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# Editorial

## LEPRA'S ELECTIVE PERIOD STUDENT PROGRAMME, 1973–1983

All medical schools in the United Kingdom include in their curriculum a so-called Elective Period (EP) during the fourth or fifth clinical year, in which the student is free to choose the subject for study as well as the place of study. With readily available air travel many students now go abroad for the EP, often to America or Canada to continue and compare clinical training at medical schools there. Others, in complete contrast, use the EP as a unique opportunity to visit and study health and living conditions and tropical diseases in Third World countries.

LEPRA's EP student programme stemmed from the recommendation in 1973 of their Medical Advisory Board (MAB) that funds should be made available to assist UK medical students who genuinely wished to pursue their EP in the Third World and undertake an approved leprosy project. The MAB's request for funds was to ensure coverage of air fares to the Third World, bearing in mind the small, if any, grants from the medical schools. Furthermore, the MAB considered that such students could make a particularly valuable contribution to leprosy by carefully co-ordinating their projects with on-going programmes or problems under study in the field of leprosy. On this basis, LEPRA's EP student programme was started in 1973 for a limited trial period. Although within the first 5 years only some 13 EP students had been awarded a LEPRA grant, the objectives of the programme were so clearly beneficial to these students as well as to the field of leprosy that LEPRA has continued, and increased, their support of EP students. The programme has been in operation now for 10 years, and in this editorial I will summarize the management and achievements during this period.

Selection of students for the EP awards has, throughout, been the responsibility of LEPRA's Medical Advisory Board (MAB) and their initial selection is judged on the applicant's proposal, *curriculum vitae* and tutor's confidential report. The final selection is decided by interview with the Chairman and/or other members of the MAB. The level of the individual's LEPRA award is determined by the air fare and local subsistence against any other grants or finances available to the student, and with the onus on the student to find the cheapest available air fare.

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**Table.** Number of elective period students and location of project by region and country

| Region | Country |
|---|---|
| Africa (18): | Botswana 1; Egypt 1; Ethiopia 5; Ivory Coast 1; Kenya 2; Malawi 1; Nigeria 1; Tanzania 3; Uganda 2; Zambia 1 |
| S.E. Asia (69): | Bangladesh 1; India 52; Nepal 12; Sri Lanka 2; Thailand 2 |
| S. America (6): | Bolivia 2; Brazil 2; Guyana 1; Venezuela 1 |
| W. Pacific (5): | Australia 1; Borneo 1; Malaya 3 |
| Total: 98 | |

In the second 5 years LEPRA's grant has been substantially increased, providing support for 15–20 students per year. Over the 10 years, 98 students (54 male and 44 female) have been awarded LEPRA grants covering a wide range of leprosy projects undertaken in 22 countries (see Table), all of which have been successfully completed. The most pleasing and encouraging feature of the programme has been the motivation, diversity of interests and high academic achievements of the students. With 14 of the successful applicants having taken a B.Sc. before going on to their clinical studies, the subject of the degree had influenced some in their choice of studies, to include more specialized projects relating to the pathology, microbiology, immunology, neurology (including electron microscopy), pharmacology and psychology of leprosy. With the overall responsibility of the MAB for the programme, their contributions have been concerned with:

1 advice and help to the student in drafting a suitable and feasible protocol for the project, bearing in mind that most EPs are limited to 7–9 weeks overseas;
2 the selection and acceptance of centres overseas most appropriate to the project;
3 provision of specialized training, equipment or reagents relevant to the project; and
4 the allocation of EP students to assist in current research programmes or problems currently under review in the field.

For the students, the programme has been successful and deeply appreciated since it has provided all 98 students with the opportunity of visiting and working in many different Third World countries, with the added satisfaction of completing a project of their own design or taking part in, and contributing to, studies designed to improve the treatment and control of leprosy. While these latter objectives were anticipated by the MAB in their recommendations to

LEPRA for initiating an EP student programme, they have been more than fully substantiated. Furthermore, 22 of the student projects have resulted in official publications as collaborative authors or as single authors (8) and these are listed in the references, with the student's name identified by an asterisk.

The acceptance for publication of 23 papers resulting from the students' projects by leprosy journals, including 5 papers accepted by specialized non-leprosy journals, is a tremendous achievement and represents an independent assessment of the high quality and current relevance of the students' projects and the success of LEPRA's EP programme. However, this wealth of publications resulting from the programme is an unexpected, but pleasing, bonus, since the essential objective of the programme was to interest medical students in leprosy by co-ordinating their projects with on-going programmes in the field or new developments, designed to improve the treatment of patients and the control of leprosy. Over the 10 years our student projects have contributed significantly to these broader objectives. For example, all the preliminary assessments and surveys on the sensitivity and application under field conditions of the dapsone/creatinine urine test as developed by Ellard, were undertaken by our students as part of their projects. There were such studies on patients in leprosy control programmes in parts of Africa and India.[1–4] Other students have undertaken field studies in connection with Ellard's studies on the pharmacology and toxicity of antileprosy drugs and the use of isoniazid as a safe and sensitive marker.[5–7] Similarly, 14 students have undertaken projects in support of Stanford's extensive and world-wide skin-test surveys using various mycobacterial antigens. These have included areas in India, Nepal and Sri Lanka, and 3 have resulted in publications.[8–10] More recently, 12 of our students have taken part in ffytche's computer-based collection of ocular complications associated with leprosy in patients in different parts of the world.[11] To date, their surveys have covered some 600 patients from centres in Brazil, India, Kenya, Nepal, Thailand and Uganda.

More specialized projects, usually determined by the student's particular interest, which have resulted in publications, include studies on the oral and nasal discharge of *Mycobacterium leprae*;[12] autonomic nerve functions and sensory testing;[14, 15] deformities related to treatment[20] and several studies on the immunological aspects of leprosy related to lepromin reactions[16, 17] and cellular[22] and antibody[23, 24] responses in different types of leprosy.

The other very considerable contribution by the students has been concerned with the treatment and control of leprosy. Several students have assisted busy and inadequately staffed control centres in going through their treatment records to identify potentially dapsone-resistant patients. Others have helped even in initiating or improving treatment programmes,[18] particularly with the introduction of multidrug therapy (MDT). Very recently, LEPRA has encouraged students to determine how well MDT has been introduced into control programmes in different parts of the world, and its acceptance by the patients.

There are already two publications on this aspect.[19, 21] Likewise, some students have studied the feasibility of integrating leprosy control into primary health care programmes.[22]

Finally, perhaps the most rewarding outcome of our EP student programme is that 4 of our earlier students, after qualifying, have already embarked on further training for a career in some aspect of tropical medicine.

*Clinical Research Centre* R J W REES
*Harrow, Middlesex HA1 3UJ*

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* Denotes elective period student

*Lepr Rev* (1984) **55,** 327–335

# The sensitivity and specificity of fluorescent leprosy antibody absorption (FLA-ABS) test for detecting subclinical infection with *Mycobacterium leprae*

JI BAOHONG,* TANG QUANKUI,* LI YENLONG,* CHEN JIAKUN,* ZHANG JIALING,* DONG LIWEN,* WANG CHENMIN,† MA JIAJU‡ & YE DALI§

**Shanghai Zeng Yi Hospital; † Hai-an Leprosy Hospital, Jiangsu Province; ‡ Hanzhong Sanitorium, Shanxi Province; § Huzhou Epidemic Prevention Station, Zhejiang Province, People's Republic of China*

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*Summary* From the examination of 854 sera from different sources by the fluorescent leprosy antibody absorption (FLA-ABS) test, the sensitivity and specificity of this test for leprosy has been confirmed. A positive FLA-ABS test in a non-leprosy individual should be considered as an indicator of subclinical leprosy infection. The subclinical infection rates of two endemic areas ranged from 11·4 to 16·3% and were at least 200 times higher than the cumulative prevalence rate of clinical infection. The combination of a positive FLA-ABS test with a negative Mitsuda reaction indicates that the individual has been infected with *Mycobacterium leprae*, but cell-mediated immunity has not been induced. Such individuals are at a greater risk of developing multibacillary leprosy and should be carefully followed up or some prophylactic measures should be considered. Since subclinical infection cannot be differentiated from very early leprosy by the FLA-ABS test alone, it is not a reliable diagnostic test of early leprosy.

## Introduction

A technique for the detection of subclinical infection with *Mycobacterium leprae* among the population of leprosy endemic areas is one of the most important requirements for leprosy control programmes. The technique should be highly sensitive and specific for leprosy, the procedures and equipments should be simple and convenient for use in the field. Abe *et al.*[1–4] have developed the fluorescent

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leprosy antibody absorption (FLA-ABS) test, using the indirect fluorescent antibody technique and improving the specificity by absorption of cross-reacting anti-mycobacterial antibodies in the serum. This test has been claimed to be useful for detecting subclinical leprosy infection.[1–6] The purpose of the present study is to evaluate the sensitivity and specificity of the FLA-ABS test.

## Materials and methods

### SERA

Approximately 0·5 ml serum was collected from each individual and stored at −20°C. Sodium azide at final concentration 0·1% was added to those specimens which had to be transported for long distances, these specimens being kept in wet-ice thermos flasks. The sera of leprosy patients were collected from Shanghai Zeng Yi Hospital, Hanzhong Sanitorium (Shanxi Province) and the leprosaria of Suzhou Prefecture (Jiangsu Province). The household contacts of leprosy patients were from Hai-an County (Jiangsu Province), Huzhou (Zhejiang Province) and Chenggu County (Shanxi Province). The healthy inhabitants of leprosy endemic areas were collected from Caoyuan People's Commune of Hai-an County and Lianshi People's Commune of Huzhou. The cumulative leprosy prevalence rates of these two areas were 4·8 and 6·2 per thousand respectively. The doubtful leprosy cases were from the Out-patient Department of Shanghai Zeng Yi Hospital and the professional contacts were the staff of the same hospital. Pulmonary tuberculosis patients were provided by the Shanghai Second Tuberculosis Sanitorium. Sera of healthy non-contacts were obtained from donors in Shanghai.

### MYCOBACTERIAL SUSPENSION

*M. leprae* suspensions were prepared from human leproma by the method of Abe *et al.* or from *M. leprae*-infected armadillo livers by Protocol 1/79. The latter *M. leprae* were provided by courtesy of Dr R J W Rees, National Institute for Medical Research, London, under the IMMLEP project of WHO. Two forms of armadillo-derived *M. leprae* were obtained: bacillary suspension at a concentration of $10^{10}$ AFB/ml and freeze-dried bacilli. The bacillary suspension was diluted to $2 \times 10^8$ AFB/ml for preparing the smear of *M. leprae* and the results were the same as in those obtained with human-derived *M. leprae*. The freeze-dried bacilli were used for the additional absorption with *M. leprae*. BCG, *M. vaccae*, *M. tuberculosis* (H37Rv), *M. kansasii*, *M. marinum*, *M. smegmatis*, *M. phlei* and *M. avium* were cultivated on Ogawa's 1% egg medium. The colonies were homogenized, washed and suspended in normal saline.

### FLA-ABS TEST

The steps of the test, including cross-reactions with other mycobacteria and additional absorption with *M. leprae* or other mycobacteria, were those described by Abe *et al.*[3, 4] A fluorescent microscope, Model BHF, Olympus Ltd, Japan, was used throughout this study. The filter system included BV and interference system, Model F-FITC, Olympus Ltd, Japan. The specificity of the green fluorescence as shown by the bacilli under the BV system were confirmed by using the interference system. The criteria for fluorescent microscopic examination were the same as Abe *et al.*[3] and two plus or more fluorescence caused by the 1:40 or higher dilution of sera were considered to be positive.

## Results

### FLA-ABS TEST AMONG LEPROSY PATIENTS

Out of 161 active leprosy patients, 146 (90·7%) were proved positive by the FLA-ABS test. The results of the tests on patients throughout the spectrum of leprosy are shown in Table 1. The positive rate was highest in lepromatous patients and gradually decreased towards the tuberculoid end. However, 73·9% of TT patients were still positive. The differences in positive rates between LL vs BT or TT, BL vs TT were statistically significant ($P<0·05$ or $P<0·01$). The distribution of the antibody titres down the spectrum of leprosy showed the same tendency as the positive rate, i.e. the mean antibody titre was highest at the lepromatous end and gradually decreased towards the tuberculoid end. The differences in mean antibody titre between each type of patient, except BL vs BB or BT vs TT, were statistically significant although there were striking variations within each type.

**Table 1.** FLA-ABS test among active leprosy patients

| Classification of leprosy | No. of cases | Positive | | Distribution of antibody titre ($10 \times 4^x$) $x=$ | | | | | Mean of $x$ | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | 0 | 1 | 2 | 3 | 4 | | |
| LL | 45 | 45 | 100 | 0 | 3 | 4 | 14 | 24 | 3·31 | 0·90 |
| BL | 50 | 47 | 94·0 | 3 | 9 | 22 | 11 | 5 | 2·12 | 1·02 |
| BB | 16 | 15 | 93·8 | 1 | 5 | 0 | 7 | 3 | 2·38 | 1·31 |
| BT | 27 | 22 | 81·5 | 5 | 7 | 12 | 2 | 1 | 1·52 | 1·01 |
| TT | 23 | 17 | 73·9 | 6 | 7 | 5 | 4 | 1 | 1·44 | 1·20 |
| Total | 161 | 146 | 90·7 | 15 | 31 | 43 | 38 | 34 | 2·28 | 1·26 |

**Table 2.** FLA-ABS test in leprosy patients; grouping by bacterial load or activity of infection

| Classification of leprosy | Group | No. of cases | Positive No. | Positive % | Positive $P$ | Distribution of antibody titre ($10 \times 4^x$) $x=$ 0 | 1 | 2 | 3 | 4 | Mean of $x$ | SD | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LL | Smear(+) | 45 | 45 | 100 | — | 0 | 3 | 4 | 14 | 24 | 3·31 | 0·90 | — |
| | Smear(−) | 33 | 30 | 90·9 | <0·05 | 3 | 3 | 11 | 8 | 8 | 2·46 | 1·23 | <0·0 |
| TT | Active | 23 | 17 | 73·9 | — | 6 | 7 | 5 | 4 | 1 | 1·44 | 1·20 | — |
| | Quiescent | 36 | 12 | 33·3 | <0·01 | 24 | 10 | 2 | 0 | 0 | 0·39 | 0·60 | <0·0 |

Table 2 suggested that the results of the FLA-ABS test were well correlated with the bacterial load of the host or the activity of the leprosy infection. The positive rate and mean antibody titre were significantly lower in the smear negative LL group than in those in the smear positive LL group, and the same tendency was observed in the quiescent TT group (where the skin lesions had subsided for at least 3 years) as compared with the active TT group.

## FLA-ABS TEST AMONG NON-LEPROSY INDIVIDUALS

Five hundred and forty-nine non-leprosy cases were examined and the results are summarized in Table 3. All sera from sputum-positive pulmonary tuberculosis patients and healthy non-contacts gave negative results. Among the healthy

**Table 3.** FLA-ABS test among non-leprosy individuals

| Group | No. of cases | Positive No. | Positive % | Distribution of antibody titre ($10 \times 4^x$) $x=$ 0 | 1 | 2 | 3 | 4 | Mean of $x$ | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| Healthy non-contacts | 30 | 0 | 0 | 30 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tuberculosis patients | 30 | 0 | 0 | 30 | 0 | 0 | 0 | 0 | 0 | 0 |
| Endemic area | | | | | | | | | | |
| Healthy adults (Lianshi) | 147 | 24 | 16·3 | 123 | 21 | 3 | 0 | 0 | 0·18 | 0·43 |
| Healthy schoolchildren (Lianshi) | 44 | 5 | 11·4 | 39 | 5 | 0 | 0 | 0 | 0·11 | 0·32 |
| Healthy schoolchildren (Caoyuan) | 117 | 16 | 13·7 | 101 | 13 | 3 | 0 | 0 | 0·16 | 0·43 |
| Household contacts of multibacillary leprosy | 88 | 58 | 65·9 | 30 | 36 | 17 | 5 | 0 | 0·97 | 0·88 |
| Household contacts of paucibacillary leprosy | 45 | 8 | 17·8 | 37 | 6 | 2 | 0 | 0 | 0·22 | 0·52 |
| Professional contacts | 48 | 20 | 41·7 | 28 | 8 | 9 | 3 | 0 | 0·73 | 0·98 |

**Table 4.** Comparison of FLA-ABS test in professional contacts: grouping by seniority

| Group | No. of cases | Positive No. | Positive % | *P** | Distribution of antibody titre ($10 \times 4^x$) $x=$ 0 | 1 | 2 | 3 | 4 | Mean of $x$ | SD | *P** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Seniority ⩾15 years | 26 | 19 | 73·1 | — | 7 | 7 | 9 | 3 | 0 | 1·31 | 1·01 | — |
| Seniority <5 years | 22 | 1 | 4·6 | <0·01 | 21 | 1 | 0 | 0 | 0 | 0·05 | 0·21 | <0·01 |
| Total | 48 | 20 | 41·7 | — | 28 | 8 | 9 | 3 | 0 | 0·73 | 0·98 | — |

* Compare with the group of seniority ⩾15 years.

inhabitants, excluding the household contacts from the two endemic areas, the positive rates ranged from 11·4 to 16·3% and the mean antibody titres ranged from 0·11 to 0·18%. No significant difference has been observed between the two areas or two age groups from the same area. Both the positive rate and mean antibody titre were very significantly higher in household contacts of multibacillary patients than in those of paucibacillary patients. The so-called professional contacts were the staff working in a leprosy hospital mainly for smear-positive patients. The total positive rate of that group was 41·7%. If subdivided according to seniority in the hospital, the positive rate and mean antibody titre were much higher among the staff with seniority ⩾15 years than in those with seniority <5 years (Table 4).

Mitsuda lepromin ($1{\cdot}6 \times 10^8$ AFB/ml) testing was undertaken immediately after blood collection in 340 healthy inhabitants or household contacts in leprosy endemic areas. The Mitsuda reaction was read at 21–28 days and was considered positive if the average diameter of the nodule was greater than 3 mm. As shown in Table 5, no correlation has been found between the Mitsuda reaction and the FLA-ABS test ($\chi^2 = 0{\cdot}264$, $P > 0{\cdot}05$). According to the results of both tests, there were four combinations, i.e. both positive, both negative, Mitsuda positive/

**Table 5.** Correlation between FLA-ABS test and Mitsuda reaction

| Mitsuda reaction | FLA-ABS test Positive | Negative | Total |
|---|---|---|---|
| Positive | 34 (10·0%) | 152 (44·7%) | 186 (54·7%) |
| Negative | 19 (5·6%) | 135 (39·7%) | 154 (45·3%) |
| Total | 53 (15·6%) | 287 (84·4%) | 340 (100·0%) |

FLA-ABS negative or Mitsuda negative/FLA-ABS positive. Nineteen (5·6%) out of these 340 individuals were Mitsuda negative but FLA-ABS positive. Seventeen had an antibody titre of 1:40 and 2 of 1:160.

### FLA-ABS TEST AMONG DOUBTFUL LEPROSY CASES

The so-called doubtful cases were those who had skin lesion(s) or neural symptoms resembling leprosy when they first appeared. FLA-ABS tests had been carried out in 75 patients of this group and the results are shown in Table 6. The

**Table 6.** FLA-ABS test among doubtful leprosy cases grouping by clinical followed up results

| Group | No. of cases | Positive No. | Positive % | Distribution of antibody titre ($10 \times 4^x$) $x=$ 0 | 1 | 2 | 3 | 4 | Mean of $x$ | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| Confirmed leprosy during follow-up | 4 | 3 | 75·0 | 1 | 2 | 1 | 0 | 0 | 1·00 | 0·82 |
| Requiring further follow-up | 13 | 7 | 53·9 | 6 | 4 | 2 | 1 | 0 | 0·85 | 0·99 |
| Ruled out leprosy during follow-up | 58 | 9 | 15·5 | 49 | 7 | 2 | 0 | 0 | 0·19 | 0·48 |
| Total | 75 | 19 | 25·3 | 56 | 13 | 5 | 1 | 0 | 0·35 | 0·67 |

total positive rate was 25·3%. They had been followed up clinically in the Out-patient Department for at least 2 years before the test. About 1 year after the test, these patients were divided into three groups, as indicated below. Histopathological examinations were carried out on a sample of two-thirds of all patients studied. Group A with 4 cases whose lesion(s) gradually progressed with unequivocal leprosy, 3 (75%) were FLA-ABS positive. Group B with 13 cases whose lesion(s) or symptoms had not significantly changed and still need further follow-up, 7 (53·9%) were FLA-ABS positive. Group C with 58 cases, in whom the diagnosis of leprosy can be ruled out, 9 (15·5%) were FLA-ABS positive. The differences in positive rate and mean antibody titre between group A vs B has no statistical significance but both groups were significantly higher than group C. To analyse the outcome in groups A and C, the $\chi^2$ test was used to check the correlation between the FLA-ABS test and the follow-up results (Table 7). The $\chi^2$ test was 7·384 and $P < 0{\cdot}01$. Thus, the FLA-ABS positive doubtful cases were more prone to develop leprosy than the FLA-ABS negative cases. Among the 9 patients who were positive to FLA-ABS in group C, 7 cases came from leprosy endemic areas but the other 2 did not. The reasons for the positive tests in the latter 2 cases are unknown.

**Table 7.** Correlation between FLA-ABS test and clinical follow up results of doubtful cases

| FLA-ABS test | Clinical follow up results Confirmed leprosy | Ruled out leprosy | Total |
|---|---|---|---|
| Positive | 3 | 9 | 12 |
| Negative | 1 | 49 | 50 |
| Total | 4 | 58 | 62 |

### CROSS-REACTION AND ADDITIONAL ABSORPTION OF POSITIVE FLA-ABS SERA

In order to show that a positive FLA-ABS test was not due to the retention of cross-reactive antibody to other mycobacteria in the sera after absorption with cardiolipin, lecithin, BCG and *M. vaccae*, 53 positive sera from non-leprosy individuals in Table 3 were tested for cross-reactivity with 6 other species of mycobacteria, i.e. *M. tuberculosis*, *M. kansasii*, *M. marinum*, *M. smegmatis*, *M. phlei* and *M. avium*. Only 5 demonstrated cross-reactivity with 1 or 2 species of mycobacteria, namely 3 to *M. smegmatis*, 2 to *M. marinum* and 1 to *M. tuberculosis*. These 5 sera were further absorbed with their corresponding mycobacteria. The cross-reaction disappeared in 4 sera but 1 was still positive to *M. smegmatis* though the antibody titre was reduced from 1:160 to 1:40. The antibody titre to *M. leprae* was not influenced by additional absorption with other mycobacteria. Ten positive FLA-ABS sera, 5 multibacillary patients, 4 household contacts and 1 professional contact, were tested by additional absorption with *M. leprae*, i.e. 0·1 ml serum absorbed by the routine procedures (resulting in a 10-fold dilution) was mixed with 0·5 mg freeze-dried *M. leprae* and incubated at 37°C for 30 min. Before absorption with *M. leprae*, the antibody titre was 1:160 in 1, 1:640 in 5 and 1:2560 in 4. After absorption with *M. leprae*, the anti-*M. leprae* antibodies were completely removed.

## Discussion

It is impossible to measure directly the sensitivity of FLA-ABS test for detecting subclinical leprosy infection, because at present no other specific reference systems are available. However, the results of the FLA-ABS test in leprosy patients and also in contacts can provide useful information. The present study revealed the following observations: (1) By the FLA-ABS test, anti-*M. leprae* antibodies have been detected in more than 90% of active leprosy patients. Even though the positive rate was least in TT patients, it still gave 73·9% (Table 1). (2)

The positive rate and mean antibody titre correlated well with the bacterial load of the host or the activity of leprosy infection (Table 2). (3) Theoretically, subclinical infection should be greater in contacts and chances of subclinical infection should correlate with the infectivity of the index case, the intensity and the duration of exposure. The positive rate and mean antibody titre of the FLA-ABS test were much higher in household contacts of multibacillary patients than in those of paucibacillary patients
contacts with longer seniority than in those with shorter seniority (Table 4). From these findings, the FLA-ABS test seems to be quite sensitive for detecting subclinical leprosy infection. The following observations suggested that the FLA-ABS test is specific for leprosy infection: (1) All specimens from sputum-positive pulmonary tuberculosis patients and healthy non-contacts gave negative results (2) Only a small proportion of positive FLA-ABS sera from non-leprosy individuals showed cross-reaction to other mycobacteria and this can be differentiated by additional absorption with corresponding mycobacteria. (3) The reaction against *M. leprae* is completely removed when positive sera are further absorbed by *M. leprae*.

Since the FLA-ABS test is quite sensitive and specific for leprosy infection, the positive reaction in non-leprosy cases may be considered as an indication of subclinical infection. Because the positive rate in quiescent TT cases was much lower than in active cases, it would seem unlikely that the FLA-ABS test could detect past aborted infections and, therefore, the subclinical infection rate detected by this test might be an underestimate. Even though the figures in Table 3 demonstrated that the subclinical infection rate was at least 200 times higher than the cumulative prevalence rate of clinical infection at the same area, they are similar to those reported by Abe *et al.*[3] A far greater proportion of the population are infected with *M. leprae* than develop clinical disease, indicating that the infections are aborted at the subclinical stage.

There was a correlation between a positive FLA-ABS test and the outcome in individuals with doubtful leprosy, in that they were more prone to develop leprosy later than those with a negative test. However, many doubtful cases came from endemic areas. It is difficult to differentiate the subclinical infection from very early leprosy by the FLA-ABS test. Hence, a positive FLA-ABS test is not a reliable indicator for the early diagnosis of leprosy.

The main purpose for detecting subclinical leprosy is to identify the individuals who have been infected and prone to develop into multibacillary leprosy. The FLA-ABS test alone can hardly fulfil this purpose because the great majority of leprosy patients are positive and the distribution of levels of antibody titres overlap between multibacillary and paucibacillary patients. It is possible to overcome this difficulty by including a lepromin test, because most multibacillary patients are in an anergic state, and therefore lepromin negative. A combination of a positive FLA-ABS test and a negative Mitsuda reaction indicates that the individual has been infected with *M. leprae* but cell-mediated immunity has not

been induced. These individuals are more likely to develop multibacillary-type leprosy and most urgently need to be protected. Abe *et al.* used the frequency of individuals in this category as an index of susceptibility to leprosy.[4] This index in the present study was 5·6%. Since the antibody titres of the FLA-ABS tests were rather low in all these individuals in our present study, we have followed them up carefully, including physical examination, lepromin and FLA-ABS tests. If this specific immunological status persists or the antibody titre tends to be increasing while the Mitsuda reaction is still negative, then prophylactic measures have been adopted.

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*Lepr Rev* (1984) **55,** 337–340

# Anti-*Mycobacterium leprae* antibodies induced by lepromin injection as demonstrated by indirect immunofluorescence

ELBA GONZÁLEZ-ABREU,
A GONZÁLEZ-SEGREDO & F DE LA CRUZ
*Departamento de Microbiologia, Instituto de Medicina Tropical 'Pedro Kourí', Calle 200 y Avenida 15. Siboney, Ciudad Habana, Cuba*

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*Summary* In Cuba the Mitsuda test is carried out on all household contacts of leprosy patients as a measure of epidemiological control. Hence, we need to know whether positivity in the FLA-ABS test can be caused by lepromin testing. The present study shows that sera from healthy individuals were positive by the FLA-ABS test up to 180 days after lepromin testing. The highest positivity rate was reached by day 21, and the highest antibody level by day 45.

## Introduction

The development of a suitable test for infection has long been awaited by those engaged in leprosy control. Sensitive serological tests capable of demonstrating antibodies reacting specifically with *Mycobacterium leprae* may become valuable for the diagnosis of early infections and if used in parallel with the lepromin test, for the identification of individuals infected but unable to develop an efficient immune response.

A number of scientists have searched for sensitive and specific techniques to detect subclinical infection in leprosy.[1–4] In 1981 the fluorescent leprosy antibody absorption (FLA-ABS) test of Dr Masahide Abe *et al.*[4] was established in our laboratory. Since then we have been working with this technique and our first results[5] correspond with those of Abe and other investigators.[6, 7] However, for a wider use in epidemiological studies the test should be sensitive enough to be positive in individuals who have been subclinically infected with *M. leprae*, whether or not this exposure leads to clinical disease.[8]

In Cuba, all leprosy contacts are given a lepromin test as one of several measures of epidemiological control.[9] Therefore we need to know whether

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positivity in the FLA-ABS test can be caused by lepromin testing. We report here the levels of antibodies induced by lepromin, and the duration of their presence.

## Materials and methods

The FLA-ABS test was carried out in 37 healthy persons with no known contact with leprosy. Lepromin, 0·1 ml ($3{\cdot}4 \times 10^7$ bacilli/ml) prepared from human leproma in our laboratory, was injected intradermally. Five millilitre blood samples were taken from each subject before, 21, 45, 90, 180 and 365 days after the lepromin injection. The sera obtained were used in the FLA-ABS test as described by Abe *et al.*[6] Abe's criteria of positivity were used to analyse the results. The sera obtained from the same group of persons before the lepromin injection were considered a negative control (0 time group) and all comparisons refer to this group. The serum of a confirmed lepromatous leprosy patient with an antibody titre of more than 1 : 2500 was used as positive control and was included in all the experiments.

A fluorescent Olympus microscope, model BHF, with interference filter (FITC) was used and the smears were observed under ×400 magnification.

## Results

The results obtained after lepromin injection can be seen in Table 1 and previous results obtained with lepromatous patients and a group of household contacts are

**Table 1.** FLA-ABS results according to time after lepromin injection

| Time (days) | *n** | Positive | % | Antibody titres −1:40 | 1:160 | 1:640 | 1:2560 | Geometric mean | SD |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 34† | 0 | 0 | 0 | 0 | 0 | 0 | — | — |
| 21 | 32 | 28 | 87·5 | 2 | 15 | 8 | 3 | 288 | 2·93 |
| 45 | 30 | 18 | 60·0 | 3 | 5 | 6 | 4 | 372 | 4·05 |
| 90 | 33 | 7 | 21·2 | 5 | 0 | 0 | 2 | 132 | 6·55 |
| 180 | 33 | 3 | 9·09 | 2 | 1 | 0 | 0 | 63·1 | 1·92 |
| 365 | 34 | 0 | 0 | 0 | 0 | 0 | 0 | — | — |
| Household contacts | 15 | 14 | 93·3 | 3 | 3 | 6 | 2 | 324 | 3·92 |
| Lepromatous patients | 48 | 48 | 100·0 | 5 | 13 | 12 | 18 | 550 | 4·17 |

* Total number of sera.

† Three individuals with detectable antibody at time 0 were excluded.

**Table 2.** FLA-ABS results according to time after lepromin injection with previous demonstrable anti-*M. leprae* antibody

| | Time (days) | | | | | |
|---|---|---|---|---|---|---|
| *n* | 0 | 21 | 45 | 90 | 180 | 365 |
| 1 | 160 | 160 | 640 | 160 | 160 | 160 |
| 2 | 640 | 2560 | 640 | 640 | 160 | 160 |
| 3 | 160 | 640 | 160 | N.S | 160 | 160 |
| Geometric mean | 251·2 | 645·7 | 407·0 | 323·0 | 158·5 | 158·5 |
| S.D | 1·92 | 3·1 | 1·92 | 2·0 | 1·0 | 1·0 |

N.S. No sample.

also shown. The responses of three persons whose sera were positive before the first lepromin injection were excluded from Table 1. As can be seen in Table 1, the positivity rate reached its highest value by day 21, while the antibody level, as expressed by the geometric mean of the antibody titre reached its highest response by day 45. The values of positivity and antibody titre decreased rapidly becoming completely negative by 365 days. The antibody response to lepromin injection was absent in a group of 4 individuals (11·8%) who were negative throughout the study.

