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# LEPROSY REVIEW

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# Leprosy Review

## A journal contributing to the better understanding of leprosy and its control

## British Leprosy Relief Association
## LEPRA





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*Leprosy Review* is published by the British Leprosy Relief Association (LEPRA) with the main objective of contributing towards the better understanding of leprosy and its control. Original papers on all aspects of leprosy, including research, are welcomed. In addition, *Leprosy Review* seeks to publish information of educational value which is of direct benefit to the control of leprosy under field conditions, and hence to the individual patient. The Journal aims to interpret what is being done in other disciplines, particularly for field workers.

From time to time the Editorial Board invites special articles or editorials from experts in various parts of the world, and gives consideration to the production of a supplement or special number devoted to a particular subject or theme of major importance.


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# Editorial

## ELIMINATION OF LEPROSY AS A PUBLIC HEALTH PROBLEM

The Forty-fourth World Health Assembly, which met in May 1991, adopted a resolution on the elimination of leprosy as a public health problem by the year 2000, and defined this elimination as attaining a level of prevalence below 1 case per 10,000 population. This landmark resolution declared WHO's commitment to attain global elimination after the Assembly noted the significant progress made with multidrug therapy (MDT) and the consequent reduction in disease prevalence, as well as the substantial support from nongovernmental organizations (NGOs), and the increased priority accorded to leprosy control by several of its Member States. The resolution, among others, further urged Member States to increase their political commitment for leprosy in order to reach the elimination goal, and requested the Director-General of WHO to strengthen technical support to Member States and to continue to mobilize and coordinate resources from NGOs and others in order to achieve the goal.

The World Health Assembly, by establishing a target for the year 2000, has drawn attention to the effectiveness of the available treatment technology, the need for leprosy-endemic countries and donor agencies to cease to regard leprosy as a permanent problem but to redouble their efforts toward leprosy control, and the need to accept leprosy as simply another health problem with a clear solution.

It is clear that MDT offers an opportunity not available before. Experience in several countries in the past 8 years or so has demonstrated convincingly that it is possible to reduce the prevalence of registered cases up to 10-fold within a period of 5 years, provided MDT is applied to at least 80–90% of registered cases. However, what is not always clear in any given situation is the extent to which the number of registered cases reflects the true situation in terms of existing cases, including the unregistered, 'hidden' cases. While this problem of unregistered cases is partly due to nonrecognition of the disease by the patient and others around him, particularly of early disease, a significant part of the problem is also due to the concealment of the known disease because of its associated social stigma, which can be quite severe, as observed in many communities. Well-organized leprosy control programmes have tried to address both aspects of this problem through health education aimed at creating awareness towards recognition of early disease and breaking down the social barriers that hinder patients self-reporting to the health services. However, the introduction of MDT, in itself, appears to have increased self-reporting in many programmes as a result of the perception by the patient and the community that it is a highly effective treatment, leading to definite cure. With this encouraging trend, it is hoped that the gap between the registered and estimated cases will steadily decrease over a period of time and that the residual unregistered cases will consist of mainly early minimal

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and mostly self-healing paucibacillary cases with a very low potential for transmission of infection.

Another consequence of the early self-reporting of patients, together with prompt administration of MDT, would be that after a period of time the prevalent cases would consist chiefly of incident cases, thus reflecting the more recent changes taking place with regard to the epidemiological situation. In this connection, the more sensitive indicators to monitoring for epidemiological changes will be changes in the incidence of leprosy in the younger age groups even though the disease might occur in all ages. This is because, while disease incidence in younger ages, as in tuberculosis, is likely to reflect recent infections, disease in older ages, particularly in persons over 30 or 40 years, is likely to be due primarily to endogenous reactivation of infections acquired in childhood. Thus, with the effective application of MDT in all patients and with an overall declining trend, it is unlikely that the continued low-level incidence of leprosy in older individuals would indicate any recent transmission of infection with *Mycobacterium leprae,* although such low-level disease incidence will make it impossible to envisage the total eradication of leprosy, even in a time span of 10 to 20 years. Hence the use of the term 'elimination of leprosy as a public health problem', clearly defining elimination as attaining a prevalence level below 1 case per 10,000 population, appears to be quite appropriate.

The elimination of leprosy as a public health problem aims essentially at the elimination of infection through MDT, thus preventing transmission. However, it should be recognized that leprosy is dreaded not because of its infection but because of the deformities it produces with their serious physical, social and psychological consequences. While MDT, through early cure, will contribute substantially to the prevention of deformities and thus will have a long-term impact, it will have very little impact on those patients who are already deformed.

It is estimated that there are about two to three million individuals in the world who are disabled physically and socially as a result of either past or present leprosy. A large proportion of these disabled persons will survive the turn of the century. In addition, a significant proportion of new cases occurring in the 1990s, and even some old patients from preceding decades, will develop deformities resulting from late diagnosis and insufficient care. Although such individuals could be cured, from the microbial point of view, through MDT and thus eliminated as cases for the purpose of public health control, the problem of disability will persist and so warrant continued care. Thus, even if elimination of leprosy as a public health problem is attained, it is clear that the problem of disability will persist well into the next century. The only way this could be mitigated is by substantial improvements in the current technologies for prevention and management of nerve damage and deformities and their application in the field. In terms of social disability, MDT appears to have a positive influence in reducing stigma against the disease. Patients, community and health workers alike now have a much better perception than ever before of the curability of the disease.

What then are the implications of the elimination strategy? First, it is obvious that elimination is not total eradication of the disease, and that we are willing to accept a small residual problem, this being defined as 1 case per 10,000 population in the hope that when such very low levels are reached the transmission of infection will be so minimal that the disease in the community will die out in the course of time. In this connection, a point often raised is what about the possibility of a resurgence of the disease after attaining low levels of prevalence? Historically, there is no evidence of resurgence of the disease in areas

where it has died out or was in the process of doing so. However, it should be recognized that in those areas the disappearance of leprosy was related more to improved social and economic conditions than to specific anti-leprosy measures. All the same, there is no reason to believe that resurgence is likely to be a serious factor as in the case of, say, malaria.

The next implication of the elimination strategy is to have a clear understanding of the level at which elimination should be attained. Is it global, regional, national, or subnational? This problem is quite important as the disease is extremely unevenly distributed among and within countries. Although the World Health Assembly resolution refers to global elimination, the inference is that such elimination should occur fairly evenly.

Another major implication of the elimination strategy is whether MDT will continue to be effective in the coming years. The elimination strategy is built around the efficacy of MDT together, of course, with case-finding. The experience with MDT over the past 6 to 8 years has given sufficient confidence in this direction. However, it is possible to foresee problems in the future with regard to treatment failure as a result either of inadequate treatment, improper application of MDT drugs leading to drug resistance or late relapses due to persisters. The indications are that the impact of such problems in leprosy control are likely to be very limited. All the same, research progress in the development of new drugs and improved MDT is sufficiently advanced so that it is quite conceivable that better MDT regimens, both from the points of view of efficacy as well as operational applicability, will become available towards the latter part of the 1990s.

The last and most important implication is whether elimination is feasible. In this connection, a point often raised is what is the basis for identifying a prevalence level of 1 in 10,000 as the required limit to be attained? The limit is clearly arbitrary but there is considerable hope and confidence that when such low levels of prevalence are reached the disease burden in the community, as well as the potential for transmission, will be extremely limited. The elimination resolution of the World Health Assembly is essentially a commitment of the Member States, with clear technical and political implications, and the goal is attainable provided leprosy control activities are intensified significantly enough so that coverage of MDT, together with case-finding, reaches the highest possible levels by the mid-1990s. Whether such intensification will be attained or not remains to be seen. Irrespective of political commitment and availability of resources, the situation is likely to be relatively more difficult in countries starting with a larger base of prevalence than in countries starting with a smaller base, warranting even more vigorous efforts.

Even as we are discussing and working actively towards our goal of elimination, we are likely to face several problems towards the latter phase of elimination. For example: difficult-to-reach cases, chronic defaulters, and possibly some relapses, all occurring within a background of a very low endemicity of around 1 in 10,000 population or less. At this time, we will require additional tools and additional strategies to deal with the remaining problems.

In conclusion, it is clear that there is still an immense amount of work that needs to be done if the target of elimination of leprosy as a public health problem is to be achieved by the year 2000, as envisaged by the World Health Assembly in its resolution adopted in May 1991. The target can be achieved provided that further, substantial, intensified

efforts are made in terms both of action and mobilization of adequate resources. Such intensification is important, particularly during the next few years. For the leprosy-endemic countries, it is an important opportunity that cannot be missed. It remains to be seen how this opportunity is exploited and thus a major public health problem solved.

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# Thalidomide's effectiveness in erythema nodosum leprosum is associated with a decrease in CD4+ cells in the peripheral blood

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*Summary* Thalidomide is well documented as being an effective drug in the treatment of erythema nodosum leprosum (ENL). The mechanism of action of thalidomide in ENL as well as the pathogenesis of ENL are yet to be fully determined.

Lepromatous leprosy patients experiencing ENL have been reported to have an increase in the ratio of CD4+ to CD8+ cells in their blood and ENL skin lesions. Thalidomide has been shown to cause a decrease in the ratio of CD4+ to CD8+ lymphocytes in the blood of healthy males. This decrease was due to a significant reduction in the numbers of CD4+ lymphocytes and an apparent increase in the numbers of CD8+ lymphocytes.

In this study, thalidomide's effectiveness in halting chronic ENL and arresting a relapse into ENL was consistently associated with a decrease in the numbers of CD4+ lymphocytes in the blood of 2 male lepromatous leprosy patients.

## Introduction

Thalidomide, α-phthalimido-glutarimide, dramatically relieves the signs and symptoms of erythema nodosum leprosum (ENL), an acute inflammatory complication of lepromatous leprosy. How thalidomide acts on ENL, and what the pathogenesis of ENL is, has not yet been fully determined.

It has been suggested that ENL is caused by an imbalance in immunoregulatory T-lymphocyte subsets.[1,2] In association with the acute phase of ENL is an increase in the ratio of helper/inducer T cells (CD4+) to suppressor/cytotoxic T cells (CD8+) in peripheral blood.[1,3,4] This imbalance in blood lymphocyte subpopulations seems to be

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unique to the ENL reactional patient and does not occur during quiescent lepromatous disease.

In a previous study, ingestion of 200 mg of thalidomide daily for 4 days caused a decrease in the ratio of Leu-3a monoclonal antibody positive (CD4+) to Leu-2a monoclonal antibody positive (CD8+) lymphocytes in the blood of healthy males.[5] This decrease was due to a significant reduction in the percentage and absolute numbers of CD4+ cells and an apparent increase in the percentage and absolute numbers of CD8+ cells.

This observation in healthy males and the reported alterations in the proportions of CD4+ and CD8+ cells in patients with acute ENL prompted us to speculate that thalidomide's effectiveness in ENL may be associated with a change in the population of CD4+ or CD8+ cells in blood.[5] After receiving informed consent from two male Ethiopian patients with chronic ENL, we tested this hypothesis.

## Materials and methods

### PATIENTS

Patient No. 943 is a 33-year-old male Ethiopian. He is classified as lepromatous with chronic ENL (LL/ENL) and had been under DDS monotherapy for 14 years before being referred to ALERT for recurring ENL. He was placed on high doses of clofazimine without improvement and was then started on steroids. He responded to high doses of steroids, but ENL reoccurred when the steroids were reduced to below 20 mg daily. He was then started on thalidomide. Upon completion of a four-day course of 400 mg of thalidomide daily, his condition improved. However, the ENL lesions reoccurred upon discontinuation of thalidomide and a similar course of treatment with thalidomide was re-initiated. His condition improved. Thalidomide became unavailable and he was returned to maintenance doses of steroids and 100 mg daily of clofazimine. This regimen continued for approximately 3 months. Then, after giving informed consent, on 21 July 1989 therapy with steroids was discontinued. He progressively lapsed into ENL and on 24 July 1989 treatment with thalidomide was once again initiated. Thalidomide (Grunenthal GMBH, 5190 Stolberg/Rhld, Germany) was taken orally in doses of 100 mg every 12 hr for 3 days. At the end of 3 days' treatment the thalidomide was stopped, and the patient progressively relapsed into ENL—7 days after the thalidomide was stopped thalidomide therapy was re-initiated with oral doses of 100 mg every 12 hr for 3 days.

Patient No. 944 is a 31-year-old male Ethiopian. He is a known LL patient since 1987 and is currently under multidrug therapy. He was referred to ALERT because of recurring ENL. He was placed on high doses of clofazimine, but in vain. He responded to high doses of steroids (up to 60 mg/day) but ENL reoccurred on lowering the dose of steroids. He was on maintenance doses of steroids and doses of 100 mg daily of clofazimine. After giving informed consent, on 21 July 1989 therapy with steroids was discontinued. He lapsed into ENL and on 24 July 1989 treatment with thalidomide was initiated. His course of treatment with thalidomide was similar to that described for patient No. 943.

### CELL SEPARATION

On four separate occasions 30 ml blood was drawn in the morning from each patient.

Approximately 10 ml blood was given to the clinical laboratory for a complete blood count, assessment of the erythrocyte sedimentation rate, and the content of haemoglobin. The remaining blood was defibrinated by shaking with glass beads for 10–15 min. The defibrinated blood was centrifuged for 20 min at $450 \times G$. The serum was removed and the pellet was diluted in 3 volumes of saline and layered on Ficoll–Hypaque. After centrifugation at $400 \times G$ for 35 min at 20°C the mononuclear cells were collected and washed using RPMI-1640.

### DETERMINATION OF T-CELL PHENOTYPES

T-lymphocyte phenotypes were determined using fluorescein-conjugated monoclonal antibodies, Leu-1 (T-cells, CD5+), Leu-2a (cytotoxic/suppressor, CD8+), Leu-3a (helper/inducer, CD4+) (Becton Dickinson, Sunnyvale, CA, USA). The fluorescence was amplified by using fluorescein-conjugated rabbit antimouse Ig (DAKOPATTS, a/s, Denmark). Absolute numbers of lymphocytes bearing a given cluster differentiation antigen (CD) were calculated from a product of (a) leukocyte counts, (b) percentage of lymphocytes from differential counts, and (c) percentage of mononuclear cells that fluoresced with a particular fluorescein-conjugated antibody.

## Results

A consistent reduction in the numbers of CD5+ and CD4+ lymphocytes was noted in both patients after effective treatment of their ENL with thalidomide whereas minimal changes in the numbers of CD8+ lymphocytes were observed (Figure 1).

After the second 3-day regimen with thalidomide, both patient 943 and patient 944 remained free of ENL. After 1 month, they were discharged from the hospital. During the past year, the patients have been seen occasionally at ALERT. Neither of the two patients has relapsed with ENL.

## Discussion

Clinically, ENL is characterized by fever and a sudden eruption of acute inflammatory lesions in areas harbouring large numbers of *Mycobacterium leprae*. Histologically, the hallmarks of ENL skin lesions are vascular necrosis, oedema, and inflammation with infiltrates of neutrophils affecting the entire dermis and subcutaneous fat.[6] The factor(s) which cause the influx of neutrophils into lesions is unknown. Immune complexes and cell-mediated mechanisms have been implicated in ENL.[2]

A disturbance in immunoregulation by T-cells is thought to be a fundamental occurrence during ENL. Patients experiencing ENL have an augmented *in vivo* responsiveness to sensitizers like dinitrochlorobenzene[7] and their lymphocytes in culture with mitogens increase in responsiveness.[1,3,8] Lymphocytes from ENL reactional patients have also been shown to respond to *M. leprae* antigens in culture.[8] Evidence for alterations in the numbers of lymphocytes expressing immunoregulatory molecules like CD4 and CD8 has accumulated from studies conducted on lymphocytes in the blood[1,3,4] and in the skin lesions[9–13] of lepromatous patients experiencing ENL.

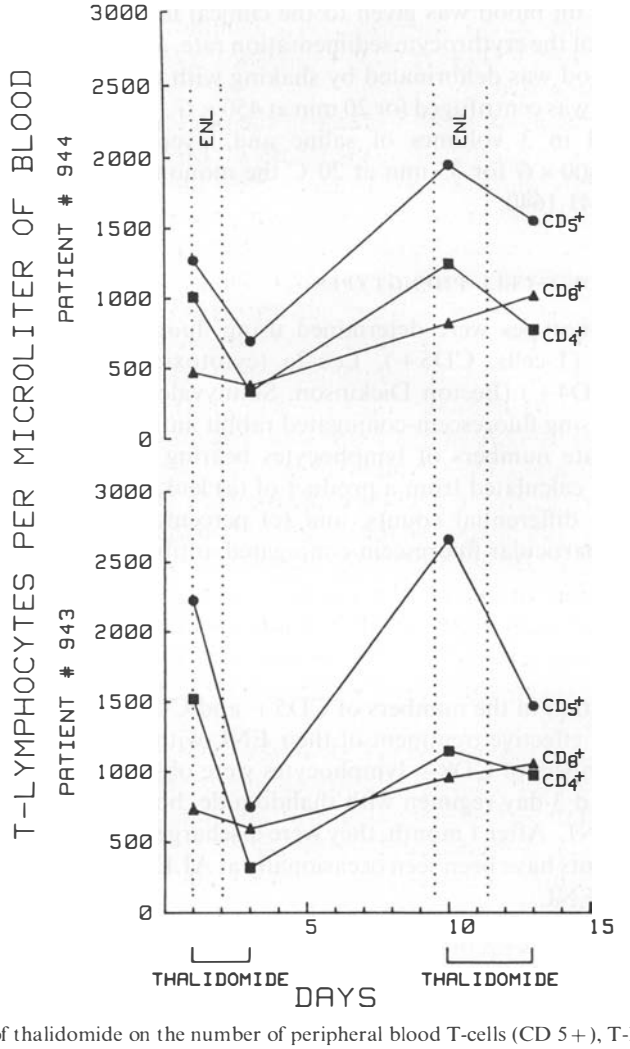


**Figure 1.** The effect of thalidomide on the number of peripheral blood T-cells (CD 5+), T-helper/inducer cells (CD 4+) and T-suppressor/cytotoxic cells (CD 8+).

In studies conducted on blood lymphocytes, lepromatous patients during ENL showed an increase in the per cent of helper cells, a decrease in the per cent of suppressor cells and a significant increase in the helper:suppressor ratio.[1,4] In a study conducted in Ethiopia, Mshana *et al.*[3] found ENL patients to have an increase in helper cells, a decrease in suppressor cells resulting in a high helper:suppressor ratio. Laal *et al.*[8] showed a relative increase in the per cent of CD8+ cells in the blood of ENL patients in comparison with patients with stable lepromatous disease. Interestingly, these investigators also reported an *in vitro* lymphoproliferation to *M. leprae* antigens in lepromatous patients undergoing ENL reactions. Contrary to the above reports Modlin *et al.*[12] showed that the percentage or numbers of T-helper or T-suppressor cells in ENL patients did not differ significantly from controls or lepromatous patients without ENL.

The skin lesions of lepromatous patients without ENL have been shown to have an excess of CD8+ lymphocytes whereas CD4+ lymphocytes are prevalent in ENL skin lesions.[9–11] A shift from CD8+ to CD4+ prevalence is also observed in patients from nonreactional LL to active ENL.[13]

The transient emergence of an increase in the per cent of T-helper cells in both the blood and skin lesions during the acute phase of ENL suggest that a target site for thalidomide in ENL may be the T-helper cell. Modulation of T-helper cells by thalidomide as a means to arrest ENL has been proposed.[14,15] This speculation is also supported by the effectiveness of cyclosporin-A (CsA) in the treatment of ENL.[14] While CsA affects several different cell types with immune potential, it consistently inhibits T-helper cell function and a CD4+ lymphocytopenia is observed during treatment with high doses of the drug.[16] Studies by Aszalos *et al.*[17] showed that the membrane potential of CD4+ lymphocytes was selectively affected in patients immunosuppressed with CsA. Vogelsang *et al.*,[18] using fluorescent-activated cell sorting, reported that a fluorescent bioactive derivative of CsA and a fluorescent hydroxylated product of thalidomide reacted with CD4+ and CD8+ lymphocytes.

Thalidomide may be able to alter the expression of CD4 molecules by binding directly to them or reducing their density on the surface of lymphocytes or macrophages. Neither thalidomide nor its pH dependent hydrolysis products were able to bind directly to CD4 molecules and inhibit or reduce the intensity of fluorescence of mononuclear cells incubated with fluorescent-conjugated antibodies with specificity to CD5, CD4, and CD8.[19] The influence of thalidomide on *de novo* synthesis of CD4 molecules or internalization of CD4 molecules on lymphocytes and macrophages are being investigated in our laboratory.

Interference with the expression of CD4 molecules by thalidomide could help explain many of the immunosuppressive properties ascribed to thalidomide. Thalidomide could also have additional sites of action as an immunosuppressive and anti-inflammatory drug in ENL. As examples, thalidomide has been shown to inhibit the production of TNF-alpha by stimulated human monocytes.[20] Thalidomide has been shown to inhibit IgM antibody synthesis.[21] It has also been shown to stabilize lysosomal membranes from rat and human liver, has anti-inflammatory properties in carageenan rat paw oedema, antagonizes certain of the chemical mediators of inflammation (histamine, serotonin, prostaglandin $E_2$ and $F_2$ alpha) and inhibits the chemotaxis of neutrophils.[22]

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## L'efficacité de la thalidomide contre l'erythema nodosum leprosum est associée à une diminution des cellules CD4+ du sang périphérique

E J Shannon, Mestawat Ejigu, H S Haile-Miriam,
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*Résumé* Bon nombre de documents ont prouvé l'efficacité de la thalidomide dans le traitement de l'erythema nodosum leprosum (ENL). Le mécanisme de l'action de la thalidomide contre l'ENL ainsi que la pathogénèse de l'ENL sont encore à démontrer.

On a décelé chez les patients atteints de lèpre lépromateuse sous la forme erythema nodosum leprosum un rapport plus élevé entre les cellules CD4+ et CD8+ dans le sang, ainsi que des lésions cutanées d'erythema nodosum leprosum. On a démontré que la thalidomide provoque une diminution du rapport entre les lymphocytes CD4+ et CD8+ dans le sang chez des subjets mâles sains. Cette diminution est due à une importante réduction du nombre des lymphocytes CD4+ et une augmentation apparente du nombre des lymphocytes CD8+.

Dans cette étude, conduite chez deux patients mâles atteints de lèpre lépromateuse, on constate une corrélation entre l'efficacité de la thalidomide prescrite pour stopper l'erythema nodosum leprosum chronique et empêcher une recidive de l'ENL et la diminution du nombre de lymphocytes CD4+ dans le sang.

## Se asocia la efectividad de la Talidomida en el eritema nodosum leprosum con una reducción de células CD4+ en la sangre periférica

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*Resumen* Se ha documentado bien la Talidomida como una droga efectiva en el tratamiento de eritema nodosum leprosum (ENL). Falta todavíva determinar completamente el mecanismo de actuación de la Talidomida en el ENL, como también la patogénesis del ENL.

Se ha informado que les pacientes con lepra lepromatosa que padecen de ENL presentan un aumento de la relación de células CD4+ a CD8+ en la sangre y las lesiones cutáneas ENL. Se ha mostrado que la Talidomida causa una reducción de la relación de linfocitos CD4+ a CD8+ en la sangre de los hombres sanos. Esta reducción se debe a una reducción significativa de linfocitis CD4+ y un aparente aumento de linfocitos CD8+.

En este estudio, la efectividad de la Talidomida en parar el ENL crónico y detener una recaída de ENL, fue asociada constantemente con una reducción en el número de linfocitos CD4+, en la sangre de los hombres pacientes de lepra lepromatosa.

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# Prevalance of IgM antibodies to phenolic glycolipid I among household contacts and controls in Korea and the Philippines

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*Summary* Phenolic glycolipid I (PGL-I) is a *Mycobacterium leprae*-specific antigen and the antibodies to the antigen may suggest an *M. leprae* infection. To compare the *M. leprae* transmission among the populations, we compared the prevalence of anti-PGL-I IgM antibodies among household contacts and controls between Korea and the Philippines. In Korea (prevalence of leprosy—0·04 : 1000), the prevalence of anti-PGL-I antibodies were 4·8% among controls and 8·0% among contacts, respectively. On the other hand, the seroprevalence rate was 10·8% among controls and 13·4% among contacts in the Philippines (prevalence of leprosy—0·70 : 1000). Interestingly, a marked difference was noted in the prevalance of anti-PGL-I antibodies among children between the countries; 10–14% among children under 10 years old and 15–18% among those aged between 10 and 19 in the Philippines compared to 0% and 2·9–6·4% in Korea, respectively. This study, therefore suggests that a high prevalance of anti-PGL-I IgM antibodies among children may indicate an active transmission of *M. leprae*, resulting in a higher incidence of leprosy in the population.

## Introduction

The prevalence or incidence of leprosy has continuously changed in a closed population along with various factors, such as coverage of leprosy control programmes, and socioeconomic status. The recent introduction of multidrug therapy[1] for leprosy patients is about to bring the incidence of leprosy down further in the near future. However, it has been difficult to determine the *M. leprae* transmission in the community partly due to a lack of specific tools to measure it.

A recent development of a seroepidemiological tool based on the phenolic glycolipid I (PGL-I),[2] an *M. leprae*-specific antigen, made it possible to detect the *M. leprae* infection

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or exposure to the organism.[3–5] In the literature, the prevalence of anti-PGL-I antibodies varied from 1·0 to 16·0% among controls[6–10] in the endemic areas of leprosy, and from 12 to 20% among household contacts.[6–9,11] However, few studies focused on the dynamics of *M. leprae* transmission among controls and contacts between countries, and correlated the prevalance of anti-PGL-I antibodies to the incidence and prevalence of leprosy among the populations under study.

This study was thus initiated to compare the seroprevalence among household contacts and controls between Korea, where the incidence of leprosy has declined rapidly, and the Philippines, where the incidence has been stable or only gradually declining during the last two decades. The age-adjusted prevalences of anti-PGL-I IgM antibodies were then compared among household contacts and controls between the countries.

## Materials and methods

### STUDY POPULATIONS

Korea has been an endemic area of leprosy for several centuries; however, since the economics of the country started to improve dramatically late in the 1960s, there has been a rapid decline in the incidence of leprosy from about 1500 new cases in 1973[12] to 106 cases in 1988.[13] There were about 25,000 registered cases in a population of 42 million. However, most of the registered patients are inactive and only about 1800 patients (prevalence; 0·04:1000) are still active, i.e. bacteriologically positive with a skin smear. When the characteristics of new patients were analysed, there was also changes in the proportion of clinical types, i.e. only 39% of new cases were lepromatous in 1973, but about 56% were lepromatous patients in 1988. Among new cases found in 1988, 72% were more than 40 years old. Only 1·0% were under 15 years old, thus indicating that Korean children now have little chance of being exposed to *M. leprae*.[13]

In the Philippines, there were about 56,000 registered leprosy cases in a population of 55 million in 1986, and about 70% (38,000 cases) of them were active patients, i.e. BI positive (prevalence; 0·70:1000).[14] The incidence of leprosy in the urban Manila area was 934 cases in 1978 and slightly decreased to 739 cases in 1986; however, total active cases increased from 6957 cases in 1978 to 11,727 cases in 1986.[14] Among the new cases, 34% were lepromatous, 27% were tuberculoid, and 38% were borderline, respectively. Interestingly, 10·5% of new cases were under 15 years old, and 27% were aged between 15 and 24, thus indicating that the substantial portion of new cases still occur in young age groups. In the Cebu City area, Philippines, there were 348 new cases in 1985, and the distribution of clinical types of new cases were as follows; tuberculoid 41·7%, lepromatous 30·2%, borderline 18·7%, and indeterminate 9·5%.[14]

### SERUM SPECIMENS

Controls from Korea consisted of 244 children who visited the paediatrics clinic at a teaching hospital in Seoul, where the prevalence of active leprosy patients is about 0·03:1000,[13] 388 residents from low endemic rural areas (prevalence; 0·02:1000), and 500 residents who were presented for reasons other than leprosy to the Catholic Skin Disease Clinic in the Kyungbuk province, which is one of the provinces with the highest prevalance of leprosy (0·05:1000). Serum samples were also obtained from 1151

household contacts residing in the resettlement villages scattered throughout the Kyungbuk province.

