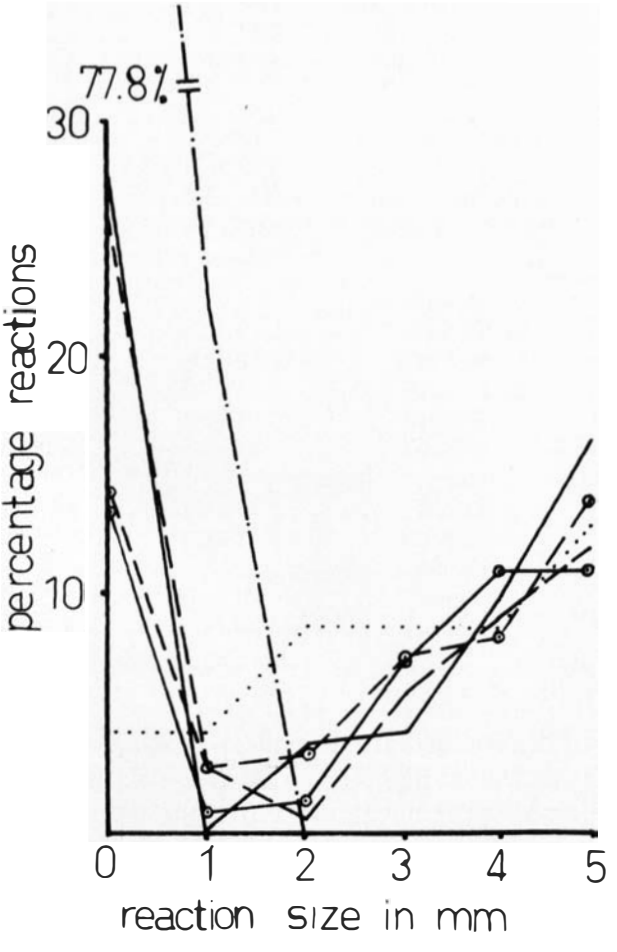


**Figure 2.** Distribution of Mitsuda reactions of 0–5 mm of the population in different localities and leprosy patients in Sri Lanka (tuberculoid leprosy, . . . . . ; lepromatous leprosy, — · — · —; Pedro, – – – o – – –; Pussellawa, ——o——; Mahagastota, ———; Galagedera, – – – – –).

**Table 2.** Mean Mitsuda reaction sizes of different categories of subjects

| Population group | Mean reaction size (mm) (numbers tested in parenthesis) | |
|---|---|---|
| | Of whole population | Of reactors only |
| I Pedro | | |
| Tamils: 1 BCG − Males | 4·13 (35) | 6·03 (23) |
| Females | 4·02 (57) | 5·31 (42) |
| 2 BCG + Males | 6·58 (27) | 7·34 (24) |
| Females | 6·44 (37) | 6·76 (35) |
| II Mahagastota | | |
| Tamils: 1 BCG − Males | 4·41 (28) | 7·27 (17) |
| Females | 2·94 (67) | 5·31 (36) |
| 2 BCG + Males | 7·17 (21) | 8·28 (18) |
| Females | 5·03 (42) | 5·89 (35) |
| III Pussellawa | | |
| Tamils: 1 BCG − Males | 5·14 (29) | 6·21 (24) |
| Females | 4·42 (63) | 6·03 (46) |
| 2 BCG + Males | 7·32 (36) | 7·99 (33) |
| Females | 6·04 (59) | 6·36 (56) |
| IV Galagedera | | |
| 1 BCG − (a) Males | | |
| Tamils | 4·9 (13) | 8·9 (7) |
| Sinhalese | 7·0 (23) | 8·4 (19) |
| (b) Females | | |
| Tamils | 3·3 (29) | 5·5 (17) |
| Sinhalese | 3·61 (54) | 6·08 (31) |
| 2 BCG + (a) Males | | |
| Tamils | 8·16 (13) | 8·84 (12) |
| Sinhalese | 6·71 (22) | 7·03 (21) |
| (b) Females | | |
| Tamils | 6·0 (25) | 6·78 (22) |
| Sinhalese | 5·44 (42) | 6·53 (35) |

trends that seem to be obtained are that males seem to have higher means than females, the BCG vaccinated higher than those not so vaccinated, and at lower elevation higher than at upper elevations. Where numbers permitted, evaluations were made (using the chi-square test) to determine the possible influence of biological variables on Mitsuda reactivity (Table 3); (examples of comparisons made—BCG + ve male Tamils at Pedro *vs* BCG + ve female Tamils at Pedro (for sex differences); BCG − ve male Sinhala at Galagedera *vs* BCG + ve male Sinhala at Galagedera; and so on). Thus at Galagedera all three variables showed no significant differences, while in the other areas the results obtained with different

**Table 3.** Influence of sex, race, and BCG vaccination status on Mitsuda reactivity

| | Number of groups evaluated showing result | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sex | | | Race | | | BCG status | | |
| Area | Not significant | Significant at 5% | Significant at 1% | Not significant | Significant at 5% | Significant at 1% | Not significant | Significant at 5% | Significant at 1% |
| Galagedera | 3 | | | 4 | | | 4 | | |
| Pussellawa | 1 | | 1 | | 1 | | 1 | | 1 |
| Mahagastota | | 2 | | | | | 1 | | 1 |
| Pedro | 2 | | | | | | | 1 | 1 |
| Total | 6 | 2 | 1 | 4 | 1 | | 6 | 1 | 3 |

groups were inconclusive, with perhaps the exception that there were significant differences between the BCG vaccinated and not vaccinated.

## THE FERNANDEZ REACTION

The frequency distributions of Fernandez reactions of the whole populations in the four different groups are presented in Figure 3. Here, while in three groups there is a general similarity of the patterns of distribution, in one group (at Mahagastota) the pattern differs completely from that of the others. In the latter, there is a marked increase in the small reactions in the 1–2 mm group, which is not seen elsewhere; the other distributions being of a more or less bimodal pattern of non-reactors and reactors. Except at Mahagastota, the mode of reactors seems to be at 3–4 or 5–6 mm.

A detailed examination of the distribution of reactions of the smaller sizes (0–7 mm) (Figure 4) shows that perhaps the best point of separation between the reactor and non-reactor component (except at Mahagastota) could be made at 3 mm—a reaction of 3 mm or more therefore being considered to be a 'reactor' ('positive') and 2 mm or less a 'non-reactor' ('negative').

In Table 4 are presented the means of Fernandez reactions in the different groups of individuals according to sex, race, and BCG vaccination status. Here too, the trends observed seem to be the same as those seen with the Mitsuda reaction (higher in males, in the BCG vaccinated and at lower elevations). The chi-square test was used, here too, to evaluate the influence of the different biological variables on Fernandez reactivity; however no significant differences were shown with sex (number of groups compared, 9), BCG status (number of

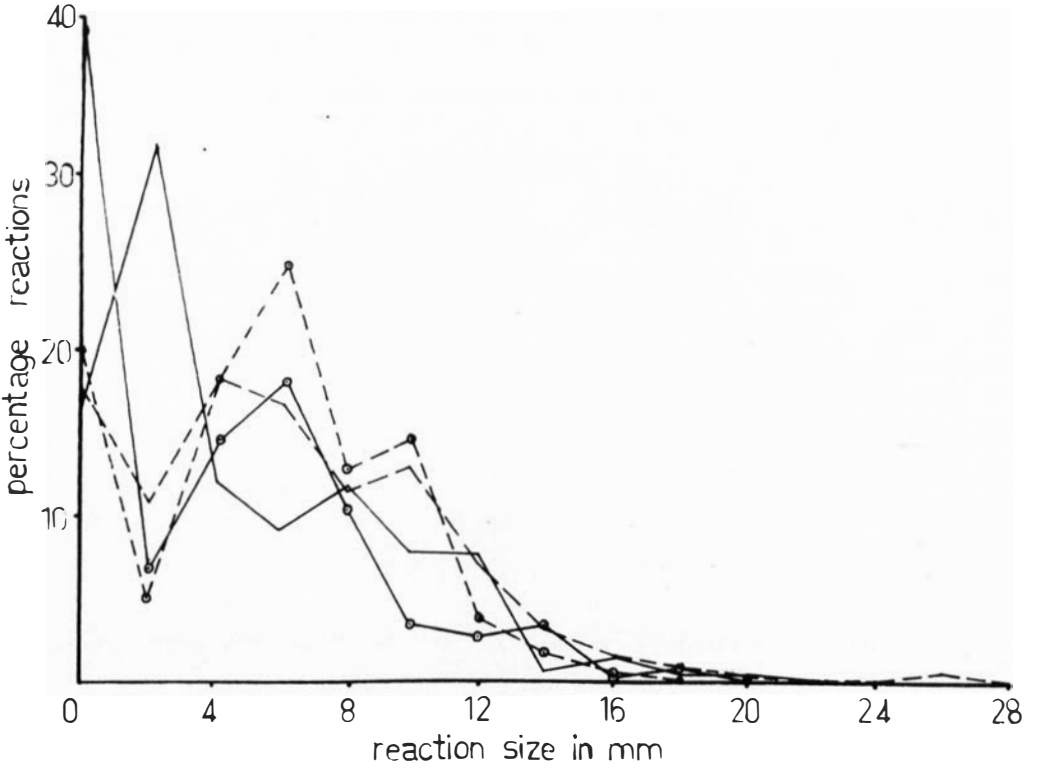


**Figure 3.** Frequency distribution of Fernandez reactions of the whole population of the different localities (Pedro, – – – o – – –; Pussellawa, ——o——; Mahagastota, ————; Galagedera, – – – – – – –).

groups compared, 7), or race (number of groups compared, 6, of which one showed differences significant at a 1% level).

The differences in the frequency distributions of Mitsuda and Fernandez reactions in the different geographical areas were also studied using the chi-square test by comparing the same subjects in the different areas. The results are presented in Table 5.

With Mitsuda reactivity in the BCG positive groups compared in the different areas, no significant differences were found showing that with the BCG vaccinated, all groups showed similar patterns of reactivity. In the BCG negative, out of 12 groups compared, five groups showed differences, with three at a 1% level and two at a 5% level. In these comparisons four of the five groups (including all three showing highly significant differences) are among females. Furthermore, four of the six significantly different groups with the Fernandez reaction, and three of the five significantly groups with the Mitsuda reaction, all involve Mahagastota, where it was earlier pointed out that, with the Fernandez reaction, the frequency distribution pattern was dissimilar to that of other areas. If the Mahagastota population is excluded from the comparisons, for Fernandez

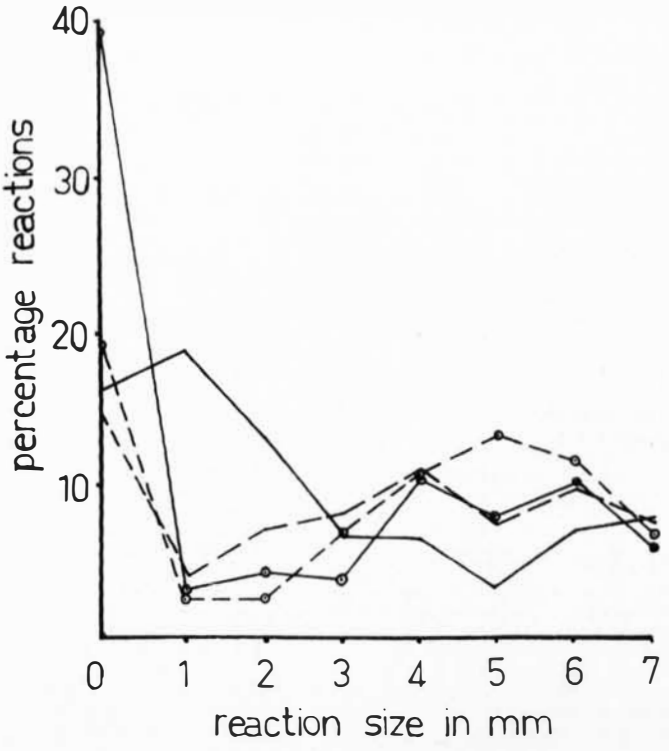


**Figure 4.** Distribution of Fernandez reactions of 0–7 mm of the population of the different localities (Pedro, – – – o – – –; Pussellawa, ——o——; Mahagastota, ————; Galagedera, – – – – – –).

reactivity only one of six groups is significant, and for Mitsuda reactivity only two of eleven groups are significantly different.

## OCCURRENCE OF ULCERATION IN THE MITSUDA REACTION

A factor which may cause individuals not to volunteer for testing during large scale population surveys with skin tests may be the occurrence of painful lesions as a result of testing. Such a lesion would be the occurrence of ulceration, which while not seen in this study with Fernandez reactivity was observed with Mitsuda reactivity. 'Ulceration' as described here, may vary from a minor and innocuous desquamation of the outer layers of the skin to deep and painful surface ulcers, sometimes more than 10 mm in diameter or sinuses leading to deeper seated cavitory lesions of similar dimensions. The incidence of such 'ulceration' (or desquamation) is presented in Table 6. While it was not possible to identify relationships of the occurrence of 'ulceration' with sex, age or geographic locality, there seems to be a significant variation with BCG vaccination status—the BCG vaccinated showed a higher incidence of 'ulceration' as compared with those not vaccinated.

**Table 4.** Mean Fernandez reaction sizes of different categories of subjects

| Population group | Mean reaction size (mm) (numbers tested in parenthesis) Of whole population | Of reactors only |
|---|---|---|
| I Pedro | | |
| Tamils: 1 BCG – Males | 5·04 (43) | 7·17 (30) |
| Females | 4·62 (61) | 6·23 (44) |
| 2 BCG + Males | 6·62 (26) | 7·42 (23) |
| Females | 5·3 (34) | 6·62 (27) |
| II Mahagastota | | |
| Tamils: 1 BCG – Males | 4·5 (24) | 6·97 (14) |
| Females | 3·38 (74) | 6·63 (32) |
| 2 BCG + Males | 7·43 (20) | 10·08 (14) |
| Females | 2·9 (45) | 5·84 (18) |
| Sinhalese: 1 BCG – Males | 3·5 (3) | 4·5 (2) |
| Females | 3·55 (11) | 5·25 (6) |
| 2 BCG + Males | 10·15 (7) | 11·59 (6) |
| Females | 5·21 (12) | 6·45 (9) |
| III Pussellawa | | |
| Tamils: 1 BCG – Males | 3·08 (31) | 5·88 (16) |
| Females | 2·31 (71) | 6·34 (24) |
| 2 BCG + Males | 4·94 (40) | 6·81 (29) |
| Females | 4·56 (46) | 7·65 (27) |
| Sinhalese: 1 BCG – Males | 3·34 (9) | 7·5 (4) |
| Females | 5·39 (38) | 7·62 (26) |
| 2 BCG + Males | 2·6 (5) | 6·5 (2) |
| Females | 4·56 (18) | 7·32 (11) |
| IV Galagedera | | |
| Sinhalese: 1 BCG – Males | 6·9 (25) | 7·5 (23) |
| Females | 4·24 (59) | 6·76 (35) |
| 2 BCG + Males | 7·76 (25) | 9·03 (21) |
| Females | 5·68 (49) | 7·39 (36) |
| Tamils: 1 BCG – Males | 6·74 (19) | 8·0 (16) |
| Females | 4·63 (32) | 6·84 (21) |
| 2 BCG + Males | 6·19 (16) | 8·0 (12) |
| Females | 6·16 (26) | 7·41 (21) |

## OCCURRENCE OF 'SOFT' MITSUDA REACTIONS

In this study it was noticed that while most Mitsuda reactions were of the characteristic nodules, some had a different character, being soft and sometimes even plaque-like. Since the significance of these were uncertain, these reactions were excluded from the foregoing analysis of Mitsuda reactions. However the

**Table 5.** Influence of geographical locality on reactivity to lepromin

| Areas between which comparisons were made | Groups on which the comparisons were made | | | | | | |
|---|---|---|---|---|---|---|---|
| | Fernandez test | | | Mitsuda test | | | |
| | BCG+M | BCG+F | BCG−F | BCG+M | BCG+F | BCG−F | BCG−M |
| Galagedera | | | | | | | |
| *vs* Pedro | Not significant | Not significant | Not significant | Not significant | Not significant | Not significant | Not significant |
| *vs* Mahagastota | Not significant | Significant (1%) | Significant (5%) | Not significant | Not significant | Not significant | Not significant |
| *vs* Pussellawa | Not significant | Not significant | | | Not significant | Significant (1%) | Not significant |
| Pedro | | | | | | | |
| *vs* Mahagastota | Not significant | Significant (1%) | Significant (5%) | Not significant | Not significant | Significant (5%) | Not significant |
| *vs* Pussellawa | Significant (5%) | Not significant | | Not significant | Not significant | Significant (1%) | Not significant |
| Mahagastota | | | | | | | |
| *vs* Pussellawa | Not significant | Significant (5%) | | Not significant | Not significant | Significant (1%) | Significant (5%) |

**Table 6.** Occurrence of 'ulceration' and 'soft reactions' in the Mitsuda reaction

| Age group in years | Occurrence of ulceration (percentages within parenthesis of those showing 'typical' Mitsuda reactions) | | | | | | | Occurrence of 'soft reactions' (percentages within parenthesis of all those whose Mitsuda reactions were read including soft reactions) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BCG−ve | | | BCG+ve | | | Total of BCG−ve and+ve | BCG−ve | | | BCG+ve | | | Total of BCG−ve and+ve |
| | F | M | Total | F | M | Total | | F | M | Total | F | M | Total | |
| ⩽20 | — | 2 | 2 | 6 | 3 | 9 | 11 | 3 | 3 | 6 | 2 | 1 | 3 | 9 |
| | (0) | (12) | (4) | (18) | (5) | (10) | (8) | (6) | (15) | (9) | (4) | (3) | (3) | (6) |
| 21–30 | 1 | 2 | 3 | 2 | 6 | 8 | 11 | 11 | 3 | 14 | 4 | — | 4 | 18 |
| | (1) | (6) | (2) | (5) | (7) | (6) | (4) | (9) | (8) | (9) | (5) | (0) | (3) | (6) |
| 31–40 | 1 | 2 | 3 | — | 7 | 7 | 10 | 10 | 1 | 11 | 4 | 1 | 5 | 16 |
| | (1) | (6) | (3) | (0) | (14) | (8) | (5) | (12) | (3) | (10) | (7) | (3) | (5) | (8) |
| 41–50 | — | — | — | 1 | 2 | 3 | 3 | 3 | 7 | 10 | 2 | 1 | 3 | 13 |
| | (0) | (0) | (0) | (8) | (9) | (9) | (3) | (6) | (25) | (13) | (8) | (8) | (8) | (11) |
| 51–60 | — | 2 | 2 | — | — | — | 2 | — | 1 | 1 | — | — | — | 1 |
| | (0) | (8) | (5) | (0) | (0) | (0) | (5) | (0) | (4) | (2) | (0) | (0) | (0) | (2) |
| ⩾61 | — | — | | | | | — | — | 5 | 5 | | | | 5 |
| | (0) | (0) | | | | | (0) | (0) | (71) | (56) | | | | (56) |
| Total | 2 | 8 | 10 | 9 | 18 | 27 | 37 | 27 | 20 | 47 | 12 | 3 | 15 | 62 |

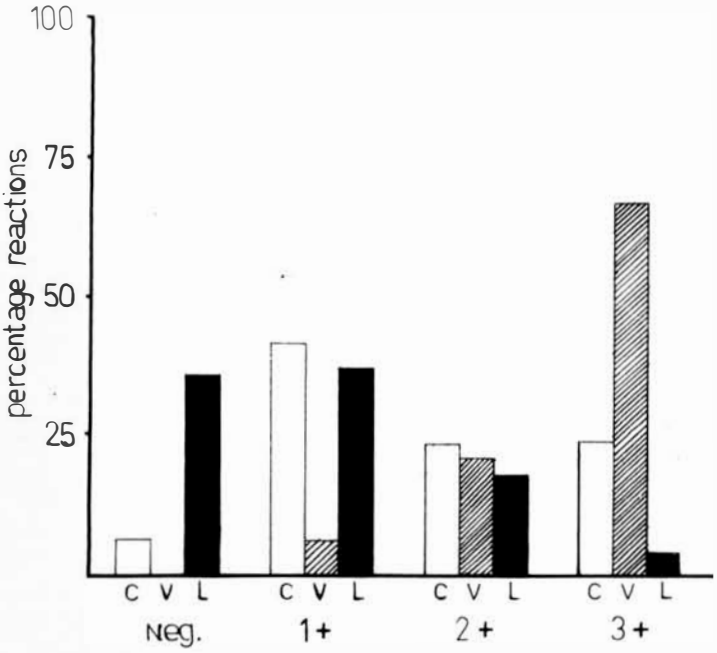


**Figure 5.** Comparison of Mitsuda reactivity in areas of low endemicity for leprosy in Sri Lanka with a nonendemic area in Chile, and an area for low endemicity in Venezuela. (C, Chile; V, Venezuela; L, Sri Lanka.)

occurrence of these is documented, as they were found in significant numbers (Table 6). While we would hesitate to draw attention to definitive patterns in the incidence of soft reactions, the data presented does seem to suggest that the occurrence of these is less in the BCG vaccinated as compared with those not so vaccinated, in contrast to the pattern of occurrence of ulcerative lesions.

## Discussion

A traditional way of classifying results of the lepromin test, has been into 'positive' or 'negative'. While such a division would be useful in clinical practice, it is less useful from the immuno-epidemiological point of view. Variable criteria for 'positive' and 'negative' have also been used, making comparisons of the work of different investigators more difficult. With bimodal distributions, as those shown by the Mitsuda and Fernandez reactions in this investigation (with one exception), it is easily possible to group the reactions into 'non-reactors' and 'reactors'. With the Mitsuda reaction the definition of a reactor in this investigation agrees well with the criteria for 'positive' (3 or 4 mm or more)[4,5,6] as defined by other workers. In the case of the Fernandez reaction, the reaction we have read is of induration, and hence different from that by some other workers (which also included erythema). The differentiation of a 'reactor' as decided in this study is at a much smaller reaction size (3 mm or more) than that (of a

'positive') used by other workers (10 mm or more) who also used erythema as an indicator of a reaction.

The effect of different biological variables on components of the reaction to lepromin (Mitsuda and Fernandez), have been studied using the chi-square test. The Mitsuda reaction showed no significant changes with these variables (sex, race, BCG status) at Galagedera (at the lowest elevation); more or less equivocal changes with sex and race at other areas, while more significant changes seemed to appear with BCG vaccination status. Fernandez reactivity in all areas did not seem to be influenced by these variables.

The highest altitude difference was between Galagedera and Nuwara Eliya (Pedro and Mahagastota)—approximately 1800 m. However there were no striking changes in reactivity of both Fernandez and Mitsuda types between the two areas. This and the other evidence presented here, suggests that in Sri Lanka altitude makes no difference to both types of reactivity to lepromin.

Another interesting finding is the fact that there is no change of reactivity with age. This leads to the conclusion that lepromin reactivity has reached maximum levels (for the population) by the age of 12 years.

At Galagedera, at the lowest elevation where populations were tested in this survey, sex, race and BCG vaccination showed no effect on lepromin reactivity of either type. (From earlier reports[2] it could be expected that this would be the area showing the highest level of environmental (non-specific) mycobacterial sensitization.) This could be because in the latter area, the population being exposed to high levels of non-specific sensitization have reached maximum levels of sensitization that can be evoked by lepromin testing (this suggestion has been made in respect of BCG vaccination, to explain why such vaccination is less effective in tropical areas, as compared with temperate zones). However, if this hypothesis is accepted, this should be manifest with significant differences in sensitization between Galagedera and other areas, which is not seen.

In Figure 5 we present a comparison of our data on Mitsuda reactivity with that of a recent similar study[7] in a nonendemic area in Chile, and an area with a low endemicity for leprosy in Venezuela in persons 15 years of age and above. The latter study had been carried out using a lepromin containing $16 \times 10^7$ bacilli/ml, four to five times the number of organisms in the preparation used in this investigation. The patterns of reactivity observed in Venezuela and Chile are different from that reported here. It is uncertain whether the differences in the results could be due to differences in antigen content, or to actual differences in reactivity of the different populations.

The necrotic reactions observed with the lepromin test were seen with the Mitsuda reaction, and were reported[8] to occur in an area of high endemicity for leprosy, but not in a village free of the disease. In this study we have observed necrotic reactions in population groups, free of the disease, in areas of low endemicity for leprosy. Though areas of large tissue swelling, often painful, were observed with Fernandez reactions, no case of vesiculation or ulceration as seen with tuberculin tests[9–11] were observed.

A further question posed is the significance of the soft reactions observed at 28 days. One possibility considered is that these are the results of faulty injection techniques—but this does not seem likely, since these reactions like the typical Mitsuda reaction, seems to occur in the same outer layers of the skin. Similar reactions were observed to develop with repeated lepromin testing,[12] in those who earlier showed typical nodular Mitsuda reactions. This raises the question whether these reactions are aetiologically different from the typical reactions.

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## References

[1] Bates LE, Busk T, Palmer CE. Research contributions of BCG vaccination programmes. II. Tuberculin sensitivity at different altitudes of residence. *Pub Hlth Reps* (*Wash*), 1951; **66:** 1427–41.

[2] Pinto MRM, Arseculeratne SN, Uragoda CG, Hemawardane DM. Differential tuberculin testing in rural populations in Ceylon. *Tubercle*, 1972; **53:** 182–97.

[3] World Health Organization. The WHO Standard Tuberculin Test. WHO/TB/Techn. Guide/3, 1963.

[4] Dubois A. La reaction de Mitsuda (notice complimentaire) *Bull Soc path exot*, 1936; **29:** 649–51.

[5] Convit J, Azulay RD, Bermudez D, Salgado P. The lepromin test in tuberculous persons in a non-endemic area. *Int J Lepr*, 1944; **12:** 60–4.

[6] Azulay RD, Convit J. The Mitsuda test in nonleprous persons in a non-endemic country. *Int J Lepr*, 1947; **15:** 264–6.

[7] Convit J, Pinardi ME, Arias Rojas F, Gonzales I, Corey G, Aruelo JJ, Monzon H. Tests with three antigens in leprosy endemic and non-endemic areas. *Bull World Health Organ*, 1975; **52:2:** 193–8.

[8] Dharmendra, Jaikaria SS. Studies on the lepromin test 2. Results of the test in healthy persons in endemic and non-endemic areas. *Lepr India*, 1941; **13:** 40–7.

[9] WHO Tuberculosis Research Office. The 5 TU versus the 10 TU intradermal tuberculin test. *Bull World Health Organ*, 1955; **12:** 169.

[10] WHO Tuberculosis Research Office. Repeated tuberculin tests at the same sites. *Bull World Health Organ*, 1955; **12:** 197.

[11] Pinto MRM, Arseculeratne SN, Uragoda CG. Vesiculation—its occurrence in the differential tuberculin test. *Cey J Med Sci*, 1972; **21:2:** 77–84.

[12] Pinto MRM, Eriyagama NB. Immunological effects of lepromin testing. I. Effects of repeated lepromin testing. *Lepr Rev*, 1987; **58,** 119–128.

*Lepr Rev* (1987) **58,** 119–128

# Immunological effects of lepromin testing in Sri Lankan population groups. I. Effect of repeated lepromin testing

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*Summary* It has been reported that lepromin testing in human subjects induces sensitization, and that with repeated testing the incidence of 'positive' Mitsuda reactions increases. On repeated testing in two Sri Lankan population groups, with Mitsuda reactions of 6 mm or less, we found that a second lepromin test at 28 days seemed to induce tolerance with reduction in reaction size or even zero reactions. This tolerance phenomenon was seen markedly with Mitsuda reactivity and less so with Fernandez reactivity. There was evidence also that while tolerance seemed to be occurring with the second test, a third test at 56 days seemed to reinduce and elicit resensitization, though weakly, with both types of reactivity. Evidence is also produced that reactors and non-reactors with both Fernandez and Mitsuda reactivity, behave differently on repeated lepromin testing, suggesting that immunologically they are different population groups.

