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Editorial

NERVE INVOLVEMENT IN LEPROSY. PREVENTION AND MANAGEMENT OF DEFORMITIES: NEED FOR A PARADIGM-SHIFT

WHY IS IT NECESSARY OR ESSENTIAL TO TALK OF PREVENTION OF DEFORMITIES?

We no more talk about leprosy control or about multidrug therapy (MDT) because these are well established, in concept, organization and operation. About deformity, disability and rehabilitation we have now started talking more and more, but neither with the same clarity, nor do we have an equally efficient action plan which has been accepted by the leaders.

We agree that leprosy is feared because of the deformities and disabilities. We have always talked of the incidence of deformity as an index of success of our control programmes. We even talk of early diagnosis and treatment as a means of deformity prevention. But in practice we find that deformities do occur in spite of early detection and treatment with chemotherapy. Deformities do develop after a patient is declared cured. We agree that whatever may be the diminishing incidence of deformities at entry, nothing would justify our neglect of Grade 1 of deformity, i.e. loss of sensation. Yet we do not have figures of WHO Grade 1 deformity, i.e. loss of sensation. We know that unless cared for with a sense of responsibility, loss of sensation leads to later deformities. These deformities, of course, occur but do not find a place either in the WHO or ILEP or National statistics. Seeing these uncared deformities leaves the patient and society dissatisfied in spite of the specialist telling them that leprosy is controlled. And that, 'leprosy soon will not be a public health problem' becomes a meaningless statement.

WHAT IS HAPPENING AND WHY?

Why is so little being done to intervene actively for disability prevention (POD) and prevention of worsening of deformity (POWD) while so much has been and is being done indirectly through control of leprosy by early and effective treatment?

We could have, but did not anticipate such a situation as exists today. In many areas of the world today there is a rapid diminution in the number of patients under treatment and at the same time an increasing cumulative number of patients with deformity and disability, an ever increasing number of unemployed because of deformity. We never looked beyond the objective of diminishing the number of active cases of the disease in the community. So many of us were shocked last year at the statement that, in a few years leprosy will not be a public health problem. What constituted a public health problem was fully defined. Why were we shocked instead of being delighted? There were

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possibly two reasons, one the recognition that a lot of work needs to be done for the prevention of deformities, of their worsening and for rehabilitation. The second reason is the fear that the flow of finances from the public may reduce substantially. Finances have up to now always been asked for a wider social benefit, to get rid of the great load of infection in society. Research up to now was mainly justified to achieve similar objectives. The structural concept, the model successfully used for action against leprosy, including fund-raising, has been a specific kind of epidemiological model, the objective being fight against infection. And it has worked. But now this model will not do.

And we, the workers, policy makers, fund-raisers did not prepare strategies, conceptual structures, paradigm for what could have been seen if we had tried to foresee. A new approach is needed.

And this is the difficulty. And change in a mind-set, a paradigm-shift, a change of approach is often a dynamic, slow and a painful process. A change of approach, to be effective has to take place at the top, in the policy makers, fund-raisers, and leaders. Then only can it percolate down. The other way is an increased demand from the public or public authority brought by a recognition that something different, something better indeed needs to be done.

IS THERE THEN SUCH A RADICAL CHANGE IN CONCEPT REQUIRED?

Table 1 shows the great difference in nature and management of disease and of disability and deformity.

This has to happen and soon enough. Otherwise, for the general public and for the patient who is disabled, eradication or control of leprosy, even when achieved by the WHO definition, will remain meaningless.

This shift in the conceptual structure has to be achieved not only by the medical persons but also their associates, namely the public and the patient and the families in all the geographical areas where leprosy work is already going on. Some examples are given in Table 2 to show what is required to know how a change of slogan would indicate a fundamental change of approach.

The phase 'care after cure', may be more appropriately rephrased as 'care with

Table 1. Differences in management

Disease	Deformity/disability
Medical problem	medical and human problem
Mass programme	individual programme
Time bound	life-long
Early diagnosis & treatment done by SET * and demands drug delivery by an active medical team and an obedient patient	early diagnosis & treatment demands early detection and drugs, measures that need active cooperation and understanding of both patient and medical persons
Evaluation: Yes or no	graded evaluation essential
On the patients part the need is of	
Acquiescence and compliance	Active responsible collaboration

A major change in the conceptual structure, is needed. For some time we, indeed, need both conceptual structures. An integration of the two paradigms is even more difficult psychologically because this requires not only a change of perception but flexibility.

* (SET, survey, education and treatment).

Table 2. Change in approach

Methodology		
Care after cure	becomes	care during treatment: POD care with respect
POWD by instruction	becomes	transfer of skills
Ulcer dressings by PM	changes	into self-care & POWD
Giving of footwear	changes	into the patient wanting foorwear
Health talks and education	becomes	health learning by patients and it spreads to other patients
Medical team's dictate	becomes	a collaborative effort

PM, paramedical; POWD, prevention of worsening of deformity.

respect' or 'care during treatment'. This care, of course, starts together with drug therapy and extends to care after stopping chemotherapy. The care procedure, like a daily bath, naturally is going to be a life-long affair and thus becomes a primary responsibility of the patient and his near ones including the medical advisor.

We have not defined how to execute 'early' and 'effective' detection and treatment as it would apply to deformities and disabilities. There are two reasons, one reason for the difficulty is because of the differences in the nature and management of the two problems, one control of the disease and the second is control of deformities and disabilities.

Disease control, as in the case of say smallpox, is a mass programme where the patient is a passive participant. He is 'given' a drug or a vaccine, and he just has to be compliant and obedient enough to 'take' it. The medical persons are the active agents, who plan and execute even to the extent of putting the tablets in the patients mouth. The indices for success relate to bacterial positivity, prevalence and incidence of disease and reduction of disability rate/incidence AT ENTRY POINT, which is a one-time statistic.

What is considered as worth recording and compiling is obvious deformation and not anaesthsia, even when everyone knows that it inevitably, unless 'cared for', leads to secondary impairments—plantar ulcers, wounds and infections and deformities and morbidity.

Disability control, on the other hand, is an individual's problem, liability and responsibility and needs his active participation, whether it be in wearing proper footwear or in taking precautions to avoid injuries to the anaesthetic hand or foot or to ask for surgical correction.

The second reason is that up to now we have used very crude methods for describing signs and symptoms of early nerve involvement. For example, we say and record that there is either sensory loss or none, deformity or no deformity. While disability has not even been defined and hence not recorded. Here 'early' has only a temporal meaning, time oriented. We can indeed have methods to record these parameters in a graded way where we can see and record improvement or worsening, e.g. by use of various nylon filaments for sensory testing.

Let me repeat why, even when there is no lack of humanness, of knowledge, of methodology, so little is being done for prevention and correction of deformities and for rehabilitation.

The most important reason is the nonrecognition of the differences in management techniques, methodology and philosophy needed for deformity prevention as compared with the control programme. Moreover instead of an exclusive vertical approach, an increasing wider or global approach is needed to bring out not only the disease but the deformities and disabilities in the mainstream of health sciences.

HOW IS THIS CHANGE OF APPROACH TO OCCUR?

The easiest is pressure by peer groups, by the leaders and by holders of the purse-strings. The first forces change of thinking, the other of practice. With the need to counteract the effects of the statement, 'Leprosy will cease to be a public health problem pretty soon', the financiers and fund-raisers have to change their approach and this could be a successful way. Instead of an appeal on behalf of a mass of leprosy patients and the society of which they form a part, it would be an appeal on behalf of individuals for whom the society has to contribute instead of the other way round.

For this we need information, for ourselves, for the leprosy workers, the authorities and the general public. We need factual data which, as we should know, does not exist, is not available for it has never been asked for by either the policymakers or governments or the public at large. Information like: What is the load of deformity in the community? How many of them are disabled? What kind of assistance do they need? What is the prevalence of loss of sensation amongst known leprosy patients? What is the natural 'progress' of such a condition? How many persons develop nerve involvement, disability and deformity AFTER starting MDT, etc has to be made available.

I find it amazing that everyone still continues to say disability, disability index, disability grading when what is meant is primarily a grading of a complex formed of impairment of sensory loss and deformities of different parts of the body. Thus THE MEANING OF THE TERM DISABILITY REMAINS UNDEFINED. We have to define and grade disability.

The basic concept, the philosophy is restoration of self-dignity and responsibility to the patient and then to motivate him to learn how he can take care of himself. The rest, 'how' of it, are details.

First comes recognition and then putting it into action, first is change of perspective, then a change of approach while planning and finally putting it into action. We, the medical people have already the knowledge and technology to work out the details of such a programme. But without first achieving the change of perspective, of approach, any number of pamphlets, articles and books published and distributed is not going to have much practical impact. They, like the excellent book by Srinivasan published by WHO,[1] and those by Jean Watson on POD,[2,3] will adorn the bookcases, mute witnesses of our inadequacy to put into practice what we write and read and talk about.

Let us then work aiming at restoration of self-dignity and responsibility to the patient and then to motivate him/her to learn methods of self-care. We have to forget our paternal role, of how wonderful we are and assume the true role of more fortunate, but still caring friends.

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References

[1] Srinivasan H., *Prevention of disabilities in patients with leprosy. A practical guide.* WHO, 1993
[2] Watson J. *Prevention of disabilities: guidelines for leprosy control programmes.* ILEP, 234 Blyth Road, London W14 0HJ, England, 1993.
[3] Watson J. *Preventing disability in leprosy patients.* The Leprosy Mission International, 80 Windmill Road, Brentford TW8 0QH, England. Reprinting.

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ILEP Statement
Elimination of Leprosy

Elimination of Leprosy as a Public Health Problem, ILEP

The following statement was made at the International Federation of Anti-Leprosy Associations (ILEP) Conference held in Hanoi, 4–7 July 1994.

1 ILEP brings together 20 non-governmental donor associations which together are the most important source of external funding for anti-leprosy work in endemic countries. Members also offer a considerable fund of expertise.

2 The Members of ILEP join with the World Health Organisation (WHO), with governments, and with local partners, in wishing to bring Multi-Drug Therapy (MDT) to people with leprosy as quickly as possible, recognizing that it is the most effective available tool for curing the disease, reducing the pool of transmission, and avoiding the disabilities that result from leprosy.

In 1990 the Members of ILEP adopted the target of MDT for All by the Year 2000. Concerned to bring the best known treatment to *every* individual who needs it; this target is in a sense even more ambitious than achieving a prevalence rate of 1 per 10,000 population.

In projects supported by Members, 64% of all registered patients and 79% of new patients were receiving MDT by the end of 1992. The ILEP Medical Commission is currently consulting projects to identify blocks to 100% coverage.

3 ILEP Members consider, however, that it is important to speak in terms of the total number of people affected by leprosy and not only in terms of those requiring chemotherapy.

The current ILEP estimate for the number of people worldwide affected by leprosy is 6·5 million.

Although there may be some overlap, this figure includes around 4 million people with or at risk of deformity as a result of leprosy (ILEP Medical Commission estimate 1992) and around 2·4 million people who are in need of chemotherapy (WHO estimate 1994).

4 Achievement of MDT for All (ILEP target) and of Elimination of Leprosy as a Public Health Problem defined as a Prevalence of 1 per 10,000 population (WHO target) will be a historic step in the battle against leprosy.

Members of ILEP believe, however, that it is most important always to keep in mind that achievement of these objectives does not mean the end of leprosy or of work on behalf of all those people who are and will be affected by the disease.

Many heavy tasks will remain beyond the Year 2000:

New cases will continue to appear and a number of fully treated cases will relapse.

Despite the positive experience of some localities that have had effective leprosy control programmes for many years, the number of new cases worldwide has so far shown no sign of decline.

It will be essential to sustain highly effective services under conditions of low endemicity, both for the individuals affected and to avoid resurgence of the disease. This will necessitate maintenance of a cadre of people expert in clinical management of the disease.

Many patients after chemotherapy remain with deformities or at risk of them because of permanent nerve damage and loss of sensation. They have a continuing need of medical services.

The tragedy of leprosy for many of those affected is the social stigma that surrounds it. Patients often have need of social and economic assistance to ensure re-integration into their community and normalization of their lives.

5 Great resources are needed to achieve MDT for All, as well as for the other continuing needs.

It would be counter-productive to present the successes achieved with MDT in such a way that those who provide resources—both governments and the hundreds of thousands of individual donors who give to ILEP Members—come to think that the race is over when many laps remain to be run.

6 Member-associations of ILEP have for decades been working against leprosy and remain committed to doing so for many years to come.

We look forward to continuing to work in partnership with governments, with WHO, and with local associations in the best interests of all who are or who will in future be affected by leprosy.

ILEP Member Organizations:

Aide aux Lépreux Emmaüs-Suisse (ALES)
ALM International (ALM)
Association Française Raoul Follereau (FF)
Associazione Italiana Amici di Raoul Follereau (AIFO)
British Leprosy Relief Association (LEPRA)
Comité Exécutif International de l'Ordre de Malte (CIOMAL)
Damien Foundation Belgium (DFB)
Deutsches Aussätzigen-Hilfswerk (DAHW)
Fondation Luxembourgeoise Raoul Follereau (FL)
Fondation Père Damien (FO)
Hartdegen Fund (HF)
Institut Cardinal Leger Contre la Lèpre (ICLL)
Le Secours aux Lépreux (SLC)
Leonard Wood Memorial (LWM)
Nederlandse Stichting voor Leprabestrijding (NSL)
Pacific Leprosy Foundation (PLF)
Red Barnet (RD)
Sanatorio San Francisco de Borja (SF)
Sasakawa Memorial Health Foundation (SJ)
The Leprosy Mission International (TLMI)

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Indeterminate leprosy: a seroimmunological and histochemical evaluation

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Summary An effort was made to differentiate indeterminate (IND) leprosy from other types of the paucibacillary (PB) group of leprosy and to identify among indeterminate leprosy cases those which may evolve to multibacillary (MB) leprosy, using serological, immunological and histochemical parameters. A total of 92 untreated, histologically classified (TT-19, BT-30, IND-32) patients, including 11 cases diagnosed as nonspecific dermatitis (NSD), which were clinically strongly suspected to be leprotic, were screened for antibodies against PGL-I, 35-kDa and LAM antigens. Lepromin tests and antigen demonstration in tissue by indirect immunoperoxidase staining were also carried out. Though a qualitative analysis did not differentiate, a quantitative analysis in terms of a cumulative index (CI) showed a higher antibody level amongst the indeterminate group of patients than the other groups included in PB leprosy. Also, the lepromin negative indeterminate group patients showed a higher CI than the lepromin positive cases, indicating that perhaps these may be the cases which may develop into MB leprosy. Thus, the semiquantification of antibody levels in the form of a CI may be a useful parameter to predict the possible evolution of a given case of indeterminate leprosy. Interestingly 64% of NSD cases had either antigen or antibody which indicated that they were probably cases of leprosy.

Introduction

Indeterminate leprosy, a clinical entity, diagnosed in conjunction with histological and bacteriological investigations, is an early and unstable form of leprosy. Its histopathological picture is that of a simple, nonspecific inflammation involving the nerve with or without acid-fast bacilli (AFB) in the nerve or in the subepidermal zone or in the arrectores pilorum muscles. The lesions of indeterminate leprosy may undergo spontaneous healing or remain unchanged for many years. They may also change to one of the more stable types of clinical leprosy,[1] which can be histologically confirmed by demonstrating either epithelioid cell granuloma or macrophage ganuloma loaded with

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bacilli.[2] Though classified under the paucibacillary (PB) group of leprosy for the purpose of managment, indeterminate leprosy (IND), thus, can potentially downgrade into the multibacillary (MB) group of leprosy. Efforts to identify parameters which can predict the evolution of a case of indeterminate leprosy have been made earlier and certain clinical, immunological and histopathological parameters have been identified.[3–8]

In the present study, we have attempted to differentiate cases of indeterminate leprosy from other types of PB leprosy, and to identify amongst them the ones which may develop into MB leprosy, using serological, immunological and histochemical parameters.