Normal controls in the Philippines also represented the heterogeneous populations consisting of 304 persons who visited the Skin Clinic of the Leonard Wood Memorial Center for Leprosy Research, Cebu City, for reasons other than leprosy and 300 persons who visited a paediatrics clinic or were blood donors or medical students in the urban Manila area. A total of 365 serum samples were from household contacts of leprosy patients in the Cebu and the Manila area.

### DETECTION OF ANTIBODIES TO PGL-I

An enzyme-linked immunosorbent assay (ELISA) described by Voller *et al.*[15] was employed with minor modification as reported previously.[3,16] However, instead of the native glycolipid, the semi-synthetic neoglycoprotein *O*-(3,6-di-*O*-methyl-β-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-methyl-α-L-rhamnopyranosyl)-(1→9)-oxynonanoyl-bovine serum albumin (natural disaccharide-octyl-BSA; ND-O-BSA)[17] was used. Briefly, 50 μl of diluted ND-O-BSA (20 ng sugar/ml) in carbonate buffer, pH 9·6, was added to the wells of U-bottom microtitre plates (Dynatech Laboratories, Inc., Alexandria, VA, USA), and incubated overnight at 37°C in a moist chamber. The wells were then washed with phosphate-buffered saline (PBS) solution, pH 7·4, containing 0·05% Tween 20 (PBST) and blocked by the addition of 100 μl of PBST-0·05% bovine serum albumin (BSA) at 37°C for 1 h. After emptying the wells, 50 μl of serum diluted 1:300 in PBST-5% normal goat serum (NGS) (Gibco Laboratories, Grand Island, NY, USA) was added to the wells which were incubated at 37°C for 90 min. After washing the wells, 50 μl of affinity-purified peroxidase-conjugated goat anti-human IgM (Behring Diagnostics, San Diego, CA, USA) diluted 1:5000 in PBST-5% NGS was added and incubation was continued at 37°C for 1 h. After another washing, 50 μl of substrate solution, $H_2O_2$-o-phenylenediamine was added to the wells which were incubated at room temperature for about 15 min. The reaction was then stopped with 50 μl of 2·5 N $H_2SO_4$ and the absorbance was read at 490 nm.

Each test was performed in triplicate and the mean absorbance of wells with BSA only was subtracted from those of wells with ND-O-BSA. Six wells in each plate were allocated for a pooled positive control serum, and plate-to-plate and day-to-day variations were adjusted based on the mean absorbance value of the positive control serum. The criteria for the seropositivity was determined by adding 2 × SD to the mean absorbance of controls, and the absorbance $\geqslant 0{\cdot}200$ was considered seropositive as reported previously.[8]

## Results

Serum specimens from controls and household contacts from Korea were examined for the presence of anti-PGL-I antibodies using ELISA. Of 1132 controls examined, 54 (4·8%) had significant anti-PGL-I IgM antibodies (Table 1). The age-specific prevalance was highest among the controls (10·1%) aged between 20 and 30 years old, and declined with increase in age. It was interesting that none of 206 controls under 10 years old and only 2·9% of controls aged 10–19 years old were seropositive to PGL-I, thus indicating

**Table 1.** IgM seroreactivity to PGL-I in sera from normal controls in Korea

| Age | No. assayed | Seropositive to PGL-I* | |
|---|---|---|---|
| | | No. | (%) |
| 1–9 | 206 | 0 | (0) |
| 10–19 | 104 | 3 | (2·9) |
| 20–29 | 169 | 17 | (10·1) |
| 30–39 | 189 | 13 | (6·9) |
| 40–49 | 167 | 10 | (6·0) |
| 50⩽ | 297 | 11 | (3·7) |
| Total | 1132 | 54† | (4·8) |

* Criteria for the seropositivity: IgM $A_{490} \geqslant 0{\cdot}200$.
† Mean ± SD $A_{490}$ of the seropositive individuals: $0{\cdot}298 \pm 0{\cdot}101$ (range: 0·201–0·708).

minimal exposure of young residents to *M. leprae* in Korea. The age-adjusted prevalance of anti-PGL-I IgM antibodies was a little bit higher among controls from the Kyeongbuk province (5·0%) than from another rural area (3·4%) (data not shown), thus reflecting the prevalance of leprosy cases in the rural areas of Korea.

Among the household contacts in Korea, 92 (8·0%) of the 1151 samples examined were seropositive to PGL-I (Table 2). The age-specific prevalence was 0% among contacts under 10 years old and 6·4% among contacts aged between 10 and 20 years, and was a stable 12–14% among contacts over 20 years old. The overall prevalence of anti-PGL-I IgM antibodies among contacts was significantly higher than among normal controls ($p < 0{\cdot}001$, $\chi^2$ test), thus indicating that household contacts in Korea had more chance of being exposed to the leprosy bacillus.

Serum samples from contacts and controls from the Philippines were also examined

**Table 2.** IgM seroreactivity to PGL-I in sera from household contacts of leprosy patients in Korea

| Age | No. assayed | Seropositive to PGL-I* | |
|---|---|---|---|
| | | No. | (%) |
| 1–9 | 45 | 0 | |
| 10–19 | 674 | 43 | (6·4) |
| 20–29 | 232 | 28 | (12·1) |
| 30–39 | 83 | 10 | (12·1) |
| 40–49 | 51 | 7 | (13·7) |
| 50⩽ | 66 | 4 | (6·1) |
| Total | 1151 | 92† | (8·0) |

* Criteria for the seropositivity: IgM $A_{490} \geqslant 0{\cdot}200$.
† Mean ± SD $A_{490}$ of the seropositive individuals: $0{\cdot}383 \pm 0{\cdot}173$ (range: 0·200–1·030).

**Table 3.** IgM seroreactivity to PGL-I in sera from normal controls from the Philippines

| Age | No. assayed | Seropositive to PGL-I* No. | (%) |
|---|---|---|---|
| 1–9 | 50 | 5 | (10·0) |
| 10–19 | 109 | 16 | (14·7) |
| 20–29 | 129 | 17 | (13·2) |
| 30–39 | 110 | 13 | (11·8) |
| 40–49 | 95 | 6 | (6·3) |
| 50⩽ | 111 | 8 | (7·2) |
| Total | 604 | 65† | (10·8) |

* Criteria for the seropositivity: IgM $A_{490} \geqslant 0{\cdot}200$.
† Mean ± SD $A_{490}$ of the seropositive individuals: 0·382 ± 0·237 (range: 0·201–1·511).

for the presence of anti-PGL-I IgM antibodies. The seroprevalence was 10·8% for controls (Table 3) and 13·4% for contacts (Table 4), respectively. There was no significant difference in the prevalence of anti-PGL-I IgM antibodies between household contacts and controls in the Philippines, thus indicating that noncontact controls had the same chance of exposure to *M. leprae* as household contacts in the Philippines. The age-specific prevalence of anti-PGL-I IgM antibodies was also high with 10–14% among controls and contacts under 10 years old, and peaked at 15–18% among those aged between 10 and 19 years old, followed by a gradual decline in the older age groups.

To overcome the differences in age distribution between the study populations, the age-adjusted seroprevalence of anti-PGL-I IgM antibodies was calculated based on the

**Table 4.** IgM seroreactivity to PGL-I in sera from household contacts of leprosy patients in the Philippines

| Age | No. assayed | Seropositive to PGL-I* No. | (%) |
|---|---|---|---|
| 1–9 | 50 | 7 | (14·0) |
| 10–19 | 94 | 17 | (18·1) |
| 20–29 | 79 | 11 | (13·9) |
| 30–39 | 69 | 6 | (8·7) |
| 40–49 | 54 | 5 | (9·3) |
| 50⩽ | 19 | 3 | (15·8)† |
| Total | 365 | 49‡ | (13·4) |

* Criteria for the seropositivity: IgM $A_{490} \geqslant 0{\cdot}200$.
† The number of samples examined was too small to be compared accurately.
‡ Mean ± SD $A_{490}$ of the seropositive individuals: 0·337 ± 0·194 (range: 0·201–1·182).

**Table 5.** Comparison of age-adjusted prevalence of IgM antibodies to PGL-I in sera from controls and contacts between Korea and the Philippines*

| | | Korea | | | | Philippines | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Controls | | Contacts | | Controls | | Contacts | |
| Age | No. compared† | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| 1–9 | 23,800 | 0 | (0) | 0 | (0) | 2,380 | (10·0) | 3,332 | (14·0) |
| 10–19 | 22,070 | 419 | (1·9) | 1,412 | (6·4) | 3,244 | (14·7) | 3,995 | (18·1) |
| 20–29 | 19,440 | 1,963 | (10·1) | 2,352 | (12·1) | 2,566 | (13·2) | 2,702 | (13·9) |
| 30–39 | 14,210 | 980 | (6·9) | 1,719 | (12·1) | 1,677 | (11·8) | 1,236 | (8·7) |
| 40–49 | 8,790 | 527 | (6·0) | 1,204 | (13·7) | 553 | (6·3) | 817 | (9·3) |
| 50⩽ | 11,690 | 433 | (3·7) | 713 | (6·1) | 842 | (7·2) | 1,847 | (15·8)‡ |
| Total | 100,000 | 4,322 | (4·3) | 7,400 | (7·4) | 11,262 | (11·3) | 13,929 | (13·9) |

* Criteria for the seropositivity: IgM $A_{490} \geqslant 0{\cdot}200$.
† Based on the population of Cebu Island, Philippines.
‡ The sample size was too small to be accurate.

age structure of the populations in the Cebu Island, the Philippines. Even after adjusting for age, the prevalance of anti-PGL-I IgM antibodies was 7·4% for contacts, which was significantly higher than that among controls (4·3%) in Korea ($p < 0{\cdot}01$) (Table 5). In the Philippines, however, there was no significant difference in seroprevalence of anti-PGL-I antibodies between controls (11·3%) and contacts (13·9%), thus indicating that controls and contacts had a similar opportunity for exposure to *M. leprae*.

The seroprevalence among controls and contacts in the Philippines were significantly higher than those in Korea ($p < 0{\cdot}001$, $\chi^2$ test). More interestingly, the magnitude of the difference in seroprevalance was greater among controls and contacts under 20 years old (Table 5). In fact, there was no significant difference in the prevalance of anti-PGL-I IgM antibodies among contacts and controls over 30 years old between Korea and the Philippines.

## Discussion

Since PGL-I is an *M. leprae*-specific antigen, the presence of antibodies to the antigen may reflect exposure to or infection with bacilli. In previous studies, the specificity of the antigen in serological tests ranged from 97 to 100% against nonendemic controls.[3–5] The cut-off values used in this study were based on the controls from the Seoul City area, where leprosy is the least prevalent in Korea, and only 1·5% of the controls exceeded the cut-off value.[8]

With this critera, the seroprevalence of anti-PGL-I IgM antibodies among household contacts and controls in the Philippines was significantly higher than those in Korea. This may reflect the higher prevalence and incidence of leprosy in the Philippines, particularly, the higher seroprevalence among young populations, which strongly suggested that transmission has taken place widely in the community regardless of intimate contacts within the families. Interestingly, household contacts aged over 30 in Korea seemed to

have a similar chance of *M. leprae* infection to those in the Philippines because the seroprevalences were comparable. This may also indicate that anti-PGL-I IgM antibodies are detectable for 10–20 years or longer after exposure if no treatment is given.

Considering that a rapid decline in the incidence of leprosy occurred during the 1970s, before the introduction of a MDT programme, the reduction of *M. leprae* transmision among controls and contacts in Korea might be partly due to the improvement of the socioeconomic status and individuals' health, because Korea had a faster growing economy than the Philippines over the last two decades. Another possible explanation is that the segregation of leprosy patients in resettlement villages was more effective in Korea, where about half of the registered leprosy patients reside currently in over 100 resettlement villages throughout the country.[13]

Interestingly, there was no significant difference in seroprevalence between contacts and controls in the Philippines, indicating that the general population was equally exposed to the leprosy bacillus. Bagshawe *et al.*[7] also reported no significant differences in seroprevalence between controls and household contacts in Papua New Guinea. In the report, controls or contacts under 20 years old had the highest seroprevalence at 25% compared with 7% among those over 20 years of age.

One of the limitations of the PGL-I antigen for measuring the degree of *M. leprae* transmission is that the sensitivity is very low (about 30–50%) among tuberculoid leprosy patients.[3–5] Therefore, any prevalence rate of anti-PGL-I IgM antibodies among controls and contacts may reflect only a portion of the individuals infected with *M. leprae*. Even with the limitation, however, this study suggests that the PGL-I based serology may be useful in determining the relative intensity of *M. leprae* transmission among controls and contacts in populations of interest. Particularly, a high seroprevalence among children may indicate high incidence and prevalence of leprosy in the population and the active transmission of *M. leprae* in the community.

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## Fréquence des anticorps IgM glycolipide phénolique I, chez des sujets d'un même foyer en contact avec l'infection et chez des témoins, en Corée et aux Philippines

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*Résumé* Le glycolipide phénolique I (PGL-I) est un antigène spécifique de *Mycobacterium leprae* et les anticorps antigène semblent indiquer une infection à *M. leprae*. Pour apprécier la transmission de *M. lepmae* parmi les populations, nous avons comparé la fréquence des anticorps anti PLG-I chez des sujets d'un même foyer en contact avec l'infection et chez des témoins, en Corée et aux Philippines. En Corée (cas de lèpre: 0,04 pour 1000), la fréquence des anticorps anti PGL-I est respectivement de 4,8% chez les sujets témoins et de 8,0% chez les sujets en contact. D'autre part, le taux de cas séro-positifs aux Philippines est de 10,8% chez les sujets témoins et de 13,4% chez les sujets en contact (cas de lèpre: 0,70 pour 1000). Une remarque intéressante a été faite concernant la nette différence dans la fréquence des anticorps anti PGL-I parmi les enfants: 10 à 14% chez les enfants de moins de 10 ans et 15 à 18% chex les enfants âgés de 10 à 19 ans aux Philippines, en comparaison avec 0% et 2,9 à 6,4% en Corée, respectivement. Cette étude semble donc indiquer qu'une fréquence élevée d'anticorps IgM anti PGL-I chez les enfants pourrait signifier une transmission active de *M. leprae* se traduisant par une augmentation de la lèpre parmi la population.

## El predominio de los anticuerpos IgM al glicolípido-I fenólico entre los contactós de domicilio y controles en Korea y las Filipinas

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*Resumen* El glicolípido-I fenólico (PGL-1) es un antígeno específico para *Mycobacterium leprae* y los anticuerpos del antígeno sugieren una infección de *M. leprae*. Para comparar la transmisión de *M. leprae* entre diferentes populaciones, comparamos el predominio de anticuerpos IgM antiPGL-1 entre los contactos de domicilio y controles, entre Korea y las Filipinas. En Korea (con incidencia de lepra de 0,04 por mil), el predominio de anticuerpos antiPGL-1 era 4,8% en los controles y 8,0% en los contactos respectivamente. De otro lado, la seroincidencia en las Filipinas fue 10,8% en los controles y 13,4% en los contactos (con incidencia de lepra de 0,70 por mil). Es interesante que hay una diferencia notable en el predominio de anticuerpos antiPGL-1 entre los niños de los dos países: 10 a 14% de los niños de menos de 10 años de edad y 15 a 18% de los entre 10 y 19 años en la Filipinas, comparado con 0% y 2,9 a 6,4% en Korea, respectivamente. Por lo tanto, este estudio sugiero que el predominio más elevado de anticuerpos IgM antiPGL en los niños puede indicar una transmisión activa de *M. leprae* que resulta en una incidencia de lepra más elevada en la población.

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# Follow-up of multibacillary leprosy patients using a phenolic glycolipid-I-based ELISA. Do increasing ELISA-values after discontinuation of treatment indicate relapse?

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*Summary* With the introduction of reproducible serological tests it was hoped that relapses in leprosy patients, after discontinuing treatment, could be detected before damaging reactions occurred and before the patients became infectious. The possible value of an ELISA using a semisynthetic analogue of phenolic glycolipid-I to detect antibodies to this antigen in order to predict a relapse in multibacillary patients was investigated. In contrast to that reported for paucibacillary patients, this test was useful to detect early relapses in multibacillary patients. In 3 out of 4 multibacillary patients who relapsed, the ELISA-values were increased. The decreased ELISA-values in the one relapsed patient could be attributed to the corticosteroid therapy. In the multibacillary patients who did not relapse after RFT, the ELISA-values were consistently low or decreased. In only one patient did the ELISA-values increase following his release from treatment and this patient was clinically suspected of developing a relapse.

## Introduction

Until recently, lepromatous leprosy patients were treated for a minimum of 10 years, but frequently longer.[1] After they were released from treatment (RFT), a certain number relapsed.[2]

With the introduction of multiple drug treatment (MDT), as advised by the WHO, it was expected that the treatment period could be shortened to 2 years. However, some leprologists advised treatment to continue after this period until a negative bacterial index (BI) was achieved.[3] There was concern, however, that despite the highly effective

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treatment relapses would still occur due to persisting bacilli. After RFT, regular follow-up, involving clinical assessments and skin smears, was therefore recommended.[4] When serological tests (Radio Immuno-Assay and ELISA) became available and were shown to be reproducible and reliable, it was hoped that these tests could be used to detect an early relapse,[5]. However, it was observed that the native phenolic glycolipid-I(PGL-I)-ELISA test was not sensitive enough to detect relapses in paucibacillary leprosy patients.[6] The test proved to be sensitive for the follow-up of individual multibacillary leprosy patients.[7]

Until recently, large numbers of multibacillary patients world-wide were allowed to discontinue the treatment, their follow-up is crucial. Early detection of relapse could help in timely therapy before any irreversible damage occurs. In this paper, the results and the value of a PGL-I based ELISA for the follow-up of multibacillary leprosy patients after RFT in the Netherlands are reported.

## Materials and methods

### MATERIALS

Combined therapy including daily rifampicin was introduced in the Netherlands in 1979.[8] The WHO-advised MDT regimen with once monthly rifampicin was implemented in 1986. Sera from patients who were RFT from 1982 onwards were stored. Sera were also obtained and stored at $-20°C$ from the 568 patients still attending leprosy clinics in Amsterdam and Rotterdam. At present only 16 of those patients who had received combined therapy have relapsed. From the multibacillary leprosy patients who had relapsed, sera were available from 4 patients before and after RFT. The sera of these 4 patients were analysed with the phenolic glycolipid-I ELISA test using a synthetic neoglycoprotein ('Gigg Disach' obtained via WHO) as described by Brett *et al.*[9] The results of the test are given in optical density (OD). Values higher than $OD = 0{\cdot}150$ are considered to be positive.[10]

#### *History of the 4 patients*

Patient 1 had suffered from lepromatous leprosy since 1956. He came to the Netherlands in 1977 from Suriname. He had been treated with dapsone, 200 mg weekly, and in 1964 the dose had been decreased to 150 mg weekly and in 1970 to 75 mg weekly. In 1971 he had been suspected of having developed resistance to dapsone and his treatment had been changed to clofazimine, 100 mg daily. From 1979 onwards he had been treated with combined therapy and he had been RFT in 1981. In 1986, at the age of 48, he developed erythematous lesions accompanied by sensory impairment on his left arm. A biopsy was taken and solid-stained AFB were seen, the BI was 5+. He was diagnosed as a relapsed borderline lepromatous leprosy patient. MDT was commenced and the lesions soon resolved. After 2 years the treatment was once again discontinued.

Patient 2, a 30-year-old man, started MDT in 1986 for borderline–lepromatous leprosy. Since he suffered from a reversal reaction he was also treated with prednisone. His medication was discontinued in 1988. One month after he was RFT he developed a reversal reaction and prednisone was restarted. It was not possible in this patient to discontinue the prednisone, because each time the dose was tapered off the reaction flared-up. In April 1988, he also developed footdrop while still on prednisone treatment.

At that time he was considered to have relapsed. Sections of biopsies with occasionally a solid-stained AFB confirmed this diagnosis and showed a BB/BL histopathology. He restarted MDT in addition to the steroid treatment and it was then possible to taper off the prednisone.

Patient 3 was 69 years old at the time of relapse. He had lived in Indonesia until 1936 and then emigrated to the Netherlands. In 1940 he had developed leprosy and had been diagnosed as having borderline–lepromatous leprosy. He had been treated with dapsone as soon as it became available in 1946 until 1964.

He was seen at the leprosy clinic again in 1985 because of sensory disturbances and ulcerations of the feet. He confided that he had been taking 100 mg of dapsone twice a week since 1964. After a complete assessment no sign of activity was observed and he was advised to discontinue the treatment. One year later he had been without any complaints or signs of relapse. After a further 6 months, however, he developed disseminated erythematous macules and the diagnosis borderline–lepromatous leprosy was made and confirmed by biopsy. The BI was 5+ and solid-stained AFB were seen in the biopsy. Upon MDT the lesions disappeared.

Patient 4, a 47-year-old man, was seen in 1986 at the leprosy clinic because of a paresis of the left foot. Shortly before, he had had an operation on this foot for osteomyelitis in the left hallux. He had been treated elsewhere from 1953 to 1966 for borderline–

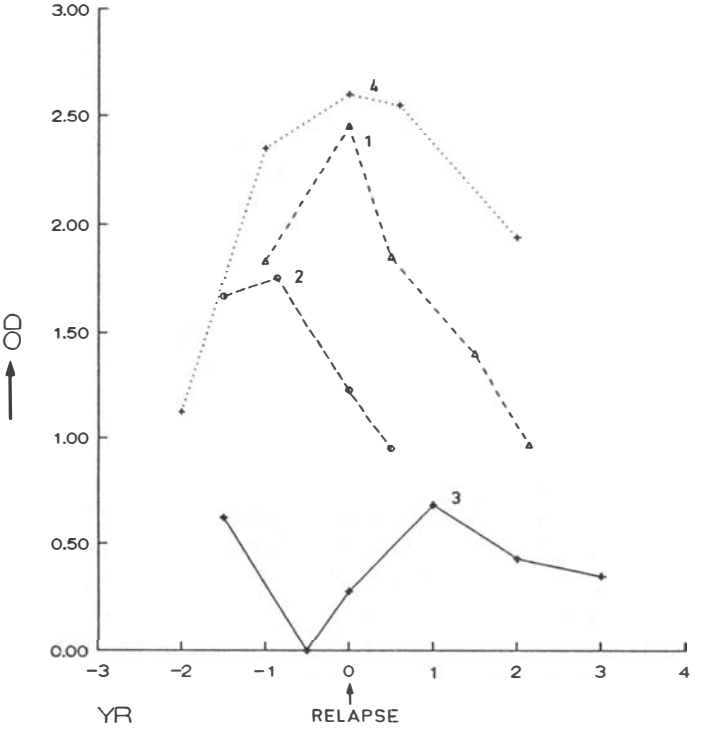


**Figure 1.** Levels of antibody in 4 multibacillary patients in whom a relapse was diagnosed. Numbers refer to patients in text.

tuberculoid leprosy. From 1970 to 1973 and from 1982 to 1984 he had taken dapsone, which had been prescribed by his general practitioner. He had been examined, and since there were no clinical signs of active leprosy, the treatment was discontinued. In 1988 he was admitted for an ulcer with cellulitis in the 3rd and 4th toe of the left foot. Since there was an increase in the PGL-I-ELISA-values skin smears were taken from his earlobes, and no acid-fast bacilli (AFB) could be observed. However, the upper arms and buttocks were positive for AFB and also solid-stained AFB were seen. At that time a biopsy was taken from a very faintly hypopigmented macule in which solid-stained AFB were also observed. He was diagnosed as having relapsed borderline–lepromatous leprosy and MDT was started.

The ELISA-values of these 4 patients with a proven relapse, were compared with the ELISA-values of multibacillary leprosy patients after RFT without an evident clinical relapse, from whom a number of serum samples were available. These patients were chosen at random.

## Results

The results of the PGL-I ELISA in the 4 patients are shown in Figure 1. The levels of antibody against PGL-I in patients 1, 3 and 4 were increased before a clinical relapse was

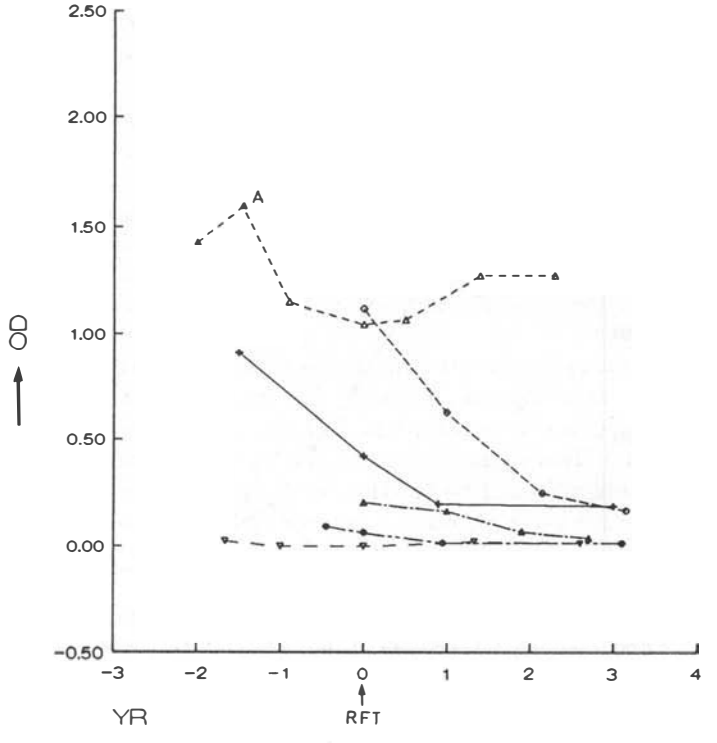


**Figure 2.** Levels of antibody in 6 multibacillary patients before and after release from treatment (RFT). Patient A is discussed in the text.

diagnosed. In patient 2 the level of antibody was not increasing when the patient was clinically considered as relapsed, although two previous serum samples showed increased levels of antibody.

The outcome of the PGL-I ELISA in multibacillary leprosy patients who had not developed a clinical relapse and from whom consecutive serum samples were available was compared with the results of the relapsed patients (Figure 2). It can be seen that the levels of antibodies against phenolic glycolipid-I declined or showed persistently low levels after RFT in these 6 patients who showed no clinical signs of relapse. The sixth patient (A) showed increased levels.

## Discussion

In patients 1, 2 and 3 the relapse was diagnosed clinically and confirmed by histopathology. In patient 4 there were no clinical signs of active leprosy. However, due to an increase in the ELISA values, a biopsy was taken and he was diagnosed as relapsed. All 4 patients were classified as multibacillary.