The results obtained with the sera of 3 individuals who were positive before the lepromin injection are shown in Table 2. In these, the geometric mean of the antibody titre reached its highest level by day 21 and returned to values comparable to their initial response, prior to the lepromin injection, at the end of the study.

## Discussion

Anti-*M. leprae* antibodies have been observed to persist for a long time in leprosy patients, even after prolonged treatment with dapsone.[10] Knowing the time of persistence of antibodies induced by a lepromin injection in healthy individuals, should allow us to decide whether antibody in the sera of leprosy household contacts is likely to be due to the Mitsuda skin test or to infection.

The geometric mean of antibody levels at 45 days after the lepromin injection is very similar to that found in our previous study with household contacts of lepromatous patients. From our results it appears that a lepromin injection can rapidly stimulate an anti-*M. leprae* response in the serum of the majority of individuals (30/34; 87·3%). Therefore, we can reasonably place confidence in the antibody result if the test is done about 1 year after the lepromin injection.

As previously mentioned, the sera of 3 individuals without known contact

were positive at the outset and remained so throughout the experiment. This means a positivity rate not due to the lepromin of 8·11% for which we have as yet no explanation.

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# The bactericidal activity of various aminoglycoside antibiotics against *Mycobacterium leprae* in mice

R H GELBER*, P R HENIKA† & J B GIBSON‡
*US Public Health Service Hospital, 15th Avenue and Lake Street, San Francisco, California 94118, USA*

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*Summary* The killing potential of various aminoglycoside antibiotics for *Mycobacterium leprae* infection of the mouse foot-pad was studied, utilizing daily intraperitoneal therapy. Kanamycin (100 mg/kg), streptomycin (150 mg/kg), and amikacin (100 mg/kg) resulted in impressive killing of bacilli (99·7%, 97% and 96% bactericidal, respectively). Gentamicin (20 mg/kg) and tobramycin (20 mg/kg) were much less active (60% and 37% bactericidal). The bactericidal activity of these very high doses of kanamycin, streptomycin and amikacin compared favourably with those of other agents previously studied in a similar manner at relatively lower dosage levels.

## Introduction

Aminoglycoside antibiotics have received only limited experimental and/or clinical attention for their potential role in the therapy of leprosy.[1–9] In 1964 the first study[8] on the activity of streptomycin in the treatment of experimental *Mycobacterium leprae* infection of the mouse foot-pad was reported. In this study, 2 mg of streptomycin injected subcutaneously 5 times weekly, continuously from the time of infection, prevented multiplication of *M. leprae* for the $15\frac{1}{2}$-month study duration. In a later study (1968)[7] *M. leprae*-infected mice were treated by the 'kinetic method' with 2 mg of streptomycin 3 times a week from day 30 to 86 following infection. The growth of *M. leprae* was found to be inhibited during the period of drug administration but resumed promptly when therapy was discontinued, suggesting that streptomycin was purely bacteriostatic. More

Present addresses:
* Seton Medical Center, 1900 Sullivan Avenue, Daly City, California 94015 (415/991-6652).
† 225 Redding Avenue, Castro Valley, California 94546.
‡ Department of Anatomy, Box 3011, Duke Univ. Med. Cen., Durham, North Carolina 27710.

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recently (1978), the activity of streptomycin against *M. leprae*-infected mice was studied.[6] It was found that 50–100 mg/kg was the minimal effective dose and that 100 mg/kg twice weekly to *M. leprae*-infected mice beginning 2 and 22 days after infection resulted in 93 and 81% killing respectively, as determined by the 'proportional bactericidal test'.[10] The only study of the activity of other agents of this class in experimental leprosy so far was published in 1967;[5] it found gentamicin 'partially' active in the treatment of *M. leprae*-infected mice by the subcutaneous route at a dose of 165 mg/kg 5–7 times weekly continuously from the time of infection. Because of the paucity of information, particularly of a quantitative nature, concerning the activity of various aminoglycosides against *M. leprae*, we initiated this study to compare the killing potential of high-dose daily therapy with a number of these agents against *M. leprae*-infected mice.

## Materials and methods

The methods used in this study to assess bactericidal activity are necessitated because *M. leprae* has not yet been successfully cultivated in artificial media or tissue culture. In this study we utilized the 'proportional bactericidal test', first used by Hilson & Banerjee[11] with *Mycobacterium lepraemurium*, as Colston *et al.*[10] adapted it previously in order to assess the activity of ingested antimicrobials against *M. leprae*. Basically, this method involves inoculating groups of mice with serial dilutions of *M. leprae* in the foot-pads, treating the mice for a limited period, and then assessing bacillary growth after sufficient time has elapsed for detectable growth to have occurred from any surviving bacilli.

For the control and each treatment, 3 groups of 10 female BALB/c weanling mice were inoculated in both hind feet with $10^1$, $10^2$ or $10^3$ *M. leprae*. Control mice were left untreated. Aminoglycosides were given as 60 daily (days 2–61) intraperitoneal injections in alternating sites, with each dose being given in 0·2 ml of sterile normal saline. Weekly average animal weights were used to maintain dosages at 150 mg streptomycin/kg (approximately 3·1 mg), 100 mg kanamycin/kg, 100 mg amikacin/kg, 20 mg tobramycin/kg or 20 mg gentamicin/kg. In addition, similar groups of mice were treated with 0·0001% dietary dapsone (the minimally effective dose[12]) or with a combination of 0·0001% dietary dapsone and daily streptomycin (150 mg/kg) injections. Generalized seizures immediately after drug administration, leading to death, occurred in up to 50% of the streptomycin and streptomycin + dapsone treated animals during the fifth week of therapy. This prompted discontinuation of streptomycin therapy in these groups on day 38.

One year after the completion of drug therapy, mice were killed and *M. leprae* were enumerated by standard techniques[13] in each of 10 foot-pads from all but 2 groups of mice. *M. leprae* from only 8 foot-pads were counted in 1 streptomycin-treated group because of early deaths, and *M. leprae* from only 8 foot-pads were

counted in 1 amikacin-treated group because of random animal mortality throughout the study period. For purposes of calculation, growth of *M. leprae* was presumed to have occurred when foot-pad counts were $5 \times 10^4$. Percent decrease in the size of the *M. leprae* population ('killing') was calculated by a 'most probable number' calculation[14] and the Spearman-Kärber calculation described by Shepard.[15]

## Results

The foot-pad results and the resultant 'percent of bacteria killed' from this study are presented in Table 1 by means of both the most probable number and the Spearman-Kärber calculation. There was remarkable concurrence in the results found by the 2 methods, the Spearman-Kärber calculation having the advantage of allowing the expression of confidence limits. Kanamycin apparently was the most active agent ($99{\cdot}7 \pm 0{\cdot}2\%$ bactericidal), but both streptomycin and amikacin had impressive activity as well ($97 \pm 2\%$ and $96 \pm 3\%$ bactericidal respectively). Gentamicin was minimally active ($60 \pm 20\%$), while tobramycin's activity ($37 \pm 22\%$) was not significantly different from controls ($P = 0{\cdot}27$). The slightly decreased activity with the addition of dapsone to streptomycin, when compared to streptomycin, is within the error limits of the experimental system ($P = 0{\cdot}40$).

**Table 1.** Aminoglycoside antibiotics foot-pad results

| | Positive/negative | | | Killed (%) | |
|---|---|---|---|---|---|
| | $10^3$ | $10^2$ | $10^1$ | Most probable No. technique | Spearman–Kärber |
| Control | —* | 10/0 | 9/1 | | |
| Streptomycin | 10/0 | 3/5 | 0/10 | 97·2 | $97 \pm 2$ |
| Kanamycin | 2/8 | 2/8 | 0/10 | 99·8 | $99{\cdot}7 \pm 0{\cdot}2$ |
| Tobramycin | —* | 10/0 | 7/3 | 28·7 | $37 \pm 22$ |
| Gentamicin | —* | 10/0 | 5/5 | 58·5 | $60 \pm 20$ |
| Amikacin | 9/1 | 6/4 | 0/8 | 97·3 | $96 \pm 3$ |
| Dapsone | —* | —* | 10/0 | | |
| Dapsone + streptomycin | 10/0 | 5/5 | 1/9 | 95·7 | $95 \pm 2$ |

* Not counted.

Table 2 allows comparison of the killing potential towards *M. leprae* of the tested aminoglycosides in very high dosage with that of other agents previously studied[10] in dosages more nearly approximating those chronically tolerated in man. It is noteworthy that streptomycin, amikacin and kanamycin, in the high doses used in this study, are more active than certain of those drugs commonly used to treat leprosy patients, particularly dapsone.

**Table 2.** Killing potential of various antibiotics by the proportional bactericidal test

| Drug (dietary concentration) | 'Killed' (%) |
|---|---|
| Thiambutosine (0·1%)* | 0 |
| Thiocarlide (0·1%)* | 0 |
| Thiacetazone (0·1%)* | 42 |
| Dapsone (0·01%)* | 78, 72 |
| Clofazimine (0·01%)* | 98 |
| Clofazimine (0·003%)* | 99, 96 |
| Prothionamide (0·1%)* | 98·6 |
| Ethionamide (0·1%)* | 98·6 |
| Ethionamide (0·2%)* | 97·4 |
| Rifampicin (0·003%)* | 99·9 |
| Rifampicin (0·01%)* | 100 |
| Streptomycin | 97·2 |
| Amikacin | 97·3 |
| Kanamycin | 99·8 |

* Data from Colston *et al.*[10]

## Discussion

This study has demonstrated the significant antimicrobial activity against *M. leprae* of very high doses of streptomycin, kanamycin and amikacin and the inactivity of gentamicin and tobramycin. Cultivable mycobacteria have been demonstrated to exhibit a similar pattern of aminoglycoside sensitivity, with kanamycin and especially amikacin being particularly effective. It has been found[17] that amikacin at clinically achievable levels inhibited all 54 strains tested of *M. fortuitum* (MIC < 2 μg/ml) and all 11 strains of *M. chelonei* (MIC < 16 μg/ml). Though kanamycin inhibited all strains of *M. fortuitum* and *M. chelonei* at 16 μg/ml, the median MIC to it was 8 μg/ml and 1 μg/ml for amikacin. However, as in our study, Wallace found gentamicin and tobramycin less active: only 28% of the *M. fortuitum* strains were inhibited by clinically achievable levels of gentamicin and tobramycin (4 μg/ml); all strains were resistant to streptomycin (MIC > 32 μg/ml). It was found[17] that strains of *M. fortuitum* were universally susceptible to < 1 μg/ml amikacin, but that *M. chelonei* required as much as 32 μg/ml for inhibition. In this study kanamycin was more active against *M. chelonei* and less active against *M. fortuitum*.

It has been found[19] that all 33 tested strains of *M. fortuitum* and *M. chelonei* were inhibited by 2 μg/ml amikacin. Another study[19] found that amikacin and kanamycin were active against the 10 tested strains of *M. marinum* and that gentamicin was inactive. It has been found[20] that all isolates of *M. marinum* tested

were sensitive to amikacin and kanamycin and resistant to gentamicin and tobramycin. It has also been found[21] that amikacin was active against all 100 strains of a wide variety of atypical mycobacteria: 69 were sensitive to 1·6 μg/ml, 30 required 3·2 μg/ml and 1 was only sensitive to 6·7 μg/ml.

Few published or pharmaceutical-company references exist for chronic administration of high doses of aminoglycosides to mice, and fewer for prolonged intraperitoneal injection of the agents (data from computer-assisted searches of literature and in-plant information, James T. Baldini, Schering Corporation, Harold W. Brinkley, Bristol Laboratories, Robert J. Petrick, Pfizer Laboratories, written communications; and Medline search). Because of this dearth of literature, dosage schedules generally had to be extrapolated from subcutaneous administration schedules in mice or rats and intraperitoneal injection data in rats. Despite the potential for neuromuscular blockade, nephrotoxicity and resultant death, mice treated with kanamycin, amikacin, tobramycin or gentamicin retained sufficient renal function to survive for the year after the protracted high-dose course of antibiotics. Mice treated with streptomycin fared well until the fifth week, when their therapy was prematurely halted because of seizure-related deaths immediately after injection. All mice treated with streptomycin and surviving this therapeutic period had enough renal reserve to live until the completion of the study.

The practicality and usefulness of aminoglycosides in the treatment of human leprosy have not yet been established. A number of studies (judged by clinical criteria alone) have shown that streptomycin is active in human leprosy.[1–4] A small pilot trial in previously untreated lepromatous leprosy patients in Malaysia, utilizing streptomycin intramuscularly in a daily dose of 0·75–1·5 g, resulted in clinical improvement comparable to dapsone, a fall in the morphological index (percent of solid-staining bacilli in skin smears, generally correlating with viability) similar to that observed with dapsone and a loss of mouse foot-pad infectivity of skin biopsy specimens that was somewhat faster than with dapsone.[9] Five of the ten dapsone-resistant patients treated with dapsone and streptomycin by Hastings *et al.*[22] relapsed clinically, and new lesions showed high morphological indices after only 23–31 months of treatment with both drugs. Unfortunately, streptomycin resistance was not proved by mouse inoculation in these cases. No leprosy trials with other agents of this class have been published.

Aminoglycosides, as a class of antimicrobial agents, may have a place in the therapy of leprosy if pharmacological and toxic problems associated with their use can be circumvented. The potential for utilization of the aminoglycosides in treatment of infectious diseases, including leprosy, is limited by the necessity of their injection and by their pronounced oto- and nephrotoxicity in acute, subacute or chronic administrations. On the other hand, rifampin and streptomycin have been found to be truly synergistic against *M. kansasii* and *M. intracellulare* infections of mice.[23] If such synergism was found for *M. leprae*, the discovery would certainly rekindle enthusiasm for a reconsideration of a clinical

role for these agents. Pattyn *et al.*[6] have found once weekly streptomycin to be equally effective in inhibiting growth of *M. leprae* in mice to twice and thrice weekly. As WHO[24] has recommended intermittent supervised combination therapy, the use of aminoglycoside antibiotics might prove especially practical, if aminoglycoside therapy could be correspondingly spaced out to monthly intervals. Experiments are currently in progress in mice to assess the combined activity of certain of these active aminoglycosides with rifampin and the efficacy of decreasing the dose and frequency of aminoglycoside administration.

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# Clofazimine and the eye: preliminary communication

A D NÊGREL, M CHOVET, G BAQUILLON & R LAGADEC
*IOTA and Marchoux Institute (OCCGE), BP 248, Bamako, Mali, Africa*

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*Summary* Fifty-seven patients, admitted to the Marchoux Institute in Bamako, Mali, were treated with clofazimine for periods varying from between 3 and 26 months. Detailed ophthalmological examination was carried out in all cases, including visual acuity; conjunctival smears for crystals; corneal sensation; the ocular fundus after pupillary dilatation. In addition, slit-lamp examination was carried out in all cases. In this preliminary study, apart from brown–red sub-epithelial pigmentation in the cornea, no untoward effects on the eye were recorded.

## Introduction

Clofazimine is of acknowledged value in leprosy, not only for the treatment of the bacillary infection, but also for the suppression of adverse immunological reaction in lepromatous leprosy, including erythema nodosum leprosum on the skin. Hastings *et al*[1] have reviewed the publications on its value in clinical leprosy and Yawalkar & Vischer have published a monograph[2] covering its chemical composition, dosage, clinical use, complications and toxicity. In recent years, WHO have recommended it for the treatment of patients with both dapsone-sensitive and dapsone-resistant lepromatous leprosy.[3]

The fact that this drug accumulates, partly in crystalline form, in the tissues of patients, has given rise in a small number of cases to intestinal and other complications and these have been reviewed by Jopling.[4] Although some of these have been serious and even fatal, the number of recorded complications from this drug since it was first introduced by Browne & Hogerzeil in 1962[5] is not large. Despite initial fears from some clinicians that its ingestion might be associated with damage to the foetus in the pregnant mother, this has not been reported—nor has any evidence so far come to light suggesting that its use may be associated with cancer in any organ. Eye damage of any significance has not been

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reported, though Oehman & Wahlberg[6] noted brown corneal deposits, which disappeared after stopping treatment. Karat[7] described a symptomatic bluish discolouration of the lens which cleared 6–12 months after treatment was stopped, and the finding of crystals of clofazimine in the iris, conjunctiva, sclera and cornea, on slit-lamp examination, 6 months after starting treatment.

In June 1980 we had the opportunity to examine a patient on long-term clofazimine in the Department of Ophthalmology of the Centre Hospitalier Universitaire, Lille, France (Director, Professor P Francois). Apart from corneal pigmentation, no significant findings were noted, but the case prompted us to review the literature and to embark on the examination of a small series of patients treated with clofazimine in Mali.

## Patients and methods

The study included 57 patients with leprosy, hospitalized in the Institut Marchoux at Bamako (OCCGE; Director Professor P St-André). There were 41 men and 16 women. Ages ranged from 14 to 60 years with a mean of 32·5. Using the Ridley–Jopling classification, 42 were LL; 7 BL; 3 BB; 4 BT and 1 TT. The total dose of clofazimine ingested by the patient varied from 13 to 170 g, covering periods of 3–26 months; the standard dose being between 100 and 300 mg daily. In each case we examined the following—visual acuity; conjunctival smears for crystals; corneal sensation; the ocular fundus after pupillary dilatation. In addition, routine slit-lamp examination was carried out in all cases. Stools and urine specimens were collected for examination for crystals in 44 cases out of the total of 57 in the study.

## Results

These are summarized in Table 1. The microcrystals of clofazimine in tears were identified from filter paper specimens smeared on microscope slides, and then examined under normal and polarized light. They had shape, dimensions and colour identical with those of the drug from capsules; their final identity is currently being studied by thin layer chromotography in Lille. In 1 case, a female of 40 years, we noted macular degeneration in 1 eye only, but without other significant abnormality; her previous ingestion of other drugs, including chloroquine, could not be established and we are therefore reluctant to associate this abnormality to clofazimine treatment. Apart from brown–red pigmentation, no significant abnormalities were noted in the cornea. No discolouration or other change, attributable to drug treatment, was recorded in the lens. (One patient previously had an operation for cataract: in 2 others there were pre-senile lens opacities.)

**Table 1.**

| Part of the eye examined | Findings | No. |
|---|---|---|
| Tears | Red microcrystals | 47 |
| Conjunctiva | Brown–red pigmentation of the bulbar conjunctiva | 29 |
| Cornea | Hudson-Stahli lines | 7 |
| | Sub-epithelial brown–red pigmentation in the form of a 'comet's tail' | 3 |
| | White–yellow deposits scattered in the stroma | 2 |

## Discussion

The pigmentary changes recorded here confirm those of previous observers and may be of some value in checking that a patient is taking the drug, or has taken it in the recent past, though it should be emphasized that pigmentation both in the cornea and elsewhere may take many months to recede after cessation of treatment. Of perhaps greater interest was the finding of red crystals in the tears in over 82% of cases in this study. Whether this occurs only during active daily or thrice weekly ingestion of the drug and ceases after treatment is stopped, we do not know; this is one of the several points which will be investigated further in an on-going study, which will include detailed observations on the retina and optic nerve. At this stage, we can record that our preliminary observations on this group of patients do not suggest any significant, untoward effect on the eyes, directly attributable to clofazimine, except corneal sub-epithelial brown–red pigmentation.

## Acknowledgments

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# The effect of intervals between surveys on the estimation of incidence rates of leprosy

K JESUDASAN*, D BRADLEY†, P G SMITH† & M CHRISTIAN*

* *Department of Epidemiology and Leprosy Control, Schieffelin Leprosy Research and Training Centre, Karigiri, South India;*
† *Ross Institute, London School of Hygiene and Tropical Medicine, London WC1E 7HT*

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*Summary* This paper examines the effect that variation in the interval between successive cross-sectional surveys may have on estimates of the incidence rates of leprosy. The results of the present study showed that when surveys of the contacts of leprosy patients were conducted in consecutive years (gap between surveys of 1 year) the estimated incidence rate of leprosy was 4·7 per 1000 person years of risk. When there was a gap of 3 years between surveys the estimated incidence rate of leprosy was only 1·9 per 1000 person years of risk. Thus when the between-survey interval increased from 1 to 3 years, the estimated incidence rate of leprosy was halved. Similar findings were obtained from the results of prevalence surveys in the general population. The implications of these findings in relation to survey work in leprosy and possible vaccine trials are discussed.

## Introduction

There is evidence that a substantial proportion of cases of non-lepromatous leprosy may heal spontaneously without treatment. For example, it has been found[9] that between 40 and 75% of early cases of non-lepromatous leprosy healed without any treatment. Similar findings have also been reported.[8, 10]

Thus estimates of the incidence rates of leprosy, based on the results of repeated and linked cross-sectional surveys of a population, are likely to vary according to the length of the interval between successive surveys. If this interval is long, some cases of leprosy will develop and resolve during the interval and thus go undetected. This has been suggested[11] but no evidence has been presented previously to show that this occurs in population-based studies.

The data presented in this paper were collected as part of the leprosy control programme at the Schieffelin Leprosy Research and Training Centre,

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Gudiyatham Thaluk in South India. The first part of the paper is based on data collected in a sample survey of the general population in Gudiyatham Thaluk, and the second part is based on data collected from repeated surveys of the contacts of leprosy patients.

### INCIDENCE RATES OF LEPROSY IN THE GENERAL POPULATION AMONG INDIVIDUALS NOT KNOWN TO BE EXPOSED TO LEPROSY IN THE HOUSEHOLD

It has been estimated[12] that the annual incidence rate of leprosy in Gudiyatham Thaluk, in individuals not known to be exposed to leprosy in their own household was 0·8 per 1000. This estimate was based on surveys done 3–5 years apart.

To examine the influence of the interval between surveys on estimates of the incidence rates of leprosy, a random sample of the population of Gudiyatham Thaluk, not known to be exposed to leprosy in the household, was resurveyed after an interval of 1 year. One centre from each of the 4 sub-divisions of the Thaluk was surveyed in early 1981. Households in which no cases of leprosy were found in 1981, were resurveyed early in 1982. The incidence rate of leprosy was calculated among them.

## Results

In the 4 centres included in the study, 27,371 individuals were examined in 1981 who showed no evidence of leprosy and who had no known household contact with leprosy. Of these persons, 23,090 (84%) were re-examined in 1982 after an interval of 1 year. There were 37 new cases of leprosy detected in the population re-examined, giving an annual incidence rate of 1·6 per 1000 persons examined.

The estimated incidence rate of leprosy calculated by Rao *et al.*, [12] with an interval between surveys of 3–5 years, was 0·8 per 1000 population examined. Thus, increasing the survey interval from 1 to 3 to 5 years, appears to halve the measured incidence rate of leprosy. It should be noted, however, that the first study[12] was conducted more than 10 years before the present one and, although both were in the same area, it is possible that some of the differences in incidence rates may be due to methodological variations in the survey techniques and some may be due to true changes in the rates of disease.

To investigate further the influence that the interval between surveys has on estimates of the incidence rates of leprosy, data from repeated surveys of the household contacts of leprosy patients in the same area were also analysed.

### INCIDENCE RATES OF LEPROSY AMONG HOUSEHOLD CONTACTS OF NON-LEPROMATOUS AND LEPROMATOUS LEPROSY PATIENTS

The data on which this analysis is based were collected as part of a study of the

risk of leprosy among the household contacts of leprosy patients. Household contacts of registered leprosy patients living in Gudiyatham Thaluk have been surveyed annually, after the first case in the household was identified and registered for treatment. This procedure was adopted as part of the control programme, as previous studies had shown that such contacts had a higher risk of developing leprosy than individuals not exposed to leprosy in the household. During each of the annual contact surveys, however, not all the contacts have been seen, although the surveys are planned to include at least 85% of the contacts. Individuals may escape examination if they are temporarily absent from the household at the time of a survey. Thus some contacts have been examined every year (between survey gap of 1 year), others after an interval of 2 years (between survey gap of 2 years) and others after an interval of 3 or more years. Estimates of the incidence of leprosy among contacts were made after different between-survey intervals.

For all 'contacts' in the study the 'person years' of follow-up of each individual were divided according to the gaps between examinations. For example, consider the survey data for an individual as illustrated in Figure 1. This

Contact Survey Number (Conducted annually)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S | S | S | S | N | S | N | N | S | N | N | S |

S, examined and found healthy; N, not examined during this survey.

**Figure 1**

person was 'at risk' of developing leprosy for a total of 12 years but was not seen on the surveys conducted in years 5, 7, 8, 10 and 11. The 12 person years at risk were divided as follows: Intersurvey gap of 1 year = 4 years at risk (between 0 and 1, 1 and 2, 2 and 3, 3 and 4); intersurvey gap of 2 years = 2 years at risk (between 4 and 6); and intersurvey gap of 3 years = 6 years at risk (between 6 and 9, 9 and 12.)

Individuals who were found to have developed leprosy at a survey were classified according to the interval that had elapsed since they were previously seen (and were healthy) (i.e. 1, 2, 3 years, etc). In computing the person years at risk it was assumed that, on average, they developed leprosy half-way through the interval. The numbers of cases of leprosy detected after different inter-survey intervals were divided by the person years at risk associated with each interval (calculated as above) to obtain estimates of leprosy incidence rates after different survey intervals.

## Results

Table 1 summarizes the findings from these analyses. When the interval between

**Table 1.** Incidence rates of leprosy among household contacts of leprosy patients according to the between-survey gaps

| Diagnosis of index case | | Between survey gap (years) 1 | 2 | 3 | 4 | 5† |
|---|---|---|---|---|---|---|
| Non-lepromatous | Secondary cases | 130 | 24 | 10 | 3 | 3 |
| | Person years at risk | 30,034 | 7277 | 5788 | 2578 | 2782 |
| | Incidence rate* | 4·3 | 3·3 | 1·7 | 1·2 | 1·1 |
| Lepromatous† | Secondary cases | 44 | 8 | 4 | 1 | 1 |
| | Person years at risk | 6964 | 1809 | 1751 | 770 | 668 |
| | Incidence rate* | 6·3 | 4·4 | 2·3 | 1·3 | 1·3 |
| Total | Secondary cases | 174 | 32 | 14 | 4 | 4 |
| | Person years at risk | 36,998 | 9086 | 7539 | 3348 | 3450 |
| | Incidence rate:* | | | | | |
| | Crude | 4·70 | 3·52 | 1·86 | 1·19 | 1·16 |
| | Adjusted (1)‡ | 4·66 | 3·63 | 1·88 | 1·19 | 1·15 |
| | Adjusted (2)‡ | 4·74 | 3·54 | 1·79 | 1·21 | 1·14 |

* per 1000 person years at risk.

† Borderline lepromatous and lepromatous leprosy combined.

‡ (1) Rates after standardizing for age and sex differences.

(2) Rates after standardizing for time since diagnosis of index case (standardization by the indirect method using the specific rates for the whole study group as standard).

surveys was 1 year, the estimated incidence rate of leprosy among household contacts was 4·7 per 1000 person years of risk. When there was a gap between surveys of 2 years the estimated incidence rate of leprosy was 3·5; when there was a gap of 3 years the estimated incidence rate of leprosy was 1·9 and when the between-survey gap was 4 years or more the estimated incidence rate of leprosy among household contacts was 1·2 per 1000 person years of risk. Thus when the between-survey gap was increased from 1 to 3 years or 2 to 4 years, the estimated incidence rate of leprosy was reduced by more than half. The decline in the estimated incidence rate with increasing inter-survey gaps is highly significant ($\chi^2$ (1 d.f. trend) = 26·6; $P < 0{\cdot}001$).

It seemed possible that some of the differences shown in Table 1 might be due to variations in the age and sex composition of the groups compared. For example, if adults were more often 'missed' in surveys than children the lower incidence rates associated with longer between-survey gaps might arise because these latter groups comprise a disproportionate number of adults (who have a lower incidence of leprosy than children). To allow for this possibility the person

years and leprosy cases in each group were classified by age (in 5-year groups up to 54 years and 1 group for older persons) and sex. Incidence rates adjusted for age and sex differences were calculated using the method of indirect standardization (with the age-sex specific rates for all groups combined as the standard). As may be seen in Table 1 this made no material difference to the trend in incidence rates with different between-survey gaps.

It also seemed possible that a spurious correlation might arise if the frequency of 'missed surveys' increased and the incidence rate of leprosy decreased as the time since diagnosis of the index case increased. To take account of this possibility the incidence rates shown in Table 1 were also standardized for the time since the diagnosis of the index case. This again, however, made no material difference to the findings.

## Discussion

The analysis of these data indicates that the more frequently surveys are conducted the higher will be the estimates of incidence rates of leprosy. This is probably because a high proportion of early cases heal spontaneously without any treatment (over 50% within 2–3 years). Surveys done infrequently will fail to pick up cases that have evolved and healed spontaneously between 2 surveys.

A consequence of this finding is that cases of leprosy detected when frequent surveys are done are likely to be less severe (i.e. are more likely to resolve spontaneously) than those that will be detected on less frequent examinations. There were only 22 incident cases detected in the group with a between-survey gap of 3 years or more, and this effect could not be demonstrated with the present data.

The apparent decline in incidence rate with increasing intervals between surveys should be strongest for those forms of the disease with the greatest tendency to spontaneous healing. Thus it might be expected that the effect would be strong for tuberculoid forms of leprosy but not for lepromatous forms. Unfortunately, we were unable to test this in the present study as only 8 of the secondary cases detected were of the lepromatous form.

In interpreting the results of this study the possibility of bias in the findings must be considered. Individuals were not allocated to be surveyed at different intervals 'at random' and it is possible that those surveyed irregularly are at low risk of developing leprosy. It is also possible that individuals were more likely to have been present for a household survey if they had recently developed leprosy. If there were this kind of selective attendance at surveys there would be a bias to find higher incidence rates associated with shorter intervals between surveys. Alternatively it is possible that new cases of leprosy may have selectively avoided attending household surveys and this would have biased the results in the opposite direction. The possibility of such selective attendance or absence cannot

be completely excluded but, in our view, the magnitude of such biases is likely to be small and a more plausible explanation of the findings is that the lower incidence rates measured in groups of individuals surveyed after longer intervals is due to the 'self-healing' of lesions.

This finding has implications both for the design of epidemiological studies of leprosy and also for the planning of control strategies. Frequent surveys done as a means of case detection will result in a large number of early cases being detected. A high proportion of these early cases probably do not require treatment and are likely to heal spontaneously if left untreated. Thus, frequent surveys may lead to the treatment of substantial numbers of early non-lepromatous leprosy cases which would otherwise regress spontaneously without treatment. Frequent surveys either of the general population or of contacts as a means of case detection are likely to be cost-ineffective and a survey once every 3–4 years (except for special purposes of examining trends etc) may be adequate.

Our findings also emphasize the importance of standardization for the between-survey gap, when the results of surveys with different survey gaps are compared. This may be especially important in vaccine trials in which the efficacy of a vaccine is assessed by a fall in the incidence rates. It is possible, for example, that the different results obtained in the BCG trials against leprosy in Uganda and Burma could be due, at least in part, to differences in the between-survey gaps in these 2 studies.