Materials and methods

A total of 92 untreated cases of clinically diagnosed leprosy attending the Central Leprosy Teaching and Research Institute (CLT & RI) outpatient department were included in the study. Histopathologically, they were tuberculoid (TT-19), borderline–tuberculoid (BT-30) and indeterminate (IND-32) types. In addition, there were 11 cases which were histopathologically diagnosed as nonspecific dermatitis (NSD) but were strongly suspected to be clinical cases of leprosy and were included in the study.

Sera from all the patients were collected and stored at −20°C for antibody assays. Sections from skin biopsy of the lesions stained by haematoxylin and eosin and Fite–Faraco methods were examined. Histochemical studies were carried out by immunoperoxidase staining of the tissue sections. A routine slit-skin smear examination from 6 sites, such as both earlobes, extensor aspect of arms and thighs, including representative active skin lesions, was made to assess the bacteriological index (BI).

Antibody assays

All the sera were screened for antiphenolicglycolipid-I (anti PGL-I), antilipoarabinomannan (anti-LAM) and anti-35 kDa antibodies.

ANTIPGL-I ASSAY

IgM antiPGL-I antibodies were measured by using the procedure reported earlier.[9] Briefly, D-BSA supplied by IMMLEP–WHO, was coated in duplicate in a 96-well flat bottom microtitre plate (Dynatec Micro-ELISA System, Germany). Sera (1 : 300 diluted) were added to both antigen and BSA coated wells. After incubation antihuman IgM peroxidase conjugate (DAKOPATTS, Denmark) was added (1 : 2000 diluted), colour was developed with o-phenylenediamine (SIGMA, USA) with H_2O_2. Reaction was stopped with $5\,NH_2SO_4$. The plates were read at 492 nm in an ELISA reader. Samples with a difference in the mean absorbance between the antigen and BSA coated wells equal to or more than 0·200 OD were considered positive.

SERUM ANTIBODY COMPETITION TEST-ELISA (SACT-E)

Antibody to the *Mycobacterium leprae* specific 35 kDa protein was detected as reported

earlier.[10] Briefly, *M. leprae* soluble extract 10 μg/ml (kindly supplied by R. J. W. Rees, IMMLEP *M. lepra* Bank) in PBS was coated in a microtitre plate (Immulon, M129 B Dynatec). Sera in 10-fold dilutions of 1 : 10, 1 : 100 and 1 : 1000 were added in duplicate and incubated for 1 hr. After removing sera, appropriately diluted peroxidase conjugated ML-04 monoclonal antibody (kindly supplied by J. Ivanyi, MRC, the Royal Postgraduate Medical School, London) was added and incubated for 2 hr. After washing, colour was developed with o-phenylenediamine substrate solution. The reaction was stopped with $5NH_2SO_4$ and a reading was taken at 492 nm in an ELISA reader. The dilution of the sera causing 50% inhibition of binding of ML-04 to the antigen (ID_{50}) was calculated. Samples with ID_{50} titres equal to or more than 10 were considered to be SACT-E positive.

ANTILAM ELISA

IgG antiLAM antibodies were measured as reported earlier.[10] Briefly LAM from *M. tuberculosis* H37Ra (kindly supplied by D. Chatterjee, Colorado State University, Fort Collins, Colorada, USA) was coated at 1 μg/ml. Control wells were coated with buffer. Sera (1 : 1000 diluted) were added to all the wells. After incubation antihuman IgG (1 : 6000 diluted) was added, then o-phenylenediamine and H_2O_2 were added as a substrate solution. The reaction was stopped and plates were read at 492 nm. Samples with a difference in the mean absorbance between the antigen and control wells equal to or more than 0·500 OD were considered positive.

Antigen detection

Antigen detection in the sections from paraffin blocks was done by indirect immunoperoxidase staining.

RAISING OF ANTIMLSE ANTIBODY

Rabbits were immunized with *M. leprae* soluble extract (MLSE), using a standard protocol.[11] The serum immunoglobulins were concentrated by ammonium sulphate precipitation and followed by extensive dialysis. This polyvalent antibody was used as primary antibody in immunoperoxidase staining.

IMMUNOPEROXIDASE STAINING

Indirect immunoperoxidase staining was done using a standard procedure.[12] Briefly, after deparaffinization and quenching with H_2O_2, the slides were blocked with 1 : 10 diluted normal swine serum. After incubation for 10 min, primary antibody (antiMLSE, 1 : 200 diluted) was added to the sections. After a further 1-h incubation, antirabbit IgG peroxidase conjugate (DAKOPATTS, Denmark; 1 : 100 diluted) was added. After washing with PBS, diaminobenzidine containing 0·02% H_2O_2 was used for colour development. After washing in water, the slides were counterstained with Harris haematoxylin, dried and mounted in DPX. Microscopially antigen appeared as a brown precipitate, within or outside the granuloma. Normal rabbit serum as primary antibody was used in controls.

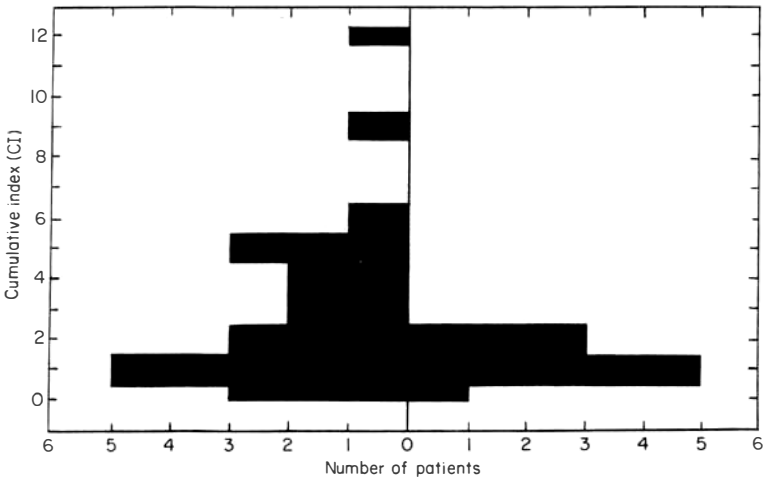

Figure 1. Histogram showing the distribution of cumulative index (CI) amongst lepromin negative (left side) and lepromin positive (right side) cases of indeterminate leprosy.

Lepromin test

Lepromin testing was done using Mitsuda lepromin (kindly supplied by M. J. Colston, MRC, National Institute for Medical Research, London). Early and late readings were taken after 48 hr and 21 days, respectively.

Statistical analysis

All descriptive and statistical analyses were carried out using SPSS/PC + and EPI-INFO software packages. The statistical significance between different groups was detected using the Chi-squared test, and Fischer's exact test was used where the expected value was less than 5. The significance of the cumulative index (CI) was determined by using Student *t*-two tailed tests. The probability value of $< 0{\cdot}05$ was considered to be significant. The data represented in Figure 1 are composed of rectangles with numbers of patients and CI.

Result

ANTIBODY ASSAY (TABLE 1)

Analysis of positivity for individual antibodies (namely, antiPGL, antiLAM and anti35 kDa) showed that there was a significant difference between IND and TT only ($p < 0{\cdot}05$; for antiLAM, p value could not be calculated for antiPGL and anti35 kDA since no case of TT was positive for both the antibodies) and not between IND and BT or NSD ($p > 0{\cdot}05$). The analysis of positivity for any of three antibodies (namely antiPGL/antiLAM/anti35 kDa) also revealed a significant difference only between IND and TT ($p < 0{\cdot}05$) and not between IND and others ($p > 0{\cdot}05$).

Table 1. Serological, immunological and histochemical parameters in indeterminate and other groups of patients

	Number of patients (%)			
Groups	IND	TT	BT	NSD
No. of cases	32	19	30	11
Positive for antiPGL antibody	10 (31)	0	5 (17) NS	2 (18) NS
Positive for anti35 kDa antibody	7 (22)	0	1 (3) NS	2 (18) NS
Positive for antiLAM antibody	13 (41)	2 (11) S	6 (20) NS	4 (36) NS
Positive for any of three antibodies	17 (53)	2 (11) S	9 (30) NS	5 (46) NS
Positive for antigen	20 (63)	6 (32) NS	20 (67) NS	5 (46) NS
Positive for any of three antibodies/antigen	26 (81)	8 (42) S	24 (80) NS	7 (64) NS
Cumulative index of three antibodies (mean ± SD)	1·812 ± 2·62	0·315 ± 0·79 S	0·733 ± 1·28 S	1·36 ± 1·8 NS
Lepromin negative (< 4 mm)	$\frac{21}{30}$ (70)	$\frac{2}{14}$ (14) S	$\frac{6}{25}$ (24) S	$\frac{6}{09}$ (67) NS

The significance of difference was observed between the referred group and indeterminate group.
NS, not significant ($p > 0{\cdot}05$); S, significant ($p < 0{\cdot}05$); SD, standard deviation.

ANTIGEN DETECTION (TABLE 1)

There was no significant difference in the positivity for antigen by immunoperoxidase staining amongst the different groups (IND—63%, TT—32%, BT-67%, NSD—46%) ($p > 0{\cdot}05$).

ANTIBODY WITH ANTIGEN (TABLE 1)

When positivity for any of the 3 antibodies and for antigen was analysed, a significant difference was observed only between IND and TT groups ($p < 0{\cdot}05$), but not between IND and other groups ($p > 0{\cdot}05$).

LEPROMIN TEST (TABLE 1)

Lepromin negativity was observed significantly more amongst the IND group than the TT and BT groups ($p < 0{\cdot}05$). But there was no difference between IND and NSD groups ($p > 0{\cdot}05$).

CUMULATIVE INDEX (TABLE 1)

An attempt was made to semiquantify the antibody levels by grading the OD/titre of the 3 antibodies. The absence of the antibody was graded 0. The different antibodies when present were graded as follows, considering the cut-off, frequency and highest OD/titre recorded for each antibody and as far as possible with equal class interval: antiPGL-I antibody, grade 1 = 0·200 to 0·400, grade 2 => 0·400 to 0·600, grade 3 => 0·600 to 0·800, grade 4 => 0·800 to 1·00; antiLAM antibody, grade 1 = 0·500 to 0·700, grade 2 => 0·700 to 0·900, grade 3 => 0·900 to 1·10, grade 4 => 1·1 to 1·3; anti35 kDa antibody, grade 1 = 10 to 100, grade 2 => 100 to 500, grade 3 => 500 to 1000, grade 4 => 1000. The grades of different antibodies of an individual patient were cumulated

Table 2. Analysis of different parameters between lepromin positive and lepromin negative groups of indeterminate leprosy

	Number of patients (%)	
Groups	Lepromin positive	Lepromin negative
No. of cases	9 (30)	21 (70)
Positive for antiPGL antibody	1 (11)	9 (43) NS
Positive for anti35 kDa antibody	1 (11)	6 (29) NS
Positive for antiLAM antibody	2 (22)	11 (52) NS
Positive for any of three antibodies	3 (33)	14 (67) NS
Positive for antigen	7 (78)	13 (62) NS
Positive for any of three antibodies/antigen	8 (89)	18 (86) NS
Cumulative index of three antibodies (mean ± SD)	0.444 ± 0.72	2.571 ± 2.94 S

NS, not significant ($p > 0{\cdot}05$); S, significant ($p < 0{\cdot}05$).

and referred to as CI for the given patient. Analysis of CI amongst the different groups revealed that cases in the IND group had significantly higher CI than cases in the other groups of PB leprosy ($p < 0{\cdot}05$). Thus, though no significant difference was observed in terms of positivity for different antibodies individually or in combination between the IND and other groups (except TT), a significant difference was observed in terms of quantification—antibody levels being higher in the IND cases.

In the light of these findings, further analysis was made to find the difference, if any, between lepromin positive and lepromin negative groups of cases of IND leprosy. Amongst IND leprosy, 21 cases (70%) were lepromin negative and 9 cases (30%) were lepromin positive (Table 2). Analysis of the positivity for individual antibodies or combination of antibodies and also the positivity for antigen did not reveal any significant difference between lepromin positive and negative groups ($p > 0{\cdot}05$), whereas, analysis of CI revealed a highly significant difference between the lepromin positive and negative groups ($p < 0{\cdot}05$), being higher in the lepromin negative group (Figure 1).

Discussion

It is well known that indeterminate leprosy is an unstable clinical entity, which can progress either to the tuberculoid or lepromatous form. Few studies have attempted to search for some clinical, immunological and histopathological parameters which can predict the probable course of a case of indeterminate leprosy.[3–8] Studies on serological responses of leprosy patients to *M. leprae* specific (PGL, 35 kDa) and mycobacteria specific (LAM) antigens have shown uniformly higher responses in the MB group of patients than in the PB groups.[13–15] Amongst the PB group an apparently higher response to these antigen was observed in the indeterminate group.[10] Using these antibody assays as well as antigen detection by the immunoperoxidase staining method, an attempt was made to differentiate the indeterminate type from other

forms of the PB group and to identify amongst the indeterminate group those who may develop into the LL form of leprosy.

The number of patients serologically responding to different antigens was comparable in all groups except in the TT group where significantly fewer responded. It has already been shown that the sensitivity of these individual antibody assays is too low to be of practical value and it is possible to increase the sensitivity without loss of specificity by using these assays in combinations.[10] Even such an analysis in this study showed a comparable increase in the sensitivity for all groups except in the TT group which was again significantly lower than the IND group. Antigen by immunoperoxidase staining was demonstrable in comparable numbers of cases in different groups including the TT group. The CI, which quantifies the antibody levels, revealed that the indeterminate group of patients had significantly higher antibody levels than other groups when qualitative analysis did not differentiate the indeterminate group from others. A positive Mitsuda skin reaction amongst the indeterminate group is known to indicate the probable evolution of the case towards the TT pole[3,4] and similarly a negative reaction towards the LL pole of leprosy.[7] In our study, a significantly higher number of indeterminate patients was found to be negative to lepromin. In both lepromin positive and negative patients of this group, the results of different antibody assays, both individually and in combination were comparable, and antigen was demonstrable equally in both the groups. But quantification in terms of CI showed significantly higher antibody levels amongst the lepromin negative group.

Earlier studies have shown that the lepromin negative indeterminate group can potentially progress to LL.[7] Flies *et al.*[6] identified certain CMI parameters, which when altered denoted downgrading of a lepromin negative indeterminate case towards the LL pole.[6] A marked dermal nerve involvement in conjunction with bacteriological and immunohistochemical markers of low resistance to infection were indicative of a probable early downgrading of the disease and these parameters could be semiquantified into an $\Sigma 3$ index, where an $\Sigma 3$ index $=> 6$ detected cases evolving to MB leprosy.[8] Our study identified higher antibody levels in terms of CI amongst indeterminate than other PB groups. Amongst the indeterminate group lepromin negative cases had higher CI. This may be the group which will downgrade to the LL form of leprosy. Further study on these lines may be more enlightening.

In our study, antigen was demonstrable equally in all the groups though all of them were PB leprosy and were negative for AFB both in skin smear and in tissue sections. This observation emphasizes the higher sensitivity of the immunoperoxidase staining method in demonstrating the presence of pathogen in the lesions.[8]

We histopathologically diagnosed as nonspecific dermatitis 11 of the cases included in the study, which had been strongly clinically suspected of leprosy. However, 64% of this group had any of three antibodies or the antigen by immunoperoxidase staining which was comparable with the indeterminate group. Even the quantification of antibody was comparable with that of indeterminate leprosy. Hence it may be stated that though they are NSD by histopathological examination, perhaps they are leprosy cases. A search for the antigen in the tissue or for the antibody in sera amongst histopathologically diagnosed NSDs, may be a useful supplement to the clinical diagnosis. Further indepth study is required to confirm this observation. These are the cases, which are probably indeterminate leprosy, but may be histologically too indefinite to be branded so. Thus when indeterminate leprosy is diagnosed and found to be

lepromin negative with higher antibody levels, close follow up will be necessary during treatment and surveillance, as these cases may subsequently develop MB leprosy. The semiquantification of antibody levels in terms of the cumulative index (CI) would be a useful parameter to predict the evolution of a given case of indeterminate leprosy.