As shown in Figure 1 patient 1 still had a very high level of antibody—even 5 years after RFT. When the diagnosis of relapse (e.g. clinical and bacteriological reactivation of the disease) was made the level of antibody had risen further. After the start of MDT the levels of antibody declined rapidly and correlated to the observed clinical improvement. It is possible that at the moment the first serum sample was taken, 5 years after RFT, the patient was already in relapse but this was clinically undetectable.

The levels of antibody on patient 2 were not increased as expected. This could be explained on the basis that the prednisone therapy the patient had received, because of the reversal reaction, also suppressed the antibody response. The patient was treated with prednisone according to the generally held view that a reversal reaction shortly after RFT, could not be a relapse, but rather reflects an increase in cell-mediated immunity due to the discontinuation of dapsone.[11,12] In this patient, however, the reversal reaction reflected a multiplication of bacilli. This multiplication was not followed by increased levels of antibody. Therefore, the patient had not received the necessary antimycobacterial therapy immediately.

The levels of antibody in patients 1 and 4, however, followed the expected pattern—a rise before clinical relapse and a decline after the initiation of treatment.

Figure 1 also shows a transient increase in levels of antibody just after the start of treatment in patient 3. This could be due to the effective treatment and consequently a sudden release of antigens from dead or dying bacilli.[11] A similar rise in levels of antibody after the start of treatment have been observed by Melsom *et al.*[13] for lepromatous patients and by Dahle *et al.*[14] for tuberculoid patients using a Radio Immuno-Assay (RIA) against *Mycobacterium leprae* antigen-7.

Figure 2 shows the levels of antibody in patients who did not relapse after RFT. One of the patients (A) showed a significant rise in the level of antibody 1·5 years after RFT. This patient had been diagnosed as having BL leprosy in 1984. He had been treated previously in Suriname for 10 years. MDT was started, but compliance of the treatment had been irregular. Nevertheless, he had been released from treatment in November 1987. Thereafter, he visited the outpatient department regularly. In August 1989, he observed an erythematous patch on his right cheek which could have been leprosy. A relapse was

suspected, however, the smear was negative, and as the patch disappeared within a few weeks it was decided to wait. The levels of antibody did not fall below an OD of 1·0 after RFT and since the level of antibody has increased further at present, he may relapse.

Among the patients presented in Figure 2, he is the only patient in whom, at a certain moment, there were clinical signs for a suspected relapse.

The results presented in this paper show that in 3 out of 4 patients with an established relapse the levels of antibody to PGL-I increased. Of the 6 patients who did not relapse after RFT, 5 showed a decrease in the levels of antibody or remained consistently low. Contrary to what had been reported for paucibacillary patients[6] in whom the levels of antibody to PGL-I had no indicative value for the diagnosis of a relapse, in multibacillary patients there seems to be a trend between the increased levels of antibody to PGL-I and a clinical relapse.

However, this trend must be confirmed in a larger group of patients in whom longitudinal serum samples are analysed before any definite conclusion concerning the predictive value of this test for relapses can be made.

## Acknowledgments

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## Suivi des patients souffrant de lepre multibacillaire au moyen de la methode ELISA sur un support de glycolipides phenoliques. L'augmentation des valeurs de la methode ELISA après l'arret du traitement est-elle indicative d'une recidive?

R A M Chin-A-Lien, W R Faber, M M van Rens, D L Leiker, B Naafs et P R Klatser

*Résumé* On espérait grâce à l'introduction des tests sérologiques reproductibles pouvoir dépister les récidives chez les lépreux après l'arrêt du traitement, avant la survenue de réactions néfastes et avant que les patients ne deviennent infectieux. On a examiné l'intérêt éventuel de la méthode ELISA en utilisant un analogue semi-synthétique des glycolipides phénoliques-I pour dépister les anticorps dirigés contre cet antigène et qui permet de prédire une récidive chez les patients multibacillaires. Contrairement à ce qui avait été rapporté dans le cas des patients paucibacillaires, ce test a permis de dépister les récidives précoces chez les patients multibacillaires. Chez 3 patients multibacillaires sur 4 qui avaient récidivés, les valeurs obtenues avec la méthode ELISA avaient augmenté. Les valeurs inférieures obtenues avec la méthode ELISA chez un des patients qui avait récidivé pouvaient être attribuées à la corticothérapie. Chez les patients multibacillaires qui n'avaient pas récidivé après l'interruption du traitement, les valeurs obtenues avec la méthode ELISA étaient basses ou avaient baissés de manière consistante. Chez un seul patient seulement les valuers avaient augmenté suite à son interruption du traitement et sur le plan clinique, on soupçonnait une récidive.

## Continuacion del estudio de pacientes leprosos multibacilares utilizando un ELISA basado en un glicolipido-I fenolico. Los valores crecientes de ELISA ¿indican una recaida despues del tratamiento?

R A M Chin-A-Lien, W R Faber, M M van Rens, D L Leiker, B Naafs y P R Klatser

*Resumen* Después de la introducción de pruebas serológicas reproducibles, se esperaba que se podrían detectar recaídas en los pacientes leprosos, después de descontinuar el tratamiento, antes de que ocurriésen reacciones dañinas y antes de que los pacientes se pusieran infecciosos. Se investigó el valor que podría tener un ELISA utilizando un producto analógico semi-sintético de glicolipido-I fenólico para la detección de anticuerpos a este antígeno, para pronosticar una recaída en los pacientes multibacilares. En contraste con lo que se ha informado sobre los pacientes paucibacilares, esta prueba fue útil para detectar recaídas tempranas en los pacientes multibacilares. En 3 de los 4 pacientes multibacilares que recayeron, hubo un aumento en los valores de ELISA. La reducción de valor ELISA en el único paciente recaído se podia atribuir a la terapia corticoesteroide. En los pacientes multibacilares que no recayeron después de descontinuar el tratamiento (RFT), los valores de ELISA erán bajos o decrecieron de una forma constante. En solamente un paciente hubo un aumento de ELISA después de descontinuar el tratamiento, y se sospechó por razones clínicas que desarrollaba una recaída.

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# Detection of a *Mycobacterium leprae* cell wall antigen in the urine of untreated and treated patients

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*Summary* A total of 90 leprosy patients, 12 household contacts and 10 normal subjects were studied for the detection of *Mycobacterium leprae* cell wall antigen in urine using monoclonal antibody ($ML30A_2$ IgG). In untreated multibacillary leprosy (BL–LL) the *M. leprae* cell wall antigen could be demonstrated in the urine of 14 (64%) patients by immunofluorescence (IF) and 22 (100%) by ELISA. In untreated paucibacillary leprosy (TT–BT), it could be demonstrated in 3 (11·5%) and in 13 (50%) patients by IF and ELISA methods respectively. All but 1 household contact (later confirmed to have BL leprosy) and all 10 normal subjects' urine was negative for *M. leprae* cell wall antigen by both methods. The same antigen was, however, demonstrated in urine of 50% paucibacillary patients who had received 6 months of treatment and in 68% multibacillary patients who had received 24 months of WHO recommended multidrug therapy. *M. leprae* cell wall antigen assays in urine will not be useful in the follow-up of leprosy patients on multidrug therapy.

## Introduction

The diagnosis of leprosy is based on cardinal clinical features like anaesthesia or hypoaesthesia, hypopigmented and/or infiltrated erythematous patches, nerve thickening and the demonstration of *Mycobacterium leprae*. Attempts have been made to diagnose clinical and subclinical leprosy by the demonstration of antibodies against *M. leprae*.[1,2] Recently, it has been found that the demonstration of *M. leprae* antigens in serum is a better indicator of infection and may help in follow-up during treatment.[3–6] Evaluation of *M. leprae* antigens excreted in urine[7–10] will be of use in the follow-up of leprosy patients on treatment, early diagnosis of relapse and in the epidemiological surveys for the evidence of subclinical infection.[11] The present study was undertaken to assess the role of *M. leprae* cell wall (CW) antigen assays in urine in the follow-up of patients on chemotherapy. The monoclonal antibody employed $ML30A_2$ IgG detects 35–70 kD cell

 0305-7518/92/0630+08 $01.00 

wall antigen named MY3. This antigen is found in *M. leprae* but is also shared by *M. welchii*, ICRC bacillus, *M. lepraemurium* and other mycobacteria.[12] *M. leprae* CW antigen assays were carried out by immunofluorescence (IF) and double antibody sandwich ELISA methods in both untreated and treated paucibacillary and multibacillary patients.

## Materials and Methods

### PATIENTS

We selected 90 leprosy patients who attended the Leprosy Clinic at the Nehru Hospital attached to the Postgraduate Institute of Medical Education and Research, Chandigarh, India for the study. These included 68 males and 22 females with disease periods ranging from 3 months to 15 years (mean 2·4 years). Out of 42 paucibacillary (TT–BT) cases 16 had received treatment with WHO paucibacillary multidrug therapy (MDT) for 6 months and the remaining 26 cases were untreated. Out of 48 multibacillary (BL–LL) patients 22 were untreated and 26 had received 2 or more years of WHO MDT.[13] We also studied 12 household contacts of the untreated patients and 10 healthy subjects. The patients were classified according to the Ridley–Jopling classification.[14] Diagnosis of leprosy was based on clinical, bacteriological and histopathological examinations and the slit-skin smears were done from 1 to 3 patches in TT–BT patients and 3 patches and both earlobes in BL–LL patients. Dharmendra lepromin (0·1 ml) was injected intradermally in the left forearm of selected patients and readings were taken initially after 48 hr and again after 4 weeks to see the lepromin response.

The renal status was assessed by routine urinalysis for albumin, sugar and microscopic examination for leucocytes, erythrocytes and casts. Urine culture for pathogenic microorganisms were done. Urine deposits obtained after ultracentrifugation were cultured into Lowenstein–Jensen media slants to look for *M. tuberculosis*. An estimation of blood urea and serum creatinine was also carried out in all patients.

Physical examination was done to rule out coexisting tuberculosis and renal diseases and a blood pressure reading was taken in all patients. A chest skiagram was carried out to rule out concomitant tuberculosis.

### DETECTION OF *M. LEPRAE* CELL WALL ANTIGEN

Midstream urine (15–20 ml) was collected in 2 sterile glass culture tubes. One of them was sent for urine culture and urine from the second tube was centrifuged at 17,000 *g* for 20 min. Smears were made in duplicate on slides from the urine deposits. One slide was used for Ziehl–Neelson staining and another used for an IF study as detailed below.

*M. leprae* CW antigen was detected by IF and by an enzyme-linked immunosorbent assay (ELISA) in the urine samples.

#### *Immunofluorescence study*

The smears were rinsed in carbon tetrachloride for 10 min at room temperature and digested with 0·1% solution of trypsin in Tris-HCl buffer (pH 8·0) at 37°C for 1 hr. The smears were fixed in ice-cold acetone for 30 min and stored at −20°C till further use.

Monoclonal antibodies ($ML30A_2$ IgG) against *M. leprae* (kindly supplied by Dr J Ivanyi, Director of Tuberculosis Research Centre, London) were applied. The smears were treated with FITC conjugated anti-mouse immunoglobulins and the IF was recorded arbitrarily as 1+ to 4+ according to the degree of fluorescence observed. Nasal and slit-skin smears from known untreated lepromatous patients were used as positive controls.

*Enzyme-linked immunosorbent assay (ELISA)*

The ELISA was performed by the double antibody sandwich method. Briefly, monoclonal antibodies diluted to 1:1000 were coated on polyvinyl microtitre ELISA plates. After thorough washing with phosphate-buffered saline (PBS) containing 1 mM $Ca^+$ and 0·02% Tween-20 (PBSCT) and blocking with bovine serum albumin, 100 $\mu$l of urine deposit samples were added to the wells and incubated at room temperature for 3 hr. After 3 washes with PBSCT the wells were again treated with 100 $\mu$l of 1:1000 monoclonal antibodies. Wash cycles were repeated 3 times followed by 100 $\mu$l of horse-radish peroxidase conjugated with rabbit immunoglobulins to mouse immunoglobulins diluted 1:5000 in PBS. Incubation was carried out at 37°C for 30 min, the wells washed 3 times and 100 $\mu$l of freshly-prepared substrate ($H_2O_2$ and orthotoluidine) were added. Incubation was done at room temperature for 30 min, the reaction was stopped by adding 100 $\mu$l of 3-N sulphuric acid. Urine samples from healthy subjects and pretitrated *M. leprae* antigen served as negative and positive controls, respectively.

Absorbance was read at 490 nm in an ELISA reader (Dynatech Laboratories Inc, VA, USA). The mean of 3 optimal density (OD) readings was recorded for each sample. A sample was considered positive if its mean exceeded the mean +2 standard deviations of the negative control samples.

## Results

All paucibacillary patients (26 untreated, 16 treated) were slit-skin smear negative. In the untreated multibacillary group (22 patients), the mean bacteriological index (BI) was 4·1+ and the morphological index was 2·3%. In the treated MB group (26 patients) all but 2 were slit-skin smear negative.

### *M. LEPRAE* CELL WALL ANTIGEN DETECTION IN URINE

*Immunofluorescence method*

*M. leprae* CW antigen was detected in 3 (11·5%) untreated paucibacillary patients, the degree of fluorescence was graded from 1+ to 2+. In multibacillary disease, the same antigen was detected in the urine of 14 (64%) untreated and 10 (39%) treated patients. The fluorescence was graded 2+ and above in the vast majority of untreated multibacillary patients (71·4%) compared with treated patients (40%) (Table 1).

All 10 healthy individuals and 11 household contacts were negative.

*ELISA method*

Half of both untreated and treated PB patients were positive by this method. All 22

**Table 1.** *M. leprae* CW antigen detected in urine of leprosy patients and controls by immunofluorescence

| Subjects | No. studied | No. negative | No. positive by IF 1+ | 2+ | 3+ | 4+ | Percent positive |
|---|---|---|---|---|---|---|---|
| I Healthy individuals | 10 | 10 | — | — | — | — | 0 |
| II Contacts | 12 | 11 | — | | — | 1* | 1 (8·3)* |
| III Paucibacillary leprosy (TT, BT) | | | | | | | |
| (a) Untreated | 26 | 23 | 1 | 2 | — | — | 3 (11·5) |
| (b) Treated | 16 | | Not done | | | | |
| IV Multibacillary leprosy (BL, LL) | | | | | | | |
| (a) Untreated | 22 | 8 | 4 | 7 | 2 | 1 | 14 (64·0) |
| (b) Treated | 26 | 16 | 6 | 3 | — | 1 | 10 (39·0) |

* Positive household contact was later found to have BL leprosy.

**Table 2.** *M. leprae* CW antigen detected in urine in leprosy patients and controls by ELISA

| Subjects | No. studied | *M. leprae* CW antigen No. negative | No. positive | Percent positive |
|---|---|---|---|---|
| I Healthy individuals | 10 | — | — | — |
| II Contacts | 12 | 11 | 1* | 8·3* |
| III Paucibacillary leprosy (TT/BT) | | | | |
| (a) Untreated | 26 | 13 | 13 | 50·0 |
| (b) Treated | 16 | 8 | 8 | 50·0 |
| IV Multibacillary leprosy (BL, LL) | | | | |
| (a) Untreated | 22 | 0 | 22 | 100·0 |
| (b) Treated | 26 | 9 | 17 | 68·0 |

* One household contact positive by ELISA was later found to have BL leprosy. He was also positive by IF method.

patients (100%) with untreated MB leprosy were positive and 17 (68%) patients who had received 24 doses of WHO-recommended MDT were also positive (Table 2).

All 10 healthy individuals and 11 household contacts were negative by ELISA. The household contact positive by both IF and ELISA was later found to have BL leprosy. The ELISA titres in different subjects are depicted in Figure 1.

*Correlation between* M. leprae *CW antigen detection by IF and ELISA*

The 3 untreated PB, the 14 untreated MB leprosy, and the 10 treated MB patients who were positive by IF were also positive by the ELISA test, but those patients positive by the

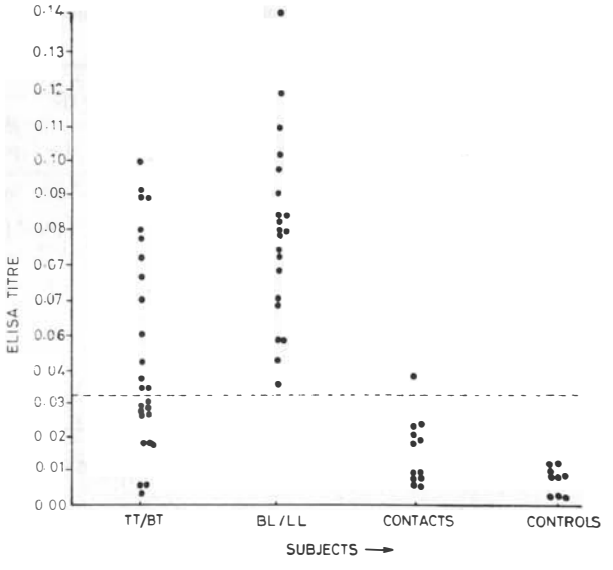


**Figure 1.** The scatterogram depicts ELISA titres in different subject groups. Each dot represents a sample. Note that specimens from all healthy controls and all but one household contact have insignificant ELISA titres whereas all BL and LL patients have titres above the cut-off line. Samples from TT and BT patients are equally distributed on both sides of the cut-off titre.

ELISA test were not positive by IF. It is apparent that the ELISA test is more sensitive in detecting *M. leprae* CW antigen in urine.

*Effect of treatment on* M. leprae *CW antigen detection in urine*

There was apparently no effect of 6 months PB treatment on the above antigen excretion in the urine. The frequency of antigen excretion was, however, reduced in MB patients who received 24 doses of WHO MDT.

## Discussion

The overt antigens of *M. leprae*, like those of all other mycobacteria, are carbohydrate based. The dominant carbohydrate epitopes of *M. leprae* are contained in 3 entities, the phenolic glycolipids (PGL), lipoarabinomannan and the arabinogalactan peptidoglycan complex. Though PGL-1 is one of the first *M. leprae* specific antigen to be isolated, PGL-II and -III have also been characterized.[15]

Ivanyi *et al.*[12] detected 4 soluble antigens of *M. leprae* using 12 monoclonal antibodies employing radioimmunoassay, labelled antibody competition test and immunoblotting taken from polyacrylamide-electrophoresis gels. These antigens were arbitrarily labelled MY1, MY2, MY3 and MY4. A protein antigen MY1 found on *M. leprae* reacted with monoclonal ML06 and had no cross-reactivity with other mycobacteria. Similarly MY3 antigen of *M. leprae* reacted with monoclonal ML30$A_2$ IgG, but this also occurs in

*M. welchii* ICRC bacillus, *M. lepraemurium*, *M. tuberculosis*, *M. bovis* and *M. scrofulaceum*. MY3 antigen is associated with protein as it is highly sensitive to digestion by subtilisin and is also associated with 5 distinct fragments (35–70 kD). Preliminary experiments indicated that MY3 antigen is associated with the cell wall as the repeated sonication of *M. leprae* cell pellet increased its yield in the supernatant fraction. The likely candidate for such a structure is the peptidoglycan cell wall.[12]

In the present experiment the coexistent tuberculosis was ruled out by clinical examination, chest skiagram and urine culture for *M. tuberculosis*. The other mycobacteria producing positive *M. leprae* CW antigen in urine is unlikely in the absence of clinical symptoms and moreover all but one of 22 controls (10 healthy controls and 12 household contacts) were negative for *M. leprae* CW antigen detection by both the IF and ELISA methods. The only household contact positive for *M. leprae* CW antigen was found to have BL leprosy.

Olcen *et al.*,[7] using radiolabelled armadillo derived *M. leprae* sonicate employing inhibition radioimmunoassay (RIA), found *M. leprae* antigenuria in 2 out of 23 PB patients and 11 out of 23 MB patients. In the present study *M. leprae* CW antigen was demonstrated in similar proportions of both PB and MB leprosy patients by the IF method. The ELISA method for detecting *M. leprae* antigenuria was, however, more sensitive, being positive in 13 (50%) PB and in all 22 (100%) MB leprosy patients. Similar high antigen positivity was found for PGL-1 detection in both urine and serum.[6,10] Olcen *et al.*[7] showed a significant correlation between the highest bacteriological index and antigen concentration in urine, contrary to our findings, even though the ELISA titres were much higher in MB patients compared to PB patients, contacts and controls (Figure 1).

Chemotherapy lead to rapid disappearance (4–8 weeks) of *M. leprae* antigen from both serum and urine correlating with a fall in the morphological index.[6,16,17] This is despite the fact that a large number of granulated or fragmented bacilli are known to persist in tissues even 4 years after treatment.[18] However, in our series *M. leprae* antigen persisted in 17 (68%) out of 26 MB and 8 (50%) out of 16 PB patients treated for 24 and 6 months, respectively, with WHO recommended MDT. This is due to the fact that the monoclonal antibody ($ML30A_2$ IgG) used by us detects a cell wall antigen (35–70 kD),[15] which probably persists despite the chemotherapy. PGL-1 is synthesized and secreted by live *M. leprae*[19] and hence its concentration falls soon after bactericidal treatment.[16,17] We therefore feel that *M. leprae* cell wall antigen assays in urine will not be of use during follow-up after treatment and for the early diagnosis of relapse.

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## Découverte d'un antigène *Mycobacterium leprae* de la paroi cellulaire dans les urines de sujets traités et de sujets non traités

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*Résumé* Une étude a été réalisée sur 90 lépreux, 12 sujets d'un même foyer en contact avec l'infection et 10 sujets sains afin de déceler dans les urines l'antigène *Mycobacterium leprae* de la paroi cellulaire, à l'aide de l'anticorps monoclonal ($ML30A_2$ IgG). Sur un groupe de sujets non traités atteints de lèpre multibacillaire (BL-LL), on a constaté la présence d'antigène *M. leprae* de la paroi cellulaire dans les urines de 14 patients (64%) avec la technique d'immunofluorescence (IF) et 22 (100%) avec la technique ELISA. Sur un groupe de sujets non traités atteints de lèpre paucibacillaire (TT-BT), la présence de l'antigène a été constatée chez 3 patients (11,5%) et 13 patients (50%) avec la méthode d'immunofluorescence et la méthode ELISA, respectivement. Les urines de tous les sujets en contact, sauf un (chez qui la lèpre a été diagnostiquée par la suite) et des 10 sujets sains se sont révélées négatives d'antigène *M. leprae* de la paroi cellulaire avec les deux méthodes. La présence de ce même antigène a, cependant, été constatée dans les urines de 50% des lépreux paucibasillaires ayant reçu 6 mois de traitement et 68% des lépreux multibacillaires ayant reçu 24 mois de médication mixte préconisée par l'OMS. La recherche d'antigène *M. leprae* de la paroi cellulaire dans les urines s'avère inutile pour le suivi médical des lépreux recevant un traitement mixte.

## La detección de antígeno de pared celular de *Mycobacterium leprae* en la orina de pacientes tratados y sin tratar

V K Sharma, S Kaur, C Vaishnavi, N Agnihotri, I Kaur y N K Ganguly

*Resumen* Se estudiaron 90 pacientes leprosos, 12 contactos de domicilio y 10 personas normales para la detección de antígeno de pared celular de *Mycobacterium leprae* en la orina, usando anitcuerpo monoclonal ($ML30A_2$ IgG). En la lepra multibacilar (BL-LL) sin tratar se pudo demostrar la presencia del antígeno de la pared celular de *M. leprae* en la orina de 14 (64%) de pacientes por inmunofluorescencia (IF) y en 22 (100%) por ELISA. En la lepra paucibacilar (TT-BT) sin tratar, se pudo detectar en (11,5%) y en 13 (50%) de pacientes por los métodos IF y ELISA respectivamente. La orina de todos menos uno de los contactos de domicilio (que más tarde se confirmó tener lepra BL) y todas (10) las personas normales fue negativa al antígeno de pared celular de *M. leprae* por ambos métodos. Sin embargo, se demostró la presencia del mismo antígeno en la orina del 50% de pacientes paucibacilares que habían sido tratado por 6 meses y en 68% de pacientes multibacilares que habían sido tratados por 24 meses, por la terapia multidroga recomendada por la OMS. Las pruebas de orina por antígeno de pared celular de *M. leprae* no será útil en el control posterior de pacientes con lepra que reciben terapia multidroga.

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# Ambulatory treatment of multibacillary leprosy with a regimen of 8 months duration

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*Summary* An ambulatory treatment regimen for multibacillary leprosy, of 34 weeks duration composed of 8 weeks daily supervised rifampicin, ethionamide (ETH), dapsone (DDS) and clofazimine (CLO) followed by 26 weeks of unsupervised ETH, DDS and CLO, introduced in 1983 has been evaluated; 268 patients were followed for a mean of 4·4 years and a total of 1188 patient years. The relapse rate was 0·33 per 100 patient years of follow up. The reduction of the duration of the combined administration of RMP + ETH reduced the hepatotoxicity to 1·4%. It is possible that both phases of the regimen studied could still be reduced, however in the near future ETH will be replaced by alternative bactericidal drugs, avoiding the hepatotoxicity.

## Introduction

Previous work from our laboratory[1–4] has shown that short course treatment, of less than 1 year's duration, is possible in multibacillary leprosy (MB) provided combined therapy with bactericidal drugs in sufficient dosage is administered.[4] Until the end of the 1980s only 2 bactericidal drugs were available: rifampicin (RMP) and the thioamides, either ethionamide (ETH) or prothionamide, but unfortunately their combined administration is hepatotoxic,[5,6] even when the duration of their combined administration was reduced to 3 months.[4]

Furthermore for the supervised daily administration of drugs in our previous studies,[1–4] patients had to be hospitalized or to reside in the proximity of the treatment centre. This was not always possible in Burundi.

We therefore decided to study the efficacy and tolerance of an entirely ambulatory regimen consisting of two successive phases: a first period of 8 weeks of a daily supervised 4-drug regimen including RMP, ETH, DDS and CLO followed by a 6-month unsupervised triple drug regimen without RMP.


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## Patients and methods

In the peripheral, rural health centre (HC), patients suspected of having leprosy were referred to the leprosy service personnel during their monthly visits, for clinical, neurological and bacteriological examinations and a skin biopsy to be fixed in 10% formalin. Slit-skin smears were taken—one from an earlobe and two from skin lesions. The biopsies together with a copy of the clinical file was sent to Antwerp, as was a copy of the treatment file when completed.

Patients were either newly diagnosed (new cases) or known cases who had been treated in the past with dapsone (DDS) monotherapy irregularly or had relapsed after DDS monotherapy had been stopped (old cases).

Patients able to visit the HC daily during the 8 weeks were included in the study and the necessary medication, in containers for daily delivery, was handed over to the responsible person in the HC. Thereafter, during the second phase of treatment, medication sufficient for 4 weeks was delivered to the HC. All administrations of drugs were noted on an appropriate form. The treatment regimen was as follows:

8 weeks: RMP 600 mg, ETH 500 mg, DDS 100 mg, CLO 50 mg daily, 6 days a week, supervised in the HC, followed by

26 weeks: ETH 500 mg, DDS 100 mg and CLO 50 mg daily 7 days a week, unsupervised, the drugs being collected from the HC once every 4 weeks.

In the present analysis only patients with a BI of 2 or more at any site, at the start of the study, are included. Treatment was considered complete if the first phase was completed within 9 weeks and the second within 30 weeks.

In the absence of any intercurrent complication follow-up examinations identical to those at intake were done yearly.

