Volume 65, Number 2, June 1994

LEPROSY REVIEW

Published Quarterly for the
British Leprosy Relief Association

ISSN 0305-7518

Leprosy Review

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

British Leprosy Relief Association
LEPRA

Editorial Office: Lepra, Fairfax House, Causton Road, Colchester CO1 1PU, England
Assistant Editor: Jennet Batten, 94 Church Road, Wheatley, Oxon OX9 1LZ, England

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.

British Leprosy Relief Association
Registered Offices: Fairfax House, Causton Road, Colchester CO1 7PU

CONTENTS

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.

Proofs are submitted to authors for immediate return by air.

Copyright/Offprints. Authors submitting a manuscript do so on the understanding that if it is accepted for publication, copyright in the paper for the United States of America shall be assigned to the Association. In consideration for the assignment of copyright, the Association will supply 20 offprints of each paper. Further offprints may be ordered at extra cost and a price list/order form is sent to authors with their proofs. The Association will not put any limitation on the personal freedom of the author to use material contained in the paper in other works which may be published in North America.

* * *

Leprosy Review is published quarterly (Mar., June, Sept., Dec.) by the British Leprosy Relief Association (LEPRA). 1995: Volume 66, 4 issues; £30, or £7.50 per copy, inclusive of postage and packing (UK and abroad). Subscription orders or enquiries should be sent to (LEPRA), Fairfax House, Causton Road, Colchester CO1 1PU, England. At its own discretion, LEPRA will continue, and also expand, its policy of sending free issues of this journal to people in various parts of the world; this will include doctors working directly with leprosy who cannot afford the above subscription, or obtain foreign currency, together with selected libraries covering tropical medicine.

Typeset and printed at Alden Press Limited, Oxford and Northampton, Great Britain

Lepr Rev (1994) **65,** 81–87

Editorial

SOME POINTS ON THE ELIMINATION OF LEPROSY

During the last decade, and on a large scale since 1987–88, the widespread use of multidrug therapy (MDT) regimens in leprosy control programmes, as recommended by WHO in 1982[5] and in 1988[6], has dramatically changed the leprosy situation.[9] While in 1986 5·3 million leprosy cases were registered worldwide, there are now 2·3 million patients registered for treatment, of whom 1,100,000 are on MDT. Since the introduction of MDT regimens, 4·3 million leprosy patients have been treated with this method and consequently classified as 'cured', with or without sequelae (with the exception of a negligible number of relapses).

However, it is recognized that, although in many countries MDT coverage is progressing, in others where operational problems exist, MDT coverage may not increase as expected. In general, the reason for such a decline in MDT expansion is that, until recently, the method has been implemented in countries or areas which have adequate infrastructure and facilities, and now it is being extended to 'difficult areas' with poor working conditions.

It was at this juncture that in May 1991 the World Health Assembly adopted a Resolution[8] to eliminate leprosy as a public health problem by the year 2000, and defined elimination as corresponding to a level of prevalence below 1 per 10,000 population.

This resolution has raised a series of questions and concerns.[2] It has also stimulated a great deal of discussion, both in WHO and in other quarters, in order to clarify a number of issues and to develop the appropriate approach for attaining the elimination of leprosy. WHO, through several consultations and meetings at various levels,[7] evolved a strategy for eliminating leprosy as a public health problem at country level.

The current leprosy situation

Based on WHO information, the current leprosy situation in the world is summarized in Table 1.

The analysis of the distribution of leprosy by country shows that, if leprosy remains a public health problem in 87 countries or areas, 25 countries have almost 95% of the leprosy burden in the world. Table 2 shows the registered prevalence and MDT coverage for these 25 most affected countries.[9]

0305-7518/94/064081+07

Table 1. Summary of the global leprosy situation

Estimated cases	3,055,210
Registered cases	2,291,581
Registered cases on MDT	1,117,508
New cases detected in 1992	653,354
Cumulative number of patients having completed MDT	4,237,712
Population living in countries with prevalence above 1 per 10,000	2,400,000,000
People with visible disabilities resulting from leprosy	2–3 million
Expectations:	
Patients to be treated between 1993 and 2000:	6–7 million
Additional cost involved in elimination strategy	US$ 420 million to US$ 600 million

The current strategy for leprosy control and the elimination strategy

CURRENT STRATEGY

The current strategy for leprosy control is based upon: (a) early identification of cases and standardized classification; (b) appropriate treatment of the same with WHO–MDT regimens; and, (c) health education directed to patients and their communities. The result

Table 2. Magnitude of the leprosy problem in the top 25 endemic countries

Countries	Year*	Registered Cases	Prevalence† per 10,000	Patients on MDT	MDT Coverage %	Completed MDT	Cumulative MDT cov.%
India	92	1459338	16·40	742988	50·91	3500000	85·56
Brazil	91	250066	16·00	62041	24·81	23008	31·15
Indonesia	92	74683	3·90	36907	49·42	74113	74·61
Bangladesh	92	19932	1·63	13007	65·26	35618	87·53
Myanmar	92	57389	11·19	31900	55·59	96181	83·40
Nigeria	92	62080	7·01	15088	24·30	2251	26·95
Sudan	92	31028	11·62	7198	23·20	2113	28·10
Philippines	92	14925	2·28	9506	63·69	28491	87·52
Iran	91	10487	1·84	10487	100·00	0	100·00
Vietnam	91	18342	2·63	11004	59·99	23284	82·37
Madagascar	92	5290	4·13	5188	98·07	8037	99·23
Egypt	91	8696	1·59	8696	100·00	8868	100·00
Nepal	92	22812	11·37	15318	67·15	22735	83·55
China	92	20003	0·17	19744	98·71	47073	99·61
Zaire	92	7736	2·04	2181	28·19	41957	88·82
Mozambique	92	19216	11·63	2360	12·28	533	14·65
Colombia	89	18983	5·54	7229	38·08	1668	43·08
Mexico	92	16732	1·81	7372	44·06	1322	48·16
Ethiopia	91	12041	2·31	11680	97·00	42938	99·34
Guinea	92	6942	11·36	6942	100·00	18366	100·00
Cote d'Ivoire	92	6483	5·01	4696	72·44	11910	90·28
Mali	92	12710	12·95	3114	24·50	3279	39·98
Chad	92	6952	11·64	761	10·95	2472	34·31
Niger	92	6468	7·84	447	6·91	1087	20·30
Pakistan	90	9611	0·74	2389	24·86	6174	54·25
Total		2178945	6·45	1038243	47·65	4003478	81·55

* Last year from which the data are available.
† Using the 1992 mid-year population data, from World Population Prospects 1990 (UN).
From *Weekly Epidemiological Record*, 1993, 68: 181–188. WHO June 1993.

of this strategy has been rapid, drastic reductions in prevalence; decreases by 90% within 5 years are common in well-organized control programmes.[3] However, parallel decreases of incidence are not observed although, in a few instances, a relative decrease in incidence has been attributed to MDT. Despite the fact that there is very little proof of the impact of MDT on the transmission of *Mycobacterium leprae*, it is hoped that the decrease in prevalence will, by reducing the sources of infection, ultimately result in a fall of incidence.[4]

In view of the contradictory results obtained in several prospective studies on the preventive value of BCG against leprosy, WHO does not recommend BCG vaccination as part of its strategy for leprosy control. However, recent case control studies may lead to a revision of this opinion. A recent prospective study in Venezuela in which a mixture of BCG and killed *M. leprae* was used as a candidate vaccine has given inconclusive results. Results of other vaccine trials using *M. leprae* mixed with cultivable mycobacteria other than BCG are expected to be available after 1995.[10]

ELIMINATION STRATEGY

The elimination strategy includes exactly the same technical components as that of leprosy control but it is different in two aspects: a time limit (the year 2000) has been added and a target (prevalence lower than 1 per 10,000) has been ascribed. In other words, the elimination strategy is just a natural expansion and strengthening of leprosy control based on MDT. If no time limit had been fixed, the step designated as elimination would have been considered as a target to be reached at any time by each individual country.

The additional constraints of 'time limit' and 'prevalence target' will, in certain areas, make it difficult for the elimination strategy to be implemented: all patients, including those difficult to reach, those reluctant to be diagnosed as having leprosy, those who do not care—not to mention those with problems of differential diagnosis—will have to be localized and then persuaded to accept a full course of an appropriate MDT regimen.

The WHO Leprosy Unit has worked out a model elimination strategy with successive phases, each of which have specific activities.[4] As part of this process, several important issues were clarified. For instance, because of the well-known uneven geographical distribution of leprosy, it was necessary to decide on a level of population for use as a denominator to monitor the decrease in prevalence and incidence rates. After discussion, it was found that, for practical reasons, elimination should be declared first at national level and, later on, at the level of regions or districts which originally had high prevalence.

Improvements to be expected from the elimination strategy

It appears that the elimination strategy could render leprosy control activities more effective in several respects, as summarized below.

IMPROVED CASE DETECTION

It is well known that, as a rule, MDT regimens attract patients much more than did the previous dapsone monotherapy. However, when careful estimates are made of the total number of existing cases in MDT-based control programmes, it is generally concluded

that the actual number of patients is significantly greater than the number of registered cases.[9] The identification of non-registered patients is obviously an essential step in the expansion of the MDT coverage if we are to reduce the gap between registered and estimated cases.

IMPROVED MONITORING OF LOW-INCIDENCE SITUATIONS

In a proportion of endemic countries the control strategy has been followed by very low prevalence and case detection levels. With the elimination strategy, prevalence and case detection rates will be further reduced to minimal levels. In the absence of a reliable test for subclinical infection, which could make the monitoring of minimal incidence situations possible, the elimination strategy has stimulated an effort to develop methods for monitoring such situations. So far, it is expected that these methods will include a set of selected indicators and, at the ultimate phase of the elimination process, the use of sentinel centres.[1]

There is one stage in the elimination process at country level which deserves special consideration. It is when the prevalence rate in its decreasing process becomes equal to the case detection rate (or when the prevalence rate becomes lower than the case detection rate, as a result of PB patients diagnosed during the first half of the year and having completed MDT by the end of the same year). This stage is most interesting; when it has been reached, in subsequent years, if MDT has an impact on incidence, taking into account cases infected before the introduction of MDT, successive annual 'incidence' rates should be decreasing.

IMPROVED MDT COVERAGE

For many reasons MDT-delivery to patients can be difficult, resulting in poor compliance of the patient. It is clearly indicated in the elimination strategy[4] that flexibility is important if we are to facilitate patients' accessibility to MDT. Adaptation to patients' constraints, in terms of time and a place for drug supply, is an obvious and simple possibility. In the more distant future, some of the new drug regimens currently under evaluation, e.g. regimens with monthly supervised intake of all drugs together and no daily unsupervised intake, could be a solution in certain circumstances.

OPPORTUNITY TO GO AS FAR AS POSSIBLE IN LEPROSY CONTROL

Improved case detection, improved monitoring of low incidence situations, and improved MDT coverage are the main technical elements of improved leprosy control. However, I strongly feel that those responsible for leprosy work should not only try to increase the impact of the available technology on the leprosy problem, but should do so within the minimum time interval.

Thus, the responsible authorities should take advantage of the ongoing control strategy to build the elimination strategy on the already existing infrastructure and facilities, this being obviously the most cost-effective option. However, there are concerns which should be taken into account, the two most important of which are, perhaps, the following:

(a) For all those involved in leprosy activities, it is of course very gratifying to see that the problem is being alleviated through MDT-based control. However, there is the

possibility that, in some programmes, the authorities might be satisfied with a reduction in prevalence of say 90% of already registered cases, and therefore may not be inclined to make special efforts to chase non-registered cases, nor to reduce the prevalence to 1 per 10,000.

(b) As a consequence of the drastic reduction in prevalence resulting from the control strategy, the donor agencies have expressed concern that fund-raising for leprosy activities could become difficult now that the size of the leprosy problem has so much decreased.[2]

In fact, at this very moment, all partners involved, especially leprosy services and donor agencies, should not relax their efforts; on the contrary, they should redouble their activities so as to achieve, as soon as possible, the maximum that can be achieved for leprosy sufferers using the existing tools.

Problems inherent to the elimination strategy

NEED FOR ADDITIONAL RESOURCES

WHO has made an estimate of the additional financial resources required to implement the elimination strategy. This estimate is from US$ 420 to US$ 600 million for the period 1993 to 2000. Although this amount is substantial, it is not beyond the possibilities of donor agencies.

NEED TO GIVE PRIORITY TO DISABILITY PREVENTION AND MANAGEMENT

Early diagnosis and appropriate MDT are the required basis for the prevention of disabilities. Other more specific activities aimed at disability prevention and management, such as early detection and treatment of nerve damage, education of patients on simple measures for protecting eyes, hands and feet, reconstructive surgery, etc., are also quite important.

Some MDT-based control programmes have taken advantage of the reduced number of patients by incorporating into their activities those related to prevention and management of disabilities. If this is not done at an early stage, these activities should be integrated into the elimination programme during its phase of consolidation.

Conclusion

To conclude, I have 3 important questions to ask.

IS THE ELIMINATION STRATEGY AN IMPROVEMENT COMPARED TO THE CONTROL STRATEGY?

As discussed above, it would appear that, if compared to the control strategy, the elimination strategy is likely to result in increased case detection, increased MDT coverage and better monitoring of progress.

The reasons for which the elimination strategy should be more effective than the control strategy are its specific components: a 'time limit' and a 'defined target'.

WHAT IS THE IMPORTANCE OF THE DRAWBACKS OF THE ELIMINATION STRATEGY?

(a) The need for additional resources does not appear a serious constraint.
(b) There will be important operational difficulties:

(1) related to activities (case detection, MDT delivery, treatment compliance, etc.); and
(2) related to monitoring of progress as we do not have an adequate indicator for measuring progress in low prevalence/incidence situations.

IS IT TIMELY TO ENGAGE IN AN ELIMINATION STRATEGY?

It seems that if the elimination strategy is implemented as a further step and natural expansion of the control strategy, there can be only advantages, such as:

(a) It can be built on the infrastructure and facilities already established for the control strategy, and can take advantage of the experience gained by its implementation.
(b) In terms of caseload, a better operational and possibly epidemiological (concerning incidence) impact than with the control strategy; in any case, the greatest impact which could be obtained from an MDT-based strategy.

It is important to note that these advantages will become effective only if the two following conditions are met.

(a) Operational methods are developed to overcome operational difficulties. This should be feasible, although unconventional solutions to some problems should be accepted.
(b) Methods for monitoring progress in low prevalence/incidence situations will have to be developed. This may cause real difficulties. However, full use should be made of the ratio prevalence/case detection rate. This indicator may prove to have a greater significance than expected.

Altogether, it seems that the advantages of implementing the elimination strategy in sequence with the control strategy, and as a natural expansion of the latter, outweighs the disadvantages. In contrast, if implementing the elimination strategy was delayed, there is no certainty that the methods required to facilitate case-detection and case-holding, and to monitor progress in low prevalence/incidence situations, would be developed without the commitment of national authorities to eliminate leprosy as a public health problem.

St Armou
64160 Morlaas
France

H. SANSARRICQ

References

[1] Daumerie D, Réseau de surveillance épidémiologique et évaluation des progrès vers l'élimination. Réunion des responsables de la lutte antilépreuse, Yaounde, 1993.
[2] Fine, PEM. Reflections on the elimination of leprosy. (Editorial) *Int. J. Lepr.* 1991; **60:** 71–80.
[3] Noordeen SK. Elimination of leprosy as a public health problem. (Editorial) *Lepr Rev*, 1992; **63:** 1–4.
[4] Noordeen SK. Global strategy for the elimination of leprosy as a public health problem. Personal communication.
[5] WHO Study Group on Chemotherapy of Leprosy for Control Programmes, Geneva: World Health Organization, 1982, Technical Report Series 675.

[6] WHO Expert Committee on Leprosy. Sixth Report, Geneva. World Health Organization, 1988. Technical Report Series, 768.
[7] World Health Organization. Report on the Second meeting of the WHO Working Group on Leprosy Control, Geneva: World Health Organization, 1992. WHO.
[8] Resolution (WHA44.9), May 1991.
[9] Progress with implementation of MDT. *Weekly Epidemiological Record, No. 21,* May 1993.
[10] Report of the Workshop on approaches to epidemiology, prevention and control, 14th International Leprosy Congress, Orlando, 1993.

Lepr Rev (1994) **65,** 88–99

Evaluation of chemiluminescence, procoagulant activity and antigen presentation by monocytes from lepromatous leprosy patients with or without reactional episodes

D. O. SANTOS*¶, P. N. SUFFYS†, A. L. MOREIRA‡, K. BONIFACIO‡, J. L. SALGADO‡, D. ESQUENAZI‡, A. L. BERTHO§ & E. N. SARNO‡

**Department of Cellular and Molecular Biology, Federal Fluminense University, Rio de Janeiro; †Biochemistry and Molecular Biology Department, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro; ‡Leprosy Unit, Department of Tropical Medicine, Oswaldo Cruz Foundation, Rio de Janeiro; §Protozoology Department, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro, Brazil*

Accepted for publication 12 October 1993

Summary In this study, we evaluated the activity of peripheral blood mononuclear cells (PBMC), isolated from treated and untreated lepromatous leprosy patients, from lepromatous leprosy patients during and after reactional episodes (erythema nodosum leprosum (ENL) and reversal reaction (RR) , and from normal healthy individuals. We determined reactive oxygen intermediate (ROI) production, procoagulant activity (PCA) and HLA-DR antigen expression of monocytes, besides lymphoproliferation, both in the presence and absence of various stimulatory agents. Phorbol myristate acetate (PMA) stimulated ROI production by monocytes from all the groups studied, with patients during reactional episodes (ENL and RR) showing a significantly higher response ($p < 0{\cdot}009$ and $p < 0{\cdot}00001$). Irradiated *Mycobacterium leprae*, although having little effect when added alone, strongly suppressed PMA-stimulated ROI production. Muramyl dipeptide (MDP) had no influence on either basal or on PMA-induced ROI production. Basal monocyte PCA, as well as *M. leprae* or concanavalin A (ConA)-induced monocyte PCA, was comparable in monocytes from all the groups studied. ConA was able to induce mitogenic activity in mononuclear cells isolated from all the groups studied. *M. leprae*, although stimulatory for normal individuals, did not induce lymphoproliferation in lepromatous leprosy patients, except for cells from patients during RR, which responded equally to *M. leprae* and to ConA. The absence of *M. leprae*-induced lymphoproliferation in lepromatous leprosy patients is not caused by the lack of basal HLA–DR expression, as PBMC from all individuals studied showed the same level of this antigen. Our results suggest an increase of spontaneous or PMA-

¶ Address for correspondence: Dr D. O. Santos, Leprosy Unit, Department of Tropical Medicine, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro, Brazil, Manguinhos, CEP 21045-900, Rio de Janeiro, RJ, Brazil.

0305-7518/94/065088+12 $01.00

induced monocyte activity, as detected by ROI production, during the reactional episode; addition of *M. leprae* suppressed this response. The increase in monocyte activity could be correlated with the increase of lymphoproliferation response to *M. leprae* during RR, but not during ENL. The importance of a possible immune suppressive action of *M. leprae* is discussed.

Introduction

Leprosy, one of mankind's oldest diseases, is characterized by a very complex immunological response which determines the disease's clinical manifestations. Depending on the capacity of the infected individual to mount an adequate immune response, leprosy appears either in a paucibacillary tuberculoid form (TL), borderline forms such as borderline–tuberculoid (BT), borderline–borderline (BB), and borderline–lepromatous (BL), or in a multibacillary lepromatous stage (LL). However, leprosy is not a stable disease and is characterized by episodes of reactional states such as the reversal reaction (RR), occurring only in borderline patients, and erythema nodosum leprosum (ENL), occurring in both LL and BL patients.[1,2] Cell mediated immunity (CMI) plays a key role in the immunological response to leprosy. In contrast to healthy individuals and TL patients, lepromatous leprosy patients do not mount an efficient CMI response against *Mycobacterium leprae*.[3,4] The absence of a functional T lymphocyte proliferative response[3] and a low level of interferon-gamma (IFN-γ) production[4] in response to infection with *M. leprae* probably results in adequate monocyte activation. Mononuclear phagocytes play a primary role during immune defence; functional deficiency of these cells has been observed in LL patients.

Microbicidal competence of phagocytes in leprosy patients is usually determined by measurement of reactive oxygen intermediate (ROI) production. However, probably because of the complexity of the interaction of macrophage and bacilli, conclusions from studies using this experimental design are highly contradictory.[5–12] One of the initial events in the cascade of steps leading to pathogen killing in the bacterially-induced CMI response is phagocytosis of the bacilli and subsequent expression of bacterial antigens on the surface of the phagocytic cell.[13] Experiments *in vitro* indicate that failure of antigen presentation in an immunogenic form, as observed in monocytes isolated from lepromatous leprosy patients, might lead to the lack of an efficient response.[14] Monocyte activation can also be determined by measuring cellular procoagulant activity (PCA).[15] *M. leprae* has been shown to induce PCA activity in monocytes from normal individuals,[16] but so far no information exists about this activity in lepromatous leprosy patients.

These data prompted us to evaluate various parameters of mononuclear phagocyte activity in patients with distinct clinical manifestations of leprosy. We were able to extend our previous observations on monocyte activity from leprosy patients[10] with new data on monocyte functions such as ROI production, PCA induction, HLA–DR expression, and on lymphoproliferation of mononuclear cells *in vitro*.

Materials and methods

SUBJECTS

All lepromatous leprosy patients were diagnosed at the Souza Araujo Ambulatory

(Leprosy Unit, Oswaldo Cruz Foundation, RJ, Brazil). Clinical diagnosis was confirmed by skin biopsy; disease classification was according to the criteria of Ridley & Jopling.[17] Of the 59 LL and BL patients in this study, 16 had only recently been treated, while 25 had not received any treatment. Another 14 were in a reactional episode (10 patients with ENL and 4 with RR), while 4 patients were in a postreactional state. Multidrug therapy (MDT) was as follows: monthly doses of rifampicin (600 mg) and clofazimine (300 mg) under supervision, as well as daily self-administered doses of dapsone (100 mg) plus clofazimine (100 mg) every other day for 24 months. Patients undergoing a reactional episode did not receive any specific treatment for reactions before blood collection. Patients in a postreactional state were treated by thalidomide and/or prednisone during the reactional episode. Blood collection of these patients was carried out in the first week after the reactional episode, when these patients no longer displayed any associated symptoms. The duration of the reactional episode was variable for each patient. We used 20 laboratory staff as normal controls.

ISOLATION OF MONONUCLEAR CELLS

Mononuclear leukocytes were isolated from heparinized venous blood using Ficoll-Histopaque (Pharmacia Fine Chemicals, Piscataway, NJ, USA) as previously described.[10]

MEASUREMENT OF ROI PRODUCTION

We incubated 1,000,000 mononuclear leukocytes on 13 mm diameter glass coverslips in 24 well microtitre plates (Becton Dickinson, San Jose, CA, USA) in RPMI 1640 medium (Gibco, Grand Island, NY, USA), supplemented with 10% foetal bovine serum (FBS)(Gibco), 2 mM glutamine (Gibco), 100 U/ml penicillin (Gibco) and 100 μg/ml streptomycin (Gibco) at 37°C in 5% CO_2. The cells were incubated with or without 20 μg/ml irradiated, armadillo derived soluble *M. leprae* sonicate (IMMLEP BANK, Mill Hill, UK) and/or 1 μg/ml muramyl dipeptide (MDP; Sigma Chemical Co, St Louis, MO, USA) for 20 h. The medium was removed and the adherent monocytes were washed 3 times with medium containing 2% FBS before use. Measurement of ROI production occurred in the presence of 50 μM luminol (Sigma) as a chemiluminescence CL probe. ROI was induced by the addition of 0·5 μg/ml phorbol-myrystate-acetate (PMA, Sigma) and measured immediately in a Packard liquid scintillation spectrometer (model 1900 CA) as previously described.[10] Results are calculated as follows: Stimulation Index (SI) CL after cell stimulation divided by CL of unstimulated cells. The percentages of basal CL were calculated as follows: (basal chemiluminescence (CL) of monocytes isolated from patients minus CL of monocytes isolated from normal individuals divided by CL of monocytes isolated from normal individuals) $\times$ 100.

DETERMINATION OF PCA

Mononuclear cells (2×10^4/well) were incubated in 96 well plates (Becton Dickinson) in RPMI 1640 medium, supplemented with 10% human serum in the presence or absence of 20 μg/ml *M. leprae* antigen or 10 μg/ml ConA (Sigma). After 20 h the supernatant was removed and the adherent cells lysed by incubation with 100 μl *n*-octyl-B-D-glucopyrano-

side (50 μM; Sigma) for 15 min at 37°C and stored at −70°C until further use. PCA of the monocytes was measured using a modified Edwards & Rickles assay.[15] Briefly, cell lysates were transferred to siliconized tubes, after which 100 μl of plasma was added and coagulation was induced by the addition of $CaCl_2$ to a final concentration of 0·03 M, followed by gentle shaking. Rabbit brain thromboplastin (Baxter Healthcare Corporation, Miama, FL, USA) was used as a standard. For determination of basal monocyte PCA, aliquots of freshly isolated mononuclear cells were sedimented at 200 g for 5 min and lysed; PCA was then determined as described above.

DETERMINATION OF HLA–DR ANTIGEN EXPRESSION

At least 5×10^5 mononuclear cells were resuspended in 20 μl of solution buffer (Earle's balanced salt solution pH 7·2, supplemented with 0·1% sodium azide and 3% FBS) and incubated with OKM1 (Becton Dickinson) or anti-DR monoclonal antibodies (National Institutes of Health, Bethesda, MD, USA), followed by incubation with fluoresceinated goat antimouse Ig polyclonal antibody (Becton Dickinson). The cells were fixed with 1% paraformaldehyde and analysed in a flow cytometer FACScan (Coulter-Miami, USA).