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References

[1] Dharmendra. *Leprosy*. Kothari Medical Publishing House, 1978; vol I: 46.
[2] Ridley DS. Indeterminate Leprosy (Editorial). *Lepr Rev*, 1974; **45:** 95–7.
[3] Bungeler W. Die pathologische Anatomie der lepra. *Virchow Arch (A)*, 1943; **310:** 493–565.
[4] Roteberg A. Valor prognostico da lepromino reacao de Mitsuda: observacao de 445 casos durante 5–6 anos. *Rev Bras Leprol*, 1944; **12:** 367–77.
[5] Bechelli LM. Indeterminate leprosy in a population survey and in the subsequent follow-ups of children in Burma. *Acta Leprol*, 1989; **7(1):** 29–36.
[6] Flies EL, Bachman AE, Sasiain M del C, Ares BR. Immunological studies in patients with Indeterminate Leprosy. *Rev Asos Argent Microbiol*, 1975; **7(3):** 81–5.
[7] Alchrome MMA, Rotberg A, Michalany J, Vargas P De O, Cassiano TP. Prognostic consideration based on a study of 38 hanseniasis patients submitted to Mitsuda tests 23 to 35 years previously. *Hansenologia Internacionalis*, 1978; **3:** 5–11.
[8] Takahashi MD, Andrade Jr HF, Wakamatsu A, Siqueira S and De Brito T. Indeterminate Leprosy: Histopathologic and histochemical predictive parameters involved in it's possible change to paucibacillary or multibacillary leprosy. *Int J Lepr*, 1991; **59:** 12–19.
[9] Dhandayuthapani S, Anandan D, Vasanthi B, Bhatia VN. Use of eluates of filter paper blood spots in ELISA for the serodiagnosis of leprosy. *Indian J Med Res*, 1989; **89:** 150–7.
[10] Sekar B, Sharma RN, Leelabai G, Anandan D, Vasanthi B, Yusuff G, Subramanian M, Jayasheela M. Serological response of leprosy patients to *Mycobacterium leprae* specific and mycobacteria specific antigens: possibility of using these assays in combinations. *Lepr Rev*, 1993; **64:** 15–24.
[11] Harboe M, Closs O, Bjorvatn B, Kronvall G, Axelsen NH. Antibody response in rabbits to immunization with *Mycobacterium leprae*. *Inf Immun*, 1977; **18:** 792–805.
[12] Mshana RN, Belehu A, Stoner GL, Harboe M, Haregewoin A. Demonstration of Mycobacterial antigens in leprosy tissues. *Int J Lepr*, 1982; **50:** 1–10.
[13] Bach MA, Wallach D, Flageul B, Haffenbach A, Conttenot F. Antibodies to phenolic glycolipid-I and to whole *Mycobacterium leprae* in leprosy patients; evolution during therapy. *Int J Lepr*, 1986; **54:** 256–67.
[14] Mwatha J, Moreno C, Sengupta U, Sinha S, Ivanyi J. A comparative evaluation of serological assays for lepromatous leprosy. *Lepr Rev*, 1988; **59:** 195–9.
[15] Chanteau S, Cartel JL, Celerier P, Plichart R, Desforges S, Roux J. PGL-I antigen and antibody detection in leprosy patients: Evolution under chemotherapy. *Int J Lepr*, 1989; **57:** 735–43.

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Effective vaccination of mice against *Mycobacterium leprae* with density-gradient subfractions of soluble *M. leprae* proteins: clues to effective protein epitopes

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Summary It had previously been discovered that intradermal mouse vaccination with a protein fraction of *Mycobacterium leprae* (called soluble proteins) in Freund's incomplete adjuvant (FIA) resulted in consistent and long-lived protection against *M. leprae* multiplication from subsequent viable footpad challenges. In this study certain density-gradient subfractions of this soluble protein, but not others, in FIA afforded vaccine protection. The results of this study suggest which *M. leprae* proteins may be involved in protective immunity, particularly 1–3 kD, 10 kD, 65 kD, and those of higher molecular weight.

Introduction

It had previously been discovered that intradermal vaccination of mice with protein subunits of *Mycobacterium leprae* protected mice from multiplication of live *M. leprae*.[1,2] When the interval between vaccination and infectious challenge was 1 month, protection was observed following vaccination both with various cell-wall fractions of *M. leprae* as well as with a partially purified protein derived from a pellet fraction of *M. leprae*.[1] Also, when the interval between vaccination and infectious challenge was 1 month, it was noted in this study that the most complex of the effective cell-wall vaccines, the so-called cell wall in soluble fraction (CWIF), afforded protection when the amount of material utilized was as little as that derived from 10^5 *M. leprae*, while 10^7 or more killed *M. leprae*, or further refined cell-wall fractions derived from 10^7 or more *M. leprae*, were required to provide protection.[1]

In subsequent studies, we found that vaccination with a sodium dodecyl sulphate

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(SDS)-soluble fraction of CWIF, 'soluble proteins', provides both unique and consistently (14 of 14 instances) prolonged mouse protection.[2] While heat-killed *M. leprae* and progressively more refined cell-wall fractions of *M. leprae* cell wall protein (CWP) and protein peptidoglycan complex (PPC) generally protected when the interval between vaccination and challenge was 1–3 months, only soluble proteins protected when the interval between vaccination and challenge was extended to 6, 9 and 12 months.[2]

In order to define further the critical protective protein epitopes in these soluble proteins, separation was first performed by SDS PAGE. However, under these conditions migration of individual proteins was not observed. In order to separate these soluble proteins and help define their effective protein components, various superose-12 density-gradient fractions of the *M. leprae* 'soluble proteins' were prepared. Here we report the results of the protective efficacy of vaccination of mice with these fractions and discuss our present state of knowledge concerning the specific proteins responsible for the protection that was observed in this study.

Materials and Methods

Soluble proteins of *M. leprae* were prepared as described previously.[2] These were passed through a superose-12 column at pH 6·8 and separated into 10 fractions, designated fraction 8, 9, 10, 11, 12, 13, 14, 15, 16 and 22.

Groups of 10 or more mice were vaccinated intradermally in the right-hind flank with 0·01 ml of Freund's incomplete adjuvant (FIA) alone, 10^7 killed *M. leprae*, and the following vaccines emulsified in FIA: 'soluble proteins' derived from 10^7 *M. leprae* and each of the 10 separate subfractions of 'soluble proteins' derived from 10^7 *M. leprae*. Two months after vaccination mice were challenged with 5000 mouse-derived and logarithmically multiplying *M. leprae* in the ipsilateral foodpad. Protection was assessed at the peak of multiplication, when the number of acid-fast bacilli from monthly footpad harvests of 3 separate mice vaccinated with Freund's incomplete adjuvant alone each reached $\geqslant 10^5$ *M. leprae* per foodpad (8 months).

Protection was assessed by comparing the number of *M. leprae* organisms in, generally, 10 right-hind footpads from each vaccine group with the number present in the negative control, FIA alone, by using the Mann–Whitney 2-sample rank-sum test and the Wilcoxon 2-tailed distribution.[3]

Results

The results of these studies are presented in Figure 1. As was found previously, vaccination with heat-killed *M. leprae* ($P < 0{\cdot}02$) and soluble proteins ($P < 0{\cdot}0001$) protected against *M. leprae* multiplication. Fractions 8, 9 and 10 afforded significant protection ($P \leqslant 0{\cdot}005$). While fractions 11 and 12 did not protect, fractions 16 and 22 resulted in significant protection, and fractions 13, 14 and 15 resulted in highly significant protection ($P \leqslant 0{\cdot}0005$). Moreover, the protection afforded by soluble proteins themselves and certain of the subfractions (8, 13, 14 and 15) was found to be significantly more profound than protection afforded by killed *M. leprae* itself.

Silver-stained SDS PAGE profiles of the density-gradient fractions are presented in

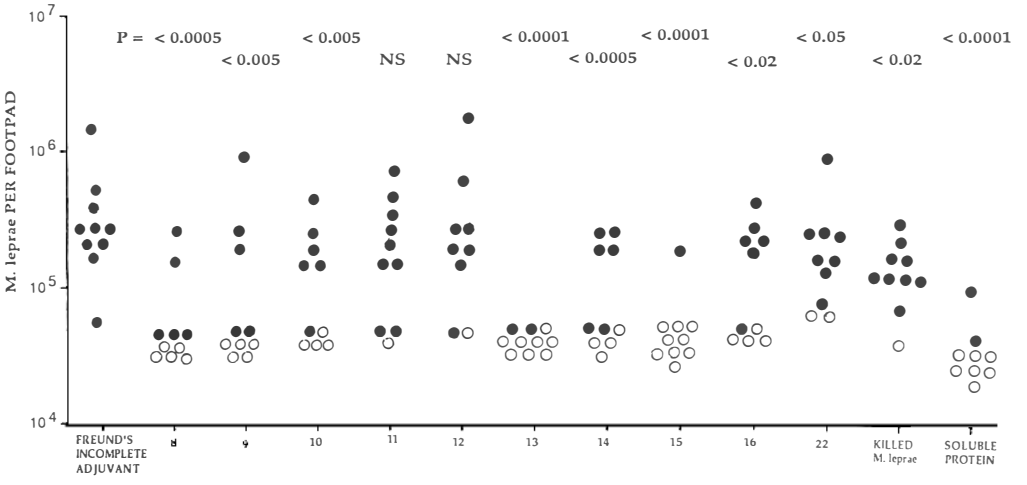

Figure 1. *Top*: Protection of mice from *M. leprae* multiplication by vaccination. *Bottom*: ● Actual number of *M. leprae*/footpad; ○ no AFB found, plotted at ⩽ the number of AFB this represents.

Figure 2. While fractions 8–10 contain only minimal amounts of various visible proteins, they mainly contain proteins of high molecular weight that do not migrate on the gels. Fractions 11 and 12 contain moderate amounts of protein but no substantial amounts of 1–3 kD or 10 kD proteins. Fractions 13–15 contain copious amounts of the major *M. leprae* 10 kD protein, a substantial amount of the 1–3 kD proteins, and also a minimal amount of what appears to be the 65 kD *M. leprae* protein. Fraction 16 contains mostly 1–3 kD proteins. Fraction 22 appears to contain a moderate amount of a single *M. leprae* protein, the 65 kD protein.

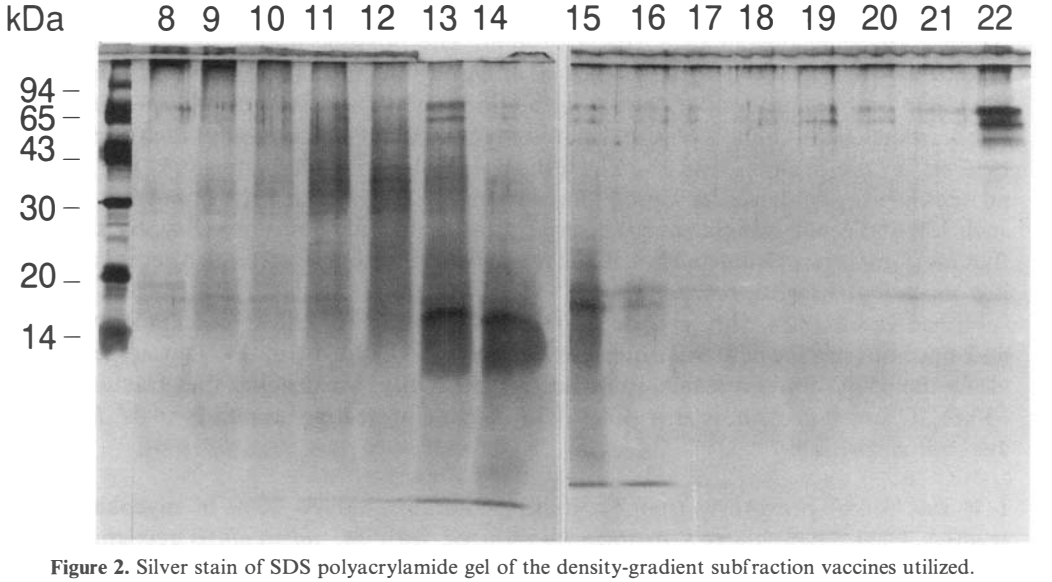

Figure 2. Silver stain of SDS polyacrylamide gel of the density-gradient subfraction vaccines utilized.

Discussion

Since the amount of protein contained in several of the protective density-gradient subfractions (particularly 8–10) was derived from less than 10^6 *M. leprae*, these findings confirm our previous results that smaller amounts of components of *M. leprae*-soluble proteins are more protective than whole killed *M. leprae* and more refined *M. leprae* cell walls.[2] More importantly, since we found in this study that while vaccination with certain density-gradient subfractions of *M. leprae* 'soluble proteins' prevented footpad multiplication of *M. leprae* following a subsequent challenge and others did not, this study provides some clues as to which *M. leprae* proteins are important for protective immunity. This study suggests that *M. leprae* protein epitopes of 1–3 kD, 10 kD, 65 kD and high molecular weight provide protective immunity.

The major finding of this study is that fractions 13–16 were all protective, fractions 13–15 being significantly more protective than killed *M. leprae*, and that the major protein constituent of all 3 of these fractions was a 10 kD protein. The likely importance of a 10 kD antigen to T-cell-mediated protective immunity found herein is consistent with that of previous studies, where it had been found that the *M. leprae* 10 kD antigen was, in general, a strong stimulus of T-cell responses:

1 It elicited PBMC responses of similar magnitude to those of *M. leprae* itself, which in patients, parallel their status in the clinical and immunologic disease spectrum.
2 It provoked PBMC responses greater than for other purified and recombinant *M. leprae* antigens with limiting-dilution analyses demonstrating that 1/3 of *M. leprae*-reactive T-cell precursors respond to its 10 kD antigen.
3 T-cells derived from lepromin skin-test-positive sites respond *in vitro* to the 10 kD antigen.
4 Like whole *M. leprae*, the *M. leprae* 10 kD protein elicited delayed-type hypersensitivity responses in *M. leprae*-sensitized guinea-pigs.[4]

Each of these protective fractions 13–16 also contains large amounts of 1–3 kD proteins, fraction 16 being devoid of a 10 kD protein. The possible importance of such low-molecular-weight proteins for protective immunity against *M. leprae* was previously suggested by the finding that peripheral blood mononuclear cells of *M. leprae*-reactive donors were found to incorporate tritiated thymidine most profoundly when stimulated by 2 *M. leprae* proteins, the 1–3 kD protein complex and the major 10 kD *M. leprae* protein.[4] Also, Andersen & Heron[5] have recently demonstrated the important role of such low-molecular-weight mycobacterial proteins in infection immunity, by showing that in *M. tuberculosis*-infected mice the majority of memory T-cells are directed at these low-molecular-weight proteins.

Since vaccination with fraction 22 resulted in lesser but still significant protection, and since the vaccine contains almost exclusively a 65 kD protein, this also suggests that alone the 65 kD protein results in protective immunity. The finding that fraction 22, a 65 kD *M. leprae* protein, is also effective in eliciting protective immunity to *M. leprae* is also not surprising:

1 It was found previously that by limiting-dilution analysis 20% of mycobacterial-reactive $CD4^+$ lymphocytes in mice immunized with *M. tuberculosis* recognize that single protein.[6]

2 We have previously found that various, largely proteinaceous, *M. leprae* cell-wall fractions provide vaccine protection in mice and that the *M. leprae* 65 kD protein is known to be cell-wall associated.[7]

Vaccination with fractions 8–10, and especially 8, each of which contains very minimal amounts of proteins and almost exclusively those of high molecular weight, all resulted in highly significant protection. In fact, mouse vaccination with fraction 8 was found to be significantly more protective than heat-killed *M. leprae* in previous studies. Such largely insoluble high-molecular-weight proteins associated with the cell wall[7] have been demonstrated to specifically elicit delayed-type hypersensitivity reactions and stimulate lymphoproliferative responses both from leprosy patients who limit their infection as well as from the contacts of leprosy patients.[8]

It is finally noteworthy in this study that fractions 11 and 12, though containing considerable *M. leprae* protein, afford no significant mouse protection and are devoid of large amounts of the 4 proteins implicated here to provide protective immunity.