When relapse was suspected, clinical, bacteriological and histological examinations were repeated and if relapse was confirmed and also if feasible, a fresh skin biopsy, on ice, was sent to the laboratory in Antwerp for mouse footpad inoculation and drug sensitivity testing. For the latter RMP 10 mg/k was administered to mice once a week during 10 weeks by gastric gavage, DDS was mixed in the food at $10^{-2}$, $10^{-3}$, $10^{-4}$%, ETH at $10^{-2}$% and CL0 at $3{\cdot}10^{-3}$.

## Results

A total of 305 patients with a BI at the start of 2 or more at any site were taken into the trial: 146 new cases and 159 old cases. Six patients died before the end of the first year from causes unrelated to leprosy. Seventeen patients (6·2%) were lost during the first phase of treatment—1 because he left the country and 16 for unknown reasons. Fourteen patients (4·5%) had to be excluded from the analysis because they failed to collect their last 1 or 2 monthly doses of drugs. Thus 268 patients were evaluated, 125 new cases and 143 old cases. They were followed for a mean of 4·4 years, and represent 1188 patient years of follow-up (Table 1). The mean BI at the start was 3·18 and declined with a mean of 0·53 per year.

**Table 1.** Follow up and incidence of relapses in patients treated with the ambulatory regimen of 8+26 weeks

| Year of follow-up | Number of patients seen | Person years of follow-up (cumulative) | Relapses | | | |
|---|---|---|---|---|---|---|
| | | | Number | Cumulative number | Incidence (%) | 95% CI |
| 1 | 268 | 268 | — | — | — | — |
| 2 | 259 | 527 | — | — | — | — |
| 3 | 242 | 769 | 1 | 1 | 0·1 | 0–0·74 |
| 4 | 197 | 966 | 2 | 3 | 0·3 | 0·06–0·92 |
| 5 | 148 | 1114 | 1 | 4 | 0·3 | 0·06–0·87 |
| 6 | 68 | 1182 | — | 4 | 0·3 | 0·06–0·87 |
| 7 | 6 | 1188 | — | 4 | 0·3 | 0·06–0·87 |
| Mean 4·4 | | | | | | |

CI, confidence interval.

Clinical evolution in all patients was very satisfactory. Four cases of hepatitis (1·4%) were diagnosed clinically at 7, 55, 68 and 208 days of treatment, with a mean of 84 days and a median of 61 days. None of them was fatal.

Four relapses, 3 in BL patients and 1 in a LL patient, have been diagnosed at respectively 31, 41, 43 and 52 months after the end of treatment, with a mean and median of 42 months. One relapse was detected in a yearly follow-up biopsy, the other 3 cases were detected clinically.

Bacilli from 3 relapses were inoculated into mice, all were sensitive to the drugs administered to the patients.

Six cases of late reversal reactions were diagnosed at respectively 29, 30, 40, 41, 56 and 57 months after the end of treatment with a mean of 42 months and a median of 40·5 months. Five had been classified as BL and one as LL.

## Discussion

The present study shows that MB leprosy can be cured by an ambulatory treatment of 8 months duration, composed of a daily supervised administration of 4 drugs, 2 of which, RMP and ETH are bactericidal, followed by 6 months of unsupervised administration of 3 drugs, one of which, ETH, is bactericidal.

The 48 doses of RMP administered during the first 8 weeks of treatment are supposed to kill all RMP sensitive organisms, while the 230 doses of ETH, DDS and CLO administered during the next 8 months should kill the remaining RMP-resistant organisms.[5] The relapse rate of 0·3% of the present 8+26 weeks (w) regimen, compares favourably with the previously studied 13w regimen for which the relapse rate was 0·28%. It must be noted however that the follow-up for the 8+26w regimen of 4·4 years or 53 months is longer than for the 13w regimen for which it was 3·5 years or 42 months. Compared with the 13w regimen,[4] the 8+26w regimen implies the administration of greater quantities of drugs during a longer time period:

8+26w RMP 48 doses within 8 weeks
ETH 230 doses within 34 weeks
DDS 230 doses within 34 weeks
CLO 230 doses within 34 weeks

13w(4) RMP 26 doses within 13 weeks
ETH 78 doses within 13 weeks
DDS 78 doses within 13 weeks
CLO 78 doses within 13 weeks

Since both regimens have a comparable efficacy, the 8+26w regimen could probably be shortened. However the main advantage of the 8+26w regimen is the significant reduction of hepatotoxicity: 1·4% instead of the 5% in previous studies[6] (4/268 versus 23/515, $p=0{\cdot}05$). This significant reduction was not observed with the 13w regimen: 14 cases among 439 patients.[4] This most probably results from the reduced duration of the simultaneous administration of RMP+ETH during 8 weeks only. How much this could still be reduced in quantity or duration may now be an obsolete question since alternative drugs such as ofloxacine,[8] minocycline[9] and macrolides may replace the use of ETH and probably avoid hepatotoxicity.

There is no evidence that the 14 patients who failed to collect their final one or two drug supplies did so because of hepatitis: they were also followed for 4–5 years and none of them developed a relapse. This supports the hypothesis and it may be possible to reduce the duration of the second phase in the present regimen, but the number of patients is too small to allow significant conclusions to be drawn.

As expected after treatment with a combined drug regimen, the strains isolated from the relapsing patients were sensitive to the drugs the patients had taken. This shows that in a small proportion of MB patients, some drug sensitive *Mycobacterium leprae* escape the action of the drugs and give rise to relapses, it is possible that a combination of more than 2 bactericidal drugs may solve this problem.

Once more the late reversal reactions, appearing in the present study after a mean of 42 months post-therapy should be differentiated from relapses on the basis of careful bacteriological and histopathological assessment.

In conclusion a treatment regimen of MB leprosy of 34 weeks duration, involving 8 weeks of daily supervised RMP, ETH, DDS and CLO followed by 26 weeks of unsupervised ETH, DDS and CLO gave most satisfactory results in terms of relapse rate while at the same time hepatotoxicity was reduced considerably.

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## Traitement ambulatoire de la lepre multibacillaire par un regime de 8 mois

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*Résumé* Une évaluation a été faite du traitement ambulatoire de la lèpre multibacillaire au moyen d'un régime de 34 semaines dont 8 semaines d'un traitement supervisé journalier à la rifampicine, à l'éthionaide (EHT), à la dapsone (DDS) et à la clofazimine (CLO) suivi de 26 semaines d'un traitement non-supervisé de ETH, DDS et CLO introduit en 1983; 268 patients furent suivis pendant une moyenne de 4,4 ans et pendant un total de 1188 années-patients. La réduction de la durée de l'administration combinée de RMP+ETH avait réduit l'hépatotoxicité à 1,4%. Il est possible que les deux phases du régime étudié puissent être encore réduites mais bientôt, ETH sera remplacé par d'autres bactéricides qui ne causent pas d'hépatotoxicité.

## El tratamiento ambulatorio de la lepra multibacilar con un regimen de duracion de 8 meses

S R Pattyn, J Bourland y Kazeze

*Resumen* Se ha evaluado un regimen de tratamiento ambulatorio de la lepra multibacilar con una duración de 34 semanas, que consistía de 8 semanas de rifampicina, etionamida (ETH) dapsona (DDS) y clofazimina (CLO) con administración diaria vigilada, seguido por 26 semanas de ETH, DDS y CLO sin supervisión, fue introducido en 1983.

Se controlaron 268 pacientes por un promedio de 4,4 años y un total de 1188 pacientes-año. La tasa de recaída fue 0,33 por 100 pacientes-año de continuación de estudio. La reducción de la duración de la administración combinada de RMP + ETH, redujo la hepatotoxicidad, a 1,4%. Es posible que se podría reducir ambas fases del regimen todavía más, pero en un futuro próximo se reemplazará la ETH con otras drogas bactericidas, para evitar la hepatotoxicidad.

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# Treatment of multibacillary leprosy with a regimen of 13 weeks duration

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*Summary* In a prospective study 559 multibacillary patients in Zaire were treated for 13 weeks with twice weekly rifampicin (600 mg) and daily ethionamide (500 mg) and dapsone (100 mg), 13-RED, or clofazimine (100 mg), 13-REC. The patients were followed for a total of 1418 person years, mean 3·2 years. The incidence of hepatitis was 3·3%. The incidence of relapses was 0·28 per 100 person years. Relapses were due to drug-sensitive organisms.

In patients who received the same drug regimens but with a reduced dosage of ethionamide to 5 mg/k bodyweight, the incidence of hepatitis was significantly lower but the relapse rate was 7·8 per 100 person years of follow-up in the RED group, no relapses were diagnosed in the REC group.

It is concluded that by the use of potent antileprosy drugs in suitable combinations and dosages, it will be possible to shorten the duration of antibacterial treatment in multibacillary leprosy to 3 months.

## Introduction

Previous studies on the treatment of multibacillary leprosy evaluated the efficacy of regimens combining rifampicin (RMP), ethionamide (ETH) and either dapsone (DDS) or clofazimine (CLO) during 12 or 6 months.[1–4] The conclusions from these studies were that the relapse rates after these regimens are extremely low: 0–0·06 per 100 patient years of follow-up, after a mean duration of follow-up of 5–6·1 years.

On this basis, a treatment regimen of shorter duration could be envisaged and the hepatotoxicity observed with the longer regimens[5] could hopefully be reduced through a reduction of the administration of the combination of RMP and ETH. A treatment regimen of 13 weeks duration was therefore applied in patients in Zaire.

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## Patients and methods

Multibacillary (MB) patients presenting at or referred to the participating centres with clinically active disease, and agreeing to stay near the centres or to be hospitalized for 13 weeks were taken into the trial. Thus all treatments were supervised.

All patients were examined clinically, neurologically and bacteriologically. A copy of the clinical file was sent to Antwerp together with a skin biopsy fixed in 10% formalin. MB leprosy was diagnosed if the bacterial index (BI) was 2 or more at any of 3 sites from which slit-skin smears were prepared (1, earlobe and 2 skin lesions) and was confirmed by histopathology.

In the absence of complicating reactions follow-up examinations are performed yearly and are identical to those at intake. Criteria for the evaluation of therapy are: absence of active clinical lesions, decrease of the BI in skin smears and biopsies, absence of solidly staining bacilli in the biopsies, decrease of the histopathological lesions and absence of side-effects.

The neurological evolution was evaluated through comparison of the disability scores (three degree WHO scoring scale)[6] and the number of hypertrophied nerves at the start of treatment and the last follow-up examination.

Patients were randomized between two treatment regimens: RMP 600 mg twice a week, together with ETH 500 mg and either DDS 100 mg (13-RED) or CLO 100 mg (13-REC) daily, for a total duration of 13 weeks. Patients previously treated with DDS monotherapy for 5 years or more and thus at risk of harbouring DDS-resistant *Mycobacterium leprae* received the 13-REC regimen.

Due to a misunderstanding 35 patients at the Museniene Hospital in Zaire were given a reduced dose of ETH, 5 mg/k bodyweight. The patients on this regimen are analysed separately.

Hepatitis was diagnosed clinically. Relapse was diagnosed clinically when new lesions appeared and was confirmed by an increase of at least 2 units of the BI in skin smears and biopsies with an important fraction of solidly staining bacilli. Furthermore, from 4 cases a skin biopsy on ice was brought to Antwerp for mouse footpad inoculation and sensitivity testing for the drugs the patients had been treated with. For sensitivity tests in mice, drugs were administered as follows: DDS in the mouse food at $10^{-2}$, $10^{-3}$, $10^{-4}$ g%, ETH in the food at $10^{-2}$ g%, CLO at $3{\cdot}10^{-3}$ g% in the food, RMP 10 mg/k once a week by gavage, during 10 weeks. Statistical analysis was done by Student $t$-test or $\chi^2$ test where appropriate. Confidence limits were taken from *Tabulae Scientificae*.[5]

## Results

A total of 556 patients were taken into the study: 268 in regimen 13-RED and 291 in regimen 13-REC. In the first group 49 (18·3%) patients were lost to follow-up within the first year, 5 (1·8%) patients died, leaving 214 (79·8%) patients for analysis. In the second group 62 (21·3%) patients were lost to follow-up during the first year and 6 (2%) patients died, leaving 220 (75·6%) patients for analysis. In both groups some patients had received a single dose of 1500 mg RMP at some time between 2 and 12 months prior to the start of the present treatment: 24 in group 13-RED and 31 in group 13-REC. There were no differences between patients receiving the 13-RED or the 13-REC regimens as regards BI, nerve involvement and disabilities.

The mean BI at intake was 3·06 and decreased with a mean of 0·55 per year. As in previous studies[2,3] all patients showed a favourable clinical evolution. Shortly after the start of therapy the clinical activity of the skin lesions subsided and continued to do so after the end of treatment. Reversal reactions during treatment were comparable in intensity and frequency with those observed with analogous treatment regimens of longer duration.[7] The treatment did not lead to an increase in disabilities nor to an increase in the number of hypertrophied nerves (results not shown).

Fourteen cases of hepatitis were diagnosed, 9 in the 13-RED and 5 in the 13-REC group, an incidence of 3·2%. The mean incubation time was 55 days, with a median of 52 days and a range of 17–84 days. There were no fatalities.

Late reversal reactions, appearing after the end of therapy, were diagnosed in 20 cases: 14 among the 13-RED group, incidence 6·5% and 6 among the 13-REC group, incidence 2·7%, this difference is not significant ($p = 0·09$). The mean interval relative to the end of antibacterial therapy was 33 months, with a range of 9–57 months and a median of 33 months.

As shown in Table 1, the total follow-up represents 1418 person years, with a mean of 39·7 months. Four relapses were diagnosed, 2 among each treatment group, giving an overall incidence of 0·28 per 100 person years of follow-up, with a 95% confidence interval of 0·08–0·99. The intervals between the end of treatment and the diagnosis of relapse were 31, 47, 53 and 58 months respectively, with a mean and median of 47 months. The original diagnoses in the relapsing patients were BL in 3 and LL in 1 patient. Two of the BL cases were new patients never treated before, the LL patient declared he had taken dapsone 3 years before for 3 months, one BL case was a patient relapsing after dapsone monotherapy.

In 2 of the BL patients relapse was signalled by the appearance of numerous small bright, red papules on an arm. Two *M. leprae* strains isolated from relapsing patients (both from 13-REC patients) were drug sensitive.

Among the group of 35 patients who erroneously received the lower dose of ETH, 2 died leaving 16 patients in the 13-RED group and 17 patients in the 13-REC group (Table 2). These patients have been followed for a total of 64 person years (mean 4 years) and 80 person years (mean 4·7 years) respectively. No cases of hepatitis were observed.

**Table 1.** Follow-up and incidence of relapses and late reversal reactions among patients treated with regimen 13-RED or 13-REC

| Years of follow-up | Number of patients seen | Person years of follow-up (cumulative) | Relapses (cumulative) | | | | Number of late reversal reactions |
|---|---|---|---|---|---|---|---|
| | | | Number | N | % | (95% CI) | |
| 1 | 434 | 434 | | | | | 4 |
| 2 | 390 | 824 | — | | | | 6 |
| 3 | 301 | 1125 | 1 | 1 | 0·08 | (0·00–0·50) | 7 |
| 4 | 215 | 1340 | 1 | 2 | 0·14 | (0·01–0·52) | 1 |
| 5 | 90 | 1430 | 2 | 4 | 0·28 | (0·08–0·99) | 2 |
| 6 | 6 | 1436 | — | 4 | 0·28 | (0·08–0·99) | — |
| Mean | | 3·3 | | | | | |

CI, confidence interval.

**Table 2.** Follow-up and incidence of relapses among 33 patients treated with either regimens 13-RED or 13-REC but with a reduced dose of ETH

| Years of follow-up | Number of patients seen | Person years of follow-up (cumulative) | Relapses | | | |
|---|---|---|---|---|---|---|
| | | | Number | Cumulative number | Incidence (%) | 95% CI |
| Regimen 13-RED | | | | | | |
| 1 | 16 | 16 | — | — | — | |
| 2 | 16 | 32 | — | — | — | |
| 3 | 13 | 45 | — | — | — | |
| 4 | 13 | 58 | 5 | 5 | 8·6 | 2·86–18·98 |
| 5 | 5 | 63 | — | 5 | 7·9 | 2·63–17·56 |
| 6 | 1 | 64 | — | 5 | 7·8 | 2·59–17·30 |
| Regimen 13-REC | | | | | | |
| 1 | 17 | 17 | — | — | — | |
| 2 | 17 | 34 | — | — | — | |
| 3 | 16 | 50 | — | — | — | |
| 4 | 16 | 66 | — | — | — | |
| 5 | 13 | 79 | — | — | — | |
| 6 | 1 | 80 | — | — | — | 0–4·51 |

Five relapses were diagnosed, all occurring in the 13-RED group giving a relapse rate of 7·8 per 100 patient years of follow-up. The difference between the RED and REC groups is significant ($p=0{\cdot}036$) as is the difference between the RED group who received a reduced dosage of ETH and the RED group who received the regular dose ($p < 10^{-3}$). The intervals between the end of therapy and the diagnosis of relapse were 39, 41, 42, 46 and 48 months with a mean of 43 months and a median of 42 months. Two *M. leprae* strains from these relapsing patients have been isolated in mice and were sensitive to the drugs the patients had received.

## Discussion

Our previous studies[1–4] have shown that it is possible to treat MB leprosy successfully with combined regimens of either 1 year or 6 months duration. On this basis and with the hope of reducing the toxicity of the association RMP + ETH, the present regimen of 3 months duration was studied in which ETH and DDS or CLO are administered daily, but RMP only twice weekly, thus reducing the administration of the combination RMP + ETH to twice weekly instead of daily as was the case in the previous studies. Pooling the results from the 13-RED and 13-REC treatment groups, the relapse rate was 0·28 per 100 person years of follow-up after a mean follow-up period of 3·3 years, which suggests that it is possible to treat MB leprosy within a period of 3 months. We do not think that the single dose of 1500 mg RMP that 9·7% of the patients received at 2 to 12 months before the start of the treatment profoundly influenced the results. Two of the 4 relapses manifested as small, bright red, papules, corresponding to what has been described by Ridley as exacerbation nodules.[8]

The incidence of hepatitis was only reduced to 3·2%, not statistically different from

that in the longer duration regimens:[5] 14/439 versus 23/515 $p$:0·41). No hepatitis was seen among the 33 patients treated with a reduced dose of ETH, the difference with the patients who received the regular dose of ETH is highly significant ($p < 0{\cdot}001$) but the reduced dosage of ETH resulted in a much higher incidence of relapses in the RED combination.

The unplanned observation of the 33 patients who received a reduced dose of ETH in error clearly illustrates two other points—the necessity besides RMP, for a second bactericidal drug, of appropriate dosage, in the treatment of MB leprosy and the higher efficacy of CLO as compared with DDS in the triple combination. The mean interval between the end of treatment and the diagnosis of relapse was 45 months. Relapses were all clinically evident and confirmed by bacteriology and histopathology, no cases were detected by the laboratory before they were clinically evident. Relapses were not due to the selection of drug-resistant organisms.

The overall incidence of late reversal reactions was 1·39 per 100 patient years of follow-up and remained fairly constant. Clinicians should be well informed about this late complication, the distinction between late reversal reaction and MB relapses being easily documented by bacteriological and/or histological examination.

The main conclusion from the present study is that it is possible to cure MB leprosy by a treatment regimen of 3 months duration, provided bactericidal drugs are given in adequate dosage. With the advent of newer and more potent drugs and hopefully less side-effects such as quinolones and/or minocycline[9,10] the future of short-course treatment regimens in MB leprosy looks very promising.

## Acknowledgments

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## Traitement de la lèpre multibacillaire par un régime de 13 semaines

S R Pattyn, G Groenen, L Janssens, L Kuykens et L B Mputu

*Résumé* Lors d'une étude prospective, 559 patients multibacillaires du Zaïre furent traités pendant 13 semaines à la rifampicine (600 mg) deux fois par semaine, à l'éthionamide (500 mg) et à la dapsone (100 mg) par jour, 13-RED, ou à la clofazimine (100 mg), 13-REC. Les patients furent suivis pendant un total de 1418 années-patients, la moyenne étant de 3,3 ans. L'incidence d'hépatite était de 3,2%. L'incidence de récidive était de 0,28 par 100 années-patients. Les récidives étaint dues à des organismes sensibles aux médicaments.

Chez les patients ayant reçu le même régime mais avec réduction de la posologie de l'éthionamide à 5 mg/k du poids corporel, l'incidence d'hépatite était nettement inférieure mais le taux de récidive était de 7,8% par 100 années-patients dans le cas du groupe RED suivi; aucune récidive ne fut diagnostiquée dans le groupe REC.

On en conclut que l'utilisation des médicaments très actifs contre la lèpre en association et suivant la posologie appropriées permet de réduire de 3 mois la durée du traitement antibactérien en cas de lèpre multibacillaire.

## El tratamiento de la lepra multibacilar con un regimen de 13 semanas

S R Pattyn, G Groenen, L Janssens, L Kuykens y L B Mputu

*Resumen* En un estudio eventual, se trataron 559 pacientes multibacilares en Zaires por 13 semanas rifampicina (600 mg) dos veces por semana y dosis diarias de etionamida (500 mg) y dapsona (100 mg), 13-RED, o de clofazimina (100 mg), 13-REC. Se controlaron los pacientes por un tiempo total de 1418 personas-año, con un promedio de 3,2 años. La incidencia de recaídas fue 0,28 por cada 100 personas-año. Las recaídas se debían a organismos sensibles a las drogas.

En los parcientes que recibieron los mismos regimenes de drogas, pero con una dosis reducida de etionamida de 5 mg/kg de peso, la incidencia de hepatitis fue significativamente inferior, pero la tasa de recaída era 7,8 por 100 persona-año en la continuación de estudio del grupo RED, mientras que no hubieron recaídas en el grupo REC.

La conclusíon fue que, usando potentes drogas antileprosas en combinaciones y dosis adecuadas, era posible reducir la duración del tratamiento antibacteriano en la lepra multibacilar a un período de 3 meses.

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# Red discoloration of the sputum by clofazimine simulating haemoptysis—A case report

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*Summary* A patient of lepromatous leprosy, who received a high dose of clofazimine as part of multidrug therapy, for chronic erythema nodosum leprosum (ENL) had frequent 'haemoptysis'. The haemoptysis was later found to be due to expectoration of clofazimine. This interesting, and perhaps first case of such an occurrence, is reported.

## Introduction

In January 1989 AA, A 17-year-old slightly-built male tailor, was first seen in the clinic with a 2-year history of a hypopigmented macule over the abdomen. The lesion had regressed without any specific treatment. For the previous 5–6 months the patient had had about 5 recurrent attacks of erythema nodosum leprosum (ENL), which lasted between 10 and 30 days. These reactional episodes were controlled by steroid tablets—2–8 per day with occasional steroid injections that were prescribed by local GPs. This treatment produced a temporary remission each time. New attacks occurred whenever the therapy was stopped. His brother has lepromatous leprosy, and almost certainly the mother had the disease too.

When he was examined, there was a diffuse shine over his face, back and buttocks, together with symmetrical, painful, tender red papules and nodules over his back and the extensor sides of the proximal parts of the limbs. There was some thickening of his earlobes. He had symmetrical nerve thickening involving ulnar, radial-cutaneous, lateral popliteal and superficial peroneal nerves. The right ulnar nerve was grossly thickened, tender to touch, and firm. He had symmetrical impairment of sensations over distal parts of his limbs. Except for a mild right ulnar nerve weakness, he had no paralytic or secondary deformities. No systemic abnormality was found.

His skin smears were +3 (Ridley) and the response to Dharmendra lepromin antigen was negative at 48 hr. He was diagnosed as a subpolar lepromatous leprosy case with chronic ENL and was put on multidrug therapy (MDT) with clofazimine (CLO) 300 mg/day along with thalidomide (300 mg/day). By day 8, the reaction had subsided. The

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dosage of CLO was reduced gradually to 100 mg/day by the end of week 5, but the patient still suffered from recurrent pain in both ulnar nerves, with more pain on the right side. The right ulnar nerve was surgically decompressed. The patient improved and was discharged.

After approximately 10 months' treatment he complained of a cough with blood-stained sputum, and breathlessness, which had lasted for about 10 days. There was no history of fever, reduced appetite or loss of weight. His chest was clear; the sputum was negative for acid-fast bacilli (AFB), both on microscopy and Lowenstein–Jensen (LJ) medium culture. A chest X-ray showed no abnormality, ruling out pulmonary tuberculosis. His total leucocyte count was 8400 $cm^2$ (polymorphs 38%, lymphocytes 32% and eosinophils 30%—total eosinophil count of 2520/$cm^2$). No parasites were seen in the blood under the microscope and the red blood cell count was normal. We diagnosed a case of tropical pulmonary eosinophilia, so put the patient on diethyl carbamazime (DEC 300 mg/day), and within 10 days there was a temporary remission of dyspnoea and 'haemoptysis'. The above investigations were repeated (eosinophilia of 14%) and he was discharged with advice to continue DEC for 10 more days. He returned again 1 month later with the same problem of blood-stained expectorate; his results, except for a raised eosinophil count, were normal. There was no growth of bacteria on a LJ medium culture, which ruled out tuberculosis. Even though red, the sputum did not show any erythrocytes (by smear) or haemoglobin (by benzidine test). No abnormal cells were seen in the sputum, which ruled out malignancy. The sputum was subjected to a CLO test using the technique of Desikan & Balakrishnan.[4] The presence of CLO was checked by a high performance thin-layer chromatographic[6] procedure which showed that the reddish-brown streaks in the sputum (Figure 1) were caused by a large amount of CLO; this was confirmed by repeat sputum examinations. For the last 4 months of treatment CLO has been replaced by prothionamide, and the reddish streaks in the sputum decreased in the following month and have been absent for this 4-month period. However, a repeat sputum examination (4 months after stopping CLO) did show some needle-shaped CLO crystals, though the sputum was clear on gross examination. The clofazimine contents of saliva spat out was 0·082 $\mu$g per gram.

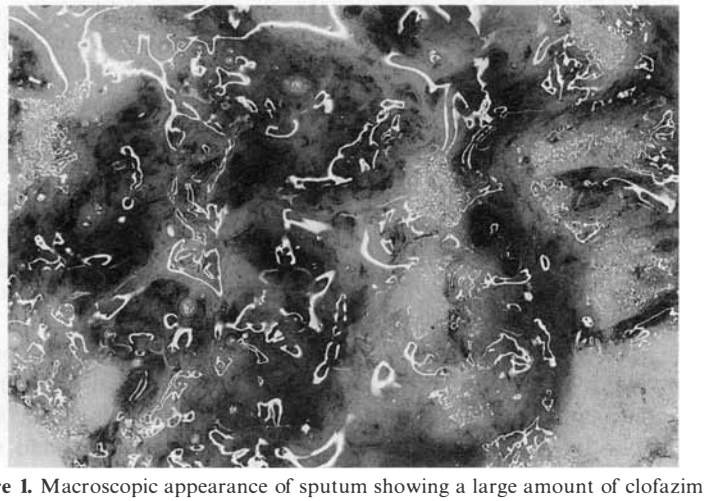

**Figure 1.** Macroscopic appearance of sputum showing a large amount of clofazimine.

## Discussion

Apart from being an effective antileprosy drug, clofazimine is also useful in the management of ENL reactions,[1] and is helpful in the withdrawal from steroids in steroid-dependent cases. However, since the anti-inflammatory effect of the drug is slow, a dose of about 300 mg/day has to be continued for a long time (about 8–12 weeks). In some reports, an even longer use of the drug in high doses was necessary to control recurrent ENL and/or steroid withdrawal.[2] It has been shown, both in mice[3] and in man,[4] that the distribution of the drug is very uneven throughout the body. In the skin itself, it is well known that the CLO levels are higher at sites of infiltration, where macrophages abound, as opposed to the uninfected skin of the same patients. Postmortem studies[4,5] have shown that the intestines and the reticulo-endothelial tissues have a far greater load of CLO than other tissues. Large amounts of CLO have been found to be deposited in the liver, gut and lung parenchyma. Concentrations in the lung of 17 mg/g of lung tissue have been reported.[4]

This patient had 'haemoptysis' after he had taken 34 g of CLO. As he did not show any particular CLO coloration of skin or symptoms suggesting any gut involvement, this suggests that in his case the lungs were possibly the site of the excessive CLO deposition.