The follow-up examinations in the vaccinated and non-vaccinated groups in the BCG trial in Uganda were, on average, at $2\frac{1}{2}$-year intervals.[6, 7] These results showed that the incidence rate of leprosy was considerably lower in the vaccinated group than in the non-vaccinated group. In the WHO BCG trial in Burma[1–3] incidence rates were calculated in both vaccinated and non-vaccinated groups based on annual re-examinations. It has been noted[1, 4, 5] that those in the vaccinated group had a higher incidence rate of leprosy in the first year of follow-up than those in the non-vaccinated group. Thus BCG may have precipitated the onset of clinical leprosy in individuals who were incubating the disease.[13]

It is possible that BCG may not prevent the development of clinical leprosy, but may enhance the healing of early leprosy lesions. Surveys done after an interval of 2–3 years would not detect cases that have developed and self-healed between surveys, whereas this effect would be much smaller if surveys were performed at annual intervals.

There has been alarm expressed in many parts of the world, where leprosy is endemic, that in spite of intensive leprosy control work, the incidence rates of leprosy remain high. A possible partial explanation of this is that intensive leprosy control results in the detection of an increased number of these early 'self-healing' cases. Thus standardization for the between-survey gap is essential for meaningful comparisons of estimates of incidence rates of leprosy and trends in the incidence rates of leprosy.

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*Lepr Rev* (1984) **55,** 361–367

# Prevalence of secondary dapsone-resistant leprosy in Upper Volta

S R PATTYN*, A YADA†, H SANSARRICQ‡
& L VAN LOO
* *Leprosy Laboratory, Institute for Tropical Medicine, Antwerp, Belgium;* † *Epidémiologiste, Ministère de la Santé Publique, Haute Volta;* ‡ *Leprosy Unit, WHO, Geneva*

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*Summary* A secondary dapsone-resistance survey was performed in 3 health sectors of Upper Volta in 1981–82, among a total population of 994 lepromatous patients. Prevalence of secondary dapsone resistance was found to be 7, 4 and 1% respectively. Analysis of the results reveals that considerable loss of viability of *Mycobacterium leprae* occurred in the specimens during transportation and was much more pronounced in the 2 sectors with the lower dapsone-resistance prevalence figures. It is therefore strongly suspected that the 7% prevalence is also representative of the sectors where the low prevalence figures were found. For other reasons discussed, the 7% figure must in its turn be a minimum.

## Introduction

Upper Volta is a land-locked country in West Africa, surrounded by Côte d'Ivoire, Ghana, Togo and Benin (South), Niger (East) and Mali (North and West) covering an area of 274,000 km$^2$ with a population of about 7 million. The capital is Ouagadougou with an international airport.

Leprosy control activities have been significantly strengthened since 1953. The whole population has been surveyed and clinically examined at regular intervals. Leprosy patients have been registered and treated.

Dapsone was administered mainly in the form of tablets distributed weekly (600 mg being taken under supervision) during the dry season (September–June) while during the rainy season patients were given 60 tablets of 100 mg dapsone (1 tablet to be taken daily). In some cases, depending on distances and density of patients, dapsone was given by injection (suspension in chaulmoogra oil, 1200 mg in 5 ml) once a fortnight.

In 1979 the Ministry of Health of Upper Volta asked THELEP whether a study on the prevalence of secondary dapsone resistance could be performed.

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## Method

By the end of 1979 2 of the authors (SRP and HS) visited Upper Volta, to investigate the possibilities, and identify 1 or more areas with a high leprosy prevalence, good records and transportation facilities. Using these factors as a basis a preliminary assessment was performed in health sector 1, Ouagadougou, sector 5, Koudougou and sector 7, Bobo-Dioulasso, the latter 2 having a daily train connection in the evening and night with Ouagadougou. In each sector 3 specialized paramedical workers were responsible for the rural leprosy control activities, there was laboratory space available, and a new binocular microscope.

A formal agreement for a research project on a survey of secondary dapsone-resistant leprosy in Upper Volta was signed by the national authorities and the Special Programme for Research and Training in Tropical Diseases.

It was decided to write a protocol detailing all activities, and to organize a 3-week training session for the 9 paramedical workers in Ouagadougou, for training in standardized clinical evaluation, smear-taking, staining slides, BI reading and biopsy taking.

The necessary equipment was provided: slides, boxes, stains, bottles, staining racks, individual patient records, registers, local anaesthetic, biopsy sets, biopsy containers, crates, vehicles and petrol.

All biopsies were to be centralized in Ouagadougou and shipped by air to the laboratory in Antwerp. The instructors of the training session were Dr Baquillon and Mr Ouologuem, both from the Institut Marchoux, Bamako, Mali. Mr Ouologuem, laboratory technician, had previously participated in a THELEP Standardization Workshop on smear-taking and reading. The session was organized in May 1980, and conducted following a specific protocol prepared by one of us (SRP). It was planned that from October to December 1980 all registered lepromatous patients, diagnosed prior to 1975 would be visited as well as all lepromatous patients who had abandoned treatment and who had presented themselves again with relapse, between 1975 and 1979, and had not been given rifampicin or clofazimine.

During this first visit a new individual patient file had to be made and smears taken from 4 sites: 2 earlobes and either 2 or 1 active skin lesions plus either forefront, thorax, back, lumbar region, arm, thigh, elbow or dorsum of a finger.

At each sector the slides were to be stained, examined and the BI calculated. During a second visit a skin biopsy was to be taken from those patients who had a BI $> 2$ at any site other than the earlobes, and sent on wet ice in a thermos flask to Ouagadougou. Each sector would take a maximum of 3 biopsies per week, in order to limit the total number of biopsies arriving weekly in Antwerp to 9.

Due to the late arrival of some supplies and other factors, the work could only start early in 1981. 62 biopsies were taken between June and September 1981, and 4 between March and June 1982.

The mouse foot-pad (MFP) technique for dapsone sensitivity testing was as described previously.[1]

## Results

Table 1 shows the overall results. In sector 1, Ouagadougou, 35 lepromatous patients, 9·8% of the total were biopsied, all biopsies contained a sufficient number of bacilli to be inoculated into mice. In 5 cases there was no multiplication in the mouse foot-pads, 5 strains were dapsone sensitive and 25 were dapsone resistant, 16 of which to the highest concentration tested: $10^{-2}$g% dapsone in the mouse diet. The overall prevalence of secondary dapsone resistance is 7%.

**Table 1.** Population, prevalence of leprosy, lepromatous leprosy and dapsone resistance in 3 sectors of Upper Volta

| | Sector 1 Ouagadougou | Sector 5 Koudougou | Sector 7 Bobo-Dioulasso |
|---|---|---|---|
| Population | 1,022,578 | 654,688 | 441,296 |
| Leprosy pat. | 9875 (9°/°°) | 4833 (7°/°°) | 1909 (4°/°°) |
| Lepromatous | 355 (3·5%) | 196 (4%) | 443 (23%) |
| Biopsied | 35 (9·8%) | 22 (11·2%) | 9 (2%) |
| Not inoc. | — | 3 | — |
| No growth | 5 (14%) | 8 (42%)* | 4 (44%) |
| S | 5 | 3 | — |
| R $10^{-4}$g% | 3) | —) | 2) |
| $10^{-3}$g% | 6) 7% | 2) 4% | —) 1·1% |
| $10^{-2}$g% | 16) | 6) | 3) |
| | 5·9% | | |

* 42% for 8 out of 19.

In Koudougou 22 biopsies, from 11·2% of all lepromatous patients, were taken. Three contained no bacilli and were not inoculated, in 8 cases there was no multiplication, 3 strains were dapsone sensitive, 8 were resistant. Based on these results the overall prevalence of dapsone resistance in the Koudougou sector is 4%.

An unexpected low number of biopsies was received from sector 7: from only 2% of the lepromatous patients. Bacilli from 2 biopsies did not multiply in mice, in 2 cases multiplication was observed in only 1 control mouse out of 5, these were also interpreted as negative for growth. Five strains were resistant. Based on these results, the prevalence of secondary dapsone resistance in Bobo-Dioulasso sector is 1·1%.

## Discussion

From 64 patients out of 66 biopsied we received also the corresponding slides of the skin smears for control. Of the 256 smears examined, 44 (17%) gave a difference of more than 1 unit in the readings, in most cases in the sense of higher scores in Upper Volta as compared with Antwerp.

Of the 66 biopsies, 3 were not inoculated because no bacilli were found in the smears from the suspensions. All 3 came from sector 5. The BI in the corresponding skin smears had been recorded 6 months earlier as 5, 0 and 3 with readings in Antwerp of 3, 2 and 3 respectively. Thus in these cases the biopsy site had been wrongly chosen. It may be advantageous to take the biopsies as shortly as possible after the skin smears have been examined.

Where the THELEP standard protocol for dapsone-resistance surveys indicates that biopsies should be taken from skin sites with a BI $\geqslant 3$, the Upper Volta Protocol stated that biopsies were to be taken from any site other than the earlobes that revealed a BI $\geqslant 2$. Four such biopsies (Table 2) were received. One multiplied regularly in mice. Three gave very weak results in the control mice, 1 of which was dapsone resistant, the 2 others have been interpreted as giving no growth. In so far that BI readings may be somewhat erroneous there may be a small advantage in including biopsies from skin smears with a BI of 2.

In 9 other cases bacterial multiplication occurred in only part of the control mice (Table 3), in only 1 case was the strain considered as dapsone sensitive, although with only 2 control mice out of 5 showing bacterial multiplication, and the mice fed the lowest concentration of dapsone not examined, this interpretation is debatable.

Multiplication in only a proportion of the mice inoculated may be the result of poor survival of *Mycobacterium leprae* in the biopsies, most probably as a result of transportation. In this respect it is remarkable that all these cases originated

**Table 2.** Results of MFP inoculation of biopsies with a BI = 2 in the corresponding skin smears

| | BI UV | BI AN | AFB/g tissue | Controls | $10^{-2}$g% | $10^{-3}$g% | $10^{-4}$g% | DDS |
|---|---|---|---|---|---|---|---|---|
| n° 1 | 2 | 3 | $2{\cdot}7\ 10^{7}$ | 5/5 | 0/5 | 5/5 | 5/5 | |
| n° 2 | 2 | 0 | $9{\cdot}10^{8}$ | 1/5 | 0/5 | 1/5 | 3/5 | |
| n° 3 | 2 | 2 | $1{\cdot}8\ 10^{8}$ | 1/5 | n.e. | 0/5 | 0/5 | |
| n° 4 | 2 | 3 | $1{\cdot}5\ 10^{7}$ | 1/5 | n.e. | 0/5 | 0/5 | |

BI UV = BI reading in Upper Volta.
BI AN = BI reading in Antwerp.
AFB: acid fast bacilli.
n.e.: not examined.

**Table 3.** Results with strains multiplying on only a proportion of the controlled mice

| Strain n° | Results in mice fed DDS 0 | $10^{-2}$g% | $10^{-3}$g% | $10^{-4}$g% | Interpretation |
|---|---|---|---|---|---|
| 319 | 2(*) | 0 | 0 | n.e. | S |
| 331 | 2 | 2 | 3 | 3 | R |
| 333 | 4 | 5 | 5 | 5 | R |
| 341 | 4 | 0 | 5 | n.e. | R |
| 346 | 4 | n.e. | 0 | 3 | R |
| 347 | 3 | 1 | 2 | 1 | R |
| 361 | 3 | 0 | 1 | 3 | R |
| 423 | 1 | 0 | 0 | 3 | R |
| 424 | 3 | 4 | 4 | n.e. | R |

(*) number of mice showing multiplication in foot-pads, always on a total of 5.
n.e.: not examined.
S: sensitive.
R: resistant.

from sector 1, Ouagadougou, from which, compared with the other 2 sectors, the lowest proportion of biopsies giving no growth were obtained (16%). However, if the number of biopsies giving 'irregular' growth and those producing no growth are added, this category represents 40% of the biopsies. This figure is of the same magnitude as the 42 and 44% biopsies from the 2 other sectors, giving no growth in the MFP. During 2 studies previously done in collaboration with the Institut Marchoux, Bamako, Mali [1,2] where the biopsies were taken to the Institute for shipment to Antwerp, respectively 14 and 25% of these failed to multiply, a significantly lower figure.

It may thus be concluded that there was a considerable loss of viability of *M. leprae* in the biopsies during this study, but that in the sector of Ouagadougou harm was limited probably due to somewhat better conditions of storage and transportation as compared with the 2 other sectors.

At first sight there seem to be considerable differences in the prevalence figures of secondary dapsone resistance in 3 nearby regions of a highly leprosy endemic country in West Africa (Table 1).

However, these differences may be more apparent than true. There was a significantly greater number of biopsies not giving rise to multiplication from sector 5 compared with sector 1 ($P=0{\cdot}04$). This was not the result of longer periods in transit or the biopsies containing a smaller number of bacilli. As discussed above this is probably the result of greater difficulties for refrigeration during transport on some occasions. If a greater fraction of biopsies from sector 5 had survived transportation and subsequently multiplied in mice, even 'irregu-

larly', it is probable that some of these would have shown dapsone resistance, increasing the prevalence figure to near that for sector 1.

The situation in sector 7 is also significantly different from that in the other 2 sectors studied. We strongly suspect that the work in sector 7 was not performed as strictly as described in the protocol. Two incidents indicate this. During the survey we were informed about difficulties encountered locally with the staining and reading of the smears. Although efforts were made to gather precise information and to give advice by cable and telex, most probably this was of little help. Furthermore, the protocol prescribed that all positive skin smears and 10% of the negative ones should be sent to Antwerp, but all the latter arrived broken.

In conclusion, it may be stated that in 1981–82 in 3 regions of Upper Volta, the mean prevalence of dapsone resistance was 3·8%, varying between 7, 4 and 1%, but that the lower figures are most probably untrue due to shortcomings in the methodology.

Furthermore, studies of this kind can make no error in producing figures which are too high, since no patients were biopsied twice. The only error possible is that some patients with dapsone resistance have not been seen, examined and biopsied. It is rather astonishing that none of the patients from whom skin smears had been taken, were missed during the second visit for biopsy taking. Therefore, the 7% prevalence of dapsone resistance must be a minimum.

During the site visit in Upper Volta in 1979, biopsies from 4 patients hospitalized in Ouagadougou and suspected of dapsone resistance were brought to Antwerp and shown to be fully dapsone resistant in the MFP test.[3] These patients were included in the 1981–82 survey, again biopsied and inoculated into mice. One did not multiply, dapsone resistance was confirmed in the 3 others.

As shown in Table 4, duration of therapy before the detection of dapsone resistance was generally long with mean durations in excess of 20 years. The earliest appearance of secondary dapsone resistance in this study was 8 years: 2

**Table 4.** Duration of previous therapy

| | | Sector 1 | Sector 5 | Sector 7 |
|---|---|---|---|---|
| R $10^{-2}$ | mean | 22·6 | 25·3 | — |
| | range | 8–35 | 19–31 | 13–30–32 |
| | median | 23 | 23 | — |
| R $10^{-3}$ | mean | 25 | 32–33 | — |
| | range | 9–33 | — | |
| | median | 27 | — | |
| R $10^{-4}$ | mean | 16·6 | — | |
| | range | 8–22 | | 17–27 |
| | median | 20 | | |

patients in sector 1, 1 with bacilli resistant against $10^{-2}$ g% dapsone and the second with bacilli resistant against $10^{-4}$ g% dapsone in the diet.

The first study on dapsone-resistant leprosy in West Africa in 1979 [1] showed a prevalence of 5·7% resistance among a population of old lepromatous cases residing near the Institut Marchoux in Bamako, Mali. A second study, performed during 1979–82 among another population in the city, revealed a prevalence of 2·3%.[2] Dapsone resistance has since been found in all countries where it has been sought:[4] it is at least 5% everywhere and on the increase. The results of the present study show that the mean prevalence of dapsone resistance in the rural areas of Upper Volta is 3·8% but in some areas reaches 7%, and such areas may be representative for the whole country rather than exceptions. This high prevalence is not unexpected since the yearly incidence of dapsone resistance has been found in both Ethiopia[4] and Mali[2] to be in the range of 2·5–3%.

As stated in the WHO Technical Report 675, Chemotherapy of Leprosy in Control Programmes, the situation concerning dapsone resistant leprosy is alarming. Furthermore, since the present study was undertaken a still more alarming, although foreseeable fact emerged, namely the very high incidence of primary dapsone resistance in both India and West Africa.[5]

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# Carcinoma in plantar ulcers in leprosy

R N FLEURY & D V A OPROMOLLA
*Hospital Lauro de Souza Lima, Rodovia Bauru-Jaú, Km 385, CEP 17.100 Bauru, Estado de São Paulo, Brazil*

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*Summary* The authors studied carcinoma arising in plantar ulcers (PUs) in 16 patients having leprosy, admitted to the Lauro de Souza Lima Hospital (Bauru, São Paulo, Brazil) from 1970 to 1982. In a study of the evolutional, clinical and pathological aspects, the main conclusions of interest were:

1 The apparent rarity of these neoplasms must be related to the fact that many observed cases are not recorded;
2 The carcinomas occur chiefly in patients of the borderline group;
3 The carcinomas have in general an ulcero-vegetating appearance, large extension and depth, and preferential situation on the proximal third of the sole of the foot;
4 Having in mind the low frequency of lesions of PUs in the foot proximal third, the incidence of carcinoma in this site can be considered relatively high;
5 From the histological point of view, the majority of tumours were well differentiated, and showed peculiarities similar to those in verrucous carcinoma, in giant condyloma acuminata and in epithelioma cuniculatum plantare;
6 The great tendency to extension of these neoplasms and the possibility of regional metastasis justify treatment by amputation.

## Introduction

The greatest problem found in leprosy is its tendency to affect the peripheral nervous system.

This tendency, in the lower limbs leads to sensory, motor and trophic disturbances leading to trophic ulcers. These, in their turn, if not adequately treated, affect the soft parts and the bones, causing progressive deformity in the foot, often leading to the need for amputation.

Plantar ulcers (PU) are a frequent complication of leprosy. Their long duration, frequent trauma, and the osteomyelitis which often follow, would be predisposing conditions for malignant transformation. The neoplasms which take place in PUs are not very common according to cases recorded in the

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**Table 1.** Clinical and pathological data

| Case | Sex | Age | Leprosy type | Leprosy duration | PU duration | Tumour duration | Location | Bone involv. | Histol. grade | Follow-up | Present condition | Initial letters |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 43 yr | TRi | 30 yr | 25 yr | 1 yr | Left P | Yes | I | 2,5 yr | Well | JGS |
| 2 | M | 68 yr | Ba | 33 yr | 6 yr | 3 mo | Left D | ? | I | ? | ? | BFG |
| 3 | M | 31 yr | Ba | 20 yr | ? | ? | Right P.M.La | Yes | II | 1 yr | Died* | LFBC |
| 4 | F | 71 yr | Bi | 17 yr | 6 yr | ? | Right P | Yes | I | 8 yr | Well | LCM |
| 5 | M | 62 yr | Bi | 30 yr | 30 yr | 5 yr | Right P | Yes | I | 6 yr | Well | SG |
| 6 | M | 61 yr | Bi | 40 yr | 25 yr | 1 yr | Left M.La | Yes | II | 6 yr | Well | JA |
| 7 | M | 73 yr | Bi | 24 yr | 13 yr | ? | Right P | No | I | 6 yr | Well | APO |
| 8 | F | 65 yr | Li | 58 yr | 31 yr | ? | Right P.M.D. | ? | II | 2 yr | Died§ | IB |
| 9 | M | 56 yr | Bi | 31 yr | 3 yr | 2 yr | Right P | No | I | 11 yr | Died† | RB |
| 10 | M | 55 yr | Ti | 20 yr | 20 yr | ? | Right P | Yes | I | 7 yr | Died‡ | DD |
| 11 | F | 71 yr | Ti | 40 yr | 23 yr | 4 yr | Right P.M. | No | I | 4,5 yr | Well | LT |
| 12 | F | 55 yr | Li | 34 yr | 1 yr | ? | Right P.La | Yes | II | 3 yr | Well | IF |
| 13 | M | 60 yr | Bi | 13 yr | 10 yr | 2 yr | Right D.La | Yes | I | 4 yr | Well | JJ |
| 14 | M | 68 yr | Li | 38 yr | 20 yr | 2 mo | Left P | Yes | I | 4 yr | Well | ABII |
| 15 | M | 65 yr | Li | 31 yr | 15 yr | 3 mo | Right D.La | No | I | 2 yr | Well | JSII |
| 16 | M | 61 yr | Bi | 23 yr | ? | ? | Left D | No | I | 1,5 yr | Well | GAS |

M, male; F, female; T, tuberculoid leprosy; TR, reactional tuberculoid leprosy; B, borderline leprosy; i, inactive; a, active; Location in plantar foot: P, proximal; M, middle; D, distal; La, lateral aspect.

* Metastasis.

† Renal insufficiency.

‡ Renal insufficiency.

§ Unknown cause.

literature.[2, 4, 7, 8, 13, 17, 21–3] However, the serious course of some of these cases, with infiltration of neoplasms in the bony parts and metastasis, justifies further study.

The aim of this work is to describe squamous cell carcinomas, which occurred in PUs in patients of the Hospital Lauro de Souza Lima (Bauru, São Paulo, Brazil) from 1970 to 1982.

## Results

Table 1 includes the main clinical and pathological data. We present some details about the clinical records of 3 patients.

*Case 1. JGS* A 43-year-old male was admitted in September 1979 for a chronic ulcer of 25 years' duration in the left heel, that had become worse 1 year ago. The patient had been under treatment for reactional tuberculoid leprosy for 30 years. His disease began with numbness in the hands and feet, right claw hands and large, elevated, red patches over the face and the limbs. The Mitsuda reaction was positive. The skin lesions disappeared after 1 year under sulphone therapy. He presented no skin lesions of leprosy but had bilateral claw hands and an ulcer with a whitish, fungating, 15-cm diameter mass, over the postero-lateral aspect of the left heel. Left inguinal lymph nodes were slightly enlarged, firm, not tender and mobile. A clinical diagnosis of squamous cell carcinoma grade I was confirmed by biopsy. A below-knee amputation of left leg and a block dissection of the left inguinal lymph nodes were carried out. The amputated leg was submitted to extensive histopathological examination including the lymph nodes. The tumour invaded all the layers of sole including the underlying bone. The lymph nodes showed no evidence of tumour metastasis. The patient had an uneventful recovery and was discharged in November 1980.

*Case 3. LFBC* A 31-year-old male was admitted in April 1975 for chronic ulcers in both feet of several years duration. Twenty years previously he had noticed erythematous patches on his trunk and right thigh. Under sulphone therapy the lesions disappeared but he took regular treatment until now. He was classified as a borderline case. On physical examination the patient was found to have hypochromic patches on his trunk and on the upper and lower extremities. Both hands showed ulnar palsy and the fingers were clawed, contracted and shortened to various degrees. The forefeet were shortened from bone reabsorption of phalanges and metatarsals. Both feet showed trophic ulcers. On the heel of the right foot there was an ulcer with proliferating granulation tissue.

As there was a clinical suspicion of malignancy a biopsy sample was taken in June 1975. It revealed a squamous cell carcinoma grade II. In July 1975 a below-knee amputation was performed. In September, enlarged, firm, tender inguinal lymph nodes were noticed and a block dissection was carried out, and a histopathological examination of the nodes showed a secondary squamous cell carcinoma. Three months later a deep, large, firm, nodule was noted over the

posterior aspect of the right thigh. A biopsy from this lesion showed again metastasis of squamous cell carcinoma. In February 1976 new metastatic nodules appeared besides the previous one. In April 1976 the patient was weak, anaemic and dehydrated. In May 1976 total fracture of 7th rib was noted and thereafter a 2 cm fast-growing metastatic nodule became obvious on the external bone. In June the patient was cachectic and wanted to go home, where he died.

*Case 9. RB* A 56-year-old male, was admitted in April 1940, and presented erythematous patches on his trunk, arms, buttocks and thighs, and wasting of his hands. Bacteriology was negative and he was classified as a borderline leprosy patient. He was discharged in May 1941. In July 1968, he was admitted with PU on his right foot and reported digestive complaints. At that time he presented muscle wasting and bone reabsorption in his hands and well-defined isolated and also confluent erythematous-hypochromic patches with marginal erythema, covering extended zones of trunk. He was under irregular sulphone therapy. In May 1970 he was admitted again with PU on the right side. The cutaneous leprosy lesions had disappeared. However, he presented muscle wasting and clawed hands, foot drop on the right side, ulceration in the right calcaneum with a vegetating base PU in that foot, PU in the left foot and bone reabsorption in both feet with amputation of some toes. There were not painful inguinal enlarged lymph nodes on the right side. The patient mentioned an increase of vegetation in PU of the calcaneum 2 years before admission, but it had been unaltered since then. In face of the clinical suspicion of carcinoma, several biopsies were performed, and the clinical assumption was confirmed after the 4th biopsy. A below-knee amputation was carried out in October 1971 and a lymph node removed from the inguinal region did not show any evidence of metastasis. The patient was without problems post-operatively, being discharged 7 March 1972. After this he was re-admitted several times due to renal insufficiency which became worse till he died, 19 February 1982.

## Discussion

### CLINICAL ASPECT

When we talk about cancer, in a general way, it does not seem that there are many differences between its incidence in leprosy patients or healthy individuals. But in relation to cutaneous and mucous neoplasms it seems that there is a greater incidence in lepromatous leprosy patients.[15]

In 1961, Leiker[12] found only 47 cases to assess and drew attention to the scarcity of references on the incidence of carcinoma in leprosy. It was noted that all related cases originated from the Iberian Peninsula and South America and that no case had been found in Africa, Indies, Philippines and some zones of the Pacific Ocean where the incidence of leprosy is very high. It was considered

unlikely[12] that there were no cases in these zones but more probable that they had simply not been recorded.

Until 1966 only 94 cases of cutaneous and mucous carcinomas in leprosy patients had been recorded; 32 of these were from Brazil.[14]

In 1966, one study[15] reviewed 40,000 biopsies on the files of the Departamento de Profilaxia da Lepra (São Paulo, Brazil) from 1930–65. This revealed 539 diagnoses of carcinomas of skin and mucous membrane in leprosy patients, bringing the total of cases found to 633.

With regard to the incidence of neoplasm in PUs there are few references in literature. This must surely be related more to the fact that cases have not been recorded than to their scarcity, as already mentioned.[12] This study[12] found no reason for the greater or lesser incidence of cutaneous carcinoma in leprosy patients than in healthy individuals of the same age, same race and similar conditions, except to confirm that the trophic lesions are very chronic and submitted to constant irritation. The first case mentioned in literature[7] was in 1942 which also referred to another similar case mentioned by Yashinobu Hayashi. Other studies,[2, 4, 8, 13, 17, 21–3] including our own, brought the number of cases described (until 1982) to a total of 33.*

It seems that neoplasma arise mainly in PUs of long duration. In our observations, the patients presented PUs from 3 to 30 years' duration and this long duration was also mentioned for all the other cases described. It is important however, to emphasize that reports from patients are often incorrect. They often report that the lesion appeared 4 or 5 years ago but during this time it healed more than once and published accounts are not always clear as to the precise identity of the foot ulcer in which carcinoma eventually develops.

The same problem occurs when we try to establish the time when malignant transformation happened; most of the information is not very precise. There are patients who get used to their lesions and do not notice changes; when asked about duration they are inclined to say that changes have taken place only recently. Others do not know whether there was any change in the appearance of the lesions. In our cases, the time of the change would seem to have occurred in 8 cases between 2 months and 4 years before the diagnosis of the neoplasm. There is, however, in some published cases greater accuracy as to the moment of this change.[8, 22]

The incidence of cases with malignant change is actually a very small number, if you take into account the high incidence of PUs in leprosy patients. In our hospital, a survey carried out in 1970, showed that 10% of our patients presented PUs. Other authors refer to a greater prevalences 15·7%[16] and 11·7%.[19] The age: of patients in whom neoplasms occur vary considerably, but all cases described were 30 years old or more. In our patients age varied between 31 and 73 years. Women are less affected than men, if we judge the available data. This could be related to a

* In 1981, a case of carcinoma in trophic ulcer is referred to[18] but the site of the lesion is not indicated.

lesser incidence of PUs in women or to the greater care they take with their lesions, lessening their chronicity.

Malignant change in plantar ulcers seems to occur more frequently in dimorphous and tuberculoid patients. The majority of our cases belonged to these clinical forms and also those described by Job & Riedel,[8] Srinivasan & Desikan.[22] Probably this would be related to the greater incidence of PUs in patients of these clinical forms due to a greater neurological involvement.

The appearance of the neoplasm is variable; in the majority of cases the border of the lesion becomes more prominent, everted and the base in general becomes vegetating. There are lesions which become bulky and rounded, adopting the 'cauliflower' aspect[22] or resembling the giant condyloma acuminatum.[3, 6, 9]

Other lesions also form exophytic masses which infiltrate through the sole forming fistulous channels, which assume a vegetating appearance when they occur in the other parts of the foot (Figure 2). These fistulae also invade the bony plane and show an identical appearance to that described in the epithelioma cuniculatum pedis[1, 5, 17, 20] (Figure 3).

Symptomatology is minimal. Some cases described refer to local pain and others to easy bleeding. Only our case No. 1 referred to bleeding, and pain was not a frequent complaint.

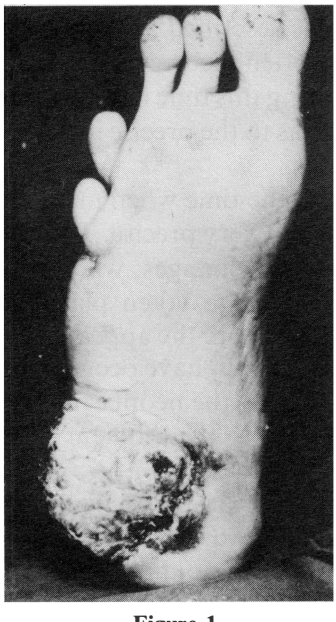

**Figure 1.**

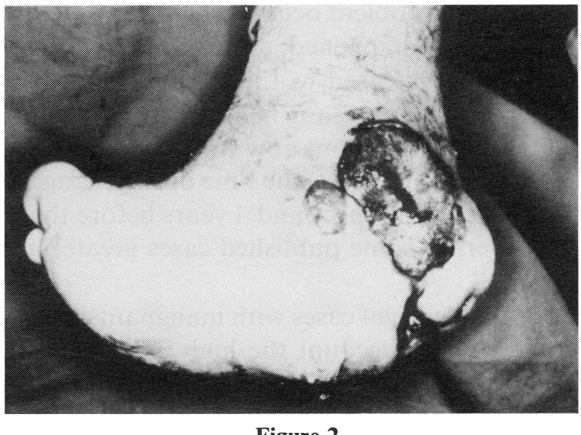

**Figure 2.**

**Figure 1.** Case 10—Squamous cell carcinoma (Grade I) Extended tumoral lesion of the foot, proximal third. Bone reabsorption at the distal third.

**Figure 2.** Case 3—Squamous cell carcinoma (Grade II) Ulcerous and vegetating tumoral lesions, proximal third and lateral aspect of the left foot.