In unpublished studies we have found that a purified and a recombinant *M. leprae* 10 kD GroEL homologue and a recombinant 65 kD *M. leprae* protein, each diluted in FIA, result in protective immunity in mice when the interval between vaccination and live *M. leprae* challenge was 1 month. Since these 2 heat-shock proteins are widely conserved across both bacterial and mammalian species, their ability to result in general immunity, species-specific immunity, and indeed autoimmunity remains both intriguing and perplexing. In order to further elucidate the issue of species-specific immunity, studies are in progress with vaccination and live *M. leprae* challenge, such as was carried out in the present study, comparing vaccine protection with: (1) a recombinant 10 kD *M. leprae* protein and the analogous recombinant 10 kD *M. tuberculosis* protein, (2) the recombinant *M. leprae* 65 kD protein and the homologous recombinant 65 kD BCG protein, and (3) wild BCG and BCG containing and expressing the 10 kD *M. leprae* protein. As in previous studies[1,2] discrimination of relative protective efficacy is being done by utilizing the strategy of assessing results both of different amounts of vaccine and by varying the interval from vaccination to live *M.leprae* challenge from 1 month up to 1 year subsequently.

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References

[1] Gelber RH, Brennan DJ, Hunter SW, Munn MW, Monson MJ, Murray LP, Siu P, Tsang M, Engleman EG,

Mohagheghpour N. Effective vaccination of mice against leprosy bacilli with subunits of *Mycobacterium leprae*. *Infect Immun*, 1990; **58:** 711–18.

[2] Gelber RH, Murray L, Siu P, Tsang M. Vaccination of mice with a soluble protein fraction of *Mycobacterium leprae* provides consistent and long-term protection against *M. leprae* infection. *Infect Immun*, 1992; **60:** 1840–4.

[3] Lehmann EL. *Nonparametric statistical methods based on ranks*. San Francisco: Holden-Day, Inc., 1975; pp. 5–13.

[4] Mehra V, Bloom BR, Bajardi AC, Grisso CL, Sieling PA, Aland D, Convit J, Fan X, Hunter SW, Brennan PJ, Rea TH, Modlin RL. A major T cell antigen of *Mycobacterium leprae* is a 10 kD heat-shock cognate protein. *J Exp Med*, 1992; **175**: 275–84.

[5] Andersen P, Heron I. Specificity of a protective memory immune response against *Mycobacterium tuberculosis*. *Infect Immun*, 1993; **61:** 844–51.

[6] Kaufmann SHE, Vath U, Thole JER, Van Embden JDA, Emmrich F. Enumeration of T cells reactive with *Mycobacterium tuberculosis* organisms and specific for the recombinant mycobacterial 64 kDa protein. *Eur J Immunol*, 1987; **17:** 351–7.

[7] Hunter SW, McNeil M, Modlin RL, Mehra V, Bloom BR, Brennan PJ. Isolation and characterization of the highly immunogenic cell wall-associated protein of *Mycobacterium leprae*. *J Immun*, 1989; **142:** 2864–72.

[8] Melancon-Kaplan J, Hunter SW, McNeil M, Stewart C, Modlin RL, Rea TH, Convit J, Salgame P, Mehra V, Bloom BR, Brennan PJ. Immunological significance of *Mycobacterium leprae* cell walls. *Proc Natl Acad Sci USA*, 1988; **85:** 1917–21.

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Ofloxacin-containing combined drug regimens in the treatment of lepromatous leprosy

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Summary A total of 26 clinically diagnosed adult patients, with active untreated lepromatous leprosy, with a Bacteriological Index of 4+ or more, were admitted to the hospital of the Central Leprosy Teaching and Research Institute, Chengalpattu, India, between 1989 and 1991. After prescribed investigations, the patients were randomly allocated in groups of 3 to 3 treatment regimens, namely: 1, clofazimine 50 mg daily and 300 mg once in 4 weeks + dapsone 100 mg daily (AA); 2, (AA)+ofloxacin 400 mg daily (BB); and 3, (AA)+ofloxacin 800 mg daily (CC). The drugs were administered for 56 days continuously under supervision. Sequential biopsy results on day 0, 7, 14, 28 and 56 in normal mouse footpad revealed no growth by day 28 and 56 in all patients treated with CC and BB regimens, respectively. Calculation of the proportion of viable *Mycobacterium leprae* through analysis of median infectious dose (ID_{50}) showed significant differences on day 7 in the percentage of kill between the ofloxacin-containing regimens and the other. Moderate to marked clinical improvement has been observed in a significantly higher proportion of patients treated with ofloxacin-containing regimens. All the 3 regimens were well tolerated. No severe complications or side-effects to the drugs were noticed with any of the regimens that required any suspension of treatment or the administration of steroids. Addition of ofloxacin to the standard WHO recommended MDT regimen for multibacillary patients may reduce the present duration of therapy. Ofloxacin may also be considered as an alternative drug in rifampicin-resistant cases or where rifampicin is contraindicated.

Introduction

The identification of bactericidal chemotherapeutic agents and the determination of their appropriate dosages and duration with and without other drugs is a priority in the quest for leprosy control, in the absence of a primary preventive measure such as an effective vaccine. There are only 4 bactericidal drugs (rifampicin, dapsone, clofazimine and thiomides) which are recommended for combined drug regimens,[1] and are widely used in the treatment of lepromatous leprosy. Each of the last 3 drugs, besides being weakly

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bactericidal, suffer from various drawbacks, such as an increased emergence of resistant *M. leprae* to dapsone,[2] skin discolouration with the use of clofazimine,[3–5] and the hepatotoxicity of thiomides.[6,7] Even resistance to rifampicin, has been reported.[8,9] Hence there is an urgent need to search for newer more potent bactericidal drugs, the detection of which might also help in reducing the duration of treatment. Several fluoroquinolones, especially ofloxacin, were found to be most active against *M. leprae in vitro*[10] and *in vivo*.[11]

Limited clinical trials concluded with ofloxacin and pefloxacin alone or in combination with other drugs reported highly favourable results in terms of tolerance, side-effects, clinical improvement and reduction in viable *M. leprae*.[12,13] A randomized clinical trial in lepromatous leprosy patients administered regimens containing dapsone, clofazimine and ofloxacin, has been conducted to find out the rate of kill of *M. leprae* in the mouse footpad model, the clinical response and the side-effects to drugs, and the results are reported below.

Materials and methods

A total of 26 clinically diagnosed, adult patients with active, untreated lepromatous leprosy were admitted to the hospital of the Central Leprosy Teaching and Research Institute, Chengalpattu, India, between September 1989 and December 1991. As well as close questioning on their first examination, a urine spot test for dapsone was conducted and we estimated their creatinine–dapsone ratio, to establish each patient's treatment status at intake. The procedures laid down in the standard THELEP protocol for examination, investigation and documentation of lepromatous leprosy patients were followed. After a thorough examination, patients received slit-skin smears for the bacteriological index (BI) and the morphological index (MI), and routine blood, urine and stool examinations, a skiagram of the chest, a lepromin test, and liver and kidney function tests were carried out. Biopsies were collected from sites with BI $\geqslant 4+$ for mouse footpad (MFP) inoculation and histopathology. Patients with either a history of ENL reactions or who had complications with other diseases such as diabetes and tuberculosis, or were over 65 years, or pregnant women were excluded from the study. Patients were allocated randomly in groups of 3^{14} to the 3 regimens, namely: 1, clofazimine 300 mg once in 4 weeks and 50 mg daily + dapsone 100 mg daily for 56 days (AA regimen); 2, AA regimen + 400 mg of ofloxacin daily for 56 days (BB regimen); and 3, AA regimen + 800 mg of ofloxacin daily for 56 days (CC regimen). Biopsies were collected from each of the patients on day 0, 7, 14, 28 and 56 of treatment from the same site. After processing, biopsy suspensions were inoculated into both hind footpads of each mouse in dilutions of 10^4, 10^3, 10^2 and 10^1 using 10 normal albino mice aged 6–8 weeks for each dilution, duly following Shepard's technique. Harvesting of footpads was done 1 year after inoculation. Smear BI and MI examination was repeated on day 28 and 56. Liver and kidney function tests and other haematological examinations were repeated at each biopsy. Prescribed drugs were administered daily under supervision and clinical progress was documented. The presence of $\geqslant 10^5$ organisms per footpad on harvesting was taken as positive for growth in MFP. The calculation for arriving at the proportion of viable organisms through the analysis of median infectious doses (ID_{50}) and significance were made as described in *Laboratory techniques in leprosy* published by

WHO.[15] If no growth had been detected after the commencement of the chemotherapy, it was assumed that growth had occurred in a footpad inoculated with the maximum concentration of inoculum for arriving at the probable proportion of the viable organism. The difference in proportion of the viable organism distribution in different regimens on day 0, median percentage of kill on day 7 between regimens and the frequency of significant reduction at day 7 were tested by Mann–Whitney and Fisher's exact tests for significance. Comparisons were not made for frequency of significant reduction beyond day 7. Clinical improvement was judged by flattening of the nodules, regression of infiltration, clearance of erythema and improvement in nasal congestion, etc. All the cases were put on the WHO recommended multidrug treatment regimen for MB patients on completion of the 56 days of trial. The study was not blind.

Results

PROPORTION OF VIABLE ORGANISMS, GROWTH IN MFP AND PERCENTAGE OF KILL

Of the 26 cases taken into the study, 3 cases (case nos 5, 11 and 12) were females and 3 were BL histopathologically (case nos 2, 5 and 15). Case no. 22 dropped out from trial after day 28. The number of MFP harvested and found positive for growth is given in Table 1. No growth was detected from day 0 of biopsy inoculation in 7 cases (case nos 1, 4, 5, 11, 12, 14 and 18) and hence they were excluded from analysis. The growth in MFP has been found to be negative in all patients treated with CC regimen by day 28 and with BB regimen by day 56 (Figure 1), whereas the growth was found positive in 1 patient on day 56 with AA regimen. However, 1 case under BB regimen showed growth in 1 MFP among 40 harvested at day 14 and 1 of 64 harvested at day 28, after attaining negativity at day 7 during the course of treatment (case no. 8).

The proportion of viable organisms, in general, was found to be very low on day 0, though inoculations were made from biopsy suspensions from sites showing BI $\geqslant 4+$. There were wide variations in the proportion of viable organisms in all the regimens. Despite randomization of patients in groups of 3, there were significant differences between the medians of proportion of viable organisms among the regimens at day 0, being highest in AA regimen (Table 2). It is observed that the lower the proportion of viable organisms on day 0, the less was the percentage of organisms killed by day 7 with any of the regimens. The maximum kill has occurred between day 0 and 7 in BB and CC regimens. The median percentage of kill has been found to be significantly higher in BB and CC regimens when compared to AA regimen (Table 2). The frequency of significant reduction of proportion of viable organisms on day 7 apparently appears to be more in BB and CC regimens compared to AA. The precise estimation of percentage of kill beyond day 7 could not be made in BB and CC regimens because no growth occurred in the footpad in most of the cases, which is perhaps due to very low proportion of viable organisms at day 0. MI and BI on day 0, 28 and 56 is shown in Table 3. In general MI at intake of cases was found to be low and even 0 in 9 cases. There has been consistent fall in MI in all the cases with progress of treatment. In 11 out of 17 cases (64·7%) the MI has reached 0·0% by day 56. No significant differences were noticed in the fall of MI between the regimens.

CLINICAL IMPROVEMENT BY DAY 56

Clinical assessment has been graded as 'nil', 'mild', 'moderate' and 'marked improve-

Table 1. Results of mouse footpad inoculation with organisms recovered from biopsy taken before and during treatment

Case no.	Regimen	0 day				7th day				14th day				28th day				56th day			
		10^4	10^3	10^2	10	10^4	10^3	10^2	10	10^4	10^3	10^2	10	10^4	10^3	10^2	10	10^4	10^3	10^2	10
2	CC	17/18	7/18	1/18	0/18	0/8	0/6	0/2	0/4	0/20	0/14	0/18	0/14	0/14	0/14	0/18	0/18	0/20	0/14	0/20	0/20
3	BB	9/18	5/18	0/14	1/16	0/14	0/14	0/18	0/20	0/18	0/16	0/16	0/8	0/12	0/10	0/8	0/18	0/18	0/18	0/12	0/10
5	AA	0/10	0/18	0/8	0/16	0/18	0/14	1/18	0/18	0/10	0/16	0/16	0/10	0/20	1/20	0/10	0/20	0/14	0/18	0/18	0/18
6	CC	2/16	0/14	1/14	0/20	0/12	1/4	0/16	0/14	1/10	0/8	0/10	1/6	0/18	0/16	0/18	0/18	0/0	0/12	0/0	0/0
7	AA	3/4	3/10	0/8	0/0	1/12	1/18	0/16	0/16	0/18	0/18	0/12	0/20	0/14	0/10	0/14	0/12	0/10	0/18	0/2	0/14
8	BB	1/14	1/20	0/16	2/20	0/16	0/18	0/18	0/18	0/12	1/16	0/6	0/6	0/18	1/14	0/14	0/18	0/18	0/18	0/18	0/18
9	CC	2/14	1/16	0/18	1/18	1/18	0/14	0/8	0/18	0/14	0/12	0/18	0/16	0/16	0/14	0/18	0/14	0/14	0/16	0/16	0/14
10	AA	7/18	0/12	0/18	0/16	3/16	2/18	0/14	0/18	7/18	0/20	0/18	0/8	2/20	0/14	0/8	0/14	0/16	0/18	0/18	0/8
13	AA	3/16	1/14	0/16	0/18	2/16	1/20	0/18	0/18	0/18	0/10	0/12	0/18	0/16	0/18	0/10	0/16	0/14	0/16	0/10	0/20
15	CC	2/16	0/14	0/18	0/8	0/20	0/16	0/18	0/16	0/18	0/20	0/18	0/20	0/16	0/18	0/18	0/18	0/18	0/18	0/20	0/18
16	AA	4/16	9/16	0/8	0/16	4/20	10/18	2/16	0/18	6/20	3/18	5/20	0/18	4/14	4/14	0/12	0/18	0/16	0/18	0/16	0/14
17	BB	4/16	7/16	1/14	0/12	0/16	0/16	0/8	0/16	0/16	0/16	0/16	0/14	0/14	0/14	0/18	0/12	0/16	0/20	0/18	0/14
19	AA	5/12	10/14	2/20	11/16	12/18	8/20	0/16	0/12	8/12	1/14	0/10	0/10	0/12	0/14	0/8	0/12	0/20	0/18	0/18	0/18
20	BB	5/16	3/18	2/20	1/16	0/12	0/14	0/12	0/8	0/12	0/12	0/14	0/10	0/14	0/12	0/14	0/12	0/14	0/16	0/18	0/10
21	CC	11/16	11/16	0/16	0/20	6/14	1/20	1/20	0/12	0/12	0/16	0/18	0/20	0/20	0/20	0/14	0/16	0/18	0/20	0/20	0/16
22	CC	7/16	3/18	0/20	0/18	0/18	0/18	0/16	0/14	0/18	0/16	0/16	0/20	0/20	0/18	0/18	0/18				
23	AA	8/20	2/20	0/18	0/20	2/18	1/18	0/20	0/18	0/20	0/18	0/16	0/14	0/12	0/18	0/20	0/14	0/20	0/12	0/20	0/18
24	BB	1/16	1/20	0/20	0/12	0/18	0/10	0/20	0/14	0/18	0/18	0/14	0/18	0/12	0/20	0/12	0/16	0/20	0/20	0/20	0/18
25	BB	14/18	0/20	0/20	0/18	4/20	2/18	0/10	0/16	0/18	0/16	0/20	0/18	0/18	0/14	0/10	0/18	0/20	0/20	0/14	0/18
26	AA	16/16	5/18	0/18	0/20	12/18	7/18	2/14	0/18	10/20	4/16	1/16	0/18	6/12	0/18	0/14	0/18	13/20	2/18	0/16	0/16

Case nos 1, 4, 11, 12, 14 and 18 were excluded since there was no growth at all periods.