## Introduction

It is now believed that the Mitsuda response observed with the lepromin test is a 'vaccination' response,[1] and that lepromin testing by itself may induce sensitization to a subsequent lepromin test. Thus it has been shown that repeated testing with lepromins of human origin[2] and also armadillo origin[3] would increase the incidence of 'positives' in the population so tested; Dharmendra and Chatterji[2] also showed that the incidence of leprosy, in those tested repeatedly—but yielding a persistently negative response on examination 16 years later, was markedly high. Further, a recent report from Cuba,[4] found that lepromin testing with lepromins of human origin, induced antibody formation detected by the FLA–ABS test persisting up to 180 days after lepromin testing. Thus the presently

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available evidence strongly supports the view that lepromin testing induces immune responses, and that these may be of both the humoral- and cell-mediated types.

The study reported here is of an investigation of the pattern of sensitization occurring with repeated lepromin testing in Sri Lanka.

## Materials and methods

The methods of skin testing and reading of results have been described in detail elsewhere.[5] The protocol followed for repeat testing was as described by the Third IMMLEP Scientific Working Group.[6] Briefly the methodology was as follows.

Two population groups in Sri Lanka were investigated (at Pussellawa and Pedro). Their characteristics and pattern of reactivity on initial lepromin testing have been described earlier.[5] After initial lepromin testing (using lepromin A with a bacillary content of $3 \times 10^7$ bacilli/ml)—after which both Fernandez and Mitsuda reactions were read; those who had a Mitsuda reaction diameter of 6 mm or less, were similarly retested on an upper volar site on the opposite arm. Following the second retest Fernandez and Mitsuda reactivity were read again. At Pussellawa, where the study was carried out first, a third retest was carried out at a lower volar site of the forearm (with a single test),* when the second Mitsuda reaction was read, the plan being, again, to retest only those showing reactions of 6 mm or less. However, only three individuals showed such increases in reaction size, and therefore with the exclusion of these individuals all the others were retested a third time. At Pedro (where testing was done after Pussellawa), only one retest with lepromin A (a second test) was carried out. On each occasion of a test (or retest), both Fernandez and Mitsuda reactivity were read.

The number of individuals in whom the results of such repeated retesting were available is listed in Table 1.

**Table 1.** Availability of results (number of persons) with lepromin retest results (including 'soft' reactions)

| | First retest results (second test) | | | Second retest results (third test) | | | Where both first and second retest results are available | | |
|---|---|---|---|---|---|---|---|---|---|
| Area | Fernandez | Mitsuda | Both | Fernandez | Mitsuda | Both | Fernandez | Mitsuda | Both |
| Pussellawa | 101 | 137 | 94 | 73 | 80 | 63 | 58 | 80 | 50 |
| Pedro | 65 | 67 | 35 | | | | | | |

* A tuberculin test had been done on the same forearm with the first lepromin test.

## Results

In Figure 1 are presented the frequency distributions of Mitsuda reactivity to lepromin A in the two areas on first testing. Figures 2 and 3 show the frequency distributions of Mitsuda reactions elicited on retesting of those showing reactions of 6 mm or less with the initial test.

Figure 4 shows the frequency distributions of Fernandez reactivity to lepromin A. Figures 5 and 6 show the frequency distributions of Fernandez reactions of those retested, whose initial Mitsuda reaction size was 6 mm or less.

The change observed here with Mitsuda reactions on retesting the first time (second lepromin test), is one of reduction in size, demonstrating the induction of 'tolerance'. In fact many reactions of larger sizes ('reactors' or 'positives' of 3 mm or more)[5] became totally negative (0 mm) (43% of the whole at Pussellawa and 25% at Pedro). Further, only approximately 10% of 'non-reactors' or 'negative' Mitsuda reactors of 2 mm or less, became 'reactors' (positive) with the first retest. Of the whole retested population in both areas only approximately 4% showed a 'significant'* increase (of more than 2 mm over the first test) in reaction size. On the other hand, approximately 60% at Pussellawa and 44% at Pedro showed 'significant' reductions in Mitsuda reaction size with the second test.

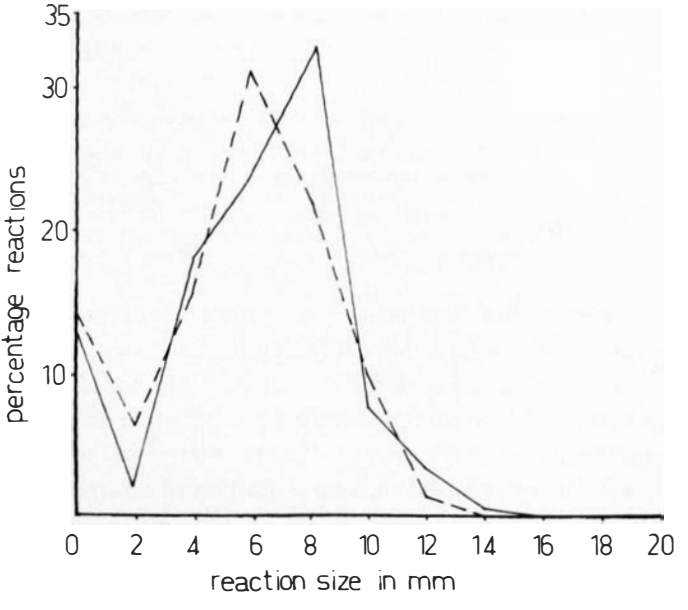


**Figure 1.** Frequency distributions of Mitsuda reactions to lepromin A with the first test at Pussellawa ( ) and Pedro (– – – – – –).

* It should be noted that 'significant' (when within quotes) refers to a change in reaction size (an increase or decrease) of more than 2 mm making allowance for possible vagaries of testing and reading procedures and does not mean significant in the statistical sense.

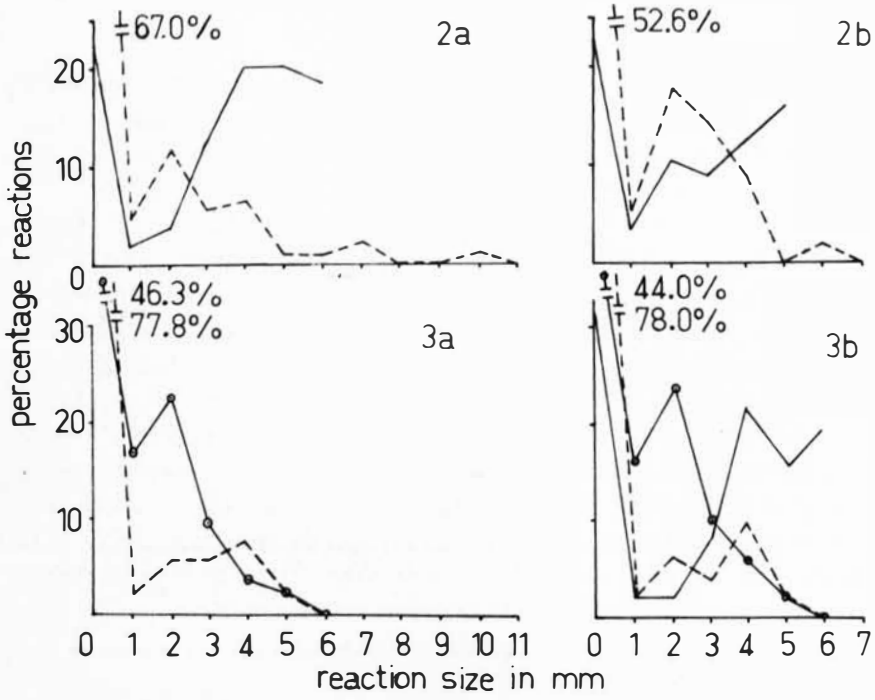


**Figure 2.** Frequency distributions of Mitsuda reactions to lepromin A of the same individuals, whose first test Mitsuda reaction sizes were 6 mm or less with the first (————) and second (– – – – – –) tests (a) at Pussellawa, and (b) at Pedro.

**Figure 3.** Frequency distributions of Mitsuda reactions to lepromin A of the same individuals, whose first test Mitsuda reaction sizes were 6 mm or less at Pussellawa (a) with the second (– – – – – –) and third (——o——) tests and (b) with the first (————), second (– – – – – –) and third (——o——) tests.

In the case of Fernandez reactivity, the picture observed with the frequency distributions is not as distinctive as with Mitsuda reactivity. While the frequency distributions show evidence of possible 'tolerance' at Pussellawa, the pattern at Pedro shows no statistically significant difference between the distributions of the first and second tests. In both areas the majority of individuals (52% at Pussellawa and 67% at Pedro) showed no 'significant' change in reaction size. A small number (17% at Pussellawa and 14% at Pedro) showed a 'significant' increase in reaction size, while reduction in reaction size was shown by 31% at Pussellawa and 19% at Pedro.

With the third lepromin test, which was carried out only at Pussellawa, both Mitsuda and Fernandez reactivity seem to be showing patterns suggestive of the recurrence or increase of reactivity. With Mitsuda reactivity the increase in reaction sizes (between the second and third tests) is of the smaller sizes in the 1– to 3-mm range, and therefore (allowing for a 2-mm variability in size), roughly the

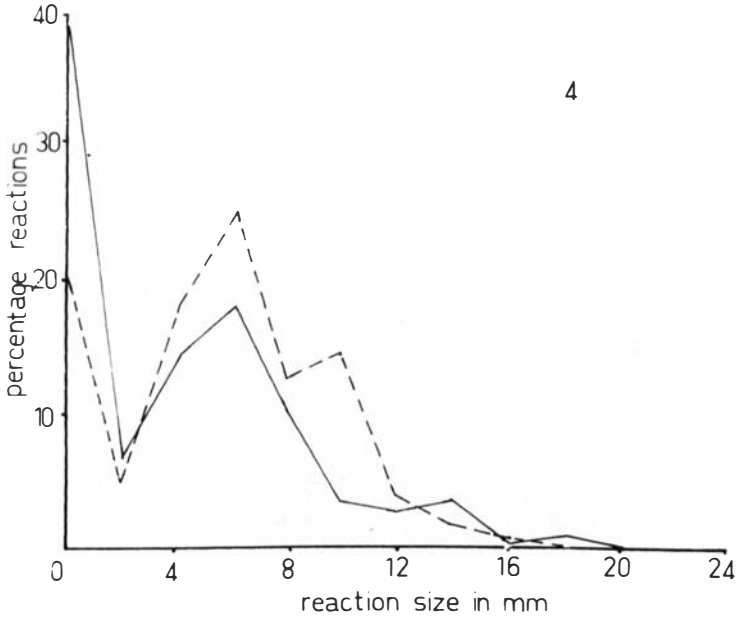


**Figure 4.** Frequency distributions of Fernandez reactions to lepromin A with the first test at Pussellawa (————) and Pedro (– – – – – –).

same small numbers of individuals (7 and 5% respectively) showed increases or decreases of reaction sizes. While the majority (54%) showed no change with Fernandez reactivity, 35% showed 'significant' increases of reaction size with 11% showing a reduction.

Comparing similarly the first and third lepromin tests, with Mitsuda reactivity, 9% showed an increase and 44% a decrease, with 47% no change. With Fernandez reactivity the numbers were 27%, 13% and 60% respectively.

The correlations between the first, second and third lepromin tests were statistically evaluated using the technique of regression analysis and nonparametric statistical methods. These analyses added further detail to the gross patterns observed in the frequency distributions. The results of the above analyses may be summarized as follows:

A *With Mitsuda reactivity*

1 There was a significant difference of the trend in the change of reactivity between the first and second tests, in the reactors ($\geqslant 3$ mm) as compared with the non-reactors ($\leqslant 2$ mm)[5].

2 The reactors showed a reduction in reactivity between the first and second tests, while the non-reactors showed no change.

3 In the subsets where the numbers of results available permitted statistical

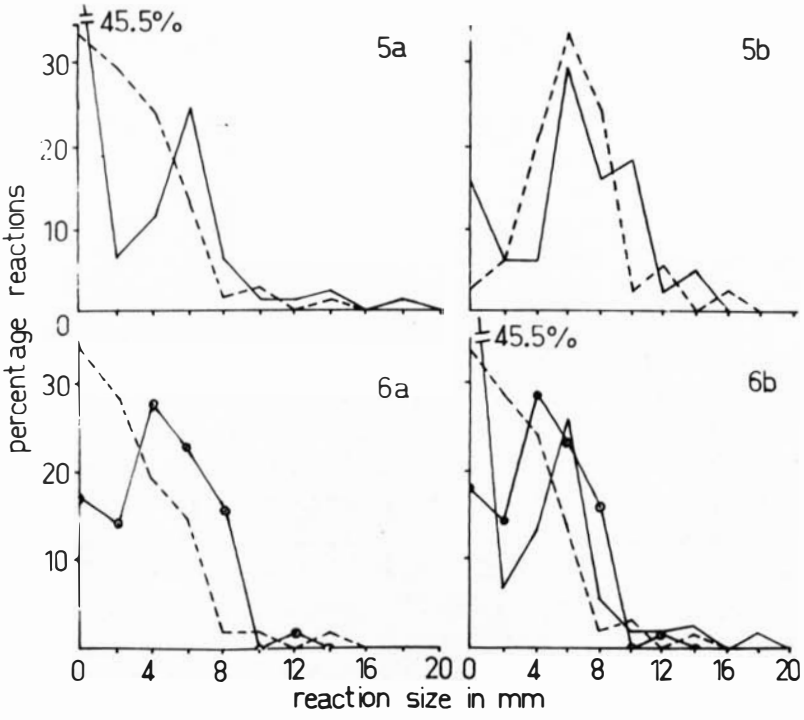


**Figure 5.** Frequency distributions of Fernandez reactions to lepromin A of the same individuals, whose first Mitsuda reaction sizes were 6 mm or less with first (————) and second (– – – – –) tests at (a) Pussellawa and (b) Pedro.

**Figure 6.** Frequency distributions of Fernandez reactions to lepromin A of the same individuals, whose first Mitsuda reaction sizes were 6 mm or less at Pussellawa, with (a) the second (– – – – –) and third (——o——) tests and (b) the first (————), second (– – – – –) and third (——o——) tests.

**Table 2.** Occurrence of 'soft' Mitsuda reactions with repeated lepromin testing. (Total number tested and read (including 'soft' reactions) within parenthesis)

| Area | With first test | With second test | With third test |
|---|---|---|---|
| Pussellawa | 1% | 17% | 15% |
| | (241) | (137) | (80) |
| Pedro | 4% | 18% | |
| | (161) | (67) | |

analysis, the difference between the second and third tests also, was that reactors in the second test showed a reduction in reaction size, while the non-reactors showed an increase in reaction size.

4 Comparison of first and third tests also showed similar patterns with an increase in reaction sizes of reactors and diminution of reaction sizes of non-reactors.

B *With Fernandez reactivity*

Again, as with Mitsuda reactivity, the trend of changes of reactivity between the first and subsequent tests was different between the reactors ($\geqslant 3$ mm) and non-reactors ($\leqslant 2$ mm).[5]

2 The difference observed between the first and the second test was a reduction in reactivity in the reactor group and an increase in reactivity in the non-reactor group (a trend different from that in the Mitsuda reaction).

3 In subsets where the numbers of results available permitted statistical analysis, the difference between the second and third tests was that reactors in the second test showed a reduction in reaction size while non-reactors showed an increase in reaction size.

4 Comparison of the first and third Fernandez tests also showed that there were increases in reaction sizes of the non-reactors and reduction in reaction sizes in the reactors.

All the above discussed changes (with both Fernandez and Mitsuda reactivity) were significant at an $\alpha \geqslant 0{\cdot}01$ level. The analysis also showed that the changes found with Mitsuda reactivity were not in any way influenced by sex, geographic location or BCG vaccination status. With Fernandez reactivity too, sex and BCG vaccination status seemed to have no influence on the results, whereas there is a possibility that geographic location does.

The relationship between the first and second, second and third, and first and third lepromin tests (in so far as Fernandez and Mitsuda reactivity are concerned) could be further examined by comparing the conversion of reactors to non-reactor status and vice versa with each subsequent test using McNemar's nonparametric statistical test for related samples.[7] With this evaluation it was found that with Mitsuda reactivity in both areas with the first retest there was a significant incidence of those changing from reactor to non-reactor status ($\alpha \geqslant 0{\cdot}01$) as compared with those showing a change from 'non-reactor' to 'reactor' status. There was no difference between the second and third tests at Pussellawa in this respect, while the first and third tests showed a similar difference to that between the first and the second. In other words the change seen between the first and second tests seemed to persist to the third test as well. With Fernandez reactivity the situation was different. There was no statistical difference in the changes of reactor/non-reactor status between first and second tests, whereas there was a significant ($\alpha \geqslant 0{\cdot}01$) increase in the incidence of reactors between the second and third tests and also the first and third tests. In other words, Fernandez reactivity shows an immunizing effect between first and third tests and second and third tests; thus while the first lepromin retest (second

test) showed no changes from the first, with the third test there was an increase in size (at Pusellawa). Thus the increase in reactivity (of both Fernandez and Mitsuda types) with the third test seen in the pattern of the frequency distributions at Pussellawa, is due to 0-mm reactions in the second test, becoming 1- or 2-mm reactions in the third test.

The foregoing analysis examines trends with repeated testing of the whole population group. At Pussellawa where three lepromin tests were carried out, the patterns of reactivity observed in each individual, with the three tests, could also be examined. Hence an individual could, in any one test, be a reactor or non-reactor, and any individual, therefore, could show any one of eight patterns of reactivity, ranging from reactor in all three tests to non-reactor in all three tests. The patterns of reactivity thus observed, showed the induced tolerance with Mitsuda reactivity clearly; and also revealed the difference between Mitsuda and Fernandez reactivity patterns with repeated testing (statistically significant at $\alpha \geqslant 0{\cdot}01$).

The above analysis of individual reaction patterns would also allow an opportunity of comparing the similarities and differences between Mitsuda and Fernandez reactivity patterns of individuals. The comparison here, showed that in any one individual, no discernible trend or correlation between Mitsuda and Fernandez reactivity patterns in the three tests could be made.

In the analysis described above only 'typical' Mitsuda reactions have been included (a well circumscribed and defined nodule was defined as 'typical'). However, some Mitsuda reactions did not manifest as above, and had a soft and sometimes plaque-like character. The significance of the latter is uncertain.[5] The occurrence of 'soft' Mitsuda reactions with the different tests is presented in Table 2. It is seen that there is a marked increase in such reactions with repeated testing.

## Discussion

The results of this study are at variance with those of studies reported earlier[2,3] which described only sensitization, or persistent non-reactivity, with repeated lepromin testing, and make no mention of the possibility of the induction of tolerance. The tolerance described here may be possibly of a transient nature but was nevertheless shown by many of those tested. Lepromin consists of killed whole *Mycobacterium leprae*, and hence this tolerance response between the 28th and 56th day (and perhaps beyond) is to the latter. It is tempting to speculate whether such tolerance could occur in the early days of natural infection with viable *M. leprae* too.

Tolerance with mycobacterial infection is a well-known phenomenon. The best-known example of this is with *M. leprae* in lepromatous leprosy. The induction of tolerance with *M. leprae* has also been demonstrated in experimental situations, where in the mouse the intraperitoneal and intravenous routes of

administration lead to tolerance, while the intradermal route leads to sensitization.[8] In the investigation reported here the intradermal route in man seemed to induce at least a transient tolerance in contrast to the finding in mice.

A distinctive finding in this study was the different behaviour of individuals of the reactor and non-reactor categories (with both Fernandez and Mitsuda reactions) on repeated lepromin testing. These two groups seem to be showing a different immunological responsiveness, and perhaps belong to two different populations. The results here also appear to validate the conclusions drawn earlier as to the points at which separation of reactor and non-reactor should be made.[5]

It was found here, regarding the change of reactor/non-reactor status, that Fernandez reactivity and Mitsuda reactivity seemed to behave differently with repeated lepromin testing. Further, the results with the initial test and with the repeated tests seemed to show differing correlations with tuberculin sensitivity with the two types of lepromin reactivity. Both lepromin reactions, though evoked by suspensions of killed, whole *M. leprae* are said to be aetiologically different.[9,10] Fernandez reactivity is considered analogous to the tuberculin response[11,12] in *M. tuberculosis* infection; and the Mitsuda reaction, to BCG vaccination, in that lepromin itself induces reactivity to itself as does the latter,[13,14] namely a 'vaccination response.'[1]

One possible explanation for the differences may be that Fernandez and Mitsuda reactivity are elicited by different antigens of *M. leprae*. Convit *et al.*[15] have shown that if the bacteria free supernatant of lepromin was used in skin tests, it produces a reactivity identical to the Fernandez reaction of whole lepromin. On the other hand Mitsuda type reactivity would be induced only by whole bacteria. If this hypothesis (of differences of antigens) be true, then antigens which manifest with Fernandez reactivity do not seem to recognize 'tolerance' as clearly, or at the same level, that is identified with Mitsuda reactivity. Also Fernandez reactivity in eliciting reactivity analogous to that of the tuberculin type, would only recognize pre-existing hypersensitivity of the latter type, and play no role in inducing the latter.

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## References


[1] Bloom BR. Rationales for vaccines against leprosy. Paper presented at *WHO TDR/SEARO/WPRO Scientific Meeting on Immunology and Chemotherapy of Leprosy*, Rangoon, 1981.

Dharmendra, Chatterji KR. Prognostic value of the lepromin test in contacts of leprosy cases. *Lepr India*, 1955; **27:** 149–52.

[3] Convit JA. Immunological effects of lepromin testing. Report of the fourth meeting of the Scientific Working Group on the Immunology of Leprosy. *WHO Document TDR/IMMLEP-SWG* (4) 1978; **78.3:**9.

[4] Gonzalez-Abreu E, Gonzalez-Segredo A, Dela Cruz F. Anti-Mycobacterium leprae antibodies induced by lepromin injection as demonstrated by indirect immunofluorescence. *Lepr Rev*, 1984; **55:** 337–40.

[5] Pinto MRM, Eriyagama NB, Pemajayantha V. Studies of reactivity of some Sri Lankan population groups to antigens of *M. leprae*. I. Reactivity to Lepromin A. *Lepr Rev*, 1987; **58:** 105–118.

[6] IMMLEP Scientific Working Group Protocol No. 9/77. Immunological effects of lepromin testing. Report of the third IMMLEP Scientific Working Group Meeting. *WHO Document TDR/SWG/IMMLEP* (3) 1977: 30.

[7] McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*, 1947; **12:** 153–7.

[8] Shepard CC, Walker LL, van Landingham RM, Shun-Shang Ye. Sensitisation or tolerance to *Mycobacterium leprae* by route of injection. *Infect Immun*, 1983; **38: 2:** 673–80.

[9] Guinto RS, Doull JA, Mabalay EB. Tuberculization and reactivity to lepromin: association between lepromin and tuberculin reactions in school children in Cordova and Opon, Cebu, Phillipines. *Int J Lepr*, 1955: **23: 1:** 32–47.

[10] Guinto RS, Wade HW. Results of tests with serial dilutions of lepromin in separate groups of normal young children, with a comparison of two lepromins and the Dharmendra antigen. *Int J Lepr* 1958; **26:** 328–45.

[11] Rodriguez JN. Observations on the Lepromin (Mitsuda) reaction. *Int J Lepr*, 1938; **6:** 11–32.

[12] Fernandez JMM. The early reaction induced by lepromin. *Int J Lepr*, 1940; **8: 1:** 1–14.

[13] Wade HW. Problems of allergy in leprosy. Festschrift Bernhard Nocht, Hamburg, Augustin, 1937; 652–5; quoted by Doull JA, Guinto RS, Mabalay MC, in *Int J Lepr*, 1959; **27: 1;** 31–42.

[14] Wade HW. The Mitsuda phenomenon, *Int J Lepr*, 1941; **9:** 101–104.

[15] Convit J, Pinardi ME, Avila JL, Aranzazu N. Specificity of the 48 hour reaction to Mitsuda antigen. *Bull. World Health Organ*, 1975; **52:** 187–97.

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# Leprosy and tuberculosis in the Blue Nile Valley of Western Ethiopia

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*Summary* Data are presented on the prevalence of leprosy and tuberculosis among different ethnic groups living under different environmental conditions in the Mendi district of the Blue Nile Valley, Western Ethiopia. The data are based on a clinical survey of 1323 persons (main study), representing Highland and Midland Oromos as well as Midland and Lowland Nilotics and on records from the local leprosy and tuberculosis programmes (additional study). It is concluded that cases of leprosy are rarely found in the highlands, whereas prevalences of 53/1000 and 92/1000, respectively, were found in two of the Lowland Nilotic villages. On the other hand, tuberculosis is 2–4 times more frequent among the Highland and Midland Oromo population (10–18/1000) than among the Midland and Lowland Nilotics (3–7/1000). In addition to the genetic difference between the Oromo and Nilotic populations, the higher temperatures, lower humidity and black soil observed at the lower altitudes might be of importance for the prevalence of mycobacterial disease. There is some evidence of an ongoing leprosy epidemic among the previously isolated Lowland Nilotics, and indications of a tuberculosis epidemic starting after their increased contact with the tuberculosis-infested Highland Oromos.

This paper is the first in a series that reports on the prevalences of several public health problems in this area, the Blue Nile Public Health Survey (BNPHS). Hence, some general information is provided on the concerned population, the geography and the organization of the public health services in the Mendi district.

## Introduction

Interactions between *M. leprae* and related mycobacteriae are important features of leprosy epidemiology, and special attention has been paid to the possible epidemiological antagonism between leprosy and tuberculosis.[1–6] BCG vaccination may provide some protection against leprosy, and crossed immunization has also been demonstrated by skin tests.[1–12] Some studies[3,5,12] suggest that the relative distribution of these major human pathogens is influenced by ecological factors such as altitude, temperature and annual rainfall as well as ethnic

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background and density of population. In order to identify such factors the logical target for investigations appear to be areas where both tuberculosis and leprosy are prevalent.

Preliminary information (Soerensen, I., personal communication) from the Mendi district of Western Ethiopia indicated that leprosy was defined to the lower altitudes, whereas tuberculosis was mainly found in the highlands. The present study was initiated to provide more reliable information on the distribution of leprosy and tuberculosis among representatives of the Mendi lowland, midland and highland, respectively.

In addition to the scientific value of such studies, the investigation was required to identify priorities within the Blue Nile Public Health Project.

## Materials and methods

### LAND, PEOPLE AND HEALTH CARE

The Mendi District is an administrative unit of about 100,000 inhabitants (1980) within Welega, the westernmost region of Ethiopia (Figure 1). The Blue Nile constitutes the northern border of the district running north-westwards at an altitude of about 700 m. From the river lowlands the country rises towards the south up to the main Mendi highland plateau, about 1700 m above sea level. In the middle of the slopes, at an altitude of about 1200 m, are the flat plains of Dalati, here called the midlands.

The lowlands are an extension of the Sudanese savannah with some forest galleries in the hillsides.[13] The soil is black and fertile, the mean temperature is high and during the dry season maximum temperatures of 40–45°C are common. Mean annual precipitation is 800–1000 mm.[13] There are no complete meteorological data available from this outpost area.

The main inhabitants are hoe-cultivating Nilotic tribes living in villages of small bamboo huts. Each family owns several huts which vary in size from 4 to 30 $m^2$, with an average of about 15 $m^2$. An average of 5 people sleep in each hut.