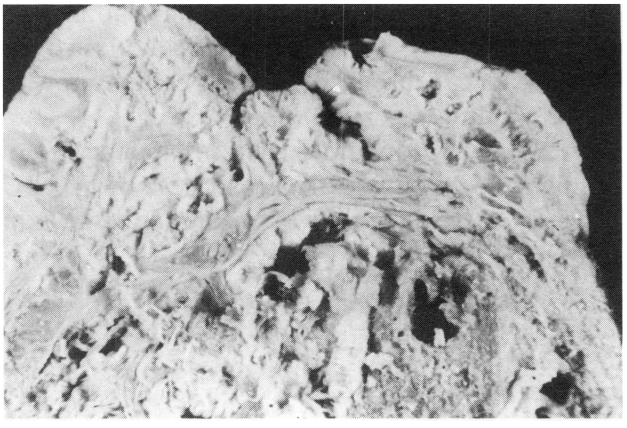

**Figure 3.** Case 14—Squamous cell carcinoma (Grade I) neoplastic extension into bone and formation of crypts.

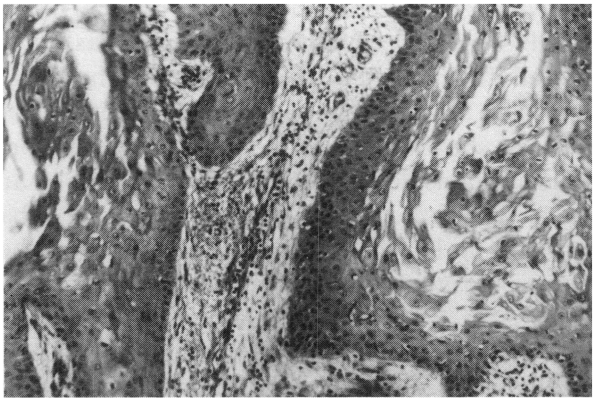

**Figure 4.** Case 11—Squamous cell carcinoma (Grade I) Disaggregation of horn cells. Initial formation of crypts.

The site of neoplasm in the sole is in general in the proximal third (Figure 1). Two cases described by Job & Riedel[8], the cases of Riedel,[21] the 2 cases of Boopalraj & Muthusami,[4] 1 of Srinivasan & Desikan[22] and 11 of our cases involved this site. Another site is in the lateral border of the foot. In these cases the patient presents his foot in echino-varo, ankylosed in that position. The support site of the foot, being not used to bear high pressures, wounds itself and the lesions open easily. Those which become malignant form vegetating masses which invade the back of the foot and open fistulae in several sites of the calcaneum. The reason for the most frequent site at the proximal third of the sole would be the greater chronicity of these lesions which lead to osteomyelitis of long duration, disintegrating the tarsus bones structure, coming even near to destruction of the tibial–tarsal joint. Lesions of the distal third of the sole are relatively of a lesser

duration because the metatarsal and the phalanx are bones with lesser size and width and because of this they can be more quickly destroyed or reabsorbed. Incidence of PU at the calcaneum level is low if compared with the other sites. About 5% in Indies;[4] 7% in our series.

Perhaps because of this, squamous cell carcinoma is not seen with the frequency which might be expected for chronic lesions like PUs. On the other hand, the incidence is relatively high if we consider only the trophic ulcers of the calcaneum.

## PATHOLOGICAL ASPECTS

The distinction between a hyperplastic pseudo-epitheliomatous reactivity and a well-differentiated carcinoma was very difficult in the pre-operative biopsies. In 1 of the cases, 6 biopsies were performed before a final diagnosis could be made. The analysis of the cytological alterations (pleomorphism, mitoses, atypical cells, etc.) was useful in only 4 cases, in which the carcinoma was considered of grade II. In the remaining well-differentiated cases (grade I), the diagnosis was mostly based in the depth and on the infiltrative features of the epithelial projections. The analysis of our cases showing extensive infiltrative tumoral masses, often involving bone, made us consider the lesions as malignant by analogy with other human neoplasms in which the diagnosis of malignancy is based on a careful evaluation of the clinical and pathological data. Examples of these neoplasms are verrucous carcinoma, the giant condyloma acuminatum and the epithelioma cuniculatum pedis.[1, 3, 5, 6, 9, 10, 20] Concomitantly, in the evaluation of the degree of malignancy of the neoplasm we found, after microscopical examination, some peculiar histological characteristics already mentioned in cases of carcinoma in this location,[1, 5, 17, 20] suggesting a possible relationship with the verrucous carcinoma, as reported by Brownstein & Shapiro.[5] The characteristics are the following:

1 Papillomatosis, hyperkeratosis and parakeratosis with formation of an actual keratinic plug which gets deeper in the depressions of the hyperplastic epithelium. In this epithelium, the intercellular bridges are not visible and the layer of squamous cells is made of voluminous, polygonal cells with abundant, homogenous and acidophilic cytoplasm. These features, described in the verrucous carcinoma and in the epithelioma cuniculatum pedis[20] were present in all but one of our cases.

2 Keratinization and disaggregation of the squamous cells forming real crypts at the level of the epithelial projections (Figure 4). This alteration was observed in 8 cases (1, 3, 4, 6, 11, 13, 14 and 15); in 6 cases (1, 4, 6, 13, 14 and 15) the crypts were macroscopically visible. Aird *et al.*[1] think these changes occur due to an excessive keratinization which is characteristic of the epithelium in this localiza-

tion. Similar changes, however, are described in the verrucous carcinoma located in the floor of the mouth and in the giant condyloma acuminatum.[1, 3, 5]

From the evolutive point of view, not even all the tumours are restricted to local growth, without metastasis and an effect on the general condition. A case of Hayashi & Fukuda,[7] 2 cases of Job & Riedel,[8] a case of Riedel[21] and 1 of our patients had metastasis and 3 of these patients died.

Summarizing, carcinoma which arises in the PUs of leprosy patients, must be more common than the literature dealing with this matter suggests, chiefly those arising in PUs of the proximal third of the sole. They can lead to death with metastasis in the regional lymph nodes and systemic sites.

The PUs of the calcaneum are easily treated with adjustments in the shoes or when they are extended, by surgical operations. When they have not been adequately treated and present malignant transformation, amputation is indicated,[5, 11] if we consider the clinical presentation of the lesion, the great extent of the ulcerous-vegetating process, and the radiological evidences of bone involvement.

The patient should be followed carefully for the development of metastasis. It is true that these patients already suffer, and with some frequency, from several kinds of mutilation and an amputation would increase their limitation to a greater extent. But preservation of life and the possibility of an efficient prosthesis justify such a course of action.

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# Multibacillary leprosy in an 18-month-old child: a case report

J NSIBAMBI, TEBEBE YEMANE BERHAN & TITIA WARNDORFF VAN DIEPEN
*All Africa Leprosy and Rehabilitation Training Centre (ALERT), PO Box 165, Addis Ababa, Ethiopia*

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*Summary* A case of multibacillary leprosy, proven on slit-skin smears and skin biopsy, is reported in a child aged 18 months in Ethiopia. The father and 2 other children were not available for examination, but the mother was a registered case of mid-borderline (BB) leprosy of 5 years' duration. The clinical, bacteriological and histopathological findings are described and discussed in relation to the accepted incubation period of leprosy and the possibility of intra-uterine infection.

## Introduction

In practice, leprosy cases in children below 2 years of age are exceedingly rare.[1] Lepromatous cases are uncommon before puberty, the great majority of cases in children being indeterminate or tuberculoid.[1] The incubation period of leprosy is on average from 2 to 5 years, but in lepromatous (multibacillary) leprosy, there is the possibility of a somewhat longer incubation period.

When lepromatous leprosy is diagnosed with certainty in a child under 2 years of age, as in the case we now report, there is obviously clear evidence for an incubation period shorter than that usually accepted. It is important to report such cases and to consider the possibilities of infection at birth, after birth or even *in utero*.

## Case report

*A male Ethiopian child* aged 18 months was presented by his mother for skin lesions which she had noticed for 2 months. The lesions started on the back and spread to other parts of the body. The mother had herself attended the clinic for a skin condition which was diagnosed as borderline leprosy (BB). The duration of

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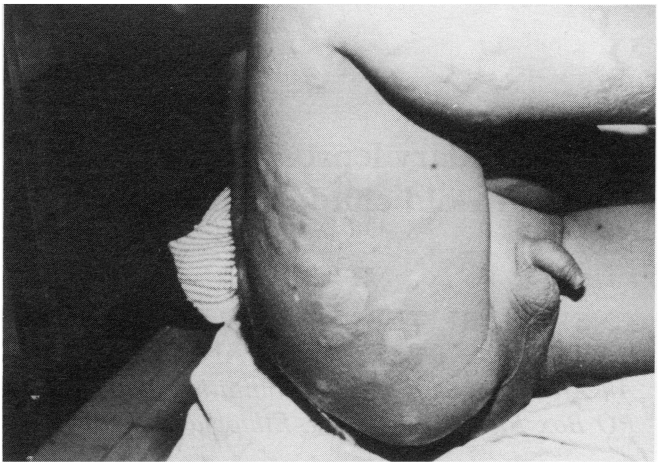

**Figure 1**

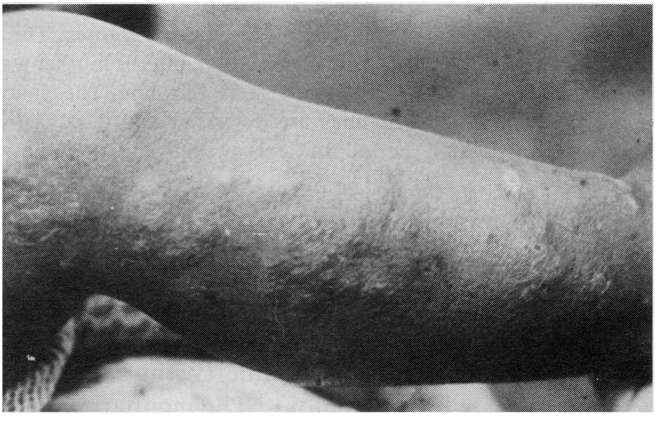

**Figure 2**

her disease was 5 years and she denied having received anti-leprosy treatment in the past. The father of the child and 2 other children in the family were not available for examination but were reported to be free from leprosy. There was no history of leprosy in the family.

Apart from the presence of the skin lesions, the child looked quite healthy. He was well nourished, of normal weight and was quite cheerful before he was subjected to the many investigations. He was not anaemic and the liver and spleen were not enlarged. There was no lymphadenopathy. There were many skin lesions present (Figures 1 and 2) consisting of small plaques (raised flat lesions) of variable sizes, mostly under 2 cm in length and looking erythematous, smooth and shiny. They were mostly distributed over the face, forehead, cheeks, upper arms and legs. Apart from a lesion on the left ear, the ears were not infiltrated and

the oral and nasal cavities were free from lesions. There was no madarosis and the eyes were normal. The hands and feet were moist and were free of any ulcers. No thickened nerves could be detected.

INVESTIGATIONS

*The bacteriological index (BI)* showed 2+, 2+, 2+ 1+ and 2+ at right ear, right eyebrow, left ear, left buttock and right thigh. Repeat examination showed 3+, 3+, 3+ and 3+ in smears taken from the most prominent lesions. The morphological index (MI) gave a figure of up to 6 in all 4 smears.

*A skin biopsy* showed a differing histological infiltrate in the upper, mid and lower zones. The upper zones had a picture resembling BL leprosy on the Ridley–Jopling classification, whilst the lower infiltrate had epithelioid cell foci, surrounded by lymphocytes and with some Langhans giant cells. Bacilli were easily found and the bacteriological index of the granuloma ranged from 2 to 4, with most bacilli-fragmented. The overall picture mainly suggested a downgrading process from BT to BL.

*Lepromin test:* positive 3 mm (Mitsuda).

*Mouse foot-pad inoculations.* A punch biopsy was performed from the lesion on the back, found earlier to yield larger numbers of *Mycobacterium leprae* with a proportion of solid forms (BI 3 and MI 6% at this site). The specimen was homogenized and the *M. leprae* recovered ($5{\cdot}2 \times 10^6$ AFB) and counted.[13] The organisms were diluted so as to provide an inoculum of $5 \times 10^3$ *M. leprae* per foot-pad and 26 locally bred Swiss albino mice were inoculated each in both hind foot-pads. One group of 8 mice served as untreated controls, whereas other groups of 6 mice were fed on a diet into which had been incorporated dapsone in a concentration of 0·0001, 0·001 and 0·01 g per 100 g diet. Harvests of *M. leprae* were performed from both hind foot-pads of 1–2 control mice beginning 6 months after inoculations. At 10 months evidence of multiplication (an average yield of $7 \times 10^5$ *M. leprae* per foot-pad) was observed in the control mice. On the other hand, the yield of *M. leprae* in any of the harvested 5 mice administered dapsone in a concentration of 0·0001 g per 100 g diet appeared to be fewer than $1{\cdot}3 \times 10^4$ organisms. The patient's *M. leprae* were therefore considered to be fully susceptible to dapsone.

*The mother* was seen for the first time when she brought her child for examination. She gave a history of skin lesions that had been present for 5 years. She also complained of burning sensation all over the body, numbness in the hands and ulcers on the feet. After delivery of the child, the lesions became red and swollen. The swelling disappeared after about 3–3½ months. She had never

received anti-leprosy treatment up to the time when she came to us. On examination, she was found to have many hypopigmented macular skin lesions, mostly on her back. There was no loss of sensation in the lesions on light cotton-wool touch. Both ulnar nerves were thickened. There was partial madarosis. BI = 1 (2+, 1+, 0, 1+, 1+ 2+). It is possible, that her leprosy had upgraded after delivery.

## Discussion

No age is exempt from leprosy[2] but, in practice, leprosy cases in children below 2 years of age are exceedingly rare.[1, 3] Two cases of borderline–tuberculoid (BT) leprosy discovered in children aged 18 months have been reported.[4] In surveys,[5] leprosy in the age group 0–1 was found, but in the age group 1–4, 8 cases in Nigeria (Katsina), 2 cases in Cameroon and 1 case in Thailand (Khon Kaen) were found. Lepromatous cases are uncommon before puberty and the great majority of cases in children are indeterminate or tuberculoid[1] Bechelli *et al.*[5] did not find any lepromatous leprosy among the age group 0–4 and no smear-positive case was found in the 4235 pre-school children examined in Bombay.[6] It is stated[7] that for a child born to a woman who has had an active relapse (of leprosy) during pregnancy there is a risk of clinical leprosy in early childhood. This is likely to be of indeterminate type and self-healing, particularly in the very young child and probably occurs more frequently than realized hitherto.

The consensus of opinion is that in most cases the incubation period is about 2–5 years.[8] Immunological investigations have revealed that most of the people exposed to leprosy will show responses suggestive of subclinical infection[9–10] and this can be found within a few weeks of exposure. Intra-uterine infection is not yet proven but immunological studies suggest that this probably takes place.[11–12]

When multibacillary leprosy is, therefore, diagnosed in an 18-month-old child 2 possibilities come to mind; the incubation period was shorter than generally believed to be in multibacillary leprosy or this was the result of an intra-uterine infection.

This case should alert health workers to examine infants of leprosy mothers and to do skin smears in all children with suspicious skin lesions.

## Acknowledgments

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# Hypersensitivity reaction to dapsone: report from Malaysia

KADER NAINA MOHAMED
*Department of Dermatology, General Hospital, Johor Bahru, Malaysia*

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*Summary* Three patients who developed hypersensitivity reaction at varying intervals after the initiation of dapsone therapy are described. Two of them had leprosy whereas the other had dermatitis herpetiformis. Their clinical manifestations were not uniform. Although fatal complications have been reported, the unique role played by dapsone in the treatment of leprosy and the importance of recognizing this reaction are discussed.

## Introduction

Dapsone is a very familiar sulphonamide to those who work in the field of leprosy. It is also used by the dermatologist for the treatment of chronic bullous disorders—dermatitis herpetiformis,[1] Hailey–Hailey disease,[2] bullous pemphigoid, and various other conditions such as subcorneal pustular dermatosis, erythema elevatum diutinum, acne conglobata and leucocytoclastic vasculitis.[3] In developing countries like Malaysia where dermatologists are actively involved in the management of leprosy patients, the beneficial effect of this drug for both skin disorders and leprosy can be easily observed and appreciated.

Dapsone is a competitive inhibitor of para-aminobenzoic acid, and thereby interferes with the synthesis of folic acid. Nevertheless, how it exerts its bacteriostatic effect in leprosy is not well established. The mechanism of action in dermatitis herpetiformis is believed to be that of inhibition of the alternate pathway in the complement system and that of polymorpho-leucocyte cytotoxicity.[4] Dapsone is well absorbed when administered orally and about 50–80% is plasma-bound.[5] It undergoes enterohepatic circulation and is subjected to acetylation and renal excretion as glucuronyl conjugate. Its half-life is around 21 h.

The side-effects of dapsone are methaemoglobinaemia, haemolytic anaemia, megaloblastic anaemia which are dose-related, agranulocytosis, peripheral neuropathy, nephrotic syndrome[6] and hypo-albuminaemia.[7] Hypersensitivity

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reactions, rarely seen nowadays were observed as early as 1950 and named as dapsone or DAPT Syndrome[8] which was characterized by fever, generalized rash, lymphadenopathy, leucocytosis involving usually the monocytes and jaundice which occurred within the first 6 weeks of dapsone treatment. Recently, the author encountered dapsone hypersensitivity in 2 patients with leprosy and 1 with dermatitis herpetiformis.

## Case reports

*Case 1.* A 17-year-old Malay girl presented with erythematous, annular rash on the right palm and dorsum of left leg with impaired sensation and thickening of the corresponding ulnar and lateral popliteal nerves with slight tenderness. The bacterial index (BI) was 2·6 and morphological index (MI) was 3·1%. Skin biopsy for histopathology and mouse foot-pad inoculation for detection of primary dapsone resistance was done. Other relevant investigations such as full blood picture, liver function tests (LFT), blood urea and Glucose-6-Phosphate-dehydrogenase (G6PD) were within normal limits. She was started on rifampicin 600 mg and dapsone 100 mg daily. Histopathology confirmed the clinical diagnosis of borderline lepromatous (BL) leprosy. On the third week of the antileprosy treatment when the MI had become 0 and the BI was 2·3, the patient suddenly developed fever, generalized rash and swelling and tenderness of cervical group of lymph nodes and bluish discolouration of lips and nails. The temperature was 40°C.

The first symptom to appear was the generalized erythematous rash whose distribution was mainly on the face, trunk and limbs with minimal involvement of the palms and soles. The eyes, mouth and the genitalia were not affected. The rash was predominantly macular with few papules scattered over the abdomen. The nerves were slightly tender, the initial skin lesions on the palm and foot did not become very erythematous or shiny; no hepatic tenderness or jaundice, ESR was 45 mm and LFT was within normal limits. Peripheral blood film showed haemolytic anaemia. There was no tender nodule and eyes were clear. Paul–Bunnell test and repeat skin biopsy were not done. The clinical picture was not that of reversal or type I lepra reaction and the chain of symptoms was more in favour of drug hypersensitivity. Therefore all drugs were stopped and general supportive treatment instituted. Within 2 days the rash faded without leading on to exfoliative dermatitis, the temperature dropped to normal, cervical lymph nodes became less tender and methamoglobinaemia disappeared. One week after she was back to normal, dapsone 25 mg was given, 6 h later she developed a temperature of 39°C with headache and no vomiting. This proved that she manifested dapsone hypersensitivity. She was started on clofazimine, 50 mg daily.

*Case 2.* An 18-year-old Malaysian Aboriginee girl was seen with an annular patch about 10 cm in diameter with a central area of hypopigmentation and

hypoanaesthesia on the right gluteal region. The BI was 0. Skin biopsy confirmed borderline tuberculoid (BT) leprosy. After performing other relevant tests she was started on dapsone 100 mg daily. The following day after she was given a second dose of dapsone she developed generalized morbilliform rash with loss of appetite and a temperature of 39°C. On the third day she developed jaundice, cervical lymph node enlargement, but no cynosis. The ESR was 62 mm, serum glutamic-oxaloacetic transaminase was 48 IU, bilirubin 5·6 mg/dl. Peripheral blood film was normal. It was not known if she had ever taken dapsone or any other sulphonamide previously. She did not warrant prednisolone and her condition returned to normal within a week on withdrawal of dapsone and on symptomatic treatment. Later she was started on clofazimine 50 mg daily.

*Case 3.* A 61-year-old Pakistani man was seen with extremely pruritic vesicles, of one month's duration, distributed over the forearms, neck and back of chest and lumbar region. Skin biopsy confirmed the diagnosis of dermatitis herpetiformis (DH). Relevant investigation which included G6PD activity were normal. He was started on dapsone 100 mg daily which was gradually increased to 200 mg daily, according to clinical response. After 4 weeks of dapsone therapy, the patient developed a high fever, 40·5°C, cervical lymph node enlargement and hepatic tenderness, but no jaundice was seen. Vesicles of DH reappeared but generalized macular or papular rash was not observed. The total white cell count was high, 21,500. No evidence of infection was noted. Dapsone was stopped and when clinical and biochemical parameters had become normal, he was given dapsone 50 mg. The following day his symptoms recurred. Subsequently he responded well to Sulphapyridine 500 mg tds.

## Discussion

In Malaysia, dapsone was used in 1948 at Sungai Buloh Leprosarium. The author's centre has about 570 leprosy patients in the follow-up, most of them receiving dapsone as maintenance therapy. The 3 patients reported here are the only cases known to have developed dapsone hypersensitivity in this region. A syndrome which included fever, mononucleosis, splenomegaly, hepatitis, and exfoliative dermatitis was first described by Lowe & Smith in 1949[9] in patients receiving large doses of dapsone. They called it 'glandular fever precipitated by sulphone therapy' as they found a rise in Paul–Bunnell titre. Allday & Barnes[8] in 1951 gave it the name 'DADPS syndrome' and were the first to put forward the view that it was a hypersensitivity syndrome. Their dosage of dapsone was 100 mg/day slowly increasing to 200 mg/day. These authors stressed that the syndrome invariably developed 5–6 weeks after commencing dapsone therapy and was sometimes fatal, and concluded that the drug was too toxic for use in leprosy. In 1956, Leiker[10] described 3 cases of the 'mononucleosis syndrome' with 1 death; he concluded that it was not glandular fever but was likely to be due to a

delayed allergic reaction. After this paper there was a lapse of 25 years with no further reports until 2 papers appeared in 1981[11, 12] describing a reappearance of the sulphone syndrome, confirming the clinical picture described by the early writers, but showing that the leucocytosis is not always a mononucleosis; for example, 1 study[11] describes a white cell count of 25,000/cu mm with 59% neutrophils, 22% lymphocytes, 10% eosinophils and 9% mononuclears, while another[12] describes a fatal case in which the number of leucocytes rose to 72,800/cu mm with 28% eosinophils. The fact that the patient who was the subject of the report[11] was receiving only 50 mg/day of dapsone emphasizes the fact that the sulphone syndrome is not dose-related.

The patients reported here developed hypersensitivity to dapsone and the G6PD activity was normal. All 3 of them—young and old—had fever, the onset was sudden, occurring 48 h, as in Case 2, to 4 weeks, as in Case 1, after the initiation of dapsone therapy and had tender cervical lymph node enlargement. Cases 1 and 2 had generalized erythematous rash which was to a great extent macular, resolved on withdrawal of dapsone without resulting in exfoliative dermatitis and preceded the constitutional symptoms. A generalized rash was not observed in Case 3. In addition, Case 1 had developed methaemoglobinaemia and Case 2 had clinical and biochemical evidence of hepatitis. In Case 1 the lepra reaction which occurs usually within 6–12 months of therapy may not be a possibility. The drug was readministered in a smaller dose for confirmation in Case 1 and to observe the dose-related effect in Case 3. The severity of the reaction in these patients was moderate and all attained resolution without the use of prednisolone, unlike those cases reported previously.[11, 12] Usually the symptoms of dapsone hypersensitivity reaction develop during the first 3–6 weeks after the start of therapy. But Case 2 developed symptoms 2 days after starting dapsone. This raises the question of whether the patient had taken dapsone in the past or developed cross-allergy to previous intake of any other sulphonamide or related drugs. Although the patient was unable to furnish details in this regard, such a justifiable possibility could not be ruled out. Case 3 had another interesting feature—a good response to another sulphonamide, sulphapyridine.

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# Multidrug therapy for leprosy in Trinidad and Tobago: a preliminary report

R F KEELER
*Hansen's Disease Control Unit, Ministry of Health and Environment, 182 Western Main Road, Cocorite via St James, Trinidad, West Indies*

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*Summary* Dual chemotherapy for multibacillary patients was introduced in Trinidad and Tobago in 1971, using clofazimine and dapsone. Since 1973, newly-diagnosed multibacillary patients have received triple therapy, at first only for a few weeks, but later for 3 months, adding rifampicin 600 mg daily to the clofazimine and dapsone already in use. In January 1982, the short-course regimens recommended by the World Health Organization (WHO) (Technical Report series, 1982) were introduced and after a period of 21 months, 531 patients had completed their courses of treatment. This paper reports preliminary results in this group.

## Introduction

Trinidad and Tobago is the southern-most island nation of the Caribbean Sea, lying close to the South American coast of Venezuela. This nation covers an area of 5128 km$^2$ and has a population of 1·1 million. Its inhabitants are primarily of East Indian and African descent in nearly equal numbers.

In 1969 the Ministry of Health abolished a policy of admitting newly-diagnosed leprosy patients to its leprosarium on Chacachacare Island, and in 1978 the Government took a decision to close the leprosarium and to find suitable accommodation in the community for the inmates. Patients have since then been treated successfully in existing health centres throughout the nation.

Dual chemotherapy for multibacillary patients was introduced in 1971 using clofazimine 100 mg and dapsone 100 mg daily in adults. Since 1973, newly-diagnosed multibacillary patients have been given triple drug therapy, at first for only a few weeks, but later for 3 months, adding rifampicin 600 mg daily to the clofazimine and dapsone already in use. After the initial 3 months of therapy, the latter two drugs were continued until the patient was bacteriologically negative

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over a period of at least 12 months, after which dapsone monotherapy was maintained indefinitely.

A vertical programme, the Hansen's Disease Control Unit, was established in 1971 with emphasis on case finding and case holding in an out-patient setting.

Three years after the unit was established, the new case rate peaked at twice the level in year 1, and it has steadily fallen since then to its present low level which is half the new case rate of year 1, or one-quarter of the peak new case rate of year 3.

Corresponding with the fall in the new case rate there has been a fall in the number of bacteriologically-positive patients (from a peak of 188 in 1974 to 35 at the end of 1982) indicating that: 1, chemotherapy was successful; and 2, the reservoir of *Mycobacterium leprae* was being reduced, thus enabling a chain of transmission to be broken.

Unfortunately we have had unacceptably high rates of non-compliance over the years, especially after the skin lesions disappeared. Too many patients defaulted before completing the recommended period of time needed to take a patient's name off the register and to consider him as released from control. Although we have had very few (3) cases of secondary drug resistance to dapsone and no known cases of primary drug resistance, we were therefore greatly interested to learn of the World Health Organization (WHO) short course, multidrug, partially supervised regimens,[1] primarily because of our compliance problems and heavy workload. Having adequate personnel, medication and mobility, we decided to start the WHO regimens in January 1982, making them available to all patients on our register, and to new patients on diagnosis.

## Patients and methods

As of 1 January 1982 we had 718 patients on our register. Thirty new patients were added in 1982 and 17 new patients were added during the first 9 months in 1983. After 21 months of following this regimen, 531 patients have completed their course of therapy.

Our standard drugs were dapsone, clofazimine, rifampicin and DADDS. For 3 patients who had proven or clinically suspected secondary drug resistance to dapsone we used ethionamide instead of dapsone and DADDS. For 1 who refused to take clofazimine we used ethionamide as the alternative drug. Our standard regimen for all patients, whether having paucibacillary or multibacillary disease, was as follows (for 70 kg adults): *once a month, under supervision:* rifampicin 600 mg, clofazimine 300 mg, dapsone 100 mg, DADDS 450 mg, i.m.; *daily, self-administered:* clofazimine 100 mg, dapsone 100 mg. We decided to add DADDS and to give dapsone under observation monthly, in addition to the rifampicin and clofazimine, because of our concern regarding compliance. Fortunately, there is minimal objection in Trinidad and Tobago to the temporary

cutaneous discolouration caused by clofazimine. However, there is moderate objection to the use of DADDS, primarily because of the pain associated with its deposition in the gluteal muscles.

We gave 6 months of multidrug therapy to patients with paucibacillary disease who were still on our register, whether their disease was active or inactive. We also gave only 6 months of multidrug therapy to patients with multibacillary disease if they had been bacteriologically negative (no AFB seen on slit smear) for 4 years or more prior to the commencement of this new regimen. We gave 12 months of multidrug therapy to patients with multibacillary disease if they had been bacteriologically negative for at least 2 years, but for less than 4 years. If patients with multibacillary disease were bacteriologically positive at any time within the preceding 2 years, they were scheduled for 24 months of multidrug therapy.

Patients were examined and given treatment at regularly held leprosy clinics in 10 health centres scattered throughout the island until 31 March 1983, when 3 of the smaller clinics were discontinued due to a lack of patients needing medication. In addition, institutionalized, aged, isolated and homebound patients were seen at their places of residence for similar care by our District Health Visitors with periodic visits also being made by our medical officers. Our field staff is composed of 2 physicians, 1 medical social worker, 1 laboratory technician, 1 physiotherapist, 1 orthopaedic shoemaker, 4 nurses (District Health Visitors), and 5 follow-up workers.

Patients who were non-compliant were pursued by letters and by personal visits. Attempts were made to meet their unique needs, even if this meant providing a time and place for examination and treatment outside of the traditional working hours and venues. As a result many received chemotherapy who otherwise would have remained out of control.

We plan to re-examine the patients who have had paucibacillary disease at 6-month intervals for 3 years prior to ending their surveillance. Patients with multibacillary disease will be re-examined also at 6-month intervals, but for a total of 5 years before terminating their surveillance.

## Results

There was excellent acceptance of the multidrug regimen by our patients. Only 3 refused to take the monthly supervised dose of medication. Nineteen others continued to refuse to take any anti-leprosy medication. We have been unable to contact 18 of our registered patients. Five patients complained of adverse responses to the multidrug, supervised regimen and 4 of these refused further treatment. The patient who continued with treatment was a 58-year-old East Indian female who reported a rash which appeared about an hour after taking her supervised medication. This occurred twice, following her second and third

monthly visits, and in each instance disappeared in 24 hours. Only clofazimine and dapsone were given on her fourth monthly visit. No cutaneous reaction was noted. Rifampicin was reintroduced on the fifth monthly visit with no adverse response. She continued then on the normal multidrug regimen until her course was completed without additional adverse responses.

During the first 21 months of pursuing the WHO's recommended multidrug, partially supervised, short-course regimen 531 patients completed their chemotherapy.

Of the 718 on the register on 1 January 1982, 514 completed their chemotherapy. Thus 72% of patients on the register when this regimen commenced have completed their treatment. Fifteen others were patients diagnosed in 1982, and an additional 2 were diagnosed in 1983.

A breakdown of the 531 patients reveals a slight preponderance of males (54%), a low proportion of children (6%), a high proportion of patients with a diagnosis made more than 10 years ago (60%), and a nearly equal division into paucibacillary and multibacillary groups (see Tables 1–4).