LYMPHOCYTE PROLIFERATION ASSAY

Mononuclear cells were incubated in 96 well plates at a concentration of 2×10^5 cells per well in 200 μl RPMI, supplemented with 10% human autologous plasma, 10 mM HEPES, 2 mM L-glutamine, antibiotics and 50 μM 2-mercaptoethanol. Cells were stimulated with 20 μg/ml *M. leprae* or 15 μg/ml ConA (Sigma). Blast formation was determined by measuring radioactive thymidine incorporation 5 days after the addition of *M. leprae* or 2 days after the addition of ConA. Briefly, cells were labelled by the addition of 1 μCi/well of [methyl-^{3}H] thymidine (5·0 Ci/mmol; Amersham, Bucks, UK) per well for 18 h. Cells were lysed on a glass filter and the amount of incorporated labelled thymidine measured in a liquid scintillation counter. The SI was calculated as follows: incorporated radioactivity in cells stimulated with antigen divided by incorporated radioactivity in unstimulated cells.

STATISTICAL ANALYSES

Significance of the difference between the values of the various groups studied was evaluated by the Student's *t*-test.[18] The *t*-test was modified to correct for the heterogeneity of variances.

Results

ACTIVATION OF MONOCYTES

Figure 1 shows the basal CL of monocytes isolated from normal individuals or from patients with different forms of lepromatous leprosy. Monocytes isolated from patients during ENL or RR showed a significantly higher CL versus normal individuals (20%, $p < 0{\cdot}0001$; and 295%, $p < 0{\cdot}004$, respectively), whereas monocytes isolated from other

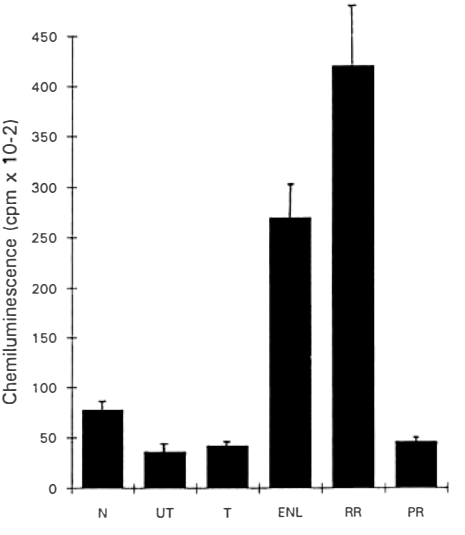

Figure 1. Basal chemiluminescence (CL) of monocytes. Monocytes were cultured for 1 day, washed and further treated for CL determination as described in the Materials and Methods. N, monocytes from normal individuals ($n = 20$); UT, untreated lepromatous leprosy patients ($n = 25$); T, treated lepromatous leprosy patients ($n = 16$); ENL, patients undergoing erythema nodosum leprosum ($n = 10$); RR, patients undergoing reversal reaction ($n = 4$) and PR, patients in post-reactional state ($n = 4$).

lepromatous leprosy patients showed a basal level of CL that was lower than that found in normal individuals ($p < 0{\cdot}04$). Table 1 shows the ROI production of monocytes, isolated from normal individuals or from lepromatous leprosy patients after stimulation with PMA and *M. leprae* or MDP. Monocytes from all individuals studied showed increased ROI production after incubation with PMA. Stimulation with PMA shows a difference in ROI response for LL and BL patients. Regardless of whether BL patients were treated or not, ROI production was comparable to that of normal volunteers; LL patients showed a much lower ROI response. Patients undergoing reaction manifestations (ENL and RR) showed the strongest CL response, differing significantly from normal volunteers. Although no significant change in basal CL was found after incubation of monocytes with *M. leprae*, ROI values were repeatedly slightly lower than in the absence of *M. leprae*. Pretreatment with *M. leprae*, however, strongly inhibited the PMA-induced CL response in all groups studied. Pretreatment of cells with MDP had no influence on either the basal or PMA-induced CL response.

MONOCYTE INDUCED PCA

PCA of monocytes from normal volunteers and lepromatous leprosy patients is shown in Table 2. PCA was only detectable after co-incubation of monocytes with other mononuclear cells (data not shown). Monocytes, isolated from all groups studied, spontaneously induced PCA; values from patients in the PR state, however, were considerably lower ($p < 0{\cdot}02$). Both ConA and *M. leprae* stimulated monocyte PCA without any significant difference between the various groups studied.

Table 1. Activation of monocytes as detected by chemiluminescence

Subjects	Chemiluminescence[a]						
Conditions at the time of the study	PMA	*Ml*[b]	*Ml*+PMA[c]	MDP	MDP+PMA[c]	MDP+*Ml*[d]	MDP+*Ml*+PMA[c]
Normal individuals ($n=20$)	14·0±6·0[e]	0·7±0·4	4·0±3·0	0·6±0·3	10·0±7·0	0·4±0·2	1·7±0·2
Untreated ($n=25$)							
BL[f]	12·0±4·0 (NS[g])	0·8±0·5 (NS)	2·0±1·0 (NS)	0·7±0·1 (NS)	10·0±5·0 (NS)	0·6±0·3 (NS)	1·7±1·1 (NS)
LL	6·0±2·0 ($p<0·01$)						
Treated ($n=16$)							
BL	13·0±3·0 (NS)	0·5±0·3 (NS)	1·8±0·9 (NS)	0·7±0·2 (NS)	20·0±10·0 ($p<0·02$)	0·4±0·1 (NS)	4·2±0·3 ($p<0·02$)
LL	5·0±3·0 ($p<0·01$)						
ENL ($n=10$)	27·0±5·0 ($p<0·0009$)	0·6±0·3 (NS)	3·1±1·5 (NS)	0·7±0·2 (NS)	29·0±11·0 ($p<0·001$)	0·4±0·2 (NS)	2·2±0·7 (NS)
RR ($n=4$)	32·0±5·0 ($p<0·00001$)	0·8±0·4 (NS)	7·2±1·2 (NS)	0·7±0·2 (NS)	25·0±8·0 ($p<0·003$)	0·8±0·3 (NS)	5·4±0·5 ($p<0·002$)
PR ($n=4$)	12·0±6·0 (NS)	0·6±0·3 (NS)	0·9±0·7 (NS)	1·5±0·7 (NS)	11·0±7·0 (NS)	0·3±0·1 (NS)	1·1±0·7 (NS)

[a] Stimulation index = chemiluminescence after stimulation/chemiluminescence without stimulation.
[b] *M. leprae*.
[c] PMA added 24 h addition of *M. leprae* MDP.
[d] MDP and *M. leprae* added simultaneously.
[e] Mean value ± standard deviation.
[f] When not specified, values from BL and LL patients were not significantly different.
[g] Not significantly different from normal volunteers.

Table 2. Procoagulant activity (PCA) of monocytes

Subjects: conditions at the time of the study	PCA (mU thromboplastin)		
		Stimulus-induced	
	Spontaneous	ConA	*M. leprae*
Normal individuals ($n=20$)	653 ± 176[a]	1737 ± 659	1509 ± 310
Untreated ($n=25$)	1058 ± 724	3038 ± 1246	2152 ± 1208
Treated ($n=16$)	510 ± 155	2513 ± 914	2012 ± 627
ENL ($n=10$)	1109 ± 1154	2435 ± 1088	2297 ± 1037
RR ($n=4$)	911 ± 892	2301 ± 568	2073 ± 291
PR ($n=4$)	256 ± 112 ($p<0{\cdot}02$[b])	1361 ± 675	1254 ± 707

[a] Mean value ± standard deviation.
[b] All other values do not significantly differ from normal individuals.

Table 3. Flow cytometric quantification of HLA–DR expression in monocytes as measured by fluorescence

Subjects: conditions at the time of the study	Fluorescence		
	% OKM1 positive cells	% DR-positive cells	% MFI[a]
Normal individuals ($n=20$)	13 ± 7[b]	16 ± 5	80 ± 15
Untreated ($n=20$)	17 ± 8	19 ± 10	77 ± 10
Treated ($n=16$)	12 ± 1	15 ± 6	75 ± 10
ENL ($n=10$)	18 ± 8	16 ± 6	77 ± 12
RR ($n=4$)	17 ± 3	15 ± 4	87 ± 14
PR ($n=4$)	12 ± 4	15 ± 3	81 ± 10

[a] Mean fluorescence intensity of DR-positive cells.
[b] Mean value ± standard deviation.

HLA–DR SURFACE ANTIGEN EXPRESSION

Expression of HLA–DR by PBMC from normal individuals and lepromatous leprosy patients is shown in Table 3. No significant differences emerged between HLA–DR surface antigen expression in any of the groups studied, and the number of monocytes within the mononuclear cell population was the same, independent of the patient's clinical status.

LYMPHOCYTE PROLIFERATION

Table 4 shows that cells from all the groups studied responded to stimulation with ConA. Patients during RR showed a stronger response. Mononuclear cells, isolated from normal individuals, also proliferated strongly after incubation with *M. leprae*. Within the population of lepromatous patients, only lymphocytes isolated from patients with RR were able to respond to the addition of *M. leprae*. Post-RR patients partially retained proliferative capacity.

Table 4. Lymphoproliferative responses of PBMCs from healthy individuals and leprosy patients

Subjects: conditions at the time of the study	ConA		*M. leprae*	
	−	+	−	+
Normal individuals ($n=20$)	1024 ± 213[a]	11733 ± 1667 (11 ± 3)[b]	2057 ± 321	12342 ± 1418 ($6 \pm 0{\cdot}5$)
Untreated ($n=20$)	678 ± 136 (NS[c])	4493 ± 1311 (7 ± 1) (NS[d])	907 ± 158 ($p<0{\cdot}04$[c])	1394 ± 300 (2 ± 1) ($p<0{\cdot}02$[d])
Treated ($n=12$)	708 ± 88 (NS)	2665 ± 199 (4 ± 1) ($p<0{\cdot}001$)	1325 ± 330 ($p<0{\cdot}04$)	1380 ± 302 (1 ± 2) ($p<0{\cdot}001$)
ENL ($n=10$)	341 ± 67 ($p<0{\cdot}04$)	3955 ± 924 ($11 \pm 0{\cdot}5$) (NS)	842 ± 218 ($p<0{\cdot}04$)	757 ± 125 (1 ± 1) ($p<0{\cdot}001$)
RR ($n=4$)	478 ± 41 ($p<0{\cdot}04$)	6597 ± 68 (13 ± 1) (NS)	369 ± 43 ($p<0{\cdot}0001$)	1845 ± 328 (5 ± 1) (NS)
PR ($n=4$)				
ENL	405 ± 51 ($p<0{\cdot}001$)	2638 ± 804 ($7 \pm 0{\cdot}8$) (NS)	412 ± 53 ($p<0{\cdot}001$)	824 ± 126 (2 ± 1) ($p<0{\cdot}001$)
RR	378 ± 137 ($p<0{\cdot}001$)	3529 ± 1204 (9 ± 1) (NS)	525 ± 75 ($p<0{\cdot}001$)	1785 ± 148 (3 ± 2) ($p<0{\cdot}001$)

[a] Mean value in cpm $\pm$ standard deviation.
[b] Stimulation index = mean cpm upon stimulation/mean cpm without stimulation.
[c] p value as compared to normal individuals.
[d] p value as compared to the stimulation index of normal individuals.

Discussion

Previous studies on ROI production by phagocytes from healthy individuals and lepromatous leprosy patients, upon stimulation with *M. leprae* and other agents, are contradictory.[5–9,11,12] We therefore measured various parameters of monocyte activity in the presence or absence of *M. leprae* from patients at given stages along the clinical spectrum of leprosy and its reactional states.

In monocytes isolated from all individuals studied, PMA induced a marked production of ROI, a process that was much more pronounced during reactional episodes. Lepromatous patients without reactional episodes displayed a weak PMA-induced CL response in comparison with normal individuals, as observed previously.[10] The PMA-induced ROI production observed in patients with ENL and RR could be linked to excessive monocyte activity. The high basal ROI seen in patients during reactional episodes strengthens this hypothesis, and the presence of extravascular complex in ENL could play an important role in monocyte activation.[1] No difference in ROI production was found in patients under treatment or not, an observation that could be generalized for all monocyte activities measured in this study. Furthermore, the CL response of LL patients was significantly lower than that of BL patients, who produced ROI to the same extent as did normal volunteers. This suggests some residual monocyte activity in BL patients—a finding that has recently been suggested by us when comparing monocyte activity from TL and LL patients.[10]

Although some groups have proposed a slow and weak ROI stimulatory capacity of *M. leprae*,[7,11,12] several reports claim *M. leprae* to be devoid of any stimulatory activity.[6,19] Such variable results could be partly explained by suppression of monocyte function by some fractions of *M. leprae*. We therefore tested whether *M. leprae* was capable of inhibiting the PMA-induced ROI response and, if so, to what degree this would vary in patients with different clinical forms of leprosy. Indeed, *M. leprae* was found to be strongly inhibitory, to a comparable extent throughout the whole gamut of leprosy patients studied. A suppressor role of various mycobacteria in skin-test responses, and an active role of suppressor factors in the so-called immune defect in LL patients, has been considered.[20] Phenolic glycolipid I (PGL1) is unique to *M. leprae* and was recently shown to decrease superoxide anion production by monocytes from normal donors stimulated with *M. leprae*.[11] It also acts as a scavenger of reactive oxygen species,[21] which may contribute to protecting the bacilli from killing by its host. PGL1 treatment does not inhibit PMA induced ROI production,[11] so it is unlikely that PGL1 alone is responsible for the suppression observed in this study. Synergistic suppression of PGL1 and other components such as lipoarabinomannan (LAM) is not unlikely. LAM has been attributed to have both macrophage stimulatory[22] and inhibitory[23] capacity. In addition, delipified *M. leprae* antigen seems to restore the ability of macrophages from leprosy patients to kill the bacteria.[24] *M. leprae* could also interfere with monocyte activity by inducing the release of prostaglandin E2, a well-known monocyte inhibitor.[25]

MDP is a synthetic analogue of Gram-positive bacterial cell wall peptidoglycan. According to Pabst & Johnston,[26] MDP retains adjuvant properties and primes macrophages to respond with increased ROI production after stimulation with PMA. In agreement with these findings, we observed that MDP exposure did not, in itself, induce ROI production by normal monocytes. However, MDP was unable to influence PMA-induced CL. These contradictory findings could be explained by the fact that the total

mononuclear cell population was incubated with MDP in our experiments. As MDP itself is a synthetic analogue of peptidoglycan, and *M. leprae* suppressed the PMA-induced ROI response when incubated with PBMC under the same conditions as MDP, we can exclude the possibility that peptidoglycan fragments present in *M. leprae* suppress the CL response.

PCA induced by monocyte thromboplastin was also used as a marker for monocyte activity. Monocytes induce an increase in PCA when activated by endotoxin, mitogens, antigens, or cytokines in the absence of lymphocytes.[27] In our study, *M. leprae* was able to induce monocyte PCA in normal individuals, a finding previously reported by Lyberg *et al.*[16] MDP also induced monocyte PCA in all individuals studied (data not shown). Surprisingly, PCA activity of monocytes, isolated from a PR patient, was significantly lower than in the other individuals studied. Perhaps the specific treatment for reaction episodes is suppressing this monocyte activity. Although PCA response to *M. leprae* and PMA was significant and comparable after 20 h of culture, we cannot exclude that PCA is more pronounced or variable between the groups studied at other time points. However, there are conflicting reports as to the time of maximal PCA after stimulation of monocytes; data ranging from 4 to 24 h have been reported.[16,28] As co-incubation of monocytes seems to sustain the PCA response, and our measurements were performed under these conditions, PCA was determined after 20 h.

There are many reports that suggest that patients with lepromatous leprosy are unable to exert a complete CMI response due to failure of their macrophages to present *M. leprae* antigens in an immunogenic form.[14] We could not find any difference in basal HLA–DR antigen expression between PBMC from normal individuals and any of the lepromatous leprosy patients. Our preliminary results indicate that stimulation with *M. leprae* has no influence on HLA–DR expression (data not shown). Comparable levels of HLA–DR expression between normal individuals, tuberculoid and long-term treated lepromatous leprosy patients were reported in another study.[29] If basal HLA–DR expression is a prerequisite for antigen presenting cells (APC) to present immunogenic *M. leprae* antigens, then, at least within this part of the complex CMI response network, APC from lepromatous patients seem to be equally functional. Native antigen presentation does not seem to be sufficient to allow induction of T-cell proliferation in response to *M. leprae*, as we found no increase in T-cell response after incubation of PBMC from lepromatous leprosy patients without reactional manifestations with *M. leprae*. It has been reported that the levels of HLA–DR expression of lepromatous patients reaches that of normal volunteers after stimulation with a combination of *M. leprae* and IFN-γ,[29] without inducing lymphoproliferation.

A T-cell proliferation response towards ConA was seen in all experimental groups studied. It has been demonstrated that the absence of T-cell responses in lepromatous leprosy patients is antigen specific.[3] Indeed, when observed, lymphoproliferation of cells from lepromatous leprosy patients after stimulation with *M. leprae* was smaller than with Con A. *M. leprae* was, however, as potent as Con A in stimulating cells from normal individuals. This is in contrast to the results of Molloy *et al.*[30] who did not observe a mitogenic response of mononuclear cells from normal individuals to *M. leprae*, which they ascribed to a generalized suppressive effect of contaminating LPS in their antigen preparation. In our study, neither treated nor untreated lepromatous leprosy patients showed a lymphoproliferative response towards *M. leprae*. The effect of treatment of lepromatous leprosy patients on CMI is still controversial; data obtained in our

laboratory demonstrate an increase in LTT after long-term treatment.[31] In contrast to this earlier study, the majority of our patients studied here were under drug treatment for only a short time. During RR, significant lymphoproliferation in response to *M. leprae* was observed. We also confirmed our earlier observations[10] that this is not the case in patients during ENL. This could be coupled with the observation of an improvement in clinical status of the patient during and after RR,[32] which probably does not occur during ENL. LTT responses were still elevated in the post-RR.

Recently, it has been proposed that the inhibitory effects of *M. leprae* for various cell functions can be correlated with the content of LPS in the preparations of *M. leprae* and its derivatives.[30] Although the LPS content in our *M. leprae* preparation might be sufficient for some of the effects observed in this study, lipids from *M. leprae* may have LPS-like activity. Sibley *et al.*[23] have demonstrated the ability of LAM to inhibit macrophage activation with a potency comparable to that of LPS. Furthermore, LPS has been shown to stimulate ROI production,[26] an activity that was not shared with our *M. leprae* preparation. Also, *M. leprae* induced a mitogenic response in mononuclear cells isolated from normal individuals and some leprosy patients. If LPS contamination in *M. leprae* preparations is involved in the suppression of mitogenic responses, it would have to be selective for cells from lepromatous leprosy patients.

Acknowledgments

This investigation received financial support from UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (TDR) and the CNPq. We thank Dr C. A. Mandarim-de-Lacerda for statistical analysis and the staff of the Souza Araujo Ambulatory at the Oswaldo Cruz Institute, Fiocruz for patient care and providing us with the clinical data. We also thank F. and C. Shapiro for critically reading the manuscript.

References

[1] Ridley MJ, Ridley DS. The immunopathology of erythema nodosum leprosum: the role of extravascular complexes. *Lepr Rev*, 1983; **54:** 95–107.
[2] Sehgal VN. Reaction in leprosy. Clinical aspects. *Int J Dermatol*, 1987; **26:** 278–85.
[3] Godal T, Mykestad B, Samuel DR, Myrvang B. Characterization of the cellular immune defect in lepromatous leprosy: a specific lack of circulating *Mycobacterium leprae* reactive lymphocytes. *Clin exp Imm*, 1971; **9:** 821–31.
[4] Nogueira N, Kaplan G, Levy E, Sarno EN, Kushner P, Granelli-Piperno A, Vieira L, Gould CV, Levis W, Steinman R, Yip YK, Cohn ZA. Defective interferon production in leprosy. Reversal with antigen and interleukin 2. *J Exp Med*, 1983; **158:** 2165–170.
[5] Sharp AK, Banerjee DR. Hydrogen peroxide and superoxide production by peripheral blood monocytes in leprosy. *Clin Immunol*, 1985; **60:** 203–6.
[6] Holzer TJ, Kenrad EN, Victoria S, Crisper RG. *Mycobacterium leprae* fails to stimulate phagocytic cell superoxide anion generation. *Infect Immun*, 1986; **51:** 514–20.
[7] Holzer TJ, Hizlaitis L, Vachula M, Wafaver CW, Andersen BR. Human phagocytic cell responses to *Mycobacterium leprae* and *Mycobaterium bovis* bacillus Galmette-Guerin. An *in vitro* comparison of leprosy vaccine components. *J Immunol*, 1989; **141:** 1701–1708.
[8] Horwitz MA, Levis WR, Cohn ZA. Defective production of monocyte-activating cytokines in lepromatous leprosy. *J Exp Med*, 1984; **159:** 666–78.
[9] Marolia J, Mahadevan PR. Reactive oxygen intermediates inactivate *Mycobacterium leprae* in the phagocytes from human peripheral blood. *Int J Lepr*, 1989; **57:** 483–91.

[10] Santos DO, Salgado JL, Moreira AL, Sarno EN. Reactive oxygen intermediates in the phagocytes from leprosy patients: correlation with reactional states and variation during treatment. *Int J Lepr*, 1992; **60:** 92–4.
[11] Vachula M, Holzer RJ, Kizaitis L, Andersen BR. Effects of *Mycobacterium leprae* phenolic glycolipid-1 on interferon-gamma of monocyte oxidative responses. *Int J Lepr*, 1990; **58:** 342–46.
[12] Vachula M, Worobec S, Andersen BR. A comparison of monocyte oxidative responses in leprosy patients and healthy subjects as influenced by mycobacterial lipid pretreatment. *Int J Lepr*, 1990; **58:** 534–39.
[13] Unanue ER, Cerottini JC. Antigen presentation. *Faseb J*, 1989; **3:** 2496–502.
[14] Hirschberg H. The role of macrophages in the lymphoproliferative response to *M. leprae in vitro. Clin exp Imm*, 1978; **34:** 46–51.
[15] Edwards RL, Rickles FR. The role of human T cells (and T cell products) for monocyte tissue factor generation. *J Immunol*, 1980; **125:** 606–11.
[16] Lyberg T, Closs O, Prydz H. Effect of purified protein derivative and sonicates of *Mycobacterium leprae* and *Mycobacterium bovis* BCG on thromboplastin response in human monocytes *in vitro*. *Infect Immun*, 1982; **38:** 855–59.
[17] Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five group system. *Int J Lepr*, 1966; **34:** 255–63.
[18] Ipsen J, Feigl P. The standard deviation and other measures of variation. 1970. In: *Bancroft's Introduction to Biostatistics*. 2nd ed., pp. 42–64.
[19] Launois P, Maillere B, Dieye A, Sarthou JL, Bach MA. Human phagocyte oxidative burst activation by BCG, *M. leprae*, and atypical mycobacteria: Defective activation by *M. leprae* is not reversed by interferon-γ. *Cell Immunol*, 1989; **124:** 168–74.
[20] Nye PM, Stanford JL, Rook GAW, Lawton P, MacGregor M, Reily C, Humber D, Orege P, Revanker CR, Terencio de las Aguas J, Torres P. Suppressor determinants of mycobacteria and their potential relevance to leprosy. *Lepr Rev*, 1986; **57:** 147–57.
[21] Chan J, Fujiwarw T, Brennan P, McNeil M, Turco SJ, Sibille JC, Snapper M, Aisen P, Bloom B. Microbial glycolipids: possible virulence factors that scavenge oxygen radicals. *Proc Natl Acad Sci USA*, 1989; **86:** 2453–457.
[22] Barnes PF, Chatterjee D, Brennan PJ, Rea TH, Modlin RL. Tumor necrosis factor production in patients with leprosy. *Infect Immun*, 1988; **60:** 1441–1446.
[23] Sibley LD, Hunter SW, Brennan PJ, Krahenbuhl JL. Mycobacterial lipoarabinomannan inhibits gamma interferon-mediated activation of macrophages. *Infect Immun*, 1988; **56:** 1232–1236.
[24] Marolia J, Robinson P, Mahadevan PR. A complex component modulating immune-deficient cells in leprosy patients leading to loss of viability of *Mycobacterium leprae*—a possible vaccine. *Clin exp Imm*, 1990; **79:** 7–14.
[25] Ridel PR, Jamet T, Robin Y, Bach MA. Interleukin 1 released by blood-monocyte derived macrophages from patients with leprosy. *Infect Immun*, 1986; **52:** 303–8.
[26] Pabst MJ, Johnston Jr RB. Increased production of superoxide anion by macrophages exposed *in vitro* to muramyl dipeptide or lipopolysaccharide. *J Exp Med*, 1980; **15:** 101–14.
[27] Szabo G, Miller-Graziano C. Induction and regulation of monocyte procoagulant activity. *Transplantation*, 1990; **50:** 301–9.
[28] Rickles FR, Hardin JA, Pitlick FA, Hoyer LW, Conrad ME. Tissue factor activity in lymphocyte cultures from normal individuals and patients with hemophilia. *J Clin Invest*, 1973; **52:** 1427–43.
[29] Desai S, Birdi TJ, Antia NH. Correlation between macrophage activation and bactericidal function and *Mycobacterium leprae* antigen presentation in macrophages of leprosy patients and normal individuals. *Infect Immun*, 1989; **57:** 1311–1317.
[30] Molloy A, Gaudernack G, Levis WR, Cohn ZA, Kaplan G. Suspension of T-cell proliferation by *Mycobacterium leprae* and its products: the role of lipopolysaccharide. *Proc Natl Acad Sci USA*, 1990; **87:** 973–77.
[31] Esquenazi D, Sampaio EP, Moreira AL, Gallo ME, Almeida JA. Effect of treatment on immune responsiveness in lepromatous leprosy patients. *Lepr Rev*, 1990; **61:** 251–57.
[32] Laal S, Mishra RS, Nath I. Type I reactions in leprosy—heterogenity in T-cell functions related to the background leprosy type. *Int J Lepr*, 1987; **55:** 481–84.

Lepr Rev (1994) **65**, 100–105

Titration of numbers of human-derived *Mycobacterium leprae* required to progressively oxidize ^{14}C-palmitic acid and release $^{14}CO_2$

E. J. SHANNON*, D. FROMMEL†,
M. GUEBRE-XABIER†‡ & H. S. HAILE-MARIAM‡
**Gillis W. Long Hansen's Disease Center, Carville, Louisiana; †Armauer Hansen Research Institute, Addis Ababa; and ‡Ali Africa Leprosy Rehabilitation and Training Center, Addis Ababa, Ethiopia*

Accepted for publication 16 December 1993

Summary *Mycobacterium leprae* was isolated from skin-punch biopsies of 2 untreated lepromatous leprosy patients. The bacteria were enumerated, diluted 10-fold and cultured in Middlebrook 7H9 medium supplemented with albumin, dextrose, catalase and ^{14}C-palmitic acid. The cultures were incubated at 33°C in a modified Buddemeyer radiorespiratory detection vessel. Those cultures containing at least 10^7 mycobacteria demonstrated a progressive evolution of $^{14}CO_2$.