Hens and goats are common, but cattle scarce due to zoonotic trypanosomiasis. Meat from hunting is sometimes added to the diet, which otherwise is based on fermented porridge of sorghum with a spiced vegetable sauce.

There is widespread social contact between the Nilotic villages. Around the major lowland village of Sirba lives the previously very isolated Saysay tribe of the Nilotic Gumuz people[13,14], in this survey called the Lowland Nilotics.

The highlands of the Mendi district are mainly eroded mountain savannah with vulcanic red soil of low fertility.[13] In 1984 the average maximum temperature was 28·7°C and the average minimum temperature 15·0°C. The total annual precipitation in the same year was 1·754 mm, mainly falling from April to October.

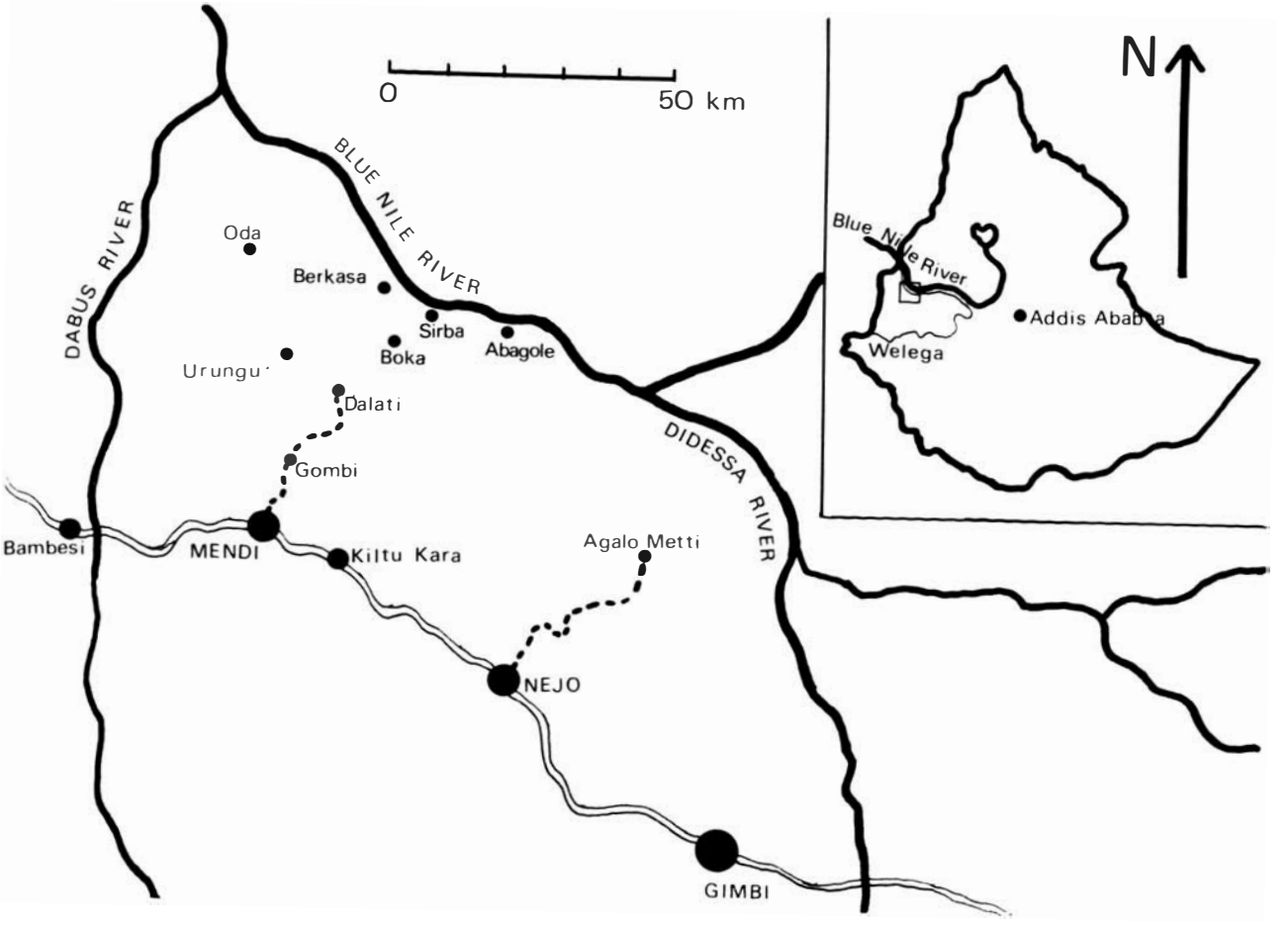


**Figure 1.** Map of the study area within the Mendi district of Western Ethiopia.

The main inhabitants are plough-cultivating Oromo people of Cushitic origin.[13,15] They live in clusters of houses made of dried mud. The average family consists of about 10 members. In most cases each family owns only one house approximately 15 to 45 $m^2$, usually with more than one room.

The main staple food consists of a fermented pancake of teff (a small, iron-rich crop exclusively found in Ethiopia) or maize with a spiced sauce of vegetables. Meat is eaten occasionally. The Oromos keep cattle, sheep and hens, but do not hunt or fish.

There is only occasional social contact between villages. The Highland Oromos live permanently in the highlands, while the Midland Oromos leave their original highland villages for about 6 months yearly to do farming at the lower altitudes around Dalati.

The midlands derive geographical and population characteristics from both areas. The area is relatively hot with maximum temperatures between 30 and 40°C. Complete meterological details are not available, but daily registrations have now been started. In 1984 the total recorded precipitation was 1,340 mm. The soil is fertile, changing from red to black. The original inhabitants are Nilotics of the Bertha group (Midland Nilotics), differing from the lowland Gumuz groups mainly by language.[13,16] In addition, a considerable number of Midland Oromos stayed in the midlands at the time of investigation.

*Communication*. The roads in the area are scarce. Between Mendi and Dalati there is a track passable by 4-wheel drive vehicles. At the time of the survey further travel had to be by foot or mule. Since 1982 4-wheel drive cars may pass from Dalati to Sirba during the dry season.

The health services of the district are coordinated from the Mendi clinic or health centre, which is staffed with 1 physician, 2 nurses and 4–6 health assistants. The physician supervises a public health team consisting of 1 nurse, 1 health assistant and 1 epidemiology worker. In addition to the community health activities offered by this team, permanent health service is provided in the lowlands by 2–3 health workers at the small clinic in Dalati. The primary health care in the villages is to an increasing extent given by community health agents and traditional birth attendants who receive short training courses.

## MAIN STUDY POPULATION

The total population of the Mendi district is approximately 100,000 of whom the lowland, midland and highland represent 5, 5, and 90% respectively. The choice of study population was made primarily to cover ethnic and cultural groups typical of the respective altitude and not to give representative samples of the whole district. Also accessibility to the villages and the attitude of village elders upon a preliminary request of cooperation influenced the decision.

In May 1982, 1,323 persons were examined for clinical and/or laboratory evidence of selected infectious diseases and malnutrition. The survey population was distributed by ethnic origin and altitude of settlement as follows:

a, 393 Highland Oromos from Gombi (1700 m); b, 455 Midland Oromos from Dalati (1200 m); c, 193 Midland Nilotics from Dalati (1200 m); and d, 282 Lowland Nilotics from Sirba (700 m).

Local elders and teachers ensured that every household member attended, once the head of the family had agreed. In the villages approached, the percentage of participation averaged 35% (20–50%). The age and sex distribution of the 1323 persons examined is given in Figure 2. Except for some overrepresentation of persons (mostly females) aged 30–40, and children (mostly boys) below the age of 10, the survey population pyramid is similar to that of the total population of the district.

The results of the leprosy and tuberculosis investigation will be given here, while the prevalence of intestinal parasites, onchocerciasis, trachoma, malaria and malnutrition will be reported elsewhere.

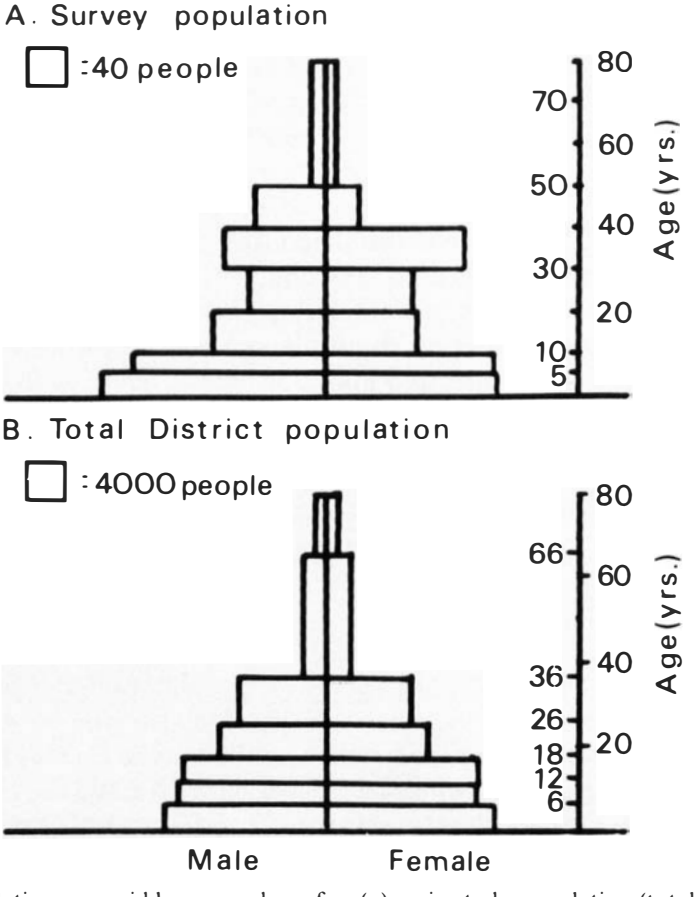


**Figure 2.** Population pyramid by sex and age for: (a) main study population (total 1323); and (b) total Mendi district population according to registration of 1980 (total 102,499).

### ADDITIONAL STUDY POPULATION

All patients already registered in current leprosy and tuberculosis programmes of the Mendi district were included in this study. Because both studies were made in the same geographical area, there was some accidental overlapping of the main and the additional study population, which will be commented on later.

### DIAGNOSIS AND CLASSIFICATION

We adopted the procedures for diagnosis and classification that had so far been used in the local programmes, which conform to what is traditionally used in rural work with limited diagnostic resources.

*Leprosy*. The diagnosis was based on clinical examination, supplemented by skin smears for microscopy of possible acid-fast bacilli. Skin smear negative cases with one or a few hypopigmented macules without any impairment of sensation and without nerve enlargement were classified as indeterminate. Paucibacillary patients with impaired sensation of lesions and/or enlarged nerves but without major sequelae were listed as tuberculoid cases. All cases showing sequelae from neuritis were grouped as borderline. A few treated initially as multibacillary patients might have been included in this group. As lepromatous leprosy were diagnosed those with multibacillary involvement of the skin with or without nodulation.

*Tuberculosis*. The diagnosis was primarily given to cases of sputum positive pulmonary tuberculosis. However, this diagnostic group also included pulmonary and extrapulmonary cases, especially children, with typical chronic symptoms that responded to tuberculostatics but not to conventional antibiotics.

*Reliability of diagnosis*. Before the study started the author evaluated the reliability of the diagnoses of leprosy and tuberculosis made by the experienced nurses and health assistants. For this purpose we thoroughly reviewed the records of the existing leprosy and tuberculosis programmes for the years 1980 and 1981 according to the above-mentioned diagnostic criteria. Fifty per cent of the leprosy patients were visited at home and re-examined, while the majority of the tuberculosis patients were re-examined in the clinics.

## Results

### MAIN STUDY

In Table 1 the leprosy results are summarized. Of the total 23 cases (17/1000), 16 were already under treatment, while 7 were new cases. Among the Highland and Midland Oromos we found prevalence rates of 3 and 9 per 1000, respectively. On the other hand, the respective prevalence rates of Midland and Lowland Nilotics were 16 and 53 per 1000.

Among the Lowland Nilotics 3 new leprosy cases were diagnosed, while the 3

**Table 1.** Main study. Distribution of leprosy cases in the Mendi district according to altitude and ethnic group

| Population | Indeterm. | Tuberculoid | Borderline | Lepromatous | Total (Prev. rate/1000) |
|---|---|---|---|---|---|
| Highland Oromos ($n = 393$) | 1 | 0 | 0 | 0 | 1 (3) |
| Midland Oromos ($n = 455$) | 3 | 0 | 1 | 0 | 4 (9) |
| Midland Nilotics ($n = 193$) | 1 | 0 | 1 | 1 | 3 (16) |
| Lowland Nilotics ($n = 282$) | 1 | 5 | 9 | 0 | 15 (53) |
| Total ($n = 1323$) | 6 | 5 | 11 | 1 | 23 (17) |

patients found among the Midland Nilotics were already under treatment. The tuberculoid end of the spectrum represented 48% of the total number of leprosy patients found in the survey.

Table 2 shows the distribution of suspected and proven tuberculosis cases found during the survey. Of totally 1323 people examined, 74 (56/1000) were suspected of tuberculosis on clinical grounds. Of these 38 (51%) came for further examination in one of the clinics. Seventeen of these were proven to have tuberculosis by sputum microscopy or cure by tuberculostatic treatment. Of the 17 proven cases 6 had previously recognized tuberculosis, 3 were on treatment while 3 were defaulters. Table 2 also demonstrates the high prevalence of tuberculosis among the Oromos of the higher altitudes. While only 1 of the 193

**Table 2.** Main study. Distribution of suspected and proven tuberculosis in the Mendi district according to altitude and ethnic group

| Population | Number examined | Suspected tuberculosis (Prev. rate/1000) | Proven tuberculosis (Prev. rate/1000) |
|---|---|---|---|
| Highland Oromos | 393 | 44 (112) | 7 (18) |
| Midland Oromos | 455 | 20 (44) | 7 (15) |
| Midland Nilotics | 193 | 8 (41) | 1 (5) |
| Lowland Nilotic | 282 | 2 (7) | 2 (7) |
| Total | 1323 | 74 (56) | 17 (13) |

Midland Nilotics (5/1000) and 2 of the 282 Lowland Nilotics (7/1000) had tuberculosis, 7 of 393 Highland Oromos (18/1000) and 7 of 455 Midland Oromos (15/1000) were found to suffer from this disease.

## ADDITIONAL STUDY

While only 1 leprosy patient was registered in the highland, 105 were registered at the Dalati clinic, serving midland and lowland population. Of these 105, 50 were re-examined by the author, and all had their diagnosis confirmed. Four had indeterminate, 22 tuberculoid, 22 borderline and 2 lepromatous leprosy, which gives a type prevalence at the tuberculoid end of the spectrum (indeterminate plus tuberculoid cases) of 52%. Of these 50, 34 claimed to have got their first patch above 30 years of age. In 14 of the 50 patients a total of 24 sequelae were registered, including infected wounds on hands (3) and feet (3), loss of fingers (8) and toes (2), clawhand (3) and other muscle atrophy of hand (3), lagophtalmos (2).

The majority (94) of the 106 leprosy patients registered in the total district inhabited six midland or lowland villages (see Figure 1) with a total population of 2405, which gives a prevalence rate of 39 per 1000. Table 3 shows the distribution of cases on these six villages. For three of the villages in the far lowland, Sirba Abaya, Boka Wau and Abagole Kuseru, the very high prevalences of 53, 73 and 92 per thousand respectively, were found.

**Table 3.** Additional study. Distribution of leprosy patients on six hyperendemic Nilotic villages in the Blue Nile Valley according to the local leprosy and tuberculosis control programmes of the Mendi district

| Village | Number of* inhabitants | Number of leprosy cases | Prevalence rate per thousand |
|---|---|---|---|
| Sirba Abaya | 759 | 40 | 53 |
| Abagole Kuseru | 272 | 25 | 92 |
| Boka Wau | 220† | 16 | 73 |
| Berkasa Mercha | 407 | 7 | 17 |
| Urungu | 235 | 4 | 17 |
| Dalati | 512 | 2 | 4 |
| Total | 2405 | 94 | 39 |

* Figures obtained from the official district registration for 1980.

† Because the figure for Boka Wau was lacking in the register, the number of inhabitants was calculated from the number of houses (44) multiplied by 5.

In Table 4 the prevalence rates for both leprosy and tuberculosis are summarized for the different parts of the Mendi district. Of the 11 leprosy patients registered outside the six hyperendemic villages, 5 were Oromos and 6 were Nilotics, all living in the midland or lowland area.

Only 6 tuberculosis patients were found among the 2405 inhabitants of the six leprosy dominated villages (3/1000). By contrast 71 of 5557 (13/1000) and 10 of 1024 (10/1000) inhabitants of the highland towns of Mendi and Kiltu Kara respectively, were registered as tuberculosis patients under treatment. Among the remaining rural Mendi district population of 93513 a total of 236 cases of tuberculosis were registered (3/1000).

**Table 4.** Additional study. Prevalence rates for leprosy and tuberculosis in different parts of Mendi district according to the local leprosy and tuberculosis control programme

| Area | Number of* inhabitants | Number of leprosy cases (Prev. rate/1000) | Number of tuberculosis cases (Prev. rate/1000) |
|---|---|---|---|
| Six mid- and lowland Nilotic villages | 2,405 | 94 (39) | 6 (3) |
| Mendi Town | 5,557 | 1 (–) | 71 (13) |
| Kiltu Kara Town | 1,024 | 0 (–) | 10 (10) |
| Remaining district | 93,513 | 11 (–) | 236 (3) |
| Total | 102,499 | 106 (1) | 323 (3) |

* Figures obtained from the official Mendi district registration for 1980.

## Discussion

In Ethiopia at large the estimated average prevalence rate for leprosy is 10/1000, and the highest local rates so far published (25–49/1000) are from the highlands of Gojjam north of Welega.[13] Systematic review of the records of the current leprosy programme (additional study population) clearly indicated a difference in the prevalence of leprosy between the highland and lowland populations of the Mendi district. Among the highland Oromos leprosy was very rare (0·2/1000) while an average prevalence rate of 39/1000 was found in six of the Nilotic lowland villages. In fact, rates as high as 53/1000, 73/1000 and 92/1000 were calculated for three of the most affected villages in the lowlands. Our investigation of the main study population confirmed that leprosy is now common among the lowland Nilotics with an average rate estimated at 53/1000,

which is far above the prevalence (5/1000) found by Fullar Torrey in 1966.[17] Moreover, 4 of the 5 cases found among the 848 Oromos were classified as indeterminate leprosy, which remains a rather inconclusive diagnosis. The low prevalence rate of leprosy in the genuine highland population is further underlined by the fact that 5 out of the 6 Oromos included in the control programme lived in the midlands most of the year.

The average prevalence of tuberculosis in Ethiopia has been estimated at 1%, although rates up to 5% have been recorded.[13] In the Mendi clinic, serving mainly a population of about 100,000 inhabitants, an average of 50–100 new sputum positive cases are diagnosed annually. According to experiences from similar programmes this corresponds to an annual incidence rate of tuberculosis of 1%.[18] Due to the limitations of this laboratory technique, insufficient medical coverage and a high defaulter rate, the true prevalence of tuberculosis in the Mendi district is certainly much higher. Interestingly, the distribution of tuberculosis within the district differed sharply from that of leprosy: among the lowland Nilotics the prevalence of tuberculosis was estimated at 3–7/1000 whereas the corresponding rate among the Oromos of the highlands was 10–18/1000. Similar differences between lowland and highland areas as regards the prevalence of tuberculosis have been reported from Erithrea.[19] On the other hand Reynolds[20] in 1963 found very high rates of clinical tuberculosis and skin reactivity among Nilotic Annuak people of Gambela, a lowland area of South Western Ethiopia.

Prevalence rates may vary considerably according to population density, as reported from South Western Ethiopia.[21] However, the clearly significant difference between the prevalence observed in the six Nilotic midland and lowland villages (3/1000) and that of Mendi town (13/1000) is not easily explained by factors such as density of housing or social and cultural habits. Also, the medical services delivered by local clinics are available to the same extent in Dalati/Sirba and in the Mendi town. On the other hand the very low prevalence found in the remaining district might simply reflect insufficient medical coverage in the remote areas.

The previous distribution of mycobacterial diseases in the Mendi district could possibly have been a consequence of immunological interplay between leprosy and tuberculosis as well as differences in altitude, temperature, annual rainfall, soil characteristics and ethnic background.[1–12] Our survey, however, has disclosed a more complex pattern: in the highlands, a previously endemic situation for leprosy now seems to be overshadowed by the high tuberculosis prevalence. Furthermore, among the lowland Nilotics, there is evidence of an ongoing leprosy epidemic[22–26] and indications of a startling increase in tuberculosis prevalence compared to the absence of this disease found in 1966.[17] Thus, if natural interplay between mycobacteria plays a role, it certainly does not seem to be a static feature of mycobacterial epidemiology.[25] More likely, the occasional introduction of one of these diseases into rather isolated populations may explain the uneven distribution of mycobacterial diseases.[22–25] Thus, the apparent rapid

increase of tuberculosis among lowland Nilotics may simply be explained by increasing contact of this traditionally isolated population with the highland Oromos, where tuberculosis is widespread.

Large field trials evaluating the protective effect of BCG against leprosy and tuberculosis have shown conflicting results.[27 28] Repeated surveys using tuberculin and lepromin skin testing,[29–32] followed by appropriate examination and, if required, treatment of positive cases, might therefore be more effective in the control of tuberculosis and leprosy than the BCG vaccination programme already launched in parts of this area.

## Acknowledgments

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## References

[1] Chaussinand R. Tuberculose et lepre, maladies antagoniques. *Int J Lepr*, 1948; **16:** 431–8.
[2] Fernandez JMM. Leprosy and tuberculosis. *AMA Arch Derm*, 1957; **75:** 101–6.
[3] Fine P. Leprosy and tuberculosis—an epidemiological comparison. *Tubercle*, 1984; **65:** 137–53.
[4] Grounds JG. Leprosy and tuberculosis: A statistical relation in South Nyanza, Kenya. *J trop Med Hyg*, 1964; **67:** 13–5.
[5] Hunter JM, Thomas MO. Hypothesis of leprosy, tuberculosis and urbanization in Africa. *Soc Sci Med*, 1984; **19:** 27–57.
[6] Nelson GS. Leprosy in the West Nile District of Uganda: An epidemiological study with special reference to the distribution of leprosy in Africa *Trans Roy Soc trop Med Hyg*, 1958; **52:** 176–85.
[7] Castro NO. Sensitization to lepromin induced experimentally with BCG. *Int J Lepr*, 1952; **20:** 221–8.
[8] Davey TF, Drewett SE. Tuberculin and lepromin sensibility in E. Nigeria. *Lepr Rev*, 1958; **29:** 81–101.
[9] Hale JH, Moleworth BD, Grove-White RJ, Sambamurthi CM, Russell DA. The relationship and significance of mantoux and lepromin reactions in leprosy. *Int J Lepr*, 1955; **23:** 139–47.
[10] Leiker DL. Studies on lepromin test. *Int J Lepr*, 1961; **29:** 488–95.
[11] Muir E. Relationship of leprosy and tuberculosis. *Lepr Rev*, 1957; **28:** 11–9.
[12] Irgens LM. Leprosy in Norway. *Lepr Rev*, 1980; (Suppl. 1), **51:** 1–130.
[13] Schaller KF, Kuls W. Ethiopia. A Geomedical Monograph. Berlin, Heidelberg, New York: Springer Verlag, 1972.

[14] Irwin L. Some notes on Saysay culture. *J Ethiop Stud*, 1968; **6:** 131–9.
[15] Ferguson CA. The Ethiopian language area. *J Ethiop Stud*, 1970; **8:** 67–80.
[16] Unseth P. Unpublished report. 1984.
[17] Fuller Torrey E. A medical survey of the Saysay people in the Blue Nile Gorge. *Ethiop Med J*, 1966; **15:** 155–9.
[18] Styblo K. The present epidemiological situation of tuberculosis in developing countries. WHO/TB/82.135, 1982.
[19] Perry A. Tuberculosis in Eritrea. *Ethiop Med J*, 1963; **2:** 31–5.
[20] Reynolds D. The tuberculosis problem in Gambela District, Illubabor Province. *Ethiop Med J*, 1963; **2:** 36–8.
[21] Fuller GK, Gemeda N, Fuller D, Demerest V. A tuberculin skin test survey in Southwestern Ethiopia. *Trop Geogr Med*, 1979; **31:** 365–73.
[22] Davey TF. Decline of leprosy in a group of Nigerian villages between 1941 and 1956. *Int J Lepr*, 1957; **25:** 329–44.
[23] Davey TF, Ross CM. Leprosy: A changing situation in Eastern Nigeria. *Brit Med J*, 1956; **2:** 65–8.
[24] Leiker DL. Epidemiological and immunological surveys in Netherlands New Guinea. *Lepr Rev*, 1960; **31:** 241–59.
[25] Skinsnes OK. Immuno-epidemiology of leprosy. Editorial. *Int J Lepr*, 1975; **43:** 145–8.
[26] Wade HW, Ledowsky V. The leprosy epidemic at Nauru: A review with data on status since 1937. *Int J Lepr*, 1952; **20:** 1–29.
[27] Editorial. BCG: Bad news from India. *Lancet*, 1980; **1:** 73–4.
[28] Noordeen SK, Sansarricq H. Immunization against leprosy: progress and prospects. *Bull WHO*, 1984; **62:** 1–6.
[29] Paul RC, Stanford JL. Multiple skin testing in leprosy. *J Hyg Camb*, 1975; **75:** 57–68.
[30] Shield MJ, Stanford JL, Paul RC. Multiple skin testing of tuberculosis patients with a range of new tuberculins, and a comparison with leprosy and Mycobacterium ulcerans infections. *J Hyg Camb*, 1977; **78:** 331–48.
[31] Stanford JL, Nye PM, Rook GAW, Samuel N, Fairbank A. A preliminary investigation of responsiveness or otherwise of patients and staff of a leprosy hospital to groups of shared or species specific antigens of mycobacteria. *Lepr Rev*, 1981; **52:** 321–7.
[32] Stanford JL. Skin testing with mycobacterial reagents in leprosy. *Tubercle*, 1984; **65:** 63–74.

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# A multicentre evaluation of a questionnaire to assess ability in the diagnosis of leprosy

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*Summary* Case finding in leprosy control programmes is dependent on the ability of field staff in the diagnosis of leprosy. However assessment of this ability in field circumstances is difficult and time consuming. In this study 20 case histories in the form of a questionnaire is evaluated as a tool to assess ability to interpret the signs and symptoms of leprosy. The study included field workers of different grades and differing experience from 6 centres in India. The validity of this method is shown by the better performance by the higher grades of staff and the correlation of performance with experience. The use of case histories in this way is a useful educational tool; it can also be used to identify individual members with major difficulties in the diagnosis of leprosy and to identify particular cases which present more general diagnostic problems.

## Introduction

In most leprosy control programmes case finding is undertaken by paramedical or basic health workers by population screening. The diagnosis of leprosy in the field is based on illiciting clinical signs and symptoms; laboratory investigations such as skin-smear examination or histopathology play a confirmatory role at a later stage if at all. The clinical diagnosis made by the paramedical staff is then usually confirmed by a more senior supervisor or medical officer before active chemotherapy is initiated.