We had a higher percentage of males than of females in our original group of 718, so we were not surprised to find a slight preponderance of males among those who had completed their chemotherapy.

Regarding children, less than 8% of our registered patients at the beginning of this multidrug programme were under the age of 15 years, so a low proportion of children was expected out of the 531 patients who completed their chemotherapy. All 31 children who completed their chemotherapy were in the 5–14-year age group.

Of the 40% whose diagnoses were made within the last 10 years, 74 patients (14% of the 531) had their diagnoses made during the last 5 years.

Since 51% of those completing the multidrug regimen had multibacillary

**Table 1.** Patients completing multidrug regimen

| Sex | Number (%) |
|---|---|
| Male | 288 (54) |
| Female | 243 (46) |
| Total | 531 |

**Table 2.** Patients completing multidrug regimen (age)

| Age group (years) | Number (%) |
|---|---|
| 0–4 | 0 |
| 5–14 | 31 (6) |
| 15–24 | 91 (17) |
| 25–44 | 131 (25) |
| 45–64 | 172 (32) |
| 65–84 | 104 (20) |
| 85+ | 2 (<1) |
| Total | 531 |

**Table 3.** Patients completing multidrug regimen (time since diagnosis)

| Years since diagnosis | Number (%) |
|---|---|
| 0–9 | 213 (40) |
| 10–19 | 149 (28) |
| 20–29 | 78 (15) |
| 30–39 | 59 (11) |
| 40–49 | 26 (5) |
| 50–59 | 5 (1) |
| 60–69 | 1 (<1) |
| 70+ | 0 |
| Total | 531 |

**Table 4.** Patients completing multidrug regimen (classification)

| Classification | Number | |
|---|---|---|
| Paucibacillary | | |
| Indeterminate | 9 | |
| Tuberculoid (TT) | 124 | |
| Borderline (BT) | 127 | |
| Sub-total: | 260 | (49%) |
| Multibacillary | | |
| Borderline (BB) | 50 | |
| Borderline (BL) | 47 | |
| Lepromatous (LL) | 174 | |
| Sub-total: | 271 | (51%) |
| Total | 531 | |

disease and since in the past we tried to keep multibacillary patients on chemotherapy for a lifetime it is not surprising to see that over 30% of the patients had been diagnosed 20 years ago or more, and that 52% are over age 44.

One 44-year-old obese female with tuberculoid disease has retained her hypopigmented lesion up to the present time (15 months after her 6 months of multidrug therapy was completed). A repeat biopsy revealed resolving granulomas, but no evidence of active disease.

Other patients with tuberculoid disease who had remaining faint hypopigmentation at the time chemotherapy was discontinued at 6 months, have all subsequently re-pigmented well, with no recurrence so far. Nine paucibacillary patients were given several months additional treatment because of prominent lesions of unresolved neuritis at the 6 months point.

Since the completion of therapy 1 patient has migrated to the United States of America, and 3 patients have died, leaving 527 for surveillance. None of the 3 deaths was related to their chemotherapy.

There was an initial increase in the attendance at clinics in early 1982, but since the latter half of 1982 there has been a considerable decline. As a result 3 smaller clinics have been closed. Patients from these areas can attend 1 of the remaining 7 clinics for their semi-annual evaluations over the next 3–5 years. Another clinic was closed 1 April 1984. Hopefully, leprosy and dermatological services could be combined in the remaining strategically located centres for the future.

Lesions definitely respond much more rapidly, clinically, in patients on multidrug therapy in which rifampicin is included than in monotherapy or dual therapy where rifampicin is absent. Easily detectable improvement occurs in less

than 2 weeks in most patients. This is encouraging to the patient as well as to the physician.

There has not been any increase in the frequency or in the severity of reactions seen in patients taking this multidrug regimen. No disabilities have developed during or after the period of chemotherapy.

## Discussion

It is too early to accurately evaluate the effectiveness of this multidrug regimen in Trinidad and Tobago. In another 2–3 years, however, I feel we should be able to satisfactorily evaluate its effectiveness in patients with paucibacillary disease. It will probably take a bit longer to adequately evaluate its effectiveness in patients with multibacillary disease.

Most patients are happy to be able to cease taking medication after a specified, relatively short period of time; a few, however, want to remain on medication indefinitely.

With three-quarters of our patients having completed their chemotherapy our staff can now concentrate more effectively on newly-diagnosed patients, bacteriologically-positive patients, non-complying patients and significant contacts. We are now able to tackle our high priorities more effectively and help our patients sense that having leprosy need only be a chapter in their lives. Their outlook on life has improved considerably as they anticipate freedom from medication and from disease in the future.

## References

[1] WHO. *Chemotherapy of Leprosy for Control Programmes. Report of a WHO Study Group.* (Technical Report series 675). Geneva: WHO, 1982.

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*SPECIAL ARTICLE*

# Treatment of leprosy in rural India as seen on a medical student elective

D N RILEY*
*Christian Fellowship Community Health Centre, Ambilikkai, Madurai District, Tamil Nadu*

*Summary* A personal report on the community and hospital treatment of leprosy in the rural villages of South India. Details are given of the present drug regimens and the practical difficulties encountered in implementing them successfully.

## Introduction

I went to India on my elective from Birmingham University Medical School with the intention of seeing medicine practised in an underdeveloped country with limited resources, and with a different spectrum of disease. One of the diseases I particularly wanted to study was leprosy. I was armed with only a standard British medical student knowledge about leprosy, and a few mental pictures of 'what leprosy did to people' from various films, charity posters and books. I had a very privileged opportunity during my short stay to see the reality of leprosy treatment in rural India, as I was able to spend much of my time in the many small Indian villages, actually amongst the Indian people themselves, as well as seeing the hospital side of leprosy care.

Tamil Nadu is one of the high prevalence areas for leprosy in the Indian sub-continent. The areas of high prevalence, 10 per 1000 or more, are found mainly in the south-eastern parts of the country. This belt of high prevalence includes Tamil Nadu, Andhra Pradesh, Orissa, Pondicherry and the Lakshadweep Islands. Tamil Nadu is hyper-endemic for leprosy with an overall prevalence rate of 19 per 1000. Out of 15 districts in the State (excluding Madras City), 14 have a prevalence rate of 10 or more per 1000 which includes the Madurai District where I spent my elective.

The leprosy control programme of Tamil Nadu is based on either Government Leprosy Control Units or missionary-supported control programmes. The Christian Fellowship Community Health Centre at Ambilikkai is the headquarters for the Leprosy Control Programme for this part of Tamil Nadu. Although the hospital has grown and spread into many aspects of medicine, surgery, cancer and tuberculosis, it started originally in 1965 to treat leprosy patients. As a missionary control unit most of the money is received from voluntary organizations outside India.

The area covered by this control programme has a population of 1·34 lakh (134,000), and is divided into 6 smaller areas, each controlled by 1 Leprosy Inspector (paramedical worker). This area has 40 main villages, or Panchat, each of which comprises 6 hamlets.

## Treatment

I will deal with the hospital facilities first. The hospital has a leprosy ward of 53 beds, which at any

* Present address: The Medical School, University of Birmingham, England.

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given time seems to have about 70% bed occupancy. Patients are admitted for the treatment of severe ulcers and reactions, and the occasional tendon transplant operation. There is also a leprosy Rehabilitation Centre where patients learn weaving, shoe-making, carpentry, welding and agriculture. The hospital has a physiotherapist who has completed a 9-month government-approved course in physiotherapy for leprosy at Vellore C.M.C. The hospital also has its own facilities for making chappels, or sandals as we call them, suitable for the leprosy patients.

Being in the hospital one could easily be deceived that the leprosy work here is successful, and that all is going well. Patients presenting with newly-diagnosed leprosy receive skin smear tests and are started on the World Health Organization (WHO) recommended drugs for their particular type of leprosy. However, these drugs had only been available free for a few weeks. This limited supply of free rifampicin and clofazimine (lamprene) has been made available by the Indian Government. Prior to that all patients were only receiving dapsone, unless they could afford to buy rifampicin and clofazimine, which for the majority of these people because they are so poor is impossible.

However, the reality is that the patients attending the hospital out-patient department are only a small percentage of the total leprosy patients, and indeed many actually come from outside the control area. The majority of the leprosy patients never come to the hospital. They are suspected, diagnosed and treated in the villages and only if they develop severe reactions and ulcers are they referred to the hospital. It must, however, be remembered that referral to hospital, and actually coming to the hospital as an in-patient do not always follow on from each other, since many of the villagers will not pay the bus fare to the hospital or cannot afford to stop working and leave their families unsupported—there is no 'signing on the sick' in India.

Treatment for the vast majority of patients is only dapsone, irrespective of the type of leprosy diagnosed, and the general policy for *treatment in the villages* is as follows:

*Lepromatous*

Dapsone 100 mg daily for 3–4 years → (Clinically inactive (negative smear)) → dapsone 50 mg daily for 10 years or life.

*Borderline*

Dapsone 100 mg daily for 18 months → (Clinically inactive) → dapsone 50 mg daily for 7 years.

*Tuberculoid*

Dapsone 100 mg daily for 18 months → (Clinically inactive) → dapsone 50 mg daily for 3 years.

*In the hospital* the drug regimens are as follows:

*1 Multibacillary*

Rifampicin 600 mg/month
Clofazimine 100 mg t.d.s. for 1 week
then 100 mg alternate days
Dapsone 100 mg daily

→ For 2 years *or* until Bacteriological Index is negative

*then* dapsone 100 mg daily; in case of lepromatous for 10 years; in case of borderline for 7 years.

*2 Paucibacillary*

| | | |
|---|---|---|
| Rifampicin | 600 mg/month | For 6 months |
| Clofazimine | 100 mg t.d.s. for 1 week then 100 mg alternate days | |
| Dapsone | 100 mg daily | |

*then* dapsone 100 mg daily for 5 years.

*3 Treatment of reactions*

The basic policy is 1, admit; 2, bed rest; 3, analgesia; 4, chloroquine; and 5, clofazimine, if not already taking it.

Steroids are used if swelling is excessive.

As already mentioned, most of the village people are only receiving dapsone for treatment of their leprosy, and it also became clear to me that many of these people are probably not even taking the dapsone. This is confirmed by a random survey of two Panchat carried out by one leprosy inspector from 15 April 1982 to 18 April 1983.

*Panchat A:* 25 cases detected in total. Of these: 7 (28%) unregistered (i.e. no treatment); 12 (48%) regular treatment; and 6 (24%) irregular treatment.
*Panchat B:* 10 cases detected in total. Of these: 2 (20%) unregistered; 5 (50%) regular treatment; and 3 (30%) irregular treatment.

In fact, in the whole of this particular area, with a population of 25,000, there are 283 known cases of leprosy (LL, 36; BL, 44; T, 203): 68 (24%) unregistered and hence no treatment; 135 (48%) regular treatment; 80 (28%) irregular treatment.

Hence the reality of leprosy treatment in rural India is as follows:

**1** Most of the detected cases of leprosy are found by the leprosy inspectors. Studying their figures though, it is only practical for them to 'examine' 75% of their population because people may be in the fields or in other villages when they visit the house on their survey or may refuse to be examined. Examination of the women is a particularly cursory affair since only exposed skin can be examined.
**2** Most of the newly-detected cases take treatment, but of the 20% who do not, they are usually of the low caste Harijans, who live in close proximity to contacts (often as many as 8 people in a small, one-roomed house), and in the most appalling unhygienic conditions with poor nutrition, i.e. conditions which are conducive to the continuing spread of an infectious disease.
**3** Taking 'regular' treatment at this hospital means that the patient attends the mini-health centre for a monthly supply of dapsone at least 9 months a year. If there is work to do in the fields, or a festival or wedding to attend, they will not come for their drugs, although it is acceptable for the patient to receive the tablets by proxy. Also the prolonged course of treatment with dapsone means these people will soon stop coming for their dapsone, perhaps because they do not feel to be getting better, or the tablets make them feel unwell, or they simply do not understand the need for long-term regular treatment. The high illiteracy of India's population makes the last reason by far the most likely cause.
**4** Even when patients do comply with treatment they are not receiving the best drugs available for their type of leprosy. The WHO recommendations of multitherapy for multibacillary cases and dapsone-resistant cases is not being carried out at present for the vast majority of patients. Indeed until 1982, patients with active leprosy were only receiving 50 mg of dapsone daily. Only since early 1982 have newly-diagnosed patients been started on 100 mg dapsone daily. Also prior to 1982 the maintenance dose was only 25 mg dapsone daily.

A summary of the treatment of leprosy in the leprosy control area based at the Christian Fellowship Community Health Centre, Ambilikkai, up to May 1983 is detailed below. The classification used at the hospital is that stipulated by the Tamil Nadu Government.

L, Lepromatous; N, Tuberculoid; N?L, Borderline and Indeterminate.

Total population, 130,000
Total number of known leprosy cases, 1913
Cases regarded as being active leprosy, 1365 (70%)
Prevalence of leprosy 14·7 per 1000 population.

| L | N | N?L | |
|---|---|---|---|
| 240 (13%) | 1227 (64%) | 446 (23%) | 1913 (100%) |

At the end of April 1983, 1461 were registered for treatment.

| L | N | N?L | |
|---|---|---|---|
| 191 | 940 | 330 | 1461 (76%) |

Total number of patients who actually took treatment was 1,013.

| | L | N | N?L | |
|---|---|---|---|---|
| Clinic | 152 | 587 | 260 | 999 |
| Domiciliary | 8 | 2 | 4 | 14 |
| | | | | 1013 (53%) |

Clearly from the above figures, only just over half the detected leprosy patients are taking regular treatment, and this is an area with a well-organized leprosy control programme.

## DRUG RESISTANCE

Resistance to dapsone is the only important drug resistance seen in this part of India. Resistance to rifampicin and clofazimine is not encountered simply because the use of these drugs at present is negligible. Drug resistance is diagnosed clinically by the patient failing to respond to dapsone monotherapy despite taking regular treatment, or developing new signs and symptoms of leprosy after showing initial improvement. Where skin smears are performed then failure of the Bacteriological Index to fall is taken as supportive evidence. To prove dapsone resistance in the mouse footpad is clearly not practical.

When a patient has failed to improve, or relapses after dapsone treatment, they are watched more closely by the leprosy inspector for a further 6 months, and encouraged to take regular treatment if they are not already doing so. If there is still no improvement they are regarded as being resistant to dapsone. However, since multitherapy is not available then the diagnosis is academic, in so far as the treatment continues at 100 mg daily. There is an overall figure of 17 suspected dapsone-resistant cases for this leprosy control area, all of which are thought to be secondary dapsone resistance. This gives a prevalence of 12·5 resistant cases per 1000 active cases.

It is a sad reality that these resistant cases are not able to attend the hospital for multitherapy for a variety of reasons. With the recently available rifampicin and clofazimine they could be treated free, or with a nominal charge. The two main reasons they will not attend are illiteracy and cost. It becomes very difficult to explain to illiterate people, who probably do not even understand the basics of their disease, the concepts of resistance and the need for different medicine. Not only do the people fail to understand why they must go to the hospital, they also see that it will cost money. In the hierarchy of personal needs, health takes a low priority in a poor person. Consequently these people are still in the villages receiving only 100 mg dapsone daily. To illustrate the cost problem, an

average poor man earns Rs 5/- daily (£1 = Rs 15/-); bus fares are approximately Rs 2/- to the hospital from a village, and one 150 mg rifampicin tablet costs Rs 4/-.

Commencing later this year is a plan to bring rifampicin and clofazimine to most of the patients who require it, i.e. multibacillary and resistant cases, which at the present time is 160 patients. This has been made possible by the donation of funds from American Leprosy Mission and WHO through the Indian Government. The plan is that all patients who are multibacillary or resistant cases *and are regular attenders*, will receive rifampicin and clofazimine according to a slightly modified WHO regimen. Since the supply of money and drugs will be limited it is felt only those patients who are known to be compliant can have multitherapy initially. The leprosy inspectors will receive monthly supplies of these drugs for patients in their area from the hospital and will take the drugs to the individual patients once a month, making sure they 'put the tablets in their mouths and swallow them'. The WHO recommendation for clofazimine will be modified to 300 mg monthly, with no alternate daily dosage, because of the extra expense and the problem of supervising patient compliance. Rifampicin will be given 600 mg once monthly with the clofazimine. Indeterminate and tuberculoid types will continue to be treated with dapsone monotherapy because of the limited resources. It remains to be seen how well this plan will work and whether or not sufficient drugs will be available.

## Discussion

The reasons why patients in the rural parts of India do not come forward with their leprosy, or refuse treatment, are complex, but are undoubtedly founded in illiteracy and poverty. More than 60% of India's population is still officially regarded as being illiterate, with a higher percentage in rural Indian villages. Seventy per cent of the population live in India's 600,000 mud-hut villages. Since the population of India is now in excess of 750,000,000 people, this means 525,000,000 people are living in rural India where medical services are at best poor. India has still not found a way to get its doctors into those areas where need is greatest, and the majority still work in the large cities and towns.

Some of the reasons which contribute to the failure of leprosy treatment at the present time are:

**1** *Ignorance*; not only about leprosy, but disease in general. The reason most patients make their initial cancer presentation with secondaries, and diabetics present with the most awful deep infected ulcers, and tuberculosis patients present with only a small percentage of their total lung capacity functioning, are all illustrations of the ignorance and illiteracy of these people. Ignorance of leprosy is just part of this picture.

**2** *Social stigma*; still a very real problem and one which again will take many years to change. Even when cured the signs of leprosy still make it very difficult for these people to be accepted back into society, and their families are regarded as being cursed by other members of the village.

**3** *The disease itself*; leprosy in its early stages has none of the symptoms which normally bring these people to a doctor, such as pain, bleeding, vomiting, dyspnoea and coughing. Also many of the people are aware that a leprosy patch may self-heal, and so may delay in presenting.

**4** *Long treatment*; which initially may not make their leprosy improve, indeed may have undesirable side-effects, and which they fear may cost money.

There are a number of positive aspects to the leprosy control programme in this part of Tamil Nadu. The system of survey, education and treatment, centred on the leprosy inspectors, is working well and people are being detected early in their disease. Treatment for these people is available locally if they attend. Also there is a hospital with good facilities for treating the complications of leprosy and for the rehabilitation of leprosy patients. Leprosy education through the leprosy inspectors, leprosy dramas (acted by staff and students from the hospital in a different village each month), and village

leaders is also having some success. I was shown some reliable figures to illustrate that in one village where intensive leprosy education had been carried out the uptake of regular treatment had increased from 38% to 60%, which is encouraging but still leaves a long way to go.

The effect of the leprosy care in this part of South India during the past 15 years is illustrated in the following figures: 1968, prevalence of 20 per 1000 population; 1979, 17 per 1000; 1982, 15 per 1000. The prevalence of leprosy in this area shows a fall of 5 per 1000 population, but the population has increased by nearly 5000 in these 14 years, to its present level of 130,000. Assuming a similar rate of fall, and no significant change in the population, it will be at least another 35 years before leprosy is eradicated in this area with the present system. Unfortunately the feeling expressed to me whilst I was in India is that this fall has been due to changing factors which were readily accessible to change, but to go from 15/1000 to complete eradication will mean altering factors which are much less accessible. For example, this will mean improving an illiteracy rate of 60%; improving unhygienic conditions, nutrition and living standards, which are at present appalling; changing many centuries of culture and religion which misguidedly makes an Indian with disease go to a temple before going to a doctor.

The Prime Minister of India, Mrs Indira Ghandi, tried to promote leprosy to a respectable level by expressing personal interest in the disease, and coined the slogan, 'leprosy eradication by the year 2000'. To indicate her seriousness she constituted a high powered committee to draw up an action plan to implement the programme. Sadly the vast size of India often means that when the Central Indian Government sets up such a plan, the help rarely reaches the people it is intended for. In a country which is still so underdeveloped, not even being able to supply clean water to the majority of its population, and indeed whilst I was in India many parts had no water at all due to failure of the monsoons, then the treatment of leprosy must be well down the list of priorities of the Indian Government, whatever the official policy may be. Undoubtedly finance is a major problem, and India is at present incapable of providing it, with so many other more important priorities. Hence the availability of foreign aid for leprosy programmes is essential. Nevertheless, we must acknowledge that however much money is made available to buy drugs and improve care, it will only be of benefit when the average Indian villager with leprosy has been educated sufficiently to understand his disease and the need to take treatment.

The spread of communicable diseases in Western countries, including leprosy, declined by improving these very factors listed above, together with the introduction of vaccines and drugs. Hence it would seem that the treatment of leprosy in India will only be successful in the long term if there is a general improvement in the standard of living and nutrition as well as the administration of the correct drugs.

**Acknowledgements**

It is with sincere gratitude that I thank LEPRA for their financial help which made my visit to India possible. My thanks also go to Dr J Cherian, Director of the Christian Fellowship Community Health Centre, for allowing me complete freedom to study the care of leprosy in his hospital and in the associated community health schemes.

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*SPECIAL ARTICLE*

# Primary defects of the hand with intrinsic paralysis

J W BRANDSMA & J G ANDERSEN
*All Africa Leprosy and Rehabilitation Training Centre (ALERT), PO Box 165, Addis Ababa, Ethiopia*

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*Summary* The primary defects of the hand that has suffered intrinsic paralysis are described.

The extent to which these defects are corrected by standard tendon transfer operations is discussed.

## Introduction

The intrinsic muscles of the hand are all innervated by either the ulnar or the median nerve. Although there are some variations in the pattern of innervation, the commonly found pattern is for the ulnar nerve to innervate the hypothenar muscles, the interossei, the two ulnar lumbrical muscles, adductor pollicis and the ulnar head of flexor pollicis brevis. The median nerve innervates the abductor pollicis brevis, radial head of flexor pollicis brevis, opponens pollicis and the two radial lumbrical muscles.

In the leprosy patient both isolated ulnar paralysis, with or without paralysis of flexor carpi ulnaris and the ulnar half of flexor digitorum profundus, and combined ulnar and 'low' median paralysis are commonly found. Distinctly less common are median paralysis, either isolated or in combination with ulnar paralysis as a 'high' median paralysis with paralysis of the extrinsic flexor muscles.

Radial paralysis is less common, but when seen is usually found in combination with intrinsic paralysis in a variety of patterns. This naturally plays an important role in the planning of surgical restoration, but this is outside the scope of this paper.

The ulnar nerve may become damaged by leprosy either proximal to the ulnar epicondylar canal or just proximal to Guyon's canal. The median nerve is usually damaged just proximal to the carpal tunnel.

Paralysis of the two ulnar innervated extrinsic muscles plays little or no role in the development of the primary defects, the immediate effects of paralysis, but may influence the development of secondary defects.

The functions of the hand may be summarized as follows:

**1** Prehensile movements. Napier[1] defined two basic prehensile movements, power grip and precision grip. Landsmeer[2] preferred to call the latter precision handling.

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**Table 1.** Primary defects of ulnar and median palsy

| | Defect | Responsible muscles |
|---|---|---|
| Ulnar | | |
| 1 | Incomplete finger extension (clawing) | Interossei–lumbricals |
| 2 | 'Reversed' pattern of finger closing | Interossei–lumbricals |
| 3 | Loss of antepulsion, 4th and 5th metacarpal | Hypothenar muscles |
| 4 | Loss of abduction and adduction of fingers | Interossei–hypothenar |
| 5 | Decreased grip-and-pinch strength | Interossei–hypothenar–adductor pollicis |
| 6 | Loss of stability of the thumb | Flexor pollicis–adductor pollicis |
| Median | | |
| 7 | Loss of opposition | Thenar muscles |

**2** Non-prehensile movements, pushing, lifting and tapping movements, e.g. those employed when typing or playing the piano.

**3** The hand is the chief organ of touch.[3] As such it also monitors the muscle power by a sensory feedback.[4] As an example of this it may be mentioned that many patients with loss of sensation but intact motor function complain of a weak hand.

**4** The hand is the chief organ of communication, next to the voice.[3] We can mention the importance of the warning hand, the greeting hand, the signalling hand, e.g. used when hitchhiking and the manifold hand gestures that vividly express the personality of the person.

Confronted with a hand with intrinsic paralysis, a surgeon will readily recognize clawing of the fingers and thenar paralysis with loss of opposition of the thumb. He may not realize that other defects are present that influence the function of the hand.

Paralysis of the intrinsic muscles is responsible for seven primary defects (Table 1).

## Primary defects

### 1 *Incomplete digital extension*

In pure ulnar paralysis the ring and small fingers inevitably develop a claw deformity. In most cases the index and middle fingers after a period of 'latent' clawing, where the 'lumbrical' position may be achieved, but where the fingers slip into clawing when power grip is attempted, will develop manifest clawing. The relative role of the interosseus and lumbrical muscles in the development of clawing has been discussed.[5] Four-finger clawing was noticed in most hands with ulnar palsy only, indicating that the lumbricals alone could not prevent finger clawing in the index and middle fingers. On the other hand clawing of index and middle finger was never encountered in pure median paralysis.

Incomplete finger extension is an obvious cosmetic defect. Functionally it prevents full opening of the hand with inability to close the hand round an object with equal pressure distribution over the whole volar surface of the fingers. The obvious claw position, metacarpophalangeal hyperextension and interphalangeal flexion makes greetings embarrassing, which may have serious social effects.

### 2 *Reversed pattern of closing*

It is stated[6] that the patient with intrinsic paralysis will close his hand in reverse pattern, i.e. distal interphalangeal flexion, followed by proximal interphalangeal flexion and finally metacarpophalangeal flexion, exactly the opposite of the normal sequence of closing. In power grip the major part

of all the pressure will fall on the tips of the fingers. Add to that the usually found loss of sensory feed back and we have the logical explanation of the progressive absorption of the fingers in the anaesthetic hand.

3 *Loss of antepulsion of the ring and small fingers*

The hypothenar muscles are responsible for the flexion in the carpo-metacarpal joints with incomplete pronation to form the cupping of the hand.

This ensures a steady grip on spherical objects and secures the grip on a cylindrical object. Grip strength is also affected by hypothenar paralysis. The flattening of the transverse metacarpal arch will proceed to complete reversal of the arch postoperatively.[7]

4 *Loss of abduction/adduction of fingers*

Few patients specifically complain of this. It is, however, a hindrance to grasping large objects, where spreading of the fingers is essential.

5 *Decreased grip-and-pinch strength*

The interosseus muscles are prime flexors of the metacarpophalangeal joints. If this function is lost, the long flexors are unable to exert their full strength. We are currently studying the influence on grip strength by tendon transfer operations in the hand with intrinsic paralysis. Paralysis of adductor pollicis and first dorsal interosseus will effect the pinch strength.

6 *Loss of stability of the thumb*

Loss of the prime metacarpophalangeal flexor to the thumb tends to cause development of the Z thumb, also called 'intrinsic minus' thumb. This usually does not develop if the articular surfaces are 'flat'. The hyperextended metacarpophalangeal joint and sharp flexion of the interphalangeal joint makes pulp pinch impossible and places overpressure on the tip of the thumb. Z-ing in 68% of patients with ulnar palsy has been found.[8] Some patients may develop a 'thrust' pinch with hyperflexion of the metacarpophalangeal joint and hyperextension of the interphalangeal joint. In appearance this is similar to the intrinsic plus thumb.

7 *Loss of opposition of the thumb*

Paralysis of the median innervated muscles results in inability of the thumb to move in the greater circle (extension, abduction and pronation) into full opposition.[9] In rare cases, where only abductor pollicis brevis is paralysed, the thumb may move in the smaller circle into a position of deficient opposition. Loss of opposition is both cosmetically and functionally a very serious defect. Opposition of the thumb is as essential to the function of the hand as a loyal opposition is for the proper functioning of a democracy.

**Surgical correction of intrinsic paralysis**

It is obviously impossible to replace the identical function of each and every one of the 19 intrinsic muscles. It is equally obvious, but not always realized, that every tendon transfer operation while it may correct one deformity may also create another.

In our unit we correct clawing of the fingers with a single-tendon transfer, preferably the extensor to flexor four-tailed graft operation of Brand.[10] The commonly-used motor is extensor carpi radialis longus.

In hypermobile hands we prefer to use the weaker palmaris longus. This will successfully correct the clawing of the fingers and reversed pattern of closing. It will supply the thumb with an

index that presents its pulp in the pinch, and will distribute pressure equally over the fingers. It will not restore antepulsion and pronation of the ulnar fingers, nor will it restore abduction/adduction of the fingers.

As already described[11] it is possible with a separate tendon transfer to re-create cupping of the hand. We do not feel that this is important enough to warrant the sacrifice of yet another function. In order to reserve the important tripod pinch between thumb and the two radial fingerpulps we routinely insert the grafts into the ulnar lateral band on the index finger and into the radial lateral band on the other fingers. Insertion into the radial lateral band on the index finger may put the pinch in jeopardy.

The unstable Z-thumb may be corrected by a metacarpophalangeal volar capsulodesis or by a recession of flexor pollicis longus to the insertion of abductor pollicis brevis, combined with a dynamic tenodesis across the interphalangeal joint.

Loss of opposition of the thumb is, in our unit, routinely corrected by a transfer of a superficialis tendon, preferably from the ring finger. In order to ensure stability and proper pronation of the thumb a two-tailed insertion is employed, into extensor pollicis longus and into adductor pollicis.

In most cases opposition in the greater circle is desired and the tendon is made to pass a pulley at the pisiform bone. In the rare cases where opposition in the smaller circle is desired, the pulley may be moved into the palm or volar carpal ligament.

Active adduction of the thumb is usually sufficient with the action of the long flexor. We do not feel that for our patients it is justified to sacrifice one more tendon to create specific adduction.

## Conclusion

The hand with uncomplicated, isolated ulnar paralysis can be corrected to virtually normal function with a one-tendon transfer operation, occasionally to be combined with a stabilizing operation for the thumb.

The hand with isolated median paralysis can be successfully corrected with a single-tendon transfer.

The hand with combined ulnar and median paralysis needs, for a successful correction, transfer of two tendons. An additional stabilizing procedure may be needed for the thumb.

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*Lepr Rev* (1984) **55,** 407–414

*SPECIAL ARTICLE*

# Leprosy immunology—some aspects of the role of the immune system in the pathogenesis of disease

T GODAL
*Laboratory for Immunology, Norwegian Radium Hospital, Montebello, Oslo 3, Norway*

We are grateful to Dr Godal for permission to present this adaptation of his slide and videotape on leprosy immunology at one of the teaching sessions of the XII International Leprosy Congress held in New Delhi, February 1984. The figures and diagrams have been taken from transparencies and we apologise for some loss of definition. Editor.

The immunology of leprosy has been a subject of extensive research for the last 15 years. Important progress has been made in a number of areas, and support for the overall concept shown in Figure 1 is steadily being accumulated. In Figure 1, time after exposure to *Mycobacterium leprae* is shown along the horizontal axis and strength of cell-mediated immunity along the vertical axis.

The concept proposes that among those who become exposed to *M. leprae*, the great majority appear to develop an effective immune response sufficiently rapidly to arrest *M. leprae* infection before overt clinical disease is precipitated. This I will call subclinical infection. Only in a minority of subjects does the disease apparently become clinically expressed. Towards the tuberculoid end, considerable evidence suggests that the immune response to *M. leprae* is the major cause of lesions, while towards the lepromatous end of the spectrum accumulation of vast numbers of bacilli in infiltrating host cells plays an important role.