Clofazimine is known to be taken up by macrophages in large amounts. Since lungs contain a large number of these cells, it is likely that the drug in the sputum came from lung macrophages. It is also possible that the patient had some lung parenchymal/alveolar damage which allowed macrophages containing CLO to escape into the bronchial tree and be coughed out with the sputum. These events appear to be episodic because the patient had a variable quantity of CLO in the sputum. In one period the patient coughed out about 4 g of sputum containing 0·298 mg/g of CLO, but at a different time, in over 24 hr, 50g of sputum only contained 0·098 mg/g, which shows the great variation in amounts.

To discover the source of this CLO discharge, bronchoscopy would have been the best method, but this was not done because it would have been invasive and not therapeutically useful to the patient. The saliva (collected after chewing sterile rubber) and the patient's gastric aspirate, which was removed 3 hours after the daily dose of CLO, were both free from CLO, therefore ruling out CLO discharge from anywhere but the lungs.

Because of 'haemoptysis' we ruled out tuberculosis, despite this being a very common problem in the tropics, especially in lepromatous patients on steroids. Another possibility, tropical pulmonary eosinophilia, was considered because the patient not only had blood-streaked sputum and mild dyspnoea but also eosinophilia. Also, the temporary remission with DEC further confused the issue. In retrospect, it seems increasingly likely that even the eosinophilia was caused by deposits of CLO in the tissues. Eosinophilia as part of eosinophilic enteritis due to deposits of CLO in the gut is well known,[7] and it is possible that similar deposits of CLO in lung parenchyma resulted in this patient's eosinophilia.

In conclusion, 'haemoptysis' in some patients with chronic recurrent lepra reactions, who are on a high CLO dosage, could be caused by the coughing out of this drug.

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## Coloration rouge des crachats par la clofazimine imitant l'hémoptisie: cas clinique

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*Résumé* Un sujet atteint de lèpre lépromateuse ayant reçu une dose élevée de clofazimine, dans le cadre d'une médication mixte contre la lèpre chronique de forme erythema nodosum leprosum (ENL), souffrait de fréquentes hémoptisies. On a découvert plus tard que cette hémoptisie était due à des expectorations de clofazimine. Ce cas intéressant est peut-être le premier cas de cette espèce signalé.

## Una descoloración roja del esputo causada por clofazimina que simula a la hemoptisis

A Girdhar, K Venkatesan, S L Chauhan, G N Malaviya y B K Girdhar

*Resumen* Un paciente con lepra lepromatosa, que recibió una elevada dósis de clofazimina como parte de una terapia multidroga para el tratamiento de eritema nodosum leprosum crónica (ENL) sufría de una frecuente hemoptisis. Más tarde, se descubrió que la hemoptisis se debía a la expectoración de clofazimina. Se señala este interesante, y posiblemente primer, caso.

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# Community-based rehabilitation: an evaluation study

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*Summary* Leprosy gives rise to two types of stigmatization, one from the disease and its neuropathetic manifestations, with their resultant disability and handicaps, and the other due to social ostracism.

The process of rehabilitation should begin from the moment the disease is diagnosed, and the earlier its detection the better the prognosis for patients.

The family unit to which the patient belongs plays a vital role in his social life, ensuring and enhancing his self-respect and dignity in society, and this fact must be recognized when evolving a strategy for rehabilitation. In no circumstances should a patient be removed from his natural home environment.

It is important that the community is made leprosy conscious and gets more involved in hastening the social assimilation of patients. Communication plays an important role throughout the rehabilitation process. One of the major functions is the removal of the social stigma in the family and in the community and this involves communication skills to ensure interaction between the staff and patients' families and the education of the community.

A highlight of community-based rehabilitation is the excellent rate of repayment of loans by the patients to whom they were made. Also of note is the extent to which former defaulters make repayments due to the continous rapport and good interpersonal relationship between the staff and patients.

Most of the subjects of this study were drawn from the lower economic strata of society and for them the most essential consideration is to make a living, however meagre. This problem is augmented in the case of leprosy sufferers, not only because of the fear and hostility which their disease excites in others, but because of their deformity and handicap. No rehabilitation programme can afford to ignore these factors which so seriously disturb the normal life of patients.

## Introduction

For centuries, rehabilitation was considered merely as an act of charity. Tracing the history of rehabilitation in leprosy we find that it originated in the 14th century in Europe and then spread to other countries. At that time the Order of Lazarus was founded to help

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leprosy sufferers; there was no effective treatment and they were treated as outcasts and were given horns, clappers and bells and known as 'horn brothers'.

Historically therefore the Lazarus homes of 14th century Europe were the forerunners of the present rehabilitation homes and projects. Times have changed. Today medical treatment combats the vagaries of leprosy, the drugs are readily available and have been proved effective and the disease can be cured and its spread contained. The principles of reconstructive surgery applied in other spheres have been tried in leprosy and found successful. Consequently, these developments have together revolutionized both the prognosis for the individual patient and public opinion concerning leprosy and the rehabilitation of those who suffer from it. Rehabilitation is now considered an essential component of the health care delivery system designed for the management and control of leprosy and, following modern scientific and technological advances, it has incorporated an element of social science, drawing up an objective and realistic plan of action for every patient from the moment he is diagnosed and registered for treatment. This plan goes hand-in- hand with all therapeutic and surgical procedures and forms an essential thread running through the whole treatment and eradication programme.

**The present study: its background and purpose**

In the Greater Madras Leprosy Treatment and Health Education Scheme (GREMALTES) large numbers of patients were registered, and it became necessary to include rehabilitation as a component in the scheme. The total number of cases in 1971–74 was 12,000 and by 1983 this had risen to 27,000. The German Leprosy Relief Association (GLRA) made a study of the conventional rehabilitation centres colonies, sheltered workshops and infirmaries, which have huge capital and recurrent financial expenditure. The institutionalization of leprosy patients was seriously questioned because of the detrimental effect of such segregation and isolation on their personality. After weighing up all the pros and cons, the GLRA conceived a new concept: domiciliary or community-based rehabilitation. A proposal was submitted by the Regional Secretariat of GLRA in India to the headquarters in Germany and they agreed to finance a pilot programme in the City of Madras. A new society, the 'German Leprosy Relief Association Rehabilitation Fund' was registered in India under the Societies Registration Act.

The aim of the rehabilitation scheme was to create opportunities for self-employment, open employment or job placement and jobs in sheltered workshops. Added to this was financial assistance to the relatives of the patients with severe disabilities unable to work to help them start in trade or to find employment, so that they could support the disabled—this was known as 'indirect rehabilitation'.

The GLRA provided the necessary core fund to give interest-free loans to patients to help them start new trades or occupations and in due course the nationalized banks came forward to give loans at a low rate of interest to patients recommended by the social workers in the programme.

Training and placement activities were also undertaken. The social workers were in contact with various job training centres and small industrial units and were therefore able to get patients trained and employed. The scheme also undertook the education of the children of patients, and service clubs—like the Rotary and the Lions—came forward to support this.

Recognizing the potential advantage of the association of social science with leprosy control, the GLRA found a role in the programme for qualified social workers and they have proved to be useful members of the team by virtue of their professional training and interdisciplinary approach to problems and the ways and means of solving them.

The study was designed to evaluate the impact of the programme and to assess the associated problems in Madras City in the period 1974–83.

## The selection of the study group

From the beginning of 1974 to 1983, a total of 972 leprosy patients were rehabilitated under this programme:

| | |
|---|---|
| Self-employment through GLRA funds | 407 |
| Self-employment through nationalized banks | 202 |
| Open employment and sheltered workshops | 363 |
| Total | 972 |

Out of this total, 78 were selected by a stratified random sampling method. A numbered list was obtained from the scheme and the first batch were drawn by lot. Every tenth person was selected from the self-employed group and every twentieth from the open employed group (see Table 1).

## Data collection

The rehabilitated patients were the primary source of data and the social and follow-up workers were the secondary source. The files, records and books maintained in the office were the documentary source.

As many patients were illiterate and needed an interpretation and explanation to some of the questions an interview schedule was used. An interview guide was used to collect data from the staff. Both these tools were finalized only after a feasibility study involving field visits and discussions with rehabilitation officers and others and pretesting on 6 persons, 2 from each group.

**Table 1.** Number of patients in evaluation study

| Programme | Number | Percentage |
|---|---|---|
| Self-employed with GLRA funds | 40 | 51·28 |
| Self-employed through nationalized banks | 20 | 25·64 |
| Open employment | 12 | 15·39 |
| Sheltered workshops | 6 | 7·69 |
| Total | 78 | 100·00 |

The data collection was by interviewing patients in their homes or places of work. The evaluation was limited to rehabilitated patients and did not include beneficiaries under the 'indirect rehabilitation scheme', i.e. the relatives of patients.

It can be seen in Table 1 that more than half of the group were rehabilitated through the self-employment scheme funded by GLRA, while the banks helped just over one quarter. The other programmes helped some 15% and 7·5% respectively.

## Evaluation of the impact of the programme

Sex: There were 61 males and 17 females.

Age: 46 (59%) were in the age group 21–40 and 29 in the 41–50 and above age group; 75 were over 31 years of age. The programme was open to all irrespective of age and sex.

Marital status: 56 (71·79%) were married, 13 (16·67%) unmarried, 5 were widowed and 4 separated.

Education: 21 (34·62%) had primary school education, 20 (over one quarter) secondary, 9 (11·54%) high school and only 3 had university education. However 19 (24·35%) were illiterate.

Duration of the disease: 51 (65·38%) had had leprosy for over 10 years, 20 between 5 and 10 years and 7 for less than 5 years.

Treatment status: 67 (85·9%) were still under treatment and the remainder having completed the prescribed course of chemotherapy had stopped treatment on the advice of their doctor.

Family size: In 30 there were less than 3 family members, in 36 4–6 members and in 12 there were more than 6 members.

Leprosy in the family: 66 (84·62%) said that no one else in the family was affected and 12 that there were one or more other cases.

## Reactions of the patients to the disease

### *At the time of diagnosis*

Only 6 were reconciled to the fact that they had leprosy, 29 were unhappy and expressed sorrow about it and 4 did not accept the diagnosis. Twenty-one considered themselves neglected by others and 18 had suicidal feelings. Generally these reactions were an indication of their underlying fear and irrational attitude.

### *After rehabilitation*

Sixty have accepted the fact that they have to live with their disease, the remaining 18 are still not reconciled to it even after rehabilitation. Possibly this is the same group that had suicidal feelings at the time of diagnosis. It is a sad irony indeed that the programme has not helped them change their attitude.

## Respect and recognition in the family

Before rehabilitation 65 (83·3%) were respected and 13 (16·67%) were not.

After rehabilitation 74 (94·87%) were respected and only 4 were not. It appears

therefore that the programme has enhanced the level of respect accorded to leprosy patients in their family.

### Occupational status

Before rehabilitation 21 (26·97%) were unemployed and a further 7 lost their jobs. Fifty patients had various occupations.

After rehabilitation none was unemployed and all had some kind of occupation. An essential aspect of the programme involved change and adaptation of occupation to take account of the physical condition of the patient, his handicap and in addition his aptitude. The social workers played a key role in motivating patients to accept such changes for their own good, so helping them to live with their disability.

### Economic benefit

The applications of loans made available to patients were:

| | | |
|---|---|---|
| to reactivate traditional occupations: | 8 | (13·33%) |
| to start new business: | 32 | (53·34%) |
| to improve old business: | 20 | (33·33%) |
| Total | 60 | (100·00%) |

The average monthly income of the patients before and after rehabilitation is shown in Table 2.

It is of note that more than one sixth of the group had no income whatever before rehabilitation. Certain changes can be seen; while the percentage of those earning less than RS 200 per month has come down from 51·29 to 15·38%, those earning up to RS 399 per month has increased from 15·38 to 44·88%, those earning up to RS 599 per month has increased from 8·97 to 21·7% and those earning RS 600 and over per month has increased

**Table 2**

| Income (Indian Rupees)* | Before rehabilitation | | After rehabilitation | |
|---|---|---|---|---|
| | Number | (%) | Number | (%) |
| Nil | 12 | 15·39 | 6 | 7·69 |
| Less than 200 | 40 | 51·29 | 12 | 15·38 |
| 200–399 | 12 | 15·38 | 35 | 44·88 |
| 400–599 | 7 | 8·97 | 17 | 21·79 |
| 600 and above | 7 | 8·97 | 8 | 10·26 |
| Total | 78 | 100·09 | 78 | 100·00 |

* 1 US$ = RS 10.40 in 1982.

**Table 3**

| Value of assets (Indian Rupees) | Before rehabilitation | | After rehabilitation | |
|---|---|---|---|---|
| | Number | (%) | Number | (%) |
| No assets | 46 | 58·97 | 19 | 24·35 |
| Less than 10,000 | 11 | 14·10 | 17 | 21·80 |
| 10,001–20,000 | 13 | 16·67 | 19 | 24·35 |
| 20,001–30,000 | 8 | 10·26 | 6 | 7·70 |
| 30,001 and above | 0 | 0 | 17 | 21·80 |
| Total | 78 | 100·00 | 78 | 100·00 |

from 8·97 to 10·26%. There has clearly been an all-round improvement in the level of income and earning capacity after rehabilitation: however there are disappointing failures, notably 7·6% of patients still had no income after rehabilitation.

The value of the patients' assets before and after rehabilitation is shown in Table 3. It is observed that more than half did not have any assets whatever before rehabilitation, but that this proportion was appreciably reduced afterwards (from 58·97 to 24·35%). Increases are observed at all levels, but of special note is that before rehabilitation there were no patients with assets in excess of 30,000, but afterwards there were 17. This indicates that rehabilitation enabled patients with some income to augment them considerably.

### THE LOANS MADE AVAILABLE

Of 60 patients studied, 40 with loans from GLRA and 20 with loans from nationalized banks, 31 were regular in repaying the loan and 29 were iregular.

Of 60 patients receiving loans from either GLRA or the banks 42 were satisfied and 28 were dissatisfied with the scheme. The reasons for dissatisfaction were insufficiency of the amounts advanced to meet all their needs and expectations.

### SAVINGS AFTER REHABILITATION

Twenty-three patients, a little over one quarter of the group, said they were able to save, but 55 said they could save nothing from their income.

### HOUSING

The study showed that before rehabilitation 39 were living in rented houses, 23 in their own houses, 3 in slum clearance board tenements, 9 in houses built on unauthorized land and 4 in leprosy beggar rehabilitation homes. After rehabilitation 39 were staying in rented houses. There was a marginal increase in the number of those owning houses—from 23 to 31. The number of patients living in slum clearance board tenements came down to 2, those living in houses built on unauthorized land came down to 6 and the 4

patients living in the leprosy beggar houses found housing elsewhere. This shows a marked improvement in housing after rehabilitation.

PROBLEMS ENCOUNTERED BY THE BENEFICIARIES

*Under the self-employment scheme:* 23 had no problems, 12 had an inadequate income, 9 complained of lack of help from other family members, 7 expressed unsteady business and 9 had health problems.

*Under the open-employment and sheltered workshop scheme:* 10 had no problems, but the remaining 8 had various complaints: a high workload for low pay, irregular work and difficulties with management.

## Effectiveness of the scheme

Forty said it was effective in helping them meet the needs of their entire family, 14 found it partially effective for family needs, 12 effective for individual needs only and 12 found it ineffective.

## Helpfulness of the rehabilitation department

Fifty-nine found the services helpful, 10 very helpful and 3 extremely helpful. Only 6 said that they were not helpful (inevitably there are always some who cannot be satisfied).

**Table 4.** German Leprosy Relief Association Rehabilitation Fund, Madras/India, 1974–83. Number of patients rehabilitated under various schemes

| No. | Centre | Year established | Loans through GLRA | Loans through banks | Job placements | Other welfare | Total |
|---|---|---|---|---|---|---|---|
| 1 | Madras (urban) | 1974 | 407 | 202 | 363 | 591 | 1563 |
| 2 | Vishakapathnam (urban) | 1974 | 100 | 27 | 97 | 299 | 523 |
| 3 | Jhargram (rural) | 1974 | 11 | — | — | — | 11 |
| 4 | Kumbakonam (rural) | 1979 | 132 | 176 | 107 | 405 | 820 |
| 5 | Pullambady (rural) | 1979 | 103 | 28 | 6 | 993 | 1130 |
| 6 | Chettupattu (rural) | 1979 | 173 | 3 | 11 | 16 | 203 |
| 7 | Bombay (urban) | 1980 | 118 | 8 | 13 | 35 | 174 |
| 8 | Tutucorin (rural) | 1981 | 25 | 6 | 11 | 9 | 51 |
| 9 | Nilakottai (rural) | 1983 | 35 | — | — | — | 35 |
| 10 | Palamner (rural) | 1983 | 22 | — | 5 | — | 27 |
| 11 | Bijapur (urban) | 1983 | — | 27 | — | — | 27 |
| Total | | | 1126 | 477 | 613 | 2348 | 4564 |

*Note:* Other welfare activities: include education of the leprosy patients and other needs.

**Social consequences of rehabilitation**

Sixty-seven patients of this study were undergoing treatment and included both infectious and noninfectious types of leprosy and some with deformities and handicaps. Before rehabilitation, some were employed in various services, some self-employed and some unemployed. A change of occupation had been necessary in some because of their physical disability or the attitude of the coworkers to their disease. As a result they suffered a reduction in their income and in some cases were unemployed at the time of rehabilitation. In a typical case, a father with family responsibilities, soon after becoming aware of having leprosy not only loses his job but also his self-confidence and interest in his family. As his income falls, his dependence on the help and charity of his already poor relatives increases, until his situation becomes desperate. It is at this point that the GLRA Rehabilitation Scheme is of obvious and dramatic benefit.

**The extension of the rehabilitation programme**

Following the encouraging results of this scheme in Madras, similar projects were developed between 1974 and 1983 in 4 urban areas and 7 rural areas in India, assisting a total of 2216 leprosy patients. Details are given in Table 4.

## Réadaptation au sein de la communauté: une évaluation

W Gershon et G R Srinivasan

*Résumé* La lèpre cause deux types de stigmatisation, l'une due à la maladie et à ses manifestations neuropathiques avec pour résultat infirmités et handicaps et l'autre causée par l'ostracisme social. Le processus de réadaptation doit commencer dès que la maladie est diagnostiquée et le pronostic des patients est d'autant meilleur que la maladie est dépistée dans les premiers stages. La cellule familiale du patient joue un rôle prépondérant dans sa vie sociale; elle garantit et renforce le respect qu'il a de lui-même et sa dignité au sein de la société. Il faut en tenir compte lors de la mise au point d'une stratégie de réadaptation. En aucun cas faut-il enlever un patient de son cadre familial naturel. Il est important que la communauté prenne conscience de la lèpre et s'efforce d'accélérer l'assimilation sociale des patients. La communication joue un rôle important dans le processus de réadaptation. Une des tâches les plus importantes est le retrait du stigmate social au sein de la famille et de la communauté et ceci nécessite des compétences en matière de communication qui garantissent une interaction entre le personnel et la famille du patient et l'éducation de la communauté.

Le grand nombre de prêts remboursés par les patients auxquels ils avaient été accordés, constitue une des réussites de la réadaptation au sein de la communauté. Il convient également de noter l'ampleur des remboursements effectués par les débiteurs, résultat des rapports continus et des bonnes relations entretenues entre le personnel et les patients.

La plupart des sujets de cette étude appartiennent aux groupes socio-économiques les moins privilégiés et ce qui leur importait le plus c'est de gagner leur vie, aussie lamentable soit elle. Ce problème est exacerbé dans le cas des lépreux tant à cause de la peur et de l'hostilité que leur maladie suscite qu'à cause de leurs difformités et handicaps. Aucun programme de réadaptation ne peut se permettre d'ignorer ces faits qui affectent profondément la vie quotidienne des patients.

## La rehabilitación basada en la comunidad: un estudio de evaluación

W Gerson y G R Srinivasan

*Resumen* La lepra produce dos tipos de estigmatización: una que resulta de la enfermedad y sus manifestaciones neuropatéticas, con la incapacidad y minusvalía que resultan, y la otra, debido al ostracismo social. El proceso de rehabilitación debe comenzar en el momento del diagnóstico de la enfermedad, y cuando antes se detecta mejor resulta el prognosis para el paciente. La unidad familial a la cual pertenece el paciente juega un papel vital en su vida social, asegurando y realzando su amor propio y su dignidad en la sociedad, y se debe reconocer este hecho cuando se prepara una estrategia para la rehabilitación. Jamás se debe retirar el paciente de su ambiente natural de casa. Es importante que la comunidad se haga más consciente de la lepra y se implique más en acelerar la asimilación social del paciente. La comunicación jeuega un papel importante en todo el proceso de asimilación. Una de las funciones más importantes es eliminar el estigma social en la familia y en la comunidad, y esto requiere habilidades de comunicación para asegurar una interacción entre el personal y las familias del paciente, y la educación de la comunidad.

Un punto sobresaliente de la Reeducación basada en la Comunidad, es la excelente proporción de reintegros de parte de los pacientes que los recibieron. También es importante el número de incumplidos que reembolsaron posteriormente, debido a la buena compenetración que existe entre el personal y los pacientes.

La mayoría de los pacientes que participaron en este estudio fueron de niveles económicos inferiores de la sociedad, y para ellos lo mas esencial es ganarse la vida, por pobre que sea. Este problema es mas serio en el caso de los que sufren de la lepra, no solamente por el temor y la hostilidad que estimula su enfermedad en los demás, pero también por su deformidad y minusvalía. Ningún programa de rehabilitación puede pasar por alto estos factores que en forma tan seria trastornan la vida normal de los pacientes.

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*SPECIAL ARTICLE*

# Early detection of damage to nerves in leprosy

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*Summary* Methods of examining and diagnosing damage to nerves commonly involved in leprosy are described. The equipment used is inexpensive, gives reliable and repeatable results and is useful in making objective assessments in terms of function in everyday living.

## Introduction

The severe disability and disfigurement resulting from the destruction of tissues by leprosy is exacerbated by the involvement of nerves. Early signs of neural involvement may be insidious and overlooked, but prompt detection and vigorous treatment of the disease in its reactional stage are essential if it is to be cured and disability avoided or minimized.

In the majority of cases there is no spontaneous pain[1] although numbness and tingling may occur. Weakness may be minimal and sensory loss dissociated in the early stages with loss of protective pain preceding loss of other modalities.[2] Patients may not only be unaware of minor alterations in function, but also may be reluctant to acknowledge them, because they fear isolation and prejudice. The need to publicize the feasibility of correcting deformities and the possibility of cure with early and conscientiously carried out treatment cannot be overemphasized.

Easily performed and rapid field tests of the function of the six nerves most commonly affected in leprosy were described by Fritschi,[3] who stressed the need for referral to an established centre for more detailed testing. The purpose of this paper is to outline such procedures and to draw attention to anomalies[4,5] and trick movements which may deceive the experienced and inexperienced.

## General considerations

Thorough examination is simple but time consuming and demands concentration by both the examiner and patient. Patients should be able to sit or lie down in comfort in a quiet and well-lit room. For bare-footed patients washing the feet is not only more comfortable, but also softens the skin. Patients should not be hungry, thirsty, or in need of the toilet.


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Ample time must be allowed for explanations and for listening to the patient's history and progress.

## EQUIPMENT

Inexpensive and reliable equipment for testing the thresholds of modalities of touch, and pain, is illustrated in Figure 1. Discrimination of textures can be assessed by using standard graded sandpaper; two-point discrimination can be measured with fine calipers and a steel rule marked in centimetres and millimetres. Testing for deep pain by needles is inappropriate, especially on the feet if the patient is habitually bare footed. Deep sensation might be tested by asking patients to walk on special mats covered with smooth pebbles of graded sizes, or by the use of calibrated pressure recording appliances. Battery operated pocket apparatus for testing thermal sensibility has been described by Srinivasan & Strumpe.[2] Intensities and rates of vibration can be measured either with a vibrometer,[6] or else tuning forks can be used. Simple electrical stimulation demonstrates the presence or absence of nerve conduction and is valuable in detecting anomalous innervation and the block to conduction in early involvement of nerves.[7] Precise measurements of rates of nerve conduction and electronmyography are objective tests and are desirable for critical assessment and research in specialized centres.

## RECORDS

The history should include the patient's age, sex, occupation, family history and possible contacts who should be traced, examined, and followed up. Symptoms should be described in the patient's own words. If they are inarticulate from fear or lack of education, questions should be helpful, but never direct, e.g. 'Is your hand as strong as it always was, or is it weaker?' is preferable to 'Have you noticed any weakness?' It is particularly important to avoid influencing suggestible individuals when discussing early sensory symptoms and signs of motor dysfunction.

A well-thought-out protocol is essential for assessing progress and planning reconstructive surgery. The power of individual muscles[8] should be graded and recorded on charts. The Medical Research Council scale is useful and simple to apply:

0, complete paralysis; 1, flicker of contraction but no movement; 2, movement of joint with gravity eliminated; 3, movement against gravity but not resistance; 4, movement against gravity and resistance, but weaker than normal; and 5, indistinguishable from normal.

From the practical point of daily living, manipulation of test objects such as those illustrated in Figures 2 and 3 is useful[9–11] and is helpful in rehabilitation since the optimum size of handles for tools can be found for each individual. In every case, contralateral parts of the body should be tested.[6] Sensory loss or abnormality can be mapped, and in the absence of photographs, indicated on dated charts. Tests should be demonstrated first on the examiner's own hand, then on a normal part of the patient's body whilst his eyes are open. The suspected and contralateral areas are examined with the patient's eyes closed or shielded. Allow frequent short pauses for relaxation.