Introduction

Until a medium capable of inducing multiplication and sustaining growth of *Mycobacterium leprae* in culture is developed, studies related to the metabolism and drug sensitivity will of necessity depend on tissue-derived organisms. The availability of *M. leprae* from the tissues of infected armadillos[1] or nude mice[2] and the competency of *M. leprae* to oxidize palmitic acid to carbon dioxide[3] has facilitated the development of *in vitro* drug sensitivity studies of established and new antileprosy drugs.[4,5]

We have shown that human-derived *M. leprae* is capable of utilizing palmitic acid as a substrate in catabolic metabolism (oxidation and release of CO_2) as well as anabolic metabolism (synthesis of ^{14}C-phenolic glycolipid).[6] In this study a large leproma was surgically removed from the eyelid of an 18-year-old male Ethiopian, enabling 2×10^8 *M. leprae* to be used in each culture. However, the appreciable amount of radioactivity recovered in the CO_2 and phenolic-glycolipid-I fractions suggested that fewer numbers of *M. leprae* might also yield satisfactory results.

After alterations of a $^{14}CO_2$ detecting Buddemeyer-type incubation vessel, we implemented the modified vessel to determine the number of human-derived-*M. leprae* capable of releasing detectable amounts of $^{14}CO_2$ from oxidation of ^{14}C-palmitic acid.

0305-7518/94/064100+06

Materials and methods

PREPARATION OF INOCULUM

The skin surfaces of 2 untreated, clinically diagnosed, lepromatous leprosy patients attending the clinic at ALERT were treated with a solution of 1% iodine in 70% ethanol. Usually 2, 4 or 6 mm punch biopsies were taken after the injection of local anaesthetic. After dissecting a small section for histological staining, the biopsies were weighed and the tissues separated at the dermal epidermal junction. Then, using a mortar and pestle, the dermis was homogenized in Middlebrook 7H9 broth (Difco, Detroit, Michigan, USA). The suspension was sonicated in an ice bath for 2 min (Sonifer, B-13 Branson Ultrasonics Corp., Danbury, Connecticut, USA). The large tissue debris was allowed to settle at $1 \times g$ for 3–5 min. The tissue remaining in suspension was centrifuged at $2000 \times g$. The pellet was suspended in 7H9 broth and the number of acid-fast bacilli (AFB) and the number of solid-staining bacteria (morphological index—MI) was determined.[7]

PREPARATION OF CULTURES AND CULTURE VESSELS

The enumerated *M. leprae* were diluted in 7H9 Middlebrook broth that had been supplemented with 10% v/v albumin-dextrose-catalase (ADC). The 7H9-ADC medium also contained 50 μg of ampicillin/ml and 2·5 μg amphotericin-B/ml. The AFB were diluted in 10-fold dilutions and placed in sterile Nunc tubes (Roskilde, Denmark). The

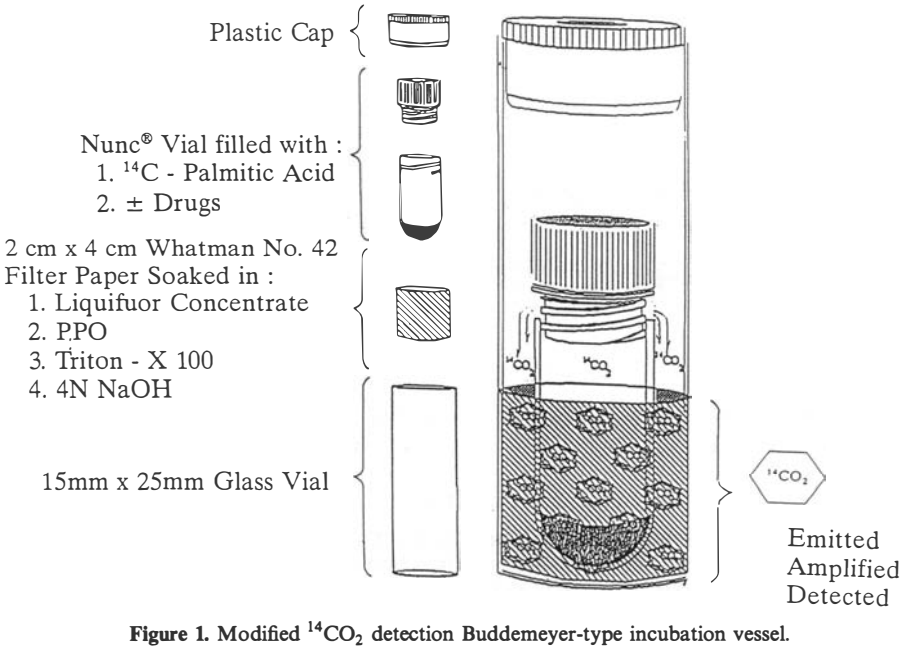

Figure 1. Modified $^{14}CO_2$ detection Buddemeyer-type incubation vessel.

tubes, with their caps tightened, were incubated at 33°C in an incubator with high humidity. On the 5th day we added 1·0 μCi of [1-^{14}C] palmitic acid (59 mCi/mmol; Amersham International plc, Buckinghamshire, UK) to each 1·0 ml of culture. The tubes with loosened caps were placed within 15×25 mm glass vials containing a dried strip of Whatman DE42 filter paper (Whatman, Inc., Clifton, New Jersey, USA). The paper had previously been dipped into a slurry of Liquifluor concentrate PPO-POPOP [2,5 diphenyloxazole-1,4-bis(5-phenyloxazoly) benzene] toluene concentrate (New England Nuclear, Boston, Massachusetts, USA); Triton X-100 and 4N NaOH.[3] The glass scintillation vials were sealed and the assembled culture vessels were returned to incubate at 33°C. The $^{14}CO_2$ captured on the filter paper was measured immediately after the addition of ^{14}C-palmitic acid and then daily using a RackBeta Liquid Scintillation Counter (LKB, Pharmacia, Uppsala, Sweden).

Results

Using the modified Buddemeyer-type detection system as illustrated in Figure 1 and in cultures containing 10^7 mycobacteria, the amount of $^{14}CO_2$ captured was proportional to the number of AFB/ml and to the time of incubation (Figures 2 and 3).

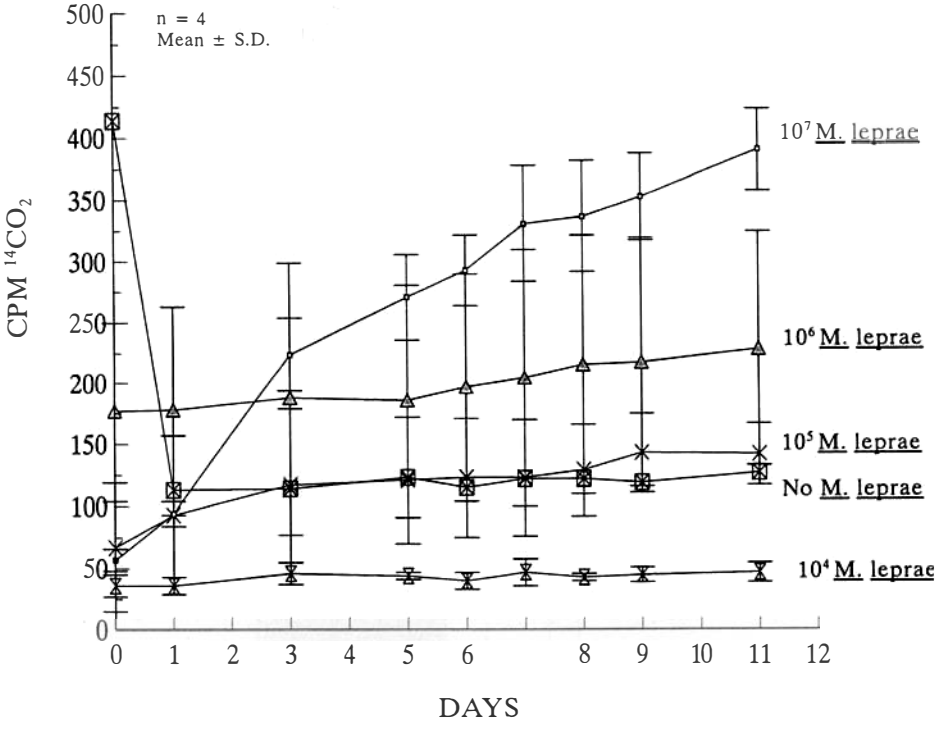

Figure 2. A 6 mm skin punch biopsy was obtained from a 35-year-old female, untreated, histologically confirmed BL/LL leprosy patient. The mean Bacterial Index from 6 sites was 5 and the Morphologic Index was 0·0; 2 × 10^8 acid-fast bacteria were recovered from the biopsy and the Morphologic Index was 0·0. On day 0, 1 μCi of ^{14}C-palmitic acid was added to each ml of Middlebrook 7H9 broth supplemented with albumin-dextrose catalase.

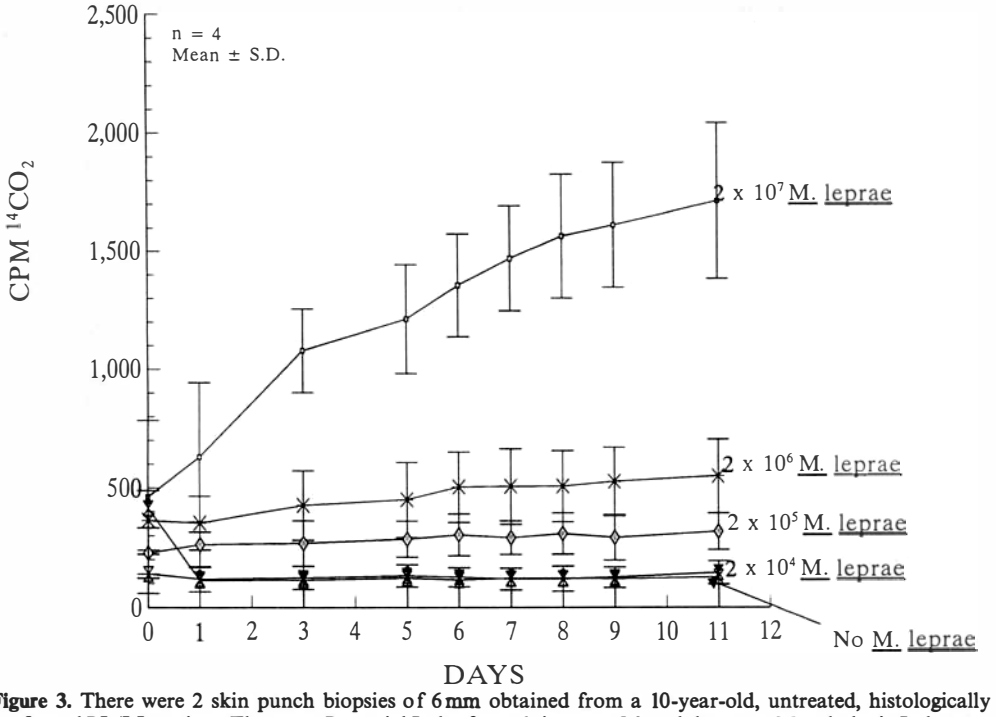

Figure 3. There were 2 skin punch biopsies of 6 mm obtained from a 10-year-old, untreated, histologically confirmed BL/LL patient. The mean Bacterial Index from 6 sites was 5·0 and the mean Morphologic Index was 0·6%; $3{\cdot}6 \times 10^8$ acid-fast bacteria with a Morphologic Index of 3% were recovered from the biopsy. There was 1 μCi of ^{14}C-palmitic acid added, as described in Figure 2.

Discussion

Inability to cultivate *M. leprae in vitro* continues to hinder leprosy research and leprosy control. A knowledge of the drug susceptibility of clinical isolates of *M. leprae* is vital to an effective control of leprosy. Clinical isolates of *M. leprae* are tested for drug sensitivity at AHRI and ALERT in a mouse footpad system. This technique is laborious and expensive, involving 6–12 months maintenance of mice as well as gram amounts of compounds. Reliable and rapid *in vitro* radiorespirometric methods (i.e. modified-Buddemeyer-type and BACTEC 640 systems) that measure, in the absence or presence of drugs, the catabolic (palmitate oxidation) capacity of *M. leprae* derived from nude mice have been developed by Franzblau *et al.*[8]

This study demonstrated that *M. leprae*, recovered from skin-punch biopsies of 2 untreated lepromatous patients, had sufficient numbers of bacteria to oxidize ^{14}C-palmitic acid in axenic culture. To detect progressive evolution of $^{14}CO_2$ the modified Buddemeyer-type assay required a minimum of 10^7 human-derived AFB. This is equal to the number of nu/nu-mouse-derived *M. leprae* used in the BACTEC system and 10-fold more than the 10^6/ml nu/nu-derived bacilli used in the Buddemeyer system.[8] To ensure sensitivity of the assay $2{\cdot}5 \times 10^7$ human-derived AFB are recommended. From a retrospective study, the number of *M. leprae* recovered from skin biopsies of clinically suspected untreated lepromatous patients attending the clinics at ALERT ranged from

Table 1. Recovery of human-derived AFB from skin biopsies of untreated multibacillary patients

AHRI Patient No.	Weight of punch biopsy in mg	Mean from 6 sites		MI of acid-fast bacilli in processed skin biopsy	No. of bacilli$\times 10^8$ recovered
		BI*	MI†		
739	ND	5·0	2·2	1·0	1·6
740	ND	2·7	0·0	1·0	5·7
752	120	4·2	0·5	1·2	6·2
783	170	3·0	0·0	6·0	4·4
853	330	3·8	0·0	3·0	5·2
873	420	4·2	0·3	4·0	0·6
881	111	4·0	0·3	4·0	6·8
817	360	5·0	1·0	6·0	13·0
917	160	4·2	0·0	3·0	0·5
919	280	4·0	0·3	8·0	68·0
924	230	4·0	1·0	4·0	4·7
959	260	3·0	0·0	0·0	1·1
960	170	4·3	0·0	0·0	6·9
962	ND	2·0	0·0	0·0	0·8
978	160	4·5	0·7	4·5	8·4
1022	70	4·3	0·0	3·0	1·8
Mean	219	3·9	0·39	3·0	8·5
SD	106	0·8	0·6	2·4	16·2

* BI, bacteriologic index.
† MI, morphologic index.

68×10^8 to $0{\cdot}6 \times 10^8$, with an average of $8{\cdot}5 \times 10^8$ AFB (Table 1). Based on these recovery data, the average radiorespirometric assay could employ 34 cultures of 1·0 ml, containing $2{\cdot}5 \times 10^7$ bacilli.

This type of assay would facilitate the rapid determination of the partial range of sensitivity of the *M. leprae* to established antileprosy drugs as well as the assessment of the efficacy of several promising new drugs.

Acknowledgments

We would like to thank the Fulbright Program for funding this study in 1988 (grant No. 88-42519) and in 1992 (grant No. 92-42519); the Norwegian National Committee for the Development of Research and Education and the Swedish International Development Agency; the members of the AHRI/ALERT Research Committee for their permission to conduct the study; Dr S. Franzblau for helpful suggestions and Mr K. White and Sister Genet Amare for technical assistance. D. Frommel is seconded from the French National Institute of Medical Research.

References

[1] Kirchheimer WF, Storrs EE. Attempts to establish the armadillo (*Dasypus novemcinctus* Linn.) as a model for the study of leprosy. *Int J Lepr*, 1972; **39:** 693–702.

[2] Chehl S, Ruby J, Job CK, Hastings RC. The growth of *Mycobacterium leprae* in nude mice. *Lepr Rev*, 1985, **54:** 283.
[3] Franzblau S. Oxidation of palmitic acid by *Mycobacterium leprae* in an axenic medium. *J Clin Microb*, 1988; **26:** 18–21.
[4] Franzblau S. Drug susceptibility testing of *Mycobacterium leprae* in the BACTEC 460 System. *Antimicrob Agt and Chem*, 1989; **33:** 2115–17.
[5] Franzblau S, Chan G. Clinical trial of Sparfloxacin in the treatment of leprosy. *Drugs*, 1993; **45:** 225–6.
[6] Shannon EJ, Harris EB, Haile-Mariam HS, Guebre-Xavier M, Frommel D. Competency of human-derived *Mycobacterium leprae* to use palmitic acid in the synthesis of phenolic glycolipid-1 and phthiocerol dimycocerosate and to release CO_2 in axenic culture. *Lepr Rev*, 1992; **63:** 101–7.
[7] Shepard CC, McRae DH. A method for counting acid-fast bacteria. *Int J Lepr*, 1968; **36:** 78.
[8] Franzblau SG, Biswas AN, Jenner P, Colston MJ. Double-blind evaluation of BACTEC and Buddemeyer-type radiorespirometric assays for *in vitro* screening of antileprosy agents. *Lepr Rev*, 1992; **63:** 125–33.

Lepr Rev (1994) **65,** 106–121

Evaluation of sensibility in leprosy—comparison of various clinical methods

W. H. VAN BRAKEL*, J. SHUTE, J. A. DIXON & H. ARZET
Green Pastures Hospital, Pokhara, Nepal

Accepted for publication 12 October 1993

Summary In order to determine whether various sensibility tests, not in common use at our hospital, are appropriate for the neurological screening of leprosy patients, an extended nerve function assessment (NFA) was done on 50 in- and outpatients who had been diagnosed as suffering from leprosy (100 hands and feet). The nerve function assessment battery consisted of Semmes–Weinstein monofilament testing (SWMT), moving 2-point discrimination (M2PD), Pinprick (PP), position sense (PS), vibration sense (VS) and voluntary muscle testing (VMT). In addition the SWMT was performed on 637 hands and 634 feet of 'field patients' in order to get a better indication of the prevalence of sensory impairment as measured with the SWMT. The SWMT has been shown to be a sensitive test of peripheral nerve function, therefore the other tests were compared with the SWMT. Results are reported separately for the ulnar, median and posterior tibial nerve. Test sites were the pulp of the distal phalanx of the index finger, the little finger and the big toe. Correlation between the SWMT and each of the other tests proved statistically significant; the closest correlations were between the SWMT, M2PD and PP for both ulnar and median nerves ($r > 0{\cdot}7$, F test > 100, $p < 0{\cdot}0001$). It is argued that the first tests to show nerve function impairment (NFI) are the M2PD and the SWMT. VS and PS were also absent in a significant proportion of patients. Arguments are presented that this may indicate advanced NFI. Results are compared with other data currently available in the literature.

Introduction

Peripheral neuropathy is the direct or indirect cause of almost all impairments, disabilities and deformities of leprosy sufferers. Potentially much of the nerve function impairment (NFI) in leprosy can be treated successfully if treatment is started during the early stages of the NFI. Effective anti-inflammatory drugs like prednisolone are now widely available, often under field conditions. Several investigators have shown that prednisolone treatment can be prescribed safely to hospital outpatients[1] or even to 'field patients',[2]

* Correspondence to: Dr Wim H. van Brakel, 98 Aberdeen Park (Flat 1), Highbury, London N5 2BJ, U.K.

0305-7518/94/065106 + 16

provided that certain basic precautions are taken. Effective treatment for nerve damage is therefore potentially available for those patients who need it, provided they can be identified while their NFI is still reversible. Because of this, the diagnosis of early, reversible NFI is of utmost importance to the patient.

This paper discusses several simple clinical tests that are potentially useful in the diagnosis of early sensory NFI.

The testing protocol was carried out at Green Pastures Hospital (GPH), a 100-bed mission hospital in Pokhara, West Nepal, run by the International Nepal Fellowship (INF) under its Leprosy Control Project (LCP), which is a joint project with His Majesty's Government/Nepal (HMG/N). GPH is the main leprosy referral hospital for the West of Nepal.

Methods

STUDY QUESTIONS

1 How appropriate are moving 2-point discrimination (M2PD), pinprick (PP), position sense (PS) and vibration sense (VS) tests for the neurological screening of leprosy patients?
2 How well do the results of these tests correlate with the results of the more established method of nerve function assessment in leprosy, the Semmes–Weinstein monofilament test (SWMT)?
3 Can any pattern be discovered in the various test results that may be predictive of 'less severe' or 'severe' NFI, i.e. that might predict a good or bad prognosis for recovery?

OUTCOME MEASUREMENTS

Question 1

The proportions of hands and feet tested that showed abnormal test results for the tests mentioned above.

Question 2

Regression coefficient, F test, correlation coefficient (r) and 'squared r' were used to express significance of linear relationship and closeness of correlation.

Question 3

The chance of getting a positive or negative test result for each of the other tests given a positive or negative result in one test.

PATIENTS

Patients were chosen without any specific selection criteria except that they had no missing limbs or digits, or stiff contractures of the fingers, that would make testing of the volar surface of the distal phalanx difficult. No randomization was applied because the

purpose of the study was to compare results of different testing methods within the same patient.

All patients had an established diagnosis of leprosy and were classified according to the Ridley–Jopling classification. Details of diagnosis and classification at GPH have been published elsewhere.[3] The patients were either taking or had been released from WHO–MDT.

NERVE FUNCTION ASSESSMENT (NFA)

NFA was done by 1 of 3 trained physiotechnicians and 3 medical students who had been thoroughly familiarized with testing techniques. The NFA battery consisted of Semmes–Weinstein monofilament testing (SWMT), moving 2-point discrimination (M2PD), pinprick (PP), position sense (PS), vibration sense (VS) and voluntary muscle testing (VMT). If any test site could not be tested for any reason, a missing value was recorded. The VMT data will not be discussed further in this paper.

SENSIBILITY TESTING

Semmes–Weinstein monofilament test (SWMT)

Patients were tested using the standard set of 5 'coloured Semmes–Weinstein monofilaments' as described by Bell–Krotoski.[4] The score per site varies from 0 to 5. A score of 5 was given when the thinnest monofilament in the test series was felt; a score of 0 if even the thickest filament was not felt. These filaments (Semmes–Weinstein numbers 2·83, 3·61, 4·31, 4·56 and 6·65) give a force ranging from about 70 mg to 300 g when applied in such a way that it bends slightly.[5] For the foot the thinnest filament used was 200 mg, while an extra filament of about 10 g was added in between the 4 g and 300 g filaments, because 10 g (SW filament no. 5·07) has been found to be the level of 'residual protective sensibility' in the foot.[6,7] The result was recorded using the colour code for the respective monofilament for each of the sites mentioned below. The 70 mg and 200 mg filaments were applied 3 times, because they tend to slip more easily than the thicker filaments. If the patient felt any of the touches the result was recorded as positive for that site. The thicker filaments were usually only applied once. The maximum score per site was 5. The following sites were tested:

Ulnar nerve: the pulp of dig. V.

Median nerve: the pulp of dig. II.

Posterior tibial nerve: the volar surface of the big toe.

Moving 2-point discrimination (M2PD)

Moving touch sensibility of the ulnar, median and posterior tibial nerves was tested with the M2PD test as described by Dellon.[8] Two prongs of a small testing device specifically marketed for testing static and moving 2-point discrimination, the Disk-Criminator™,*

* Available through P.O. Box 13692, Baltimore, Maryland, 21210, USA.

were moved from proximal to distal over the volar/plantar surface of the distal phalanx, giving as little pressure as possible. Randomly 2 or 1 prongs were applied and the patient was asked whether he felt 1 or 2 prongs. The smallest distance between the prongs that was still detected by the patient as 2 prongs was recorded in millimetres for that site. The smallest distance tested was 2 mm. The test sites were the same as for the SWMT.

The score was calculated as '15 minus the minimum distance between the 2 "prongs" of the testing device (in millmetres) that was still perceived as 2 points'. The maximum score was therefore 13, if the patient could still feel 2 separate points at an interprong distance of 2 mm. If the testing device was not felt at all, the score was recorded as 0. If the device was felt, but only as 1 moving point, a score of 1 was given.

Pinprick (PP) score per nerve

Pain sensation was tested using standardized wooden toothpicks. The toothpick was applied randomly with the sharp end or the blunt end and the patient was asked to indicate whether he felt 'sharp' or 'blunt'. The sites to be tested with the PP test were the same as the sites for the SWMT test. The score per site was the number of correct responses out of 5 trials.

Position sense test

'Proprioception' or position sense was tested in the same digits as the SWMT. While the middle phalanx was fixed between the thumb and the index finger of the examiner, the examiner gently moved the distal phalanx either up or down from the neutral position. The patient was asked to indicate whether he felt his finger/toe go up or down. The score per site was the number of correct responses out of 5 trials. The maximum score was therefore 5 for each site.

Vibration sense test

Vibration sense in the nerves and sites described under the SWMT were tested using a 128 Hz tuning fork. A supramaximal stimulus was given to the tuning fork and then the prongs were immediately applied to the volar–plantar surface of the distal phalanx of the digit to be tested. The patient was asked to describe what he felt. Any description of a vibrating, 'electrical' or similar sensation was taken as a positive test (score 1). If the tuning fork was felt without any special sensation, the test was negative (score 0).

NERVE FUNCTION IMPAIRMENT (NFI)

A patient was diagnosed as having NFI using the following criteria:

SWMT: a score for any site of 3 or less;
M2PD: a score of 10 or less for any site on the hand and 9 or less on the big toe;
PP: a score for any site of 0 or 1 (values of 4 and 5 were counted as normal, while the values 2 and 3 were left out of the analysis);
PS: same as for PP;
VS: a score at any site of 0.

Table 1. Proportions of nerves with abnormal test results (i.e. nerves with NFI) as detected with each of the NFA methods (n = 100)

nerve	SWMT*		M2PD*	PP*	PS*	VS*
	GPH†	FIELD‡				
Median	10	23	16	5	2	2
Ulnar	26	31	42	23	10	11
Posterior tibial	29	37	69	36	10	21

* SWMT = Semmes–Weinstein monofilament test, M2PD = Moving 2-point discrimination, PP = pin prick, PS = position sense, VS = vibration sense.
† GPH = Green Pastures Hospital.
‡ n = 637 hands and 634 feet.