This approach to case detection uses standard screening methodology and it is thus appropriate to apply screening criteria[1] to assess the detection of leprosy in control programmes. The paramedical staff perform the standard screening test while the senior staff act as the standard and valid diagnostic test. Thus the screening examination can be assessed for specificity, sensitivity and overall agreement. The re-examination by senior staff of cases positive by the screening examination gives an estimate of the false positives. However to estimate the numbers of false negatives it requires the senior staff to repeat the population

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screening at a similar point in time but independent from the paramedical workers examination, this has been undertaken in special surveys and it has been suggested that 5–10% of the population be regularly resurveyed.[2] Such re-examination is costly and programme directors may not be convinced of their necessity.

The whole procedure of population screening is complex, it is dependent on community co-operation, a high level of coverage, the ability to conduct a full examination in a good light under difficult circumstances, and the expertise to interpret the findings in making a diagnostic decision. It is, however, possible to identify parts of the process and assess these rapidly and inexpensively in isolation. Such methods can detect problems and be part of quality assurance in leprosy control work as well as contributing to the ongoing in-service training of field staff in leprosy control programmes.

In this study the efficacy of a simple questionnaire to assess the ability of leprosy control programme staff to interpret clinical findings in the diagnosis of leprosy is evaluated. The validity of the tool is assessed by examining the results from different programmes with staff of different grades and levels of experience.

## Methods

Twenty case histories of typical problems encountered in case detection in a leprosy control programme were prepared. These twenty were chosen to represent common problems and are therefore not necessarily typical of all suspected cases. The 20 case histories are given in the Appendix along with the standard answers used in the analysis. Each member of the field staff reads each history and then writes down his diagnosis as one of three categories, affected, not affected or suspected, as is the standard method in population screening.

Copies of the 20 case histories were completed independently by the field staff of 6 different leprosy control programmes throughout India and by paramedical workers undergoing initial training. A set of 'correct' answers were prepared and each worker's responses were compared with this standard. The agreement between the field worker and the standard is expressed as a percentage of all cases. The number of cases considered suspects is presented as a percentage of all the cases. Cases considered affected by the field worker and not affected by the standard are described as false positives and are expressed as a percentage of all diagnosed not affected by the standard. Similarly false negatives were those considered unaffected by the field worker but affected by the standard. The performance of each worker was thus assessed for overall agreement, the proportion of suspects, false positives and false negatives.

The standard answers used in the analysis have been compared with the majority answer. Difficulty and discrimination indices have also been calculated for each of the 20 cases based on the findings.

**Table 1.** Performance of the six centres

| Centre | Number of staff | Agreement (%) | Suspects (%) | False negatives | False positives |
|---|---|---|---|---|---|
| 1 | 14 | 53 | 31 | 8·3 | 11·4 |
| 2 | 26 | 48 | 32 | 12·2 | 15·4 |
| 3 | 7 | 62 | 27 | 4·8 | 11·4 |
| 4 | 11 | 56 | 30 | 4·5 | 5·4 |
| 5 | 17 | 55 | 34 | 10·8 | 8·2 |
| 6 | 9 | 55 | 36 | 11·2 | 11·2 |
| Total | 84 | 53 | 31 | 9·5 | 11·2 |

**Table 2.** Performance in the 4 grades of staff

| Grade | Number of staff | Agreement (%) | Suspects (%) | False negatives | False positives |
|---|---|---|---|---|---|
| Trainees | 21 | 46 | 29 | 11·8 | 18·0 |
| Paramedical workers | 51 | 54 | 32 | 9·5 | 11·0 |
| Non-medical supervisors | 6 | 67 | 26 | 0 | 0 |
| Medical officers | 6 | 62 | 34 | 11·2 | 0 |
| Total | 84 | 53 | 31 | 9·5 | 11·2 |

## Results

The 20 case histories were completed by 84 field workers from 6 centres including 21 trainee paramedical workers, 51 trained paramedical workers (PMW), 6 non-medical supervisors (NMS) and 6 medical officers (MO). The results from each centre are shown in Table 1. The pattern in each centre is similar. Centre 2 contained the 21 trainees and thus had the lowest agreement and highest percentage of false negatives and positives. Each centre was a mixture of staff of differing grades and of different experience.

The performance of the 4 grades of staff is shown in Table 2. The performance of trainee paramedical workers when compared with the standard shows the least agreement and the most false diagnoses. The performance of the supervisors and medical officers is better than that of the paramedical workers. The effect of experience in the field of leprosy on performance is assessed in Table 3. Five participants failed to give details of their experience. There is a general trend of

**Table 3.** Performance and years of experience

| Experience in years | Number of staff | Agreement (%) | Suspects (%) | False negatives | False positives |
|---|---|---|---|---|---|
| 0 | 22 | 47 | 32 | 12·2 | 17·2 |
| 1 | 7 | 62 | 35 | 7·2 | 5·8 |
| 2 | 18 | 52 | 34 | 13·0 | 12·2 |
| 3 | 15 | 54 | 31 | 6·7 | 8·0 |
| >3 | 17 | 61 | 29 | 6·0 | 3·6 |
| Total | 79 | 54 | 32 | 9·5 | 10·4 |

(5 failed to give details of their experience)

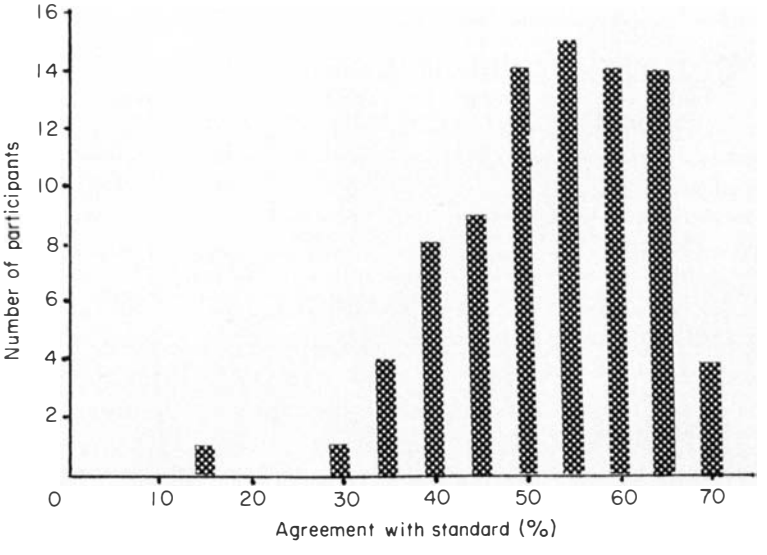


**Figure 1.** The distribution of the agreement with the standard for the 84 participants.

improved performance with increasing years of experience. The correlation coefficient of experience against agreement ($r = +0{\cdot}4$) and experience against false positives ($r = -0{\cdot}3$) are both statistically significant ($p < 0{\cdot}05$).

Each participant's response was assessed for serious deviation from the standard. Serious deviation was considered as any one of the following 6 parameters; failure to detect half the true positives or half the true negatives, more than 1 false negative or false positive, agreement in less than 8 of the 20 cases, and 10 or more suspects. Serious deviations from the standard were detected in 29

individuals, 14 of whom were trainees. Ten of the remaining 15 had one deviation, 2 had two deviations, 2 had three deviations and one had 5 deviations.

The distribution of the agreement with the standard for each of the 84 participants approximates to normal (Figure 1). From this distribution it is possible to identify the characteristics of those with high (65% or more) and low (40% or less) scores. The 14 with low scores included 9 trainee PMWs and 5 trained PMWs (2·5 years average experience). The 18 with high score included 1 trainee PMW, 7 trained PMWs (5·5 years average experience), all 6 of the NMSs and 4 out of the 6 MOs.

The standard answers were compared with the majority answer for each of the 20 questions. There was agreement in all but 3 questions (4, 10 and 19) where in each case the standard was 'suspect' but the majority went for 'unaffected'. A difficulty index was calculated for each question based on the lack of agreement between the 84 participants; where less than 50% agreed on the answer it was classed difficult and where more than 80% agreed on the answer it was classed as easy. Using this method, 6 questions were assessed as difficult (1, 8, 9, 12, 14 and 20) and 3 were classed as easy (3, 6 and 15). Each question was then assessed by a discrimination index based on the proportion of participants giving either false positive or false negative diagnoses. Using this index there were 3 questions where more than 10% gave false positive answers (5, 7 and 20) and 2 where more than 10% gave false negative answers (13 and 18).

## Discussion

The analyses of the results of this multicentre evaluation of 20 case histories as a method of assessing ability in the diagnosis of leprosy show a consistency in the responses. The validity of this method of assessment is confirmed by the better performance, across a number of parameters, of the higher grades of staff and those with more experience. This pattern exists for the overall agreement with the standard responses as well as the number of false negatives and false positives. Further, as would be expected in any valid assessment, those in training had the poorest results for all the measures.

The group with the lowest scores includes, along with the trainees, 5 trained PMWs who have low scores and a number of serious deviations from the standard. This ability to identify field staff in service who have problems in the diagnosis of leprosy is an important feature of this case history method. The responses to the questions have also been used to identify problem areas. Early lesions in children seem to present a common difficulty; variation in the response to such cases would lead to apparent differences in the leprosy prevalence amongst children in different regions. The discrimination index is useful in identifying important problems, such as case history No. 13, which the majority diagnosed as leprosy but more than 10% passed over as unaffected; and those with any skin such as case No. 5 where more than 10% diagnosed as leprosy.

The need for operational research in leprosy control programmes has been well recognized for many years.[3,4] However there are only a few reports of such work being undertaken.[5,6] Perhaps the main reasons for this gap in field work is that such work is extremely laborious and directors of field work are apprehensive about getting into this area in fear of what may be uncovered. This study suggests a simple and inexpensive method of approaching the problem by picking out one particular aspect of leprosy control work and assessing it in isolation. A good performance with this method does not imply that there are no problems but a poor performance does signify that serious problems do exist which deserve further examination.

These case histories can also be used as a method of in-service training by stimulating discussion between staff in these difficult areas. In-service training or any teaching programme could also be assessed by repeating the case histories on the same group at a later stage. New series of case histories could also be compiled and used in a similar way. Use of the case histories may also help to convince programme directors of the need for regular quality assessment in the diagnosis of leprosy in control programmes.[2]

**Acknowledgments**

I would like to thank the staff from the 6 centres who willingly helped in this evaluation.

**References**

[1] Hart CR. Screening in general practice. Churchill Livingstone. Edinburgh; 1977: p. 12.
[2] Kumar A, Durai V, Sivaprasad N, Sirumban P. Diagnostic efficiency of paramedical workers in leprosy. *Lepr Rev*, 1985; **56:** 309–14.
[3] Noordeen SK. The need for operational studies in leprosy control. *Lepr India*, 1977; **49:** 6.
[4] Meade TW. Growing points in leprosy research—epidemiology. *Lepr Rev*, 1974; **45:** 15.
[5] Neelan PN, Noordeen SK, Desikan KV, Ramu G, Prabhu KPM, Christian M. Inter-observer variations in diagnosis and classification of early lesions of leprosy. XI Biennial Conference of the Indian Association of Leprologists, 1979.
[6] Kumar A, Durai V, Sirumban P. Diagnostic efficiency of paramedical workers involved in leprosy case detection programme. *Ind J Lepr*, 1984; **56:** 626–32.

## Appendix

**Questionnaire—Leprosy case detection**

Read the following 20 case descriptions as if they were people you had met in the

course of survey work and mark them as either Not Affected (N), Affected (A), or Suspect (S). Do not discuss your answers with others until you have completed the questions. No smears or other tests are available.

Letters in circles represent the standard responses used in the analyses.

A 7-year-old boy has a few pale patches on his face with no anaesthesia. His father has lepromatous leprosy. (S)

2 A 4-year-old boy has two pale patches on his buttocks but he will not co-operate and so sensation is not tested. (S)

3 A 32-year-old woman with slight loss of eyebrows. Her face, back and limbs show redness and infiltration. (A)

4 A 7-year-old boy has a few pale patches on his face with no anaesthesia. He has been kept a suspected case for 3 years but there is no improvement. (S)

5 A 24-year-old woman has several raised patches with a white, scaly surface. There is no anaesthesia. (N)

6 A 19-year-old boy has a single anaesthetic patch on his left hand. (A)

7 A 70-year-old man has only loss of eyebrows. No other signs. (N)

8 A 7-year-old girl has a few pale patches on her face with no sensory change. (S)

9 A 14-year-old boy has a patch on his chest which he says is a birthmark but on testing there is sensory change. (A)

10 A 29-year-old man has a left drop foot but has no patches or loss of sensation. (S)

11 An 8-year-old girl has two patches on her face with no sensory change. She has been a suspect for 1 year but now the patches are more well defined. (S)

12 A 7-year-old boy has a few patches on his face. There is no sensory change. (N)

13 A 27-year-old man has thickening of both ulnar and lateral popliteal nerves but no patches or sensory change. (A)

14 A 14-year-old boy has a single well-defined patch on his back with no sensory change. (S)

15 A 50-year-old man has had very white patches on his legs for about two years. (N)

16 A 27-year-old woman has numerous patches on her body and loss of sensation on her feet and hands. (A)

17 A 7-year-old boy has a few pale patches on his face. There is no loss of sensation. His father has tuberculoid leprosy. (S)

18 A 5-year-old boy has a few pale patches on his buttock. Sensation is not tested. His mother has tuberculoid leprosy. (A)

19 A 30-year-old woman has many itchy patches with loss of sensation over these patches. (S)

20 A 70-year-old woman has tingling in her hands and feet. There are no patches or loss of sensation. Ⓝ

Staff Grade .....

Experience in Leprosy ..... years

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# Seroreactivity against the *Mycobacterium leprae* phenolic glycolipid I in Mycobacteria infected or stimulated groups of individuals

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*Summary* The enzyme-linked immunosorbent assay (ELISA), was applied in a group of sera of lepromatous leprosy patients, tuberculosis patients, BCG vaccinated children and bloodbank donors using the phenolic glycolipid I, isolated by Hunter and Brennan, for the determination of specific antibodies.

Positive results were found in the group of leprosy patients while the majority of the sera of the other individuals were negative.

Slight cross-reactivity was encountered in a few individuals.

At the same time a study was carried out in healthy persons without a known contact with *Mycobacterium leprae*. These received a lepromin injection (Mitsuda test) and blood samples were taken before and 21, 45 and 90 days afterwards. In this case evidence was shown that the lepromin injection did not influence the results of the test.

## Introduction

During the immune reaction to *Mycobacterium leprae* infection, humoral response which is generally accepted as non-protective, arises. This characteristic may be of importance to analyze the variable course of infection, the immunogenic structure of the bacilli and for the detection of subclinical infection.[4,8]

Harboe *et al.* have suggested that if antibodies arise after infection and before symptoms appear it may be possible to study the epidemiology of leprosy infection instead of the epidemiology of the disease and its complications as has been done previously.

Several investigators[3–5,10] have shown that antibody concentration is higher in multibacillary leprosy than in the paucibacillary type which may relate antigenic load to antibody titres. This relationship might be important for the early

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diagnosis and control of the individuals responsible for the transmission of the disease in the community.

Recently, Hunter and Brennan[6] obtained an antigen which is considered species specific for *M. leprae* and might be useful for the serological screening in high risk population by the ELISA test.[2,6] Since the phenolic glycolipid I has been made available to us by the courtesy of Dr P Brennan, we have examined its activity against sera from lepromatous leprosy patients, tuberculosis patients, BCG vaccinated children, lepromin tested healthy volunteers and bloodbank donors.

## Materials and methods

Sera of 32 lepromatous clinically and histologically classified patients were included in this study. Of these, 9 were under DDS treatment. Also the sera of 27 tuberculosis patients, 24 BCG vaccinated children and 195 bloodbank donors were studied.

Simultaneously 33 healthy Cuban volunteers, without known contact with leprosy patients, received a lepromin injection (0·1 ml/$40 \times 10^6$ bacilli/ml Lepromin A from Carville USA). Blood samples were taken just before the injection and 21, 45 and 90 days thereafter and their sera tested by the ELISA technique.

ELISA conditions:[1] The phenolic glycolipid I antigen was suspended in ethanol to a concentration of 2 $\mu$g/ml and 50 $\mu$l added to wells of polysterene plates which were incubated overnight at room temperature. Plates were washed with phosphate buffered saline (PBS), blocked with PBS containing 5% bovine serum albumin (PBS/BSA) and incubated at 37°C for 1 h in a moist chamber, after which the PBS/BSA was aspirated. Fifty microlitres of serum diluted 1:300 with PBS containing 20% normal calf serum (PBS/NCS) was added and incubated at 37°C for 1 h. Later, plates were washed with PBS and goat antihuman immunoglobulin M (IgM) peroxidase conjugate (Cappel Laboratories) diluted 1:1000 in PBS/NCS was added. After a 1 h incubation the plates were washed and 50 $\mu$l of $H_2O_2$–Ophenylendiamine substrate in citrate-phosphate buffer were added and incubated at room temperature for 20 min in the dark. The reaction was stopped with 2·5N $H_2SO_4$ and the absorbance read at 492 nm using a Multiskan MC reader (Flow Lab).

Reference sera, positive and negative were included in each plate to correct the sample readings.

Statistical analysis was carried out using the $\chi^2$ test.

## Results and discussion

Two-fold dilutions from 1:20 to 1:2560 of negative sera and 2 positive sera were

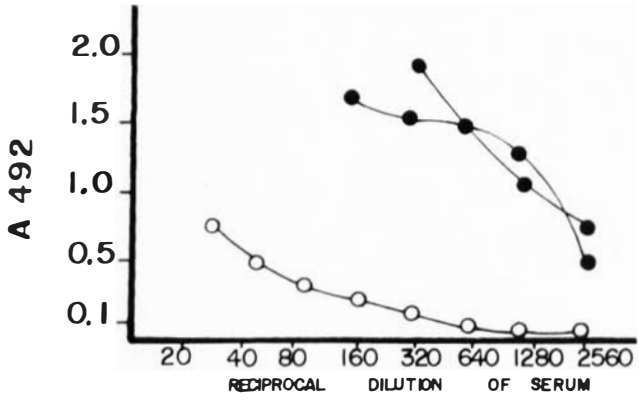


**Figure 1.** IgM activity against phenolic glycolipid in serial dilution of lepromatous sera (●——●), and negative human serum (○——○).

used to standardize the ELISA test (Figure 1). We chose 1:300 as working dilution since its combination with the antigen gave the maximal separation between positive and negative test samples but still showing low negative values. A total of 300 sera of bloodbank donors were analyzed and compared to negative human control sera to determine the cut-off value at $\bar{x} \pm 2$ SD ($0{\cdot}060 \pm 0{\cdot}124$). The study of 23 sera of untreated lepromatous patients demonstrated a high positivity (100%) using the phenolic glycolipid I in the ELISA test. These results agree with those encountered by other investigators[3–5,9] in which reference is made between bacillary load and antibody production, both of which are very high in patients presenting this clinical form of leprosy (Table 1 and Figure 2). The results obtained with 9 treated lepromatous patient sera, demonstrated a similar behaviour to that found by others[3–5,7,10] in patients with DDS treatment, who point out that antibody titres decrease in relation to the time of treatment. At the

**Table 1.** Seroreactivity to phenolic glycolipid I.

| Sera | No. positive/negative | X ± SD (A492) | Positivity (%) |
|---|---|---|---|
| Multibaciary patients not treated | 23/0 | $1{\cdot}51 \pm 0{\cdot}655$ | 100 |
| Multibaciary patients treated | 7/2 | $0{\cdot}903 \pm 0{\cdot}766$ | 77·7 |
| Tuberculosis patients* | 2/27 | $0{\cdot}073 \pm 0{\cdot}073$ | 7·41 |
| BCG vaccinated children* | 1/23 | $0{\cdot}088 \pm 0{\cdot}050$ | 4·34 |
| Bloodbank* | 10/185 | $0{\cdot}170 \pm 0{\cdot}062$ | 5·12 |

* $\chi^2 = 0{\cdot}313$ $P > 0{\cdot}01$.

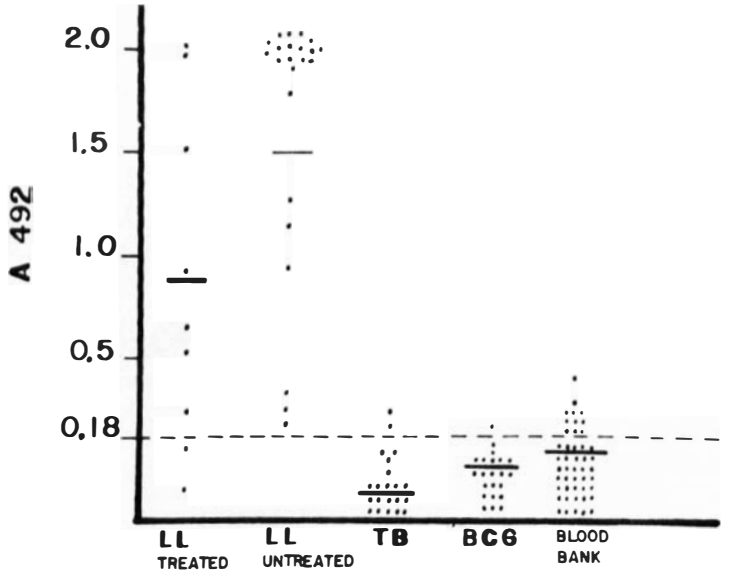


**Figure 2.** IgM antibody activities against Phen Gly I in human sera. The solid lines represent the mean values and all points above the dashed line are considered positive.

**Table 2.** Seroreactivity to phenolic glycolipid I in treated LL patients.

| Sera | Bacteriological Index (BI) | Time of treatment (years) | OD |
|---|---|---|---|
| 1 | 0 | 21 | 0·04 |
| 2 | 0 | 12 | 0·16 |
| 3 | 1 | 5 | 0·25 |
| 4 | 3 | 4 | 2·00 |
| 5 | 4 | 2 | 0·89 |
| 6 | 2 | 2 | 2·00 |
| 7 | 2 | 2 | 0·55 |
| 8 | 3 | 2 | 0·70 |
| 9 | 3 | 1 | 1·54 |

same time a tendency towards a reduction in the Bacteriological Index (BI) is observed although certain differences are seen among these patients (Table 2).

In the study of the group of tuberculosis patients and BCG vaccinated children the results in general are negative as can be observed in Table 1. Nonetheless, we cannot ignore a discrete positivity in both groups: 7·4% in the tuberculosis patients and 4·2% in the BCG vaccinated children.

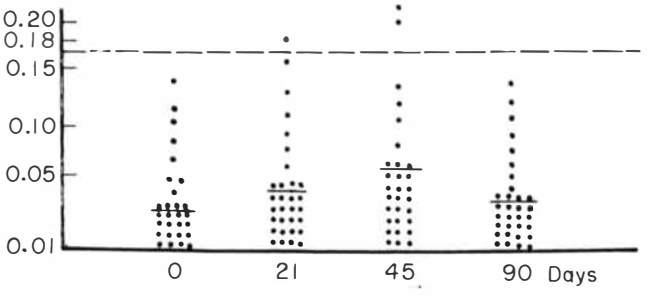


**Figure 3.** Lepromin influence in healthy people. The solid lines represent the mean values and all points above the dashed line are considered positive.

The sera of supposedly healthy bloodbank donors also demonstrated slight positivity of 5·1% which is comparable to the results reported by Young and Buchanan with healthy individuals in their work in Mexico (4%) and Sri Lanka (9%).[9]

The positive results of those individuals who do not present the disease, were analyzed by the $\chi^2$ test which demonstrated that there was no significant difference ($P > 0{\cdot}01$) between them while a significant difference was found when compared to the leprosy patients ($P < 0{\cdot}01$). These positive results may be due to a discrete cross-reactivity, or as a result of contact with *M. leprae*, or instead, simply false positive reactions.

Among the persons who received a lepromin injection (Mitsuda test) (Figure 3), a slight positive result can be observed in one individual at 21 days and in two at 45 days, while all persons in the study were negative by 90 days. The negative results with the lepromin test seem to confirm the view about the poor immunogenicity of the phenolic glycolipid I[3] since the injection of $4 \times 10^6$ dead organisms was not enough to elicit a positive response.

Our results seem to confirm that ELISA using the phenolic glycolipid I is potentially a highly specific procedure for the detection of antibodies against leprosy infection without complications arising from BCG vaccination or previous infection with *M. tuberculosis* and encourage us to undertake a more extensive trial among contacts of leprosy patients aimed to detect early stages of the disease and to assess its predictive value.

## Acknowledgments

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## References


[1] Cho S, Yanagihara D, Hunter S, Gelber R, Brennan P. Serological specificity of Phenolic Glycolipid I from Mycobacterium leprae and use in serodiagnosis of leprosy. *Infect Immun*, 1983; **41:** 1077–1083.

Brennan P. New-found Glycolipid antigens of Mycobacteria. *Microbiol*, 1984; 366–375.

[3] Brett SJ, Draper P, Payne S, Rees RJW. Serological activity of a characteristic phenolic glycolipid from Mycobacterium leprae in sera from patients with leprosy and tuberculosis. *Clin Exp Imm*, 1983; **52:** 271–279.

[4] Harboe M. Significance of antibody studies in leprosy and experimental models of the disease. *Int J Lepr*, 1984; **50:** 337–340.

[5] Harboe M. Radioimmunoassay and other serologic tests and their application in epidemiological work. *Lepr Rev*, 1981; **52:** Suppl, 275–288.

[6] Hunter S, Brennan P. A Novel Phenolic Glycolipid from Mycobacterium leprae. Possibly Involved in Immunogenicity and Pathogenicity. *J Bac*, 1981; **147:** 728–735.

[7] Melson R, Harboe, M, Naafs B. Class specific anti-Mycobacterium leprae antibody assay in lepromatous leprosy (BL-LL) patients during the first two of four years of DDS treatment. *Int J Lepr*, 1982; **50:** 271–281.

[8] Young D, Buchanan T. A serological Test for Leprosy with a Glycolipid Specific for Mycobacterium leprae. *Science*, 1983; **221:** 1057–1059.

[9] Young D, Buchanan T. *The Phenolic Glycolipid from Mycobacterium leprae: Use in Serological Tests*. Proceedings of the workshop on serological tests for detecting subclinical infection in leprosy. Tokyo: Sasakawa Memorial Foundation, 1983.

[10] Yoder D, Naafs B, Harboe M, Bjune G. Antibody activity against Mycobacterium leprae antigen 7 in leprosy. Studies on variation in antibody content throughout the spectrum and on the effect of DDS treatment and relapse in BT leprosy. *Lepr Rev*, 1979; **50:** 113–121.

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# Viral challenge in leprosy: viraemia, interferon, and specific antibody production

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*Summary* Following 17-D yellow fever vaccination, viraemia and specific neutralizing antibody production were assessed in groups of 12 healthy Malay controls and Malay tuberculoid and lepromatous leprosy patients. Subsequent viraemia was found in 10 healthy subjects, 9 tuberculoid patients and 8 lepromatous patients. Neither the time of appearance, chronicity, nor titre of viraemia was different amongst the three groups. Nine or 10 individuals from each of the 3 subject groups developed specific neutralizing antibody. Prior to vaccination, the ability of peripheral blood leucocytes to produce interferon *in vitro* after stimulation with Newcastle Disease Virus, was studied. Leucocytes from all the healthy subjects and patients produced significant amounts of interferon. Neither lepromatous nor tuberculoid patients' leucocytes produced levels of interferon different from healthy controls. A tendency was observed for lepromatous patients to produce decreased amounts of interferon *in vitro* as compared to tuberculoid patients ($P=0{\cdot}06$).