Autonomic function can be recorded either qualitatively or quantitatively by noting the colour, temperature and moisture of skin. Skin resistance is measured by a

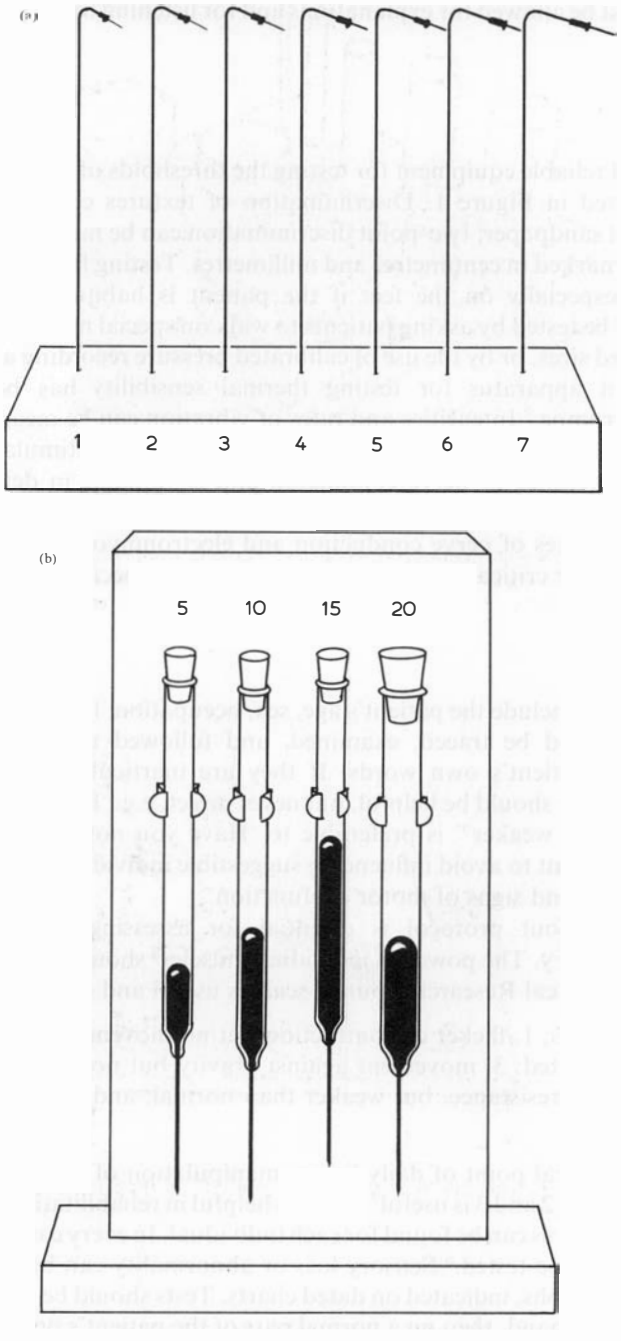


**Figure 1.** (a) Home-made *vs* Frey hairs (as modified by the late G Weddell). These graded suture materials are mounted on spokes of bicycle wheels which are angulated. 1 cm lengths project freely. To conform with previously recorded work[18] No. 3 should be equivalent to 1 g pressure. Other grades should be noted and calibrated on an accurate balance and replaced at intervals. (b) Cutting needles are mounted on weights of 5, 10, 15 and 20 g which run freely, either in glass tubing, or better still, rigid polythene tubes.

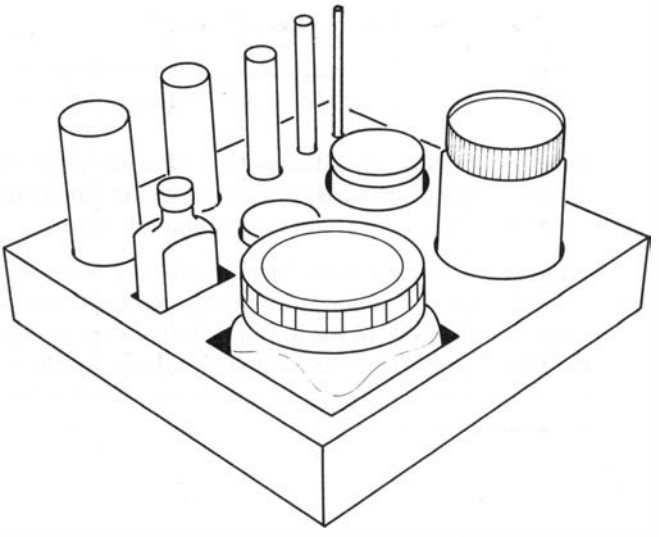

**Figure 2.** Home-made equipment, wooden rods of different diameters, test the optimum size of handles for tools, also timed taking and replacing in the slots can give semi-objective test of dexterity. Square jars in square holes are useful for patients who are either one-handed, or who have very weak hands.

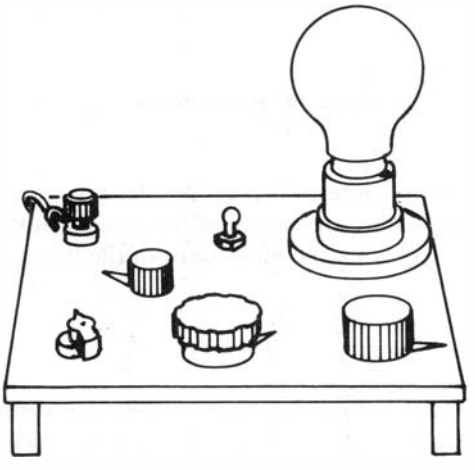

**Figure 3.** Light bulbs require precision for engaging lugs, power for seating in sockets. The knobs and switches require precise manipulation.

dermometre which is a simple and inexpensive instrument consisting of an ohmmeter, an indifferent electrode and a mapping one with a head of $\frac{1}{2}$ to 1 cm diameter. In hot climates sweating is often visible and there is no need for ninhydrin or quinizarin tests. It can be enhanced by application of a sphygomamometer, inflating the cuff above systolic pressure for 1–2 min.[12]

EARLY SYMPTOMS AND SIGNS OF NEURAL INVOLVEMENT

Spontaneous discomfort or pain may be aggravated by movement of related joints or muscles, and there may be localized tenderness and swelling of the nerve and referred paraesthesia.

2 Partial and developing sensory loss are often associated with spontaneous tingling in the distribution of the nerve 'like insects crawling over the skin' and with hyperaesthesia which feels 'uncomfortable', 'nasty' or 'unlike anything felt before'.

Parts of limbs may feel heavy or even absent. Movement may become clumsy, and the subject became tired too quickly, or suffer from cramp. Cramp, occasionally spontaneous, may waken a patient from sleep. In the lower limb there are alterations in gait and weight bearing.[13,14] Weakness and fully developed paralysis results in characteristic paralytic deformity due to imbalanced activity of unaffected muscles. An early sign is the inability to sustain an end position.

OBJECTIVE CHANGES IN SKIN

These are varied; there may be altered pigmentation; transient hyperhydrosis, hypo- or anhydrosis; altered colour and temperature due to vasomotor disturbance. In long-established cases the pulps of fingers and toes may atrophy, with alterations in curvature and thickness of nails and flattening and blurring of papillary ridges. Loss of sensation increases the risks of painless ulceration, burns and secondary infection with a devastating loss of tissue.

## Early symptoms and signs of damage to specific nerves

THE ULNAR NERVE

Damage, with or without a tender swelling, commonly occurs at or just above the posteromedial aspect of the elbow, or just above the anterior surface of the wrist, or in the dorsal cutaneous branch supplying the inner third of the hand, the little finger, and half the ring finger.

### *History*

With high lesions, sensory disturbance is found on palmar and dorsal surfaces of the inner third of the hand and medial $1\frac{1}{2}$ digits. Symptoms are increased by the stretching of the nerve, by flexion of the elbow and by compression in the cubital tunnel during active ulnar deviation of the wrist. The dorsal branch escapes in lesions at the wrist. Whatever the level of damage, there is increasing weakness and fatigue of sustained grip and clumsiness of skilled and precise movement of the fingers; implements tend to slip from the hand; turning off taps, wringing out towels and loosening tops of jars become difficult. Clawing of fingers impedes removing things from pockets.

### *On Examination*

The early paralytic deformity and later wasting of intrinsic muscles of the hand, especially the first dorsal interosseous, are characteristic. Clawing is less pronounced in higher than

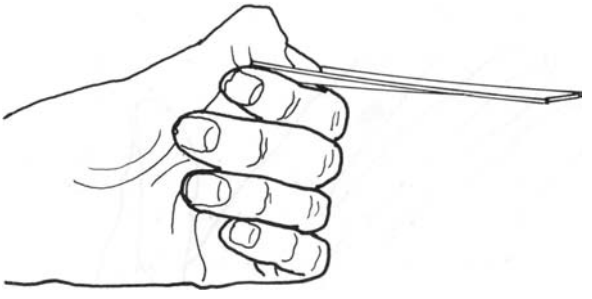

**Figure 4.** A positive Froment's sign using flexor pollicis longus instead of adductor pollicis.

in lower lesions where flexor digitorum profundus is unaffected. The hypothenar eminence and medial aspect of the thenar eminence overlying adductor pollicis are soft in early paralysis and atrophied later. The distal transverse metacarpal arch is lost, or diminished at rest, and this loss is accentuated when attempting to extend the fingers of the outstretched hand. Active adduction of fingers is lost, but trick abduction is possible due to the pull of divergent tendons of the long extensors. The paralytic abduction deformity of the little finger is one of the earliest signs to appear and the last to disappear in recovery as the small fourth palmar interosseous has to counteract the long flexors and extensors and abductor minimi digiti. Adduction is tested by slipping a sheet of paper between fingers and asking the patient to resist when it is pulled away. Loss of adductor pollicis can be compensated by trick flexion of flexor pollicis longus (Figure 4). Straight finger flexion at the metacarpophalangeal joints is only possible with intact ulnar intrinsic muscles (Figure 5).

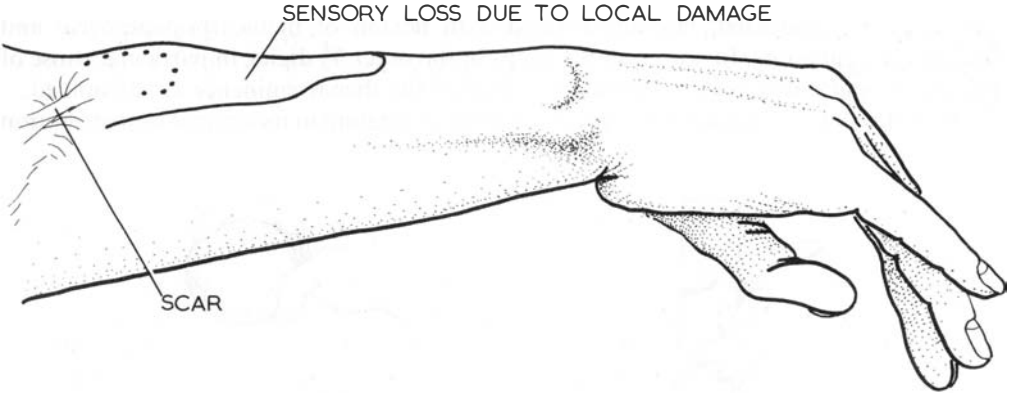


**Figure 5.** Paralysis of posterior interosseous branch of the radial nerve; note persistent extension of interphalangeal joints and inability to extend metacarpophalangeal joints.

## THE MEDIAN NERVE

The common site of damage is just above the wrist crease.

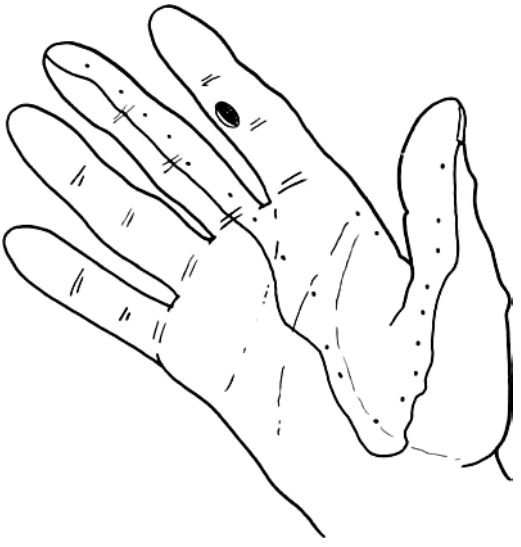

**Figure 6.** Anomalous sensory supply with a complete division of the median nerve; note the deep painless burn.

*History*

In such low lesions knocks and chaffing by coat cuffs can produce tingling in the hand and outer $3\frac{1}{2}$ digits. Increasing difficulty is experienced in picking up small objects, doing up buttons, holding a pen or small tool, putting keys into locks, threading needles, and recognizing coins in pockets.

*On examination*

The thumb is adducted, laterally rotated with flexion of metacarpophalangeal and interphalangeal joints. In late cases the pulps of the outer $3\frac{1}{2}$ digits, in particular those of the thumb and index finger, and the outer half of the thenar eminence are atrophied.

Palpation of the swollen nerve produces pain or tingling in its cutaneous distribution

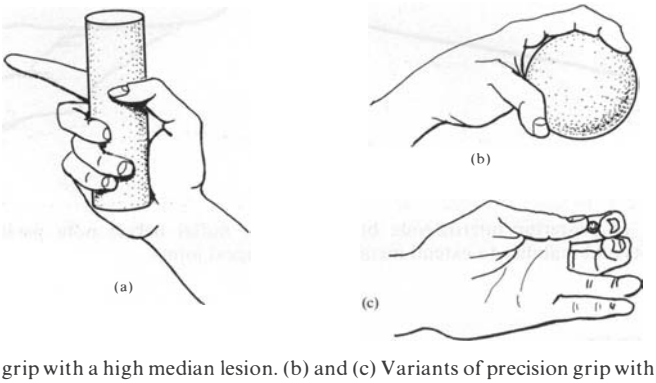


**Figure 7.** (a) Power grip with a high median lesion. (b) and (c) Variants of precision grip with a median lesion at the wrist.

in which sensation is either diminished or absent. Anomalous motor and sensory supply by median and ulnar nerves must be borne in mind[4] (Figure 6). Even with anomalous innervation, it is impossible to sustain abduction of the thumb at right angles to the palm and a pulp-to-pulp grip between the index finger and thumb is impossible (Figure 7).

## RADIAL NERVE

Power and precision grips are weakened as radial extensors fail to stabilize the wrist.[9,11] Extension of the metacarpophalangeal joints is weak or lost, although extension of interphalangeal joints persists, provided the ulnar nerve is intact. The area of loss of cutaneous sensibility is notoriously variable (Figure 8(a) and (b)) and may be important if the back of the hand is subjected to knocks at work, e.g. harvesting by hand with a sickle.

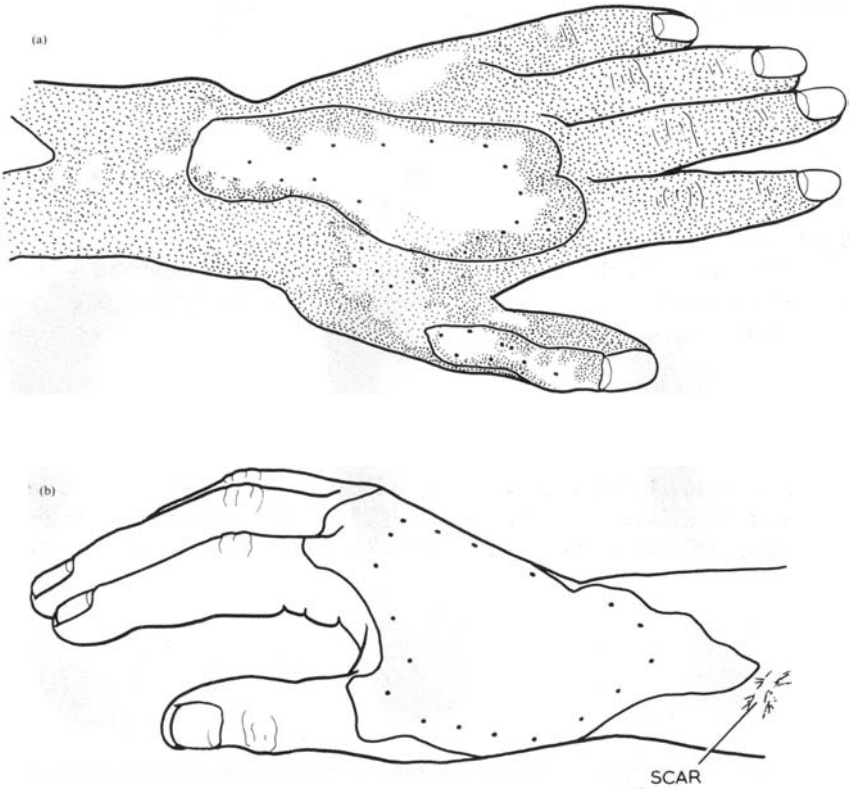


**Figure 8.** (a) Quinizarin sweating test and map of anaesthesia to 1 g *vs* Frey hair, ——; analgesia to light pen prick, · · · · · · after complete section of radial nerve. (b) Sensory loss mapped as in Figure 10(a) after section of the superficial radial nerve.

## THE COMMON PERONEAL NERVE

The common peroneal nerve is usually affected in the region of the neck of the fibula.

*History*

The patient may 'catch his foot' or 'turn the ankle' on both flat and rough surfaces due to foot drop and loss of the evertors of the foot.

*On examination*

In advanced cases the anterolateral aspect of the leg and extensor brevis digitorum are wasted. Callosities may develop under the 5th metatarsal head if the unopposed action of tibialis posterior is not corrected by an appropriate 'lively' splint. There is weakness or loss of dorsiflexion of the ankle and metatarsophalangeal joints. If no active splint is used there will also be a contracture of the calf muscle and disturbance of weight bearing and gait that are reflected in footprints (Figure 9), wear of shoes and incidence of callosities (Figure 10(a). Loss or altered sensitivity is found on the lateral aspect of the leg and dorsum of the foot.

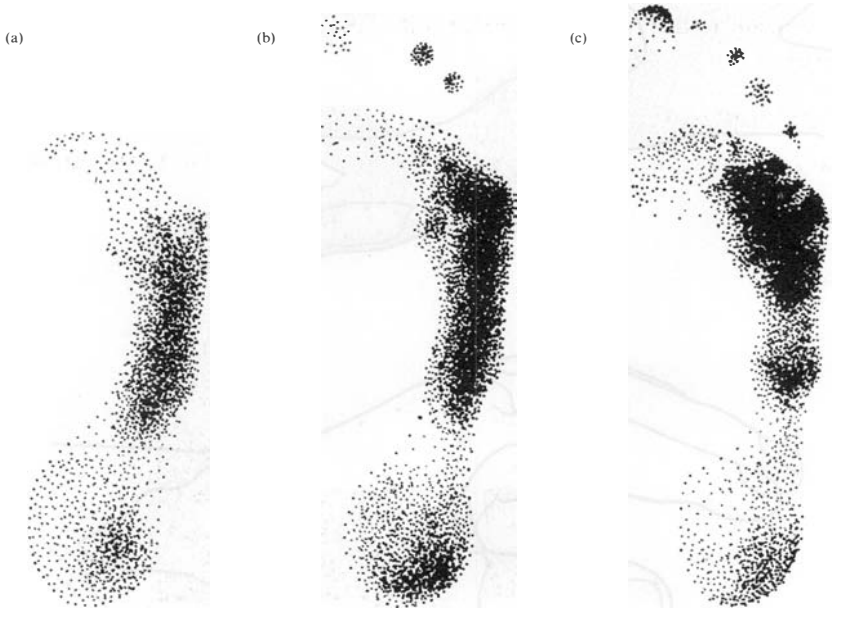


**Figure 9.** Footprints of patient with common peroneal palsy (without lively splint). (a) standing on both feet; (b) standing on affected foot; (c) walking print.

## THE TIBIAL AND SURAL NERVES

The tibial nerve is commonly involved in the medial retromallealar fossa and the sural in its long subcutaneous course from mid-calf, behind the lateral malleolus and along the lateral border of the foot.

*History*

Patients who wear shoes may notice increasing clawing of toes with painful callosities over the proximal interphalangeal joints. Bare-footed patients may have painless ulcers; sometimes the first symptom may be painful lymph nodes in the vertical inguinal group. If patients sit cross-legged, ulceration is also common on the side of the 5th metatarsal head in the area supplied by the sural nerve.

*On examination*

The clawing of toes is marked, and callosities may be found under all metatarsal heads (Figure 10(b)). The transverse metatarsal arch is flattened, and ulceration is common under the 1st metatarsal head due to the pressure of toeing off with a grinding movement in which eversion is involved. The intrinsic muscles on the sole are soft or, in long-standing cases, atrophied. Inability to pick up crumpled paper is an early sign of weakness of intrinsic muscles. Weak toe spreading is possible by the pull of divergent tendons of the long extensors and flexors. Loss of sensation is serious as it involves the weight bearing of the foot and the lateral border of the foot if the sural nerve is affected.

As in lesions of the peroneal, the normal pattern and rhythm of gait are lost, and weight bearing is disturbed with consequent abnormal wear of footwear[12–14] (Figure 10(b)–(d)).

TRIGEMINAL NERVE

Corneal sensitivity must be tested, using a wisp of cotton wool. Diminution or loss are

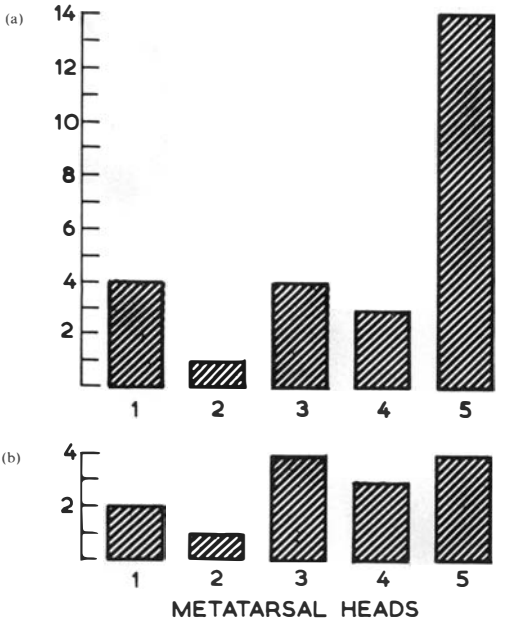


**Figure 10** (a) Incidence and distribution of calosities in 24 patients with paralysis of the common peroneal nerve and inadequate correction of foot drop. (b) Incidence and distribution of calosities in 14 patients with tibial nerve paralysis (note the foot falls into inversion during foot strike because of the structure of the talus).

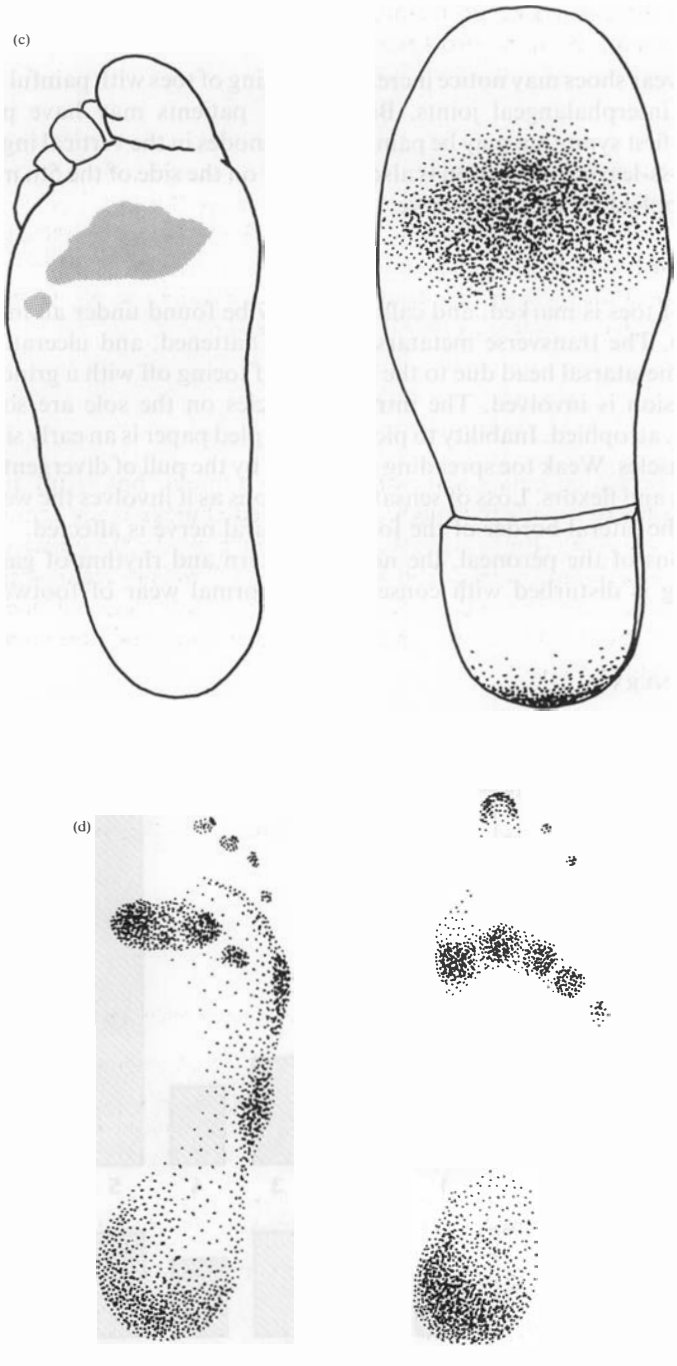


**Figure 10** (c) Foot of patient with paralysed intrinsic muscles showing calosities. Shoe wear is excessive under metatarsal heads. (d) 1 Footprints of two patients with paralysed intrensics. Note wasted foot which increases pressure of weight bearing per sq cm; 2 Note excessive pressure under metatarsal heads, especially under the first.

dangerous and there is risk of ulceration, scarring or even rupture followed by escape of aqueous and vitreous humors, prolapsed iris and retinal detachment.

### FACIAL NERVE

Involvement of this cranial nerve also has serious consequences. The disfigurement of paralysis is socially embarrassing, but the danger to the eye[15] is of overwhelming importance as there is a weakness which leads to the loss of the protective blink reflex and ability to close the eyelids. Emergency treatment is needed, particularly if there is associated corneal anaesthesia. Protective goggles and the use of eyedrops to prevent drying are imperative. Tarsorraphy may be indicated.[15]

## Conclusion

Sophisticated electronic equipment is a valuable adjunct, but is no substitute for a carefully taken history, with thorough and recorded clinical examination. In addition, enlisting active co-operation of patients will minimize incidental formation of contractures, trophic ulcers and burns. The importance of regular follow-up examination, conscientious taking of drugs and wearing corrective and protective appliances cannot be over emphasized. Sound advice prevents unnecessary inactivity, and rehabilitation goes hand in hand with treatment.[16,17]

## Acknowledgment

Thanks are due to Mrs Audrey Besterman for illustrations drawn from photographs of patients, actual equipment and footprints.

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*SPECIAL ARTICLE*

# Considerations in the integration of eye care into leprosy care services

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*Summary* Little attention has been directed to the development, management and evaluation of eye care programmes for leprosy patients. This paper examines when an eye care programme for leprosy patients is needed, methods for integrating eye care into leprosy control programmes and lists of available ocular leprosy teaching materials.

## Introduction

Leprosy control programmes began as vertical programmes and still exist as such today in many places. Vertical health programmes often result in a lack of comprehensive care for the patient, and eye problems in leprosy patients have often been neglected. Leprosy patients with visual loss form a particularly disadvantaged group because of other disabilities from the disease and the difficulties and delay in receiving appropriate eye care. In recent years ocular leprosy has been the focus of increasing scientific investigation. Nevertheless, little attention has been directed to the development, management, and evaluation of eye care programmes for leprosy patients.[1]

Ocular complications of leprosy often develop slowly; minor pathology is frequently overlooked or neglected with the result that serious problems develop. However, many of the blinding complications of leprosy are preventable or treatable by simple means and at low cost.

## When is an eye care programme needed?

How should a programme manager determine if an eye care programme is needed? Population-based surveys give the most accurate information,[2] but are costly. A more practical approach may be to review the clinical status of patients in a leprosy control

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programme. An answer of 'yes' to any of the following indicates that there may be a significant prevalence of eye disease.