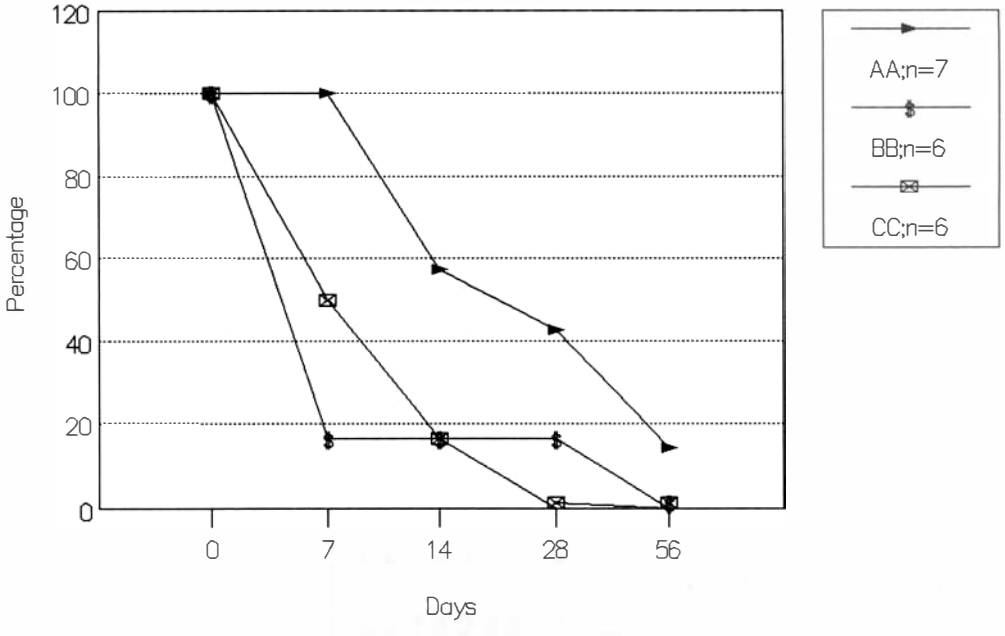

Figure 1. Cases showing growth in mouse footpad in relation to regimen.

ment'. None of these cases showed deterioration. All cases in the ofloxacin regimens (BB and CC), except 1 case in CC regimen, showed improvement (11 out of 12), a majority of them being moderate to marked (88%), whereas the majority in AA regimen showed no improvement at all (6 out of 9). The difference between AA and the other 2 regimens was found to be significant. All cases taken into the trial were analysed except case no. 22.

Table 2. Distribution of proportion of viable organisms on '0' day of different regimens and their percentage of kill at different period of trial by range and median

	Day									
	0		7		14		28		56	
Regimen	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median
AA	0·004 to 0·1443	0·0144	−18·91 to 88·0	25·0	0·0 to 91·68	63·8	20·8 to 98·26	63·0	37·5 to 98·26	70·9
BB	0·0029 to 0·048	0·0105	>13·91 to >94·8	>67·8	>13·8 to >94·88	>75·3	>13·8 to >94·8	>75·3	>13·8 to >94·8	>75·3
CC	0·0029 to 0·0536	0·0070	−12·7 to >95·3	61·4	−18·5 to >95·3	>61·4	>14·9 to >95·36	>61·4	>14·9 to >95·3	>50·9

Table 3. Average BI and MI Results on day 0, 28 and 56 by regimen

Case no.	Regimen																		
	AA						Case no.	BB						Case no.	CC					
	MI	BI	MI	BI	MI	BI		MI	BI	MI	BI	MI	BI		MI	BI	MI	BI	MI	BI
1	1·25	4·16	ND	ND	0·35	3·67	3	2·16	5·00	1·16	5·50	0·83	5·00	2	1·5	5·50	1·0	4·16	1·0	4·35
5	1·67	5·16	1·33	4·33	0·5	4·83	4	1·5	5.33	0·87	4·83	0·83	5·16	6	1·83	6·00	0·5	6·00	0·5	5·33
7	0·83	4·33	0·5	4·67	0·0	3·67	8	1·50	5·50	0·0	4·00	0·0	3·50	9	0·33	4·83	0.33	5·33	0·0	4·00
10	1·17	5·17	0·0	5.50	0·0	5·16	12	0·5	4·16	0·0	4·00	0·0	3·33	11	0·5	4·00	0·0	4·00	0·0	4·00
13	1·3	3·67	0·0	4·16	0·1	3·83	14	0.0	4·33	0·0	4·83	0·0	3·67	15	0·5	3·17	0·0	2·33	0·0	3·00
16	0·0	4·33	0·0	3·67	0·0	4·00	17	0·0	4.16	0·0	4·00	0·0	4·16	18	0·0	5·33	0·0	4.67	0·0	4·00
19	2·0	4·00	0·0	3.16	0·0	3·33	20	0·1	3·83	0·1	3·50	0·0	3·67	21	0·0	5·16	0·0	4·83	0·0	4·33
23	3·5	4·83	0·0	4.67	0·0	4·17	24	0·0	4.33	0·0	4·83	0·0	5·16	22	0·0	5.16	0·0	4·16	0·0	
26	0·0	3·17	0·0	3·67	0·0	0·7	25	0·0	3·67	0·0	3·33	0·0	3·00							

Table 4. Complications and side-effects of drugs

Regimen	AA	BB	CC
Complications			
Type I reaction	–	1	–
Type II reaction	1	1	4
Neuritis	1	3	–
Total complications	2	5	4
Side effects			
Headache	1	2	–
Giddiness	–	3	–
Pain in legs	1	1	1
Vomiting	–	2	1
Pain abdomen	1	1	1
Diarrhoea	–	1	–
Itching	–	–	2
Total cases suffered	3	7	4
Total cases in trial	9	9	8

*Some cases have suffered from more than one side-effect.

Significance:

Fisher's exact test.

Complication:

Between AA and BB ($p = 0{\cdot}33$);
BB and CC ($p = 0{\cdot}99$)
AA and CC ($p = 0{\cdot}33$)
AA and BB, CC ($p = 0{\cdot}21$)

Side-effects:

Between AA and BB ($p = 0{\cdot}15$)
BB and CC ($p = 0{\cdot}33$)
AA and CC ($p = 0{\cdot}63$)
AA and BB, CC ($p = 0{\cdot}22$)

COMPLICATIONS AND SIDE-EFFECTS

Complications in the form of mild Type I and II reactions and neuritis; and side-effects to drugs such as headache, giddiness, pain in the legs, vomiting, pain in the abdomen, loose stools and itching occurred in more patients treated with BB and CC regimens, compared to AA, but the differences were not significant. Complications responded to symptomatic treatment without steroids and drug side-effects were found to be mild and these cleared with the appropriate symptomatic treatment (Table 4). All the cases taken into the trial were analysed.

OTHER INVESTIGATIONS

No significant abnormalities were noticed in haematological and biochemical investigations at intake and during the course of trial.

Discussion

Loss of infectivity in MFP has been reported on administration of 28 daily doses of 400 mg ofloxacin in all untreated lepromatous leprosy patients.[13] The results of the

present study indirectly corroborates the above findings with 800 mg of ofloxacin (CC), since growth positivity was noticed from biopsies treated with other regimens (BB and AA) on day 28 and beyond. But for the ambiguous MFP result of 1 patient in 'BB' regimen (case no. 8), a daily dose of 800 mg ofloxacin does not appear to be more active against *M. leprae* than 400 mg. A killing rate of *M. leprae* of > 99% has been reported with ofloxacin in normal mice by 28 daily does.[13] A lower rate of > 75% was noticed in the present study because of the very low proportion of viable organism in day 0 biopsy. The present duration of WHO recommended MDT treatment for MB patients for a minimum of 24 months was based on the fact that dapsone and clofazimine are weakly bactericidal in dealing with the possible rifampicin-resistant mutants. In view of the effectiveness of ofloxacin in making *M. leprae* non-infective in MFP by day 28 and the fast rate of kill, it should be theoretically possible to reduce the duration of therapy, if ofloxacin is added to the present WHO recommended MDT for MB leprosy. The MI appears to be useful only for monitoring the response to chemotherapy, since it was found to decline consistently with the progress of therapy. The faster clinical improvement noticed in patients who received ofloxacin-containing drug regimens has also been reported by others.[13] The slow clinical response with clofazimine[16] or dapsone is well known. Even when they were given together (AA) the majority (66·7%) of patients showed no clinical improvement. Complications in the form of reactions and neuritis have not been reported by others either with ofloxacin or pefloxacin, but were noticed in the present study.[12,13] However, similar drug side-effects of a mild nature were reported as noticed in the present study, and the regimens were reported to have been well tolerated as in the present study.

Conclusions

The ofloxacin containing combined drug regimens were well tolerated by lepromatous leprosy patients. The complications and side-effects were of a mild nature.
Moderate to marked clinical improvement was noticed in a short period with ofloxacin-containing regimens.
Ofloxacin if added to the currently used WHO recommended MB–MDT regimen may shorten the duration of treatment.
Ofloxacin may be considered as a suitable alternative in suspected/proven rifampicin-resistant cases and where rifampicin is contraindicted.

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References

[1] WHO, Technical Report Series No. 675, 1982: **19:** 22.
[2] Ji BH, Drug resistance in leprosy, a review. *Lepr Rev*, 1985; **56:** 265–78.

[3] Petit JH, Rees RJ. Studies on sulfone resistance in leprosy. 2. Treatment with riminophenazine derivative (B663). *Int J Lepr*, 1966; **34:** 391–7.
[4] Petit JH, Rees RJW, Ridley DS. Chemotherapeutic trials in leprosy. 3. Pilot trials of a riminophenazine derivative B.663 in the treatment of lepromatous leprosy. *Int J Lepr*, 1967; **35:** 25–33.
[5] Yawalkar SJ, Vischer W. Lamprene (clofazimine) in leprosy. *Lepr Rev*, 1979; **50:** 135–44.
[6] Ji BH, Chen JK, Wang CM, Xia GA. Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev*, 1984; **55:** 283–9.
[7] Pattyn SR, Janssens L, Bourland J, Saylan T, Davis EM, Grillone S, Ferraci C and The Collaborative study group for the treatment of leprosy. Hepatotoxicity of the combination of rifampicin—ethionamide in the treatment of multibacillary leprosy. *Int J Lepr*, 1984; **52:** 1–6.
[8] Jacobson RR, Hastings RC. Rifampicin-resistant leprosy. *Lancet*, 1976; **2:** 1304–5.
[9] Guelpa-Lauras CC, Grosset JH, Constant-Desportes M, Brucker G. Nine cases of rifampicin resistant leprosy. *Int J Lepr*, 1984; **52:** 101–2.
[10] Franzblau SG, White KE, Comparative in vitro activities of 20 fluoroquinolones against *Mycobacterium leprae. Antimicrob Agents Chemother*, 1990; **34(2):** 229–31.
[11] Grosset JH, Guelpa-Lauras CC, Perani EG, Beoletto C. Activity of ofloxacin against *Mycobaterium leprae* in the mouse. *Int J Lepr*, 1988; **56(2):** 259–64.
[12] N'Deli LN, Guelpa-Lauras CC, Perani EG, Grosset JH. Effectiveness of Pefloxacin in the treatment of lepromatous leprosy. *Int J Lepr*, 1990; **58(1):** 12–18.
[13] Grosset JH, Ji BH, Guelpa-Lauras CC, Perani EG, N'Deli LN. Clinical trial of Pefloxacin and Ofloxacin in the treatment of lepromatous leprosy. *Int J Lepr*, 1990; **58(2):** 281–95.
[14] Pocock SJ. *Clinical trial—A practical approach*. A Wiley Medical Publication, John Wiley & Sons, 1984; 76–7.
[15] WHO/CDS/LEP 86.4 *Laboratory techniques for leprosy*. 1987; 100–4.
[16] Jamet P, Traore I, Husser JA, Ji B. Short-term trial of Clofazimine in previously untreated lepromatous leprosy. *Int J Lepr*, 1992; **60(4):** 542–8.

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Reactions in Leprosy: an Epidemiological Study of 386 Patients in West Nepal

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Summary This paper presents epidemiological data on reversal reaction (RR) and erythema nodosum leprosum reaction (ENL) from a retrospective study of 386 leprosy patients newly registered at Green Pastures Hospital, Pokhara, West Nepal. The average follow-up time was 21 months. The prevalence of RR at first examination was 28% (23–32), and the prevalence of ENL reaction was 5·7% (2·3–9·2). The overall incidence rates among the 335 patients that were available for follow-up were 8·7 (6·5–12)/100 person years at risk (PYAR) for RR and 3·2 (1·5–6·7)/100 PYAR for ENL. Relapse of RR was common (1·4/patient). In all, 52% of RR were complicated by new nerve function impairment, against 59% of ENL reactions. The finding of other investigators that most RRs occur during the first year of treatment was confirmed by this study. The most significant risk factor for RR was extent of clinical disease measured by a count of body areas with clinical signs of leprosy. The risk of developing a RR for patients with 'extensive disease' (3 or more out of 9 body areas involved) was 10 times that of patients with limited disease (Rate Ratio 10 (1·3–76), $p = 0{\cdot}026$).

The study indicated that the following categories of patients in Nepal are at high or increased risk of developing a RR: 1, borderline patients during their first year of MDT; and 2, patients with more extensive clinical disease as described above.

Introduction

Although leprosy reactions are a very common phenomenon, very few data have been published on their epidemiology—the 5 publications by Duncan & Pearson,[1] Becx-Bleumink *et al.*,[2,3] Roche *et al.*[4] and Lockwood *et al.*[5] are notable exceptions. Up to now, no prospective studies have been published that were designed to establish the incidence rates of the various forms of leprosy reactions. The available epidemiological information is therefore still quite patchy and incomplete, despite a growing amount of literature on the treatment of reactions in leprosy.[6–11]

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Green Pastures Hospital (GPH) is a 100-bed mission hospital in Pokhara, West Nepal, run by the International Nepal Fellowship under its Leprosy Control Project, which is a joint venture with His Majesty's Government/Nepal. GPH is the main leprosy referral hospital for the West of Nepal. Because of good record keeping combined with fairly constant methods of nerve function assessment, it was thought that the data thus accumulated would form a useful database for a retrospective study of reactions and peripheral neuropathy in leprosy. This paper discusses the prevalence and incidence of reversal reactions (RR) and ENL reactions (ENL). The significance of a third type of reaction, Silent Neuropathy, will be discussed in a separate paper.[12] We also attempted to analyse possible risk factors for RR.

Methods

STUDY QUESTIONS

1 What is the prevalence at registration and incidence of leprosy reactions (RR, ENL) in the study patient population?
2 Can any risk factors for RR and ENL be identified?

OUTCOME MEASURES

For question 1:
The number of patients with RR and ENL stratified by classification, severity of reaction, leprosy treatment and time of onset of reaction.

For question 2:
The association between leprosy reactions/neuritis and age, sex, classification, extent of disease (number of skin lesions, nerves and body areas involved in the disease), PGL-1 serology results, and type of leprosy treatment: MDT *vs* DDS monotherapy.