The criteria for the SWMT and the M2PD are based on normal values found in a normative study conducted recently by a team from our hospital (to be published elsewhere).[9]

STATISTICAL METHODS

The significance of the difference between the various proportions was tested using the standard normal deviate (SND) for unpaired samples and McNemar's paired χ^2 test for paired samples as described by Armitage.[10] The significance of an association between 2 tests was tested with an F test (linear regression). A p-value of less than 5% was used as level of statistical significance. The 95% confidence interval is given of the most important proportions or ratios, e.g. 4·19 (2·14–8·25) means that there is a 95% chance that the ratio actually lies between the values 2·14 and 8·25%. Predictive values for positive and negative tests were calculated according to Armitage. Analysis was done using Epi Info software, version 5·01.[11] The terms 'sensitivity' and 'specificity' are not used in the correct sense, because no 'true diagnosis' or 'golden rule test' is available for NFI in leprosy. The meaning, however, is the same, but is used in a qualitative rather than quantitative sense.

Results

We chose 50 patients for the study—6 female, 44 male—i.e. 100 hands and 100 feet. There was no significant difference in test results between left and right, or between male and female. The mean age was 40·6 (SD 12·3, range 16–65, median 41·5).

Table 1 and Figure 1 show the proportions of abnormal test results, i.e. nerves with NFI, as detected with each of the NFA methods. The highest proportions of abnormal test results were found for the M2PD (16%, 42% and 69% for the median, ulnar and posterior tibial nerve, respectively). The difference between the SWMT and M2PD results were not significant for the median nerve (McNemar's test, $z = 1{\cdot}73$, $p > 0{\cdot}05$). However, the differences were highly significant for the ulnar and posterior tibial nerves ($z = 3{\cdot}41$ and 6·58, respectively, $p < 0{\cdot}001$). The lowest, but still not insignificant proportions were found for the position sense and vibration sense tests. Overall the posterior tibial nerve was the most frequently affected nerve.

The significant linear relationship and correlation between the SWMT results and the results of each of the other NFA methods is shown in Table 2. The closest correlations

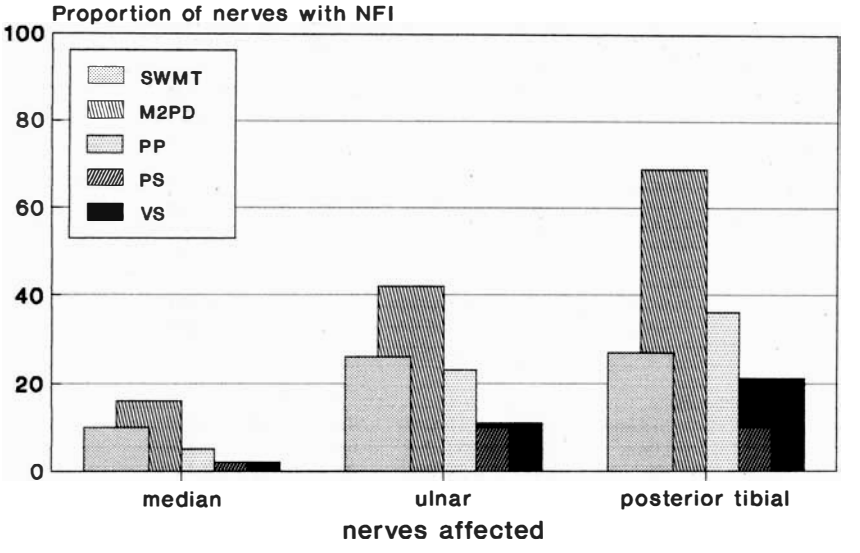

Figure 1. Proportions of nerves with NFI detected by various sensibility tests.

were between the SWMT and M2PD and PP for both ulnar and median nerves and SWMT and VS for the median nerve only ($r > 0{\cdot}7$, F test > 100, $p < 0{\cdot}0001$). A similar pattern of correlation was found between the M2PD and the other tests, but mostly the correlation coefficients were slightly lower (data not shown).

Table 3 shows the chance of finding NFI with each of the other tests if one of the tests shows NFI. The high predictive value of the absence of vibration sense or position sense is separately illustrated in Figures 2 and 3.

The chance of getting normal test results with each of the other tests if one of the tests is normal is shown in Table 4. The predictive value was high for normal results of the pinprick test, the moving 2-point discrimination test and the Semmes–Weinstein monofilament test. This is illustrated separately in Figures 4, 5 and 6, respectively.

Discussion

The importance of the early detection of NFI is based on the assumption that early detection will lead to improved treatment prognosis. Until now scientific evidence for this assumption is lacking. Our ability to detect peripheral neuropathy obviously depends on the sensitivity of the instruments used during the nerve function assessment (NFA). Sensory testing in the field is usually done with the 'ballpen test', as recommended by Jean Watson.[12] This test, along with the 'field VMT', certainly brought a great improvement to many field programmes where no NFA was done at all, but they are probably not sensitive enough to detect less severe NFI. In one study only 61% of patients with foot ulcers had sensory NFI according to the ballpen test, while 95% tested positive using a single SW monofilament (no. 5.07).[7] The variance of test results on repeated testing with the ballpen has been shown to be very large.[5] It should be remembered, though, that the ballpen test was originally introduced to determine whether or not a patient had WHO

Table 2. Correlation between SWMT results and results of the other nerve function assessment methods respectively, using linear regression

nerve	r†	95%ci	r^2	F‡	β§
M2PD					
Median	0·73	0·62–0·81	0·53	111	0·216
Ulnar	0·8	0·72–0·86	0·64	176	0·252
PT*	0·57	0·42–0·69	0·33	47	0·203
PP					
Median	0·77	0·67–0·84	0·59	142	0·641
Ulnar	0·82	0·74–0·87	0·67	179	0·684
PT	0·68	0·56–0·78	0·47	86	0·621
PS					
Median	0·56	0·41–0·68	0·32	45	0·607
Ulnar	0·65	0·52–0·75	0·43	72	0·668
PT	0·41	0·23–0·56	0·17	20	0·44
VS					
Median	0·73	0·63–0·81	0·54	114	4·76
Ulnar	0·64	0·51–0·74	0·41	68	3·27
PT	0·61	0·47–0·72	0·38	59	2·5

* PT = posterior tibial.
† r = correlation coefficient.
‡ F test results are all highly statistically significant ($p < 0{\cdot}001$).
§ β = regression coefficient.
Other abbreviations, see Table 1.

disability grade 1 (anaesthesia), and *not* to screen for early NFI. Reliability of the ballpen test may well be improved by careful testing giving standard instructions like 'only use the weight of the ballpen as pressure' or, 'give as little pressure as possible' (Jean Watson, personal communication). Some evidence of this was recently presented from Ethiopia and Nepal. Lienhardt *et al.*[13] found the coefficients of agreement (Kappa statistics) to be between 0·54 and 0·74 (max. value = 1) for ballpen testing in the hands of 'trained observers'.

A range of simple but useful neurological tests is available that can be used under field conditions. A detailed protocol and suggested scoring system for the use of these tests was published by Pearson as early as 1982.[14] As yet no prospective studies have been reported using this protocol or a similar testing protocol. The use of a more extensive and sensitive NFA battery may shed more light on the sequence in which different nerve function modalities get affected in leprosy. This may well have prognostic consequences.[15] The sequence in which modalities disappear and reappear after treatment in nerve injuries and compression syndromes has been well described.[8,16] But there seems to be no general consensus among leprologists concerning this issue. Some investigators have found touch tests to be 'the least sensitive among perception tests,[17] while others have found that fine touch is lost 'early',[18] or before temperature discrimination,[19] and that there is a 'close correlation of manual (Semmes–Weinstein monofilament) and electrophysiological tests of the upper extremity.[20,21] Good correlation between graded nylon filament results and motor conduction velocity measurements was also reported by Naafs & Dagne.[22]

Table 3. Predictive value (percents) or chance of getting a positive test result (NFI) for each of the tests on the top row, given a positive result of the test in the first column

nerve	n*	SWMT	M2PD	PP	PS	VS
VS						
Median	2	100	100	100	100	
Ulnar	11	91	100	100	55	
PT†	21	86	100	100	42	
PS						
Median	2	100	100	100		100
Ulnar	10	90	100	90		60
PT	10	80	90	100		80
PP						
Median	5	100	100		40	40
Ulnar	23	87	96		43	48
PT	36	75	92		24	53
M2PD						
Median	16	44		33	13	13
Ulnar	42	55		58	26	26
PT	69	36		59	14	30
SWMT						
Median	10		70	63	20	20
Ulnar	26		88	87	39	38
PT	29		93	100	31	62

* n = the number of nerves found to have NFI according to the results of the test in column 1.

† PT = posterior tibial.

Other abbreviations, see Table 1.

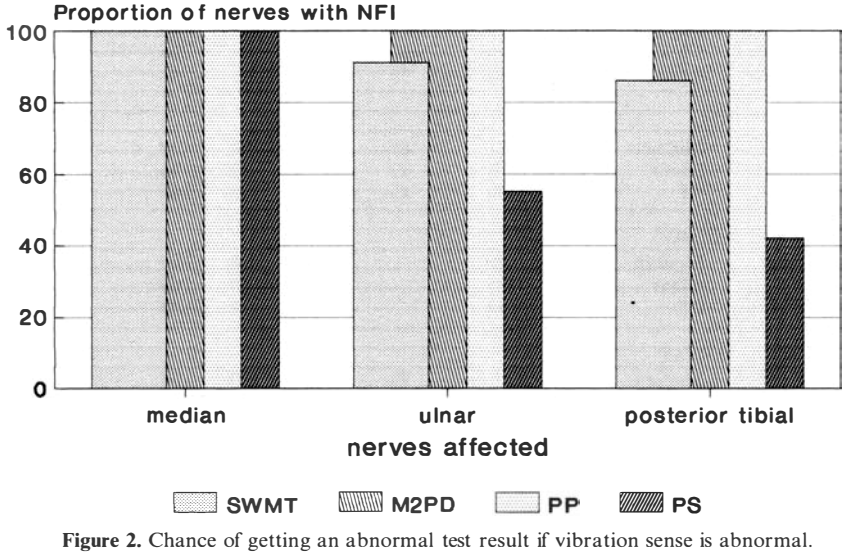

Figure 2. Chance of getting an abnormal test result if vibration sense is abnormal.

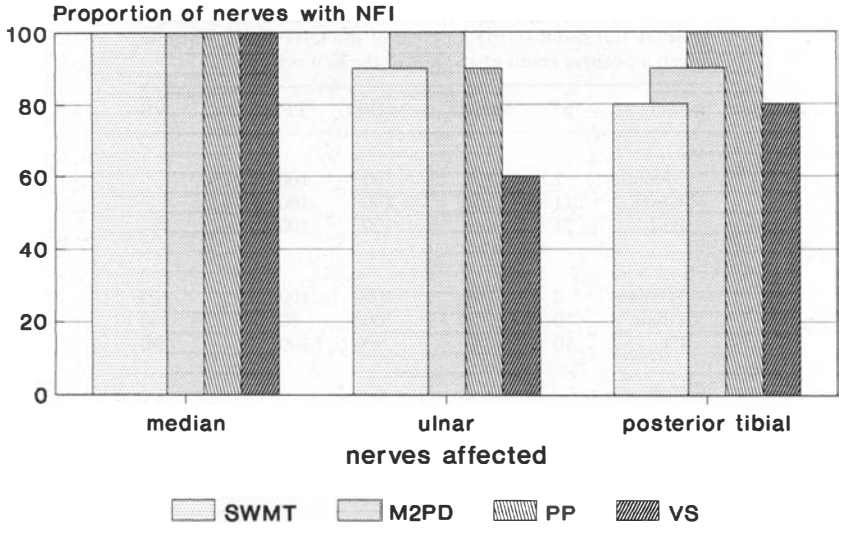

Figure 3. Chance of getting an abnormal test result if position sense is abnormal.

Table 4. Predictive value (percentages) or chance of getting normal test results for each of the tests on the top row, given a normal result for the tests in the first column

	n*	SWMT	M2PD	PP	PS	VS
VS						
Median	98	92	86	97	100	
Ulnar	89	82	65	85	95	
PT†	79	86	39	71	97	
PS						
Median	95	92	85	97		100
Ulnar	85	98	67	85		95
PT	86	79	35	63		87
PP						
Median	90	97	89		100	100
Ulnar	70	94	77		99	100
PT	42	100	45		100	100
M2PD						
Median	84	96		100	100	100
Ulnar	58	95		98	100	100
PT	31	94		86	97	100
SWMT						
Median	90		90	100	100	100
Ulnar	74		74	94	99	99
PT	71		40	82	97	96

* n = the number of nerves with a normal function according to the results of the test in column 1.

† PT = posterior tibial.

Other abbreviations, see Table 1.

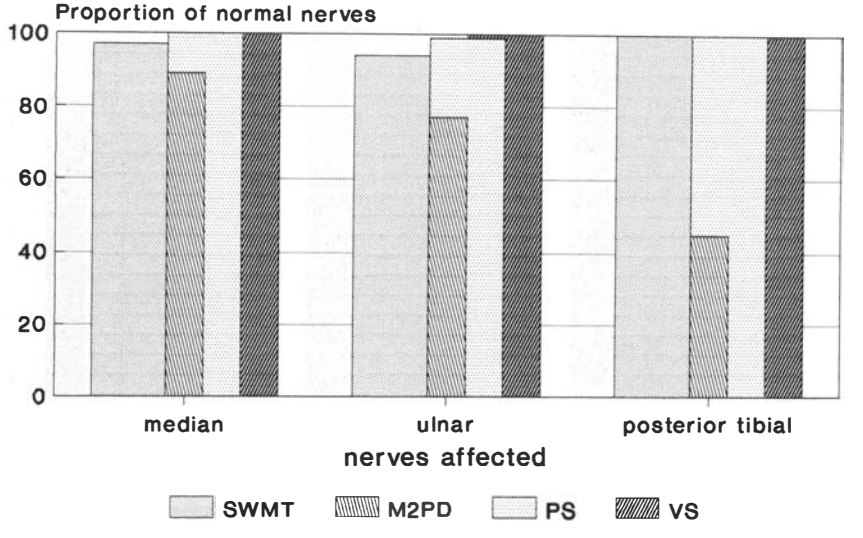

Figure 4. Chance of getting a normal test result if the pinprick test is normal.

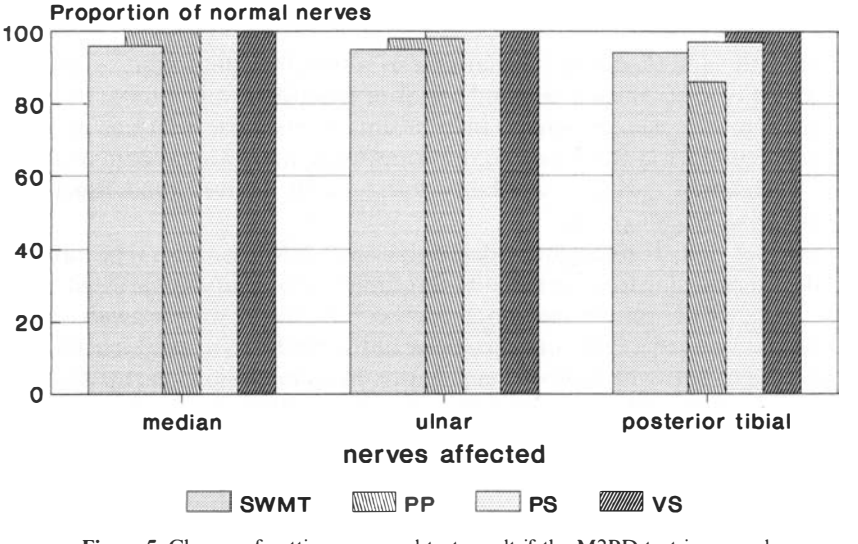

Figure 5. Chance of getting a normal test result if the M2PD test is normal.

SEMMES–WEINSTEIN MONOFILAMENTS AND MOVING 2-POINT DISCRIMINATION

The use of graded nylon monofilaments has been found to be a sensitive and repeatable method to detect less severe nerve damage in leprosy and to monitor the treatment response of NFI.[5,7,18,20,22–24] The main problem is the limited availability of standardized filaments. Other practical problems with this test include: loss of the filaments or failure to replace them after they become bent, the extra time involved in this more elaborate test, and the difficulty of finding a quiet place, free from distraction, in many field situations.

It has been claimed (in nonleprosy patients) that there may not be a good enough

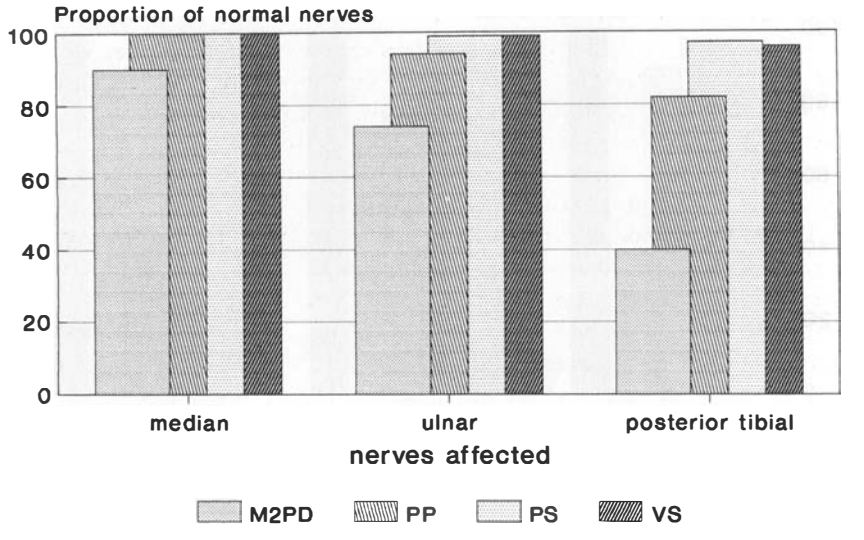

Figure 6. Chance of getting a normal test result if the SW monofilament test is normal.

correlation with hand function.[8] The latter is of course very important because, from the patient's point of view, the actual hand and foot function is much more important than passive touch-test thresholds. Judith Bell[25] claims a very close relationship between the SWMT and actual hand function. To our knowledge there are no data available in the literature correlating 'passive' sensibility testing with 'active' hand function tests in subjects suffering from leprosy.

It seems that there is sufficient evidence that the SWMT is valid, repeatable, sensitive and specific for assessing touch sensibility thresholds, provided standardized filaments are available and that the proper technique is used.[26] As far as we are aware, however, no quantiative data on sensitivity and specificity of the SWMT are available that have been determined in patients with leprosy neuropathy. In compression neuropathy the SWMT correlates very well with measurements of sensory fibre conduction and electronic vibrometry.[27] The 'coefficient of variation' (SD divided by the mean) of measured application force was less than 10% in 2 separate studies.[5,26] This was confirmed recently by our own normative study (to be published elsewhere). We chose the SWMT, therefore, as a reference test against which to compare other clinical tests of sensibility. In a recent study by Dellon *et al.*[28] testing healthy volunteers with a new computer-linked electronic device called the pressure-specifying sensory device (PSD),* static 1-point discrimination was found to have the lowest threshold for pressure perception (0·1 g/mm^2) when compared with moving 1-point and static and moving 2-point discrimination.

In our study the SWMT appeared slightly less sensitive than the M2PD in picking up leprosy NFI. The proportion of nerves testing positive with the M2PD, i.e. showing NFI, was consistently the highest of all tests (Figure 1). In a subsequent study, however, this

* Available through NK Biotechnical Engineering Company, P.O. Box 26335, Minneapolis, Minnesota 55426, USA.

was no longer the case (to be published later). The predictive value of a normal SWMT result was less good than that of the M2PD and the PP. Until studies with even more sensitive electronic testing instruments become available, the question of which instrument is the most sensitive in screening for leprosy neuropathy may well remain unanswered. But the monofilaments are very easy to use and results have been shown to have only limited interobserver variability.[5] This feature makes the SWMT particularly suitable for serial testing, such as in the monitoring of NFI treatment.

The M2PD was introduced by Dellon as a test of the quickly adapting fibre system which mediates 'moving touch' and is therefore claimed to be a test of 'functional sensibility'. The test can be done with a paperclip if necessary, but for this study we used the instrument specifically marketed for static and moving 2-PD testing, the Disk-Criminator™. Both static and moving 2-PD have been criticized for their inability to produce repeatable pressure stimuli in an electronic testing setup.[29] However, the fact that the normal values found by different investigators, particularly for the M2PD, have been very consistent and with little variance, it seems that this criticism may not be valid in the clinical testing situation.[8,9,30]

In the current study we found a very good correlation between SWMT and M2PD, particularly in the hand. In compression neuropathy the M2PD is only affected much later than the SWMT.[27] It has been suggested by Lundborg *et al.*[31] that the reason for the latter may be that 2-point discrimination involves higher cortical integration, which needs only a minimum of peripheral input for correct interpretation. One explanation for our observation might be that the SWMT does not actually selectively stimulate the slowly-adapting fibre system (static touch) and the M2PD does not only selectively stimulate the quickly-adapting fibre system (moving touch), as has been claimed,[8] but each test cross-stimulates mechanoreceptors of both systems. It has been shown that handheld instruments for sensibility testing always produce a whole range of stimulus frequencies.[29] Another explanation for the observed good correlation between the 2 tests might be that in leprosy neuropathy individual fascicles are affected, producing a 'patchy' pattern of impairment. This may equally affect touch thresholds as well as innervation density (moving 2-point discrimination), and therefore give a good inter-test correlation (Dr A. Lee Dellon, personal communication).

The difference between the M2PD and the SWMT was the largest on the foot (69% *vs* 29%) and it may be that the M2PD is less reliable for testing sensibility there. In a recent study we found the coefficient of variation to be as high as 50% for normal values of M2PD on the foot.[9] A possible explanation could be that the higher cortical integration, required for interpretation of 2-point discrimination, is less well developed for the sole of the foot than for the fingertips. Weinstein suggested that this would be the reason behind the lack of correlation that he observed between static 2PD and monofilament thresholds, which are apparently registered at a lower cerebral level.[32] Callous on the footsole may be another reason why M2PD may be more affected than the pressure sensibility.

A normal M2PD result had the highest predictive value for finding normal results with the others tests. Our data therefore suggest that M2PD may be a very sensitive test of NFI in leprosy. This supports the finding of Lewis that (static) 'two-point discrimination was lost early'.[18] However, it was found that M2PD was the test most difficult to explain to the patients and the most prone to misunderstanding of those used in this study. Therefore the clinical usefulness, particularly the intra- and interobserver reliability, will still need to be confirmed in a follow-up study.

PINPRICK

Pinprick (pain) sensation is mediated by 'free nerve endings' of small myelinated and unmyelinated fibres. But again a prick with a pin or toothpick will cross-stimulate all other touch receptors as well. It has been observed to be often present while static touch sensibility is either diminished or absent.[18] In the present study we found a very strong correlation between SWMT and PP results (Table 2). This directly contradicts the findings of Oommen *et al.*[33] who found no association between the loss of touch perception and the loss of pain perception in 76 ulnar nerves of 38 patients. It is not possible to explain this discrepancy because Oommen *et al.* do not give any details of their testing techniques or of their criteria for 'loss of perception'. A normal PP result had a high predictive value for a normal SWMT result (Figure 4), while the SWMT was often still normal when the PP was already affected. The PP may thus be a useful screening test for NFI in leprosy, especially under field conditions. It is easy to carry out and was found to be easily understood by the patients.

The disadvantage is the great potential variability in the stimulus strength (more or less pressure given on the pin), which actually influences the patients' perception of 'sharp' or 'blunt'. This could be overcome by the use of weighted sliding, or spring-loaded pins as described by Palande & Bowden,[34] and Jain *et al.*[35] Availability may again be a problem with these instruments, as is the use of metal needles, because of the risk of a perforating injury, with an associated risk of infection. The use of a pointed wooden pin, such as a tooth pick, is therefore preferred over an actual pin.[15]

POSITION SENSE AND VIBRATION SENSE

In a recent study by Jennekens,[15] 33% of the examined leprosy patients had an abnormal position sense of 1 or more digits in 1 or more limbs. 'It reflects a severe impairment of the distal, thick sensory fibres.'[15] In our data this percentage was 19% (data not shown). This difference could be because the patients studied by Jennekens were inpatients, with advanced leprosy only, while our group contained both in- and outpatients and both advanced and 'less severe' cases. The fact that an abnormal PS reflects severe NFI is illustrated by our finding that if the PS is abnormal, there is a very high chance that the other tests will also be abnormal. Whether an abnormal PS is also a bad prognostic sign for the chance of recovery after treatment of NFI is currently being investigated in a prospective study at our hospital. The test was found to be easy to perform and easy to understand by the patient and does not need any instrumentation.

Electronic vibrometry is currently widely accepted as a very sensitive method of assessing nerve function.[36–40] We are aware of only one systematic study where vibration perception was measured to assess peripheral nerve function in leprosy.[7] In this study Hammond & Klenerman found that vibrometry, using a handheld biosthesiometer, is a sensitive method of detecting sensory impairment in the feet of leprosy patients. In our study VS was affected in a similar proportion of nerves as the PS. The predictive value of an abnormal test result was equally high as for the PS, indicating that loss of vibration perception to a handheld tuning fork (a strong stimulus) may also be a sign of advanced NFI.

It would be very worthwhile to further investigate the value of controlled electronic vibratory stimuli in the diagnosis of less severe NFI in leprosy. There is a need for a

sensitive, reliable instrument for the diagnosis of NFI in leprosy, against which the sensitivity and specificity of other simple clinical tests can be calculated.

One important sensory modality that was not included in our study for operational reasons is temperature discrimination. This is an important modality in leprosy neuropathy as it has been claimed that it is affected in the early stages of the disease,[33,41] but temperature discrimination is difficult to test reliably because of the difficulty of maintaining constant temperatures for 'hot' and 'cold', particularly in hot climates and under field conditions. Schreuders & Kuipers[42] tried to use the WHO-supplied portable temperature testing device (the Thermal Sensibility Tester) for testing temperature discrimination on the hand, but it was found that 24–50% of healthy Thai people could not distinguish the difference between the hot and the cold tip of the device. If a more reliable instrument becomes available this modality should certainly be tested, as temperature sensibility plays an important role in protective sensibility. Burns are one of the most frequently sustained injuries in patients with leprosy NFI.