## Introduction

Clinicians generally agree, and a number of studies have supported the view, that leprosy patients appear to handle other infections normally[1] and are not predisposed to immunologically mediated disease or malignancy.[2–4] As a prerequisite for leprosy vaccines to prove effective, individuals at risk in endemic countries should be capable of responding in a normal fashion to unrelated infectious agents. In order to experimentally test this issue, we performed a study in Malaysia utilizing well classified lepromatous and tuberculoid patients and healthy controls, which assessed *in vitro* leucocyte interferon production and *in*

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*vivo* viraemia and specific neutralizing antibody development, following the challenge of subjects with a non-endemic virus, live attenuated yellow fever.

## Materials and methods

### SUBJECTS

Subjects included 12 healthy Malay staff members of the National Leprosy Control Center, Sungei Buloh, Malaysia, 12 Malay lepromatous leprosy patients, and 12 Malay tuberculoid leprosy patients. None of the subjects had a prior history of yellow fever vaccination, encephalitis, dengue or travel outside Malaysia. Disease classification was based on clinical and histologic findings (Ridley, D.S.) and lepromin skin testing. Subjects were vaccinated subcutaneously with 0·5 cc of a 17-D vaccine strain of yellow fever. Viraemia was assessed prior to vaccination and 4 or 5 days, and in some instances 6 days later, and circulating neutralizing antibody were determined and quantitated prior to vaccination and 4, 5 and 12 days later. Prior to vaccination, the ability of peripheral blood leucocytes to produce interferon *in vitro* was assessed.

### VIRAEMIA

Viraemia following yellow fever vaccination was assayed in pig kidney (PS) cells grown in Leibovitz L15 medium with 3% inactivated foetal calf serum following the method of Madrid and Porterfield[5] with minor modifications. Undiluted human serum was added to a suspension of $3 \times 10^5$ PS cells/ml, using 0·1% ml serum to 2·5 ml cells in one 50 mm plastic petri dish or 0·05 ml serum to 0·5 ml cells in each of two wells in disposable FB-16-24 plastic containers, and cultures were overlaid with an equal volume of carboxymethyl cellulose overlay 2 h later. After 5 (or occasionally 7) days incubation at 35°C, preparations were rinsed with normal saline, stained with naphthalene black, and any plaques visible were counted.

### YELLOW FEVER ANTIBODY

Neutralization tests were performed in disposable plastic trays. One volume (0·2 ml) of an appropriate dilution of yellow fever vaccine suspension was mixed with one volume of heat inactivated (56°C/30 min) human serum diluted, 1:10, 1:40, 1:160 and 1:640, and the serum virus mixtures were held in the wells of plastic plates overnight at 4°C. Two volumes of PS cells (0·4 ml of $3 \times 10^5$/ml) were then added, and the mixtures incubated at 35°C for 2 hs after which 0·4 ml of carboxymethyl cellulose overlay was added to each well, and the preparations incubated at 35°C for 5–7 days. Confluent or semi-confluent plaques developed in

the absence of yellow-fever neutralizing antibodies; sera which reduced the plaque count to below 50% of that produced in control wells were recorded as positive.

### INTERFERON PRODUCTION *IN VITRO*

From each subject 20–25 ml of venous blood with phenol-free heparin (30 iu/ml) were placed in a vessel to which 6% dextran (4 to 5 ml) was added. Ten millilitre portions in sterile screw-capped tubes were inclined at 45° and incubated at 37°C for 40 min. The plasma was then removed, pooled, and centrifuged at 1000 rpm for 10 min at room temperature. The leucocyte containing sediment was suspended in Eagles media plus 10% foetal calf serum. Cell counts were adjusted to $3 \times 10^6$ cells/ml in screw-capped tubes and inocculated with 0·2 ml of undiluted allantoic fluid containing Newcastle Disease Virus (NDV1) with viral hemagglutinin titres of 1/640 or greater. After 24-h incubation in a roller drum at 37°C the fluid was harvested for interferon assay.

Interferon was assayed on fluid dilution by assessment of inhibition of rhinovirus cytopathic effects on WI38 human diploid lung cells utilizing the method of Wheelock.[6] In each test a standard interferon preparation was incorporated.

## Results

### VIRAEMIA

The results are presented in Table 1. Some early sera were toxic to the cell cultures; consequently it was impossible to detect viraemia in these samples. As expected, viraemia was never present on day 0, but was present in 6 samples on day 4, in 26 samples on day 5, and in 15 samples on day 6. Viraemia was detected at least once in 10/12 normal subjects, in 8/12 patients with lepromatous leprosy and in 9/12 patients with tuberculoid leprosy. There were no significant differences between these three groups in the time of appearance, duration or magnitude of the viraemia.

### YELLOW FEVER ANTIBODY

The results are presented in Table 1. Neutralizing antibody titres of 10 or less were regarded as negative, and titres of 20 and above as positive. By these criteria, 9 of the pre-vaccination samples (day 0) appeared to have neutralizing antibodies against yellow fever virus. Since none of the subjects had received prior yellow fever vaccine, and since yellow fever does not occur in nature in Asia, these positive findings presumably reflect cross-protection produced by antibodies

**Table 1.**

| Clinicopathologic classification | Mitsuda ± (induration) | Yellow Fever viraemia* days | | | | Yellow Fever antibody days | | | | Newcastle Disease Virus induction of leucocyte interferon (reciprocal of plaque formation) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 4 | 5 | 6 | 0 | 4 | 5 | 12 | |
| All L | | | | | | | | | | |
| (#12) L | −(5) | ? | ? | 20 | 10 | 10 | 10 | < 10 | 20 | $10^{-3}$ |
| (#14) L | −(0) | 0 | 0 | 0 | 0 | < 10 | < 10 | 10 | 80 | $10^{-2.5}$ |
| (#15) BL | −(5) | 0 | SC | 5 | 20 | 10 | 10 | 10 | 80 | $10^{-1.85}$ |
| (#17) L | +(9) | 0 | 0 | 0 | 0 | < 10 | < 10 | 10 | 80 | $10^{-2.25}$ |
| (#18) BL | −(5) | ? | ? | 10 | 15 | 10 | < 10 | < 10 | 80 | $10^{-3}$ |
| (#27) BB/BL | −(0) | 0 | 0 | 0 | | < 10 | < 10 | < 10 | 20 | $10^{-2.1}$ |
| (#28) L | −(5) | 0 | Conf | 10 | | < 10 | < 10 | < 10 | 40 | $10^{-2.27}$ |
| (#29) BL | +(8) | 0 | 0 | 3 | | 20 | 20 | 20 | 40 | $10^{-2.9}$ |
| (#31) BL | −(0) | 0 | 0 | 4 | | 20 | 20 | 20 | 80 | $10^{-3.25}$ |
| (#32) L | −(2) | ? | ? | 15 | | 20 | 20 | 20 | 20 | $10^{-2.7}$ |
| (#33) L | lacking | ? | ? | 15 | | 20 | 20 | NT | 20 | $10^{-2.3}$ |
| (#35) L | −(0) | ? | ? | 0 | | 10 | 10 | 10 | 40 | $10^{-2.5}$ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| All T | | | | | | | | | | |
| (#1) BT | −(3) | | | 20 | 5 | NT | NT | <10 | 10 | $10^{-3}$ |
| (#9) T | lacking | | | 4 | 3 | NT | NT | <10 | 20 | $10^{-2\cdot}$ |
| (#10) T | + (14) | | | 0 | 0 | NT | NT | 10 | 40 | $10^{-2\cdot8}$ |
| (#11) BT | +(10) | 0 | SC | 12 | 10 | 20 | <10 | 10 | 20 | $10^{-3\cdot5}$ |
| (#13) T | +(8) | ? | ? | 3 | 8 | 10 | 10 | 10 | 20 | $10^{-2\cdot7}$ |
| (#16) T | lacking | 0 | Conf | 10 | 10 | 20 | 20 | 20 | 20 | $10^{-3}$ |
| (#19) BT | −(4) | 0 | 0 | 0 | 0 | <10 | <10 | <10 | 80 | $10^{-3\cdot15}$ |
| (#21) T | +(10) | 0 | SC | 0 | | <10 | <10 | <10 | 80 | $10^{-2\cdot1}$ |
| (#23) T | +(14) | ? | ? | 20 | | 20 | 20 | 20 | 40 | $10^{-2\cdot}$ |
| (#25) T | +(12) | 0 | 0 | 10 | | <10 | <10 | <10 | 20 | $10^{-2\cdot7}$ |
| (#26) BT | +(9) | 0 | 0 | 3 | | <10 | <10 | <10 | 80 | $10^{-2\cdot75}$ |
| (#34) T | +(11) | 0 | 0 | 0 | | 10 | 10 | 10 | 20 | $10^{-4\cdot3}$ |
| All normal | | | | | | | | | | |
| (#2) | +(10) | 0 | 0 | 10 | 2 | <10 | <10 | <10 | 40 | $10^{-2\cdot}$ |
| (#3) | +(18) | ? | ? | 8 | 10 | <10 | <10 | <10 | 10 | $10^{-2\cdot4}$ |
| (#4) | +(7) | ? | ? | 20 | 20 | 10 | 10 | 10 | 40 | $10^{-2\cdot}$ |
| (#5) | +(9) | | | Conf | 2 | NT | NT | 10 | 40 | $10^{-3\cdot3}$ |
| (#6) | +(9) | 0 | 0 | SC | SC | 10 | <10 | <10 | 10 | $10^{-3\cdot15}$ |
| (#7) | +(10) | 0 | 0 | 5 | 3 | <10 | <10 | <10 | 40 | $10^{-3\cdot5}$ |
| (#8) | +(20) | | | Conf | Conf | NT | NT | <10 | 20 | $10^{-2\cdot35}$ |
| (#20) | +(12) | ? | ? | 0 | | <10 | 10 | 10 | 20 | $10^{-2\cdot}$ |
| (#22) | +(10) | 0 | Conf | 5 | | 20 | 20 | >20 | 80 | $10^{-2\cdot2}$ |
| (#24) | +(9) | 0 | 0 | 0 | | <10 | <10 | <10 | 80 | $10^{-2\cdot}$ |
| (#30) | +(10) | 0 | 0 | 8 | | 20 | 20 | 20 | 40 | $10^{-3}$ |
| (#36) | lacking | ? | ? | 1 | | 10 | <10 | 10 | 40 | $10^{-2\cdot3}$ |

?, toxic; SC, semi-confluent; Conf, confluent; *, plaques per 0·1 ml serum; NT, not tested.

against antigenically related flaviviruses which do occur in Malaysia, of which dengue and Japanese encephalitis viruses are the two most probable candidates. The day 4 and day 5 samples gave results virtually indistinguishable from those obtained with the day 0 samples, but by day 12 only 3 sera remained antibody negative, and these came from subjects who were viraemic on days 5 and 6. Antibody titres tended to be higher in the lepromatous leprosy patients than in the other groups. All the subjects who failed to produce a detectable viraemia nevertheless responded with the production of yellow fever antibodies.

### INTERFERON PRODUCTION *IN VITRO*

All of the subjects studied produced significant amounts of interferon *in vitro* following stimulation of peripheral blood leucocyte cultures. For normal subjects interferon production averaged $10^{-2\cdot73\pm0\cdot27(\text{S.D.})}$, and correspondingly tuberculoid patients $10^{-2\cdot95\pm0\cdot30(\text{S.D.})}$, and lepromatous patients $10^{-2\cdot55\pm0\cdot18(\text{S.D.})}$. These differences in interferon production between the three groups of patients were not significant. However, lepromatous subjects' interferon production was less than tuberculoid patients' ($P=0\cdot06$).

## Discussion

Wheelock *et al.*[7] demonstrated previously that viraemia could be identified in 10 of 15 normal subjects following vaccination with the 17-D strain of yellow fever virus, and by 10 days following vaccination, yellow fever antibody was detectable in all the subjects. These current studies are in essential accord with those findings. In our studies the titre and period of viraemia, following viral challenge *in vivo* and the production of specific neutralizing antibody appears to be normally generated in both lepromatous and tuberculoid patients. Also, these studies demonstrate that production of interferon to viral challenge by peripheral blood mononuclear cells *in vitro* in leprosy patients across the spectrum, does not appear aberrant. Control of viral infection involves a complex network which includes antibody, cellular immunity, and interferon which act in an integrated manner. These studies support that in leprosy patients this network is generally intact.

Though patients with lepromatous leprosy are known to produce a polyclonal hyperglobulinemia[8–11] that can result in a wide variety of falsely positive serologic tests,[12–16] antibody production in leprosy is not, however, conceived to be generally aberrant. In fact lepromatous patients were found to produce higher titres of agglutinins to H-antigens, in response to typhoid vaccine, than healthy military recruits.[17] Indeed, antibody to a *Mycobacterium leprae*-specific phenolic glycolipid is regularly produced in lepromatous leprosy and in high titre.[18] Our studies further support the concept that antibody to specific pathogens is not abnormally generated in leprosy patients.

Glasgow and Bullock[19] previously demonstrated that mice heavily infected with *M. lepraemurium* following intraperitoneal challenge with chikungunya virus produced distinctly lower levels of interferon than control mice, uninfected with *M. lepraemurium.* Mixed peritoneal cells from infected mice also reflected these *in vivo* findings and demonstrated decreased interferon production to chikungunya virus. It has been postulated that human lepromatous leprosy might also be associated with a defect of interferon producing capacity or other responses to viral challenges. In this respect a number of clinical reports have indeed suggested that lepromatous leprosy patients are more susceptible to variola[20] and demonstrate slow resolution of inoculation lesions and vaccinia gangrenosa following vaccination,[21,22] an indication of impaired cellular immunity. The present study found leprosy patients had no observed aberrancy in protective immunity to yellow fever. The decreased production of interferon *in vitro* by lepromatous as compared to tuberculoid patients ($P = 0{\cdot}06$) found in these studies is, however, of some interest.

Though interferon production has been classically considered to be induced by viruses, parasites,[23–26] and bacterial products, including endotoxin[27–30] tuberculin,[31] and poly RI–poly IC[32–35] are potent interferon inducers. Interferon has also been shown to inhibit *in vivo* multiplication of various intra- and extracellular pathogens other than viruses including pneumococci,[36] listeria,[37] trachoma,[38] cryptococcus,[19] *P. berghei*,[39] and certain tumours not known to be caused by viruses.[40] Levy *et al.*[41] found that the potent interferon inducers poly IC and Tilerone inhibited mouse footpad multiplication of *M. leprae.* Nogueira *et al.*[42] found peripheral blood mononuclear cells from lepromatous leprosy patients, even those on long-term therapy, deficient in their capacity to release gamma interferon *in vivo* in response to both mitogen and *M. leprae.* In those studies interleukin 2 was found to restore the decreased gamma interferon production of lepromatous leprosy in response to specific antigen or mitogen. Gamma interferon is evoked by specific cellular memory and these studies do not clarify if this fraction, especially that induced by *M. leprae* and potentially protective, is deficient.

There is considerable evidence on both sides of the issue of whether the immune defect in lepromatous leprosy is due to a specific defect[43–46] in host defence mechanisms against *M. leprae* or secondary to some more generalized anergy.[47–51] There has also been conjecture that certain individuals are genetically incapable of mounting an appropriate protective response thereby being predisposed to the development of leprosy, or alternatively, that the development of leprosy is due entirely to environmental exposure to the bacillus, wherein possibly the timing, route, and degree of exposure are crucial factors in determining whether overt disease does or does not become manifest. Certainly these two propositions need not be mutually exclusive and most likely both heredity and environmental factors interplay to determine the outcome in

individuals exposed to *M. leprae*. In any event these current studies lend support to the concept that leprosy patients do not present a generalized immune defect.

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## References

[1] Sansonetti P, Lagrange PH. The immunology of leprosy. Speculations on the leprosy spectrum. *Rev Inf Dis*, 1981; Vol. 3, 422–469.

[2] Purtilo DT, Pangi C. Incidence of cancer in patients with leprosy. *Cancer*, 1975; **35:** 1259–1261.

[3] Olenic A. Altered immunity and cancer risk: a review of the problem and analysis of the cancer mortality experience of leprosy patients. *J Nat Cancer Inst*, 1969; **43:** 775–781.

[4] Turk JL, Waters MFR. Leprosy. In: *Immunological diseases.* Samter M (ed), 3rd ed, 1978. Little Brown, Boston, Vol. 1, 627–638.

[5] Madrid AT, Porterfield JS. 'A simple micro-culture method for the study of group B arboviruses'. *Bull World Health Organization*, 1969; **40:** 113–121.

[6] Wheelock EF. Virus replication and high-titred interferon production in human leukocyte cultures inoculated with Newcastle Disease Virus. *J Bact*, 1966; **92:** 1415–1421.

[7] Wheelock EF, Sibley WA. Circulating virus, interferon and antibody after vaccination with the 17-D strain of yellow-fever virus. *N E J M*, 1965; Vol. 273, 194–201.

[8] Bullock WE, Ho MF, Chen MJ. Studies of immune mechanisms in leprosy. *J Lab Clin Med*, 1970; **75:** 863–870.

[9] Waters MFR, Turk JL, Wemambu SNC. Mechanisms of reactions in leprosy. *Int J Lepr*, 1971; **39:** 417–428.

[10] Jha P, Balakrishnan K, Talwar GP, Bhutani LK. Studies of humoral immune response in leprosy. *Int J Lepr*, 1970; **39:** 14–19.

[11] Sheagren JN, Block JB, Trauttian JR, Wolff SM. Immunologic reactivity in patients with leprosy. *Ann Intern Med*, 1969; **70:** 295–302.

[12] Abe M, Chinone S, Hirako T. Rheumatoid-factor-like substance and antistreptolysin O antibody in leprosy serum: Significance in erythema nodosum leprosum. *Int J Lepr*, 1967; **35:** 336.

[13] Bonono L, Dammacco F, Pinto L, Barbieri G. Thyroglobulin antibodies in leprosy. *Lancet*, 1963; **2:** 807.

[14] Bonono L, Tursi A, Trimigliozzi G, Dammacco F. LE cells and antinuclear factors in leprosy. *Br Med J*, 1965; **2:** 689.

[15] Cannefax GR, Ross H, Bancroft H. Reactivity of the RPCF test in leprosy compared with other syphilis tests. *J Pub Health Rep*, 1959; **74:** 45.

[16] Cathcart ES, Williams RC, Ross H, Calkins E. The relationship of the latex fixation test to the clinical and serologic manifestations of leprosy. *Amer J Med*, 1961; **31:** 758.

[17] De Almeida JO, Brandao H, de Lima EG. Enhanced serologic response of lepromatous patients to antityphoid vaccination. *Int J Lepr*, 1964; **32:** 292–296.

[18] Cho Sang-Nae, Yanagihara Donna L, Hunter SW, Gelber RH, Brennan PJ. Serological specificity of phenolic glycolipid I from *Mycobacterium leprae* and use in serodiagnosis of leprosy. *Infect and Immunity*, 1983; Vol. 41, 1077–1083.

[19] Glasgow LA, Bullock WE. Impairment of interferon production in mice infected with *Mycobacterium lepraemurium*. *Proc Soc Exp Biol Med*, 1972; **139:** 492–496.

[20] Denney OE, Hopkins R. 'Specific leprous reactions and abnormal vaccin-induced in leprosy by smallpox vaccination'. *J Pub Health Rev*, 1922; **37:** 3141–3143.

[21] Browne SG, Davis EM. 'Reaction in leprosy precipitants by smallpox vaccination'. *Lepr Rev*, 1962; **11:** 252–387.

[22] Saha K, Mittal ML, Ray SN. Consequences of small pox vaccination in leprosy patients. *Infect Immun*, 1973; **8:** 301–308.

[23] Rytel MW, Jones TC. Induction of interferon in mice infected with *Toxoplasma gondii*. *Proc Soc Exp Biol Med*, 1966; **123:** 859–862.

[24] Freshman MM, Merigan TC, Remington JS *et al.* *In vitro* and *in vivo* antiviral action of an interferon-like substance induced by *Toxoplasma gondii*. *Proc Soc Exp Biol Med*, 1966; **123:** 862–866.

[25] Huang K-Y, Schultz WW, Gordon FB. Interferon induced by *Plasmodium berghei*. *Science*, 1968; **162:** 123–124.

[26] Rytel MW, Marsden PD. Induction of an interferon-like inhibitor by *Trypanosoma cruzi* infection in mice. *Am J Trop Med Hyg,* 1970; **19:** 929–931.

[27] Stinebring WR, Youngner JS. Patterns of interferon appearance in mice infected with bacteria or bacterial endotoxin. *Nature (Lond)*, 1964; **204:** 712.

[28] Ho M. Interferon-like viral inhibitor in rabbits after intravenous administration of endotoxin. *Science*, 1964; **146:** 1472–1474.

[29] Youngner JS, Stinebring WR. Interferon appearance stimulated by endotoxin, bacteria, or viruses in mice pretreated with *Escherichia coli* endotoxin or infected with *Mycobacterium tuberculosis*. *Nature (Lond)*, 1965; **208:** 456–458.

[30] deSomer P, Billiau A. Interferon production by the spleen of rats after intravenous injection of Sindbis virus or heat-killed Escherichia coli. *Arch Gesamte Virusforsch*, 1966; **19:** 143–154.

[31] Green JA, Cooperband SR, Kibrick S. Immune specific induction of interferon production in cultures of human blood lymphocytes. *Science*, 1969; **164:** 1415–1417.

[32] Hilleman MR. Double-stranded RNAs (Poly 1 : C) in the prevention of viral infections. *Arch Int Med*, 1970; **126:** 109–124.

[33] Colby C, Duesberg PH. Double-stranded RNA in vaccinia virus infected cells. *Nature (Lond)*, 1969; **222:** 940–944.

[34] DeMaeyer E, DeMaeyer-Guignard J, Montagnier L. Double stranded RNA from rat liver induces interferon in rat cells. *Nature (New Biol) (Lond),* 1970; **229:** 219–222.

[35] Merigan TC. Interferon stimulated by double-stranded RNA. *Nature (Lond)*, 1970; **228:** 219–222.

[36] Regelson W, Munson A. The reticuloendothelial effects of interferon inducers: polyanionic and non-polyanionic phylaxis against microorganisms. *Ann NY Acad Sci*, 1970; **173:** 831–841.

[37] Vilcek, J, Jahiel RI. Action of interferon and its inducers against nonviral infectious agents. *Arch Int Med*, 1970; **126:** 69–77.

[38] Hanna L, Merigan TC, Jawetz E. Effect of interferon on TRIC agents and induction of interferon by TRIC agents. *Am J Ophthal,* 1967; **63:** 1115–1119.

[39] Jahiel RI, Vilcek J, Nussenzweig RS. Exogenous interferon protects mice against plasmodium berghei malaria. *Nature (Lond)*, 1970; **227:** 1350–1351.

[40] Levy HB, Law LW, Rabson AS. Inhibition of tumour growth by polyinosinic-polycytidylic acid. *Proc Natl Acad Sci USA*, 1969; **62:** 357–361.

[41] Levy L, Aizer F, Ng H, Welch TM. The effects of tilorone on mycobacterial infections of mice. *Lepr Rev*, 1978; **49:** 215–222.

[42] Nogueira N, Kaplan G, Levy E, Sarno EN, Kushner P, Granelli-Piperno L, Vieira L, Gould VC, Levis W, Steinman R, Yip YK, Cohn ZA. Defective interferon production in leprosy. Reversal with antigen and interleukin 2. *J Exp Med*, 1983; **158:** 2165–2170.

[43] Mohagheghpour N, Gelber RH, Larrick JW, Sasaki DT, Brennan PJ, Engleman EG. Defective cell-mediated immunity in leprosy: failure of T cells from lepromatous leprosy patients to respond to mycobacterium leprae is associated with defective expression of interleukin 2 receptors and is not reconstituted by interleukin 2. *J Immun*, 1985; Vol. 135, 1443–1449.

[44] Rea TH, Quismorio FP, Harding B, *et al.* Immunologic responses in patients with lepromatous leprosy. *Arch Dermatol*, 1976; **112:** 791–800.

[45] Convit J, Pinardi ME, Rojas FA. Some considerations regarding the immunology of leprosy. *Int J Lepr*, 1971; **39:** 556–564.

[46] Ulrich M, deSalas B, Convit J. Lymphocyte transformation with phytomitogens in leprosy. *Int J Lepr*, 1972; **40:** 4–9.

[47] Talwar GP, Krishnan AD, Mehra VL, *et al.* Evaluation of cell-mediated immune responses in untreated cases of leprosy. *Clin Exp Imm*, 1972; **12:** 195–203.

[48] Bullock WE. Studies of immune mechanisms in leprosy: 1. Depression of delayed allergic responses to skin test antigens. *N Engl J Med*, 1968; **278:** 298–304.

[49] Turk JL, Waters MFR. Cell-mediated immunity in patients with leprosy. *Lancet*, 1969; **2:** 243–246.

[50] Mehra VL, Talwar GP, Balakrishnan K, Bhutani LK. Influence of chemotherapy and serum factors on the mitogenic response of peripheral leucocytes of leprosy patients to phytohemagglutinin. *Clin Exp Imm*, 1972; **12:** 205–213.

[51] Nath I, Curtis J, Bhutani LK, Talwar GP. Reproduction of a subpopulation of T lymphocytes in lepromatous leprosy. *Clin Exp Imm*, 1974; **18:** 81–87.

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# Problems encountered in treating one leprosy patient in a developing country: a case report

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*Summary* We describe multiple problems encountered in the management of 1 patient suffering from lepromatous leprosy in a developing country, and these include Type II lepra reaction, intercurrent infection, shortage of experienced colleagues to consult, laboratory shortcomings, and side-effects of chemotherapy. It is postulated that the development of pustular and acneiform skin lesions in our patient is a new and previously unreported side-effect of dapsone.

## Case history

A 36-year-old Thai male had been treated for active lepromatous leprosy with dapsone for 1 year, and when first seen on 6 September 1983, he was receiving 100 mg/day. He had also been receiving prednisolone 20 mg/day for almost the same period of time because of small skin eruptions in the form of papules and pustules, which he referred to as 'reaction'; he was unable to give exact details regarding the duration, etc., of these eruptions, but he could recollect that they appeared within a few days of starting dapsone and persisted almost continuously since then. There was associated burning sensation over the affected skin areas, and he also complained of frequent fever and myalgia. He was sent to this hospital because of the recent appearance of large erythematous painful nodules and necrotizing lesions associated with severe systemic symptoms in addition to the earlier papules and pustules.

## On examination

The patient was febrile and looked ill. Cushingoid features including central obesity and 'mooning' of face were present. There were few large erythematous tender nodules, some of them ulcerating, suggestive of ENL. The face as well as

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both upper extremities were covered with numerous small (1–2 mm) papules and pustules, distributed bilaterally and symmetrically. Upper portions of chest and back also had similar lesions, but less in number, and most of them resembled acne; other parts of the body had an insignificant number of lesions. The patient looked moderately anaemic. There was no oedema of extremities. There was generalized lymphadenopathy, but the nodes in the left axilla were relatively very large and matted as well as tender. Bilateral epididymo-orchitis was present. There were no clinical abnormalities in heart, lungs or abdomen, and his urine was normal. Chest X-ray appeared normal. BI of smears was 4+.

## Treatment

Dapsone 100 mg/day was continued, and in addition he received clofazimine (Lamprene) 300 mg/day, thalidomide 300 mg/day, analgesics and hematinics. Prednisolone 20 mg/day was continued, but was tapered off over the next 4 weeks.

## Progress

The ENL and epididymo-orchitis subsided well within the next 2 weeks, but the small skin eruptions persisted, together with a continuous low-grade fever. By this time it was observed that these papules and pustules appeared in crops, individual lesions lasting 2 or 3 days, then subsided leaving hyperpigmented areas but no crusting or scarring. A few episodes of epistaxis occurred during his first few months in hospital.