The precise detection of subclinical infection is of fundamental importance to a more complete epidemiological understanding of leprosy. This has not yet been achieved. However, significant advances have been made recently in this area by development of *M. leprae*-specific serological techniques as pioneered by Abe. More recently the employment of a chemically defined and unique antigen of *M. leprae*, namely the phenoicglycolipid identified by Brennan and his co-workers, appears promising. In this and related areas the development of monoclonal antibodies is rapidly becoming important to leprosy immunology. The difference between conventional and monoclonal antibodies is illustrated in Figure 2. As you see in Figure 2, if an animal is immunized with an antigen, the antiserum will contain antibodies to many different structures on the antigen. However, each lymphocyte in the animal produces only one type of antibody. This is utilized in the production of monoclonal antibodies. This is illustrated on the right side of Figure 2. In the production of monoclonal antibodies each lymphocyte is fused with a myeloma cell and cloned. In this way antibodies of identical specificities are produced. Moreover, they can be produced in unlimited amounts, because the myeloma cell has conferred immortality on the lymphocyte.

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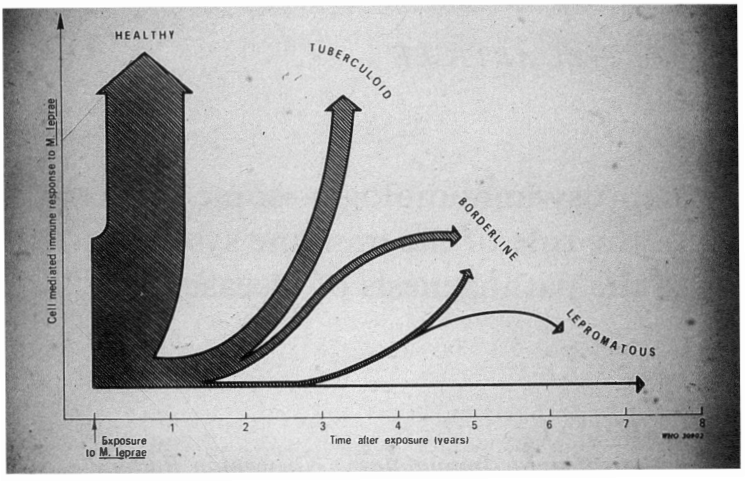


**Figure 1.** From Godal *et al. Bull L'Inst Pasteur*, 1979; **72:** 273.

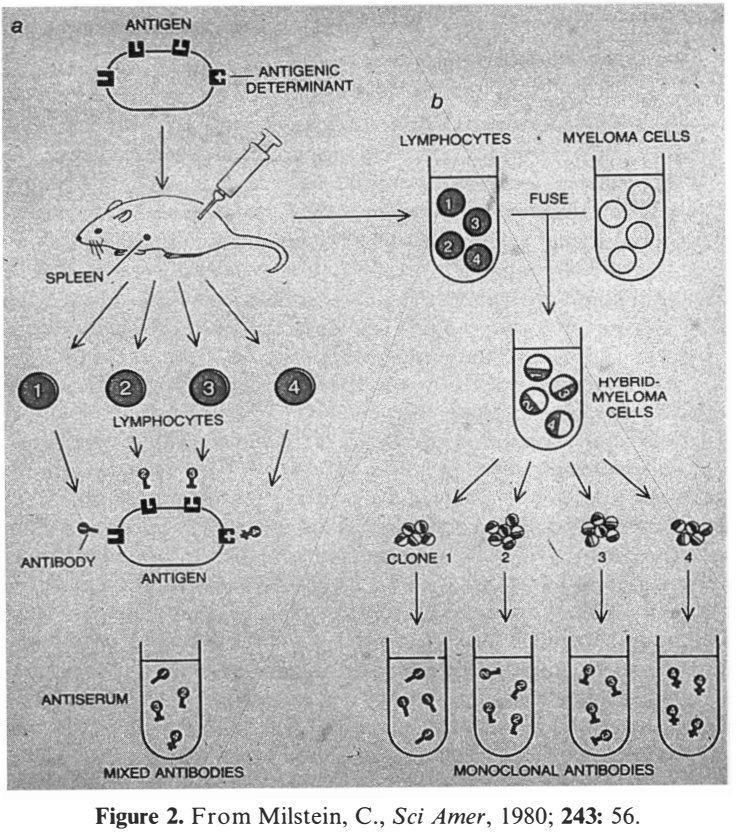


**Figure 2.** From Milstein, C., *Sci Amer*, 1980; **243:** 56.

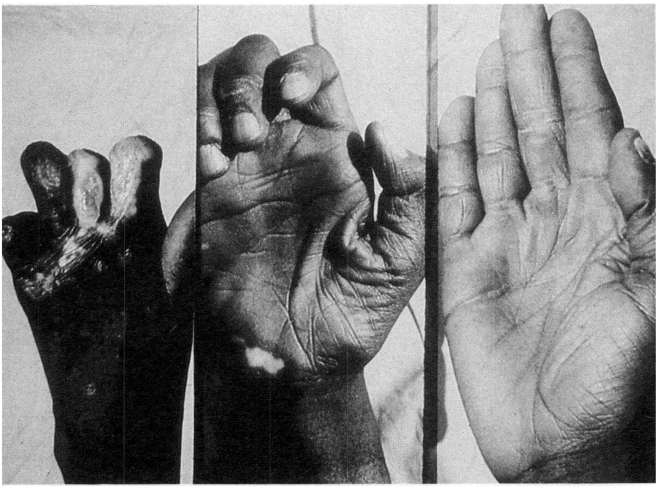

**Figure 3**

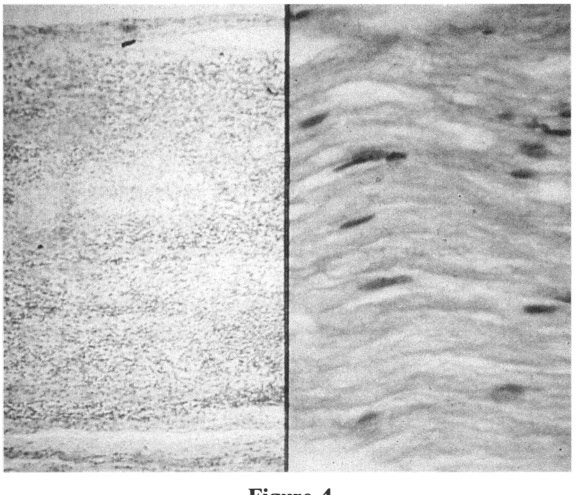

**Figure 4**

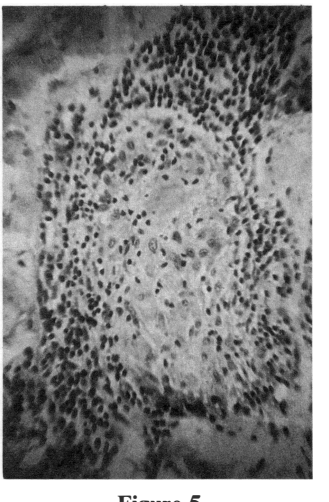

**Figure 5**

Two aspects of leprosy immunology are focused upon, namely nerve damage in borderline and tuberculoid patients, and the nature of the immunological deficiency in lepromatous leprosy.

Nerve damage in leprosy is of key importance, since this, as illustrated in Figure 3, is a major cause of deformity. Deformity often results from loss of sensation and loss of motor nerve function. If one looks histopathologically at damaged nerves in borderline and tuberculoid patients, as shown in Figure 4, the regular cable-like structure may be completely broken down by infiltrating inflammatory cells. Actually, as shown in Figure 5, there is granuloma formation within the nerves with lymphocytes, macrophages and epithelioid cells. A considerable body of evidence suggests that this granuloma formation within the nerves results from immunological attack from the host on leprosy bacilli hiding within the nerves. Thus, whenever recognized by the host immune system, T lymphocytes will become attracted to these sites and release various factors called lymphokines,

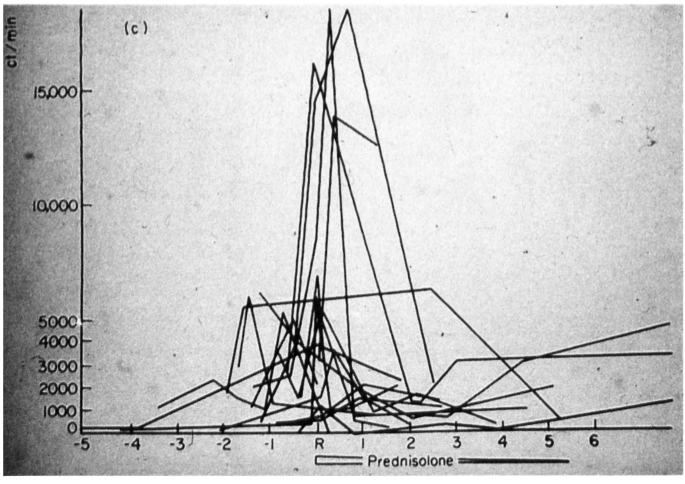


**Figure 6.** From Bjune *et al. Clin exp Imm*, 1976; **25**, 85.

which in turn will attract and activate monocytes to kill bacteria that they will engulf. However, this attack will, as an unfortunate side-effect, also distort and damage nerve fibres and function. It is important from a clinical point of view that this type of nerve damage in leprosy may occur very rapidly. This is especially seen in reversal reactions, where there may be a rapid build up of immunological attack on leprosy bacilli. This is shown in Figure 6 taken from a prospective study carried out by Barnetson, Bjune and co-workers. Along the horizontal axis you see time in months before and after the development of reaction and along the vertical axis lymphocyte proliferation to *M. leprae* as measured by radiolabelled thymidine incorporation. The close association between reaction and lymphocyte proliferation is indeed very striking. It is therefore very important to treat such patients adequately as soon as possible, that is, they really have to be considered as emergency cases, otherwise nerve function may be permanently lost.

Let us now turn to lepromatous leprosy. The central question here is, what is going wrong in lepromatous leprosy? Why does the host system fail to attack the leprosy bacilli, which are thriving in the tissues in vast numbers?

It is well known from earlier studies that this immunological defect is remarkably specific to leprosy bacilli. This is illustrated in Figure 7. Here you see 3 treated patients and their lymphocyte proliferative response to *M. leprae*, BCG and PPD. As you can see, the patients responded strongly to BCG and PPD, but were completely negative to *M. leprae*. Thus, the defect is what we

| Patient No. | Antigens | | |
|---|---|---|---|
| | BCG | PPD | *M. leprae* |
| 322 | 6·6 | 12·4 | 0·3 |
| 327 | 35·7 | 82·4 | 0·6 |
| 328 | 16·2 | 66·3 | 0·7 |
| Mean | 19·5 | 53·7 | 0·5 |

**Figure 7.** Lymphocyte transformation (uptake of $^{3}H$ thymidine, T/C ratio) in leukocyte cultures of treated lepromatous patients. (From Godal *et al. Scand J Immunol*, 1972; **1**: 311.

immunologists call antigen specific. Since it is well known from a large number of studies, including studies on T-cell-deficient animals, that it is the T-cell that has the capacity to mediate specific immunity to intracellular bacilli such as the leprosy bacillus, one has for a long time suspected that T-cells play a central role in the defect of lepromatous leprosy. The mechanisms involved in T-cell activation and T-cell-mediated intracellular killing of mycobacteria have advanced considerably during recent years and allow a more detailed analysis of the defect in lepromatous leprosy. Thus, we will here now first consider the basic concepts of T-cell activation and then discuss recent findings, which suggest more precisely the nature of the defect in lepromatous leprosy.

The T-cell response may be subdivided into three parts (Figure 8), the afferent limb or inductive

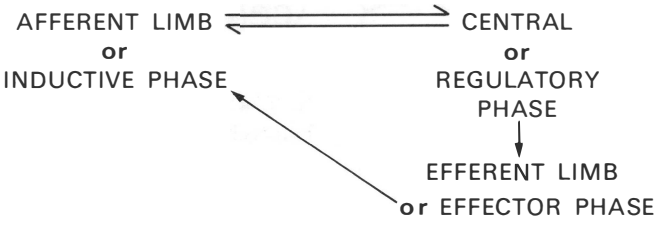


**Figure 8.** T-cell response to *M. leprae*.

phase, the central or regulatory phase or level, and the efferent limb or effector phase. With regard to the afferent limb, we have known for a number of years that T-cells do not see antigen alone, but that antigen is presented to the T-cell by other cells, so-called antigen-presenting cells, which include monocytes, macrophages or dendritic cells. The Langerhans cells of the skin also belong to this cell category.

How antigen-presenting cells interact with T-cells is not yet a fully understood process. It appears they actually talk to each other, that is to say, it is a mutually dependent, highly sophisticated process (Figure 9). The antigen-presenting cells have on their surface antigen derived from, in our case, *M. leprae* and high concentrations of HLA-DR molecules, both of which are required for T-cell activation. In addition there is evidence that the antigen-presenting cell produces a factor, interleukin 1 (IL-1), which is required for T-cell activation. However, the production of IL-1, as well as the level of HLA–DR expression, may actually be under T-cell control, as illustrated to the left by the $T_1$ cell. The activation of T-cells leads to two clearly distinguishable phenomena: 1, one subset of T-cells, here called $T_2$, starts to produce a factor required for T-cell proliferation and production of lymphokines. This factor is called interleukin 2 (IL-2); and 2, some T-cells, here called $T_3$, will develop receptors for IL-2 and thereby become able to respond to IL-2.

Although I have for simplicity depicted three T-cell functions as located to three subsets of T-cells ($T_1$–$T_3$), they may actually be largely overlapping populations.

This part of the immune response, the *afferent limb*, sets the stage for T-cell proliferation and interleukin production, which may be called the *central level* of the immune response. The central level may also be called the regulatory level, because T-cells are controlled by other T-cells, so-called suppressor cells, and this regulation is often called the suppressor circuit (or the suppressor circus! because there are many unclear aspects and controversial issues about the suppressor circuit) (Figure 10). These suppressor cells may have the T4 or the T8 phenotype and are thus not limited to T8 cells. Suppressor cells may interfere with T-cell activation in various ways, for example by blocking induction of IL-2 receptors or by blocking IL-2 production.

Let us now consider the third part of the T-cell response, the so-called *efferent limb* (Figure 11). How do T-cells effect their attack on *M. leprae* and related organisms? It appears that T-cells mainly

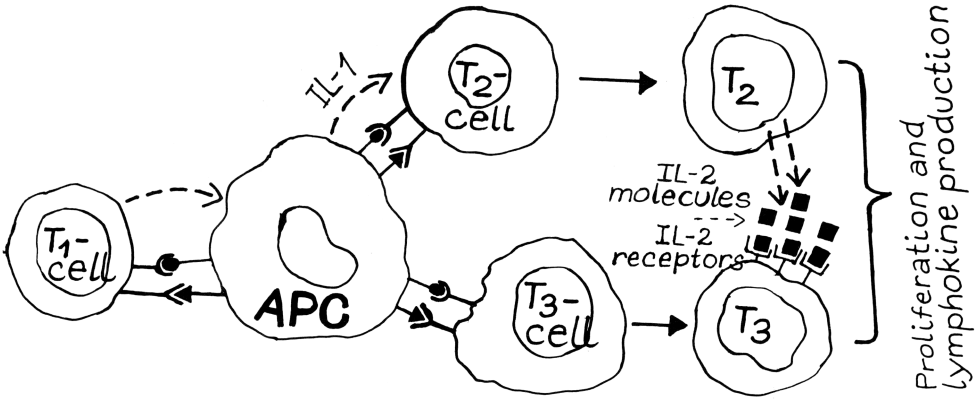


**Figure 9.** Afferent limb. ●, HLA-DR molecule ('Ia'); ▲, antigen; APC, antigen presenting cell (monocytes, macrophages, dendritic cells, Langerhans cells, B-cells etc.) IL-1, Interleukin 1; IL-2 Interleukin 2 (or T-cell growth factor).

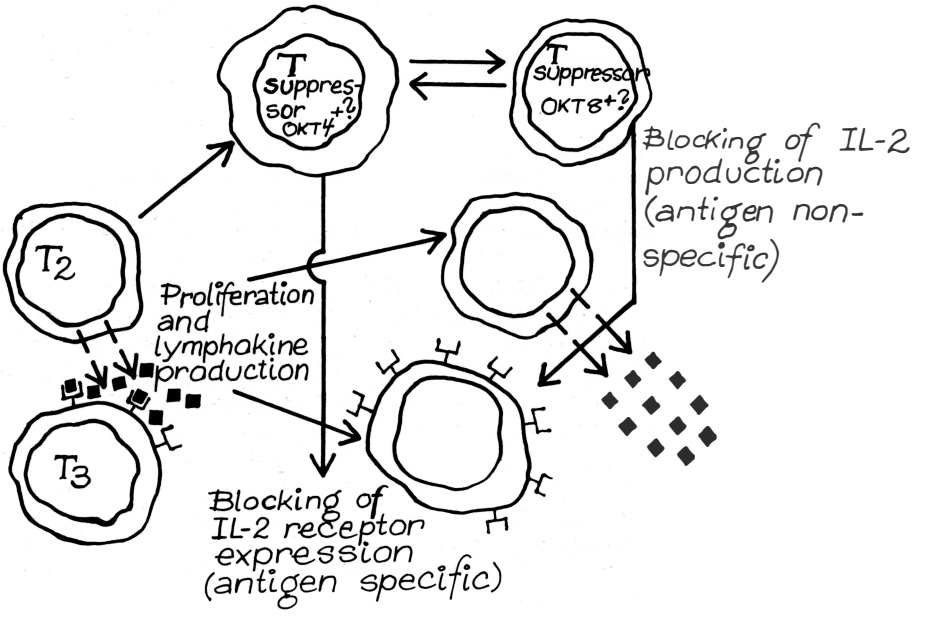


**Figure 10.** Central or regulatory level with suppressor circuit.

orchestrate or conduct the attack by production of lymphokines, some of which have chemotactic properties and attract monocytes from the blood into the sites where *M. leprae* has been detected; and other lymphokines, one called macrophage activation factor (MAF), probably identical with $\gamma$-interferon, activate the macrophage to kill and digest the bacteria they have internalized.

We may now return to the question of what is going wrong in lepromatous leprosy. It would be apparent that there are many places where things could go wrong: 1, the antigen-presenting cells may be compromised; 2, T-cells may lack receptors for *M. leprae* antigens; 3, patients may have developed an overwhelming suppressor circuit that could suppress IL-2 receptor induction or IL-2 production; and 4, there could be a defect in the efferent limb.

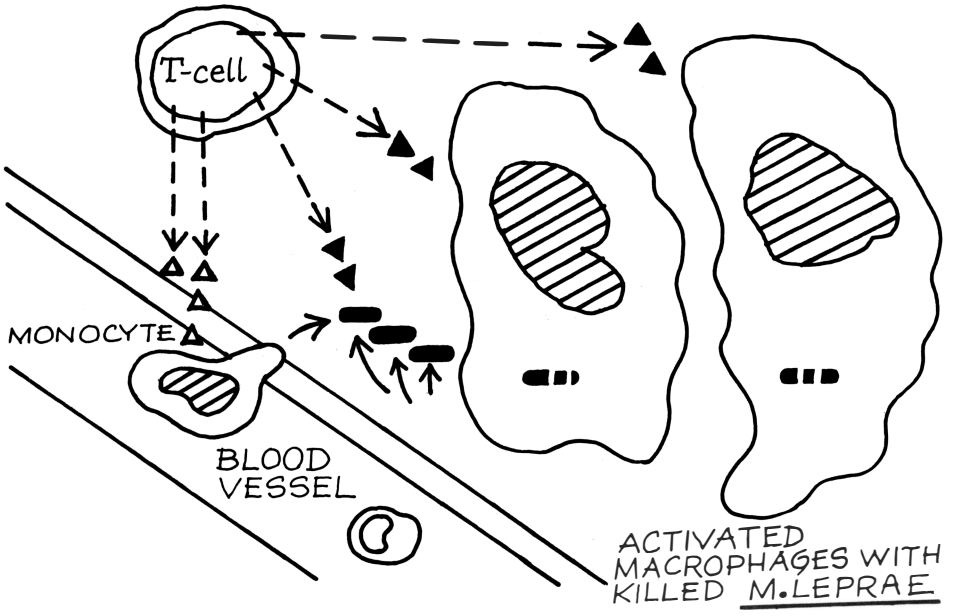


**Figure 11.** Efferent limb. ▬, live *M. leprae*; △, chemotactic factors; ▲, macrophage activation factor ($T_\gamma$-Interferon?).

Space does not allow us to consider in detail all the experimental data which may be considered for or against any of these possibilities. However, data have steadily accumulated in recent years that provide further evidence that the defect is located at the central or regulatory level (Figure 12). Several investigators, especially Mehra and Bloom, have detected suppressor cells in lepromatous leprosy. Finally, Haregewoin in Addis Ababa in collaboration with Salim Mustafa and myself has shown that lepromatous T-cells fail to produce IL-2, but if given IL-2 from external sources to lepromatous T-cells, the T-cells will now mount a proliferative response to *M. leprae*.

Combined these findings suggest that suppression of IL-2 production may be of central importance. A proposal for the nature of the defect is outlined in Figures 10 and 13. Figure 10 shows the normal regulatory compartment and Figure 13 the aberrancies in lepromatous leprosy. These findings are encouraging because they suggest that these studies on the immunological nature of defect in lepromatous leprosy may lead to new approaches for restoring immunological competence in such patients. Hopefully some day termination of chemotherapy and prevention of drug resistance may become feasible in such patients.

**(1) Defect in afferent, regulatory or effector compartment.** Present evidence suggests that the defect is localized to the regulatory compartment. The two main reasons are:

**(a)** Increased suppressor cell activity ($OKT8^+$, antigen non-specific suppressor cells) has been observed in LL (Mehra & Bloom).

**(b)** Proliferative T-cell response to *M. leprae* can be restored *in vitro* with IL-2 (Haregewoin *et al.*). Thus, the afferent limb appears intact and *suppression* of IL-2 production appears to be of key importance.

**Figure 12.** What is going wrong in lepromatous leprosy?

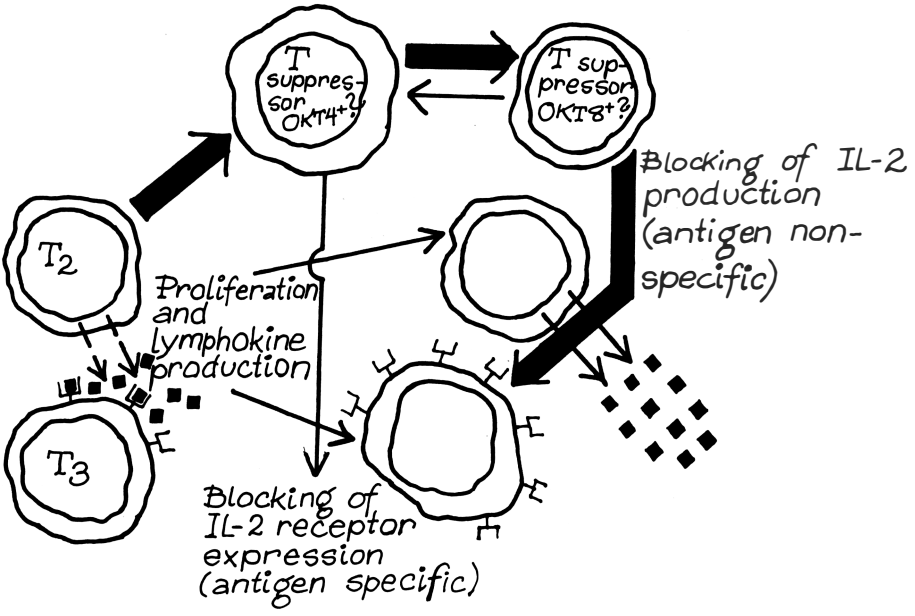


**Figure 13.** Defect in lepromatous leprosy.

In conclusion, the immune system is of central importance to the pathogenesis of various disease manifestations in leprosy. The main contribution of leprosy immunology so far has been at the conceptual level. But as you may well have noted during the XII International Congress of Leprosy, the stage is now set in a number of areas for exploring more direct contributions to leprosy control.

*Lepr Rev* (1984) **55,** 415–420

*SPECIAL ARTICLE*

# Five-day course on clinical leprosy for medical officers

JEANETTE HYLAND
*United Mission to Nepal, PO Box 126, Kathmandu, Nepal*

(We are extremely grateful to Miss Hyland for the submission, some considerable time ago, of a detailed account of this 5-day course, which was planned and carried out in Nepal. We hope that the following abridged version will adequately describe the most important aspects of this initiative and that its publication will lead to the development of similar courses in other countries. EDITOR)

## PURPOSE OF THE COURSE

'. . . To suitably acquaint medical officers from His Majesty's Government, Nepal health services (and other health professionals), working in the Western and Middle Western Regions, with the care and control of leprosy, in order to strengthen the leprosy control programme in these areas and to make present cooperation and future integration a more realistic aim.'

## BROAD OBJECTIVES

At the end of the course participants will:

**1** Diagnose leprosy with no false positives, differentiating it from other similar conditions; classify it according to Ridley and Jopling and infectious and non-infectious systems.
**2** Manage uncomplicated leprosy under their own work conditions, selecting appropriate management regimes according to guidelines recommended by the National Leprosy Control Programme (NLCP).
**3** Diagnose and manage complications commonly arising in leprosy, which do not require referral facilities, according to guidelines recommended by NLCP.
**4** Select cases requiring referral because of severe complications, referring them to appropriate centres according to the set-up of NLCP and criteria of referral recommended by NLCP.
**5** Explain the goals and mode of operation of NLCP, particularly the district level case-finding and case-holding methodology; cooperate with NLCP, assisting where possible in implementing leprosy control, provide informal advice and guidance to NLCP workers in the area for which they are responsible.
**6** Provide moral support to patients, representing them to their families and communities and other health workers, explaining the nature of the disease, its treatment and control so as to allay anxiety and promote acceptance of patients.

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These will now be considered in detail:

*Broad objective 1*

At the end of the course, the participants will *diagnose* leprosy clinically with no false positives, *differentiate* it from other similar conditions, *classify* it clinically according to Ridley & Jopling and infectious/non-infectious systems.

In order to be able to do the above, the participants need to have the following:

| *Knowledge* | *Skills* | *Gained by means of:* |
|---|---|---|
| **1** Describe the cardinal signs of leprosy. | Recognize the cardinal signs of leprosy. | Demonstration of patients and slides; how to examine skin, nerves, hands, feet and eyes. |
| **2** Describe the process of diagnosis of leprosy. | | Check list. |
| **3** Describe the Ridley & Jopling classification. | Recognize the clinical picture of different types of leprosy and classification correctly. | Demonstration of patients and practice at examining and classifying according to chart given. |
| **4** Describe infectious/ non-infectious classification. Skin smear taking, fixing and reading and interpretation of results, routine sites. | | Demonstration of procedure of taking skin smears and their fixing and reading. |
| **5** Detail conditions commonly confused with leprosy and detail their differentiation. | | Illustrated by slides and discussion and demonstration of patients, if any. |
| **6** Natural history of leprosy treated and untreated. | Take a history and assess progression of patient's condition. | Case study of a patient with a long history. |

*Broad objective 2*

At the end of the course the participants will *manage* uncomplicated leprosy under their own work conditions, *selecting* appropriate management regimes according to guidelines adopted by LCP.

In order to be able to do the above, the participants need to have the following:

| *Knowledge* | *Skills* | *Gained by means of:* |
|---|---|---|
| **1** Detail drug regimes for leprosy as set down in LCP linked to drug action on *Mycobacterium leprae*. | | Class and discussion and list. |
| **2** Describe assessment of patients' progress over years. | Assess patients' progress from history and record of smear, annual examinations and physical examinations. | *Case study* to (a) pick out progression from clinical record; (b) physical examination of patient. |

| | | |
|---|---|---|
| **3** Describe signs of active and inactive leprosy and criteria for release from control. | Recognize signs of activity and inactivity.<br>Write up physical examination and history according to recording procedure of LCP. | Examination of patients, slides, deciding on findings and discussion. |
| **4** Outline the structure and function of LCP in the field. | | Chart of LCP. |
| **5** Advise patients about their disease, its treatment and control and measures to take for their own self care and means to prevent complications and what to do if complications arise. | Interpersonal skills hopefully already present in the participants. | Talking with patients of their case study. Discussion and chart on education for self-care in whatever condition of patient. |

*Broad objective 3*

At the end of the course the participants will *diagnose* and *manage* complications commonly arising in leprosy, which do not require referral facilities, according to the guidelines offered by LCP.

In order to be able to do the above, the participants need to have the following:

| *Knowledge* | *Skills* | *Gained by means of:* |
|---|---|---|
| **1** Describe complications in leprosy | | |
| (a) based on immunological response in the patient: i, ENL, neuritis, iritis; and ii, reversal reaction and their management. | Recognize signs of serious complications, select suitable treatment regimes. | Class, discussion, case demonstration, slides. |
| (b) based on neural damage: i, paralysis (motor); ii, anaesthesia (sensory); and iii, anhydrosis (autonomic) and their management. | Recognition and recording of deformity grading, primary and secondary deformity.<br>Care of feet and prevention of plantar ulcers and infections. | Patient demonstration of deformities and ulcers. |
| (c) based on 'leper' phenomenon—psychological and social disability and rehabilitation philosophy. | Ability to listen and sympathize with patients.<br>Kind and sympathetic acceptance of patients as people. | Discussion in small groups of patients' problems and how leprosy has affected their lives. |
| (d) based on bacteriological response to therapy: i, relapse, and ii, drug resistance and their management. | Suspect relapse and drug resistance and to manage all cases with appropriate multidrug regimes | Discussion, anecdotes, patient demonstration, if any. |

*Broad objective 4*

At the end of the course the participants will *select* cases for referral because of severe complications, *referring* them to appropriate centres according to criteria for referral and set-up of LCP.

In order to be able to do the above, the participants need to have the following:

| *Knowledge* | *Gained by means of*: |
|---|---|
| **1** Outline of referral centres and their capabilities. | List of referral centres. |
| **2** List of criteria for referral of cases. | List of criteria, discussion. |

*Broad objective 5*

At the end of the course the participants will *explain* the goals and mode of operation of LCP, particularly the district level case-finding and case-holding methodology; *cooperate* with LCP, *assisting* where possible in implementing leprosy control, *provide* informal advice and guidance to LCP workers in the area for which they are responsible.

In order to be ready to do this, the participants need the following:

| *Knowledge* | *Attitudes* | *Gained by means of*: |
|---|---|---|
| **1** Outline the principles of leprosy control. | Willingness to cooperate. | Illustrated talk introducing principles and structure of LCP. |
| **2** Explain the structure of the LCP in Nepal and the individual responsibilities of both Basic Health Service (HMG) and Leprosy Control Programme (vertical) staff. | Belief that leprosy control is essential and that they have a role. | Written notes on LCP structure, LCP referral centres and what they do. |
| **3** List referral centres and detail the kinds of cases they can cope with.<br>**4** Discuss how effective links can be established between BHS and LCP services for leprosy control. | Good relationships with the LCP workers. This objective will only be achieved through building good relationships with participants both during and after the course. | Group discussion on how to forge effective links between LCP and BHS and answering this question—'How can you in your particular situation get involved in leprosy control and contribute to establishment of effective links between LCP and BHS for mutual help in leprosy control?' |
| **5** Outline the status of leprosy control in the districts they come from. | | Notes on state of leprosy control in their own district. A copy of last fiscal year annual statistics given. |

*Broad objective 6*

At the end of the course the participants will *provide moral support* to patients, *representing them* to their families, communities and other health workers, *explaining* the nature of their disease, its treatment and control so as to allay anxiety and encourage their acceptance.