Considerations for practical application

The aim of this study was to examine whether the abovementioned tests are suitable as screening tests for leprosy neuropathy, *not* whether they are suitable for field use, in the hands of multi-purpose health workers. To determine their operational suitability, further studies will need to be carried out.

When applying the above tests in clinical practice, we usually test more than the 3 sites used in this study. A minimum of 3 sites per tested nerve is common; for the sole of the foot 5–10 may be used.

According to the above results it seems unnecessary to use all 5 of the tests described when screening a leprosy patient for NFI. A combination of the M2PD and the SWMT, or alternatively the PP if no standardized filaments are available, virtually excludes sensory NFI if both tests are normal and indicates definite NFI if both tests are abnormal. If at least 1 of the tests is abnormal there is an indication to perform some additional tests. Finding absence of vibration perception or position sense indicates severe sensory nerve damage and possibly a poor treatment prognosis, but the latter will still need to be confirmed in a prospective study.

Meanwhile no effort should be spared to train health workers in nerve function assessment techniques, using the locally most appropriate methods, to detect impairment as early as possible.

Conclusions

1 Correlation between the SWMT and each of the other tests proved statistically significant; the closest correlations were between the SWMT, M2PD and PP for both ulnar and median nerves.
2 The proportion of nerves testing positive with the M2PD (i.e. showing NFI) was consistently the highest of all tests.
3 Our data suggest that the M2PD is a sensitive screening test of NFI in leprosy. However, care should be given to ensure that the patient understands the test well.

4 When screening patients for NFI a combination of the M2PD with either the SWMT or PP is likely to be highly sensitive and specific.
5 There was evidence that absence of position sense and /or vibration sense indicated advanced damage to the nerve trunk and this may therefore be a sign of 'severe' NFI.

Acknowledgments

We are indebted to the staff of the Physiotherapy Department at Green Pastures Hospital who spend much of their time performing detailed nerve function assessments, without which this study would not have been possible. We are grateful to Professor F. G. I. Jennekens, Dr A. Lee Dellon and Dr J. W. Brandsma for their encouragement and helpful comments during the preparation of this manuscript. The work at Green Pastures Hospital is dedicated to the service and glory of God.

References

[1] Kiran KU, Stanley JNA, Pearson JMH. The outpatient treatment of nerve damage in patients with borderline leprosy using a semi-standardized steroid regimen. *Lepr Rev*, 1985; **56:** 127–34.
[2] Becx-Bleumink M, Berhe D, 'T Mannetje W. The management of nerve damage in the leprosy control services. *Lepr Rev*, 1990; **61:** 1–11.
[3] van Brakel WH, de Soldenhoff R, McDougall AC. The allocation of leprosy patients into paucibacillary and multibacillary groups for multidrug therapy, taking into account the number of body areas affected by skin, or skin and nerve lesions. *Lepr Rev*, 1992; **63:** 231–45.
[4] Bell-Krotoski JA. 'Pocket' filaments and specifications for the Semmes-Weinstein monofilaments. *J Hand Ther*, 1990; Jan–Mar: 26–31.
[5] Bell-Krotoski JA, Tomancik E. The repeatability of testing with Semmes–Weinstein monofilaments. *J Hand Surg*, 1987; **12A:** 155–61.
[6] Birke JA, Sims DS. Plantar sensory threshold in the ulcerative foot. *Lepr Rev*, 1986; **57:** 261–7.
[7] Hammond CJ, Klenerman P. Protective sensation in the foot in leprosy. *Lepr Rev*, 1988; **59:** 347–54.
[8] Dellon AL. *Evaluation of sensibility and re-education of sensation in the hand.* Baltimore: John D. Lucas Printing Co, 1988.
[9] Kets M, van Leerdam M, van Brakel WH, Khawas IB, Gurung KS. Normal values for several sensibility tests of hand and foot in healthy volunteers in West Nepal (in preparation).
[10] Armitage P, Berry G. *Statistical Methods in Medical Research.* 2nd ed. Oxford: Blackwell Scientific Publications, 1987: 121–4.
[11] Dean AG, Dean JA, Dicker RC. *Epi Info, Version 5: a word processing, database, and statistics program for epidemiology on microcomputers.* USD, Inc, Stone Mountain, Georgia, 1990.
[12] Watson JM. *Essential action to minimise disability in leprosy patients.* The Leprosy Mission International. Stanley L. Hunt (Printers) Ltd, 1988.
[13] Lienhardt C, Pasquier R, Le Maitre C, Wheeler J. Comparability of ball pen and nylon filaments in testing sensory function of patients with leprosy in Nepal and Ethiopia. Paper presented at the 14th International Leprosy Congress, Florida, 1993. (abstract RE 80 in 'Abstracts').
[14] Pearson JMH. The evaluation of nerve damage in leprosy. *Lepr Rev*, 1982; **53:** 119–30.
[15] Jennekens FGI, Jennekens-Schinkel A. Neurological examination of patients suffering from leprosy: is it worthile? *Lepr Rev*, 1992; **63:** 269–76.
[16] Moberg E. Objective methods of determining functional value of sensibility in the hand. *J Bone Joint Surg (UK)*, 1958; **40:** 454–66.
[17] Oommen PK, Srinivasan H, Rajakumar C. Neurophysiological correlates of peripheral neural deficits in leprosy and their clinical significiance. In: *Proceedings, XII International Leprosy Congress.* New Delhi, 1984: 377–9.
[18] Lewis S. Reproducibility of sensory testing and voluntary muscle testing in evaluating the treatment of acute neuritis in leprosy patients. *Lepr Rev*, 1983; **54:** 23–30.
[19] Bell-Krotoski JA. Hand screen for early detection and monitoring of peripheral neuropathy part II. *The Star*, 1992; **51**(3): 3–7.

[20] Kaplan M, Gelber RH. Nerve damage evaluation. In: *Proceedings, XII International Leprosy Congress.* New Delhi, 1984: 455–61.
[21] Brown TR, Kovindha A, Wathanadilokkol U, Piefer A, Smith T, Kraft GH. Clinical assessment of early leprous neuropathy with electrophysiologic correlation. Paper presented at 14th International Leprosy Congress, Florida, 1993. (abstract RE35 in 'Abstracts').
[22] Naafs B, Dagne T. Sensory testing: a sensitive method in the follow-up of nerve involvement. *Int J Lepr*, 1977; **45:** 364–8.
[23] Mehta LN, Shetty VP, Antia NH, Irani PF. Quantitative, histologic and ultrastructural studies of the index branch of the radial cutaneous nerve in leprosy and its correlation with electrophysiologic study. *Int J Lepr*, 1975; **43:** 256–64.
[24] Lehman LF, Orsini B, Nicholl A. The development and adaptation of the Semmes–Weinstein light touch/deep pressure sensory test in Brazil. Paper presented at the 14th International Leprosy Congress, Florida, 1993. (abstract RE20 in 'Abstracts').
[25] Bell-Krotoski JA. Light touch-deep pressure testing using Semmes–Weinstein monofilaments. In: *Rehabilitation of the hand*, 3rd ed. Hunter *et al.* (eds) C. V. Mosby Co., 1989; 585–93.
[26] Levin S, Pearshall G, Ruderman R. Von Frey's method of measuring presure sensibility in the hand: an engineering analysis of the Weinstein–Semmes pressure aesthesiometer. *J Hand Surg*, 1978; **3:** 211–6.
[27] Szabo RM, Gelberman RH, Williamson RV, Dellon AL, Yaru NC, Dimick MP. Vibratory sensory testing in acute peripheral nerve compression. *J Hand Surg*, 1984; **9A:** 104–9.
[28] Dellon ES, Mourey R, Dellon AL. Human pressure perception values for constant and moving one- and two-point discrimination. *Plast Rec Surg*, 1992; **90 (1):** 112–7.
[29] Bell-Krotoski JA, Buford Jr WL. The force/time relationship of clinically used sensory testing instruments. *J Hand Ther*, 1988; Jan–Mar: 76–85.
[30] Louis DS, Green TL, Jacobson KE, *et al.* Evaluation of normal values for stationary and moving two-point discrimination in the hand. *J Hand Surg*, 1984; **9:** 552–5.
[31] Lundborg G, Gelberman RH, Minteer-Convery M, Lee YF, Hargens AR. Median nerve compression in the carpal tunnel—Functional response to experimentally induced controlled pressure. *J Hand Surg*, 1982; **7:** 252–9.
[32] Weinstein S. Fifty years of somatosensory research: from the Semmes–Weinstein monofilaments to the Weinstein Enhanced Sensory Test. *J Hand Ther*, 1993; Jan–March: 11–22.
[33] Oommen PK, Srinivasan H, Rajakumar C. Neurophysiological correlates of peripheral neural deficits in leprosy and their clinical significance. In: *Proceedings, XII International Leprosy Congress.* New Delhi, 1984: 377–9.
[34] Palande DD, Bowden REM. Early detection of damage to nerves in leprosy. *Lepr Rev*, 1992; **63:** 60–72.
[35] Jain GL, Pasricha JS, Guha SK. Objective grading of the loss of pain and touch sensations in leprosy patients. *Int J Lepr*, 1986; **54:** 525–9.
[36] Elderson A, Gerritsen van der Hoop R, Haanstra W, Neijt JP, Gispen WH, Jennekens FGI. Vibration perception and thermoperception as quantative measurements in the monitoring of cisplatin induced neurotoxicity. *J Neurol Sci*, 1989; **93:** 167–74.
[37] Lundborg G, Lie-Stenstrom A, *et al.* Digital vibrogram: a new diagnostic tool for sensory testing in compression neuropathy. *J Hand Surg*, 1986; **11A:** 693–9.
[38] Dyck PJ, Zimmerman IR, O'Brien PC, Ness A, Casky PE, Karnes J, Bushek W. Introduction of automated systems to evaluate touch pressure, vibration and thermal cutaneous sensation in man. *Ann Neurol*, 1978; **4:** 502–10.
[39] Goldberg JM, Lindblom W. Standardised method of determining vibratory perception thresholds for diagnosis and screening in neurological investigation. *J Neurol Neurosurg Psych*, 1979; **42:** 793–803.
[40] Bloom S, *et al.* Use of a biosthesiometer to measure individual vibration thresholds and their variation in 519 non-diabetic subjects. *Br Med J*, 1984; **288:** 1793–5.
[41] Antia NH, Mehta LN, Shetty VP, Irani PF. Clinical, electrophysiological, quantitative, histologic and ultrastructural studies of the index branch of the radial cutaneous nerve in leprosy. I. Preliminary report. *Int J Lepr*, 1975; **43:** 106–13.
[42] Schreuders T, Kuipers M. Thermal sensibility tester. Can it be used to find early nerve damage in leprosy? *Lepr Rev*, 1992; **63:** 294.

Lepr Rev (1994) **65,** 122–129

A survey to determine the prevalence of leprosy in a community in East Trinidad

M. SUITE, N. B. EDINBOROUGH, M. LEWIS* & J. TOLLEFSON†

*Hansen's Disease Control Unit (Ministry of Health), 182 Western Main Road, Cocorite, Trinidad; *Public Health Laboratory (Ministry of Health), Jamaica Boulevard Federation Park, Trinidad; and †Caribbean Epidemiology Centre (PAHO/WHO), Jamaica Boulevard, Federation Park, Trinidad*

Accepted for publication 12 October 1993

Summary A house-to-house survey was conducted in a community in East Trinidad, where a clustering of cases had been observed. There were 1355 residents, of whom 73·5% had a complete visual skin examination.

No new cases of leprosy were found but a variety of skin disorders were diagnosed. The most common disorder was pityriasis versicolor, which is one of the differential diagnoses of hypopigmented skin lesions. This has serious implications for the delayed diagnosis of leprosy.

In all, 5 of the 9 old cases residing in the survey area suffered from paucibacillary disease, and had a history of contact with a lepromatous case. They were not listed initially as contacts of this index case. Contact lists should therefore include nonfamilial persons having frequent contact with an index case. The definition of 'frequent' should be determined by each programme.

It may also be necessary to review the duration of surveillance of contacts. The survey was estimated to have cost about US $2,500 and was not considered to be cost-effective.

Introduction

Leprosy exists at low endemic levels in Trinidad and Tobago, as is demonstrated by the annual prevalence rates (measured by cases registered for treatment) which have fluctuated from 6 to 10 per 100,000 population between 1985 and 1990. It has been noted that the county of St George East in northern Trinidad has the highest leprosy incidence rate for the country, providing about 40% of new cases annually between 1985 and 1990, while accounting for about 16% of the population of Trinidad and Tobago. Clustering of cases has been observed in some communities but not all of it has been familial.

The main aim of the study was to assess the true prevalence of leprosy in a community in St George East county where clustering had been observed. We also

0305-7518/94/064122+08

wished to determine whether active case-finding by means of a house-to-house survey in such an area is an effective means of detecting new cases. In addition, the study was to provide a service of consultation for nonleprosy skin diseases.

Material and methods

The survey was conducted by 3 teams of investigators in February and March 1991, and 1 week before the survey commenced householders were notified by a public address system that a 'skin survey' was to take place. No mention was made of leprosy. An explanatory letter (Figure 1) was presented to each householder and a standardized questionnaire was given to those who accepted this. Household members who agreed had a visual examination of the entire skin, or exposed areas of face, arms and legs if this was preferred.

Sensory testing (light touch and pinprick) was conducted if thought necessary, but nerves were not examined for enlargement. People with suspicious lesions, as well as those desiring consultation, were referred to the Dermatology Clinic. Investigators were allowed to make up to 3 visits to the household in order to obtain maximal coverage.

Results

Of 286 eligible households, 2 refused to participate; 35 premises in the survey area were either unoccupied or demolished and were not included. Data were available for up to 1355 people from 284 households.

Leprosy prevalence for the survey area based on the 2 known cases still on the treatment register was 14·8 per 10,000 population. No new cases were found and the estimated prevalence was not altered by this survey.

DEMOGRAPHIC DATA

Gender data was recorded for 1328 people, and 47·4% were male and 52·6% female. Age data were available for 1329 people and 32·9% (446/1329) were under 15 years old (Table 1), a similar distribution to that of Trinidad and Tobago as a whole, where children represent 31·3% of the population (Central Statistical Office—1990). About

Dear Householder,
The Ministry of Health is conducting a survey of skin diseases in your area. You are kindly asked to cooperate with the interviewer as necessary. A brief examination of the entire skin will be done, free of charge. With your consent, the health worker will examine your skin and ask a few simple questions. Persons who have skin disorders requiring treatment or further tests will be given a referral to the nearest skin clinic or to the skin clinic at the General Hospital, Port of Spain (free of charge). You may refuse to be examined if you are uncomfortable about it. However, it will greatly assist us if you allow yourself and your family to be examined. All information will be kept strictly confidential.
Thank you.

Figure 1. Introductory letter to householders.

Table 1. Age distribution of population

Age (years)	No. of persons (%)
0–14	446 (32·9)
15–29	410 (30·3)
30–44	242 (17·9)
45–59	147 (10·8)
60–74	61 (4·5)
75–89	22 (1·7)
90 and over	1 (0·1)
Not recorded	26 (1·9)
Total	1355 (100·1)

50% were Africans (670/1335) and 30% were East Indians (404/1335), which is not significantly different from the statistics for the whole county (African, 50·3%; East Indian, 25·1%) but differs significantly from the general population, where Africans account for 40·8% of the population and East Indians 40·7%; 19% were of mixed race.

OCCUPATION OF HEAD OF THE HOUSEHOLD

About 23% of household heads had occupations in the community social and personal services, 14% were unemployed and close to 10% were employed in each of the manufacturing, agriculture and transport and communications sectors or were retired from jobs. Fewer breadwinners were employed in other sectors such as petroleum, construction, restaurants and the utilities.

LENGTH OF RESIDENCE

The period of residence in the survey area for household members varied from a few months to 79 years. People who had lived in the household for less than 3 months were not included in order to rule out transients (Table 2). Just over 50% were spouses and children of the head of the household.

Table 2. Length of residence in the survey area

Length of residence (years)	No. of persons (%)
3–9 months	625 (46·1)
10–29	365 (26·9)
30–39	227 (16·8)
40–49	82 (6·1)
50–59	22 (1·6)
60–79	11 (0·8)
Not recorded	23 (1·7)
Total	1355 (100·0)

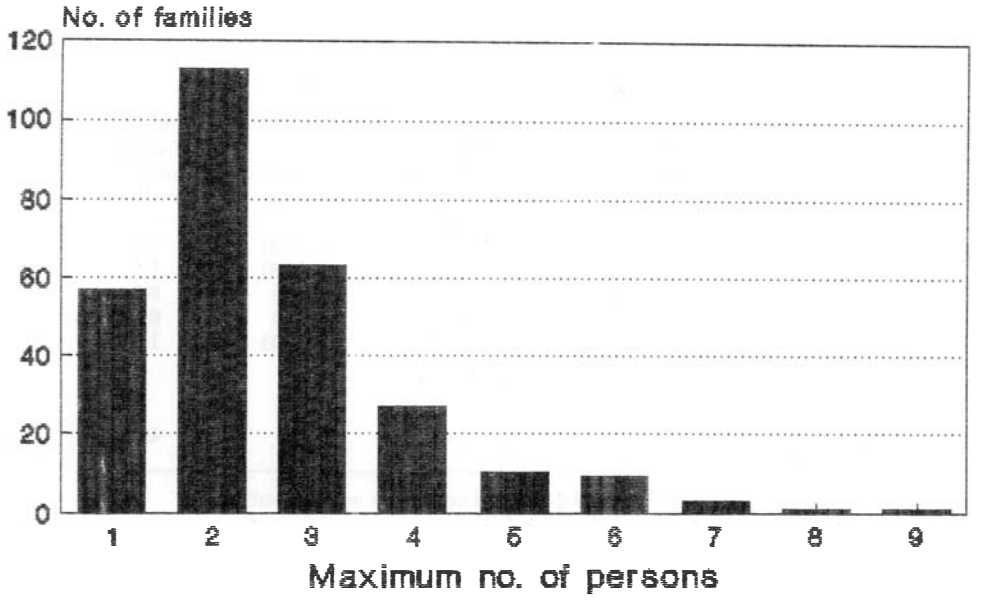

Figure 2. Occupancy of sleeping rooms.

SANITARY FACILITIES

About 77% of the households had a regular pipeborne water supply. No household received a truck-borne supply nor did any collect water from springs or rivers. Toilet facilities were adequate, with 211 households (74·3%) having WC systems unlinked to a sewer; 73 (25·7%) had pit latrines.

SLEEPING FACILITIES

Sleeping rooms were considered crowded if 4 or more people slept in them, regardless of size. By this standard, 16·9% of households had overcrowded sleeping rooms (Figure 2), which corresponds to the national average of 17% of households with 4 or more persons per sleeping room.

RESULTS OF SKIN EXAMINATION

We did not examine 120 of the 1355 subjects (8·9%); either they were not at home when the household was surveyed, or an examination was refused.

FULL SKIN EXAMINATION

A total of 995 people (73·5% of the eligible population) had a complete skin examination and were found to be normal; 90 people had disorders which were not conclusively diagnosed by the field workers; 1 was considered to suffer from leprosy, but subsequently in the clinic she was diagnosed as suffering from an achronic naevus. She was the granddaughter of a deceased case who had been discharged.

Table 3. Distribution of diagnoses made in the field and in the dermatology clinic

Skin disorder	Field diagnosis		Clinic diagnosis	
	No. of persons (%) (n = 183)	Percent of sample examined (n = 1235)	No. of persons (%) (n = 52)	Percent of sample examined (n = 1235)
Pityriasis versicolor	66 (36·1)	5·3	16 (30·8)	1·3
Eczema	9 (4·9)	0·7	19 (36·5)	1·5
Scabies	8 (4·3)	0·6	4 (7·7)	0·3
Acne	5 (2·7)	0·4	4 (7·7)	0·3
Naevi and others	4 (2·2)	0·3	12 (23·1)	1·0
Psoriasis	1 (0·5)	0·1		
Unknown	90 (49·2)	7·3		
Total	183 (99·9)	14·7	55*	4·4

* There were 3 subjects who had 2 different conditions on examination.

EXAMINATION OF EXPOSED AREAS ONLY (FACE, ARMS, LEGS)

A total of 48 people (3·8%) allowed a partial examination; 7% (93/1355) had skin problems either recognized by the field workers or they had information from previous medical consultations available. Pityriasis versicolor was the most common diagnosis (Table 3) and 1 subject had an undiagnosed skin disorder but it was not thought to be leprosy.

REFERRALS

A total of 99 people (7·3% of the population) were referred to the Dermatology Clinic but only 52 presented for assessment by the medical officer. The final diagnoses are shown in Table 3.

OLD CASES

There were 9 known leprosy cases and the relevant details are shown in Table 4.

The longest diagnosed (Case 9) had moved to the area from the leprosarium 39 years before. She was bacteriologically negative in 1971 and on subsequent examination.

Cases 2 and 3 (mother and daughter) had definite contact with a lepromatous case (GC, diagnosed in 1984 and now deceased), who had shared their premises for about 18 years, but they were not listed as his contacts. These 2 women had also cared for him in his later years while he was bacteriologically negative. Case 5 was diagnosed 2 months before Case 6 and 9 months before Case 7, both of whom were her nephews. They all had tuberculoid disease and were discovered to have been frequent visitors of GC (referred to above) who lived next door, but they also were not listed as his contacts. Of the 8 cases that were diagnosed between 1981 and 1990 who were still living in the survey area, 5 had a definite history of contact with GC, an active case of leprosy.

Table 4. Characteristics of 'old' cases

Case no.	Age at time of survey (years)	Sex	Ethnic origin	Year of diagnosis	Type	Resident survey area at time of diagnosis	History of contact	Period of residence in survey area (years)	Status at time of survey
1	36	F	EI	1987	BT	No	Yes (inactive)	$1\frac{1}{2}$	Had MDT
2*	58	F	AF	1990	TT	Yes	Yes	25	On MDT
3*	41	F	AF	1990	BT	Yes	Yes	25	On MDT
4	29	F	EI	1985	TT	No	No	5	Had MDT discharged
5*	29	F	AF	1984	TT	Yes	Yes	29	Had MDT discharged
6*	12	M	AF	1985	TT	Yes	Yes	12	Had MDT discharged
7*	14	M	AF	1984	TT	Yes	Yes	14	Had MDT discharged
8	15	F	AF	1983	TT	Yes	No	12	Had MDT discharged
9	79	F	EI	1930	TT	No	No	39	No MDT

*Same index case—Lepromatous.
AF, African; EI, East Indian; MDT, multidrug therapy.

Discussion

In this control programme, we relied almost entirely on notification, voluntary reporting and contact examination to discover new cases. Our largest surveys were of the populations of the schools attended by the index cases, and this method has not been productive in the past.

The survey was undertaken as a pilot study to assess the prevalence of leprosy in a community where a clustering of cases had been noted. The prevalence remained the same because no new cases were found as a result of the survey. Another aim of the study was to determine whether this survey format could be followed by others in similarly affected areas. It has been suggested that active case-finding by means of surveys is time consuming and expensive and is not likely to be productive in areas of low endemicity.[1] The survey lasted for 35 working days (each day about 8 hours and each team averaging 12 days) and the estimated cost was about US $2,500. No new cases were found and we do not believe that the exercise was cost-effective.

The reception given to the investigators was good and it is encouraging that as many as 91·1% of participating individuals had their skin examined either totally or partially. Co-operation may have been improved by not mentioning leprosy. Since 120 subjects were not examined and 48 did not allow a complete examination, our data can be considered incomplete. A review of surveys conducted in Bombay, India[2] determined that 60% of lesions were found on the covered areas of the body, suggesting that examination of the entire skin is of considerable importance, but compliance is more likely to be favourable if exposed parts only are examined.

Our field workers had considerable experience in contact examination and only 1 had less than 6 months' experience in leprosy control activities. No examination of nerves was required because the incidence of purely neural disease is believed to be low in our population (3·1% of all new cases from 1986 to 1990). In addition, the assessment of nerve enlargement is subject to much interobserver variation. W. Bhakti[2] has commented that although nerve enlargement was often present in lepromatous cases, emphasis

was infrequently placed on its importance in case detection. This is worthy of further consideration since, in Trinidad and Tobago, we tend to emphasize the presence of a hypopigmented spot as an early presenting sign and then proceed to demonstrate any sensory deficit. Other signs, e.g. cutaneous infiltration, if subtle, may not be perceived by field workers as being abnormal, but when these cases are examined later they may be found to have nerve enlargement and to be smear positive.

Pityriasis versicolor, an often hypopigmented skin disorder, was a common diagnosis (30·8%—66/183) made in the field and was the most common clinically diagnosed condition overall. In our experience, patients frequently admitted that they believed leprosy lesions to be 'lota' (a local term for pityriasis versicolor) and had applied therapy thought to be appropriate for this disorder. They have also volunteered that this diagnosis was made by their physicians. Misdiagnosis of hypopigmented lesions bears important implications for the detection of early disease.

Although no new cases were found, we were able to examine more closely some of the characteristics of the known cases. Social and economic conditions for the area as a whole were quite satisfactory. Households where 8 of the 9 'old' cases resided had pipe-borne water and a WC. Overcrowding of the sleeping accommodation occurred in households where 2 of these cases resided. The classification of occupation by employment sector did not give any indication of economic status.

Of the 'old' cases, 8 could conceivably have contracted their illness while resident in the survey area. Close contact was definite in 5 cases with nonlepromatous disease and the likely source of infection was lepromatous. This is consistent with findings elsewhere[3] which indicate that the occurrence of disease in contacts of lepromatous cases is higher than that in contacts of nonlepromatous cases. The source was nonfamilial and new infection occurred in 3 different households. It is conceivable that other factors apart from genetics and household contact are operating within this cluster. The features of the 'old' cases reinforce the need to examine the contact situation carefully, and to extend the definition of 'close' contacts to include persons having frequent contact, but not living in the same household. Such persons should be regularly examined, as well as educated about signs of disease. Admittedly, it is difficult to determine what is frequent contact and thus many contacts are inadvertently omitted from contact lists. This would have to be determined for each programme.

This programme examines contacts yearly for 5 years after diagnosis of the index case. For leprosy an incubation period of 2–5 years is accepted but a wide range has been reported.[4] Because of this factor, as well as the likelihood of missed contacts, our current period of surveillance may be inadequate.