In the 5th week after admission, when the patient was off prednisolone and thalidomide for a week, there was a recurrence of epididymo-orchitis, but ENL was absent. In addition he developed pain and tenderness involving the muscles of both thighs, and admitted having experienced similar episodes over the previous few months. We had observed, on admission, that there was moderate wasting of some thigh muscles, and he had a clumsy gait, but these findings were attributed to be part of a cushingoid syndrome secondary to prednisolone. Prednisolone was re-started with a dose of 30 mg/day, and later was gradually tapered off. It was observed at this time that the fever, skin eruptions and muscle symptoms disappeared, along with signs of epididymo-orchitis, whenever the patient was on the larger doses of prednisolone, and as treatment progressed it was noted on many occasions that skin lesions and muscle symptoms reappeared whenever prednisolone was reduced to less than 20 mg/day. On these grounds we ruled out the possibility of steroid acne and of steroid myopathy.

Lymph node biopsy (left axilla) in the 8th week after admission revealed changes of tuberculosis adenitis, so a 3-months course of anti-tuberculosis treatment was given consisting of rifampicin 600 mg/day and 1 tablet of IT/day

(each tablet consisting of isoniazid 300 mg and thiacetazone 150 mg). The tuberculous lymph nodes subsided, but the pustular and acneiform skin lesions persisted. Pus from the lesions showed no growth on culture and VDRL was negative.

After 9 months of hospital treatment his condition was very pathetic, with pustules covering his face, upper extremities, and upper back, with very painful and tender thigh muscles which were remarkably wasted, causing a weak and clumsy gait, and continuous fever. There was no involvement of calf muscles, nor any sign of foot drop. Tendon reflexes were equivocal. At this time he was on dapsone 100 mg/day, clofazimine 100 mg/day, and hematinics. He had not received prednisolone for a few weeks. Because of the possibility that his skin lesions represented a hypersensitivity to dapsone, this drug was stopped, but clofazimine and hematinics were continued. Prednisolone was re-started in a dosage of 30 mg/day. Within 2 weeks of stopping dapsone, remarkable improvement was noticed. There was no flaring up when the dosage of prednisolone was reduced, and in the 5th week while on prednisolone 10 mg/day, only an occasional pustule could be seen. It was also observed that on exposure to sunlight there was exaggeration of lesions associated with burning sensation.

Two months after stopping dapsone the patient was completely off prednisolone and was free from skin lesions. He was not febrile and feeling well, his gait had improved, and there was no pain or tenderness in thigh muscles, although wasting was unchanged. He was now given a trial dose of dapsone 100 mg. Five or 6 hours later he was febrile and complained of pain and burning sensation all over the body, but there were no skin lesions. Next morning, after about 20 hours,

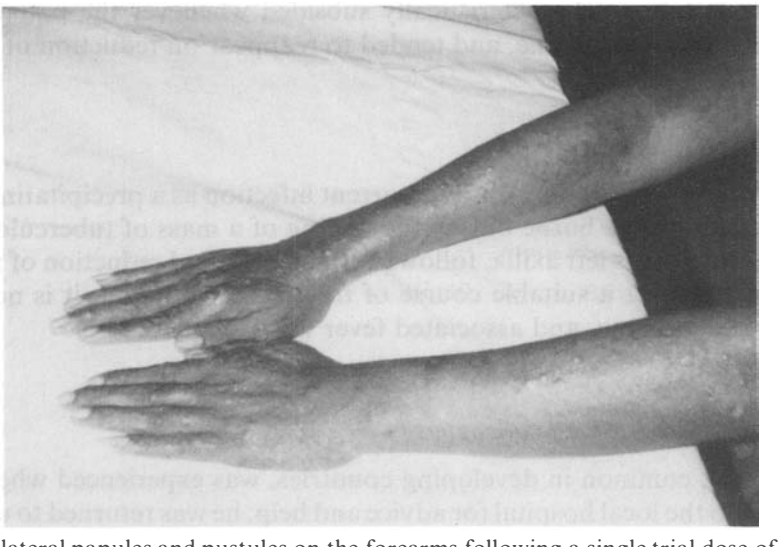

**Figure 1.** Bilateral papules and pustules on the forearms following a single trial dose of dapsone.

there were numerous papules associated with severe itching and burning, and few pustules; lesions were mostly on face, upper extremities (Figure 1) and upper back. It was interesting to note that on intentional exposure to sun, there were fresh lesions and exaggeration of itching and burning over the involved areas. One more dose of dapsone was given on the next day, and many new papules and pustules appeared. No more dapsone was given and these symptoms subsided within 1 week after a short course of prednisolone. Thereafter he had no significant complaints and was discharged, one year after admission, on clofazimine 100 mg/day. Two months later, at follow-up examination, he was feeling well, and appeared healthy and strong. Although his thigh muscles remained thin, he had no muscle pain or weakness. Affected skin areas looked hyperpigmented, but there was no pitting or scarring. Skin smears contained granular bacilli.

## Discussion

This case emphasizes the multiplicity of problems which can be associated with the management of lepromatous leprosy in a developing country, and these can be described as follows:

### 1 *Type II reaction*

Manifestations of Type II reaction included bouts of ENL, sometimes becoming necrotic, moderate anaemia, epididymo-orchitis, myositis, epistaxis, and fever. These manifestations characteristically subsided whenever the patient was on higher doses of prednisolone, and tended to reappear on reduction of dosage to less than 20 mg/day.

### 2 *Intercurrent infection*

The importance of searching for intercurrent infection as a precipitating cause of Type II reaction[1] was borne out by the finding of a mass of tuberculous lymph nodes in the patient's left axilla, followed by an all-round reduction of reactional manifestations after a suitable course of treatment. However, it is noteworthy that the pustuloderma, and associated fever were unaffected.

### 3 *Shortage of experienced colleagues*

This problem, common in developing countries, was experienced when we sent our patient to the local hospital for advice and help; he was returned to us with the message that he had been given treatment for syphilis!

4 *Laboratory shortcomings*

Another handicap when treating leprosy in a developing country is that requests for laboratory investigations may go unreported, or, if reports are received, they may be unreliable. We sent pus from the enlarged lymph nodes for AFB culture, and the sputum was examined at the hospital, but no reports were received. Our patient's Hb was reported to be 4·0 g % on the first occasion, and 4·5 g % on the second, results which we refused to accept as the patient did not appear to be profoundly anaemic. On the 3rd occasion we were informed that the Hb was 13 g %. The report on lymph node biopsy carried the diagnosis of 'lepromatous leprosy' in spite of the presence of 'masses of epithelioid cells, so we drew our own conclusions as to the true diagnosis of tuberculosis. It was because of laboratory unreliability that we omitted investigations such as differential white cell counts and liver function tests.

5 *Side-effects of Chemotherapy*

(a) *Prednisolone.* Our patient had signs of Cushingoid syndrome when first seen with moon face and central obesity.

(b) *Dapsone.* We propose that the pustuloderma was part of a hypersensitivity reaction to dapsone; not only was there associated fever and generalized lymphadenopathy, but there was a history of onset of symptoms a few days after commencing treatment with dapsone. Furthermore, there was a good response to prednisolone and to withdrawal of dapsone. Pustuloderma reappeared following a single trial dose of dapsone. These circumstantial evidences support a direct association between the drug and the skin manifestations. Drug reactions have a remarkable ability to mimic other diseases. They may take the form of vascular, eczematous, follicular, ulcerating, vegetating, gangrenous, furunculoid, carbunculoid, as well as pustular lesions.[2] Hypersensitivity to drugs such as sulphonamides, iodides and bromides, is known to be among the non-infectious causes of pustular skin eruptions,[3] and comparable cases have been reported with chloramphenicol, piperazine, pyrimethamine and frusemide.[4] A recent report has incriminated carbamazepine,[5] and the authors suggest that pustuloderma can be induced by a drug-induced toxic erythema which has progressed to erythroderma, the inflammation of the skin being so intense that toxic pustulation occurs. Although a number of skin complications may occur as part of a hypersensitivity reaction to dapsone[6,7]—exanthematous skin eruption,[8,9] exfoliative dermatitis,[10] toxic epidermal necrolysis,[11] and Stevens-Johnson syndrome,[12]—pustular and acneiform skin eruptions have not been described previously, although there is a report of a patient who developed papular and pustular skin lesions, later followed by exfoliative dermatitis.[13]

In the differential diagnosis of our patient's skin eruptions we must consider necrotic ENL (erythema necroticans), steroid acne, papulonecrotic tuberculids, and pustular syphilids.

Necrotic ENL can be excluded because as mentioned earlier, the larger lesions suggestive of ENL as well as the epididymo-orchitis subsided completely while on treatment with prednisolone, thalidomide and high doses of clofazimine, whereas the small eruptions kept recurring even when the patient was on high doses of clofazimine for over 3 months, and when the lesions subsided with stoppage of dapsone, the patient was only on 100 mg/day; moreover, these lesions showed no ulceration or crusting as do necrotizing ENL. Steroid acne can be ruled out as the lesions subsided with higher doses of prednisolone, and *vice versa*. Papulonecrotic tuberculids were excluded when the lesions failed to respond to 3 months of anti-tuberculosis treatment; moreover, tuberculid lesions are papules and nodules which undergo central necrosis, and heal spontaneously with pitted scarring.[14] Normally, typical pustules are absent. Pustular syphilids are mainly on the trunk, forehead and extremities; pustules arise from red infiltrated bases, they involute slowly, resulting in a rather persistent crust-covered superficial ulceration.[15] In our patient there was no ulceration, crusting or scarring, VDRL was nonreactive, and there was no response to anti-syphilis treatment.

The exaggeration of the cutaneous manifestations on exposure to sunlight could be due to a possible photoallergic and phototoxic effect of dapsone, since such adverse effects are known to be caused by many drugs including sulphonamides.[16]

## Acknowledgment

We are very grateful to Dr W H Jopling for his kind help, assurance and support, especially for revising the typescript and providing additional reference materials. Our grateful thanks are due to Dr K Ramanujam for supplying reference materials. Finally we thank our patient for bearing with us during the long period taken to establish the diagnosis.

## References

[1] Jopling WH. *Handbook of Leprosy*, 3rd edn. Management of lepra reaction. London: William Heinemann Medical Books Ltd, 1984, p. 97.

[2] Domonkos AN, Arnold HL, Odom RB. *Andrews' Diseases of the skin* P, *Clinical Dermatology*, 7th edn. Drug reactions. Tokyo: W B Saunders Company, Igaku-Shoin/Saunders, 1982, p. 137.

[3] Fitzpatrick TB, Haynes HA. *Harrison's Principles of Internal Medicine*, 9th edn. Skin lesions of general medical significance. Isselbacher-Adams-Braunwald-Petersdorf-Wilson. Tokyo: McGraw-Hill Kogakusha Ltd, 1980, p. 241.

[4] Macmillan AL. Generalised pustular Drug Rash. *Dermatologica*, 1973; **146:** 285–91.

[5] Staughton RCL, Harper JI, Rowland CME, McMichen H. Toxic Pustulo-derma—a new entity?. *J Roy Soc of Med*, Supplement No. 4, 1984; **77:** 6–8.

[6] Bryceson A, Pfaltzgraff RE. *Leprosy*, 2nd edn. Side effects of dapsone. Longman Inc. N.Y and associated companies, 1979, p. 45.

[7] Jopling WH. Side effects of antileprosy drugs in common use. *Lepr Rev*, 1983; **54:** 261–70 and 1985; **56:** 61–70.

[8] Kader Naina Mohamed. Hypersensitivity reaction to dapsone: report from Malaysia. *Lepr Rev*, 1984; **55:** 385–9.

[9] Tomecki KJ, Catalano CJ. Dapsone Hypersensitivity. *Arch Dermatol*, 1981; **117:** 38–9.

[10] Sardari Lal, Garg BR. Sulfone induced exfoliative dermatitis and hepatitis. *Lepr India*, 1980; **52:** 302–5.

[11] Katoch K, Ramu G, Ramanathan U. Toxic epidermal necrolysis (Lyell syndrome): a case report. *Lepr India*, 1983; **55:** 133–5.

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

[13] Ramanujam K, Ramu G. Toxic reactions to parent sulfone: report of four cases. *Lepr India*, 1968; **40:** 1.

[14] Domonkos AN, Arnold HL, Odom RB. *Andrews' Diseases of the skin, Clinical Dermatology*, 7th edn. Mycobacterial diseases. Tokyo: W B Saunders Company, Igaku-Shoin/Saunders, 1982, p. 415.

[15] Domonkos AN, Arnold HL, Odom RB. *Andrews' Diseases of the skin, Clinical Dermatology*, 7th edn. Intermediate and late secondary syphilis. Tokyo: W B Saunders Company, Igaku-Shoin/Saunders, 1982, p. 453.

[16] Madhukar A, Pathak, Fitzpatrick TB, Parrish JA. *Harrison's Principles of Internal Medicine*, 9th edn. Photosensitivity and other reactions to light. Isselbacher-Adams-Petersdorf-Wilson. Tokyo: McGraw-Hill Kogakusha Ltd, 1980, p. 255–62.

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*SPECIAL ARTICLE*

# Field detection of early neuritis in leprosy

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*Summary* Five field tests for detecting early damage to peripheral mixed nerve trunks in leprosy, are described. The regular monthly use of these tests will assist in reducing deformity. The whole set can be administered in less than ten seconds.

Neuritis in leprosy is frequently the precursor of irreversible sensory and motor loss. But, if the condition is detected early enough, deformity can be averted.

Unfortunately the term 'Neuritis' is usually associated with pain or tenderness. Srinivasan[3] has pointed out that in his study, 47 out of 58 patients (81%) gave no significant history of pain or tenderness in the affected nerves. This is also the experience of two other workers.[1,2]

It is therefore not sufficient to be only on the look-out for painful tender nerves. One of the most reliable signs of early neuritis is some degree of loss of function.

It is not necessary to have a detailed knowledge of the anatomy of the extremities, in order to detect early weakness of muscles, and correctly attribute this to the particular nerve involved.

It is not possible to spend a lot of time grading muscles on a quantitative scale in the field. There is not enough time for any of the field clinic staff to do this.

Therefore a set of easy tests have been devised which aims at revealing early weakness of groups of muscles.

There are only six mixed nerve trunks commonly affected in leprosy. To reveal early weakness in any of these, on either side, using the following tests, will take less than 10 seconds. When weakness is suspected the field worker must refer the patient immediately to the referral centre for detailed motor and sensory evaluation of nerve function, and early treatment with steroids, if the muscle weakness is confirmed.

Test 1 *Facial nerves*

The patient is asked to close both eyes (Figure 1). Any delayed or incomplete closure is suggestive of facial nerve involvement.

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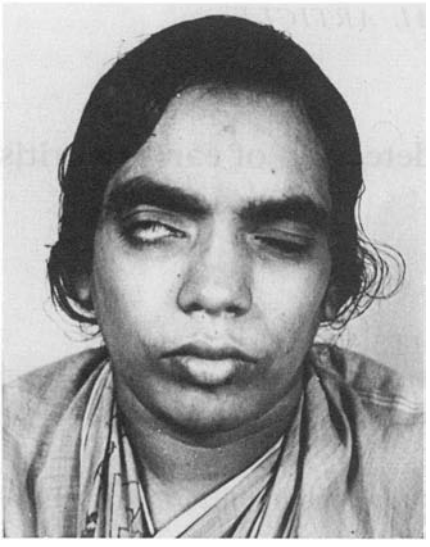


**Figure 1.** Patient with one eye lagophthalmos attempting to close both eyes. Note right eye paresis.

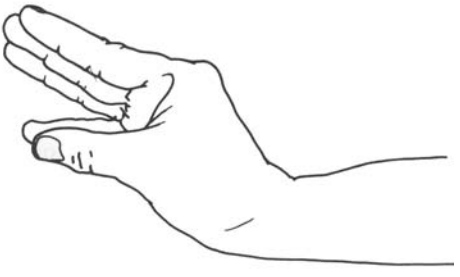
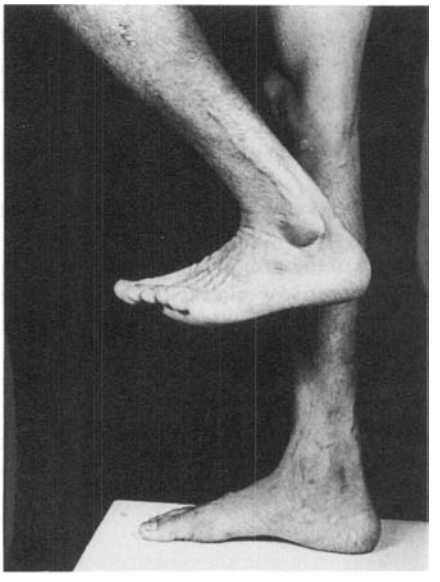


**Figure 2.** The Indian Classical dance pose which tests all three nerves of the forearm and hand. Dorsiflexion of wrist, radial nerve; extension of fingers, ulnar nerve; and abduction of thumb, median nerve.

**Figure 3.** Diagrammatic representation of the ulna–median radial gesture viewed from the radial side.



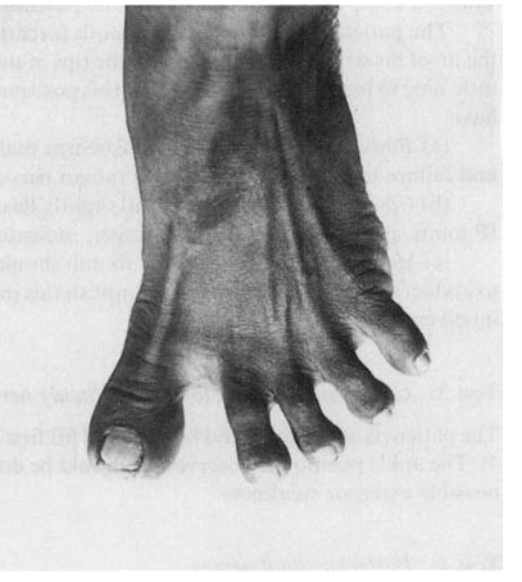


**Figure 4.** Test for lateral popliteal nerve paralysis. Note ankle and toe dorsiflexion.

**Figure 5.** Spreading of toes, test for intrinsic muscles of the foot—posterial tibial nerve.

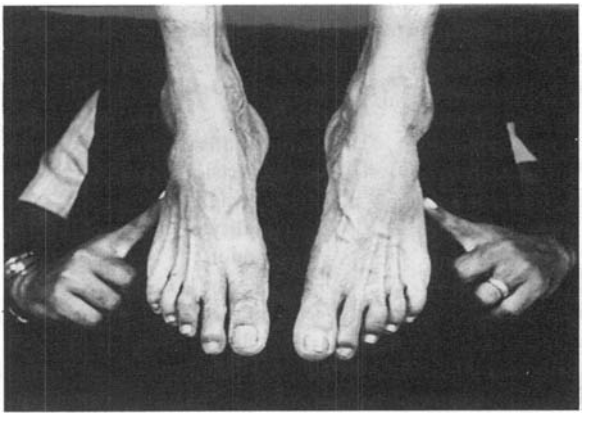


**Figure 6.** The sensory test for posterial tibial nerve paralysis.

Test 2 *Ulna median and radial nerves*

This is a composite test achieved in one position (Figure 2).

The patient is asked to pronate both forearms, raise both wrists, extend all fingers and touch the tip of his straight little finger with the tips of the thumbs of the same hand (Figure 3). It takes very little time to teach an illiterate patient this position. Analysing this in terms of the nerves involved we have:

(a) *Radial nerve.* The pronated forearm makes the wrist extension an antigravity movement, and failure to achieve this indicates radian nerve involvement.

(b) *Ulna nerve.* The fingers are all slightly flexed at the MP joints and failure to straighten all the IP joints, particularly in the little finger, indicates weakness of ulna supplied muscles.

(c) *Median nerve.* The tip of the thumb should touch the tip of the straight little finger. Inability to abduct and flex the thumb to accomplish this indicates thenar muscle weakness and median nerve involvement.

Test 3 *Common peroneal (lateral popliteal) nerves*

The patient is asked to extend his toes and lift first one and then the other foot off the ground (Figure 4). The ankle position is observed. It should be dorsiflexed. Inability to dorsiflex the ankle indicates possible extensor weakness.

Test 4 *Posterior tibial nerves*

This is the only one which may present some difficulty. The patient is asked to remove his slippers and spread his toes (Figure 5). If he cannot do that (and some normal persons especially in a shoe-wearing population have difficulty), then the observer may gently stroke the lateral border of both feet together (Figure 6) and ask 'Do you feel this normally and the same on each side?'. Weakness of

**Table 1.** Below is a summary of Tests 1–4

| Test | Instruction to patients | Observation | Nerve |
|---|---|---|---|
| 1 | 'Shut your eyes' | Rate and completeness of closure | Facial |
| 2 | 'Do this' (demonstrate the position) | 1 Dorsiflexion of wrist | Radial |
| | | 2 Extension of fingers, especially little finger | Ulnar |
| | | 3 Ability of thumb to abduct | Medial |
| 3 | 'Lift your foot' . . . . . 'Now the other foot' | Ankle and toe dorsiflexion | Lat. popliteal |
| 4 | 'Spread your toes' | Any flickers of toe separation or metatarso phalangeal flexion | Post. tibial |
| | *or* | | |
| | Touch both lateral borders of feet with a light touch | Any difference in sensory appreciation | |

the intrinsic muscles of the foot predisposes to forefoot ulceration due to undue prominence of the metatarsal heads on the plantar surface.

Even a busy field worker can afford the 10 seconds it takes to carry out these tests.

It is important that he should apply these tests to patients who have had no obvious nerve damage, especially to multiple lesion cases of borderline leprosy.

A word to the doctor in the referral centre. Never discourage or ridicule your field worker if he refers a case who, on detailed examination, turns out not to have any nerve damage. The early detection of nerve damage is essential if we are to prevent deformity. Early detection depends on early suspicion by the person in the team who sees the patient first and most regularly. Encourage him!

**Acknowledgments**

The author acknowledges with thanks the assistance of several of his patients and staff in modelling the illustrations, to Mr Sanjay Agrawal and Mr Ramadoss for the photographs and Miss Shanthi Sivaprakasam for typing the manuscript.

**References**

[1] Fritschi EP. *Reconstructive Surgery in Leprosy*. John Wright and Sons, p. 11, 1971.

[2] Ross FW. Neuritis. In *A Manual of Leprosy*, 3rd edn, Thangaraj RH, p. 170, The Leprosy Mission, New Delhi, 1983.

[3] Srinivasan H, Rao KS, Shanmugam N. Steroid Therapy in Recent "Quiet Nerve Paralysis". *Lepr India*, 1982; **54:** 412–9.

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*SPECIAL ARTICLE*

# The 'Mozlep' System: a renewed proposal for a combined clinico-epidemiological follow-up of the leprosy patient

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The 'Mozlep' System originated in Mozambique (hence the name) in 1983, at the time of the start of the National Leprosy Control Programme. The aim was to implement locally the OMSLEP System,[1] trying at the same time to reduce to a minimum the number of forms necessary for a correct and complete follow-up of the patient, not only on epidemiological but also on clinical grounds. The goal of the 'Mozlep' System was therefore to supply something simple enough to fulfil the OMSLEP requirements and comprehensive enough to collect all the essential information as compactly as possible.

Apart from the inevitable administrative forms, the routine papers for the leprosy worker are basically two: The Clinical File (A Pasta) and the Clinico-epidemiological Individual Form (Ficha Individual). These are to be the subject of the present paper.

The Clinical File consists of a three-page file.* On the front page the usual headings identify the patient as a member of the community: name, surname, sex, tribe, date and place of birth and so on. At the bottom there is a section devised to follow-up the patient during his/her transfers.

At the back of the first page four anamnestic sections of records: the first for reactions and their characteristics (date, type, duration, treatment and outcome); the second for any hospitalizations, also with date, duration, diagnosis and outcome (each hospital has in addition its own recording forms); the third only for specific surgical treatments and application of prostheses; and lastly the fourth, with the date and description of up to four biopsies. Finally, on the third page there is a full description of the WHO classification of disabilities and disability grading,[2] with room for up to 10 different evaluations of the hands, feet and eyes, both right and left.

The Clinico-epidemiological Individual Form (Ficha Individual) consists of a double-sided form, the front of which repeats the OMSLEP IF with only minor changes. As in the OMSLEP IF, we find three rows of boxes: the upper one for the first examination at detection, the other two, identical to each other, for the follow-ups. The numbers written on top of the boxes are exactly the same as in the OMSLEP system, so that there is no problem in filling in the Detection Form (DF) and the Annual Statistics Form (ASF).

In box no. 5, first row, we added the age on onset, when known, for retrospective epidemiological studies. In box no. 6, the bacteriological status was modified, replacing globi, AFB and SB with BI and MI because this is current practice in Mozambique.

* This and all the other forms referred to are in Portuguese and available from the author: Via A. Vespucci 26/3, 30173, Mestre, Venice, Italy.

0305-7518/87/058178+04 $01.00  

Furthermore, a 'box A' was added after box no. 9, due to the local situation: very many of the patients known at the time of the Portuguese Administration had disappeared in 1983 and it seemed wise to know, as far as possible, at the time of registration in the new National Programme, how many of the supposed 'new patients' were already included in the old one. So a square was introduced for 'old case' (caso antigo), one for their clinical status and one for the presence or absence of reactions at the moment of the second registration.

In the other two rows, boxes 13 and 23 were modified as for box no. 6; in boxes 15 and 25 the attendance for treatment was expressed in terms of percentage: less than 50%, from 50 to 75%, more than 75% (with the present MDT, this should be probably reformulated); and in boxes 16 and 26 the name of the leprosy reactions were introduced in detail.

Now, the new concept is that *only two of these rows should be filled in, and at six-month intervals.* For the new patient (i.e. first form = page no. 1, top left-hand corner) row no. 2, for instance, will remain blank whilst, for the next ones, row no. 1 will of course be left behind. The reason for that is shown on the back page of the form, which is probably the most interesting of the whole system (Figure 1).

It collects virtually all the essential clinical information of the leprosy patient. It consists of two identical halves to be also filled in at six-monthly intervals. A gap of six months was chosen because it allows us to use one form for the first semester and *then a single form altogether per year.* Being almost completely comprehensive, no other forms will be necessary (except that for contacts).

Each half is made of three sections. In the top section the front and the back of a human body are inscribed in a box, divided in turn into small squares, identified by numbers and capital letters,[3] for statistical purposes. Here the skin lesions should be drawn. On the right side, a couple of hands and feet are depicted with some marks indicating where sensation of the palms and soles should be tested, according to the method derived from ALERT Leprosy Control Programme.

In the middle section, there is a picture of a face for the graphical recording of its lesions. On the right side are the main clinical features of a leprosy lesion, with three possible answers each arranged in such a way that tuberculoid features are towards the left, lepromatous the right.

The third section concerns the nerves. The clinical assessment for the most important of them: facial, great auricular, ulnar, median, radial, lateral-popliteal and posterior tibial, according to a number of characteristics: normal, enlarged, hard, nodular, tender, paralytic. Moreover, the presence or absence of corneal sensitivity and a simplified Voluntary Muscle Testing (VMT) are included, again according to the ALERT Leprosy Field Programme.