CRITERIA FOR INCLUSION OF PATIENTS

Only new, previously untreated patients who registered for treatment in GPH during the period January 1988–January 1992 were included in the study. Pure neuritic patients were excluded from the analysis, because our criteria for reaction were mainly based on skin signs.

DIAGNOSIS AND CLASSIFICATION

After registering at GPH, each patient was examined in the Outpatients Department by either of the 2 experienced leprosy supervisors. The examination included a full history, full body charting, palpation of all major peripheral nerve trunks and disability grading according to the 'old' WHO grading system (0–3).[13] Patients were classified according to the Ridley–Jopling system[14] and our 'body area system' (PB/MB categories for treatment purposes),[15] in which a patient with more than 2 out of 9 body areas is classified as multibacillary (MB).

If there was any doubt concerning the leprosy diagnosis, the classification, or

whether the patient had had recent nerve function impairment (NFI), he was referred to the medical officer. In patients admitted to hospital their blood pressure and body weight were also recorded. The allocation of patients to MDT or DDS monotherapy regimens depended largely on whether a patient lived near enough to be able to attend for supervised treatment at least once every 2 months.

HISTOLOGY

From September 1990, all newly registered patients and all patients admitted for reaction and/or nerve function impairment treatment in GPH had a skin biopsy taken from an active lesion. Tissue was fixed in formalin, processed to paraffin and sections stained with haematoxylin and eosin and Wade–Fite stains. Histological classification of leprosy followed the standard Ridley–Jopling system.[14]

DIAGNOSIS OF REACTIONS AND NERVE FUNCTION IMPAIRMENT

REVERSAL REACTION (RR)

A patient was diagnosed as having a RR if he showed the following clinical signs:

Skin: redness and swelling of (usually already existing) lesions, sometimes tender in the lesions.
Nerves: often signs of neuritis: swelling, pain (shooting or burning), tenderness, paraesthesia or nerve function impairment.
General: sometimes oedema of hands, feet or face, occasionally fever.
The skin signs were obligatory; the nerve signs and general signs optional.

For this study, histopathology was not designed to contribute inclusion/exclusion criteria for RR. For both reversal and downgrading reactions, dermal oedema on skin histology was considered a feature. Positive features for a reversal (upgrading) reaction were increased numbers of large Langhans' giant cells, formation of discrete granulomas, epidermal erosion, fibrinoid necrosis of granulomas, and (for multibacillary leprosy patients) a reduction in the expected number of acid-fast bacilli.[16,17]

ERYTHEMA NODOSUM LEPROSUM (ENL)

A patient was diagnosed as having ENL if he showed the following clinical signs:
Skin: multiple, usually small, tender nodules, with or without ulceration, particularly on the arms and legs.
Nerves: often signs of neuritis: swelling, pain (shooting or burning), tenderness, paraesthesia or nerve function impairment.
General: fever, oedema, involvement of other organs, e.g. iritis, orchitis, arthritis.
The clinical diagnosis was supported by finding, on skin biopsy, multibacillary leprosy with an acute inflammatory cell infiltrate and oedema.[16]

SILENT NEUROPATHY (SN)

A patient was diagnosed as having SN if he showed the following clinical signs: evidence

of *recent* (see below) sensory or motor nerve function impairment without skin signs of RR, ENL, obvious spontaneous nerve pain or nerve tenderness.

NERVE FUNCTION IMPAIRMENT (NFI)

A patient was considered to have NFI if there was a deterioration of >2 points in his VMT score, or 2 points or more in his TST score compared to the previous result. NFI of less than 6 months duration was recorded as 'recent', while NFI of longer duration was recorded as 'old'. If no previous VMT and TST results were available, the patient history regarding the onset of the muscle weakness and/or impairment of sensation was used to determine whether the nerve function impairment was 'recent' or 'old'.

The decision whether or not to initiate corticosteroid treatment for any given recent NFI was usually made by the medical officer, or, in his absence, by the nursing superintendent.

NERVE FUNCTION ASSESSMENT

NFA was done by either of 2 trained physiotechnicians over a period of 4 years at the following intervals: at the first examination, at every clinic visit for outpatients, at annual examinations during treatment and after release from treatment, every 2 weeks for patients receiving treatment for reaction or NFI.

VOLUNTARY MUSCLE TEST (VMT)

A full VMT was performed using the modified MRC scale as described by Brandsma.[18] The VMT score (0–5; 0 = paralysed, 5 = normal strength) consisted of the sum of 2 individual muscle scores for the ulnar, median, radial and lateral popliteal nerve (max. score 10). For the facial nerve only the orbicularis oculi muscle was tested (max. score 5).

TOUCH SENSIBILITY TEST (TST)

Touch sensibility of the ulnar and median nerves was tested on the palm of the hand using a nylon monofilament giving a force of approximately 10 gm when pressed until it bent. The result was recorded as felt or not felt for each of the sites mentioned below. Touch sensibility of the posterior tibial nerve was tested in a similar way using a thicker monofilament, giving a force of about 75 gm. The TST score consisted of the sum of TST scores given for individual sites (2 = monofilament felt, 1 = doubtful, 0 = not felt). We tested 3 sites for the ulnar nerve (max. score 6), 4 for the median (max. score 8) and 10 for the posterior tibial nerve (max. score 20).

LABORATORY TESTS

Serum of all patients was sent to the Mycobacterial Research Laboratory at Anandaban Hospital, Kathmandu, for ELISA testing of phenolic glycolipid-1 (PGL-1) antibody titres. The first (highest) result obtained was used for analysis. An absorbance of >0·199 was considered positive.[4]

STATISTICAL METHODS

The significance of the difference between proportions was tested with using a Yates-corrected χ^2 test or Fisher's exact test. The difference between 2 unpaired sample means was tested using the Student's *t*-test. For the calculation of the person years at risk denominator patients were censored as soon as they were diagnosed as having a RR. They were also censored from the denominator if they died, were transferred, or were otherwise lost to follow-up. Patients who had a reaction at registration were not excluded from the analysis, because they remained at risk of further reactions. The significance of various risk factors for reaction was examined with Cox's proportional hazards regression. The results are expressed as rate ratios. The adjusted rate ratio is the ratio obtained when age, sex, treatment, bacteriological index, PGL-1 status, and each of the extent-of-disease indicators in turn were entered together into the model. It may be interpreted as an estimate of the increase in risk associated with a particular risk factor after controlling for the other factors. A *p*-value of less than 5% was used as level of statistical significance. Of the prevalence, incidence rates and rate ratios the 95% confidence interval is given. For example, 4·1 (2·1–8·2) means that there is a 95% chance that the true value lies between 2·1 and 8·2. In computing the 95% confidence limits for rates a normal approximation was used if the number of observed reactions was 20 or more. For smaller numbers an exact method based on the Poisson distribution was used. Epi Info software, version 5.01[19] and SPSS for Windows, version 6 were used for the analysis.

Results

PATIENTS

A total of 386 patients were included in the study—the mean age was 41 years (range 2–88, standard deviation 16), and 70% were male. Only 335 patients were available for follow-up (the remainder was transferred after diagnosis). The average follow-up time of these patients at the start of data analysis was 20·7 months (range 1–49).

The distribution of the study patients according to the Ridley–Jopling classification was as follows. Two tuberculoid (TT), 202 borderline tuberculoid (BT), 7 borderline (BB), 133 borderline lepromatous (BL), and 42 lepromatous (LL).

PREVALENCE

Tables 1 and 2 show the prevalence and incidence rates of RR and ENL. The prevalence of RR was 28% at the time of diagnosis. For ENL this figure was 5·7%. In all categories more reactions were diagnosed at the start of treatment than during or after treatment. The distribution of prevalence over classification sub-groups is illustrated in Figure 1.

Of the BT patients who presented in reaction, 14 had a biopsy and 9 showed features of a RR. Of the BL patients who presented in reaction and were biopsied, 5/7 had histological features of RR with Langhans' giant cells (3 patients) and focalized granulomas (all 5 patients), in addition to the less specific dermal oedema. These were similar to the appearances of the biopsies taken from BL patients in reaction on MDT (which are, by definition, RR).

Table 1. Prevalence and incidence rates of RRs among 386 new patients of leprosy at GPH

	Prevalence at registration				Incidence rates			
Classification	Number	% (95%Cl)[a]	Severe reactions	Reactions with new NFI[b]	Number	per 100 PYAR[c]	Severe reactions	Reactions with new NFI
TT	0/2	0	0	0	0/2	0	0	0
BT	69/202	30 (24–37)	34/61	30/61	21/182	6·8 (4·4–10)	11/21	11/21
BB	2/7	29 (0–62)	2/2	2/2	1/4	20 (2·8–141)	1/1	1/1
BL	41/133	31 (23–39)	21/41	20/41	23/106	15 (10–23)	14/23	14/23
LL	3/42	7·1 (0–15)	1/3	1/3	0/34	0	0	0
Total	107/386	28 (23–32)	58/107	53/107	45/325[d]	8·7 (6·5–12)	26/45	26/45

[a] 95% confidence interval, [b] nerve function impairment, [c] incidence expressed as the number of episodes of RR per 100 person years at risk (PYAR), [d] the number of patients that was available for follow-up.

INCIDENCE RATES

The overall incidence rate of RR was 8·9/100 PYAR and 116 out of the 335 new patients who were followed up had a RR at registration or during or after treatment. Altogether, they had 160 episodes of reaction (1·4/patient). The incidence rate of ENL was 3·2/100 PYAR. The proportion of patients with severe reactions was 26/45 (66%) and 7/7 (100%) in the RR and ENL groups, respectively. There was little difference in the severity of reactions between the classification sub-groups. shows the incidence rates of reaction in the different classification groups.

TIME OF ONSET

The occurrence of reactions by time of onset is shown in Figure 3 and Table 3. The great majority of RR that were diagnosed after the start of treatment occurred during the first 6 months of treatment (40/66); 4/12 ENL reactions occurred after the first year.

Table 2. Prevalence and incidence rates of erythema nodosum leprosum (ENL) among 175 new borderline lepromatous and lepromatous patients at GPH

	Prevalence at registration				Incidence rates			
Classification	Number	% (95% Cl)[a]	Severe ENL	ENL with new NFI[b]	Number	per 100 PYAR[c]	Severe ENL	ENL with new NFI
BL	4/133	3·0 (0·1–5·9)	2/4	1/4	1/106	0·58 (0·08–4·1)	1/1	1/1
LL	6/42	14 (3·7–25)	3/6	3/6	6/31	13 (5·6–28)	6/6	5/6
Total	10/175	5·7 (2·3–9·2)	5/10	4/10	7/137[d]	3·2 (1·5–6·7)	7/7	6/7

[a] 95% confidence interval, [b] nerve function impairment, [c] incidence expressed as the number of episodes of ENL per 100 person years at risk (PYAR), [d] the number of patients that was available for follow-up.

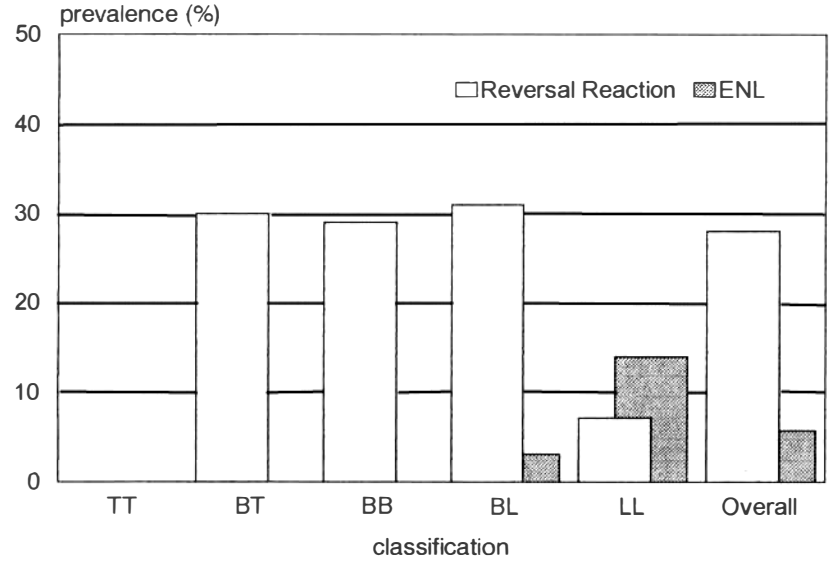

Figure 1. Prevalence of RR and ENL at the first examination in 386 new cases at GPH.

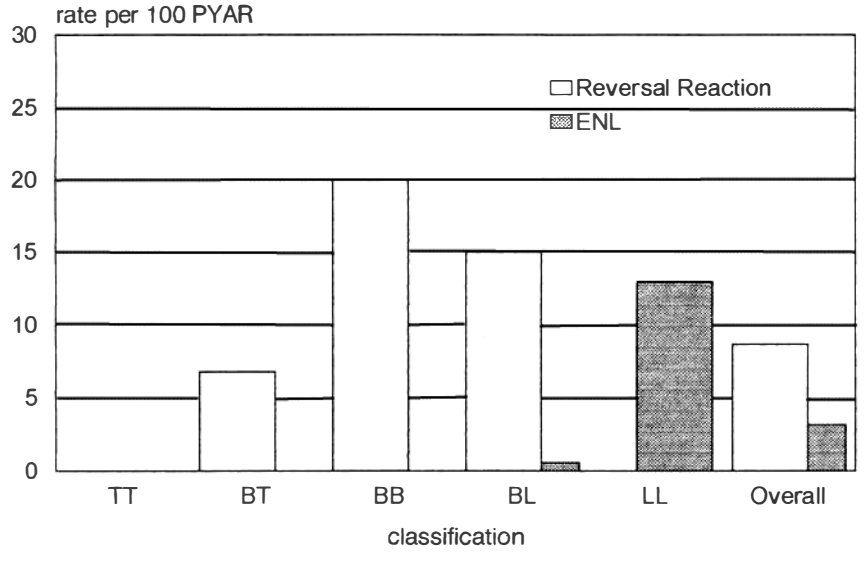

Figure 2. Incidence rates of RR and ENL per 100 person years at risk (PYAR) among 335 new patients at GPH.

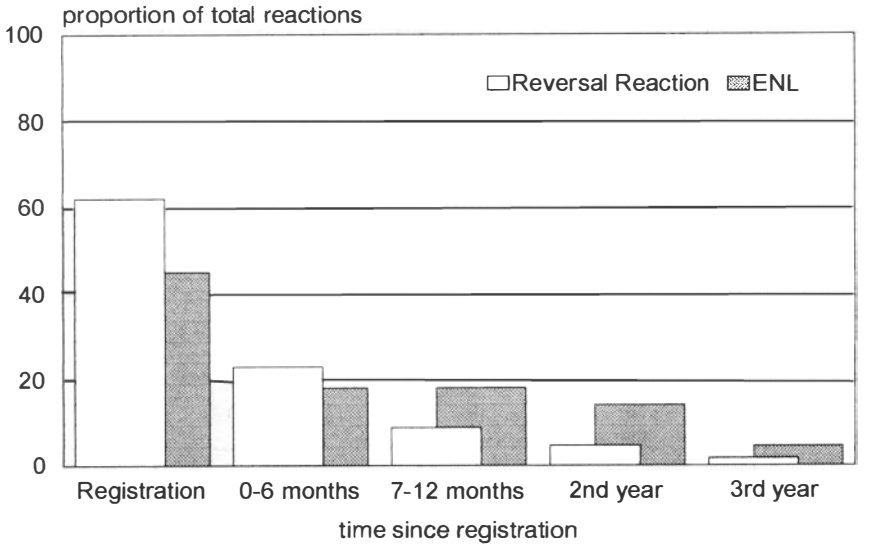

Figure 3. Occurrence of RRs and ENL by time of onset among new patients at GPH.