Acknowledgments

We wish to acknowledge the contribution of the staff of the Epidemiology Department at the Caribbean Epidemiology Centre and the field and office staff of the Hansen's Disease (Leprosy) Control Unit without whom the survey would not have been possible. We also wish to thank Mrs Y. Holder, Dr R. Paul and Dr D. Quamina for their helpful comments. Dr Jan Tollefson participated in this study as a final year resident in Community Medicine, University of British Columbia. She was attached to CAREC as an epidemiologist in training.

References

[1] *WHO Guide to Leprosy Control*. 2nd Edition. Geneva 1988, pp. 14–16.
[2] Bhakti W. Case detection: are the present survey methods effective? A review of leprosy surveys in Bombay. *Lepr Rev*, 1988; **59:** 239–44.
[3] WHO Technical Report Series 716. *Epidemiology in relation to control*. Geneva, 1985. p. 20.
[4] Noordeen SK. The epidemiology of leprosy. In: *Leprosy*, Hastings RC (ed.). Edinburgh: Churchill Livingstone, p. 24, 1989.

Lepr Rev (1994) **65,** 130–136

The influence of operational factors in the profile of monolesional leprosy cases in South India

P. KRISHNAMURTHY, P. S. RAO, M. SUBRAMANIAN & INDERPARKASH
Division of Epidemiology and Statistics, Central Leprosy Teaching and Research Institute, Chengalpattu 603 001, Tamil Nadu, India

Accepted for publication 2 November 1993

Summary A comparison of the profile of monolesional cases among new PB cases detected in a Government Leprosy Control Unit (GLCU) and the field area of a Central Leprosy Teaching and Research Institute (CLTRI), both located in South India, demonstrates that the proportion of monolesional cases among new cases detected between 1987 and 1991 was higher in children than adults, higher in females than males (only in the CLTRI)—over 95% were the tuberculoid type. A significantly increasing trend in this proportion could be seen in the GLCU but not in the CLTRI; an explanation of this is based on the difference in operational aspects in case detection methodology adopted by the 2 areas—e.g. intersurvey interval and mode of case detection. Such studies, focusing on single skin lesions, help us in understanding the role of various possible operational factors in influencing the behaviour of the disease.

Introduction

There is considerable controversy and uncertainty over the natural history of leprosy, but there is general agreement that treatment of single-lesion patients may assist an early diagnosis of leprosy.[1] If untreated this lesion may persist, progress or disappear. There is a renewed resurgence of interest in single-lesion cases. Though their ability to transmit infection in the community is unknown their significance in the context of leprosy control is undeniable. The proportion (and significance) of single-lesion cases among the new PB cases detected, the trend of this proportion over a period in areas where multidrug therapy (MDT) has been implemented, and any factors influencing this trend, are some of the features that need to be explored and examined to be able to understand better the behaviour of the disease. The control and treatment of leprosy could be altered if such an investigation suggests the necessity for it.

An attempt was made to study the profile the trend of monolesional cases and the factors influencing this trend in high endemic areas using data from the field area of the Central Leprosy Teaching and Research Institute (CLTRI) and also from a Government Leprosy Control Unit (GLCU) in the state of Tamilnadu in South India.

0305-7518/94/065130+07

Materials and methods

Data was taken from patient care cards of all the cases newly detected between 1987 and 1991, both in the field area of the CLTRI and the GLCU, have been computerized and analysed for this study. Data from these 2 units are regularly collected and updated as a part of a computerized management information system developed at the CLTRI. The population of the field area of the CLTRI is 112,000 (1991) and that of the GLCU area is 413,000 (1991). Pulse therapy was started in the field area of the CLTRI in November 1986 and in the GLCU in April 1987. The prevalence of leprosy at the start of MDT in the CLTRI area was 27·7 per 1000 and in the GLCU area 15·6 per 1000. About 1000 new cases in the GLCU area and 200 in the CLTRI area are being detected annually. The intersurvey interval in the CLTRI is $1-1\frac{1}{2}$ years and in the GLCU 3–4 years. In the CLTRI case detection is through a total population survey, special surveys (field research projects) or voluntary. In the GLCU it is through a total population survey, annual contact and school survey, sample survey, special surveys and voluntary mode.

Monolesion is defined as a single skin lesion, hypopigmented/erythematous, with or without infiltration and definite sensory loss, and without trunk nerve involvement. Biopsy was not done.

χ^2 test for linear trend (1988–91) and χ^2 (Yates' corrected) for a 2×2 contingency table was applied to test for significance using the EPI INFO package.

Results

About 61% of the total new PB cases detected between 1987 and 1991 in the CLTRI area and 56% in the GLCU area were single skin lesion (Table 1). The proportion of monolesion cases among new PB cases was higher among children than adults in both the CLTRI area ($\chi^2 = 23{\cdot}77$, $p = 0{\cdot}0001$) and the GLCU area ($\chi^2 = 220{\cdot}65$, $p = 0{\cdot}000$), higher among females than males in the CLTRI area ($\chi^2 = 11{\cdot}24$, $p = 0{\cdot}0008$) but not in the GLCU area ($\chi^2 = 1{\cdot}65$, $p = 0{\cdot}198$) (Table 2). Over 95% of monolesional cases in both the areas were the tuberculoid type (Table 2). About 4% (45/1022) and 6% (240/3840) of new cases detected in the CLTRI and GLCU areas, respectively, between 1987 and 1991 were multibacillary.

Table 1. Distribution of skin and nerve lesions among new PB cases detected in GLCU and CLTRI (1987–91)

	GLCU (nerve involvement (PB))			CLTRI (nerve involvement (PB))		
	0	1	>1	0	1	>1
No patch	3 (0·1)*	13 (0·4)	10 (0·3)	0	5 (0·5)	2 (0·2)
Patch (single)	2027 (56·3)	45 (1·2)	4 (0·1)	595 (61)	76 (8)	14 (1·4)
Patch (>1)	1180 (33)	168 (4·7)	150 (4·2)	179 (18·3)	71 (7·3)	35 (3·4)
Total		3601 (100)			977 (100)	

*Numbers in parentheses are percentages.

Table 2. Proportion of monolesional cases among new PB cases detected between 1987 and 1991 in CLTRI and GLCU by age, sex and type

Characteristics	CLTRI	GLCU
Total	595/977 (61)*	2027/3599 (56)
Age		
Child	294/433 (68)	933/1280 (73)
Adult	301/574 (55)	1094/2319 (47)
Sex		
Male	280/502 (56)	1006/1820 (55)
Female	315/474 (66)	1021/1777 (57)
Sub-type		
I	13 (2·2)	
TT	567 (95·3)	2005 (99)
BT	15 (2·5)	22 (1·0)

* Numbers in parentheses are percentages.

Table 3. Relapse rates in mono and multilesion PB cases in CLTRI and GLCU

	Relapse rate	
Characteristics	CLTRI	GLCU
Monolesion	5/446 (1·1)*	5/1256 (0·4)
Multiple	8/282 (2·8)	13/1080 (1·2)

* Numbers in parentheses are percentages.

There was no difference in treatment regularity (two-third clinic attendance in a given period) between monolesion and multiple lesion PB cases (85% and 83% in the GLCU area and 85% and 80% in the CLTRI area, respectively). Relapses were seen in monolesion cases but they were significantly less than the multiple lesion cases ($\chi^2 = 3{\cdot}86$, $p = 0{\cdot}049$) (Table 3).

The proportion of monolesion cases was higher among children than adults in both the CLTRI and GLCU areas throughout the period under consideration. The proportion of single lesion cases in all new cases detected between 1988 and 1991 shows an interesting trend in the GLCU but not in the CLTRI area (Figure 1). This trend in the GLCU area is obvious only in the adult ($\chi^2 = 9{\cdot}07$, $p = 0{\cdot}0026$) but not in the child cases ($\chi^2 = 0{\cdot}087$, $p = 0{\cdot}76$), in males ($\chi^2 = 5{\cdot}045$, $p = 0{\cdot}024$) but not in females ($\chi^2 = 1{\cdot}65$, $p = 0{\cdot}213$) (Table 4(a) and (b)).

No clear linear trend could be discerned in the proportion of MB cases in the new cases detected (Table 5).

In the GLCU area there was a significant rise in the number of monolesional cases detected among adults through the different survey modes of others,(e.g. sample survey, referral, special selective surveys) ($\chi^2 = 4{\cdot}191$, $p = 0{\cdot}040$) (Table 6(b)), whereas the linear

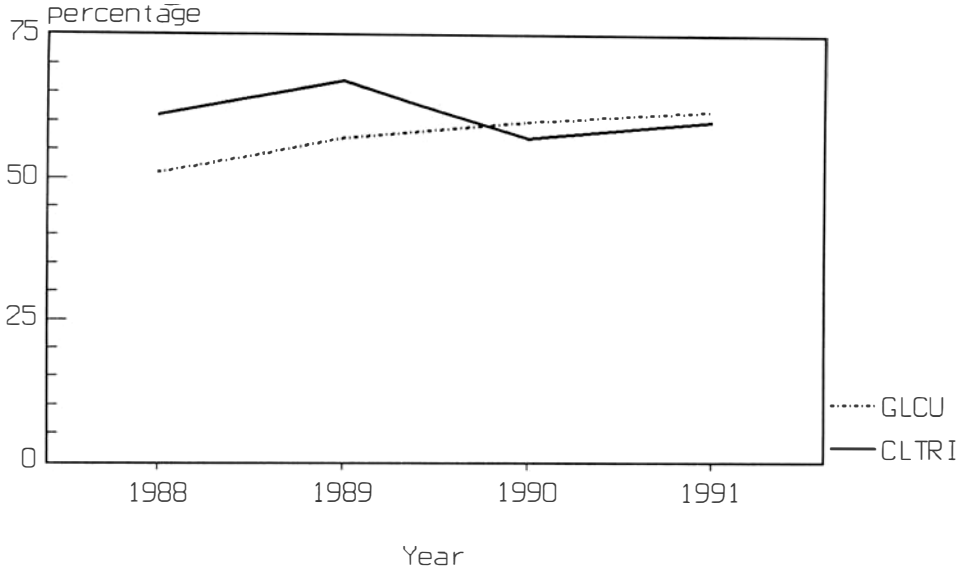

Figure 1. The proportion of monolesional cases among new PB cases between 1988 and 1991.

increasing trend seen in a general survey among adults is not significant ($\chi^2 = 1{\cdot}291$, $p = 0{\cdot}25$). Intensification of case detection through an annual sample survey by an independent agency, camps, etc. might have contributed to some extent to this trend. In the CLTRI area there is a gradual but not significant fall ($\chi^2 = 1{\cdot}355$, $p = 0{\cdot}24$) in the proportion of monolesional cases detected by voluntary mode over the specified period (Table 6(a)). Parallel active surveys as a part of research projects which began in 1988 diagnosed cases which would otherwise have been detected by the voluntary mode.

Discussion

The upsurge in interest shown in single skin lesion leprosy cases, especially in India, in the face of reports of a rising proportion of monolesional PB cases from various leprosy project districts, is understandable. Such a trend, if evident, could either signify an epidemiological drift in the disease profile, or reflect merely an operational process, or both.

The 2 areas selected for the study are similar in being highly endemic for leprosy but dissimilar in the case detection strategy that they adopt. In both a preponderant proportion of new PB cases was shown to be monolesional. The proportion of monolesional cases among PB was higher in children than in adults in both the areas, possibly due to a greater susceptibility of children to infection[2] and a higher occurrence of benign lesions (including mono) among them, coupled with the intense case detection activity that is focused on this age group. Interestingly enough the monolesional proportion is higher in females than in males in the CLTRI area, due perhaps to better examination coverage through the involvement of a female health worker.

An increasing trend in the proportion of monolesional among new cases was

Table 4. Proportion of monolesional cases among new PB cases by age and sex detected in (a) CLTRI and (b) GLCU (1987–91)

(a) CLTRI	Year of detection					
Age	1987	1988	1989	1990	1991	
Child	70/105 (67)	67/102 (66)	60/77 (78)	42/66 (64)	55/83 (66)	$\chi^2 = 0{\cdot}028$ $p = 0{\cdot}86$
Adult	66/126 (52)	82/143 (57)	63/105 (60)	35/70 (50)	55/100 (55)	$\chi^2 = 0{\cdot}14$ $p = 0{\cdot}70$
Total	136/231 (59)	149/245 (61)	123/182 (67)	77/136 (57)	110/183 (60)	$\chi^2 = 0{\cdot}10$ $p = 0{\cdot}75$
Male	67/122 (55)	79/127 (62)	57/95 (60)	37/74 (50)	40/84 (48)	$\chi^2 = 1{\cdot}61$ $p = 0{\cdot}20$
Female	69/109 (63)	70/117 (39)	66/87 (76)	40/62 (64)	70/99 (70)	$\chi^2 = 0{\cdot}32$ $p = 0{\cdot}57$
(b) GLCU	Year of detection					
Age	1987	1988	1989	1990	1991	
Child	58/84 (69)	195/280 (70)	217/287 (76)	211/285 (74)	252/344 (73)	$\chi^2 = 0{\cdot}087$ $p = 0{\cdot}76$
Adult	56/210 (27)	228/542 (42)	216/471 (46)	242/471 (51)	352/623 (56)	$\chi^2 = 9{\cdot}07$ $p = 0{\cdot}0026$
Total	114/294* (39)	423/822 (51)	433/758 (57)	453/756* (60)	604/967* (62)	$\chi^2 = 6{\cdot}11$ $p = 0{\cdot}013$
Male	47/145 (32)	210/424 (49)	210/375 (56)	233/394 (59)	306/482 (63)	$\chi^2 = 5{\cdot}045$ $p = 0{\cdot}024$
Female	67/149 (45)	213/398 (53)	223/383 (58)	220/362 (60)	298/485 (61)	$\chi^2 = 1{\cdot}65$ $p = 0{\cdot}213$

* Age and sex particulars for one case each in 1987, 1990 and 1991 are not available.

Table 5. New cases detected (1987–91) by type of leprosy in (a) CLTRI and (b) GLCU

(a) CLTRI	Year of detection				
Type	1987	1988	1989	1990	1991
PB	231	245	182	136	183
MB	11 (4·5)*	9 (3·5)	10 (5·2)	16 (10·5)	9 (4·7)
(b) GLCU	Year of detection				
	1987	1988	1989	1990	1991
PB	295	822	758	757	968
MB	44 (13)	40 (4·6)	52 (6·4)	45 (5·6)	59 (5·7)

* Numbers in parentheses are percentages.

Table 6. Proportion of monolesional PB cases detected by various modes and age: 1987–91 in (a) CLTRI and (b) GLCU

(a) CLTRI		Year of detection				
Mode of suvey		1987	1988	1989	1990	1991
General survey	Child	57/83 (69)‡	58/87 (67)	51/64 (80)	25/39 (64)	35/53* (66)
	Adult	57/101 (56)	72/120 (58)	58/90 (62)	25/48 (52)	38/61* (62)
Other	Child	— (0)	— (0)	— (0)	3/4 (75)	12/15 (80)
	Adult	— (0)	— (0)	0/1 (0)	3/4 (75)	9/12 (75)
Voluntary	Child	13/22 (59)	9/15 (60)	9/13 (69)	14/23 (61)	9/16 *(56)
	Adult	9/25 (36)	12/23 (52)	7/14 (50)	7/18 (39)	7/25 *(28)
(b) GLCU		Year of detection				
Mode of survey		1987	1988	1989	1990	1991
General survey	Child	17/23 (74)	37/50 (74)	50/64 (78)	19/26 (73)	62/90 *(69)
	Adult	12/30 (40)	74/145 (51)	102/189 (54)	82/143 (57)	148/241* (61)
Contact survey	Child	3/3 (100)	9/15 (60)	5/8 (62)	5/6 (83)	14/17* (82)
	Adult	5/13 (38)	15/28 (54)	4/13 (31)	11/19 (58)	13/24* (54)
School survey	Child	10/13 (77)	82/109 (75)	97/120 (81)	113/153 (74)	93/115* (81)
	Adult	1/1 (100)	7/8 (88)	11/15 (73)	19/29 (66)	13/18* (72)
Others	Child	4/11 (36)	18/25 (72)	28/35 (80)	33/45 (73)	26/38* (68)
	Adult	8/39 (20)	31/85 (36)	36/81 (44)	63/118 (53)	85/144* (59)
Voluntary	Child	22/32 (69)	45/75 (60)	35/57 (61)	25/38 (66)	31/48* (21)
	Adult	27/122 (22)	95/265 (36)	59/162 (36)	49/125 (39)	54/138* (39)

* Not significant, $p > 0.05$.
† Significant, $p < 0.05$.
‡ Numbers in parentheses are percentages.

recognizable in one area, not in the other. Any epidemiological explanation for this drift could only be exceptional for 3 reasons: (a) the time span is too conservative to produce such a change; (b) it did not emerge in an area of similar endemicity and ethnicity; and (c) the MB proportion among new cases remained virtually stable during this period in both the areas.

Monolesional cases are believed to indicate early leprosy or early diagnosis. Delay in detecting cases does occur in the leprosy control programme, in which a total population survey lasts 3–4 years. Since a good segment of the child population (5–14 years) is covered through annual school surveys it is easy to understand why there is less delay in case detection in this group. This lag, therefore, is limited to adult cases and it gets gradually curtailed as case detection efficiency shows an upswing,[3] either through better coverage by a routine general survey, or special surveys, or through increased voluntary reporting brought about by health education. This may result in a gradual increase in the monolesional case proportion among new cases over a period of time. This is clearly reflected in the GLCU area. The manifestation of the trend only in adult males, though

not clear, could perhaps indicate a culturally-motivated difference in utilization of services offered by the programme and an unchanging ascertainment bias among the workers. The trend is not visible in the CLTRI area because even though a lag in case detection may occur it is minimal both in magnitude and proportion and does not show any year-to-year variation when considering a 20-year-old ongoing programme of an annual intense survey with an extensive examination coverage. Obviously, any differences are due to the mode of operation. A thorough understanding of the various operational elements in the programme is needed before a comprehensive explanation of the pattern of the disease in a particular direction could be made.

The study of the monolesional cases and their trend may be useful in understanding the disease. But the influence of case detection methods on the patterns of monolesional cases is great so that only studies using rigorously standardized methods of case detection can help us in understanding the disease process.

Acknowledgments

The authors are thankful to Mr Muthukumar, Mr Balakrishnan and Mr Pugazhendi for their assistance in the data entry and computerization process.

References

[1] WHO/LEP/CTD/LEP/90.2. Report of the consultation on the early diagnosis of leprosy: 1990.
[2] Jopling WH, McDougall AC. *Handbook of leprosy*, 3rd edn (1984). CBS Publishers & Distributors, New Delhi.
[3] Lechat, MF. Epidemiological indicators in leprosy control programmes. WHO/LEP/SG/WP/83.4: 1983.

Lepr Rev (1994) **65,** 137–142

A longitudinal study of alveolar bone loss around maxillary central incisors in patients with leprosy in Malaysia

KRISHNAN SUBRAMANIAM*,
SEANG HOO NAH* & SANDY C. MARKS†‡
** Department of Anatomy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; and †Department of Cell Biology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA, USA*

Accepted for publication 16 December 1993

Summary The loss of alveolar bone supporting the maxillary central incisors and the general periodontal conditions were evaluated after 14 years in the 12 patients remaining from an original group of 47 under treatment in Malaysia. Alveolar bone loss was minimal during this period even in the presence of periodontal inflammation. These data suggest that treatment protects patients with leprosy from alveolar bone loss and suggests that other skeletal deformities might respond similarly.

Introduction

Skeletal involvement is a major complication in advanced leprosy[1,2] because of the net loss of bone.[3] Moller-Christensen, in evaluating medieval skulls excavated from a Danish cemetery, first noted and documented a tripartite resorption phenomenon in the maxilla involving the palatine process, alveolar bone supporting the incisor teeth and the anterior nasal spine which he described as *facies leprosa*.[4] Contemporary studies on osseous resorption around these sites in the maxilla have confirmed that resorption of the alveolar process of the maxilla is a characteristic feature of the disease.[5,6] In a study initiated in 1977 on patients under treatment at the National Leprosy Control Centre in Malaysia we demonstrated that loss of alveolar bone was maximal in the maxillary anterior region, that patients with lepromatous leprosy had a greater degree of alveolar bone loss compared to those with borderline or tuberculoid leprosy[7] and that this resorption of bone was mediated by osteoclasts.[8] A follow-up study on 22 patients (from the original patient pool of 47) 4 years later showed that the rate of alveolar bone loss was minimal in patients with lepromatous, borderline or tuberculoid leprosy[9] and similar to that seen in larger populations without leprosy.[10,11]

‡ Correspondence: S. C. Marks.

0305-7518/94/065137+06

The purpose of the present study was to extend our earlier observations[9] after a lapse of 10 years to determine if the risk of accelerated bone loss observed in untreated lepromatous leprosy[12] is greatly reduced in patients maintained on treatment, as seen in other skeletal and soft tissue deformities of this disease.

Materials and methods

The patients still available from the original group[7] were recruited for this study. All patients up to 1987 were on 50 mg dapsone daily with a supervised monthly dose of 100 mg. Multidrug (MDT) therapy was begun at the National Leprosy Control Centre in Malaysia in 1987. Patients with multibacillary disease received a pulse dose of rifampicin (600 mg), clofazimine (100 mg) and dapsone (100 mg) on day 1 followed by clofazimine (100 mg) and dapsone (50 mg) for 27 days. This cycle was repeated for 2 years after which treatment was stopped and patients were followed for up to 4 years. Patients with paucibacillary disease received the same regimen without clofazimine. All patients had received this regimen and showed no evidence of relapse. Written consent was obtained after the procedures were explained to each patient.

Alveolar bone loss in the maxilla was measured radiographically[13] as described previously[7] using periapical radiographs taken with the paralleling long-cone technique.[14] The angle between the plane of the film and the X-ray beam was adjusted to between 50° and 60° for each patient because angulations within this range have been shown to have little effect on the calculation of alveolar bone support from multiple assessments.[13] Radiographs were magnified 10× and measurements from the root apex to the cemento-enamel junction and to the alveolar crest were made to the nearest 0·05 mm on each side of the maxillary central incisors using needle callipers and a micrometer. Duplicate measurements differed less than 3%. The reduction in alveolar bone support (which translates to bone loss) was expressed as a percentage by subtracting the current bone height related to the root length of the maxillary central incisor, from that present initially, which can be presumed to be the full root length, up to the level of the cemento-enamel junction.[9] The difference in the values between the present data and those obtained in 1982 (both of which were performed under identical conditions) was calculated to determine the percentage of loss of bone height over the last 10 years and the mean value for each disease type was translated into actual loss of bone height and expressed in millimeters.

Clinical examination of each patient included testing for tooth mobility, periodontal pocketing and gingival recession[15] on the maxillary central incisors and an assessment of the general periodontal condition including the extent of calculus deposits. Statistical evaluation was performed using the Student's *t*-test.[16]

Results

Table 1 summarizes the loss of alveolar bone height (alveolar bone loss) expressed as a percentage observed for each patient, and also compares similar data observed on the same patients in 1978[7] and 1982.[9] A 59-year-old lepromatous patient had his incisors missing, precluding measurements. However, the corresponding data from 1978 and

Table 1. Maxillary anterior alveolar bone loss and periodontal measurements

	Age of patient		Percent alveolar bone loss*			Maximal periodontal measurement‡		
Disease Type	(1992)	1978	1982	1992	Mobil	Pocket	Recession	Calculus
Lepromatous	59	37	37	—	—	—	—	—
	64	22	22	24	0	1	4	1
	68	32	36	36	0	2	3	2
	69	26	30	29	1	4	0	3
	70	23	27	37	1	2	3	2
Borderline	46	10	10	19	0	3	0	3
	53	20	25	31	1	2	0	3
	54	13	17	22	0	2	0	2
	58	17	17	16	0	3	2	2
	64	17	19	22	1	3	0	2
Tuberculoid	58	14	14	15	0	4	0	3
	62	29	29	33	1	2	4	2
	66	23	25	30	1	2	4	2

* Values rounded to nearest whole number.

‡ Largest periodontal measurements of maxillary central incisors: mobility = 0, 1, 2, or 3; periodontal pocketing and recission in mm; calculus = 1 (slight), 2 (moderate) or 3 (heavy).

1982 for this patient are included for comparative purposes. He also had the greatest bone loss, but had no net loss of bone over the initial 4-year period. The mean alveolar bone loss observed for the lepromatous patients in the present study (31·5 ± 5·3%) is significantly greater ($p < 0·05$) than that seen in patients with borderline leprosy (22 ± 5·0%) but not for those with tuberculoid leprosy (26 ± 7·8%). This observation also holds true for similar data recorded in 1978 and 1982. A qualitative assessment also showed that, in general, the loss in alveolar bone height is either static or minimal, considering that it extends over a decade. In order to assess this more accurately, the difference in the amount of alveolar bone lost in each disease type was calculated over the period of study. These data were then compared with those obtained for the same patient group over the earlier 4-year period (1978–82) and summarized in Table 2. From the combined data in Table 2, it is possible to estimate the percentage bone loss over a period of approximately 14 years. The loss in alveolar bone height over this period was 5·2% (lepromatous), 6·6% (borderline) and 4·4% (tuberculoid). An interesting observation in Table 2 is, despite lepromatous patients as a whole registering the greatest total loss in alveolar bone height (from the onset of our study in 1978), the *rate* of bone loss is the lowest (2·8%) when compared to patients with tuberculoid (3·3%) or borderline (4·4%) leprosy. The presumed loss in bone height over the 10-year period was also calculated based on an assumed mean root length of 13 mm for central incisors plus 3 mm being the height of the curvature of the cervical line.[17] The rate of loss of alveolar bone height was calculated at 0·06 mm per year for lepromatous or tuberculoid leprosy and 0·08 mm per year for borderline leprosy.