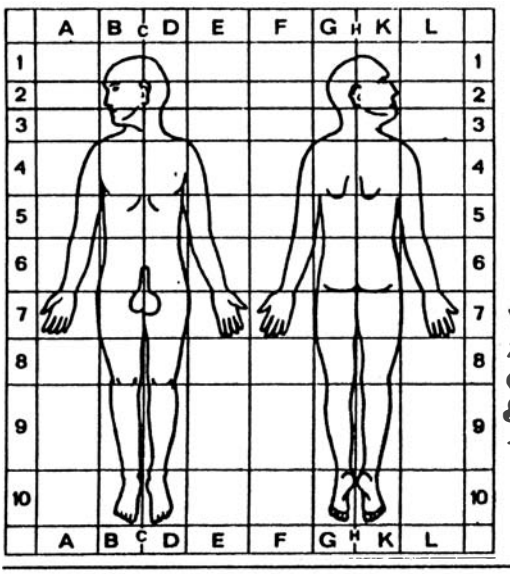
Lastly the Ellis test, derived from Zimbabwe; a simple test to assess the presence of a subclinical neuritis in the limbs (see *Leprosy Review*, **58,** 00 1987).

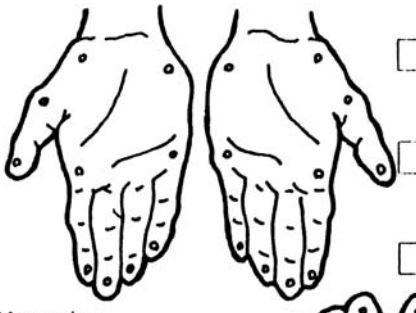
**Comment**

I think there is evidence that the Mozlep System was designed to help both the clinician in the field and the epidemiologist at his desk. For the leprologist engaged in the field, in fact, it has the same function as the clinical file for the doctor in a hospital ward. Furthermore it should be valuable for the follow-up of the leprosy patient since it has been designed to record all really relevant data; it reduces to a minimum the number of documents and records; it is not in contrast with the OMSLEP System, since the same baselines are followed and the same information requested. It could however be argued that the system is not so simple as to please everybody. This may be true and it has to be recognized that its effective use calls for some kind of general as well as specific knowledge.

The Mozlep system has been devised for a leprosy supervisor, or a doctor. This does not mean that we should exclude unqualified staff from participation, but it would be unrealistic to expect from them what they have neither the knowledge nor the time to do.

Until training can be extended and improved in Mozambique for the more junior grades of leprosy worker, it is probably wise to limit the amount of information which has to be recorded and



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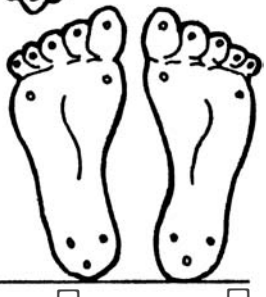

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| PLACAS | :AUSENTES | ☐ | PRESENTES | ☐ | LEVES | ☐ |
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| TRANSPIRAÇÃO | :AUSENTE | ☐ | DIMINUIDA | ☐ | PRESENTE | ☐ |
| PERDA DE SENSIBILIDADE | :MARCADA | ☐ | MODERADA | ☐ | AUSENTE | ☐ |
| ALOPECIA | :PRESENTE | ☐ | LIGEIRA | ☐ | AUSENTE | ☐ |
| BORDO | :BEM DEF | ☐ | DERRAM. | ☐ | MAL DEF | ☐ |
| CURA CENTRAL | :MARCADA | ☐ | LEVE | ☐ | AUSENTE | ☐ |

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SENSIBILIDADE CORNEAL

PRESENTE ☐ AUSENTE ☐

OUTRAS OBSERVAÇÕES: (TRATAMENTO, ETC.)

ASSINATURA:

ELLIS TEST

| | D | E |
|---|---|---|
| POS | ☐ | ☐ |
| NEG | ☐ | ☐ |

**Figure 1.** MOZLEP; form for comprehensive clinical information. (See *Editor's note* overleaf.)

analysed. It is hoped that the System described here will be of practical value to the further development of the National Leprosy Control Programme.

**Acknowledgments**

To the Italian Leprosy Relief Association, 'Amici di Raoul Follereau', Bologna, Italy, who sponsored the work, and to the 'Studio Pubblicitario Busetto' Mestre-Venezia, Italy, who provided technical assistance with the production of the Mozlep forms.

**References**

[1] OMSLEP. Recording and reporting system for leprosy patients. Lechat MF, Misson CB, Walter J. Catholic University of Louvain, Brussels.
[2] WHO. *A guide to leprosy control*, 1980.
[3] Boerrigter, G. Grid system and body diagram for leprosy. *Lepr Rev*, 1983; **54:** 115.

*Editor's note.* The author kindly supplied all the forms referred to in the text, but, partly because of shortage of space and partly because they are in Portuguese, we print only the above, which is the most important.

Note that Figure 1 is one half of the entire form (the left half). The entire form has a duplicate right half. Reading from above downwards, the words under the hands mean—sensitive, insensitive, scar, wound or ulcer, shortening or mutilation and clawing. In the middle section, the titles from above downwards mean—number of lesions, symmetry, nodules, plaques, hypopigmentation, sweating, loss of sensation, hair loss, border, central healing.

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*SPECIAL ARTICLE*

# Clinical, bacteriological and histopathological assessment of multibacillary leprosy cases after 1 and 2 years multidrug therapy. Preliminary communication*

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Accepted for publication 2 October 1986

*Summary* Seventy-three multibacillary leprosy patients in Bombay who had completed 12 and 24 monthly doses of multidrug therapy (MDT) were subjected to clinical, bacteriological and histopathological assessment. Only one in 17 of the 12 dose group with initial Bacterial Index (BI) $\geq 2$ was rendered smear negative. This increased to more than 50% in the 24 dose group with the same BI. A number of discrepancies were noted in the correlation between clinical, bacteriological and histopathological findings in treated cases in both the 12 and the 24 month group and the possible reasons are discussed. This report is preliminary and long-term studies on a larger scale are clearly needed for more accurate assessment, but the data so far available suggest that considerable emphasis should be given to the BI, as the least subjective test, in deciding when to stop chemotherapy.

## Introduction

The Bombay Leprosy Project began to use multidrug therapy routinely for the treatment of multibacillary leprosy following the recommendations of the World Health Organization in 1982.[1] The Indian Association of Leprologists (IAL) made similar recommendations[2] but the drug regimens differed slightly.

In view of the importance of information pertaining to clinical, bacteriological and especially histopathological changes after different durations of multidrug therapy (MDT), a preliminary assessment of patients who had completed one and two years' treatment (12 and 24 monthly doses) was carried out under urban conditions, which have already been described.[3]

* This study was carried out as part of an elective period supported by LEPRA.
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## Material and methods

The Bombay Leprosy Project (BLP) is a field-based control programme run largely by trained paramedical workers, with limited facilities available for advanced laboratory research work.

A total of 73 multibacillary (smear positive) cases were selected for the study, 28 of whom had previously received dapsone monotherapy, the remainder having had no previous treatment. Thirty were living in leprosy colonies on the outskirts of Bombay. The rest attended their nearest BLP clinics in a hospital or urban health centre.

A period of 7 weeks was spent assessing patients who had just completed 12 or 24 monthly doses of MDT. Most of these patients received the regimen recommended by the IAL, i.e. an initial course of 21 days continuous rifampicin was administered under supervision. However, patients who had a poor record of compliance or who attended clinics with inadequate facilities were given the usual WHO drug regimen (Table 1).

### CLINICAL ASSESSMENT

A clinical assessment of each patient was made to assess the activity of the disease. This information was used to classify each patient's condition after MDT as 'active', 'regressing' or 'inactive' on purely clinical grounds. This was based on standard criteria for assessing the activity of the disease.[4] Clinical 'inactivity' is defined as absence of signs of activity in the skin (no new lesions, extension of old lesions, erythema, infiltration, non-traumatic ulceration or persistence of nodules) and absence of activity in neural lesions (nerve tenderness or progression of anaesthesia or muscle paralysis).

This assessment was compared with the initial clinical status report available in the patient's records.

### BACTERIOLOGICAL ASSESSMENT

The slit-skin smears from a minimum of four sites were taken and compared with the initial (pretreatment) BI available from the patient's records in order to determine the extent of decline of the BI over the treatment period. All originally smear positive cases were considered for the study regardless of duration of disease or previous treatment.

### HISTOPATHOLOGICAL ASSESSMENT

The skin biopsy was taken using a standard 6-mm circular punch. The sample was preserved in buffered formalin and processed at the BLP laboratory. The slides were read by an independent

**Table 1.** Allocation of leprosy patients

| | Drug regimen | | |
|---|---|---|---|
| No. doses | WHO | IAL | Total |
| 12 | 7 | 15 | 22 |
| 24 | 14 | 37 | 51 |
| Total | 21 | 52 | 73 |

histopathologist and the reports classified as being consistent with 'active', 'regressing' or 'inactive' disease. The criteria used were based on descriptions by Ridley.[5]

Finally, the correlation between the clinical, histopathological and smear status of each patient was examined.

## Results and discussion

Of the 73 patients, 22 had completed 12 pulse doses and the rest had taken 24 doses.

### CLINICAL ASSESSMENT

Clinical assessment showed that only 2 cases became inactive and 4 were still showing clinical activity in the 12-dose group (Table 2(a)), whereas in the 24-dose group 14 became inactive and 8 were still showing activity (Table 2(b)). This assessment was done irrespective of smear status.

### BACTERIOLOGICAL ASSESSMENT

For bacteriological assessment patients were classified into 2 groups with BI $< 2$ and BI $\geqslant 2$. Only 1 in 17 of the 12 dose group with an initial BI of $\geqslant 2$ was rendered smear negative (Table 3(a)). This increased to more than 50% of patients in the 24 dose group with the same BI and 12 out of 13 (92%) with BI $< 2$ became smear negative after 24 doses (Table 3(b)). Smear conversion rate was faster in cases with BI $< 2$.

**Table 2**

(a) *12-dose group*

| Total no. of cases | Active | Regressing | Inactive |
|---|---|---|---|
| 22 | 4 | 16 | 2 |

(b) *24-dose group*

| Total no. of cases | Active | Regressing | Inactive |
|---|---|---|---|
| 51 | 8 | 29 | 14 |

**Table 3**

| | Before MDT | | | After MDT | | | | |
|---|---|---|---|---|---|---|---|---|
| BI | Total No. of cases | Cumulative BI | Mean BI | Cumulative BI | Mean BI | Mean change BI | Mean % change BI | Number negative |
| (a) 12 pulse dose group | | | | | | | | |
| $< 2$ | 5 | 6·05 | 1·21 | 1 | 0·2 | 1·01 | 86·7 | 4 |
| $\geqslant 2$ | 17 | 52·9 | 3·11 | 33·4 | 1·96 | 1·15 | 38·8 | 1 |
| (b) 24 pulse dose group | | | | | | | | |
| $< 2$ | 13 | 12·4 | 0·95 | 0·33 | 0·019 | 0·931 | 94·9 | 12 (92%) |
| $\geqslant 2$ | 38 | 125 | 3·29 | 36·6 | 0·962 | 2·33 | 73·8 | 20 (53%) |

**Table 4.** Number smear negative after MDT

| No. of doses | BI | No. of negative cases | No. of previous negative smears | | | No. with 3 negative smears and clinically inactive |
|---|---|---|---|---|---|---|
| | | | 0 | 1 | 2 | |
| 12 | <2 | 4 | 3 | 0 | 1 | 0 |
| | ⩾2 | 1 | 1 | 0 | 0 | 0 |
| 24 | <2 | 12 | 3 | 3 | 6 | 4 |
| | ⩾2 | 20 | 9 | 4 | 7 | 3 |
| Total | | 37 | 16 | 7 | 14 | 7 |

Thirteen patients in the 24-dose group had a total of 3 or more consecutive negative smears, though only half of these were also classified as having clinically inactive disease.

The criteria used by the Bombay Leprosy Project for discontinuation of multidrug therapy require that 3 consecutive sets of skin smears (from at least 4 sites at monthly intervals) are negative in addition to clinical inactivity. Therefore, only 7 (14%) patients out of 51 would stop treatment, but 6 others may be considered if the subjective nature of clinical assessment were taken into account.

Only one case in the 12-dose group had 3 consecutive negative smears.

*Histopathological Assessment*

A total of 60-skin biopsies were taken for histopathological assessment. The results are shown in Table 5 (a) and (b).

One case in the 12-dose group was histopathologically inactive while 18 (44%) patients were inactive after 24 doses with only 2 (5%) patients still active.

**Table 5**

| BI | Total no. of cases | Active | Regressing | Inactive |
|---|---|---|---|---|
| (a) 12-dose group | | | | |
| <2 | 5 | 4 | 1 | 0 |
| ⩾2 | 14 | 1 | 12 | 1 |
| Total | 19 | 5 (27%) | 13 | 1 (5%) |
| (b) 24-dose group | | | | |
| <2 | 12 | 1 | 3 | 8 |
| ⩾2 | 29 | 1 | 18 | 10 |
| Total | 41 | 2 (5%) | 21 | 18 (44%) |

However, only 2 of those found histologically inactive had 3 negative smears and neither of these had been classified as clinically inactive.

In the 24-dose group, out of 8 clinically active cases only 2 were showing activity in histopathology. The rest were showing histopathological regression.

Five (14%) out of 37 smear negative cases were showing histopathological activity.

## Comment

This was a field-based study with limited facilities and expertise. This undoubtedly accounts to a large extent for the poor correlation between the clinical, bacteriological and histopathological assessments.

However, most leprosy control programmes have to work under similar conditions and the various forms of assessment will be subject to the same observer error. Therefore, in view of the discrepancy between different methods of assessing disease activity, perhaps the main emphasis in the criteria for discontinuing therapy should be the bacterial index in smears which is the least subjective test.

Despite the limitations of this study we consider that these preliminary results are encouraging. Large numbers of multibacillary patients are rendered smear negative after 2 years of multidrug therapy.

Long-term follow-up studies on a larger scale are obviously required for a more accurate assessment of the efficacy of MDT. This would also allow estimates to be made of the number of patients relapsing during, and after stopping, drug therapy.

## Acknowledgments

We are grateful to the paramedical workers, especially Mr D D Naik of BLP and student volunteers Mr Raju Vartak of RRE Society of The Acworth Leprosy Hospital for their invaluable help in this study.

## References

[1] WHO Study Group. *Chemotherapy of Leprosy for Control Programmes.* Technical Report Series No. 675, 1982.

[2] Indian Association of leprologists (1982). Proceedings of the Consensus on treatment regimens in leprosy and problems of drug delivery. *Ind J Lepr*, 1984; 56–158.

[3] Ganapati, R, Revankar, CR, Gawade, PB. MDT for Multibacillary Leprosy—Experience in Bombay, 1984.

[4] WHO. A Guide to Leprosy Control, 26–27, 1980.

[5] Ridley, D. Skin Biopsy in Leprosy, Documenta-Geigy, Ciba-Geigy, Basel, 1977.

Proceedings of the 12th International Leprosy Congress, New Delhi, February 1984; 225.

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# Obituary

## **DAVID MOLESWORTH,** MD, OBE
1913–1986

Dr David Molesworth, OBE, who dedicated his life to the treatment of leprosy, died on December 15. He was 73.

Brownlow David Molesworth was born on February 10, 1913. He was educated at Emmanuel College, Cambridge, and studied medicine at the London Hospital. After qualifying in 1937, he was appointed medical officer to the Grenfell Mission, which worked to improve the health of eskimos. He spent the following year in Labrador working with them, in particular advising on dietary matters. But he spent most of his career in the tropics. In 1939 he joined the Colonial Medical Service and was sent to Singapore as general duty medical officer. But his work there was cut short with the Japanese invasion in 1942, and he spent the next three years in a PoW camp.

It was only by chance, while awaiting repatriation from Singapore, that he became interested in leprosy. He heard of a vacancy for an officer in charge of the leprosarium at Sungai Buluh, Malaysia. He got the job, and remained there for the next decade. On his arrival he found many patients near death from malnutrition, a sight that he never forgot. But the timing of his appointment to Sungai Buluh was auspicious. There were, on the one hand, several thousand severely ill and deformed patients, for whom there was no known treatment; on the other hand, recent tentative claims were made that such leprosy had responded favourably to a sulphone drug, dapsone. He pioneered the use of this, conducting successful programmes of mass treatment while never losing interest in individual patients.

In 1956 he went for two years to Geneva as adviser to the World Health Organization's leprosy section. From there he went to Ghana where he was director of the government's leprosy service at Elmina. His final post, in 1966, was as director of the British Leprosy Relief Association's control project in Malawi. He retired in 1979.

Molesworth was an extrovert personality with a "George the Fifth" beard. He was a good teacher, and his enthusiasm for his subject inspired his colleagues. He was also a keen ornithologist, especially knowledgeable about the bird life of Malawi.

His wife, Rosemary, whom he married in the late 1930s, survives him, together with their two sons and two daughters.



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After working in Malaya with people suffering from leprosy and as a consultant with WHO, Geneva, David Molesworth joined the Ghana Leprosy Service in 1959 to take charge of that Service. He was able to build on the relatively new concept of mobile treatment work until the whole of the country was covered. He also introduced reconstructive surgery at the Ankaful Leprosarium and, with his superb skill as a surgeon, many patients benifited from his work. With his knowledge of WHO and UNICEF he was able to procure much equipment and medical supplies for the Service which was to prove invaluable when economic stringency was affecting the country.

Early in 1966 David transferred from Ghana to Malaŵi to direct the Lepra Control Project which had been established in the south of the country. So successful was this Project that the Malaŵi Government asked Lepra to expand its work to cover the whole of Malaŵi and, under David's direction this was done. With far sighted planning the country was divided into regions and each region established mobile treatment work, in most cases supervised by a doctor with appropriate support facilities.

In addition, and due to the absence of a dermatologist in Malaŵi, David inaugurated a general skin clinic at the central hospital in Blantyre where patients were referred to him for advice and treatment. In this way David was able to make the fact of a leprosy treatment centre in the middle of Blantyre acceptable to the general public thus overcoming hostility to the Project when it was first mooted.

David was exceptional in all that he did. He was an expert ornithologist and an ardent angler. He took an active part in the Malaŵi Fauna Society. Photography was one of his delights.

He will be missed by many people and there are leprosy patients throughout the world who will be saddened by his death, for David's endearing characteristic was his genuine friendliness and concern for all he served. He inspired great confidence in his patients, whoever they were, and his name was always on their lips.

Those who worked with him have lost a very kind friend and counsellor.

J ELDON

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# Letter to the Editor

## SOME PROBLEMS ARISING FROM UNCERTAIN ELECTRICITY SUPPLY

Sir,

In this country, and indeed in most countries in the West, the public give little thought, if any, to problems which could arise from an unreliable electricity supply. It is usually required that electricity supply be maintained within the statutory limits of a very small percentage of the declared voltage and frequency. Alas, this is not so in most of the Third World and developing countries. The only problem we meet is when the supply is cut off, temporarily, due to overloading in severe winters, when some load sharing may be necessary at times of major breakdown of plant.

I met some of the problems first in Africa and later in India where failure of the supply is a daily expectation and it is surprising how the communities in these countries have learned to live with these conditions, to accept them as normal and so often without a word of complaint. It is now over 10 years ago that I met in India what was quite a new problem to me, namely, dangers arising not from cuts but from sustained periods of low voltage. I was staying with the Medical Superintendent of a large leprosy hospital in South India, when he, realizing that I was an electrical engineer, appealed to me for help, not in overcoming the problem of the supply but in protecting his equipment from damage. The first and obvious answer was to tackle the problem of the supply and that could be done by installing generating plant, preferably with automatic starting and switching so that when the mains electricity dropped in voltage (or rose) below (or above) pre-determined safe values, the auxiliary generator cut in. He accepted this but still wanted to know what protection could be given in situations where there was no auxiliary generator. First he explained what happened in low voltage and two main items seemed to be affected. First, all single-phase motor driven equipment including refrigerators, air conditioners and the like, suffered burn out of their motors resulting in total loss, long delays and high cost. He was concerned particularly about the problems in hospital laboratories where cultures, etc. were used in experiments and medicines kept cool and preserved for treatment. The other problem was minor in comparison, namely the rapid reduction in the life of fluorescent lighting tubes. The cause of failure was the same in both cases, and fluorescent tubes revert to starting conditions when the voltage drops, starting currents are much heavier than full normal running currents and hence burn out results. I made certain suggestions to him on the installation of simple overload current trips.

Electrically, the problem is very simple, all that is required is to insert in the circuit a device which either will cut off the supply when the current exceeds a safe value, or apply to the circuit an under or over voltage relay which will cut off the supply before the current rises dangerously. Three devices are listed below:

### A OVERCURRENT TRIPS

#### 1 *Thermal trips*

These consist simply of a bi-metallic strip with heater. They can be given a variety of characteristics from slow to quick operation, automatic or manual resetting. They are marketed as subminiature

circuit breakers at ratings from 0·5 to 5 amps, single hole mounting, dimensions (body) 28L, 19H, 11W (in mm). They cost £2 each and one would be needed for each piece of equipment to be protected.

2 *Thermal/Magnetic trips*

These are largely as above but with added advantages, including more rapid action on dangerous surges and auxiliary terminals for battery operated warning devices such as tell-tale light (showing on or off, or both) audible warning and timing. The medical superintendent insisted he would want to be warned that the equipment had been cut off, and if it occurred at night, for how many hours it had been off. These are rated from 0·5 to 10 amps, they measure L59, H40, W19 (mm) and cost £7 each. Again, one would be needed for each piece of apparatus to be protected. They have manual resetting only.

B UNDER OR OVER VOLTAGE RELAYS

Before describing them, may I point out that serious over-voltage does occur. Again the above medical superintendent told me they had often experienced the 230 voltage rising to 400 and staying there for a day!

These relays are electronic costing approximately £30 each, and are designed to measure the supply voltage and to interrupt the supply under, for example, the following conditions. (i) Trip out of the voltage falls from a normal 240 volts to 170 volts and stay out until it rises again to 185 volts and stays there, or above for a pre-determined safe period of say 2–3 minutes. The circuit would then close. (ii) Trip out of the voltage rises above 285 volts and stay out until the voltage falls to 270 volts or below and then close the circuit after 2 or 3 minutes. (iii) If required, automatic closure can be replaced by manual setting. (iv) Auxiliary contacts can be supplied as in A 2 above. (v) These are rated up to 30 amperes and can protect any number of devices on the same circuit up to the normal rating of 30 amperes. (vi) They come in plastic boxes, roughly $150 \times 90 \times 50$ mm.

So far, these comments have related to single phase AC circuits but 3-phase electron motor protection relays are available. The manufacturer's information sheet states that 'these relays make up a system of overload stalled current and phase failure protection that offer benefits over the conventional bi-metallic (thermal) or solenoid overload devices. These are too complicated for further details here but information is available.

The name of the young man who supplied me with the goods and most of this information is: Mr Derek Huff, Integrated Design Ltd, 201 Fulwell Park Avenue, Twickenham, Middx TW2 5HD. He will, I know, be happy to give any help needed and to supply equipment or name the suppliers as may be required.

*73 Delamere Road*
*Ealing, London W5 3JP*

J E RICHARDSON

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# Leprosy Control and Field Work

## Leprosy control in Burma; Annual Report, 1985

The Health Unit of OXFAM in Oxford has kindly sent a copy of the latest annual report from Burma. The introductory paragraph describes how, since the implementation of the Peoples Health Programme, all routine leprosy control activities have been integrated into the Basic Health Services in all 314 townships of the country. The 'special rifampicin treatment programme', conducted in all highly endemic areas since 1983, is carried out by Leprosy Control Teams. All registered leprosy patients throughout Burma receive domiciliary treatment with dapsone monotherapy, but in the highly endemic areas (Magwe, Mandalay, Sagaing, Pegu, Rangoon, Irrawady Divisions and Shan State), multibacillary cases are given rifampicin 1200 mg once a month for 6 consecutive months, followed by 1500 mg annually. Numerous tables give detailed information about prevalence, incidence, deformity rates, and numbers of cases on dapsone monotherapy, and on rifampicin. During 1985 6600 new cases were detected and the impression gained from this excellent report is that there is still a formidable pool of cases, many of them multibacillary, awaiting diagnosis and treatment. A contact for further information is: Dr Tin Myint, Department of Leprosy Control, Department of Health, Theibyn Road, Rangoon, Burma.

## A microscope in every village; the portable, plastic McArthur model

A user's handbook available from Eritrean Relief Association Public Health Programme, BCM Box 865, London WC1V 6XX, describes the development and intended use of this plastic version of the well-known McArthur portable microscope. The following is extracted from the preface:

The Eritrean Relief Association, a British Registered Charity, inaugurated an extensive public health programme in 1981 as part of its attempt to provide a framework for longer term development in its programme area, where the population have been afflicted by war for over 20 years and, for the last five years, by a severe drought. In May 1982 a decision was taken in the Eritrean Public Health Programme (EPHP) that a considerable input of microscopes and microscopy skills would be required in order to change disease patterns in the areas of Eritrea where the programme was operative. Since this involved approximately 200 villages at the time, a project for purchase of this number of microscopes was drawn up. A large number of instruments were reviewed, and the design made initially by Dr John McArthur in 1982 was chosen as the most suitable. The first commercially available instrument appeared in 1933, since which time it has been refined and added to. EPHP took responsibility for redesigning it in plastic.

The purchase price of 200 of these instruments covers the entire cost of establishing a production line, making a settlement with the designer and hiring a draftsman to redesign the instrument for mass production. Funding for this scheme was obtained by EPHP from ICCO, the Dutch Protestant inter-church development agency, co-financed by the Dutch government. By the end of 1983, the first 1000 sets of components had been produced. One year later, components for a further 10,000 sets were made.

This small handbook is intended for use in conjunction with a manual of techniques for specimen collection and preparation. Used in this context, it should go some way towards explaining the particular microscope design adopted for the 'Microscope in Every Village' project.

(We would welcome information from any area where this low-price, highly portable instrument has been tried out. Further enquiries to: Dr Neil Andersson at the above address.)

## Essential Drugs Monitor, WHO

The Essential Drugs Monitor is a newsletter produced and distributed by the WHO Action Programme on Essential Drugs and Vaccines. Since the Action Programme was launched in 1981, more than 80 countries have either drawn up essential drugs lists or started projects in support of primary health care, providing reliable essential drugs and vaccines which:

Meet people's common health needs; have significant therapeutic value; are acceptably safe; and offer satisfactory value for money. All correspondence should be addressed to the Editor, Essential Drugs Monitor, World Health Organization, CH-1211 Geneva 27, Switzerland.

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In Number 3, 1986, a particularly interesting item concerns the choice of injection equipment for the Expanded Programme of Immunisation; joint guidelines issued by WHO and UNICEF. Their opening paragraphs read: 'Since the possibility exists that unsterile needles and unsterile syringes can transmit not only LAV/HTLV-III (AIDS-related virus) but other infectious agents including hepatitis viruses, immunization programmes have the obligation to ensure that a sterile needle and a sterile syringe are used with each injection', (EPI Global Advisory Group, November 1985).

Countries which for many years have tolerated unsterile immunization and injection techniques are becoming increasingly aware of the risks they run.