In order to be able to do the above, the participants need the following:

| *Knowledge* | *Attitudes & Beliefs* | *Skills* |
|---|---|---|
| | **1** Leprosy is a disease. | Interpersonal and communication skills. |

| | | |
|---|---|---|
| | **2** It must and can be treated.<br>**3** Patients are people who can be victims of prejudice.<br>**4** Doctor's role is to stand by patients.<br>**5** Doctor's role is to control disease. | |
| Describe the:<br>**1** Principles of the control of leprosy based on present knowledge of epidemiology. | | Class and discussion. |
| **2** Principles of patient and public health education in terms of communication, appropriate language and illustrations. | Acceptance of difference and belief that people can learn when things are communicated to them in terms they are familiar with. | Gained through means of: Discussion and meeting patients and listening to them and communication games and through their case study. |

*Allocation of time*

The total time of the course amounted to 30 hours; 6 hours per day for 5 days. This was allocated as follows:

| | | |
|---|---|---|
| **1** Welcome, tour, farewell functions | 1 hr 30 min | = 5% of total time |
| **2** Pre- and post-tests—review/ preview, question time | 2 hr | = 7% |
| **3** Films (movie) | 1 hr 30 min | = 5% |
| **4** Basic leprosy theory | 3 hr 45 min | = 12% |
| **5** Complications in the broadest sense | 7 hr 45 min | = 26% |
| **6** Practical sessions—with patients and in the hospital | 8 hr 15 min | = 27% |
| **7** Education and communication | 1 hr 45 min | = 6% |
| **8** Leprosy control in Nepal | 3 hr | = 10% |
| **9** Administrative matters | 30 min | = 2% |
| | 30 hours | 100% |

*Teaching—learning experiences used*

The principle of involving the participants in *active learning* situations was behind the planning of the whole course.

For example: One of the main objectives of the course was that at the end the participants would *provide moral support to patients*. Thus, a lot of the course and the experiences planned for the participants aimed at allaying their own anxiety about being with leprosy patients and building a positive attitude to patients as *people* with a very difficult problem to live with.

With this end in view:

**1** The film, 'Rehabilitation in Leprosy' was shown.

**2** Each participant took part in a small group meeting with a patient on the first day during which

the patients were encouraged to answer questions which high-lighted what having leprosy meant to them as people, how the fact of having leprosy had affected their lives.
**3** The visit to the Rehabilitation Department told of patients' social problems and how these could be dealt with.
**4** The second day each participant was assigned an individual patient to meet and talk with, etc., daily in the hope that some sort of relationship might form (case study).
**5** Each day participants met and examined patients.
**6** The teaching and hospital staff set an example of acceptance and respect for patients which it is hoped might be emulated.
**7** Discussion was held with participants asking them how they could best help patients learn to cope with their condition in their circumstances.

*Use of aids and materials*

**1** *Patients.* Leprosy patients kindly agreed to participation in class and in the hospital as well as being assigned to participants for case studies. Patients were chosen according to their signs and their story to illustrate the specific topic being taught at the time.
**2** *Teaching and hospital staff* were their own best 'visual aid' when it came to trying to convey to the participants the desirable ways of relating to patients as people, of acceptance, conversation, respect and touch.
**3** *Books.* (a) The excellent small booklet *Essentials of Leprosy* (1980) from ALERT, Ethiopia, was used as the basic text. A copy of this booklet was given to each participant at the beginning of the course. Each day reading was given for the next day's class topics. (b) *Leprosy for students of medicine.* Bryceson & Pfaltzgraff (1979) second edition, was offered for sale at a reduced price. (c) ALERT publication *Guide to Leprosy for Field Staff* was also given to each participant and used as reference for most of the practical aspects of the course.

*Duplicated notes.* Notes prepared in Pokhara on various relevant topics were handed out at the appropriate class.
**4** *Slides.* Slide set 'Leprosy in Children' (TALC) was used as a general introduction on the first day. This stimulated a lot of questions.

*Selected clinical slides (few only) of local patients* were used to illustrate the classes: a, cardinal signs of leprosy; b, classification of types of leprosy; c, complications based on immunological response—ENL, reversal reaction, neuritis, iritis, etc. and d, complications based on neural damage to show typical deformities.
**5** *Movie films.* These movies were shown during the course as an overall introduction to the leprosy problem and a glimpse of its presence as a world problem, not just a local one.

The film '*Rehabilitation in leprosy*' was used first as it presents a message of some hope and attempts to deal with patients as people. The second film, '*Sarbamangalam*', made in Nepal by NSL is basically an appeal to the public to show compassion to leprosy patients; it gives some idea of the leprosy work being done in Nepal, is basically aimed at the public and contains very little technical information. Thirdly, '*Leprosy*' by DAHW was used as a summing up of the course; condensing as it does so much technical information into so short a time it is a useful rounding-off film. The parts of it which are now 'dated' were pointed out to the audience.

*Lepr Rev* (1984) **55,** 421–428

# Domiciliary and Field Work

## Blink-Bell-Blindness

J W Brandsma, Physical Therapist, Consultant: Rehabilitation Research Department, National Hansen's Disease Center, Carville, Louisiana 70721, USA.

The body's reaction to the leprosy bacillus may damage two nerves that are very important for a proper function of the eye and the eyelid muscles. The importance of the muscles that close the eye and the importance of sensation of the eyeball and how they relate to each other in blinking were beautifully described more than 150 years ago:

> The mechanical, and more obvious mechanism for the protection of this organ (the eye), is a ready motion of the eyelids (blink) and the shedding of tears, which coming as it were from a little fountain, play over the surface of the eye, and wash away whatever is offensive (facial nerve). But for the action of this little hydraulic and mechanical apparatus there is required an exquisite sensibility to direct it—not that kind of sensibility which enables the eye to receive the impressions of light—but a property more resembling the tenderness of the skin, yet happily adapted, by its fineness, to the condition of the organ (trigeminal nerve).
>
> This nerve extends over all the exterior surfaces of the eye, and gives to those surfaces their delicate sensibility. Now it sometimes happens that this nerve is injured and its function lost; the consequences of which are very curious—smoke and offensive particles, which are afloat in the atmosphere, rest upon the eye; flies and dust lodge under the eyelids, without producing sensation, and without exciting either the hydraulic or the mechanical apparatus to act for the purpose of expelling them. But although they do not give pain, they nevertheless stimulate the surfaces—so as to produce inflammation, and that causes opacity in the fine transparent membranes of the eye; and the organ is lost, although the proper nerve of vision (optic nerve) remains entire.
>
> I have seen many instances of the eye being thus destroyed for lack of sensibility to touch, and it has been curious to remark, on these occasions, that when the hand was waved or a feather brought near the eye, the person blinked; yet he did not shut his eye on rubbing the fingers across the eyeball. In those cases, when vision gave notice of danger to the organ, the patient blinked to avoid it, but when something touched the eye or eyelids, the sense of touch gave no alarm, and was followed by no action for the protection of the organ.[1]

Sir Charles Bell referred here to patients who had loss of sensation only but could still close their eyes. In leprosy we very often find patients who have damage to both the trigeminal and facial nerve. If patients are not instructed on eyecare when you find insufficient blink, they may develop corneal ulcers and eventually become blind. This is a serious condition in leprosy patients who may have to rely on their vision to compensate for the loss of feeling which they very often have in hands and feet. They are then unable to inspect their hands and feet for injuries.

### *Examination and care for the paralysed and insensitive eye*

*Observe* the patient and see if he blinks. Do not stare at the patient because he may stare back at you and it is then difficult to know if he has a regular voluntary blink. As you are writing your notes or

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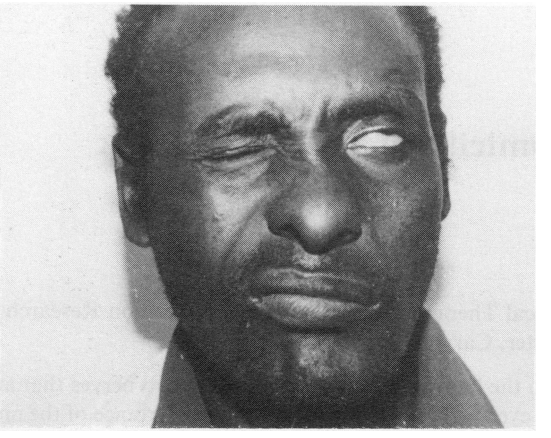

**Figure 1.** Total facial palsy left side. Notice facial asymmetry and Bell's phenomenon as patient attempts to close his eye.

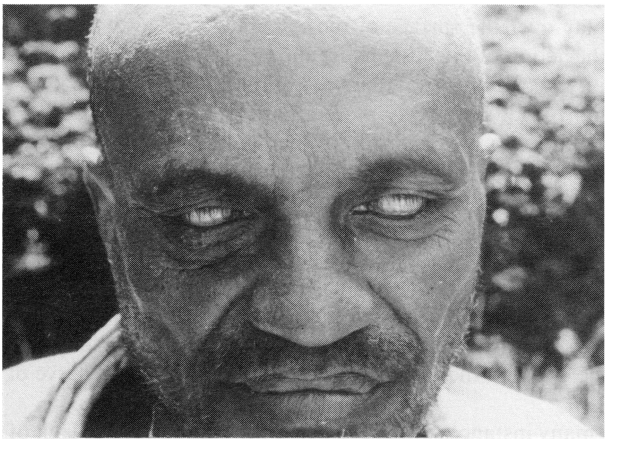

**Figure 2.** Bilateral lagophthalmos showing Bell's phenomenon.

examining other parts of the body or attending to other patients, you may look from the corner of your eye and note if the patient has a regular blink. The eyes will not be in danger if the patient has a regular blink. If you notice that the patient does not close his eyes or has incomplete eye closure then . . .

*Ask* the patient to close his eyes. You may now notice two things.

A *Patient is able to close his eyes*

Many patients are able to close their eyes when they think of it. These patients, however, have lost the sensory 'trigger' for automatic regular eye closure (blink).

These patients need to be conditioned into a 'Think-Blink' habit of eye closure in order to prevent exposure damage to the eye. Try to give practical instruction for each individual patient, e.g. 'close your eyes whenever you meet somebody, when you pass a tree, when you have ploughed one length of your field'. Try to relate the instruction to the daily activities of the patient.

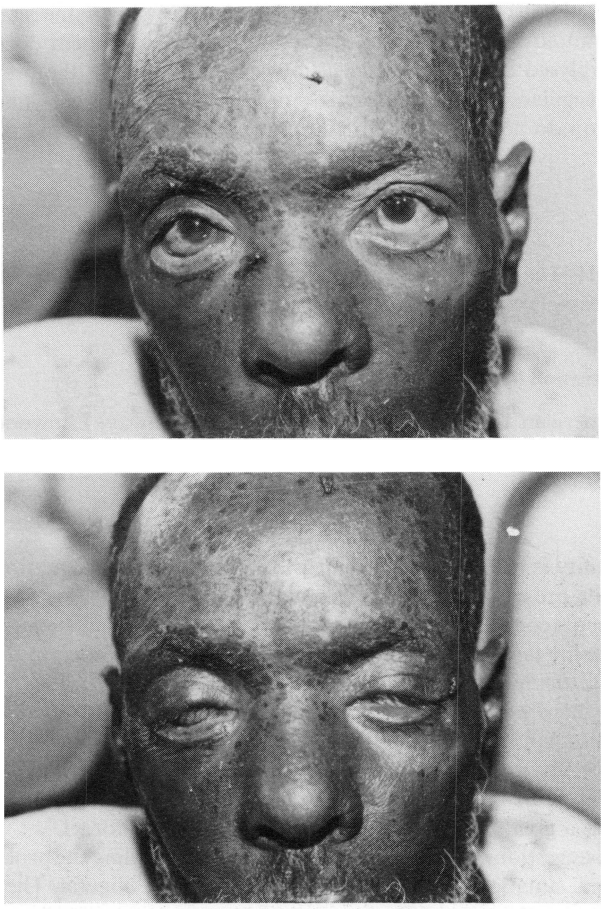

**Figure 3(a)** and **(b).** Eyes open and closed in same patient. Notice sagging of lower eyelids and flies!

Instruct these patients also to close their eyes 10 times powerfully 5 times every day. This may strengthen weak eye muscles so that full eye closure might be obtained.

B *Patient is unable to close his eyes*

As the patient tries to close his eyes you will notice that the eyeball 'rolls up' under the upper eyelid (this is known as Bell's phenomenon (reflex), after the very same Bell who has been quoted earlier.)

In patients with lagophthalmos (inability to close the eye) or severe weakness and an *insensitive* cornea this will usually only happen when the patient tries to close his eyes. It therefore needs to be explained to these patients that as they try to close their eyes the eyeball rolls up and that is the way the cornea is moistened and foreign bodies are washed from the cornea.

Instruct these patients to try to close their eyes as often as they can, but at least a few times every hour (see also 'A'). This reflex will usually happen 'spontaneously' in patients with eyelid weakness or lagophthalmos and a *sensitive* cornea. The eye is then not in so much danger.

It is important that the patients who do not have a regular blink are instructed to wear (sun) glasses and a hat with a large brim that will prevent the wind from blowing into their eyes and the sun from shining directly into their eyes.

The patient should also be taught to inspect his eyes daily for redness and foreign bodies. A spouse or relative should be instructed to inspect the eyes if the patient does not have a mirror. Surgery for the paralysed eyelid muscles will only partially help in the prevention of exposure damage to the eye. Regular eye inspection and exercises will have to be continued after surgery also.

*Remember* if you do not see a *blink*, it should ring a *bell* for you to take action in order to prevent *blindness.*

*Reference*

[1] Bell, Charles KGH. *The Hand.* First printed in London by William Pickering, 1833. Reprinted 1979, The Pilgrims Press, Brentwood, Essex, England.

**Management of ulceration in anaesthetic extremities**

R E Pfaltzgraff, American Leprosy Missions Inc., One Broadway, Elmwood Park, New Jersey 07407, USA.

*Introduction*

Whenever an extremity is insensitive to pain it will unwittingly be traumatized to the extent that tissue damage readily progresses to actual ulceration.

Leprosy is the most common cause for insensitivity leading to such damage, but other causes of neuropathy can have the same end result. The patient attributes the injury to the underlying disease rather than simply to the insensitivity.

The fact that there are many treatments and procedures proposed for management of neuropathic ulceration indicates that as yet we do not have a really good solution to the problem.

The subject is briefly reviewed in *Leprosy* by Bryceson & Pfaltzgraff.[1] The matter is fully dealt with by Brand in *Insensitive feet*.[2] I suggest that leprosy workers should re-read *Insensitive feet* annually. It contains a great deal of information that we tend to forget.

The following suggestions offer some alternative ways of tackling the problem. They have been found to work in one situation—at Garkida in Gongola State, Nigeria. They may contain some suggestions to help solve this very difficult aspect of leprosy management.

**1** Immobilization is vital. Use a splint for the hand or arm. Splint or use crutches for a foot. If there is bilateral foot involvement use a wheelchair or have the patient scoot on the floor using 'hand-sandals' made like small slippers but with a single strap.

**2** The total contact walking cast, as described by Brand, works in some situations and is excellent, but was seldom satisfactory in our unit.

**3** If possible make shoes at an early stage so they are available when the patient is ready for them. This cannot be done if there is too much oedema initially, or if the foot will be altered by surgery.

**4** Control infection. Elevate infected limbs. Use appropriate antibiotics. The most practical seems to be penicillin and, if infection is especially severe, add streptomycin, or add later if infection is not rapidly controlled by penicillin.

**5** Dressing. The most satisfactory all round dressing is done with silver nitrate 0·5% wet dressings. No bacteria can develop tolerance to silver nitrate ($AgNO_3$). The crystals of $AgNO_3$ are placed in a brown-coloured bottle and the requisite amount of water added. Water can usually be used directly from the tap. If there is a precipitate when water is added to the silver crystals then it may be necessary to use rain water or distilled $H_2O$ instead.

The $AgNO_3$ solution is self-sterilizing, but should always be kept in a dark bottle and should not be stored so long that a precipitate develops. If there is a significant precipitate, it should be discarded. The dressing material can be gauze, or cotton (or even raw, unprocessed cotton) that

does not require sterilization as it is rendered sterile by the silver. No bacilli can grow in a solution of silver nitrate that has not reacted with tissue proteins, yet it does not damage living tissues.

$AgNO_3$ dressings should be occluded with a sheet of polyethylene plastic extending beyond the dressing, and wrapped with a bandage. Dressings *must* be changed twice daily. One-half per cent $AgNO_3$ can also be used on clean postoperative wounds where there may be potentially infected tissues or where there may be bleeding. It seems to help to stop postoperative oozing. But for this use it is not occluded with plastic and the dressing allowed to dry. Such a dry dressing can be kept in place for up to a month (possibly longer) until sutures are removed. This, for example, is a good postoperative dressing after arthrodesis of the ankle.

The only disadvantages of using $AgNO_3$ are unrelated to its value for patients. It stains the skin of both patients and staff, as well as linens, the floor and furniture, so that it looks unsightly. There is no practical way to remove the stain, but the colour, of course, is lost as the epidermis is shed. We have had one staff member who seemed to develop an intolerance to the solution, getting fissured, dry, inflamed fingers. This can be suppressed with corticosteroid ointments.

**6** Debridement—remove *only*: a, dead bone unattached to tissues, or a bone that will definitely impede plantigrade walking or foreward propulsion of the foot. *Be conservative*; b, *dead* skin; c, protuberant granulation tissue; and d, functionless tissues that cannot possibly be used for weight bearing can be amputated. Preferably, however, fillet and rotate to cover an area of ulceration or scar.

Excise areas of ulceration, or scar tissue that has ulcerated repeatedly. Good footwear allows more conservatism in surgery. So the surgery that is indicated will relate to the potential for prosthetic footwear. A good shoe programme is *vital*.

Malignant growths can be radically excised if not extending to bone. If deep and fungating, with multiple sinuses, the tumour probably involves bone and amputation is indicated. Leave the stump as long as possible, but do not leave the malleoli. Rarely do these tumours metastasize. Exposed bone, even with a rough surface, can be saved. Patience will be rewarded by a slough of the dead surface of the cortex leaving vital granulation tissue over which it is possible to apply skin grafts.

A very severe infection, especially with gangrenous tissue requires urgent debridement, possibly followed by a second debridement. Otherwise delay debridement until infection has mostly cleared.

**7** Skin grafting. Grafting skin onto defects of the hand, foot or lower limb are rewarding. Split thickness or pinch grafts can be used. Graft only when there is healthy, dry, dark red granulation after dressing with $AgNO_3$. Exuberant granulations occasionally need to be touched with a $AgNO_3$ stick, or alternatively a period of dressing with Iodoform powder. For scars that repeatedly break down, it is preferable to excise completely to normal tissues under tourniquet-controlled haemostasis. Seldom is there excessive bleeding and sometimes a split graft can be applied primarily. More frequently grafting needs to be done later. Perforate split grafts with the tip of a scalpel, making slits at about a centimetre apart, and apply the graft carefully with mosquito forceps. Usually it need not be sutured in place. If bleeding is likely, delay grafting and dress with $AgNO_3$.

All grafted patients should be given antibiotics from prior to the procedure until almost completely healed.

Closely woven cloth impregnated with Vaseline and then sterilized can be placed over the graft for the first few days to prevent the $AgNO_3$ dressing adhering to the surface.

Where there are no facilities to make split grafts; when conditions are not ideal or with a wound that is not completely clean, pinch grafts may be used successfully. Prepare the area to be grafted and the donor site and drape, using sterile technique. Procaine or other local anaesthetics can be used for the donor area, none is required in the graft site.

A small stiff needle is required to pick up the skin. A hypodermic needle will serve, but a Hagedorn needle is better. Pick up the skin on the point and cut off a circle of skin about 3 mm in

diameter. Carry it to the ulcer site and with a downward pressure on the needle push the piece of skin under the surface of the granulations. The consistency and depth of the granulations determines the technique for burying the graft adequately. It takes a bit of trial and error to develop the technique. The needle is held at about 25° to the skin, then while pushing the point down into the granulations the back of the needle is elevated while the point is moved slightly forward—a combination of rotation around an axis at the middle of the needle, and forward advancement.

When the graft is buried in the granulations place the back of the scalpel blade over the shaft of the needle just at the place where it enters the granulations and pull out the needle in the line of its shaft. The scalpel will hold the graft in the granulations if they are adequate. If they are not healthy or too fibrous, the graft may pop back out. In that case it is better to continue dressings with $AgNO_3$ for a few more days.

The donor site can be dressed with $AgNO_3$ without the plastic occlusion and left to dry. At about 1 week it will have healed.

The grafted site should be dressed with $AgNO_3$ and plastic occlusion and changed twice daily, beginning 6–12 h after surgery. Penicillin is used to prevent infection, beginning prior to surgery and continuing until almost complete healing.

Grafts can be placed slightly less than 1 cm apart. If one attempts too close a placement, those previously buried will be disturbed. On about the third or fourth day the grafts will move up to the surface, flatten out, and begin to grow.

If there is any question of movement of the area grafted, or if on a weightbearing surface, a posterior plaster slab should be applied to immobilize nearby joints.

**8** 'Small cast'. A small ulcer that is not infected, yet does not heal can sometimes be cured by use of a 'small cast'. This is made by applying one roll of 6-inch plaster, with a single small dressing with a bit of antibiotic applied right over the ucler. This thin cast immobilizes, keeps clean and prevents walking. If the patient walks it becomes dirty or breaks! The cast usually is removed after 2 weeks, and if the ulcer is not fully healed can be replaced for a further 2 weeks.

**9** Graded walking. Gradually increasing walking *under supervision* is important. The first day 5 min of walking is enough, the second day two 5-min periods gradually increasing until the patient is ready for discharge. This cannot be timed, but varies depending upon the severity of the ulcer, the deformity, the amount of scar, etc.

Warning. No bandage should ever be placed on a foot and then the foot forced into a properly fitted shoe!

*Conclusion*

If patients are cooperative, with this programme any ulcer that has not undergone malignant degeneration will heal. If it does not heal either there is malignancy, which will express itself as a fungating growth, or more patience is required.

*References*

[1] Bryceson A & Pfaltzgraff RE. *Leprosy*. Edinburgh: Churchill-Livingstone, 1979.
[2] Brand P. *Insensitive Feet*. The Leprosy Mission, 1981.

**WHO: Blindness prevention; training auxiliary personnel in eye care**

The *WHO Chronicle*, **34:** 332–5 of 1980 carries an article on the above subject with the following summary:

> Unless active measures are taken to combat blindness, much of which is preventable or curable, it is expected that by the year 2000 the number of blind in the world (at present 30–40 million)

will increase considerably. Auxiliary health personnel have an indispensable role to play in the delivery of eye care and in preventing blindness. Last year a WHO task force met in Bethesda, Maryland, and discussed the training of such auxiliaries for blindness prevention and for providing eye care to all populations through the primary health care services. This article is based on the report of that meeting.

Emphasis is given to the idea that much blindness is avoidable. The main headings are: peripheral level; the primary health workers' tasks; intermediate level; duties of health personnel; training auxiliaries; examples from three countries (Guatemala, India and Kenya).

***Primary eye care manual for health workers*; Kenya**

Through correspondence with Mr John Macharia Waruhiu, Field Training Officer, Kenya Rural Blindness Prevention Project, Kenya Society for the Blind, Barclay House, Langata Road, PO Box 46656, Nairobi, Kenya, we have received a copy of this manual—one of a range of materials produced by the International Eye Foundation in the USA. The manual is on A4-sized paper, 7 pages only, extremely clearly printed and illustrated with black and white diagrams. It is designed for primary eye care within the context of primary health care, and is based on the belief that over 75% of all blindness in Kenya is preventable or treatable. Dr Randolph Whitfield Jr, Ophthalmic Consultant, Central Province, Kenya has written to explain that the International Eye Federation (PO Box 1323, Nyeri, Kenya; 7801 Norfolk Avenue, Bethesda, Maryland 20804, USA) has also produced teaching manuals on other aspects of ophthalmology which have been field tested and printed for nurses, clinical officers, teachers and students in rural health training centres.

**International Agency for the Prevention of Blindness; IAPB**

Dr Carl Kupfer, President of the IAPB (National Eye Institute, Building 31, Room 6A03, Bethesda, Maryland, USA) has kindly written to us with a copy of the latest IAPB News (No. 4, Spring 1984). This excellent newssheet has information on eye disease and blindness prevention from over 30 different countries, including articles, notices, announcements of meetings, research and primary eye care. The current issue has items on: successor to Sir John Wilson in the Royal Commonwealth Society for the Blind; prevention of blindness in Tanzania; Christoffel-Blindenmission in Tanzania; Helen Keller International; 'tips on eye care' from Bwino, the quarterly health magazine in Zambia; International Eye Foundation projects in Kenya and Malawi; a list of recent WHO meetings.

**'Eye Camps' in South India; Kasturba Kusuta; Nivaran Nilayam**

We are most grateful to Professor Jagadisan ('Sankaran', No. 38, First Main Road, CIT Colony, Mylapore, Madras, 600 004, India) for the following information about eye camps held in South India:

> We conducted two eye camps, one in April 1982 and another in February 1983. My good friend Dr Raja Savarirayan of the Christukula Ashram, Tirupattur, North Arcot, who has been engaged in ophthalmic work for half-a-century, was good enough to conduct the camps with grants from Christoffel-Blindenmission, West Germany. The cataract operations were done by an expert ophthalmic surgeon of Salem Dr K G Gurubatham and Dr Raja Savarirayan. A number of trained and experienced ophthalmic assistants came with the surgeons. Our own staff, doctor, nurse and others, gave their help. These eye camps benefited our leprosy patients for whom poor vision is a 'double' blindness because of their insensitive fingers. But these camps also benefited a considerable number of non-leprosy cataract patients. The first camp, from 23

to 30 April 1982, benefited 56 patients, of whom 11 were leprosy patients, the rest being general cases. The second camp was held from 16 to 25 February 1983. This camp benefited 49 general cataract patients and 10 leprosy patients. Thus, 21 leprosy patients and 94 patients from the general population (non-leprosy) were benefited by these camps. The results have been very good because of the intensive care before and after operations that Dr Raja Savarirayan and his colleagues bestowed upon the patients. Moreover, since the patients came from neighbouring villages, they could come to our hospital for treatment of any complications and for long-term follow-ups. The holding of these camps here has increased the awareness of the medical, nursing and para-medical staff to the eye problems of leprosy patients, and much care is taken to relieve eye complications and to prevent poor vision. The holding of these camps at which leprosy patients (a minority) are operated on the same table and treated in the same wards as the non-leprosy cataract patients of the general population (the majority) has been a striking step towards integration, both medical and social, of the leprosy patients with society. It is also one plank among many in our new scheme through leprosy work to better living and better health care.

**'Slide-text' Colour Transparency Teaching Sets on Leprosy**

We have recently reviewed those which are known to this office and take this opportunity of recording the following information:

**1** *India. Leprosy I and Leprosy II.* Authors Parekh, Ganapati and Chetan Oberai. Produced by Medical Education Department, Glaxo Laboratories (India) Ltd, Worli, Bombay 400 025, India. Each set has 24 colour slides, with text, covering virtually the whole subject of leprosy. Apply to Dr Phatnani at the above address.

**2** *India. Reconstructive Surgery in Leprosy*, prepared by N H Antia and S G Kamat. 1, Opponens plasty. 2, Correction of clawed fingers. These excellent slide sets describe two of the most important operations for deformities of the hand in leprosy. The first has 24, and the second 48 colour slides of high quality, which are designed '. . . to provide an easy introduction to the subject and stimulate interest for further reading and for undertaking surgery.' The text is extremely clear for both operations and could be used either for self-instruction or teaching others. The cost of (1) is Rs 250 and of (2) Rs 500. Enquiries to Dr N H Antia, Ben Nevis, Bhalabhai Desai Road, Bombay-400 036, India.

**3** *USA.* National Hansen's Disease Center, Carville, Louisiana 70721, USA. Dr R O'Connor, Chief of the Training Branch can supply information and documents on a wide range of teaching material available from this centre, and this includes a comprehensive slide-text set on *Clinical Aspects of Leprosy* with 60 slides.

**4** *Europe.* The WHO Regional Office for Europe have produced a set of *Leprosy in the Light-Skinned*, prepared by Dr D L Leiker (Amsterdam). This includes a 21-pp booklet as the descriptive text and there are 50 slides. Enquiries to Dr B Velimirovic, Regional Officer for Communicable Diseases, at the WHO Regional Office for Europe, 8 Scherfigsvej, DK-2100, Copenhagen, Denmark.

**5** *The Netherlands.* In the 'MEDDIA' series, a very comprehensive set of colour slides is available, either as conventional 35 mm transparencies, or on microfiche (with viewer); and there is a full text to accompany the set. Royal Tropical Institute, 1092 AD, Amsterdam, The Netherlands.

**6** *United Kingdom.* As 'an activity of the Tropical Child Health Unit', Institute of Health, 30 Guildford Street, London WC1N 1EH, TALC (Teaching Aids at Low Cost) produce a wide range of teaching–learning materials, including a comprehensive series of slide-text sets, at remarkably low cost. There are two on leprosy: Lp, *Leprosy In Childhood*; LpCn, *The Classification of Leprosy* has 24 slides, with full text.

*Lepr Rev* (1984) **55,** 429–436

# Reports, News and Notes

## LEPRA's contribution to the fight against leprosy. A talk given at the 1984 Annual General Meeting of LEPRA by S G Browne, Vice-President of LEPRA

It may sound presumptuous to entitle this talk 'LEPRA's contribution to the fight against leprosy', as if a relatively small voluntary organization without vast financial resources or massive political pull could make any significant contribution towards the continuing struggle against an entrenched foe. The whole idea may at first sight seem rather absurd, yet I am daring to suggest that LEPRA has over the years in many respects been able to play a key role in this battle, complementing and supplementing the efforts of larger and better-funded organizations, and of governments and supranational bodies like the WHO. We are not suggesting that all LEPRA's geese are swans, but we do have a number of genuine swans in the activities of the organization whose 60th Anniversary we celebrate today.

To me personally, the preparation of this rapid historical review has been a fascinating and nostalgic journey into the past, since at several points I have had the privilege of acquaintance with some of the principal protagonists in LEPRA's unfolding story.

Let me remind you briefly of the situation 60 years ago. Leprosy was slowly emerging from the unscientific mists of the previous centuries. Although the young Norwegian doctor, Hansen, had demonstrated the causative organism some 50 years previously, and although Christian Missions were doing their best to alert the conscience of Christendom to the plight of leprosy sufferers, governments on the whole had done little to contain the scourge or alleviate the lot of leprosy's victims except enact repressive and coercive legislation. After all, what can you do with a condition that was still half-disease, half-myth, whose victims were despised and shunned, regarded as being especially guilty or especially dirty, useless encumbrances in society?