In general, the periodontal status (Table 1) in these patients was not different from

Table 2. The rate of alveolar bone loss in the anterior maxilla by disease type

	Mean loss of alveolar bone			
	Period: 4 years		Period: 10 years	
Disease Type	%	mm*	%	mm*
Lepromatous	2·4	0·38	2·8	0·45
Borderline	2·2	0·35	4·4	0·70
Tuberculoid	2·1	0·34	3·3	0·53

*Based on a mean alveolar bone height of 16 mm adjacent to the proximal and distal surfaces of maxillary central incisors (see text for details).

our observations in 1982. Maxillary central incisors had little or no mobility and other parameters of periodontal inflammation were of slight to moderate magnitude. The most severe were calculus deposits around the maxillary central incisors which were moderate to heavy in all patients except a 64-year-old lepromatous male who had no visible deposits. Gingival recession up to 4 mm around the maxillary incisors was seen in lepromatous and tuberculoid patients. Periodontal pocketing greater than 3 mm was found in only 2 patients.

Discussion

These data show that continuity of treatment has a beneficial effect on maxillary alveolar bone loss in patients with leprosy and suggest that it may also reduce other skeletal deformities. It has been shown that alveolar bone resorption in the anterior maxilla is a characteristic skeletal deformity of leprosy[2,4,5] and that it is greatest in untreated patients with lepromatous disease,[7,8,9,12] who by the 4th decade have the same alveolar bone loss as patients in Malaysia without leprosy who are in their 6th decade.[7,18] While alveolar bone loss around the maxillary incisors was initially greater in patients with lepromatous leprosy when compared with the other 2 types, the rate of loss in the present study was lowest in this group (Table 2). Patients with borderline leprosy recorded the highest rate of bone loss over the same period, about 30% greater than patients with lepromatous or tuberculoid leprosy. Thus our data suggest that successful treatment of the disease greatly reduces alveolar bone loss in patients with leprosy. These observations support our earlier findings[9] and infer that the longer the duration of untreated disease, the greater the tendency for alveolar bone loss in the anterior maxilla.[12]

Upon closer examination, it was noted that the rate of loss in these patients with leprosy with poor oral hygiene is similar to that in younger patients without leprosy with good oral hygiene.[10,11] Loe *et al.*[10,11] studied more than 1000 subjects younger than 40 years old in Norway and Sri Lanka over 6 years to assess periodontal status and loss of alveolar bone. The rate of attachment loss (which varies directly with loss of alveolar

bone support over long periods) was 0·08 mm and 0·29 mm per year for Norwegians and Sri Lankans, respectively. The difference between the 2 groups was attributed to the relative oral health status. The Norwegians had much less plaque and gingival inflammation and better oral hygiene than the Sri Lankans. The rate of alveolar bone loss seen in the present study is similar to that of the Norwegians but the oral hygiene in our leprosy patients is poor (similar to the Sri Lankans). The incidence of calculus and gingival inflammation in these patients with leprosy (Table 1) is similar to those in age-matched Malaysians without leprosy but the rate of alveolar bone loss in treated patients with leprosy is considerably less.[9,12] Thus, the correlation between the reduced rate of bone loss and poor oral hygiene in the patients in our study is a paradox since plaque accumulations and periodontal disease are directly related to alveolar bone destruction in populations without leprosy.[10,11,13,15,19]

What then is the reason for the initial susceptibility of patients with lepromatous leprosy to maxillary anterior bone loss? The suggestion that bone loss is directly attributable to some local effect of *Mycobacterium leprae* concentrations in the nasal mucosa is appealing and conceptually simple. A recent observation suggests that bone loss could be preceded by erythema nodosum leprosum (ENL).[20] It has been suggested that the immunologically mediated destructive ulceration arising from severe ENL reactions could initiate or aggravate bone destruction in the premaxilla,[21] or other bones.[22] Initiation and continuity of treatment may protect alveolar bone from this destructive influence in patients with leprosy. It is also possible that the specific immune derangements that make patients susceptible to leprosy in the first place may also protect them from alveolar bone loss associated with periodontal disease.[12] These possibilities need to be examined.

Acknowledgments

This work was supported by the University of Malaya (grant No. 135/77), the Heiser Program for Research in Leprosy, and Colgate-Palmolive/Malaysia.

We thank the director and staff of the National Leprosy Control Centre, Malaysia for their support. Our special thanks go to Mr Chiew Hock Koon for his chairside assistance, the patients who participated in the study and Mr Zulhisham, Professional Relations Manager of Colgate-Palmolive Co.

References

[1] Lechat MF. Bone lesions in leprosy. *Int J Lepr*, 1962; **30:** 125.
[2] Moller-Christensen V. *Ten lepers from Naestved in Denmark. A study of skeletons from a medieval leper hospital*. Copenhagen. Danish Science Press Ltd., 1953. p. 160.
[3] Paterson DE. Bone changes in leprosy: their incidence, progress, prevention and arrest. *Int J Lepr*, 1961; **29:** 393.
[4] Moller-Christensen V, Bakke SN, Melsom RS, Waaler E. Changes in the anterior nasal spine and the alveolar process of the maxillary bone. *Int J Lepr*, 1952; **20:** 335.
[5] Michman J, Sagher F. Change in the anterior nasal spine and the alveolar process of the maxillary bone in leprosy. *Int J Lepr*, 1957; **25:** 217.
[6] Southam JC, Venkataraman BK. Oral manifestations of leprosy. *Br J Oral Surg*, 1973; **10:** 272.
[7] Subramaniam K, Marks SC. Alveolar bone loss in leprosy. *Lepr Rev*, 1978; **49:** 287.
[8] Marks SC Jr, Subramaniam K. The cellular basis for alveolar bone loss in leprosy. *Lepr Rev*, 1978; **49:** 297.

[9] Subramaniam K, Marks SC, Nah SH. The rate of loss of maxillary anterior alveolar bone height in patients with leprosy. *Lepr Rev*, 1983; **54:** 119.
[10] Loe H, Anerud A, Boysen H, Smith M. The natural history of periodontal disease in man: the rate of periodontal destruction before 40 years of age. *J Period*, 1978; **49:** 607.
[11] Anerud A, Loe H, Boysen H, Smith M. The natural history of periodontal disease in man: changes in gingival health and oral hygiene before 40 years of age. *J Periodontal Res*, 1979; **14:** 526.
[12] Nah SH, Marks SC, Subramaniam K. Relationship between the loss of maxillary anterior alveolar bone and the duration of untreated lepromatous leprosy in Malaysia. *Lepr Rev*, 1985; **56:** 51.
[13] Schei O, Waerhaug J, Lovdal A, Arno A. Alveolar bone loss as related to oral hygiene and age. *J Clin Period*, 1959; **30:** 7.
[14] Lang NP, Hill RW. Radiographs in periodontics. *J Clin Period*, 1977; **4:** 16.
[15] Rateitschak KH, Rateitschak EM, Wolf HF, Hassell TM. In: *Color Atlas of Dental Medicine*, Vol. 1, *Periodontology*. 2nd Ed. Rateitschak KH (ed). New York, Thieme, 1989.
[16] Armitage P. *Statistical Methods in Medical Research*, New York, J. Wiley, 1971, p. 104.
[17] Wheeler RC. *Dental Anatomy: Physiology and Occlusion.* Philadelphia, W. B. Saunders, 1974. p.136.
[18] Subramaniam K. Marks SC Jr, Nair S, Ho KH. Profile of periodontal disease in an urban adult population in Malaysia. *J Malaysian Soc Health*, 1985; **5:** 97.
[19] Socransky SS, Haffajee AD, Goodson JM, Lindhe J. New concepts of destructive periodontal disease. *J Clin Periodontol*, 1984; **11:** 21.
[20] Scheepers A. Erythema nodosum leprosum: a possible cause of oral destruction in leprosy. *Int J Lepr*, 1992; **60:** 641.
[21] Rendall JR, McDougall AC. Reddening of the upper central incisors associated with periapical granuloma in lepromatous leprosy. *Br J Oral Surg*, 1976; **13:** 271.
[22] Moller-Christensen V. *Bone Changes in Leprosy*. Copenhagen, Munksgaard, 1961, pp. 14–15.

Lepr Rev (1994) **65,** 143–150

Letters to the Editor

HEREDITARY CAMPTODACTYLY: A CONDITION MIMICKING CLAWHAND DUE TO LEPROSY

Sir,

Hereditary camptodactyly is a rare type of fibromatosis with an autosomal dominant inheritance that affects both sexes equally. It begins in childhood, involving the little fingers (bilateral), producing persistent flexion of the proximal interphalangeal joints with sparing of the metacarpophalangeal joint.[1] Sometimes the other fingers are also affected.[2] The resulting deformity closely simulates clawhand[3] caused by leprosy. Because leprosy is a major cause of clawhand in a leprosy-endemic country like India, identification of this entity is essential to prevent the misdiagnosis of cases of 'Camptodactyly' as clawhand due to leprosy. We have recently seen 2 patients suffering from hereditary camptodactyly who were initially suspected as clawhands because of nerve damage due to leprosy.

Both patients (a 16-year-old girl and a 45-year-old man) presented with flexion deformity of the little finger of both hands that they had suffered from birth. The man also had similar deformities of the ring fingers. In both cases there was no history of hypopigmented patch, sensory deficit or neuralgic pain anywhere on the body, including the fingers. The first patient's father and the second patient's mother suffered from similar deformities. Local doctors first suspected both cases to be 'leprosy', and the girl received anti-leprosy treatment for 6 months, without benefit.

Examination revealed fixed flexion deformity of the proximal interphalangeal joint of the little fingers of both hands in the female patient and the little and ring fingers of both hands in the male patient. All modalities of sensations were preserved. There was no wasting or weakness of the small muscles of the hand. In both cases there was no thickening of the ulnar, median or radial cutaneous nerves, and no thickening of the palmar fascia. Systemic examinations and relevant laboratory investigations produced results that were within normal limits in both cases.

Both patients were diagnosed as suffering from 'Camptodactyly' with an autosomal dominant inheritance. Their real condition was explained to them and they were reassured.

Both the above cases were misdiagnosed/suspected as clawhand due to leprosy. The same observation was made by Pavithran.[3] In ulnar clawhand due to leprosy, the deformity consists of hyperextension at the metacarpophalangeal joints and flexion at the interphalangeal joints of the affected fingers. In addition there is a sensory deficit in the distribution of ulnar nerve and wasting and weakness of the small muscles of the hands supplied by the ulnar nerve. However, the 'bilateral' nature of clawing, the absence of any sensory or motor deficit and a family history of flexion contracture is an aid in diagnosing 'Camptodactyly' and helps to rule out leprosy. Camptodactyly is also to be differentiated from Dupuytren's contracture and Sterbiodactyly.[1] Camptodactyly has been associated with Marfan's syndrome, pectus excavatum, scoliosis, ptosis, Dupuytren's contracture, knuckle pad[4] and taurinuria.[5] However, no such associations were observed in our patients.

The idea of this communication was to emphasize two facts. First, 'Camptodactyly' is probably not as rare as is suggested in the standard textbooks because many cases are being diagnosed as 'leprous clawhand', as happened to our patients. Secondly, in an endemic area for leprosy,

physicians, leprologists and field workers must be made aware of this condition in order to avoid the psychological trauma and 'stigma' caused by incorrectly diagnosing patients as 'leprous clawhand'.

Department of Dermatology
Venereology and Leprology, PGI
Chandigarh-160 012, India

SANDIPAN DHAR &
BHUSHAN KUMAR

References

[1] Burton JL. Disorders of connective tissue. In: *Textbook of Dermatology*, Champion RH, Burton JL, Ebling FJG (eds.). 5th edition, Volume 3. Oxford: Blackwell Scientific Publications, 1992; 1803.
Welch JP, Temtamy SA. Hereditary Camptodactyly. *J Med Genet*, 1966; **3:** 104–7.
[3] Pavithran K. Camptodactyly simulating clawhand in a patient with indeterminate leprosy. *Ind J Lepr*, 1991; **63:** 232–4.
[4] Pavithran K. Camptodactyly with knuckle-pad. *Ind J Dermatol Venereol Leprol*, 1986; **52:** 222–3.
[5] Nevin NC, Hurwitz LJ, Neill DW. Familial Camptodactyly with taurinuria. *J Med Genet*, 1966; **3:** 265–8.

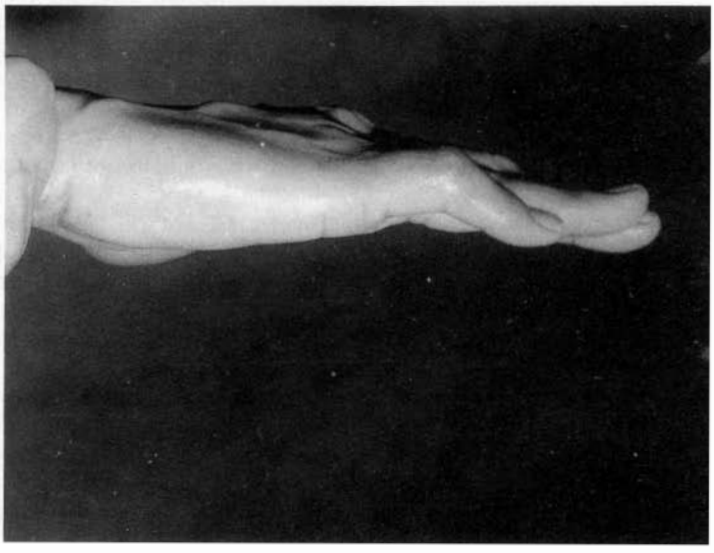

Figure 1. Showing a fixed flexion deformity of the proximal interphalangeal joint of the right hand.

A CASE OF TUBERCULOID LEPROSY WITH EITHER WIDESPREAD NERVE INVOLVEMENT OR A SECOND NEUROLOGICAL DISEASE—A CASE REPORT

Sir,

We wish to present the case of a 50-year-old Bhutanese farmer, who suffered numbness and tingling of the whole of the right arm and left leg, commencing in April 1992. He was admitted 5 days after onset to a general hospital in East Bhutan where he stayed for 3 months, with an interval of 2 weeks at home. No records are available from that time, but according to information we received from the hospital, he underwent anti-leprosy treatment, although no cardinal signs of leprosy were found. During hospital admission he developed weakness in the hands and feet and was unable to walk 'after an injection' (probably Vitamin B-complex). He was referred to our hospital in early August 1992.

There was no family history of leprosy or neurological disease and no history of poison intake or handling. On examination all muscles in the arms and legs were hypotonic and muscle strength was decreased. Because of weakness of the quadriceps muscle on both sides he was unable to walk. The tendon reflexes were absent and there was sensation loss in the arms and legs. There was tenderness over the lower part of the spine. Cranial nerves were intact. Neither enlarged nerves nor skin patches could be found, therefore on clinical grounds he was judged not to have leprosy and so referred the same day to the national referral hospital in Thimphu.

He was referred back to us with swelling of the face, hands and feet 3 weeks later. On examination we found 2 swollen and red, anaesthetic patches on the back and right shoulder, and several enlarged nerves (right ulnar, both lateral politeal, left radiocutaneous, left greater auricular). Tendon reflexes were still absent, but the abdominal skin reflexes remained. Position sense seemed impaired, but that could be due to language problems (as he could take a match out of a box and strike it without much difficulty). Detailed VMT showed bilateral weakness of the ulnar, median, lateral popliteal and posterior tibial nerve innervated muscles as well as right side radial nerve paresis. Weakness was also noted in the quadriceps femoris muscles bilaterally. Facial nerve was intact. Sensation loss was found in both forearms and both legs from the groin downwards as well as the lower part of the buttocks. Pressure sores were present over both greater trochanters. Skin smears for AFB were negative. VDRL was weakly positive, but the Rapid Plasma Reagin card test was negative.

The patient was diagnosed as having type I leprosy reaction and he was put on Prednisolone 60 mg OD as well as MB MDT (WHO) on 2 September 1992—2 new patches on the back and left upper arm appeared 2 days later, but subjectively he improved soon after the start of treatment.

Skin and nerve biopsies were performed. The skin biopsy was badly damaged during transport to the UK and showed 'inflammation, not inconsistent with leprosy'. The nerve biopsy of left radiocutaneous nerve showed 'a florid neuritis with some granulomas but no AFB. This must be leprosy, tuberculoid.' A neurologist we consulted believed that it was most likely a case of Guillain–Barré polyradiculitis or polyneuropathy. The CSF taken on 19 September 1992 showed normal protein, sugar and cell contents, but this does not exclude Guillain–Barré syndrome. Electric diagnostic studies of peripheral nerves are not possible in Bhutan.

During the following months muscle function improved slightly, but on discharge he was still unable to walk due to weakness of the thigh muscles. His sensation did not improve.

In summary, this appears to be a case of histopathologically confirmed tuberculoid leprosy with either widespread nerve involvement including the femoral nerves or, more likely, with a second neurological disease (Guillain–Barré syndrome?—which however did not improve significantly). We were unable to find a similar case that had been reported.

The possible cause could be leprosy involvement of the central nervous system, but 'ordinarily *M. leprae* do not invade the central nervous system in humans. There are only 3 instances in the literature in which leprosy bacilli have been detected in the central nervous system. *M. leprae* have been found in the interstitial tissue in dorsal root ganglia, Gasserian ganglia and also in anterior horn cells, but never in the cerebrum. There was no evidence of destruction of neuronal cells to cause any sensory or motor nerve changes.' (Dr C. K. Job, personal communication.)

It is possible that the presenting disease was not leprosy, but that the tuberculoid leprosy became manifest only after the commencement of anti-leprosy treatment. This is observed in other patients as well. (Dr M. F. R. Waters, personal communication.)

Gidakom Hospital
The Leprosy Mission
P.O. Khasadrapchu
Butan

F. J. MOET &
STEEN M. ANDERSEN

Acknowledgement: Dr Sebastian Lucas kindly prepared and examined the biopsies.

COMMENT: LEPROSY CONTROL AND THE IMPLEMENTATION OF MULTIPLE DRUG THERAPY AND THE PREVENTION OF DISABILITIES

Sir,

The suggestion under 'Further simplification' in the above Editorial, published in *Lepr Rev*, 1992; **63:** 193–8[1], to separate case detection and chemotherapy from disability prevention and management calls for comments. Do the authors[1,2] really mean that the prevention of disabilities (POD) should be achieved by a different person (agency) than the people administering MDT?

POD is an essential component of any leprosy control programme, as is, for example, chemotherapy. Disappointing experiences when combining the above-mentioned components into an integrated leprosy control service should not lead to the decision to abandon (separation, simplification) POD at PHC/DHP level altogether. The overall objective should be that no disabilities should occur apart from those that are irreversible at diagnosis.[3]

Renewed efforts could be directed, for example, at the introduction of only the most essential POD components at PHC/DHP level and at strengthening the supervisory structure.

In my opinion POD at peripheral health service level should at least consist of:

Health education of new patients (and patients released from treatment) concerning the risk of reactions and about prevention of disabilities.

2 Recognition of early nerve damage.

3 Prompt treatment of severe reactions with prednisolone.[4]

4 Teaching of simple self-care: for example care for insensitive hands and feet, simple exercises, advice on suitable commercially available footwear, etc.

I can easily agree with separating physical and social rehabilitation activities (e.g. footwear for patients with deformed feet, orthopaedic appliances, physiotherapy, reconstructive surgery, vocational training, etc.) from case detection and chemotherapy.

In order to combine case detection and chemotherapy with POD, the supervisory and supporting structure (including a referral system) has to be strengthened. The leprosy control supervisor should visit each clinic at least once every 3 months. An important task for the supervisor will be to give on-the-job training regarding, for example, diagnosis and classification, chemotherapy, POD, etc.

MDT implementation with early case detection considerably improves disability prevention. It is, however, inconceivable that when giving health education to new patients no attention is paid to the risk of reactions and the prevention of disabilities. Instead of separating POD (and especially referring to the above-mentioned essential POD components at peripheral health service level) from case detection and chemotherapy, more attention should be paid to strengthening the supervisory structure of an integrated leprosy control programme.

Medical Advisor, Leprosy Control Centre, Zone 6 P. A. M. SCHREUDER
P.O. Box 58
Khon Kaen 40000
Thailand

References

[1] McDougall A. Leprosy control and the implementation of multiple drug therapy: to what extent can the operational strategy be simplified for primary health care? *Lepr Rev*, 1992; **63:** 193–8.
Yuasa Y. MDT for all; target oriented leprosy control program in the 1990s. *Int J Lepr*, 1991; **59:** 624–38.
[3] Watson J. Preventing disability in leprosy patients. London: The Leprosy Mission International, 1986.
[4] Becx-Bleumink M, Berhe D, 't Mannetje W. The management of nerve damage in the leprosy control services. *Lepr Rev*, 1990; **61:** 1–11.

COMMENT: THE SERODIAGNOSIS OF LEPROSY

Sir,

We have read the Editorial 'The serodiagnosis of leprosy' by Dr P. G. Smith, published in *Lepr Rev*, 1992; **63:** 97–100, with great concern.

In Cuba, where the elimination of leprosy as a public health problem is defined by WHO has almost been achieved, we are already discussing how to eliminate *Mycobacterium leprae* transmission, its causative agent. The WHO strategy is based on the administration of MDT to at least 80–90% of registered cases and the encouragement of early self-reporting of cases, and aims essentially at the elimination of infection, thus preventing transmission.[1] MDT was implemented in 3 Cuban provinces in 1989 and was extended to the whole country in 1990, but in fact the therapeutic regimen (600 mg daily RMP given for 6 and 3 months to MB and PB patients, respectively, followed by monthly injections of 225 mg DADDS, all administered by health personnel) that had been used since 1977 until it was substituted by MDT proved to be effective. Only 6 of 1211 MB patients treated for at least 5 years were discovered to be relapsed in a drug resistance study conducted just before MDT implementation (A. B. González, unpublished observations). Such treatment was given to most of the patients but this does not seem to have made any obvious impact on *M. leprae* transmission because in the period 1972–90 the annual case detection rate is represented by a practically flat curve with a very slight declining trend (R. Gil, unpublished observations).

From the above-mentioned facts it could be believed that the elimination of *M. leprae* transmission could take longer than would be expected if the only method was to treat confirmed cases. Therefore, early diagnosis together with prompt treatment appears to be crucial to achieve elimination. But, besides the fact that early diagnosis is not always easy to attain due to many very well-known reasons, it should be ascertained how early this should be. Perhaps individuals incubating the highly infectious forms of the disease are capable of acting as a source of transmission for varying periods before their leprosy becomes manifest and these could pass on the disease to others before they themselves are diagnosed. We have some evidence that this might occur.[2] In Cuba, on average during the last few years, around 60% of the cases have been diagnosed less than 12 months after the onset of the clinical signs and only 10% after 5 years and more, so that in order to interrupt transmission it will definitely be necessary to detect these cases even earlier.

It is generally accepted that patients at the lepromatous area of the spectrum make the major contribution to the spread of *M. leprae*, therefore in order to interrupt transmission what is really important is the early detection and treatment of as many *M. leprae* transmitters as possible. In this respect the PGL-I ELISA is useful because it is virtually 100% sensitive in lepromatous leprosy. The usefulness of this serodiagnostic test should be discussed and evaluated in relation to particular epidemiological situations. Marked differences in the distribution of leprosy types between the populations of different geographical areas have been observed due to unknown reasons. Because of this, it is not too surprising that a great deal of work would have to be done, for instance, in Malawi, where 95% of the patients are PB,[3] to find a few presumably infected individuals who are suspected of incubating MB leprosy because of the observation of elevated PGL-I antibody levels. It seems important to us that in the study by Chanteau[4] only 1 of 10 individuals who developed leprosy among a group of 1123 contacts in Polynesia, followed up for up to 6 years, was lepromatous and that he/she showed a high PGL-I antibody level between 20 and 30 months before being diagnosed. We do not agree with Dr Smith's observation on the results of the Venezuelan study[5] that it was a striking finding that most of the 20 cases occurred in those who had not had elevated antibody levels. The results (OD readings) for each individual serum sample were expressed as a proportion of the value observed for the positive control sample in each microtitre plate—a pool of sera from 6 patients with LL or BL leprosy with known high levels of antibody to PG-I. If a cut-off value had been set at 0·25 sample/positive control ratio, 14 of the 20 cases (70%) would be considered seropositive, but the seropositive proportion of all sera would be 33·4% which

is somewhat higher than that commonly found for leprosy contacts in published reports on this subject, and if the cut-off value were at a 0·5 ratio (which could, in our opinion, undoubtedly be regarded as 'elevated') 35% of the developed cases would show antibody levels above this value and the total seropositive proportion would only be 5·8% which is at the low end of the range commonly reported. On the other hand, 13 (65%) of these cases developed paucibacillary disease (2 TT, 1 BT and 10 I) and it is well known that this assay is of low sensitivity in these leprosy types. Again, 2 of the 3 cases who developed lepromatous leprosy (1 LL and 1 BL) showed very high antibody levels, and the third one (BL) still showed a value of 0·37.

It is true, as Dr Smith writes, that even with a test which had a specificity of 95%, if only 1/1000 of those screened really had leprosy, there would be 50 times as many false positives as true positives in detecting cases. But the lepromin test might provide a useful means for discovering those who are at risk of developing MB leprosy and becoming new sources of infection in the community. We fully agree with Dr Smith in that there is little to be gained by extending case-finding activities if currently identified cases are not properly treated. Nonetheless, we workers on leprosy must not be in a hurry to throw this tool into the waste basket.

Instituto de Medicina Tropical
'Pedro Kouri'
Apartado 601, Zona Postal 13
Ciudad de la Habana, Cuba

ANGEL B. GONZÁLEZ
ELBA GONZÁLEZ-ABREU

References

[1] Noordeen SK. Editorial: Elimination of leprosy as a public health problem. *Lepr Rev*, 1992; **63:** 1–4.

[2] González-Abreu E, Mora N, Perez M, Pereira M, Perez J, González AB. Serodiagnosis of leprosy in patient's contacts by enzyme-linked immunosorbent assay. *Lepr Rev*, 1990; **61:** 145–50.

[3] Ponnighaus JM, Fine PEM. Leprosy in Malawi: 1. Sensitivity and specificity of the diagnosis and the search for risk factors for leprosy. *Trans Roy Soc Trop Med Hyg*, 1988; **82:** 803–9.

[4] Chateau S, Cartel JL, Spiegel A, Plichart R, Roux J. La détection des IgM anti-PGLI pour le serodiagnostic des malades hanséniens et la surveillance des sujets contacts en *Polynésie. Bilan sur 5 ans. Bull Soc Path Ex*, 1990; **83:** 649–57.