Is there a large number (or proportion) of leprosy patients with multibacillary disease?
2 Is there a large number (or proportion) of 'cured' leprosy patients (multibacillary or paucibacillary) over 50 years of age or with a period of over 25 years since initial diagnosis?
3 Is the average period of time between onset and diagnosis over 5 years among most newly diagnosed patients or, do many newly diagnosed patients have moderate to severe (grade 2–3) disabilities?

The above criteria are based on the assumption that patients who receive a complete course of multidrug therapy are not likely to develop potentially blinding ocular pathology. Anecdotal reports suggest this may not be the case. Leprosy control programmes that discharge leprosy patients with inadequate follow-up after completion of multidrug therapy will be likely to place many 'cured' leprosy patients beyond the supervision necessary to avoid further eye complications and blindness. Nevertheless, until more information is available, attention to ocular disease should be provided at least in those settings described in 1–3 above.

## Integration of eye care into leprosy control programmes

Eye care in developing countries is usually available only in tertiary care facilities. A few leprosy centres do provide ophthalmology services. Most of these institutions have an ophthalmologist whose primary responsibility is the ocular treatment of leprosy patients. While high quality tertiary care is available, patients self-present only, follow-up is variable, and there is no relationship between leprosy control activities in the field and ocular care in the institution. The challenge is to devise a system that integrates eye care activities into leprosy control programmes in the field to provide a comprehensive eye care programme.

In a number of developing countries paramedical eye workers have been shown to be an effective group capable of providing primary eye care; they form an essential segment of the eye care infrastructure in ophthalmologist-poor areas of Africa and Asia.[3–7] In the past few years some attempts have been made to develop programmes utilizing leprosy paramedical workers as the front line for ocular care for their patients.[8] The fact that most pathology in ocular leprosy is in the anterior segment of the eye makes it particularly appropriate for detection by leprosy health workers with minimal training and equipment. Patient education in ocular complications of leprosy can be integrated into existing disability prevention programmes and be a component of a health worker's regular patient visits.

Training of primary health workers provides basic technical skills but is only one component of a comprehensive eye care programme. Primary health workers must be supported by an appropriate and efficient referral system in order to gain the confidence of the patient. Adequate examination equipment and drugs are also required to maintain a successful programme. To this end, political and administrative support of eye work within the leprosy programme is mandatory. To establish an adequate referral system collaboration between leprosy control programmes and general eye care services is almost

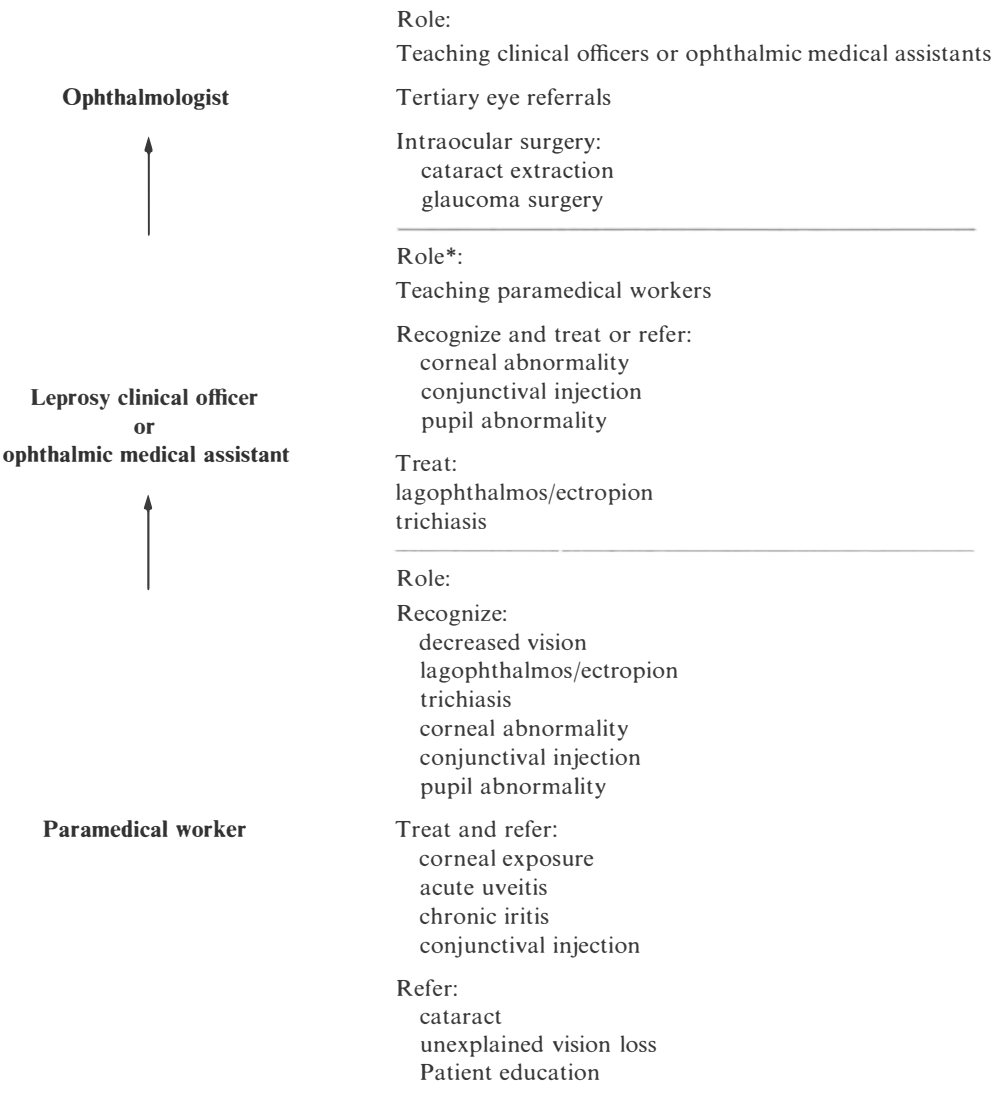
always essential. Additional and specific education of the ophthalmology community about leprosy may be necessary to achieve this; only in the special settings where a 'leprosy ophthalmologist' is found can the general eye care services be disregarded by the leprosy programme. Collaboration may be furthered by the establishment of a consultative group composed of both leprosy control and ophthalmology personnel. This group may establish tertiary services for leprosy patients at general eye care facilities, conduct seminars on eye care for leprosy health workers and hospital staff, and evaluate programmes in eye care.

## Conclusion

An eye care programme for leprosy control programmes in developing countries should be affordable to the country concerned and acceptable and accessible to all the leprosy patients. It should comprise various levels of health care with a well-structured referral chain allowing transferrals from the paramedical level through secondary services up to tertiary care for those who need it. Teaching materials and curriculums available for both the health worker and the trainer/ophthalmologist are listed in Table 1. There are certain aspects of leprosy control programmes that facilitate the integration of eye care into the programmes. There is already a system of paramedical workers established in the field and the additional training for them to learn primary prevention of eye disease is not great. Training paramedical workers, however, is only the first step. They must be supported in their duties by the administrators of the leprosy control programme and by a referral

**Table 1.** Ocular leprosy teaching materials

| Title and author | Source |
|---|---|
| *Care of the eye in Hansen's disease* (Brand, M) | The Star, Gillis Long Center, Carville, LA 70721, USA |
| *Leprosy of the eye: A general outline* (Joffrion VC, Brand M) | Gillis Long Center, Carville, LA 70721, USA |
| *Eye care in Hansen's disease: A screening tool for nurses* (Brand, M, Courtright P, Demarest V) | Gillis Long Centre, Carville, LA 70721, USA |
| Slide set on ocular leprosy | American Leprosy Missions, 1 ALM Way, Greenville, SC 29601, USA |
| Video:<br>1 The red eye<br>2 Eye in leprosy<br>3 Keep blinking | Schieffelin Leprosy Research & Training Centre, SLR Sanatorium, P.O. PIN 632 106, N. Arcot, Tamil Nadu, India |
| Video: Health workers and blindness prevention in leprosy | Project ORBIS, 330 W. 42nd Street, New York, NY 10036, USA |
| *Guide to ocular leprosy for health workers* (Courtright P, Lewallen S) | German Leprosy Relief Association, Postfach 110462, D-8700 Wurzburg, 11 Germany (available 1992) |
| *Training health workers to recognize, treat, refer and educate patients about ocular leprosy* (Courtright P, Lewallen S) | German Leprosy Relief Association, Postfach 110462, D-8700 Wurzburg, 11 Germany (available 1992) |




* To be fulfilled by an ophthalmologist in the absence of an eye-trained leprosy clinical officer or ophthalmic medical assistant.

**Figure 1.** Hierarchy of eye care services for leprosy patients.

structure which includes the ophthalmology community. Ocular disability prevention can be integrated into existing leprosy control services through collaboration between leprosy paramedical workers, leprosy clinical officers, and ophthalmologists (Figure 1).

## Acknowledgments

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# Obituary

## DAVID AKINWUNMI AKINTONDE MA, MB, CHB, BAO, DPH, JP

## 1923–1991

Dr David Akinwunmi Akintonde was born on 23 April 1923 (Easter Day) and died on 18 May 1991 (Pentecostal Day). He was the first widely known Nigerian leprologist and worked in the field for 30 years (1961–1990).

His education began at ONIPE in Oluyole Local Government, from where he moved to Ibadan Grammar School. He completed his secondary education at the Igbobi College, Lagos (1935–1940) where he passed his Cambridge School Leaving Certificate Examination with exemption from London Matriculation.

On 20 May 1944 he sailed (that was the only available means of transport to Europe in those days) to Trinity College, Dublin in the Republic of Ireland where he had already obtained admission to study medicine. He passed his examinations with credit, obtaining the following degrees: BA, MB, CHB and BAO. He later obtained an MA.

On his return to Nigeria, he served in the UCH Ibadan for a year as House Officer under Professor Jolly. He was employed by the Government of the Western Region of Nigeria and posted to Benin Province as the Medical Officer for the Ishan Division.

In 1960, Dr Akintonde returned to the United Kingdom for a course in Public Health, which he passed with distinction. On his arrival home in 1961 he was posted to his former zone as the chief Consultant Leprologist of the Western Region. When Bendel State was created in 1963 he was posted back to the Western Region and in 1975, when the Western Region was split into States, he moved to Ogun State where he was the Chief Consultant Leprologist until 1977, when he retired. His services were still very much needed by the two States Ogun and Oyo. He opted to serve in Oyo State as a contract officer until 1990.

In 1979 he was appointed a member of the committee on the prerogative of mercy by His Excellency, Governor Bola Ige of Oyo State. His experience was gratefully acknowledged by the Government of Oyo State by a decision in which medical opinion was paramount.

In 1981 he was appointed a Justice of the Peace.

Dr Akintonde was a devoted and painstaking pioneer leprologist. Being a pioneer was difficult but Papa (as we used to call him) took things in his stride. His leprosy publicity campaigns were very effective without being too flamboyant. His achievements at Ossiomo in the former Bendel state of Nigeria are still there for all to see. Then 'the vineyard was large but the labourers few'. His fatherly advice and motivation has greatly helped to increase the number of 'labourers'.

In a society where the stigma attached to leprosy is high, for him to have ventured into the field and remain there showing total commitment (even in retirement) for 30 years is no mean achievement. We are all aware that he left not only for reasons of health but also because he was able to get a devoted successor.

We grieve with his beloved wife, Mrs O Akintonde, a retired Director of Nursing services, and their four children and we take consolation in the fact that Papa was a guiding light to we younger leprologists and that to the last he obeyed the 'Golden Rule', i.e. 'Do unto others as you would want others to do unto you'.

T O MAJOROH

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# Letters to the Editor

## AN INEXPENSIVE SLIDE MARKER MADE FROM A DENTAL BUR AND A PLASTIC PEN

*Sir*,

At a recent meeting of the Ciba-Geigy Leprosy Fund in Basle, Switzerland, Professor S Pattyn (Antwerp, Belgium) drew attention to the existence of a slide marker which can be made from a metal dental bur and a (discarded) plastic pen (Figures 1 and 2). It was thought this had originated in Turkey and Professor Turkan Saylan (Istanbul) has now confirmed that it was indeed first devised by Professor Melih Tahsinoğlu of the Department of Pathology, University of Istanbul. It consists of an ordinary 'Bic' or similar plastic pen (used and discarded), into the tapered end of which can be inserted a round-tipped dental bur, about 15 mm long. The tip of the plastic pen has to be melted to insert and secure the bur and the procedure should be carried out in an extraction cabinet since the fumes are toxic. Discarded drills can easily be obtained from dentists and they mark glass clearly, even though unsatisfactory for drilling teeth. Markers of the kind illustrated have been in use for many years in the Dermatopathology Department of the Istanbul Medical Faculty and in the leprosy control programme, based at the hospital at Bakirköy. This simple device, using materials which would otherwise be thrown away, seems to be highly satisfactory, and it costs nothing. By contrast, the current list price of a diamond marker in the UK is £6.00 Sterling (approximately USA $12.00).

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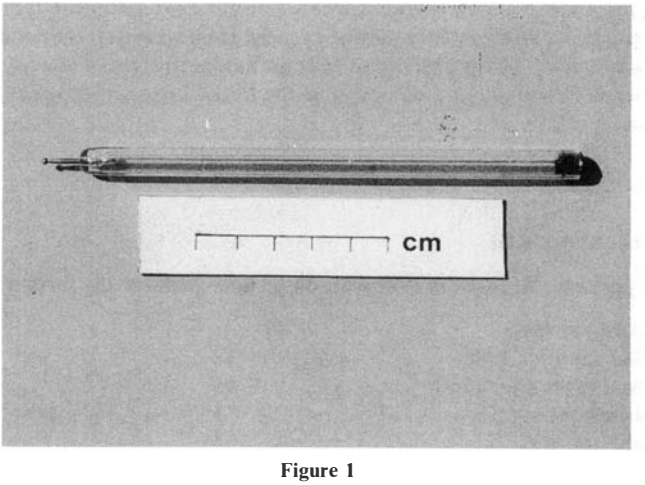


**Figure 1**

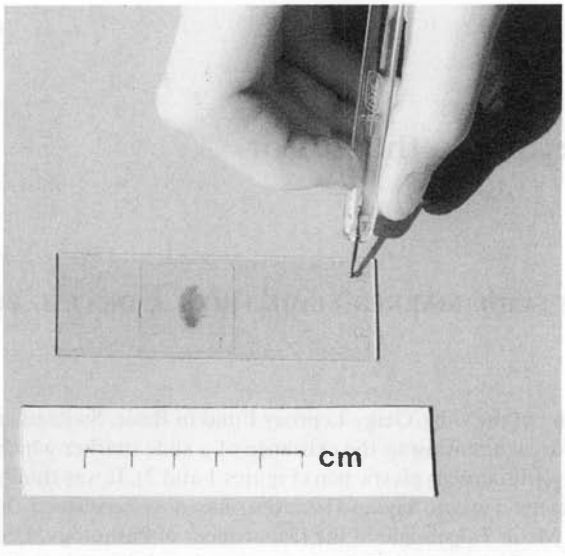


**Figure 2**

## EIGHT YEARS OF FOLLOW-UP OF PAUCIBACILLARY PATIENTS TREATED WITH SHORT-COURSE REGIMENS

Sir,

Previously we presented the results of treatment, between 1980 and 1982, of 825 paucibacillary patients in Central Africa with regimens consisting either of a single supervised dose of 1500 mg rifampicin (RMP) followed by 1 year of daily 100 mg dapsone (DDS) (unsupervised) (regimen A) or 10 weekly supervised doses of 900 mg or 600 mg RMP (292 patients) (regimen B).

We have been able to follow many of these patients until early 1990. In the absence of histopathologic cure and when new lesions appeared or old ones reappeared, patients were seen at regular intervals and skin biopsies were examined yearly. Here we report the results of this long term follow-up. Cure was defined by the absence of histopathological signs of leprosy, and relapse as the reappearance of signs of leprosy in a biopsy after the initial histopathological cure.

### Cure rate

ZAIRE–RWANDA–BURUNDI

About half of the patients not cured in 1986 were cured later without any further specific treatment:

| | | |
|---|---|---|
| Patients not cured in 1986 | 48 | |
| histological cures after 1986 | | 18 |
| no histological cures after 1986 | | 15 |
| patients lost to follow-up | | 3 |
| patients died | | 4 |
| patients retreated | | 8 |

Thus the final cure rates for the groups considered in the previous paper[1] are:

| | |
|---|---|
| Accessible patients, −3 lesions, regimen A | 100 |
| Accessible patients, +3 lesions, regimen A | 94·6 |
| Accessible patients, −3 lesions, regimen B | 100 |
| Accessible patients, +3 lesions, regimen B | 99·3 |
| Inaccessible patients (regimen A) | 96·5 |

*Comores*

Of the 12 patients not cured in 1986, 3 died subsequently and 9 others were cured.

**Relapses** (Table 1)

**Table 1.** The number of relapses

| | n | Patient (yr) | Number before 1986 | Number after 1986 | rate |
|---|---|---|---|---|---|
| *Zaire–Rwanda–Burundi* | | | | | |
| Acc −3 1 A | 39 | 166 | 1 | 1 | 0·6 |
| Acc +3 1 A | 106 | 555 | 5 | 8 | 1·4 |
| Acc −3 1 B | 48 | 202 | 2 | 2 | 0·9 |
| Acc +3 1 B | 108 | 440 | 4 | 5 | 1·1 |
| Inacc A | 109 | 426 | 8 | 11 | 2·6 |
| *Comores* | | | | | |
| −3 1 B com | 159 | 539 | 1 | 2 | 0·4 |
| +3 1 B com | 133 | 450 | 0 | 4 | 0·9 |

Whenever there was any doubt between relapse and (late) reversal reaction, a case was categorized as relapsed, so the figures represent the worst.

Although the differences between the groups are not statistically significant, the patients with less than 3 lesions seem less likely to relapse and the inaccessible patients, who may have been the worst treatment compliers, present more relapses.

Table 2 presents the time of occurrence of relapses in years after cure.

The frequency of relapse diminished from year to year, and more than half appeared within the first 2 years. The results show that all three regimens studied are efficient both in terms of cure and relapse rates. However, 15·9% of patients were cured only 2 or more years after the end of therapy, and although the development between dermatology and histology is not always completely parallel, these long delays are not readily accepted by many patients, paramedical workers and even physicians. Thus the search for efficient short course paucibacillary regimens needs to be continued.

**Table 2**

| Years after cure | Number | Cumulative (%) |
|---|---|---|
| 1 | 12 | 36·4 |
| 2 | 8 | 60·6 |
| 3 | 5 | 75·6 |
| 4 | 5 | 90·1 |
| 5 | 0 | 90·1 |
| 6 | 3 | 100 |

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## AGRANULOCYTOSIS DURING MULTIDRUG THERAPY (MDT) OF LEPROSY

Sir,

Agranulocytosis is a recognized side-effect of dapsone but until recently had not been reported during leprosy treatment.[1] In 1986 the first case of agranulocytosis complicating the treatment of leprosy was reported in a Melanesian from Papua New Guinea.[2] I would like to report another case of agranulocytosis during multidrug therapy (MDT), in a Melanesian from Vanuatu.

A 29-year-old woman with a family history of leprosy was seen in the Outpatient Department of the Vila Central Hospital with foot drop, sensory loss of the lower leg and nerve enlargement. Skin smears for acid-fast bacilli were negative. A diagnosis of paucibacillary leprosy was made and MDT, including 100 mg dapsone daily, was started.

After 5 weeks she was admitted to the same hospital, having developed a fever and rash. She was pyrexial with an axillary temperature of 39·4 C. Her sclera were yellow and she had a generalized erythematous rash. Her liver was enlarged and tender and she had a palpable spleen. The sulphone syndrome secondary to dapsone was diagnosed, leprosy treatment was stopped and treatment with prednisone 60 mg daily was started. Investigations on admission included a haemoglobin of 8·6 g/dl with a white blood count of 29,300/mm$^3$. Blood film examination was interpreted as showing a left shift with atypical lymphocytes. Serum bilirubin was 478 micromol/l (normal range < 17) with very high transaminases, and 3 days after admission her skin began to desquamate. She remained very sick for several days but gradually improved.

She developed a fever 11 days after admission, and a cough with purulent sputum. There were a few crackles audible at the right base but a chest radiograph showed clear lung fields. Amoxycillin

500 mg 3 times daily was commenced, and 3 days later, 2 weeks after being admitted, her condition rapidly deteriorated, she began to cough blood and her blood pressure fell to 60/40 mmHg. Intravenous fluids were started and cloxacillin, gentamicin and chloramphenicol given. A repeat chest radiograph showed right upper lobe consolidation. Her white blood cell count was only 700/mm, with no neutrophils visible. Unfortunately she did not respond to treatment and died a few hours later.

Although there have been several reports of agranulocytosis due to dapsone, nearly all of these have been in patients taking dapsone for a reason other than leprosy. The first case of agranulocytosis secondary to dapsone occurred in a patient being treated for dermatitis herpetiformis.[3] A total of 16 US soldiers serving in Vietnam developed agranulocytosis while taking 25 mg dapsone daily as malaria prophylaxis,[4] of whom 8 died. Agranulocytosis has also been reported with weekly Maloprim (100 mg dapsone, 12·5 mg pyrimethamine) prophylaxis.[5]

Serious reactions, numbering 103, with 11 deaths, were reported to the national registers of Sweden and the UK during 1965–1988,[6] and 7 deaths were attributed to agranulocytosis. The incidence of serious reactions appeared to increase with higher doses.

In the last 4 years in Vanuatu we have been seeing a high incidence of the dapsone syndrome during leprosy treatment with nearly a quarter of patients reacting to dapsone (P Reeve *et al.* unpublished data). This usually rare syndrome has been reported in 2 brothers in Papua New Guinea[7] and in an Aboriginal mother and son in Australia (J. C. Hargrave, personal communication). It is interesting that the only other case of agranulocytosis complicating leprosy treatment was reported in a Melanesian, and it is possible that there could be an increased susceptibility to dapsone reactions in Melanesians.

Because of the high incidence of reactions to dapsone all new leprosy patients in Vanuatu are being admitted to hospital for the first 2 months of treatment for close supervision.

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P REEVE

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## COMMENT: RECENT ADVANCES IN THE ANTIMICROBIAL CHEMOTHERAPY OF LEPROSY

Sir,

Ji & Grosset must be congratulated for an illuminating editorial.[1] It was comforting to know that there are many anti-*Mycobacterium leprae* drugs already available for testing, but a few other aspects of their account raised some questions for me.

**Ofloxacin trials**

The authors suggest that not much more than a month of multidrug therapy (MDT), including daily ofloxacin and rifampicin, should be sufficient for lepromatous patients. This seems to be more optimistic than the evidence permits. Viable *M. leprae* in patients treated with ofloxacin at 400 mg/day[2] are unlikely to decline at an exponential rate greater than 0·56 per day or less than 0·11 per day, according to standard calculations.[3] Therefore, most optimistically, lepromatous patients with $5 \times 10^{11}$ viable *M. leprae* are predicted to need at least 6 weeks of daily ofloxacin and rifampicin, for viable *M. leprae* to be eliminated. A shorter duration seems unduly adventurous, although it may suffice in patients with a smaller initial number of *M. leprae*. More cautious investigators may wish to assume the most pessimistic rate of bacterial decline, by which the corresponding safe duration of daily ofloxacin with rifampicin is up to 8 months. These calculations disregard re-infection and persisters, both of which can be dealt with by subsequent treatment.

The authors suggest that trials of new regimens should include patients treated up to 1 year with dapsone monotherapy. This is a mistake which would seriously weaken any inferences drawn from the trials. Viable *M. leprae* decline at a rate of no less than 0·032 per day[4] in the presence of $>750$ ng/ml dapsone, according to evidence from mouse tests.[5-7] Even 6 months of dapsone monotherapy is therefore predicted to give a 3000-fold reduction in the number of viable *M. leprae*, and a whole year of dapsone a 10 million-fold reduction.

The inclusion of dapsone-treated patients in trials of new regimens is expected to exempt the regimens from serious testing. This mistake has already been made once in the THELEP trials of WHO–MDT (which mainly included smear-negative patients who had previously received several years of dapsone monotherapy). It would be a pity to repeat that mistake.[8]

**Shorter MDT with rifampicin, clofazimine and dapsone**

The authors claim that MDT with rifampicin, clofazimine and dapsone should not be shortened below 2 years. This is unduly pessimistic. The measured rates of decline in viable *M. leprae* during treatment with each of these drugs suggest that, even most pessimistically, as little as 14 months of clofazimine and dapsone with rifampicin included for an initial 100 daily doses should be sufficient to eliminate viable non-persister *M. leprae* in lepromatous patients.[1] The most optimistic assumptions suggest that as little as 3 months of daily rifampicin and clofazimine or even 5 months of regular daily clofazimine and dapsone following a single initial rifampicin dose could prove sufficient against viable *M. leprae* in lepromatous patients.[4]

MDT with rifampicin, clofazimine and dapsone is itself fairly expensive. Trials to shorten such MDT seem to deserve a higher priority than the authors seem to concede. Enthusiasm for more expensive drugs should not stand in the way of trials to establish the minimum required duration of MDT with rifampicin, clofazimine and dapsone.

**Dapsone monotherapy of limited duration**

So far a glaring deficiency in nearly all trials of MDT has been the omission of a control group on dapsone monotherapy of limited duration. Quantitative analysis suggests that 3 years of regular full-dose dapsone monotherapy could prove more than sufficient for the elimination of non-persister viable bacteria in lepromatous patients.[4] This prediction may only rarely have been tested[9,10] but remains to be refuted. Dapsone monotherapy using monthly injections[11] also provides the only opportunity at present for fully supervised intermittent anti-microbial chemotherapy in leprosy.

The objections to dapsone monotherapy in leprosy do not bear scientific scrutiny. It is believed that campaigns of dapsone monotherapy were losing efficacy by the late 1970s, where the evidence

shows that their efficacy was undiminished or even increasing.[12–14] It is believed that 'primary dapsone resistance' was unknown before 1977,[15] whereas mouse tests in the early 1960s[16] demonstrated that the equilibrium frequency of 'full-dose' dapsone-resistant mutants lies between 1 in 100 and 1 in 10,000.[4]

Wherever mouse tests are done, dapsone-resistant *M. leprae* are found, as expected. Nevertheless, wherever dapsone is taken regularly and in adequate dosage by patients, it succeeds, except in a handful of 'slow-responding' lepromatous patients who do poorly on any regimen including MDT. Dapsone-resistant *M. leprae* probably decline in patients on dapsone monotherapy because dapsone reduces the relative fitness of the resistant mutants[4] and because leprosy patients (unlike mice with small bacterial inocula) show significant rates of bacterial clearance.

Dapsone monotherapy is observed to be adequate for about 99% of all patients starting treatment in India (where nearly half of the registered leprosy patients in the world live), since the cumulative probability that dapsone will fail within 20 years of starting monotherapy is observed to be under 10% for L patients[17,18,4] and under 1% for all leprosy patients in India. In 1991, millions of patients in India and elsewhere remain on dapsone monotherapy without the predicted catastrophe of widespread failure of dapsone monotherapy. The measured incidence of dapsone-resistant failure of treatment among L patients[19] is so low (0·76%/year $\pm$ 0·104, 95% c.i.[17,4]) that dapsone-resistance will probably continue to present an infrequent threat to dapsone monotherapy in the foreseeable future.