According to some few people, the time was ripe to enlist the support of influential figures outside the Churches, to encourage research into leprosy, and to organize treatment on a wide scale with remedies then available. A meeting was called at the Mansion House on 31 January 1924, when the British Empire Leprosy Relief Association was publicly inaugurated. I was not present, but I did have contact with two of the illustrious founders of BELRA. I met the Rev Frank Oldrieve at a meeting in London that same year, when he had been appointed as BELRA's first Secretary, and afterwards I was in touch with Sir Leonard Rogers of the Indian Medical Service, a man already renowned for his researches in malaria, cholera, kala-azar and plague. The third member of that famous trio was Sir Frank Carter, an eminent Calcutta philanthropist. All three were highly motivated Christian gentlemen who wanted desperately to eradicate leprosy from the countries coloured red on the world-maps of those days—the British Empire.

The Mansion House appeal met with a most disappointing financial response. Nothing daunted, the triumvirate decided to attempt to enlist the support of the Viceroy of India, Lord Reading. He made his appeal, simply, and with conviction; he said: 'Contributions are urgently needed for the extension and support of institutions . . . and for further research.'

The parent body in Britain may have got off to a shaky and uncertain start, despite the interest and advocacy of HRH the Prince of Wales, but its Indian offspring—afterwards (in 1950), under the inspiring leadership of Professor Jagadisan, to merge into the Hind Kusht Nivaran Sangh—became a strong infant in the most populous (and most leprous) of the countries comprising the British

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Empire. Frank Oldrieve was the indefatigable midwife in India and elsewhere. He had a simple message, 'Rid the Empire of leprosy', and he advocated a simple remedy, chaulmoogra oil, either pure, or chemically modified. Sir Leonard Rogers supplied seeds of *Hydnocarpus wightiana* to leprosy hospitals in India and Africa, and instructed doctors and auxiliaries in the preparation and administration of the pure oil and its diverse derivatives. He bludgeoned medical workers into acceptance of his medical products and his ideas. Just before his death at the ripe old age of 94, he was in enthusiastic correspondence with me at Uzuakoli about drug trials with a combination of his pet chaulmoogra oil and the sulphones. He considered that the sulphones alone would never eradicate leprosy.

To bring this part of LEPRA's story right up to date, I should mention that I gave to Professor Stumpf of the University of Los Angeles, California, some fruits from chaulmoogra trees grown at Oji River (Nigeria) from seeds supplied by Sir Leonard Rogers; the seeds germinated in the USA, and oil expressed from the ripe fruits provided Professor Louis Levy with hydnocarpic acid: he investigated the mycobacteriostatic and lymphotactic properties of various derivatives of the acid in an attempt to synthesize compounds that would attack the multiplying organism at a novel and vulnerable point. Sir Leonard, being dead, is thus still speaking to research workers today.

Although BELRA had begun with such high objectives and expectations, its early days were hampered by shortage of funds and a blunting of ideals. Then something happened. Tubby Clayton was the agent of change. Having seen for himself the human tragedies of neglected leprosy sufferers in West Africa, he returned to this country on fire with two ideas; enlisting laymen in the fight against leprosy, and ensuring adequate financial support for BELRA. As Padre of Toc H, he was in touch with idealistic young men whom he pressed into service. They went to Itu in Nigeria, to Sierra Leone, to The Gambia, to India. And their enthusiasm revivified the organization. At last, BELRA was getting on the map, and its finances were being put on a sounder basis. Its serious medical aims were becoming recognized, with men like Ernest Muir and Robert Cochrane ensuring its scientific respectability. Somewhat later, James Ross Innes joined the medical team, as Medical Secretary. As a voluntary agency, BELRA could also emphasize the human and humanitarian aspects of the problem of leprosy—and it did so.

Another major contribution of BELRA to the fight against leprosy was in the provision of literature. Frank Oldrieve began it, with the regular production and distribution of five thousand copies of his *Leprosy Notes*, which merged into *Leprosy Review*—a much respected journal, still going strong, under the able editorship of Dr Colin McDougall. In the early days, BELRA published small scientific monographs from time to time—a practice that continues today.

Two events mark the sixties: the first, on 1 January 1964, as an acknowledgement that the 'E' in BELRA (representing the Empire) was slowly disintegrating and disappearing, LEPRA rose Phoenix-like from the anachronistic ashes of BELRA; the second event, the Medical Advisory Committee of LEPRA, through its Chairman, Dr Dick Rees, recommended that a Project for the control of leprosy over a wide area in Malaŵi should be inaugurated. This imaginative proposal would demonstrate that by utilizing jeeps and bicycles, and trained and supervised medical auxiliaries, it would be possible within a delimited area to control, and eventually even to eradicate, leprosy. When Medical Secretary of LEPRA, I visited the Project more than once to advise and encourage. Very impressed with the standard and coverage of these activities, the Malaŵi Government authorities requested LEPRA to incorporate an additional area into the scheme. Today, with the implementation of the fashionable multidrug therapy in the Project, LEPRA will once again be in the news: in collaboration with the WHO, the LEPRA records will be extracted and analysed for critical report. There is talk, too, of Malaŵi being chosen for the initial field trials of a protective vaccine against leprosy when this becomes available. Still in the forefront, and still making a strategically valuable contribution to the fight against leprosy.

In many other ways, too, LEPRA is making its presence felt. Gone are the days when a charitable body such as ours could be ruggedly independent. When the International Leprosy

Association was founded in Manila in 1931, BELRA was closely involved through Ernest Muir and Robert Cochrane—both in the administrative set-up and in the editing and publication of the *International Journal of Leprosy*. This complementary and cooperative activity was also shown with the Mission to Lepers, which was renamed The Leprosy Mission in 1966.

Another organization with which LEPRA was to have close links was the Leprosy Research Unit, later to be called The Leprosy Study Centre. Doing 'good by stealth', as ever, Sir Frank Carter helped supply the finance to ensure the survival of this brain-child of Robert Cochrane, and LEPRA was represented on its Governing Body until its sad demise in 1980. I was its Director from 1966.

Pursuing still further its cooperative links with outside bodies, LEPRA became in 1976 a full member of ILEP, the International Federation of Anti-Leprosy Associations: before that year, I had had the honour of representing LEPRA on ILEP as an observer.

In two directions LEPRA has shown commendable initiative: I refer, first, to the encouragement of medical students to interest themselves in leprosy by organizing an Essay Competition; and second, to helping medical students financially when they wish to spend an elective period at a Leprosy Centre overseas.

Another activity with which BELRA, and later LEPRA, has especially identified itself is research in leprosy. As one of its original objectives, research has always figured largely in the projects sponsored and the sums earmarked every year for this purpose. From the early encouragements of Sir Leonard Rogers, to the support of the Leprosy Research Unit at Uzuakoli in Eastern Nigeria (of which I had the privilege of being Director from 1959 to 1965), and the subsidizing of research at the (British) Medical Research Council (Dr Dick Rees), the Department of Anatomy at Oxford (Dr Colin McDougall) and the Immunology Unit at the Royal College of Surgeons here in London (Professor John Turk and Dr Jill Curtis) LEPRA has over the years sought to identify and support medical research likely to prove of original or seminal significance—a magnificent record for a relatively small organization.

LEPRA's links with Buckingham Palace are among its most treasured connections. The very active help of its first Patron, HRH the Prince of Wales, assured the imprimatur of royal approval, and the continued genuine personal interest of Her Majesty the Queen as our present Patron is a much-appreciated token of the concern of the Monarchy for the well-being of the unfortunate victims of leprosy in the countries of the British Commonwealth and beyond.

If progress is to be reckoned by distance travelled, and not by point attained, then this brief and superficial excursus into 'LEPRA's contribution to the fight against leprosy' indicates that real advances have been made in the understanding and control of this scourge, and summarizes the honourable and by no means insignificant role that LEPRA has been able to play in these advances.

Crystal-gazing is admittedly a hazardous pursuit, but we must ask ourselves the question, What of the future? Will LEPRA be celebrating its Centenary in 40 years' time, or will leprosy have been banished for ever by then from God's earth? Who knows? Its control and eventual eradication will prove much more difficult than smallpox, or even tuberculosis. Meanwhile, there is much to learn, and much to do, as we face the future challenges with confidence and hope.

### *British National Formulary* No. 7, 1984

This compact and valuable source of information on drugs and prescribing, published jointly by the British Medical Association and the Pharmaceutical Society of Great Britain, now runs to 484 pages, including a detailed index. The main text consists of classified notes on drugs and preparations used in the treatment of diseases and conditions. These notes are split into 15 chapters, each of which is related to a particular system of the human body or to another main subject (infections, vaccines, etc.). Each chapter is divided into sections which begin with appropriate *notes for prescribers*. These notes are intended to provide information to doctors, pharmacists, nurses,

etc., to facilitate the selection of suitable treatment. The notes are followed by details of relevant drugs and preparations.

The opening pages of general information, including sections on prescribing for children, prescribing during pregnancy, adverse reactions to drugs, are extremely well written. (Leprologists will be interested to see that pregnancy is given as a contraindication to the use of dapsone and that the advised dose of this drug in leprosy is '. . . 25–50 mg weekly, gradually increasing to 400 mg twice weekly or 100 mg daily'.) Obtainable from the British Medical Association, Tavistock Square, London WC1H 9JP.

**WHO: Advertisement for the post of scientist (Education Specialist) in malaria, 1984**

Although the title does not in fact specify malaria, the duties of the post include: assessment of existing training facilities and future training needs of malaria control and related vector-borne disease control programmes in Member Countries of Asia; promotion of national training programmes through cooperation in the preparation of learning objectives and curricula for different types of training courses, developing the training of national teachers, and coordinating and providing technical support for the organization of regular courses, seminars and workshops; organization and provision of technical and administrative support to national training programmes by (a) coordination of consultant services and exchange of teaching personnel (b) cooperation in the monitoring of training activities, whenever advisable, including budgetary and financial aspects, selection of trainees, recruitment of lecturers, preparation of course curricula, timetables and lecturing (c) evaluation of training activities; collection and distribution of information on malaria and related vector-borne disease training activities in Asian countries; promotion of applied field research; assistance in the management and administration of the project as necessary; assistance in the preparation, implementation and evaluation of the Project Plans of Action; assistance in the preparation of the project technical and administrative reports.'

[With slight changes, the wording of this advertisement could be modified for tuberculosis, leprosy and many other diseases, most of which call for a similar approach to the subjects of education and training. In the case of leprosy, where it is now abundantly clear that the safe and effective implementation of multiple drug therapy depends crucially on the quality of the medical staff, a systematic and professional approach of the type outlined above would surely be of considerable value. *Editor.*]

**UNESCO coupons in place of foreign currency**

In many countries the shortage of foreign currency hinders the importation of books, publications and scientific material.

In some of these countries, Unesco Coupons, whose value is expressed in United States dollars, are sold for national currency to educators, research workers and students who use them to pay for their foreign purchases. The Coupons are issued in the following values: $1000, $100, $30, $10, $3, $1; 'blank' Coupons, which can be made out by the distributing body for amounts from 1 to 99 US cents, are also available.

Here are some examples of material that can be purchased with Unesco Coupons. As a general rule, all publications, films and material intended for educational, scientific or cultural purposes can be purchased with Unesco Coupons:

*Publications* books, school textbooks, periodicals, medical or scientific journals, maps, copies of courses, reproductions of works of art, sheet music.
*Materials: audio-visual material* films and prints, filmstrips, colour slides, movie projectors, raw

film, screens, records, record-players, tape-recorders, tapes, photographic material, developing material, film, radio and television sets.
*School material* exercise books, paper, ink, pencils, india-rubbers, rulers, paints, typewriters, demonstration apparatus, drawing tables, musical instruments.
*Scientific material* optical instruments and equipment, laboratory equipment and instruments, chemical products, electrical and acoustical measuring instruments, analytical and clinical testing apparatus, electrical and electrotechnical equipment, hand and machine tools, meteorological geodetical and topographical instruments.

Unesco Coupons can also be used to pay subscriptions to educational, scientific or cultural institutions, and university registration fees and copyright dues.

The list of 'Distributing Bodies for UNESCO Coupons' covers most of the countries or major areas in which leprosy is endemic. This system should be invaluable to many of those who have difficulty in obtaining the foreign currency for the items noted above. Further information from the United Nations Educational, Scientific and Cultural Organisation, 7 Place de Fontenoy, 75700, Paris, France.

**English for foreign students; English for medicine; University of Edinburgh**

We have received information from the Institute of Applied Language Studies, 21 Hill Place, Edinburgh EH8 9DP on various courses in English, several of which may be of value to students from abroad. Short courses (days to weeks) are held on Elementary Medical English; English for Medical Students; English for Medical Practice in Great Britain; English for Clinical Medicine; English for Biomedical Sciences. Long courses (weeks to a few months) are on General and Medical English. Further details and brochure from the above address.

**English Language Book Society (ELBS); 1984 catalogue**

The ELBS Student Editions are low-priced editions of British publishers' books, chosen by an advisory committee for their value to students in developing countries. They are priced at between one third and a half of the price of the cheapest publishers' editions and are made available to students by a subsidy from the British Government in approximately 80 countries:

*Africa* Benin, Botswana, Burundi, Cameroon, Chad, Congo (Brazzaville), Djibouti, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Ivory Coast, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mauritania, Mauritius, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, Swaziland, Tanzania, Togo, Uganda, Upper Volta, Zaire, Zambia, Zimbabwe.
*Asia* Bangladesh, Brunei, Burma, Hong Kong, India, Indonesia, Laos, The Maldives, Malaysia, Nepal, Pakistan, Singapore, Sri Lanka, Thailand.
*Pacific* Fiji, Kiribati, Papua New Guinea, Solomon Islands, Tonga, Tuvalu, Vanuatu, Western Samoa.
*West Indies and Atlantic* Antigua, Bahamas, Barbados, Belize, British Virgin Islands, Cayman Islands, Dominica, Guyana, Jamaica, Monserrat, St Kitts-Nevis, Anguilla, St Lucia, St Vincent, Surinam, Trinidad and Tobago, Turks and Caicos Islands, St Helena.
*Middle-East* Egypt, Jordan, Sudan.

The main subjects covered are: social sciences, pure sciences and applied sciences. Under medical sciences (p 25) and medical microbiology (pp 27/28) alone, there are numerous entries of considerable interest. Many important books, including several on laboratory work in developing countries, etc., are either available or under development or revision. In countries where there is a

British Council Library, an exhibition set of these ELBS books is usually kept for consultation. Books cannot be supplied free: they should be purchased direct from local booksellers. Source: ELBS, The British Council, 11 Portland Place, London W1N 4EJ.

***Revista Argentina de Dermatologia (Spanish), Buenos Aires, Argentina***

We have recently received the latest issue of this journal from the Editorial Office, Hospital Ramos Mejía, Gral. Urquiza 609, 1221 Buenos Aires, Argentina. As usual, quite a number of the original articles and other sections refer to leprosy, or the use of drugs such as thalidomide and colchicine in various dermatological disorders. Like other journals from South America and from Mexico, this journal in Spanish is full of good illustrations and interesting observations, including many on 'tropical dermatology'.

**International Symposium on Mycobacteria of Clinical Interest, Cordoba, Spain, 1985**

Professor M Casal has written to inform us of this symposium, to be held from 27 to 28 September 1985, in Cordoba. The themes to be discussed include the following: immunopathology of leprosy and tuberculosis; modern methods for the rapid diagnosis of tuberculosis; human mycobacterioses; therapy of tuberculosis and leprosy; experimental chemotherapy of new anti-microbial agents; modern automatized systems in mycobacteriology; new knowledge about *Mycobacterium leprae.*

Further details from; Secretariat, International Symposium on Mycobacteria of Clinical Interest, Department of Microbiology, School of Medicine, Avda, Menéndez Pidal, s/n, Cordoba-4, Spain.

**XVII World Congress of Dermatology, Berlin, 1987**

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

***Partners in Portuguese: 'Companheiros'***

It is a pleasure to report that *Partners*, a magazine produced by the Leprosy Mission International (50 Portland Place, London W1N 3DG), is now available in Portuguese. In Brazil, where its value should presumably be very considerable, enquiries may be addressed to: CERPHA, Rua Conde de Bonfim, 232, sala 613, CEP 20520 - Caixa Postal 24046, Rio de Janeiro, Brazil.

***Revista Goiana de Medicina*; a medical journal from Brazil (Portuguese)**

We are grateful to the Editorial Office of this journal (Associação Medica de Goiás, Av. Portugal, Es. Av Mutirão Setor Bueno, Caixa Postal 254, 74000 - Goiânia, Goiás-Brazil), for vol. 28, nos. 1/2,

January/June, 1982—which in fact includes an interesting article on lymphadenitis in lepromatous leprosy. The contents list is entirely in English and there is a good English summary of each article. The journal may well be of value and interest to those working in Portuguese-speaking areas of Africa.

**Histopathology Services for Developing Countries**

For the last 15 years the Department of Histopathology at St Thomas' Hospital has provided a free, postal, diagnostic service for a number of hospitals, both government and mission, in developing countries. It was originally envisaged that the need for such services would decrease as they were built up locally. For a variety of reasons, differing from country to country, this has not happened and the need is still there and likely to continue. To meet these problems and to provide histopathological expertise in parasitic, communicable and other tropical diseases in the UK a consultant histopathologist post has been created jointly with the London School of Hygiene and Tropical Medicine and University College Hospital Medical School. This post has been filled by the appointment of Dr S B Lucas who has spent 2 of the last 4 years in this unit and who is keen to maintain or increase diagnostic services, including leprosy histopathology. Specimens should be sent to Dr S B Lucas, Department of Morbid Anatomy, School of Medicine, University College London, University Street, London WC1. (Tel: 01-387-9300.)

***Technical Guide for Smear Examination for Leprosy by Direct Microscopy***

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

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

**BIREME and the Index Medicus Latino-Americano**

We are indebted to Kioko Shiraishi, Publication Section, in BIREME; Centro Latino-Americano de Informação em Ciencias da Saude, Rua Botucatu, 862, Caixa Postal 20381, Vila Clementino, São Paulo, Brazil for the following information:

> In 1968, the Pan American Health Organization set up the Regional Library of Medicine and Health Sciences (BIREME) in the Paulista Medical School in São Paulo under an agreement with the Government of Brazil.
>
> BIREME is doing an outstanding job not only of searching for and disseminating scientific information and training specialized staff, but also of promoting the establishment of national biomedical information subcenters (there are already 18 in Brazil). It is also the hub of the Latin American network of biomedical and health information. With the help of the National Library of Medicine of the United States, BIREME has succeeded in developing into a center of high prestige in its field. Its most notable accomplishments include the compilation of the *Index Medicus Latinoamericano*, which is published semiannually since 1979 and embraces the output of 250 scientific publications, thereby filling the major gap that had existed in this field.

**Medical Student Electives in the Third World; Action Health 2000, Cambridge, UK**

We are most grateful to the Director, Dr M Kapila, Action Health 2000, for the following information about his organization and more specifically about the 'Scheme for Medical Student Electives'. This is a voluntary, charitable society concerned with health care issues in the Third World; the general purpose is to work towards the WHO target of making basic health care accessible to the world's poorest peoples. The main lines of work may be summarized as follows: (1) *Practical support* (financial, technical, personnel) for appropriate health and development programmes in the Third World. (2) *Study and research* into issues related to health care in the Third World. (3) *Information and education.* Action Health is committed to creating greater awareness about the inequitable distribution of health care resources in the world, especially amongst health professionals here. (4) *Training and service.* Opportunities are being created for short-term and long-term placements in selected overseas health programmes for nurses, doctors and other health workers. This is valuable experience for individuals as well as a contribution to health care in the Third World. One such scheme is for 'Medical Students Electives in the Third World'.

A 6-page document is available describing these electives under the following headings: background, placement, orientation course, organization, follow-up and support.

Action Health 2000 organizes comprehensive Orientation Courses in conjunction with the Department of Infectious and Tropical Diseases, Addenbrooke's Hospital, Cambridge. The Course is usually over a weekend (Friday to Sunday) and consists of an intensive programme of seminars, films, slide-shows and simulation games. There is the opportunity to meet returned elective students and doctors/nurses who have worked in developing countries.

Chairman: Dr A Rubenstein, Cambridge. Advisers: Professor D Morley, Drs J Yudkin and D McLaren. Further information is available from Dr M Kapila, Action Health 2000, 35 Bird Farm Road, Fulbourn, Cambridge CB1 5DP.

**Video-tape: 'Chemotherapy of Leprosy for Control Programmes'**

The Department of Medical Illustration in Oxford has produced a 14-minute video-tape describing recent regimens of drug treatment for leprosy, based on the Report of a World Health Organization Study Group entitled *'Chemotherapy of Leprosy for Control Programmes'*, published by WHO in Geneva in 1982 in the Technical Report Series, Number 675. The system used is VHS PAL 625. English language. 14 min. The intended audience includes—medical students, medically qualified doctors, senior personnel in ministries of health in leprosy-endemic countries, tutors and teachers in medical and para-medical schools, programme planners, leprosy control officers and supervisors, senior staff in pharmacies, drug supply and distribution.

The subject matter covers the classification of leprosy according to both Madrid and Ridley-Jopling systems; definition of pauci- and multi-bacillary leprosy; unit dosage and regimens of dapsone, rifampicin, clofazimine and the thioamides for the treatment of both pauci- and multi-bacillary cases. In order to ensure the safe and effective implementation of multiple drug therapy for as many patients as possible and with the minimum of delay, repeated emphasis is given to the importance of the training, retraining and supervision of the health personnel concerned. Cost £12 sterling ($16 US dollars), plus Value Added Tax (VAT), but inclusive of postage. Apply directly to—Department of Medical Illustration, the John Radcliffe Hospital, Headington, Oxford OX3 9DU, England.

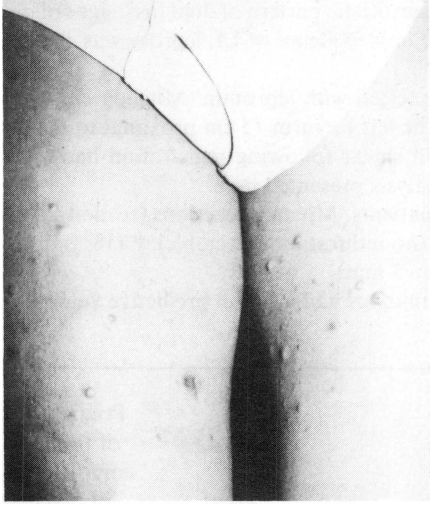
*Lepr Rev* (1984) **55,** 437–439

# Letters to the Editor

## REPLY. RELAPSED LEPROMATOUS LEPROSY IN KOREA; OCCURRENCE OF MULTIPLE SMALL 'UMBILICATED' LESIONS OF BORDERLINE TYPE

Sir,

It was with pleasure that we read Do-Il Kim's letter,[1] in which he pointed out that numerous centrally dimpled, small sized and bilateral, symmetrically distributed lesions were unusual and did not correspond to published accounts of patients with lepromatous leprosy who are known to relapse with features of borderline leprosy. He further stressed that it could be yet another type of leprosy, as seen in Korea, which seems to be dapsone-resistant and relapse.



We saw similar lesions in a male 20-year-old Egyptian patient in 1981. The lesions were small (1–2 cm in diameter), raised, arising from normal looking skin, erythematous and centrally umbilicated (Figure). The patient had noted the lesions for only 2 months and said that he had not taken any antileprotic treatment. Histology of the lesion was that of histoid leprosy. The patient was given rifampicin and dapsone with considerable improvement, but was unfortunately lost to follow-up after 6 months. The clinical picture was unusual and an initial diagnosis of viral exanthem was in fact made. It was only after biopsy and slit smear that the diagnosis was clinched. Retrospectively, we wonder if this could have been a case of dapsone-resistant leprosy, presenting with lesions somewhat similar to those described by Dr Do-Il Kim.

*Department of Medicine*
*Division of Dermatology*
*University of Garyounis*
*PO Box 6674 Benghazi, Libya*

MALKIT SINGH
A J S KANWAR
Y K MALHOTRA

### Reference

[1] Do-Il Kim. Relapsed lepromatous leprosy in Korea; occurrence of multiple small 'umbilicated' lesions of borderline type. *Lepr Rev*, 1983; **54:** 76.

## CLASSIFICATION OF TREATED LEPROSY PATIENTS IN THE ABSENCE OF ADEQUATE RECORDS

Sir,

Facing the problem of having in our treatment register several hundred patients who had a history of anti-leprosy treatment prior to registration with us but whose original classification and signs of leprosy were unrecorded, we wished to evaluate the accuracy of our classifications. We hoped to develop for our paramedical workers guidelines for classifying such patients more accurately.

We took a random sample of 56 patients from those who remained on treatment because their most likely classification was considered to be LL leprosy. This classification was made 7–9 years after their beginning treatment with us, on the basis of either repeatedly positive slit skin smears or clinical findings conventionally considered as residual indicators of LL leprosy, namely: madarosis; nasal collapse; pattern of anaesthesia; pattern of digit loss; signs of old papules, nodules, infiltration or ENL; history. Where the only evidence of LL leprosy was clinical, indicators from at least two categories were required.

These 56 patients were tested with lepromin (Mitsuda H, supplied by courtesy of Dr R J W Rees) on the volar side of the left forearm 15 cm proximal to the most distal wrist crease. Eleven patients whose first slit skin smear following registration had shown a BI greater than 1+ are excluded from the short analysis presented here.

For the remaining 45 patients, Mitsuda reactions (read at 26–36 days after injection) were as follows: 27 (60%) negative (no induration detectable); 8 (18%) doubtful (induration 1–3 mm); 10 (22%) positive (induration > 3 mm).

The following clinical findings had a useful predictive value for a negative Mitsuda reaction:

| | | Total no. of patients with this sign | Predictive value of this sign for complete absence of detectable cell-mediated immunity against *Mycobacterium leprae* (within this group) (%) | No. of patients with this sign and little or no cell-mediated immunity (Mitsuda reaction 1–3 mm) |
|---|---|---|---|---|
| | Definite flattening of nasal bridge | 9 | 67 | 3 (33%) |
| 2 | Anaesthesia on nose | 6 | 67 | 1 (17%) |
| 3 | 'Lepromatous face'— flattened nasal bridge +some loss of eyebrows +earlobe abnormality suggesting old infiltration or papules | 4 | 75 | 1 (25%) |
| 4 | Definite anaesthesia of both cornea | 4 | 75 | 1 (25%) |
| 5 | Anetoderma suggestive of old papules/nodules (but excluding ears) | 12 | 75 | 3 (25%) |
| 6 | Definite loss eyebrows | 12 | 75 | 2 (17%) |

| | | | | |
|---|---|---|---|---|
| 7 | Two out of three of signs no. 4, 5, 6 | 6 | 83 | 1 (17%) |
| 8 | History of papules or nodules consistent with leprosy lesions | 16 | 75 | 3 (19%) |

Surprisingly, the pattern of anaesthesia, the pattern of loss of digits and signs of previous thickening of (or nodules in) the earlobes showed no correlation with Mitsuda reaction sizes.

Thus it would seem that on clinical grounds alone without the help of lepromin testing, it is difficult to correctly identify previously treated and inactive lepromatous patients with no detectable cell-mediated immunity. Since this is a group which in the past might have had to receive lifelong dapsone monotherapy and now should perhaps be considered to require triple therapy before discharge or lifelong surveillance without treatment and whose identification therefore is desirable, our findings might be of interest to some of your readers.

*185 Rochdale Road*
*Edenfield, Ramsbottom, Lancashire*
ALISON SUMMERS

*LEPRA Evaluation Project,*
*PO Box 46, Chilumba*
*Karonga District, Malawi*
J M PONNIGHAUS

*P O Bachlaan 44*
*438 415 Vlissingen*
*Holland*
C BURGGRAAFF

**ILEP MEETING ON MULTIDRUG THERAPY (MDT), DELHI, 1984**

Sir,

I would like to make some comments on the report of the ILEP Meeting on Multidrug Therapy in *Lepr Rev* (1984) **55:** 215–220, as regards the brief report about Ethiopia.

In my written and oral report to the Meeting I indicated that a number of problems were encountered during the first months of implementation of the MDT programme in a pilot area. The problems were especially due to the fact that the MDT programme was initiated without sufficient preparation and detailed written instructions.

I mentioned these problems with the intention of underlining that it is absolutely imperative that a MDT programme is properly planned and organized before its implementation. This important conclusion is not included in your published account.

I also mentioned that the problems we faced could be corrected some months after the introduction of the programme. Furthermore, I showed that the implementation of MDT programme had been quite satisfactory, which is, e.g. expressed in a cumulative attendance of 92·3% during the first 6 months for the 3140 patients who were put on MDT. The percentage of paucibacillary patients who had successfully completed their 6 months course of MDT was high; 85% ten months after the start of the programme.

In the report referred to, I miss any mention of the latter points, which were given by me during the Meeting.

The report therefore gives an incomplete picture of what I submitted in writing to ILEP and reported during the Meeting in New Delhi about the implementation of MDT in an area which is under the responsibility of the ALERT Leprosy Control Programme.

*Director, ALERT Leprosy Control*
*PO Box 165, Addis Ababa, Ethiopia*
MARIJKE BECX-BLEUMINK

# ®Lamprene Geigy

(= 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)

# Leprosy Review Index

VOLUME 55 (1984)

# A Note from the Editor to Contributors of *Leprosy Review*

During the past year we have occasionally had problems with the receipt, acknowledgement, posting and preparation of manuscripts, and we take this opportunity to draw attention to a few points which may ease the editorial 'process'.

*1 Envelopes and packaging.* Quite a number of manuscripts have been received with the envelope frayed, or even open along the edges. A strong envelope is essential and the use of plastic 'grips' or spines to hold pages together should be avoided, since they cut through the paper.

*2 Originals and copies.* We need a clear (black) original and an equally clear copy. We usually have to make at least two additional copies and this is impossible from a faint or poor quality original. Good quality photostat copies are preferable to carbon copies. Artwork, especially lettering, should be sufficiently clear to stand a reduction of about 60%.

*3 Return of manuscripts to authors.* The current costs of correspondence and air mail postage incurred by this Journal are already considerable. We regret that it is not possible, except under exceptional circumstances, to return manuscripts, photographs or artwork to authors. If a paper has not been found suitable for publication, we retain it here for reference for a period of 1 year, after which it is discarded.

*4 Addressing.* All matters to do with *manuscripts*, *publishing*, *printing* and the *editorial 'process'* should be addressed to the Editor or Editorial Assistant at the Slade Hospital, Headington, Oxford OX3 7JH, England. All matters to do with *subscriptions to the Journal*, *postage* and *distribution*, should be referred to LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. On several occasions, authors have changed address without letting us know. Please indicate your address for reply or any likely change of address in the near future.

*5 Titles.* Both for the purposes of our own indexing of this Journal, but even more importantly for general indexing and abstracting systems, it is important in most instances to get 'leprosy' (or some related word) into the title as a general guide to the subject matter.

*6 Summaries.* Authors, especially those working in pure or basic science, are asked to keep in mind that this Journal has a wide-ranging readership. Many subscribers do not appreciate the significance of scientific data *per se* and it would be of great help if authors could include in their summaries a brief note explaining *why* the study was undertaken and *what the results mean*, in terms which are likely to be comprehensible to the reader whose background is not scientific.

Thank you,
*EDITOR*

# CONTENTS



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