[5] Ulrich M, Smith PG, Zuniga M, Sampson C, Centeno M, Garcia V, Manrique X, Salgado A, Convit J. IgM antibodies to native phenolic glycolipid I in contacts of leprosy patients in Venezuela: epidemiological observations and a prospective study of the risk of leprosy. *Int J Lepr*, 1991; **59:** 405–15.

REPLY: THE SERODIAGNOSIS OF LEPROSY

Sir,

My contention is that serological tests for the diagnosis of early leprosy are still at the research stage and, in particular, the use of elevated antibodies for PGL-1 as a screening test for early leprosy is likely to be of little value in most leprosy control programmes. The experience in Cuba may represent an exception, but convincing evidence for this is not presented in the letter from Drs González and González-Abreu (see previous letter).

If it is hypothesized that incipient cases of lepromatous leprosy are the major reservoir of infection in Cuba (and this hypothesis itself may be questioned as non-lepromatous cases may also be infectious and be important in maintaining transmission, if their numbers are large enough) then identifying these cases and treating them may speed the reduction in transmission rates. Even if antibodies for PGL-1 are a very sensitive indicator for these cases (and we do not know this, as most published studies report elevated antibody levels in lepromatous patients who already have clinical leprosy), we know that they are not a very specific indicator and there remains the problem of

differentiating the true early cases from the much larger number of 'false-positives' in order to know which individuals to treat (even before they have clinical signs of disease). It is not clear that the lepronim test will provide the necessary discrimination.

Prospective studies of the populations that are being serologically tested in Cuba may shed light on some of these issues. For example, with an extensive testing programme it will be possible to document those cases of leprosy which are *not* picked up by the serological screening programme.

Department of Epidemiology and Population Sciences
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

P. G. SMITH

COMMENT: DISAPPOINTING EXPERIENCES WITH BLISTER–CALENDAR PACKS

Sir,

I am sure that you will have had a number of letters concerning the problem raised in a previous Letter to the Editor published in *Lepr Rev*, 1993, **64,** 171, by P. Lever and H. Boutmy. First I was disturbed to read that crushed dapsone powder could be used specially for those who are allergic to dapsone. We have also found that patients are unable to remove medication, and on my white wall I have an area of lamprene that refuses to be removed. First we used folic acid, but this also had its problems as one can grow fungi even in air-conditioned rooms. Baking soda and baking powder have all been tried so I too would be very grateful if anyone can help.

Direct sunlight here causes the temperature to rise to over 50°C and the humidity is also very high. For those who cannot manage to remove the tablets from the blister pack, we remove them ourselves. That is why I have no fingernails to speak of!

It is most important not to overload containers---even tobacco tins in third world countries are airtight, although the availability of these is restricted as many people do not smoke.

Disease Control Unit
Raihu Health Centre
Box 13 Aitape
Sandown Province
Papua New Guinea

JACQUELINE ELDRED

COMMENT: DISTINGUISHING POST-KALA-AZAR DERMAL LEISHMANIASIS FROM LEPROSY: EXPERIENCE IN THE SUDAN

Sir,

I write with reference to the above article *Lepr Rev*, 1993; **64,** 53, on methods to distinguish lepromatous leprosy (LL) from post-kala-azar dermal leishmaniasis (PKDL).

Between 11 January and 14 April 1993 I worked in the Dharbhanga District of Bihar. The work was called 'cleaning of records operation'. We came across many cases of PKDL. In the beginning some were mistaken for lepromatous leprosy because we had no previous experience of PKDL. However, it is easy to distinguish PKDL from lepromatous leprosy for the following important reasons:

non-involvement of nerves;
2 non-involvement of mucosa of the upper nose and throat;
3 non-involvement of eye and testes in PKDL; and
4 skin-smear negativity.

The lesions also dramatically improve after starting treatment with sodium slibanate. (I have seen a patient who improved after only 1 week's treatment. The skin lesions in PKDL can be macules, maculopapular, and nodular lesions.)

Eyebrows are not lost, ears may not be involved—no prominence of the great auricular nerve will be present.

These patients had suffered from Kalazar for between 1 and 5 years and had not received a complete course of treatment. L.D. bodies could not be demonstrated in skin smears or from a blood sample. Formaldehyde tests of urine were also negative. However, a splenic biopsy of parasitic forms can confirm diagnosis under field conditions. A course of sodium slibanate as a therapeutic test rapidly clears the lesions.

V. V. GURUNATHA BABU

Leprosy Training Centre
Hyderabad (Urban)
Andhra Pradesh
India 500 012

Lepr Rev (1994) **65**, 151–152

Book Reviews

***The Surgical Management of Deformities in Leprosy and Other Peripheral Neuropathies.* Noshir H. Antia, Carl D. Enna and Behman M. Daver**

This is an excellent textbook on the surgical management of leprosy-related deformities, written by international experts in the field of leprosy surgery.

The book begins with chapters on the pathogenesis and pathology of deformities in leprosy, and changes in the skin and peripheral nerves, which provide foundational knowledge on the destruction and mutilations that manifest this disease. The chapters relating to the deformities of the face and hands and their management are particularly outstanding, with a complementary section on applied anatomy. There are also separate chapters on the management of foot deformities, complications and secondary deformities and surgical rehabilitation which includes motor and sensory re-education, and foot-care.

The greatest strengths of this book are the clarity of presentation, good illustrations and the selection of topics which covers virtually all conditions seen by the leprosy surgeon. However, this work would have been more complete if data had been given on the results of the various procedures, showing the advantages of one technique over the other. The one area with which I would disagree relates to the use of vascularized muscle graft for the correction of lower facial palsy, where the use of sural nerve in the 1st stage cannot be justified because of possible mycobacterial infiltration.

In summary, this is a concise, well-referenced textbook, and although written primarily for the leprosy surgeon, it also has useful chapters which would be of interest to orthopaedic and hand surgeons. The lifetime experiences of these acknowledged experts is recommendation enough, and this reasonably-priced book should be an essential purchase by all those practising leprosy surgery.

Jerome H. Pereira

Oxford University Press, Bombay, 1992. 162 pp.

***Leprosy. A Reference Guide for Medical Practitioners, Programme Managers and Leprosy Workers.* R. S. Misra**

Dr R. S. Misra, consultant dermato-venereologist and leprologist in Safdarjung Hospital, the Government of India, New Delhi, has produced a book (Hardback, 352 pages) which is described by the publishers as giving an assessment of the current situation in leprosy (global, regional and high endemic), with particular attention to India. The main chapter headings include: 'Global View', 'The Indian Scenario', 'Problems in Leprosy Management' and 'Facets of Leprosy Eradication'. There is an excellent bibliography and index, together with 26 appendices under the headings of 'National Leprosy Eradication Programme (NLEP)', 'Implementation of NLEP' and 'Useful Background Information'. Apart from a few contributors from the UK and Brazil, the rest are from agencies or institutes in India, including the Bombay Leprosy Project, the Central JALMA Institute for Leprosy (Agra), the Sacred Heart Leprosy Centre (Coimbatore, Shieffelin Leprosy

Research and Training Centre, Karigiri), the Lala Lajput Rai Memorial College (Meerut), the Maulana Azad Medical College (Delhi), the Central Health Education Bureau, Government of India (Delhi), the Grant Medical College and the Sir J. J. Group of Hospitals (Bombay), the German Leprosy Relief Association (Madras) and the National Institute of Immunology (Delhi). The personal contributions by Dr Misra repeatedly underline the importance of uniform multiple drug therapy implementation, irrespective of the level of endemicity in any particular state or district. Especially concerning leprosy in India, this is almost certainly the most up-to-date and informative book available. The appendices alone run to over 100 pages and they are a mine of valuable information on operational definitions, statistical and epidemiological data in the NLEP. The author, already well known for his contributions to research in dermato-venereology and leprosy, has assembled in this book a remarkable combination of wisdom and practical advice, which will surely prove invaluable as a reference guide and handbook, especially in India. The book is published and printed by Ashok Kumar Mittal, Concept Publishing Company, A/15–16, Commercial Block, Mohan Garden, New Delhi 110059, India.

A. Colin McDougall

Concept Publishing Company, New Delhi, 1993. Rs. 500

Lepr Rev (1994) **65,** 153–156

Teaching Materials and Services

WHO 'Core Library'

WHO has developed a 'core library' for doctors working in small hospitals. This library, which consists of seven clinical manuals, was established following the recommendation of a study group concerned with hospital functions at the first referral level. The group specifically asked WHO to 'select and promote a short list of manuals that are considered indispensable to hospitals at first referral level and could form the nucleus of a hospital library'.

Three surgery manuals (*Anaesthesia at the District Hospital*, *General Surgery at the District Hospital* and *Surgery at the District Hospital*) were selected because they describe new life-saving procedures, as was the new pocket guide on *Management of Severe and Complicated Malaria. Respiratory Infections in Children: Management in Small Hospitals* was included because of its direct relevance to a major problem in hospitals, and *Manual of Radiographic Interpretation for General Practitioners* was selected as representing the most complete set of radiographic images for clinical use. Finally, *Cancer Pain Relief* was added to the list because many patients in developing countries are hospitalized because of intractable pain; when the cause is cancer, the disease may be so far advanced that pain relief is the sole treatment option.

To help make the library affordable, WHO has reduced the price by 65%, meaning the books, valued at Sw.fr.125, can be purchased for only Sw.fr.44. Since 4 of the books are large-format, weighty manuals, the price is, in effect, just enough to cover postage.

There are already signs that this special offer will be successful. The first order (from a Geneva address) arrived the day after promotion began, and many other orders have come in since; 2 NGOs are considering purchasing core libraries for all hospitals within selected countries, and the International Hospital Federation will be promoting the library in its newsletter and journal.

Available in English and French from: the World Health Organization, Distribution and Sales, 1211 Geneva 27, Switzerland.

TALC, U.K.: Libraries for district hospitals and health workers

TALC (Teaching Aids at Low Costs) already sends out large numbers of subsidised books, but knows that there is also an urgent need for many hospitals and health clinics in the developing world to have an up-to-date range of medical and health books. Because of the situation TALC is making 2 libraries available which have both been selected by experts to provide the best range of information possible.

The first library for district hospitals costs £85 including postage and packing by surface mail worldwide. It contains 17 books ranging from 2 on primary surgery, to an AIDS handbook and the latest book on tuberculosis.

The second, aimed at district health workers, has 14 books and costs £60 including postage and packing by surface mail. The books include 'Where there is no Doctor', a revised book on nutrition and a book on obstetric emergencies.

Anyone interested in participating in this scheme who would like further details should contact TALC at: PO Box 49, St Albans, Herts. AL1 4AX, U.K. Telephone No: 0727 853869.

Disability Information Service, AHRTAG, U.K.

The Disability Information Service is specifically for disabled people in developing countries and those working with them.

It provides ready access to an extensive range of written materials on disability and rehabilitation, including books, manuals, conference proceedings, journal articles and unpublished reports.

The emphasis is on materials that cover the community based approach to rehabilitation, particularly those produced in developing countries.

The service has been set up jointly by AHRTAG (Appropriate Health Resources and Technologies Action Group Ltd) in the U.K., and the International Child Health Unit (ICH) at Uppsala University, Sweden.

These organizations liaise closely with the United Nations Disabled Persons Unit in Austria. The Unit is setting up a clearing-house on disability and rehabilitation worldwide which will co-ordinate a worldwide network of resource centres and databases.

Just write in with details of what specific area you are interested in receiving information. Please be as precise as possible, so that we can ensure that any information sent to you is relevant to your particular needs.

Universities, libraries and all enquirers from the Nordic countries should write to:

Disability Information Service
ICH
University Hospital
S-751 85 Uppsala
Sweden

Development projects, other organizations and individuals should write to:

Disability Information Service
AHRTAG
1 London Bridge Street
London SE1 9SG
U.K.

World Orthopaedic Concern (WOC)

WOC exists to improve standards of orthopaedic care and education by:

- training orthopaedic surgeons in their own countries to the highest standards appropriate to the challenges they may meet;
- training undergraduates and other medical staff to face the same challenges;
- sending both junior and senior orthopaedic staff from Britain to hospitals abroad to assist in training and care programmes;
- sending equipment and medical literature, as needed, to hospitals abroad;
- establishing a 'reserve pool' of medical personnel to respond to major disasters worldwide;
- working with others—surgeons in other medical disciplines, anaesthetists, orthotists and prosthetists, physiotherapists and nurses—involved in developing surgical services abroad.

Contact: World Orthopaedic Concern at the British Orthopaedic Association, 35–43 Lincoln's Inn Fields, London WC2A 3PN, U.K. Tel: 071 405 6507. Fax: 071 831 2676.

Where there is no doctor, a village health care handbook, 1992

This revised edition of the handbook, 446 pp, by D. Werner with C. Thuman and J. Maxwell, describes a wide range of illnesses and factors that affect the health of the villager in developing countries, from diarrhoea to tuberculosis. It now includes information about additional health

problems, such as AIDS, dengue, abortion complications and drug addiction. Advice is updated on other topics, with emphasis on cleanliness, healthy diet and vaccinations. Childbirth and family planning are covered in detail.

The book explains which medicines are most useful for specific sicknesses and which are useless or dangerous. Risks and precautions are carefully described and guidelines given for the sensible use of both traditional and modern medicines. The handbook is aimed at villagers remote from medical centres, and village storekeepers and pharmacists selling health care supplies. Its important and clearly written information will also interest village health workers, teachers, mothers and midwives.

Available in more than 50 languages. Contact: The Hesperian Foundation, P.O. Box 1692, Palo Alto, CA 94302, U.S.A.

The Prescriber; guidelines on the rational use of drugs

The first issue of the newsletter appeared in January 1992 and it is intended to provide information on the rational use of essential drugs to community health care workers in developing countries. Each issue of *The Prescriber* concentrates on a particular health issue. Topics to date have included sexually transmitted and AIDS related diseases, drug use in pregnancy and most recently, diarrhoeal diseases.

Available in English, French, Spanish and Portuguese from: UNICEF, 3 United Nations Plaza, New York, NY 10017, U.S.A.

Leprosy—basic information and management, Ciba-Geigy (now in Urdu)

This 42-page booklet, originally in English, has been translated into French, Spanish, Bengali, Indonesian and recently Urdu. (Copies in Urdu may be obtained on writing to the Superintendent, Rawalpindi Leprosy Hospital, Zafar-ul-Haq Road, Rawalpindi 46000, Pakistan.) It is distributed free, in reasonable numbers to *bona fide* applicants, on application to: The Medical Department, Ciba-Geigy, Basle 4002, Switzerland.

Multidrug therapy: questions and answers, WHO (now in Bengali)

This valuable booklet deals with commonly arising questions in the implementation of multiple drug therapy (MDT)—and gives answers. It will be distributed in West Bengal and Bangladesh.

Apply to: Dr D. S. Chaudhury, Director, Greater Calcutta Leprosy Treatment and Health Education Scheme, 23 Market Street, Calcutta 700 087, India.

Master of Public Health (MPH) Course, Leeds, U.K.

The MPH for warm climate countries was established in 1981. The course is designed to help medical practitioners in positions where medical skills alone are not enough, including individuals taking charge of districts, and district medical officers moving to provincial level. The course also seeks to prepare doctors for more senior administrative positions and for movement to academic posts in university departments.

'The district' is the focus of the teaching—it is at this level that the vital link between policy and community takes place and theory is turned into practice.

The Design of the Course

Principles of preventive and community medicine as opposed to the curative approach will be emphasized.

The Leeds MPH has an interdisciplinary approach to its teaching, drawing on the departments of Public Health Medicine, Civil Engineering and the Nuffield Institute from the University and that of Health Education from the Polytechnic. There is also an extensive programme of visiting speakers providing information on the most recent advances of their subjects.

A variety of lively teaching methods are employed. Interaction between course members from different parts of the world is one of the most valuable features. Tutorials are given for small group teaching and a personal tutor is available to help. Staff specifically attached to the course aim to foster a spirit of caring and encourage both academic and social activities.

Course Content includes:

- public health medicine;
- epidemiology and statistics;
- demography;
- planning and management;
- health promotion;
- health engineering;
- family and urban health;
- occupational health;
- use of personal computers (Epi Info will be taught and used).

Further options will be added to reflect student needs.

Apply: MPH Course Coordinator, Dept of Clinical Medicine, Academic Unit of Public Health Medicine, 20 Hyde Terrace, Leeds LS2 9LN, U.K.

Video on Multidrug Therapy (MDT) for Leprosy, WHO

This film is intended to create an enhanced awareness among decision-makers, public health managers, health workers and the public, of the importance and effectiveness of MDT in the control and treatment of leprosy. It was produced in 1991, VHS, 20 mm, English and French. Cost: Sw fr. 40 (USA $36.00); developing countries, Sw fr. 28. Order No. 1650058. Apply: WHO, Distribution and Sales, 1211 Geneva 27, Switzerland.

Health Action: Newsletter from AHRTAG, U.K.

Health Action is published by the Appropriate Health Resources and Technologies Action Group (AHRTAG).

It is a quarterly newsletter that covers the key issues in management and practice of primary health care, highlighting the links between health and other aspects of development. It provides a new forum for discussion of the issues that affect the future implementation of primary health care—and the well-being of millions of people.

Who is it for? . . . all those who implement primary health care programmes or work in related fields. It will be useful to those involved in planning, supervision and training, particularly within health districts, as well as people in government or multilateral organizations who support these workers.

Regular features include:

- Combating inequality—focusing on the opinions and experiences of people who are challenging inequalities in health and society;
- Reviews and Resources—a useful page of information about publications, videos, conferences and courses;
- Feedback and letters—a chance for you to air your views;
- Challenge—in each issue we pose a question on a primary health care issue so that you can tell us about your experiences.

How much does it cost? . . . If you live or work in a developing country, it is free. For other people, there is an annual subscription charge (details available from AHRTAG).

To become a regular reader, please contact: Health Action, AHRTAG, 1 London Bridge Street, London SE1 9SG, U.K.

Lepr Rev (1994) **65,** 157–159

News and Notes

Essential Drugs Monitor, WHO

The Essential Drugs Monitor is produced and distributed by the WHO Action Programme on Essential Drugs. It is published in English, French and Spanish, and has a global readership of some 200,000, to whom it is free of charge. The Monitor carries news of developments in national drug policies, therapeutic guidelines, current pharmaceutical issues, educational strategies, and operational research.

WHO's Action Programme on Essential Drugs was established in 1981 to provide operational support to countries in the development of national drug policies and to work towards the rational use of drugs. The Programme seeks to ensure that all people, wherever they may be, are able to obtain the drugs they need at the lowest possible price; that these drugs are safe and effective; and that they are prescribed and used rationally.

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

Resource list of international newsletters, 1992/3

Details of 110 newsletters, free of charge to readers in developing countries, are contained in the latest edition of AHRTAG's resource list of free international newsletters published this month. Details of a further 14 recommended newsletters and journals available on subscription are also included.

The newsletters cover a wide range of primary health care related issues including disease control, AIDS, mother and child health and health education, and are indexed by subject, language and geographical focus.

Copies of this resource list are available from AHRTAG, 1 London Bridge Street, London SE1 9SG, U.K.

Price:

free (developing countries)

£3.50 (including postage and packing) to U.K./Europe/U.S.A.

For further information, please contact Margaret Elson.

The Newsletter of the WHO Global Programme on Aids, 1992, No. 2

As part of WHO's commitment to the overall care of people with the AIDS virus, GPA has developed an innovative handbook entitled *Guidelines for the clinical management of HIV infection in adults.* The 100-page guide sets out diagrammatic plans for treatment—by symptom, not by disease—at local health centres, district or regional hospitals, or at central level.

'At present, the lack of clear guidelines for clinical management may lead to inaccurate clinical diagnosis, inappropriate treatment and unsuitable resource planning', says Dr Rudolf Wabitsch, of GPA's Health Care Support Unit. 'We hope this book will help countries, especially in the developing world, to formulate national treatment norms for HIV infection and AIDS in accordance with their own particular needs and resources.'

The handbook offers guidance for clinical management at three different levels of health care: Level A, where no laboratory or X-ray is available—a dispensary, or primary health care clinic, for example; Level B where a small laboratory is available, and chest X-rays and microscopy might be possible (e.g. a district hospital); and Level C, where the laboratory and other diagnostic facilities of a major hospital are at hand.

Where practicable, the guidelines are presented in the form of decision maps. For each level of care, and for each symptom (fever, diarrhoea, or lymph node enlargement, for example), different shaped boxes linked by arrows designate the initial state, the decision to be taken and the consequent action. Other guidelines for the clinical management of HIV and AIDS have addressed specific diseases. The new handbook has chosen to address symptoms because many diseases are difficult to identify without expensive diagnostic procedures unavailable or inappropriate in countries with scarce resources.

Field tests in Malawi, Burundi and Barbados have shown that the guidelines are sound in form and content, and that they can be adapted successfully according to differing resources, health systems and clinical presentations.

IDRC Reports, Canada

IDRC Reports is published quarterly by the International Development Research Centre (IDRC) of Canada. Its aim is to keep an international readership informed about the work IDRC supports in developing countries as well as other development issues of interest. The magazine is also available in French as *Le CRDI Explore* and in Spanish as *El CIID Informa.*

Through support for research, Canada's International Development Research Centre (IDRC) assists developing countries in creating their own long-term solutions to pressing development problems. IDRC is a public corporation created by the Parliament of Canada in 1970, and it is guided by an international Board of Governors. IDRC has regional offices in Cairo, Dakar, Johannesburg, Montevideo, Nairobi, New Delhi, and Singapore.

Copies are available free of charge to controlled groups in developing countries. Paid subscription is AD$16 for 4 issues.

Contact: Distribution and Marketing Unit, Corporate Affairs and Initiatives Division, IDRC, PO Box 8500, Ottawa, Canada K1G 3H9.

St Francis Leprosy Guild, London

The St Francis Leprosy Guild was founded in 1895 to help missionaries, doctors, nurses and others to care for patients with leprosy. Its current activities include: nursing care, multidrug treatment, surgery, preventive medicine and hygiene, physiotherapy, rehabilitation, special footwear, wheelchairs, X-ray equipment, long-term hospitalization, and assistance in securing employment. The 1993 report to benefactors includes an account of how funds were distributed in 1992. (Over £400,000, covering most leprosy-endemic countries worldwide.) Address: 21 The Boltons, London SW10 9SU, U.K.

India: Report of the 4th Independent Evaluation of the National Leprosy Eradication Programme

This Report gives a full account of the objectives, methodology observations, conclusions and recommendations of the 4th Independent Evaluation of the NLEP, which covered 24 of the states/union territories in December 1991. Copies are available from the Leprosy Division, Directorate of Health Services, Ministry of Health, New Delhi 110001, India. (See also, 'National Strategy for the Elimination of Leprosy in India' by B. N. Mittal, *Ind. J. Lepr*, **64,** 513–20.)

Sir Rickard Christophers award to Drs Jopling and Ridley

We are delighted to report that Drs William Jopling and Dennis Ridley, both past members of the Editorial Board of *Leprosy Review*, have been jointly awarded the Sir Rickard Christophers Medal

by the Royal Society of Tropical Medicine and Hygiene for their 'outstanding contributions to the understanding of leprosy'. This award is made every 3 years and Drs Jopling and Ridley are to receive their medal on 16 June 1994 at the Society's headquarters.

Welcome leprosy news from Japan

Dr Jopling has kindly sent the following item on Kumamoto, Japan. It is especially welcome as so little is known in the West about the leprosy situation in Japan.

'Dr Ichiro Kikuchi reports from Kikuchi Keifuen Leprosarium in Kumamoto, Japan, that an official ceremony took place in that city on 6 April 1993 to honour the names of two English Protestant missionaries, Miss Hannah Riddell and Miss Ada Hannah Wright, by the founding of a 'Riddell–Wright Honouring Association'. Miss Riddell went to Japan in 1890, and in 1895 she established the first hospital in Kumamoto to give sanctuary to the neglected leprosy sufferers who marginally survived by begging near a temple. On her death in 1932 she was succeeded by her niece, Miss Wright, until the hospital closed in 1941.'

Dr Kikuchi's paper 'Hansen's disease patients: responses to stigma and segregation in Kumamoto, Japan' has been published in the *International Journal of Dermatology* (1994) **33** (No. 2), 142–5.

International Leprosy Meeting for Missionaries and Auxiliary Staff, 10–22 October 1994; Paramedicals 7–12 November 1994

For further details of the above meetings, both of which cover a wide range of topics, write to: Dr Jose Terencio de las Aguas, Santorio San Fco. de Borja, 03791 Fontilles, Spain.

CBM/LEPRA Ophthalmic Course, Karigiri, India 1994

The ninth annual 5-day ophthalmic teaching module was held at the Schieffelin Leprosy Research and Training Centre, Karigiri from 14 to 19 March 1994. This course, which was again sponsored jointly by the Christoffel Blindenmission and LEPRA, was designed to give instruction to leprologists on the detection, prevention and management of the ocular complications of leprosy by means of a series of lectures, clinical and surgical demonstrations, videos and slide-tapes.

Teaching included presentations on basic anatomy, physiology and pathology of the eye with special emphasis on leprosy: in addition there were lectures on the clincial signs and management of lagophthalmos, corneal ulcers, intra-ocular inflammation and infiltrative lesions, together with discussions on 'high risk eyes', ocular manifestations of relapsed disease, rehabilitation and the global aspects of blindness in leprosy.

The course, which was attended by 14 participants working in India, Burma, Nepal and the Cape Verde Islands, was run by Dr Margaret Brand of the Leprosy Mission and Mr Timothy ffytche from St Thomas's Hospital, London, together with Dr Ebenezer Daniel, Dr Mary Jacob and Dr Prem Kumar of Karigiri.

The Director and staff of Karigiri and The Leprosy Mission are to be congratulated on their continued support for this important and popular contribution to teaching. We would also like to acknowledge the contribution made by Allergan who donated pen-torches with blue filters to all participants on the course.

Reviews of publications on leprosy in Spanish

The *Revista de Leprologia de Fontilles*, Volume XVIII, No. 6, 1992, is a reminder of the extensive reviews in Spanish of recent publications on leprosy from the world literature which appear in each issue. The headings include bacteriology, immunology, pathology, biochemistry, animal and experimental leprosy, clinical aspects and diagnosis, therapeutics, surgery, physiotherapy, prevention, control, psychological aspects, education and rehabilitation. Contact: Sanatorio de Fontilles, Alicante, Spain.