## Guidelines on Treatment; National Leprosy Eradication Programme, India, 1985

We have received this excellent booklet from the Leprosy Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi 110011, India. It comprises operational guidelines on case detection, treatment, follow-up and reporting forms. Compared with the WHO recommendations ('*Chemotherapy of leprosy for control programmes*'; Report of a WHO Study Group; *Technical Report Series 675*, WHO, Geneva, 1982), the important differences in the Indian recommendations for MDT are as follows:

*1 Multibacillary patients.* There is an initial, supervised, 'intensive phase' of 14 days, during which drugs are given as follows (adult doses)—rifampicin 600 mg daily; clofazimine 100 mg daily; dapsone 100 mg daily. This is followed by a 'continuation phase', given for a period of at least 2 years, consisting of rifampicin 600 mg monthly, supervised; dapsone 100 mg daily, unsupervised; clofazimine 300 mg once monthly supervised and 50 mg daily unsupervised. (This phase is thus identical with the basic WHO regimen for multibacillary patients).
*2 Paucibacillary patients.* Under the heading of treatment for this group of patients (page 12), two choices are given: (a), dapsone monotherapy with 100 mg daily, self-administered (adult dose), to be continued until the patient is declared 'inactive'; and (b), multidrug treatment, using rifampicin 600 mg once monthly, supervised (adult dose) with dapsone 100 mg daily, self-administered; to be continued until 6 monthly doses have been administered. The concluding paragraphs in this section are as follows: 'Clinical inactivity cannot be achieved with chemotherapy for 6 months. The objective of short course chemotherapy is to render the patient free from viable bacilli and to initiate regression of lesions. Resolution of skin and nerve lesions will occur gradually, promoted by the high cell mediated immunity in this type of patient. It must also be appreciated that some lesions are partially or totally irreversible and may persist. Rarely, lesions of a trophic or degenerative nature may occur much later and should not be considered as evidence of activity.

Occasionally on completion of adequate treatment (6 supervised doses of rifampicin), the lesions may show no evidence of regression and, on the contrary, new lesions may appear. This is liable to occur especially in patients who are smear negative and have multiple lesions widely disseminated symmetrically or bilaterally. The diagnosis must then be carefully reviewed by a medical officer after detailed clinical and bacteriological examination for errors in classification. If the classification is correct, the treatment should be continued with rifampicin and dapsone in the same dosage for a further period of 6 months. If the patient was classified wrongly, the treatment should be changed to that recommended for multibacillary leprosy.'

Although perhaps not fundamental, there are nevertheless some important points of difference in the Indian recommendations for MDT, compared with those of WHO. These guidelines from Delhi should be studied in the original, particularly by those who believe that meaningful 'comparisons' between MDT programmes can be made by computer, or other means.

## AHRTAG: Low cost packaging of drugs for developing countries

Late in January 1987, a meeting was held in the offices of AHRTAG (Appropriate Health Resources and Technologies Action Group Ltd), 85 Marylebone High Street, London WIM 3DE, to discuss the production of various forms of container (packaging) for the issue of drugs to patients in developing countries.

Based on a pilot field test in Bangladesh, Mr Jon Vogler described the production and possible use of: 1, paper envelopes; 2, simple boxes made out of card; 3, small plastic pots, made from scrap plastic; 4, bottles or jars made locally from clay (i.e. pottery); and 5, paper tubes. Simple machinery has already been developed for pressing out the plastic and for cutting card into appropriate shapes for small boxes. He has contacted the WHO Essential Drugs Programme in Geneva, who have encouraged further efforts for the better presentation of drugs in developing country situations. Discussion included the need to train and re-train pharmacists, so that any containers developed are used to best advantage. It is now planned to extend these pilot studies to several other countries, and also to consider the production of simple stamping machines in the UK, and their export through ECHO and similar agencies. This initiative has direct relevance to the use of dapsone, clofazimine and rifampicin for leprosy, especially where these drugs are issued 'loose', i.e. not as a fixed combination or in a blister (calendar) pack. Further enquiries to Mr Ken Ritchie, Director, AHRTAG, at the address above.

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# Teaching Materials and Services

## Orientation in Leprosy for Doctors; New Delhi, India

Once again, we draw attention to this excellent booklet from India, 28 pages and about quarto size, written by Dr and Mrs Thangaraj, with Dr K C Das, A D G Leprosy, Assistant Director of Health Services, Nirman Bhavan, New Delhi 110011. The aim is 'To give a short orientation in leprosy to all medical doctors and to ensure their involvement in the National Leprosy Eradication Programme'. The main clinical findings are described, followed by differential diagnosis, reactions, and care of the feet, hands and eyes. Both the WHO and Government of India regimens for multiple drug therapy are described. The booklet is well illustrated in colour throughout. It is succinct, easily read and should surely be of great value for the better orientation of doctors (and medical students) in a country where the leprosy problem is so formidable. Published by HKNS, 1 Red Cross Road, New Delhi 110001, India.

## Leprosy of the Eye by Van Joffrion and Margaret Brand

This general outline, originally published in *Leprosy Review* (1984), **55**, is still available from the Gillis W Long National Hansen's Diseases Center, Carville, LA, 70721, USA, but it is also now in French, mainly for distribution in Africa. Apply to the Director of Education and Training at the above address.

## Primary Eye Care; TALC teaching aids, London

Yet another text with a colour transparency teaching set has been produced by Teaching Aids at Low Cost (TALC), PO Box 49, St Albans, Herts AL1 4AX, England. 'Primary Eye Care' has the usual 24 colour slides, with detailed text and questions. There is also a valuable glossary of ophthalmological terms. This material has been produced by Victoria Sheffield, Program Officer, Helen Keller International Incorporated, New York, with Dr Felicity Savage of the Institute of Child Health in London, in association with the International Eye Foundation. In line with previous sets, this one is sold at the remarkably low price of £2.50 for self-mounting sets, or £3.60 mounted. Further enquiries to Mrs B Harvey at the above address.

## OXFAM—LEPRA: Packs of Teaching–Learning Materials for Leprosy; 1982–86

In early 1982, following a discussion between representatives of OXFAM and LEPRA (British Leprosy Relief Association) in Oxford, it was decided to assemble a pack of English-language teaching–learning materials for leprosy, mainly as a service of information, but also for nursing and paramedical tutors, doctors and other senior staff with responsibility for teaching.

In the first instance, 25 packs were made up. A few were donated to key institutions and international agencies, but the majority were sold at about £15.00 per pack plus the cost of postage. However, there was an unexpected and continuing demand. During the two years 1982 and 1983, 200 were assembled and sold to individuals, training centres, control programmes and institutions in virtually all the leprosy-endemic areas. In late 1983/early 1984, it was decided to phase out the 20-document pack, largely because of its considerable weight and cost of postage, but also because more appropriate documents had become available. The smaller pack of 10 documents costs £10.00 and contains the following: 1, Chemotherapy of Leprosy for Control Programmes (1983) Technical Report Series 675. 1211 Geneva 27, Switzerland; 2, Questions and Answers 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 Pfalzgraff, published by Churchill Livingstone, Edinburgh, UK; 4, The Diagnosis and Management of Early Leprosy (1983) by Browne, published in 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 in the Leprosy Mission International, London, UK; 7, Technical Guide for Smear Examination for Leprosy by Direct Microscopy (1983) by Leiker and McDougall, published by Leprosy Documentation Service (INFOLEP), Amsterdam, Netherlands; 8, Atlas of Leprosy (1983) Published by the Sasakawa Memorial Health Foundation, Tokyo, Japan.

0305-7518/87/058193+03 $01.00  

A few advance copies were distributed in 1983; 132 in 1984; 200 in 1985 and 207 in 1986. In the period 1982–86, over 10,000 documents have been distributed from the OXFAM Health Unit in Oxford. Despite limited publicity and advertising, there is clearly a continuing demand from many parts of the world and it is intended to continue the service more or less indefinitely. (Orders to: Health Unit, OXFAM, 274 Banbury Road, Oxford OX2 7DZ, England.)

## KLEP: Karigiri Leprosy Education Programme, South India

Three booklets have recently been produced by KLEP in South India: 'Diagnosis and clinical manifestations of leprosy'; 'Differential diagnosis of leprosy'; and 'Case taking in leprosy'. These are each about 20 pages in length, paperbound, inexpensive in format but very clearly printed, and well illustrated with colour pictures and diagrams. They have presumably been written and planned for work in South India, but they could be of value, not only in other parts of South East Asia, but in other leprosy-endemic countries. Schieffelin Leprosy Research and Training Centre, Karigiri 632 106, South India.

## Medical Education Newsletter Number 35, Dundee, Scotland, UK

We are grateful to the Centre for Medical Education, The University, Dundee, DD1 4HN, Scotland, UK for continued deliveries of this Newsletter on such a wide range of topics. Number 35 includes information on: academic links with China; computers as teaching tools; article and book reviews; distance learning; courses for doctors and paramedics; and, tips for teachers. This Centre also runs numerous courses on teaching, learning, syllabus design, etc—many of which are relevant to third world situations.

## Self-instructional packages; SIP

The latest Newsletter (July–September 1986) from the School of Medical Education, The University of New South Wales, has an article with this title by May Wong, Lecturer, Department of Biological Sciences, Cumberland College of Health Sciences, Sydney, Australia. The subject headings include: A definition of SIP; How can the SIP be used?; What are its advantages?; What are the difficulties and disadvantages?; A list of media which can be included in the SIP; What key factors should be considered when preparing the package?; and, How can SIP be evaluated?. There is a short but useful reference list.

## Community-based rehabilitation in developing countries: a diploma in London

The Tropical Health Unit, Institute of Child Health, University of London, 30 Guildford Street, London WC1N 1EH, has sent details of their course leading to a diploma for teachers and Planners of Community based rehabilitation in developing countries. A booklet covers the aims of this course; the work of the unit; duration of the course and eligibility; and, teaching methods and course content. Apply to the Course Principal at the above address.

## Health Education in leprosy; a flip-book; HKNS, India

We are indebted to Mrs E S Thangaraj, Medical Coordinator, The Leprosy Mission, Southern Asia, CN1 Bhavan, 16 Pandit Pant Marg, New Delhi 110001, for sending a copy of this interesting flip-book, which is in A4 size, has colour, and text. There are 18 pictures or themes, intended mainly to identify false beliefs and wrong ideas; give correct information; and, change attitudes and behaviour. There are instructions on the first page for its proper use and each picture is accompanied by a brief, clear statement of the most important points to be considered. The pictures are bright, positive and encouraging. This is the first flip-book of its kind we have seen for some years and we wish it all success in the important realm of health education in leprosy.

## ILEP Catalogue on Training, 1987

We are grateful to the General Secretary of ILEP in London for permission to publish the following list. Address all enquiries to the 'contact' of the relevant centre.

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

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

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

Telephone, 22.51.31. Contact, Dr M Nebout, Directeur, Dr B Grossetête, Chef Unité Enseignement. Aeroport, Bamako. Logement, Internat. Bourses d'Etudes, Octroyées soit par les gouvernements des élèves, soit par les différents organismes comme l'OMS et les Associations-membres de l'ILEP, dont l'Association Française Raoul Follereau. Les demandes de bourse auprès de ces organismes doivent être présentées au Secrétaire général

de l'OCCGE (Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies, B.P. 153, Bobo-Dioulasso, Haute-Volta). Langue, Français.

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

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

**CARACAS:** Instituto de Biomedicina, Apartado Postal 4043, Caracas 1010A, Venezuela.

Contact, Dr Jacinto Convit, Director. Airport, Caracas. Language, English. Recognition of courses, WHO, CEPIALET.

**CARVILLE:** Gillis W Long National Hansen's Disease Center, United States Public Health Service Hospital, Carville, LA 70721, USA.

Telephone (504) 642.77.71. Contact, H Austin Hayes, Director of Education and Training. Nearest airport, Ryan Airport, Baton Rouge, LA. Accommodation available. Language, English. Recognition of courses, By Government, and American Medical Association.

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

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

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

Telephone, 22.36.15. Contacts, Dr J Millan, Directeur ILAD and Dr J C Naudin, DAHW-SENEGAL. Aeroport, Dakar-Yoff. Logement, A l'ILAD: 8 chambres individuelles (pas de repas, mais facilités proches), En ville: logement en hôtel aux frais des intéressés.
Frais d'inscription, Seulement pour le certificat de Léprologie de l'Université de Dakar 50,000 francs CFA. Les autres cours et stages sont gratuits grâce au soutien financier de Amici di Raoul Follereau, et de l'Ordre de Malte. Bourses d'Etude, L'Institut ne prenant en charge ni le voyage ni les frais de séjour des stagiaires, ceux-ci peuvent solliciter des bourses d'étude auprès de leur gouvernement, de l'Ordre de Malte, de l'OMS ou d'une Association-membre de l'ILEP. Langue, Français. Reconnaissance des cours, Le Certificat de Léprologie est délivré par la faculté de Médecine de Dakar. Responsables, Directeur de l'ILAD, Responsable médical DAHW.

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

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

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

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

**MEXICO:** Centro Dermatologico Pascua, Dr Vertiz, 464 Esq Av Central, Delegacion Cuauhtémac, CP 06780, México DF, México.

Telephone: 538-70-33 ou 519-63-51. Contact, Dra Obdulia Rodriguez, Directora. Aeroport, México. Logement, Hôtels. Language: Espagnol.

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

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

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# News and Notes

## International Meeting on Voluntary Organisations in Leprosy, Bombay, 1986

The theme paper prepared by the Gandhi Memorial Leprosy Foundation (GMLF) discussed the issues of the meeting in the light of the following objectives:

1 To foster cooperation among voluntary organizations.
2 To pave the way for an effective linkage between the voluntary organizations at international, national and local levels.
3 To build a bridge of understanding between Government and Non-Government organizations.
4 To develop better understanding between national agencies, providing funds and technical support, with those at the grass root level whose experiences and experiments need to be documented for ensuring effective leprosy control and rehabilitation.
5 To develop a forum for all types of international voluntary organizations for exchange of ideas and experiences.

In his summary of the congress Professor Mutatkar concluded:

'It was decided to form a formal network of voluntary organizations who are operating leprosy work in various aspects on an inter-country basis to develop meaningful partnership with governments funding voluntary organizations in leprosy.'

*Excerpts from speeches held at the Congress:*

*Dr S K Noordeen, Chief Medical Officer, Leprosy Division of Communicable Diseases, World Health Organization, Geneva, Switzerland* brought out WHO recognition of the need for coordination between Governments and NGO's and recommended this meeting to look into the establishment of appropriate coordination mechanisms. He made it clear that elimination of leprosy as a public health problem, in the forseeable future, was not possible without major contributions from voluntary sector. He commended the evolution of the role of voluntary organizations from care of disabled and social support to patient, to establishing trend-setting, cost-effective comprehensive projects, health education approaches and aids, training and promotion of cause of leprosy at decision-making levels of governments.

*Dr R S Sharma, Vice-President, National Leprosy Organization India, Gandhi Memorial Foundation, Wardha, India* expressed happiness over the sharing of modern knowledge by the international community and thanked countries like Japan and the Federal Republic of Germany for their anti-leprosy work, particularly in India.

*Professor Dr T Saylan, University of Istanbul, Medical Faculty of Istanbul, Leprosy Centre, Istanbul, Turkey* 'As is well known, leprosy patients belong to the lowest socio-economic group and if a security of living for the future is not provided, diagnosis and treatment alone usually do not suffice. Therefore, social rehabilitation of leprosy patients is gaining more and more importance.'

*Mrs Mathilde Gruner, Managing Director, AHM Aussätzigen-Hilfswerk München, Leprosy Relief Organization Munich, Munich, West Germany* stressed the need to satisfy the donor's interest: 'Above all, he wants to be sure that the charitable organization that he supports is reliable and efficient, and that the measures to contain and eradicate leprosy are well-planned and effective. This is the responsibility of the Funding Agency towards the donating public, and it is best met when we are supplied with reports of work-in-progress and examples of increasing success in raising leprosy consciousness among the general public, the medical associations and the governmental administrations. Enquiries to Leprosy Relief Organisation Munich ev, Zenettistrasse 45, D-8000, München 2, West Germany.

## Governments and voluntary agencies in leprosy control programmes

The *STAR* of November/December 1986 carries a full-length article by Dr Harold Wheate, 34 Upland Road, Sutton, Surrey SM2 5JE, England, on the subject of collaboration between governments and voluntary agencies, which complements the Editorial in this issue of the journal from Dr K C Das in Delhi. Dr Wheate

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reviews what has already been achieved in this area and goes on to consider the present and future potential under the following headings: Coordination; staff training; health education; specialised services and referral facilities; rehabilitation and staff re-deployment. One of his concluding paragraphs is particularly apt:

'In many countries, of course, the HD [leprosy] treatment program has been integrated, at least at the peripheral level, into the general health service and this problem does not arise. Where it does exist, however, it should be addressed at as early a stage as possible. The first step is to stop any further recruitment of monovalent workers and fill any vacancies by staff seconded from the general health service, after appropriate orientation. Monovalent auxiliaries with the prospect of several years active service ahead of them can be given the opportunity for additional training, for example in the fields of tuberculosis, endemic disease control or the care of disabilities. At all stages there is need for close cooperation between the government and the VAs to ensure that this highly motivated cadre can continue to be fully utilized.'

## The Wellcome Tropical Institute, London

The Wellcome Tropical Institute is funded by the Wellcome Trust and was established in 1984 to develop the Wellcome Museum of Medical Sciences, to work with governments and universities in the tropics to support their own courses in tropical medicine, and to develop continuing education for medical officers away from teaching hospitals. Thus the Institute intends to complement the work of the two British Schools of Tropical Medicine and will develop work outside the normal functions of these Schools.

The Institute is a logical development of work started by Sir Henry Wellcome, to generate research in tropical medicine, to communicate its results to students of medicine and to provide a focus in London where those who work in the tropics can meet each other.

The Institute is pleased to collaborate with any individuals or organizations involved in the development of tropical medical education, both in the United Kingdom and abroad. Overseas we work with the institutions which need support for their teaching in tropical medicine. In the United Kingdom, we hope to generate an increased and informed interest in tropical medicine, chiefly, but not solely through our Museum and its exhibitions.

*The Museum*

It is our aim to maintain and improve the collections and exhibitions of the Museum. Much thought has recently been given to increasing the stimulus and information imparted by the displays to all levels of students and visitors. Existing material is being completely revised and we are continually aware of the need to acquire fresh material which will ensure that the Museum remains topical, relevant and current as a teaching information centre.

A new venture is to establish Museum displays in appropriate institutions in this country and abroad. Links have been established with a number of African medical schools, in particular Nairobi, Addis Ababa and Kumasi. Teaching and display materials are being produced on a variety of topics concerning health and disease in a form which can be exported and presented in institutions overseas. We hope to assist medical schools to develop their own Distance Learning and Training Programmes through advice and expertise available at the Institute.

*Distance Learning Programme*

Recent discussions between the Commonwealth Secretariat and the Wellcome Trust about the needs of district and rural medical officers overseas, and British participation in their education and training, has led to the development of the Wellcome Tropical Institute Distance Learning Programme as a means of promoting continuing postgraduate education. This programme, targeted at district medical officers, is being compiled in collaboration with governments and universities, initially in African countries. The aim of this programme is to strengthen rural health services by giving active and continual support to medical staff in rural areas where they work. We hope that the material provided will reinforce the medical training of doctors, and will also serve to stimulate interest in the areas of Tropical Health Care, Community Development, and Education and Research. Great care is being taken to present the programme modules in the most appropriate and sympathetic form of self-instruction. The presentations may include non-paper media such as slide-sound and video. The Distance Learning Programme will emphasize practical problem solving activities in the following areas: clinical practice, administration and management of resources, and Community Health Care.

*The Library*

The Library contains primary and secondary sources relating to the History of Tropical Medicine, and is rapidly developing through the cooperation of the London School of Hygiene and Tropical Medicine, the British Medical Association, Royal Army Medical Corps, Royal Society of Tropical Medicine and Hygiene, and the Wellcome Institute for the History of Medicine, all of which have placed major parts of their collections on permanent loan. Special private collections include those of Colonel D G Crawford of the Indian Medical Service and Drs C M Wenyon and C A Hoare of the Wellcome Museum of Medical Science. The Library also maintains a large and increasing number of current books, reprints and periodicals on Tropical Medicine.

*The Archive Centre*

The Archive is established to administer and exploit various collections which have been transferred and presented to the Institute.

The aims of the Archive have been identified as the building up of a comprehensive collection of material, documenting work in the History of Tropical Medicine, and representing a broad spectrum of current trends and developments in tropical medicine and health care, together with education in these areas.

The Archive collects the personal and working papers of academics and practitioners active in all areas of tropical medicine. It is also developing links with many of the non-government agencies and organizations which have a vital role in the dissemination of medical aid and teaching in tropical countries. The Archive hopes to receive, on deposit for research purposes, the records of these agencies. Where it is not feasible to acquire such records we plan to make detailed surveys of the material, so that its existence is documented for future research needs.

Further enquiries: Sue Bramley, The Wellcome Tropical Institute, 200 Euston Road, London NW1 2BQ, Tel: 01-387-4477.

## Leprosy Control Seminar for Tutors in Zambia, September 1986

The second national Seminar for Tutors was held at Mwachasimpola Health Demonstration Zone from September 8 to 13 1986, and it was organized by the Leprosy Specialist for Zambia, Dr Richard de Soldenhoff. The Seminar was attended by 21 tutors and trainees from different training institutions in Zambia. Participants included 8 tutors from Enrolled nurse training schools; 5 from Registered nurse training schools; 3 from laboratory technician and assistant schools; a lecturer from the School of Physiotherapy, Evelyn Hone College, Lusaka; a lecturer in Community Health, Lusaka; 2 tutors involved in health inspector and clinical officer training; and a Leprosy Control Supervisor.

The purpose of the Seminar was: 1, To ensure that each training institution had a resident staff member with an appropriate understanding of leprosy control in Zambia; 2, To identify the tasks of the different health workers in the leprosy control programme and ensure that their training was suitable; and 3, To present two other national programmes to participants, i.e. the National Nutritional Surveillance Programme, and Control of Diarrhoeal Diseases.

*Programme*: The first three days were spent on leprosy and the remaining two days on the other national programmes. Topics covered included epidemiology of leprosy; signs, symptoms and classification; reactions; treatment of leprosy; nerve function testing; disability prevention and understanding leprosy from the patients' point of view. Participants did a task analysis relating to leprosy control work in a rural health centre (deciding 'who does what'). Subsequently, they divided into groups and each one had to produce a set of learning objectives relating to the list of tasks. By the end of the seminar there were learning objectives for teaching leprosy in the following courses: registered nurses, enrolled nurses, laboratory workers, and community health workers. This was an important piece of work and one that is seldom attempted at national level.

During the evenings, films on different topics were shown. There was also a book table which was well used by participants between sessions. (We are most grateful to Miss P. Jane Neville of The Leprosy Mission International, London, for this account.)

## Hansen Institute for Research and Information, Würzburg

The German Leprosy Relief Association and the Medical Mission Institute decided to set up a 'Hansen Institute for Research and Information' in Würzburg. The two organizations hope that with this foundation they will make a contribution to specific medical help for the countries of the Third World.

The Institute's three main areas of activity are: 1, To take charge of projects during the introduction of the combination therapy within the framework of the world-wide fight against leprosy; 2, To set up a laboratory to demonstrate simple equipment and techniques as they will be used under the difficult conditions of the project countries; and 3, To make available teaching material and specific information on the medical questions of the projects.

The Research and Information Centre is being built with the agreement of the Medical Mission Institute in Hermann-Schell-Straße in Würzburg. It is planned to be completed by the end of 1986. It was named by the sponsors in memory of the Norwegian researcher, G H Armauer Hansen (1841–1912), who discovered *Mycobacterium leprae* in 1873.

Further information: German Leprosy Relief Association, Dominikanerplatz 4, D-8700, Würzburg 11, West Germany.

## The NH Swellengrebel Laboratory of Tropical Hygiene, The Netherlands

The following is extracted from *Tropical and Geographical Medicine*, **38,** number 4, 1986: The study of leprosy is a priority of the Department of Tropical Hygiene of the Royal Tropical Institute. It is studied in very diverse fields, ranging from health services research, project management, documentation and information to

microbiological research in the laboratory. The laboratory research is focussed on the early diagnosis of leprosy. We have three important reasons to be concerned with the demonstration of the disease in its early phase. First, it would permit early treatment, which could prevent or at least reduce severe nerve damage and other pathological phenomena. Secondly, early treatment would reduce the spread of the disease by an infective patient. The third reason is related to drug resistance of *Mycobacterium leprae*; early demonstration of relapses would allow a timely adjustment of therapy. Immunity is of decisive importance to the course of leprosy. Immunological diagnosis, which is our main field of interest, is addressed to the detection of the manifestations of humoral and cellular immunity. We approach the problem along three roads:

1 *M. leprae* antigens are identified and characterized with monoclonal antibodies and T-cell clones directed against *M. leprae*.
2 *M. leprae* antigens are isolated and purified with chromatographic methods.
3 *M. leprae* antigenic determinants are chemically synthesized.

So far we have achieved the most tangible results in the field of humoral immunity. Using an *M. leprae*-specific monoclonal antibody, we have developed an ELISA-inhibition test which has shown a satisfactory degree of sensitivity and specificity, surprisingly also in patients with tuberculoid leprosy in whom humoral immunity is supposed to be poorly developed. This test has passed the laboratory phase and is ready for field testing. Similarly, satisfactory results have been obtained with a serological test using synthetic antigenic determinants coupled to a protein carrier molecule, which is now ready to be tried out in parallel with the ELISA-inhibition test in a field study.

The road to the development of a skin test to measure cellular immunity is long. We have isolated and purified several promising fractions of *M. leprae* which will be tested in lymphocyte transformation tests, migration-inhibition tests and in skin tests, firstly in experimental animals and finally in humans. In the foreseeable future there will be a great shortage of *M. leprae* antigens because the microorganisms from which they are isolated are available only in small quantities. Therefore we will soon start to explore the possibility of preparing important protein antigens with recombinant-DNA technology, which together with synthesis of antigens holds a promise for the future.

Address: National Institute of Public Health and Environmental Hygiene, (RIVM), Bilthoven, The Netherlands.

## WHO Health Literature Services Programme Newsletter, November 1986

Number 11, November 1986 from the Office of Library and Health Literature Services, WHO, 1211 Geneva 27, Switzerland, includes information on: a London data base on AIDS; international codes for country names and currencies; audio-visual materials in biomedical and health fields; health science libraries in Ethiopia; fellowship for medical librarians; biomedical information programme, Manila; health libraries in the Philippines; WHOLIS, the data base of WHO library, Geneva. (Could it be that this is the network through which a systematic attempt should be made to ensure that all libraries in leprosy-endemic countries have appropriate books and other documents for medical students, doctors and scientists? *Editor*.)

## Meetings, Congresses, September 1988

1 *International Society of Dermatology, Tropical, Geographic Ecologic, with The International Society of Dermatopathology*; 4–8 September 1988; in Oxford, England. Organizing secretary; Mrs Christine Cherry, Department of Dermatology, the Slade Hospital, Headington, Oxford OX3 7JH, England.
2 *XIII International Leprosy Congress*; 11–17 September, 1988 in the Hague, The Netherlands. Co-sponsored by the World-Health Organisation. Organizing secretary: Mr H E M de Bok, NSL, Wibautstraat 135, 1097 DN Amsterdam, The Netherlands.
3 *XII International Congress for Tropical Medicine and Malaria*; 18–23 September, 1988; International Congress Centre RAI, Amsterdam, The Netherlands. Congress Secretariat: XIIth International Congress for Tropical Medicine and Malaria, c/o OBA bv, Europaplain 12, 1078 GZ Amsterdam, The Netherlands.

## 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 3 travel fellowships each year to a maximum value of £1200 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.

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(= clofazimine)

## The highly effective antileprosy drug with anti-inflammatory[1] properties

## For the prevention[2] and treatment[3] of lepra reactions (ENL)

## Suitable for use in combined regimens for the prevention and treatment of dapsone-resistance in lepromatous and dimorphous forms of leprosy[4]


1. Browne, S. G.: Lepr. Rev. *37*, 141 (1966)
2. Azulay et al.: Lepr. Rev. *46* (Suppl.), 99 (1975)
3. Schulz, E. J.: Lepr. Rev. *42*, 178 (1972)
4. Yawalkar, S. J., Vischer, W. A.: Lepr. Rev. *50*, 135 (1979)


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

Further information is available on request.