RISK FACTORS

The potential risk factors for RR and their significance is shown in Table 4. The skin lesion count was not an independent risk factor, but was strongly correlated to the body area count which was a stronger risk indicator. 'Extensive disease' was defined as: 3 or

Table 3. Occurrence of reactional episodes by time of onset among 384 new leprosy patients registered at GPH

	BT		BB		BL		LL	
Period	number	%[a]	number	%[a]	number	%[a]	number	%[a]
Reversal reactions								
At registration	61	69	2	66	41	53	3	100
0–6 months	15	17	1	33	24	31		
7–12 months	7	7·9			8	10		
2nd year	4	4·5			4	5·1		
3rd year	2	2·2			1	1·3		
Total	89		3		78		3	
ENL reactions								
At registration					4	40	6	50
0–6 months					2	20	2	17
7–12 months					2	20	2	17
2nd year					1	10	2	17
3rd year					1	10		
Total	0		0		10		12	

[a] Column percentages.

Table 4. Risk factors for RRs occurring after the start of antileprosy treatment among 335 new patients in GPH

Risk factor	Category of patients	Rate ratio[a]	*p*-value
Sex	all	1·7 (0·85–3·3)	0·14
	BT	4·7 (1·7–13)	0·0027
Treatment (MDT *vs* DDS)	all	1·7 (0·51–5·5)	0·40
Extent of clinical disease			
> 10 skin lesions	all	2·8 (1·01–7·5)	0·047
> 3 nerves enlarged	all	1·4 (0·51–3·9)	0·51
> 2 body areas involved	all	10 (1·3–76)	0·026
Bacteriological index	all	0·76 (0·34–1·7)	0·50
PGL-1	BT	1·1 (0·4–3·3)	0·80

[a] Rate ratio adjusted for the influence of age, sex, treatment, bacteriological index, PGL-1 positivity, and each of the 3 indicators of extent of clinical disease in turn.

more out of 9 body areas with primary or secondary signs of leprosy, or more than 10 skin lesions, or more than 3 peripheral nerve trunks enlarged. A highly significant association was found between the risk of developing a RR and the extent of 'clinical' disease. The most effective indicator of 'extensive disease' was the body area count (rate ratio 10 (1·3–76)). This finding will be discussed below in relation to its potential importance for the identification of patients at a risk of reaction. The incidence rate of reversal reaction in patients with 3 or more body areas involved was 10/100 PYAR. The rate among those with limited disease was approximately 1/100 PYAR. There was no significant difference in incidence of reaction between different age groups. Among BT patients, women had a significantly increased risk of developing reversal reaction (rate ratio 4·7 (1·7–13), $p = 0{\cdot}0027$). This sex difference in incidence rates was not significant in the whole patient group.

Discussion

Reversal reaction (RR), ENL, and what we have called silent neuropathy (SN) are the main causes of disabling nerve damage in leprosy. SN will be discussed in a separate paper. The main publications on occurrence of reactions are summarized in Table 5. To our knowledge, the present study is the first to present incidence rates of RR and ENL reaction in new patients. For the sake of comparison with other studies cumulative prevalence figures have been included in Table 5. It should be noted that cumulative prevalence figures can only be compared if they refer to an equal duration of follow-up.

REVERSAL REACTIONS

The impression of Pfaltzgraff & Bryceson[20] that more than 50% of BT patients develop a

Table 5. Overview of publications on the occurrence of leprosy reactions

Author	Type of patients, average duration of follow-up and classification	Type	Proportion of patients who developed a reaction (year) Registration %	1 (%)	2 (%)	Cumulative[a]
Pfaltzgraff & Bryceson[20]	type? follow-up?					
	BT	RR		> 50		
	BB	RR		> 50		
	BL	RR		50		
		ENL				25
	LL	ENL				50
Rose & Waters[10]	all DDS patients, follow-up 5 years					
	BL	RR		33		50
	LLs	RR				10
Boerrigter *et al.*[21]	503 field patients (new)	RR	2·2	1·4	3·0[b,c]	6·6[c]
	TT/BT				(7·3)	(8·3)
Groenen *et al.*	new + old patients, follow-up: max. 3 years (?)					
	335 PB	RR		6		
	280 MB	RR		48		
		ENL		12		
Roche *et al.*[4]	New hospital out-patients, average follow-up: 21 months (range 7–35)					
	51 BT	RR				20
	13 BB	RR				46
	62 BL	RR				39
Lockwood *et al.*[5]	New hospital out-patients, follow-up: 6 years					
	77 TT	RR				3·8
	218 BT	RR				11
	3 BB	RR				100
	67 BL	RR				15
	123 LL	RR				2·4
Becx-Bleumink & Berhe[3]	New field patients, follow-up: 24 months					
	438 BT	RR	3·4	10[b]	7·3[b]	21
	266 BL	RR	4·9	26	12	44
		ENL	0·8	1·1	0·8	2·7
	109 LL	RR	0	13	6·4	19
		ENL	2·8	5·5	2·8	11
van Brakel *et al.*	New hospital out-patients, average follow-up; 21 months (range 1–49)					
	182 BT	RR	32	8·2	2·2	39
	4 BB	RR	50	25	0	75
	106 BL	RR	29	13	3·8	38
		ENL	1·9	0	0	1·9
	31 LL	RR	6·5	0	0	6·5
		ENL	16	9·7	6·5	32

[a] Cumulative prevalence of patients with a leprosy reaction. [b] Actually, during PB MDT and during the first year after release from PB MDT. [c] Refers to 'marked' RRs needing steroid treatment. The figure in parentheses includes also mild RRs.

RR is not confirmed by more recent studies. Roche *et al.*[4] and Becx-Bleumink & Berhe[3] report a cumulative percentage of about 20% in the BT group. The difference between their findings and ours (20% *vs* 36%) may be explained by the fact that Roche *et al.*[4] and Becx-Bleumink[3] only included patients with severe reactions, while our figures include all reactions. Since only 55% of RR in our study were severe, the proportion of BT patients with severe reaction was about 21%. The reactions described by Becx-Bleumink occurred among field patients and were therefore likely to be less common than among hospital outpatients like those in our study. This may also explain the difference in TT/BT patients found by Boerrigter *et al.*[21] and us (8·3% *vs* 36%). An ethnic difference may also be involved.

The high cumulative prevalence (19%) of LL patients with RR found by Becx-Bleumink[3] is surprising, particularly since only severe reactions were included. Rose & Waters[10] found 10% among LL patients treated with DDS over a 5-year period, while we recorded only 7·1% among 42 LL patients treated with MB MDT. An ethnic difference seems unlikely as in the other classification groups the trend is the reverse. A possible explanation would be that a number of patients that we would have classified as BL were classified as LL in the ALERT field programme. A low cumulative prevalence (2·4%) was found among 123 LL hospital outpatients in Hyderabad, India, during a 6-year follow-up period.[5]

Another difference between the Ethiopian data and our data is the proportion of RR present at the time of diagnosis (7·9% *vs* 59%). Most of our patients are self-reporting and therefore this indicates that RR was likely to be a reason for a patient to seek treatment, and even to go to a referral hospital rather than to a field clinic. This idea was already suggested by Naafs & Wheate,[22] reporting on Ethiopian hospital outpatients, who found that a large proportion of the reactions that occurred in BT/BB patients were present at the time of diagnosis (62%). In the series described by Lockwood *et al.*[5] 57% of reactions occurred before or at the time of first diagnosis. The finding of Naafs & Wheate[21] that in BL patients the occurrence of RRs is spread out over a much longer period than in the BT/BB group is not confirmed by our data (see Table 3). This could be due to the fact that most of our patients were on MDT, while their patients were taking DDS monotherapy. The rapid bactericidal effect of rifampicin may cause RRs to occur earlier in the course of treatment.

In the untreated BL patients, the nature of the reactions was not always clear. Some may have been downgrading, but by histological inference (they share features of paucibacillary patients and treated multibacillary patients in reversal reaction[17]), some were RR. There are no published studies that formally evaluate the sensitivity, specificity and predictive values of the proposed histopathological features of hypersensitivity reactions.[17,23,24] Such an evaluation, with appropriate controls, is overdue.

ENL REACTIONS

ENL was relatively rare in both Ethiopian and Nepali BL patients (2·7% *vs* 1·9%). These figures are significantly lower than the 25% reported by Pfaltzgraff & Bryceson.[20] This is probably because of the protective effect of clofazimine against ENL.[3] This would also explain the much lower ENL 'incidence' found in LL patients on MB MDT (50% *vs* 11% and 32%). The difference between Ethiopian and Nepali LL patients could again be due to the difference of field patients *vs* hospital outpatients.

RISK FACTORS

The only risk factors that have been convincingly demonstrated are PGL-1 antibody 'positivity' and a positive lepromin test in borderline patients.[4] Despite the fact that our patients' sera were analysed in the same laboratory at Anandaban Hospital in Kathmandu, our data did not confirm this finding. This is surprising since our patients matched those described by Roche *et al.*[4] closely in terms of age and sex distribution. The explanation may be a difference in diagnostic criteria for RR. Roche *et al.*[4] majored on the presence of (acute) neuritis, including neuritis without skin signs of RR. These criteria indicate that only more severe patients were included. We emphasized skin signs for the diagnosis 'RR', because these are the signs by which a RR is usually recognized and distinguished from ENL. But even modelling our data to include severe reactions only, also including SN, or both, did not change the result.

Among our patients we found a consistently significant association between the extent of clinical disease, measured by the number body areas (out of 9) with clinical signs of leprosy, and the risk of developing a RR. A cut-off point of 3/9, i.e. when a patient with 3/9 or more body areas involved was classified as having 'extensive disease', showed a 10-fold increase in the risk of developing a RR when compared with patients with 'limited disease' (adjusted rate ratio 10, $p = 0{\cdot}026$). It could be argued that 'body areas' may just be a proxy indicator for bacteriological index or classification, i.e. that the risk of reaction increases towards the lepromatous end of the leprosy spectrum. However, a similar association was found within the BT patient subgroup (who were almost all skin smear negative), indicating that the body area count is a useful indicator of the risk of RR. We are not aware that this has been reported in the literature and submit that this finding, with its element of quantification (counting) is potentially of considerable importance for control programmes, for the identification of patients at risk of reaction. In programmes where workers are not familiar with body area counts a skin lesion count could be used as an indicator of the underlying risk factor, which is 'extensive disease'. Our data suggested more than 10 skin lesions' as the optimum cut-off point above which a patient should be classified as having 'extensive disease'.

In order to estimate the incidence rate among field patients, we calculated the rates for patients with extensive and with limited disease separately. Among 904 field patients newly registered by our Western Regional Mobile Clinic during 1990–92, 71% had extensive disease. With a rate of 10/100 PYAR for these patients and 1/100 PYAR for patients with limited disease, the expected incidence rate of RR in the field would be around 7/100 PYAR. In other words, 7 patients with RR out of every 100 per year. Similarly, a field programme with only 5% patients with extensive disease would have an estimated incidence rate of 1·5/100 PYAR.

We observed that in a number of patients a RR or ENL reaction that existed at the time of diagnosis got worse after the patient received the first dose of rifampicin. In a few patients an ENL relapse occurred every month 3–5 days after the patient had taken his or her monthly dose of MDT. Groenen *et al.*[25] concluded from their study 'that rifampicin may enhance type 1 reactions ..., especially in previously untreated MB patients.' Our data were compatible with an increased risk of RR in patients on MB MDT as compared to patients on DDS, but this was not statistically significant. There was no difference in the proportion of severe reactions between the 2 treatment categories (data not shown).

New potent bacteriocidal drugs or drug combinations should be carefully tested to see if they produce an increased risk of reactions and or nerve damage. This is particularly true for regimens that will further reduce the duration of treatment and hence, potentially, the time of effective follow-up. This was expressed in the recent *Consensus development statement on chemotherapy in leprosy*.[26] 'In evaluating any new treatment regimen, the incidence of disabilities during and after chemotherapy is as important a measure of the value of a new regimen as the relapse rate.'

It has been our policy to delay the first monthly dose of rifampicin if a patient presented with a reversal or ENL reaction (or SN) at the time of diagnosis (usually for only 1 month) until the reaction was under control.

The only other group that appeared to be at increased risk was female BT patients. An increased risk of RR may be expected in female patients of childbearing age, due to an increase of the cell-mediated immunity after delivery, triggering off upgrading reactions.[1] The observed increase in risk is, therefore, probably not due to classification but by placing an increased proportion of women who had a recent delivery in this group. Information on pregnancy or lactation was unfortunately not recorded systematically. It was therefore not possible to check this assumption. None of the factors in Table 4 was significant as a risk factor for ENL reaction, but the numbers were very small.

TREATMENT OF REACTIONS

The treatment of reactions will not be discussed here. In most patients the important part is the treatment of the accompanying nerve function impairment. Patients with a mild reactions of any type (no nerve function impairment or involvement of other organs) were treated with a combination of aspirin and chloroquin. The patients (except women of childbearing age) with severe ENL were treated with thalidomide (starting dose 200 mg twice daily). Women of childbearing age, as well as RR and SN patients with nerve function impairment, are treated with prednisolone, starting with 40 mg od and gradually tapering every 2 weeks. The duration of the standard regimen is currently 16 weeks.

Conclusions

RR and ENL are common complications in Nepali leprosy patients, often leading to nerve function impairment.

Certain categories of patients appeared to be at high risk of developing a RR: 1, borderline patients during their first year of MDT; and 2, patients with extensive clinical disease (defined as 3/9 or more body areas with clinical signs of leprosy). They should be monitored with great care, including a nerve function assessment at every clinic visit, at least during their first year of treatment with MDT.

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References

[1] Duncan ME, Pearson JMH. Neuritis in pregnancy and lactation. *Int J Lepr*, 1982; **50:** 31–8.

[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] Becx-Bleumink M, Berhe D. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the Leprosy Control Program of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Ethiopia. *Int J Lepr*, 1992; **60:** 173–84.

[4] Roche PW, Theuvenet WJ, Britton WJ, Risk factors for type I reactions in borderline leprosy patients. *Lancet*, 1991; **338:** 654–6.

[5] Lockwood DNJ, Vinayakumar S, Stanley JMA, McAdam KPWL, Colston MJ. Clinical features and outcome of reversal (type 1) reactions in Hyderabad, India. *Int J Lepr*, 1993; **61:** 8–15.

[6] Naafs B, Pearson JMH, Baar AJM. A follow-up study of nerve lesions in leprosy during and after reaction using motor nerve conduction velocity. *Int J Lepr*, 1976; **44:** 188–97.

[7] Naafs B, Pearson JMH, Wheate HW. Reversal reaction: the prevention of permanent nerve damage. Comparison of short and long term steroid treatment. *Int J Lepr*, 1979; **47:** 7–12.

[8] Pearson JMH. The use of corticosteroids in leprosy. *Lepr Rev*, 1981; **52:** 293–8.

[9] Touw-Langendijk EMJ, Brandsma JW, Andersen JG. Treatment of ulnar and median nerve function loss in borderline leprosy. *Lepr Rev*, 1984; **55:** 41–6.

[10] Rose P, Waters MFR. Reversal Reactions in leprosy and their management. *Lepr Rev*, 1991; **62:** 113–21.

[11] Naafs B. Leprosy reactions. *Quad Coop San*, 1992; **12:** 67–72.

[12] van Brakel WH, Khawas IB. Silent neuropathy in leprosy: an epidemiological description. *Lepr Rev*, **65,** in press.

[13] *WHO Expert Committee on leprosy, Fourth report*. WHO Technical Report series. No. 459. WHO, Geneva, 1970.

[14] Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five group system. *Int J Lepr*, 1966; **34:** 255–73.

[15] 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.

[16] Ridley DS. *Skin Biopsy in Leprosy*, 3rd edition. Ciba-Geigy Ltd, Basle, Switzerland, 1990.

[17] Ridley DS, Radia KB. The histological course of reactions in borderline leprosy and their outcome. *Int J Lepr*, 1981; **49:** 383–92.

[18] Brandsma W. Basic nerve function assessment in leprosy patients. *Lepr Rev*, 1981; **52:** 161–70.