The objections to monthly injections of dapsone seem unduly pessimistic. Injections are so frequently and widely demanded (and conceded) in India that it is doubtful whether the risk of infection with HIV can be lowered significantly by the avoidance of monthly dapsone injections (which need not be administered by untrained staff).

Up to 30 million US dollars per year would be freed in India alone if 3-year dapsone monotherapy were used instead of WHO–MDT.[4] In fact, 3-year fully supervised dapsone monotherapy is so suited to Indian needs that its omission from trials seems not only unscientific but also economically unwise. The cost and sustainability of regimens of antimicrobial chemotherapy deserve more attention than they have received: the enthusiasm and prosperity of donors cannot be relied upon.

**Does antimicrobial chemotherapy reduce the spread of *M. leprae*?**

Reduced transmission of *M. leprae* has so far seemed to depend more on secular factors than on antimicrobial chemotherapy. Since infective patients are generally diagnosed well after they have become infectious[20–21] (possibly because lepromatous leprosy can have inconspicuous signs) and since *M. leprae* can survive indefinitely outside human hosts (reviewed[22]) antimicrobial chemotherapy is expected to generally have only a trivial impact on the secular decline of leprosy. This prediction has yet to be refuted by any report with an adequate description of methods, and 3-year dapsone monotherapy would give the same cosmetic reduction in number of patients on antimicrobial chemotherapy as does WHO–MDT, but at far lower cost and with far less risk of selecting *M. leprae* resistant to rifampicin and to multiple drugs.

**Are some disabilities attributable to antimicrobial chemotherapy?**

The authors overlook important new evidence on the positive association between the risk of disability and the regularity of antimicrobial chemotherapy.[23] It has long been suggested[24] that tuberculoid patients can be classified on the basis of simple prognostic criteria (e.g. single well-defined patch, positive lepromin reaction, no nerve involvement). Self-healing is known to occur in up to 75% of persons developing tuberculoid signs of infection with *M. leprae*.[25–30] Could the risk of disability in patients with 'low-risk' tuberculoid signs be increased by the inclusion of antimicrobial

chemotherapy in their treatment? A double-blind trial (such as that already suggested[4]) could answer this important question.

**Research priorities in antimicrobial chemotherapy**

The priorities for research in the antimicrobial chemotherapy of leprosy seem to go beyond the testing of newly available drugs. In particular, the authors may wish to consider the need for:

a careful predictions of cost for various strategies of antimicrobial chemotherapy;
b trials to test the predicted minimum duration for MDT (with clofazimine and dapsone, including daily rifampicin for an initial period);
c quantitative theoretical models to suggest appropriate durations and subjects for trials of new regimens;
d a controlled double-blind trial to refute the suggestion that antimicrobial chemotherapy increases the risk of disability among persons with signs of low-risk tuberculoid infection; (and, perhaps most importantly for countries such as India):
e the inclusion of a control group on 3-year fully supervised dapsone monotherapy in trials of more expensive regimens.

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## REPLY: B JI and J-H GROSSET

Sir,

The following is in response to the above letter from Dr Almeida regarding our editorial entitled 'Recent advances in the chemotherapy of leprosy'.[1]

The backbone of the current multidrug therapy (MDT) regimens is rifampicin (RMP) because of its great potency; the major objective to combine it with other drugs is to prevent the selection of RMP-resistant mutants during RMP-monotherapy, due to the huge bacterial population in untreated multibacillary (MB) leprosy patients.[1] Both pefloxacin and ofloxacin displayed very powerful bactericidal activities in lepromatous patients: 99·99%, or 4 'logs', of organisms viable on D0 were killed by 22 doses of either pefloxacin 800 mg or ofloxacin 400 mg[2]; and the average size of RMP-resistant *Mycobacterium leprae* in an untreated lepromatous patient is no more than $10^4$, or 4 'logs'. By definition, RMP-resistant mutants should be killed by fluoroquinolones at the same speed as RMP-susceptible organisms, thus, all the RMP-resistant mutants may be eliminated after 22 doses of either pefloxacin or ofloxacin. It is, therefore, possible that the combination of RMP and ofloxacin may considerably shorten the duration of MDT.

However, we have never claimed that 1 month of ofloxacin will be able to eliminate $5 \times 10^{11}$ viable (non-persister) *M. leprae* as described by Dr Almeida. Because of the limitations of the tools, we know that at best, we are only able to measure the initial 5 or 6 logs of the killing even using nude mice for monitoring the bactericidal activity.[2]

Dr Almeida has calculated the declining rates of viable organisms during treatments with various drugs. It is difficult to verify the validity of these calculations simply because of the lack of a sensitive tool. Nevertheless, it is unlikely that the declining rate of viable organisms remains the

same as the initial killing, at least during the course of treatment with RMP.[3] In addition, unless one can demonstrate that 3 months of clofazimine can kill about 4 logs of organisms in a previously untreated lepromatous patient, it seems over-optimistic to assume that 3 months of daily RMP and clofazimine could be sufficient for the treatment as suggested by Dr Almeida.

Plenty of information has already demonstrated the seriousness of dapsone-resistant leprosy, and that its prevalence increases with time if dapsone monotherapy is continued.[4] The later results[5] from other areas were entirely consistent with the earlier assessments. The dapsone susceptibility of the *M. leprae* strains isolated from previously untreated patients had changed significantly: the primary dapsone-resistant *M. leprae* was virtually nonexistent before 1977;[6] whereas the organsims from one-third[4] to one-half[5] of the MB patients diagnosed in the 1980s were resistant to dapsone. In addition, regular administration of dapsone in an adequate dosage could not effectively prevent the relapse, because after 20 years of supervised sulphone therapy, in which a majority of the patients had received the dapsone equivalent of at least 100 mg daily, the annual relapse rate still remained 1%.[7] Therefore, it was clear that the attempts to control leprosy by dapsone monotherapy were failing, and the justification to further evaluate the 3-year dapsone monotherapy, as proposed by Dr Almeida, is weak.

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## COMMENT: 'IMMUNOLOGICAL UPGRADING WITH COMBINED IMMUNOTHERAPY AND CHEMOTHERAPY IN A LEPROMATOUS LEPROSY PATIENT: A CASE REPORT'

Sir,

The above article, which was published in *Lepr Rev* (1991), **62,** 297–302, is intriguing. However, we feel that there are some points that should be discussed to avoid any possible misunderstandings.

Skin test conversion responses to killed vaccines prepared from cultivable mycobacteria, namely *Mycobacterium avium* (the 'ICRC' bacillus and *Mycobacterium w*) are well conceived,[1,2] but have not been conclusively proved in experimental animals.[3] Such a conversion may also occur through:

1, multidrug therapy (MDT);[4,5] 2, repeated lepromin testing;[6] 3, spontaneous upgrading; and 4, injection of cytokines *per se*[7,8] or antigenic challenges that induce cytokine activation. More significantly, it has been documented that delayed-type hypersensitivity may not parallel specific immunity in mycobacterial infections.[9,10] Hypersensitivity and protective immunity may be directed towards separate mycobacterial antigens.[11] These factors were not focused upon in the article. It is, therefore, imperative to enlarge the study, keeping in view the 3 groups, namely MDT alone, MDT and vaccine, and vaccine alone. Also these groups should be interchanged during trials. The findings in the present case should, therefore, be viewed with caution. We look forward with keen anticipation to the publication of the conclusive results of the study being undertaken by the authors.

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## COMMENT: REVERSAL REACTIONS IN LEPROSY AND THEIR MANAGEMENT

Sir,

Dr Rose and Dr Waters in their Editorial (*Lepr Rev*, 1991; **62:** 113–21) drew attention to the importance of the recognition of reversal reaction (RR) in the borderline group of leprosy and its management towards deformity prevention. I should like to make the following points on RR and its management.

1 The recognition of Type I, i.e. RR, downgrading reaction is a known clinical entity, more specifically observed in BB cases downgrading to BL and BL cases to LL cases. Such phenomenon is seen mostly in untreated BB cases, the 2nd and 3rd trimester of pregnancy, and in those with viral infections, which lower the cell-mediated immunity, are especially at risk. This RR downgrading is not strikingly symptomatic, but some signs are: oedema over the dorsal aspect of hand and foot; frequent appearance of new dermal lesions: and slow deterioration of the sensory and muscular

component of an affected nerve. The management of such cases does require steroids, but only 10–15 mg to begin with and then decreasing to 2·5 mg over 4–6 weeks.

2 In Type I, i.e. RR, upgrading reaction, the use of rifampicin as part of an antileprotic therapy is a matter for concern, especially in cases of BL downgraded from BT, where a parental clinical group shows a thickened nerve. This may even result in acute paralysis, with a marked increase of tenderness in the trunk nerve. This is because of further bacterial breakdown and availability to overcharged cell-mediated response in RR. Many cases of BT, BB and BL have developed foot drop and lagophthalmos. Undiagnosed leprosy cases are reported from leprosy endemic areas, which are being treated for tuberculosis with rifampicin and that have developed neuritis.

3 The concomitant use of rifampicin during RR is scientifically questionable. Rifampicin is known to reduce the cortisol level of the body by enhancing the production of the hepatic microsomal enzyme, which in turn increases the metabolic degradation of steroids and reduces the pharmacological effectiveness. Hence the steroid dosage may be required in a higher quantity.

4. Surgical management of RR for neuritis is a rewarding experience when 40–60 mg of steroid is administered for 4–5 days, with the requisite splints. If the pain does not subside, the case must be subjected to external neurolysis to prevent nerve damage. Leprosy centres should have surgical facilities and remain certain that such procedures prove to be highly beneficial. The ILEP Medical Commission should plan leprosy surgery workshops or courses for potential leprosy physicians.

5 Nonsurgical treatment should attract as much attention as steroid therapy in the management of RR cases. In India, more specifically Government controlled units, 20-bed hospitals for leprosy do not practise the splinting procedure.

Measures aimed at preventing the formation of deformities are: paralysed muscles should be rested in a functional, relaxed position and that inflamed nerves should be protected from mechanical injury for a period of 2 weeks. This should be followed by exercises, in the form of passive movements followed by active exercises. Maintaining a full range of passive movement of smaller joints—e.g. interphalangeal, metacarpophalangeal and intercarpal—in the hand and respective joints in the foot prevents the development of contractures. Massage helps in maintaining the blood supply and circulation to the affected area.

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# Teaching Materials and Services

## Centre for Social Science Research on Leprosy, India

Dr A. M. Kurup, Chief Research Scientist, has supplied the following information on this Centre:

Following the philosophy of the Mahatma, the father of the Indian nation, one of the many innovative approaches to leprosy control adopted by the Gandhi Memorial Leprosy Foundation (GMLF) was the establishment of a Centre for Social Science Research on Leprosy (CSSRL), in September 1985. The idea of establishing such a Centre evolved at the National Seminar on Social Aspects of Leprosy organized by the GMLF in 1982, followed by suggestions made by working groups constituted by the Government of India and the State Government of Maharashtra. Realizing the importance of social science input in leprosy eradication, from 1988/89 the World Health Organization (Tropical Diseases Research) assisted the Centre with a long-term Institutional Development Grant. Before this, the Leprosy Relief Organisation, Munich, had been modestly complementing the efforts of the GMLF.

The formative stages of the CSSRL was guided by Professor R. K. Mutatkar, a reputed medical anthropologist, of the University of Poona, who continues to be associated with its activities. In January 1988, the responsibility of leading the Institution fell on the present Chief.

The prime objectives of the CSSRL revolve around the application of social science research input for leprosy eradication (see box below). For achieving these objectives the Centre, besides its multi-disciplinary Faculty, solicits co-operation with like-minded institutions and individual experts, both within the country and abroad. Leprosy-related issues as a potent field for social science research not only need to be promoted among social scientists, but also the results of such research require to be utilized in disease management.

CSSRL aims to do this by: organizing national and international forums of social and health scientists to stimulate research; identifying and involving research scientists and institutions to instil interest in them; establishing a computer-based information and retrieval system; and undertaking research independently and on a collaborate basis.

In view of the expanding activities of the CSSRL a Managing Committee consisting of senior social scientists, leprologists and leprosy managers was constituted to steer the activities of the Centre in October 1989, headed by Professor M. S. Gore, Chairman of GMLF, and a veteran sociologist of repute. A Scientific Advisory Committee guides the research activities of the Centre.

*Objectives*

- To conduct and promote social science research, disseminate and utilize research results in planning, programming, evaluation and training;
- To survey existing social science research and examine their relevance to the National Leprosy Eradication Programme;
- To identify gaps in social science research with reference to national needs;
- To equip and orient social scientists and health scientists for health behaviour research in the field of leprosy; and
- To document research information and data.

Further enquiries: Centre for Social Science Research on Leprosy, Gandhi Memorial Foundation, Hindi Nagar, Wardha 442 103, India

## School of Medical Education, NSW, Australia

The following publications are available from the School of Medical Education, University of New South Wales, PO Box 1, Kensington, Australia 2033:

***Teaching Skills: A Guide for Teachers of Health Workers,*** third revision by *Christine E Ewan* MBBS, MA, PhD. This edition is a revised version of the Teaching Skills Development Manual first published in 1982 in collaboration with the World Health Organization, Geneva. ($AUS15.00 each)

***Self-Assessment for Managers of Health Care: How Can I be a Better Manager?*** WHO Offset Publication No 97 by *Arie Rotem* and *Joe Fay*. ($AUS10.00 each)

***Educational Processes for Trainers of Primary Health Care Workers.*** Exchanging experiences in relation to primary health care (Workshop Forum 1981). Edited by *Mick Bennett* and *Christine E Ewan*. ($AUS5.00 each)

***Management Training for National Health Development.*** Defining ways of strengthening the capabilities of teaching institutions in the implementation of health management (Workshop Forum 1984). Edited by *Charles Boelen*, *George Dorros* and *Arie Rotem*. ($AUS5.00 each)

***Designing Appropriate Training Programs.*** Educational planning in the health professions (Workshop Forum 1985). Edited by *Raja Bandaranayake* and *Susan S. Irvine*. ($AUS5.00 each)

***Evaluation of Training Programs for Primary Health Care.*** Identifying the nature of data to be collected, designing the evaluation plan and choosing methods of data collection and analysis (Workshop Forum 1983). Edited by *Arie Rotem* and *Raja Bandaranayake*. ($AUS5.00 each)

***Management of Change in Training Institutions.*** Focusing on the management of change in educational institutions (Workshop Forum 1986). Edited by *Arie Rotem* and *Katja Janovsky*. ($AUS5.00 each)

***Management of Human Resources in Health.*** Providing a framework for planning, exchanging of experiences, reviewing constraints in development of strategies and identifying realistic entry points for improvement in the management of human resources in health (Workshop Forum 1989). Edited by *Arie Rotem*. ($AUS5.00 each)

***A Manual on Teacher Training for Teachers of Primary Health Care Workers.*** This Manual provides a resource for teacher training programs for the field trainee. By *Raja Bandaranayake*, *T. D. Vijitha Perera*, *S. Dulcie de Silva* and *Rukmal Seneviratne*. ($AUS12.50 each)

## A leprosy course in Maputo, Mozambique

For the first time since Mozambique's independence in 1975 a 4-week course was held in Maputo commencing on 2–3 September. In the past many short-course seminars have been held but they mainly covered a limited number of selected topics for health personnel at district or provincial level.

Due to economic and organizational problems, which are considered secondary to the persistent Civil War that creates urgent priorities, leprosy and its problems have been underevaluated and 'forgotten'.

Multidrug therapy was introduced in Mozambique in 1984, but since then has only reached

about 8·5% of the 18,200 patients on the register, mainly because the prescription of such therapy was mostly the preserve of the provincial supervisors.

The first course had 16 participants—health workers already engaged in the National Leprosy Control Programme. The aim of the course was: 1, to give up-to-date knowledge of the most important topics dealing with leprosy; and 2, to provide sufficient skills so that the Programme can be run at more peripheral levels.

Basic instruction on the following areas was included to refresh the participants' knowledge: anatomy and physiology of the skin and nerves, topographic anatomy, physiopathology of inflammation, pathology of skin lesions and of the peripheral nerves, and a short account of general and applied microbiology and the essentials of immunology applicable to leprosy.

This was preliminary to the clinical criteria for suspecting, diagnosing and classifying leprosy in dark-skinned patients, with particular reference to the aspects of control of the disease in southern Africa. In particular, the criteria for the introduction/extension of MDT was given, taking into account the existing social situation and the degree of training of the health workers. Probably the most important outcome of the course is that a real extension of MDT treatment may begin.

The course was preceded by a 76 multiple-choice question test, to evaluate the basic knowledge of the attendants. As a mean, only $54 \pm 19\%$ of the questions were correctly answered. At the end of the course, the students underwent a final evaluation, with a 119-question test: a minimum score of 70% was necessary to pass and $81 \pm 11\%$ of the questions obtained a correct answer (maximum 91% and minimum 44%—only one student failed).

The course was held thanks to co-operation between the National Leprosy Programme of the Department of Epidemiology and Endemies at the Ministry of Health and the Italian Association of Amici di Raoul Follereau who gave financial and organizational help.

Further courses will be held twice a year, in February and August.

Consideration is being given to the inclusion of a tuberculosis component and also to open the courses to students from other Portuguese-speaking countries.

For further information, please contact: Secção de Lepra, Ministério da Saúde, MAPUTO, Moçambique; or Dr L. Compostella, A.I.FO., c.p. 4344, MAPUTO, Moçambique.

### *Leprosy: basic information and management*—now in Indonesian

This 42-pp booklet, published by Ciba-Geigy Ltd, CH-4002, Basle, Switzerland, is available free of charge to *bona fide* applicants. It is already available in French, Spanish and Bengali and has now been translated into Indonesian. The current English edition (2nd, 1989) has sold out, but a third edition will be available in the near future.

### *Essential Drugs Monitor*; WHO

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

meet people's common health needs; have significant therapeutic value; are acceptably safe; offer satisfactory value for money.

All correspondence should be addressed to the Editor, *Essential Drugs Monitor*, World Health Organization, CH-1211 Geneva 27, Switzerland.

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# News and Notes

## New, improved 'genetic vaccines' for tropical diseases

The following is extracted from *The Guardian* newspaper, 27 September 1991:

A new application of genetic engineering has resulted in a better way to make vaccines for tropical parasitic diseases.

Conventional vaccines are made from viruses or bacteria grown outside the body and chemically killed or weakened to render them harmless, but in some such vaccines a few organisms may escape the treatment and emerge still able to cause disease; and with parasitic diseases, parasites cannot usually be grown in bulk outside the human body, because they are so well adapted to it.

An alternative method involves taking genes for individual antigens—proteins that stimulate immunity strongly—from micro-organisms, implanting the genes in laboratory cell cultures and using the cultures to produce the antigens to use in vaccines. But the problem in the case of tropical parasitic diseases is that single antigens generally do not stimulate immunity nearly as strongly as vaccines from whole organisms. For immunity to be strongly stimulated, parasite antigens need to be 'seen' by the immune system in the context of neighbouring antigens.

Instead of taking genes out of parasites to produce vaccines, Professor Lex van der Ploeg and Dr Mary Gwo-Shu Lee at Columbia University in New York, are inserting genes into parasites. The genes are targeted so precisely that they either delete or replace one or more of the parasite's own selected genes. In this way, Ploeg and Lee have shown they can produce parasites which, while perfectly healthy living in the laboratory, are doomed to die after only a day or two in their human host. The deletion of a gene for a vital enzyme has left them unable to feed themselves in the human body.

Such vaccines, being made of whole parasites, should stimulate immunity more strongly than vaccines made from individual antigens, and should stimulate cell-mediated as well as antibody-mediated immunity. And because the techniques used to insert or delete genes are so precise, the vaccines should end any risk of people contracting diseases from imperfectly treated micro-organisms.

By deleting specific genes in known sites on chromosomes, and observing the effect of each deletion on the organisms, Ploeg and Lee are building up information about the roles of different genes in the life of the parasite. As well as identifying genes which, when deleted, make it impossible for a parasite to survive long in its human host, this work will, it is hoped, identify genes which when deleted or replaced, may allow the parasites to breed and grow outside the human body so they can be cultured on the large scale needed to make vaccines.

The technique has been used by other scientists to target genes to specific sites on the chromosomes of sheep and cattle to create new breeds of transgenic farm animals able to produce valuable pharmaceutical proteins in their milk. The technique, called homologous recombination, depends on the natural ability of two identical sequences of DNA to join together. This can be used to replace a gene with a very similar gene but one which has one or two vital alterations. Or, by using just a short homologous sequence to target a so-called anti-sense sequence of the gene, it can delete

the gene completely. (Anti-sense genes are mirror images of genes which have the effect of literally cancelling out the corresponding gene's message.) This work will also be useful in identifying new targets for drugs. By specifically deleting genes and so discovering the functions of the proteins they code for, the enzymes that a parasite possesses that are different from those of its human host can be identified. Drugs to attack these enzymes could then be designed which would be harmless to the human host and so free of side effects.

The Columbia team have worked mainly with trypanosome parasites, one species of which causes African sleeping sickness and others leishmaniasis and Chagas' disease, conditions common in central and Latin America and the Middle East.

## ActionAid *Disability News*, India

ActionAid *Disability News* is a bi-annual newsletter of the Disability Division, ActionAid-India. The newsletter is meant for private circulation only, for planners, administrators, professionals, funding organizations and implementing agencies involved in disability and rehabilitation programmes.

The major emphasis of the newsletter would be on articles related to policy development, concept clarification, development of methodology in areas of service delivery, training of manpower and programme evaluation, and development of technology related to rehabilitation.

Other information related to rehabilitation of disabled people that may be of use to funding organizations and implementing agencies are also welcome.

The views expressed in the newsletter are those of contributors and not necessarily of ActionAid.

Copies of the newsletter are mailed free of cost on request.

We are interested in exchanging copies of this newsletter on a reciprocal basis, with other rehabilitation publications and in gathering information on programmes and research findings related to disability and rehabilitation.

Articles sent to us will be published subject to their suitability and may also be published elsewhere if so desired. Two copies each (typewritten, double spaced, on bond paper) of articles, letters, comments and other communications meant for publication may be sent to the address given below.

Disability Division, ActionAid, P.B. 5406, 3, Resthouse Road, Bangalore 560 001, India.

## Psoriatic lesions measure, Thames Laboratories, UK

Thames Laboratories of Abbey House, Wrexham Industrial Estate, Wrexham, Clwyd LL13 9PW, Wales, UK have produced a 'psoriatic lesion' measure, which consists of a piece of thin Perspex (or similar) material, into which are traced a number of black concentric rings. The centre ring is 10 mm in diameter, the next 15 mm, and so on, until the outer ring reaches a diameter of 45 mm. By simply placing this device over a lesion, even if it is not circular or regular in outline, diameters can be easily measured and recorded. Intended for use in psoriasis, this measure might have other applications, e.g. monitoring the changes in size of a skin lesion that is suspected to be early or indeterminate leprosy.

## International Leprosy Seminar, Istanbul, Turkey, September 1991

The first International Leprosy Seminar was held in Istanbul on 2–3 September 1991 and was jointly organized by the Leprosy Centre of the Istanbul Medical Faculty, University of Istanbul (Professor Turkan Saylan) and the Regional Office of the World Health Organization for Europe. The main objective of the meeting was to bring together people working in leprosy from the neighbouring countries of Eastern Europe, the Middle East, North Africa and Malta, to exchange information,

with particular emphasis on the following: 1, a review of the present state of knowledge, including new approaches to leprosy control, epidemiology and social aspects; and 2, the teaching of leprosy in medical schools and the wider involvement of teaching staff.

Delegates came from Albania, Egypt, Greece, Iran, Israel, Kuwait, Malta, Romania, the USSR and the Yemen. Dr S. K. Noordeen, Chief, Leprosy, Division of Control of Tropical Diseases, WHO, Geneva, opened the meeting with a review of the present state of leprosy worldwide, including a description of the remarkable changes which have resulted from the implementation of multiple drug therapy (MDT). From a total world figure for registered cases, i.e. the world prevalence, of 5·3 million in 1986, the figure declined to 3·7 million in 1990 and is currently 3·4 million. It is expected that there will be a steady decline towards about 400,000 cases by the year 2000. Dr Colin McDougall (Oxford, UK) described basic diagnosis, classification, reactions, treatment and the evaluation of patients in leprosy control programmes. Miss Jean Watson (London, UK) spoke on the prevention and treatment of disability and Professor Turkan Saylan the social aspects of leprosy. The second day was devoted to a visit to the Istanbul Leprosy Hospital at Bakirkoy with full discussion of the facilities available there for diagnosis, drug treatment, disability prevention and management, eye examination and prosthetics. The final session dealt with the teaching of leprosy to students in medical schools and the greater involvement of medical staff in various faculties. Regardless of the extent of the leprosy problem, it transpired, from information presented by delegates, that medical schools in the countries represented at this meeting allocated about 1 hour to leprosy in the entire curriculum. Recommendations were made for: 1, a longer period, including clinical or field work in countries with a continuing and significant problem; 2, the greater involvement of teachers in departments such as neurology, dermatology, orthopaedics and community medicine; and 3, the wider of use of videos, especially in situations where experienced and capable teachers are not readily available. The entire range of TALMILEP teaching and learning materials for leprosy was on display throughout the seminar, including the video catalogue.

## Implementing multiple drug therapy for leprosy, OXFAM, UK

OXFAM's description of this 45-pp paperback is as follows:

'The system of multiple drug therapy for leprosy recommended by the World Health Organization in 1982 is an extremely effective treatment which, if widely introduced and effectively operated, could result in a dramatic reduction of the incidence and severity of leprosy throughout the world. This book, written in the form of extended answers to a series of questions, deals with a variety of aspects of the care and management of patients undergoing multiple drug therapy. It is aimed essentially at those in senior positions concerned with teaching health workers, programme planning and implementation of leprosy control programmes.'

In the original English language version, over 5000 copies were sold and the 4th edition (1988) recently sold out, and is being reprinted now. CERPHA (Comissao Evangelica de Reabilitacao de Pacientes de Hanseniase, Rua Guapeni 54/101, Caixa Postal 24046, Rio de Janeiro, Brazil) translated and distributed 2000 copies in Brazil. Copies in Spanish are available from Centro de Investigacion de Enfermedades Tropicales, Apdo 25-A, Acapulco, Guerrero, Mexico. Copies in Bengali can be obtained from Dr D. S. Chaudhury, Greater Calcutta Leprosy Treatment and Health Education Scheme, 23 Market Street, Calcutta 700 087, India. The price for an English edition, from OXFAM, Banbury Road, Oxford, England, is £3.50 (US $7) plus postage.

## Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Professor J. L. Turk, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

It is understood that the paper is offered to *Leprosy Review* alone, that it will be subject to editorial revision, and that its copyright becomes the property of the British Leprosy Relief Association. Manuscripts should be typewritten, in double spacing, on one side of A4 (297 × 210 mm) paper, with wide margins (4 cm all round). Contributors must send three complete copies of the text, tables and figures. On a separate sheet give the title, short title, name and postal address of the author, together with the name of the institution where the work was done. Abbreviations of titles of journals should follow the list of journals indexed in *Index Medicus*. References to books should include the editor(s), publisher and place of publication. Once manuscripts have been accepted a copy on disk that matches the hard copies exactly would be very much appreciated.

*Units and Abbreviations*. The Journal recognizes the adoption of the Système International d'Unitès (SI Units) proposed in *Units, Symbols and Abbreviations* (1972) published by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Abbreviations should only be used for unwieldy names, and only when they occur frequently.

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