[19] 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.

[20] Pfaltzgraff RE, Bryceson A. Clinical leprosy. In: Hastings RC. (ed) *Leprosy*. Edinburgh: Churchill Livingstone, 1985.

[21] Boerrigter, G, Ponnighaus JM, Fine PEM. Preliminary appraisal of a WHO-recommended multiple drug regimen in paucibacillary leprosy patients in Malwai. *Int J Lepr*, 1988; **56:** 408–17.

[22] Naafs B, Wheate HW. The time interval between the start of anti-leprosy treatment and the development of reactions in borderline patients. *Lepr Rev*, 1978; **49:** 153–7.

[23] Sehgal VN, Gautam RK, Koranne RV, Beohar PC. The histopathology of type I (lepra) and type II (ENL) reactions in leprosy. *Ind J Lepr*, 1986; **58:** 240–3.

[24] Lazaro-Medina A, Tianco EA, Avila JM. Additional markers for type I reactional states of borderline leprosy. *Am J Dermatopathol*, 1990; **12:** 417–21.

[25] Groenen G, Janssens L, Kayembe T, Nollet E, Coussens L, Pattyn SR. Prospective study on the relationship between intensive bactericidal therapy and leprosy reactions. *Int J Lepr*, 1986; **54:** 236–44.

[26] *Consensus development statement on the chemotherapy of leprosy*. ALM International, 1992.

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Nerve damage in leprosy: an epidemiological and clinical study of 396 patients in west Nepal – Part 1. Definitions, methods and frequencies

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Summary A historic cohort study was performed to determine the prevalence and incidence rates of nerve function impairment (NFI) as demonstrated by sensory testing with a nylon monofilament and standard tests of motor function. The records of 396 new leprosy patients registering at Green Pastures Hospital, Pokhara, between January 1988 and January 1992 were analysed. The mean follow-up period was 21 months.

In all, 36% (141/396) of patients had either sensory or motor function impairment at their initial examination. For each nerve the prevalence of sensory and motor impairment is reported separately. The posterior tibial nerve was the most frequently affected (sensory) nerve (21%). Sensory impairment of the ulnar nerve was found in 17% of the patients; 8·8% had sensory impairment of the median nerve. The overall incidence rate of motor function impairment was 7·5 (5·4–10) per 100 person years at risk (PYAR). Sensory impairment had a significantly higher rate of 13 (10–17)/100 PYAR (rate ratio (1·8 (1·2–2·7), $p = 0{\cdot}0076$). Bl patients had a significantly higher incidence rate of nerve function impairment than BT patients (rate ratio 2·3 (1·4–3·7), $p = 0{\cdot}006$). Altogether 152/396 (39%) of the patients required corticosteroid treatment for 'recent' or 'acquired' impairment, and 78 of the patients (20%) developed severe nerve function impairment during or after antileprosy treatment. Analysis of potential risk factors for nerve function impairment showed a significant association with the extent of clinical disease expressed as the number of body areas (out of 9) with primary or secondary signs of leprosy (rate ratio 5·0 (1·5–17), $p = 0{\cdot}0091$).

It was concluded that nerve function impairment is a serious problem, often occurring during or after multidrug therapy. The extent of clinical disease expressed as a count of body areas involved, or of skin or nerve lesions may identify patients who are at increased risk of nerve damage.

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Introduction

Leprosy is a disease of the peripheral nervous system and most of the serious complications are due to peripheral neuropathy.[1–3] As Naafs stated: 'Leprosy would be a rather innocent skin disease were it not for the nerve damage and subsequent loss of sensation and muscle power and secondary ulcerations and deformities, which make the leprosy patient an outcast from society.'[4]

Mycobacterium leprae is the only known bacillus able to invade the peripheral nervous system. It is said to be the most common cause of treatable peripheral neuropathy in the world,[5] but there are surprisingly few studies of the epidemiology of peripheral neuropathy in leprosy. Amongst these are reports from Bell-Krotoski[6] on 'Nerve Involvement in Leprosy', McLeod *et al.*[7] on nerve conduction velocity results, Duncan & Pearson[8] describing nerve function impairment (NFI) among pregnant and lactating women, and Becx-Bleumink *et al.*[9,10] on nerve damage detected among control programme patients.

Despite much basic neuropathological research in the 1960s, 1970s and early 1980s, particularly by Weddell *et al.*,[11] Boddingius,[12–14] Antia *et al.*,[15–18] Dastur *et al.*,[19,20] Chopra *et al.*,[21] Job,[22] Sabin[23,24] and Swift,[25] many clinicoepidemiological questions remain unanswered. These include defining methods of detecting treatable neuropathy, and of preventing neural impairment, as well as means of improving the treatment of neuropathy of recent onset.

Green Pastures Hospital (GPH) is a 100-bed mission hospital in Pokhara, West Nepal, run by the International Nepal Fellowship (INF) under its Leprosy Control Project (LCP), a joint project with His Majesty's Government/Nepal (HMG/N). GPH is the main leprosy referral hospital for the West of Nepal. Good record keeping with fairly standardized methods of assessment have provided data for this retrospective study of the incidence of peripheral neuropathy and reactions in leprosy.

The aims of the present study were to determine:

the prevalence and classification of neural impairment by age and sex, and in specific nerves, at the time of registration;
the incidence rate of neural impairment, occurring during and after anti-leprosy treatment; and
to identify risk factors which are of prognostic value.

Definitions

Considerable difficulty in studying the peripheral neuropathy in leprosy, and in comparing the results of treatment, is caused by confused terminology and incomplete reports of the methods used (Charosky *et al.*[3]). Unfortunately these defects have persisted. To facilitate comparison with other related studies, the terms used are defined below.

NERVE INVOLVEMENT

May be defined as 'anything from the presence of a leprosy bacillus in a nerve to the total

destruction of the nerve.[26] In the former case the nerve is affected before this can be detected by ordinary physical examination.[7,27]

PERIPHERAL NEUROPATHY

A general neurological term indicating, 'Any disorder that causes structural damage to nerve fibres within the peripheral nervous system'.[28] It does not indicate the aetiology or nature of the disorder or disease. Early in the disease process the 'damage' may be functional rather than structural.

NERVE DAMAGE

An imprecise but common term for 'neuropathy', which is also used in relation to trauma. Here it indicates clinical or subclinical damage to a nerve, whether reversible or irreversible.

NEURITIS

A condition in which inflammatory cells are found in the nerve.

ACUTE NEURITIS

A clinical term, used here to mean: acute inflammation of a peripheral nerve trunk detectable by swelling and/or functional impairment (NFI, see below) with spontaneous nerve pain and/or nerve tenderness on palpation. Nerve pain or tenderness may or may not be accompanied by paraesthesia.

SILENT NEUROPATHY (SN)

A clinical term used for neuropathy with neural impairment but without the other clinical signs and symptoms of acute neuritis. In this paper it refers to those episodes of neuropathy that cause clinical nerve damage within a period of days or weeks and not to the chronic destructive neuropathy of leprosy.

NERVE FUNCTION IMPAIRMENT (NFI)

Clinically detectable impairment of motor, sensory or autonomic function.

NERVE PAIN

Spontaneous pain in the distribution of a peripheral nerve trunk either at rest or during movement of the affected limb.

NERVE TENDERNESS

Pain in a peripheral nerve trunk elicited by palpation of the nerve, which was considered to be significant only if it was spontaneously mentioned by the patient or if it could be 'seen' on the patient's face.

PARAESTHESIA

Symptoms of tingling, 'pins and needles', burning or 'electrical' sensations in areas supplied by the affected peripheral nerve.

ANAESTHESIA OR HYPOAESTHESIA

Complete or partial impairment of tactile sensibility.

VOLUNTARY MUSCLE TESTING (VMT)

A manual test assessing the strength of individual muscles or groups of muscles in the upper and lower extremities.

SENSORY TEST (ST)

Use of this term includes the 'ballpen test' or use of a piece of thin paper, a feather, a wisp of cottonwool or nylon (mono)filaments, for light touch or the 'pin-prick test' for pain sensation.[29] It would be preferable to use the name of the actual test used.

SENSIBILITY TESTING

The testing of any sensory modality. The following separate modalities are nowadays recognized: static touch, moving touch/vibration sense, pain, and temperature.

IMPAIRMENT

This is defined as, 'Any loss or abnormality of psychological, physiological, or anatomical structure or function.'[30]

DISABILITY

'Any restriction or lack (resulting from impairment) or ability to perform an activity in the manner as within the range considered normal for a human being'.[30]

HANDICAP

'A disadvantage for a given individual resulting from an impairment or disability, that limits or prevents fulfilment of a role that is normal, depending on age, sex and social and cultural factors for the individual.'[30]

DEFORMITY

Secondary structural changes of the eye, hand or foot resulting from impairment of

sensory, autonomic and/or motor nerve function: joint stiffness, bone absorption, and mechanical imbalance such as 'clawing'.[16]

Methods

OUTCOME MEASURES

The number of patients with peripheral neuropathy as evidenced by clinical signs of motor and/or sensory impairment.

The number of patients developing nerve function impairment at any stage during or after treatment.

The association between leprotic neuropathy and age, sex, classification, extent of disease (no. of skin lesions, nerves and body areas involved in the disease), phenolic glycolipid-1 (PGL-1) serology results and antileprosy treatment regimens (multidrug therapy (MDT) *vs* dapsone (DDS) monotherapy).

DIAGNOSIS AND CLASSIFICATION

Methods of diagnosis, classification, using both the Ridley–Jopling classification, as well as our 'body area classification system', laboratory examinations and histology have been described in detail in a previous paper.[31]

DEFINITION OF NERVE FUNCTION IMPAIRMENT (NFI)

A patient was considered to have nerve function impairment if there was a deterioration of >2 points in his VMT score, or 2 points or more in his TST score compared to the previous result. NFI of less than 6-month's duration was recorded as 'recent', while impairment of longer duration was recorded as 'old'. If no previous VMT and TST results were available the patient's history was used to determine whether the impairment was 'recent' or 'old' (using the same numeric criteria for VMT/TST deterioration as mentioned above).

NERVE FUNCTION ASSESSMENT (NFA)

A NFA was done by either of 2 trained physiotechnicians at the first examination, at every visit as an outpatient, at annual examinations during treatment and after release from treatment. For patients receiving treatment for a reaction or nerve function impairment that was performed fortnightly.

VOLUNTARY MUSCLE TEST

A full VMT was performed using the modified MRC scale[32] as described by Brandsma.[33] The VMT score consisted of the sum of individual scores (0–5; 0, paralysed; 5, normal strength) for certain muscles innervated by the:

Facial nerve; orbicularis oculi (only)—max score 5: ulnar nerve; first dorsal interosseus ('index finger out') and abductor digiti minimi ('little finger out')—max score 10: median

nerve; abductor pollicis brevis and opponens pollicis ('thumb up')—max score 10: radial nerve; extensor carpi ulnaris ('wrist up') and extensor digitorum communis (extension of metacarpophalangeal joints)—max score 10: lateral popliteal nerve; extensor hallucis longus and peroneus longus and brevis ('lateral foot up')—max score; 10.

If any particular muscle could not be tested, e.g. because of joint stiffness or previous surgery, or if test data were not available for any particular follow-up time, the other findings from that occasion were excluded from the analysis.

TOUCH SENSIBILITY TEST (TST)

Touch sensibility of skin sites (see below) innervated by the ulnar and median nerves was tested using a nylon monofilament giving a force of approximately 10 g when pressed until it bent. The result was recorded as 'felt' or 'not felt' for each of the sites mentioned below. If the patient sometimes felt the touch and sometimes not, the result was recorded as 'partial'. Touch sensibility of the posterior tibial nerve was tested in a similar way using a thicker monofilament, giving a force of about 75 g. The TST score consisted of the sum of touch sensibility test scores given for individual sites (2, monofilament felt; 1, doubtful; 0, monofilament not felt); the number of sites depending on the nerve tested:

Ulnar nerve; 3 sites on the pulp of the little finger, over the MCP 5 joint and on the hypothenar eminence respectively—max score 6: median nerve; 4 sites on the pulp of the thumb, over the MCP 2 joint, the pulp of the index and middle finger respectively—max score 8: posterior tibial nerve; 10 sites on the footsole: on the tip of each toe, over the MTP 1 and 5 joints, the instep, the lateral border and the heel—max score 20.

If there was an ulcer on the test site a score of 0 was given for that site. If the number of sites for any particular nerve was not complete, e.g. if a digit was missing, the score was recorded as a missing value. Missing data were handled as described above.

CRITERIA FOR INCLUSION AND EXCLUSION OF PATIENTS

All new, previously untreated patients who registered for treatment in the GPH during the period January 1988 to January 1992 were included in the study. Patients whose treatment for reaction/neuropathy was started elsewhere more than 1 week before arrival the GPH were excluded.

STATISTICAL METHODS

The significance of the difference between proportions was tested using the Standard Normal Deviate (SND) for unpaired samples and McNemar's paired χ^2 test for paired samples.[34] The significance of an association between nerve function impairment and any risk factor was examined with Cox' proportional hazards regression and is expressed as rate ratios. Incidence rates were calculated as the number of patients developing new nerve function impairment during the follow-up period divided by the cumulative person years at risk. Patients were censored as soon as new impairment had occurred. For patients for whom the exact time between registration and onset of neural impairment was not known it was assumed that it had occurred half way during their follow-up

period. Patients lost to follow-up due to death, defaulting or transferral only contributed person years to the denominator for as long as they were still followed up. Significance of the difference between rates was calculated using the appropriate SND test. A p-value of less than 5% was used as level of statistical significance. For the most important proportions or ratios the 95% confidence interval is given in parentheses after the ratio, e.g. 4·1 (2·1–8·2), means that there is 95% chance that the ratio actually lies between the values 2·1 and 8·2. We used Epi Info Software, version 5·01,[35] for analysis.

Results

PATIENTS

We included 396 new patients in the study. The mean age was 41 years (range 2–88, standard deviation 16); 277/396 were male. Only 335 patients were available for follow-up (the remainder were transferred elsewhere after diagnosis). Their average follow-up time was 21 months (range 1–49), 71 patients were taking dapsone monotherapy, 256 and 68 were on or had been released from WHO multidrug therapy (MDT),[29] for multibacillary and paucibacillary patients, respectively, and 1 patient was on a different multidrug regimen.

NERVE FUNCTION IMPAIRMENT

Table 1 shows the prevalence at first examination of motor and sensory impairment in the Ridley–Jopling classification subgroups. This is illustrated in Figure 1. The only 2 TT and 7 BB patients had no NFI and are therefore not included in Figure 1. In all patients, except the pure neuritic (PN) patients, the prevalence of sensory impairment was a little higher than motor impairment (overall 29% *vs* 24%, respectively). This difference was not significant at the 5% level ($p = 0{\cdot}11$, SND test).

Incidence rates are shown in Table 2 and Figure 2. BL patients had a significantly higher rate than BT patients (29 *vs* 12/100 person years at risk (PYAR), rate ratio 2·3

Table 1. Prevalence of nerve function impairment at first registration in 396 previously untreated patients at Green Pastures Hospital

		Motor impairment		Sensory impairment		Either	
Classification	Total patients	Number affected	Prev (%) (95% CI)[a]	Number affected	Prev (%) (95% CI)	Number affected	Prev (%) (95% CI)
TT	2	0		0		0	
BT	202	49	24 (18–30)	59	29 (23–35)	69	34 (28–41)
BB	7	0					
BL	133	37	28 (20–35)	45	34 (26–42)	56	42 (34–50)
LL	42	6	14 (3·7–25)	10	24 (11–37)	11	26 (13–39)
PN	10	4	40 (9·6–70)	2	20 (0–45)	5	50 (19–81)
Total	396	96	24 (20–28)	116	29 (25–34)	141	36 (31–40)

[a] Prevalence per 100 patients +95% confidence interval.

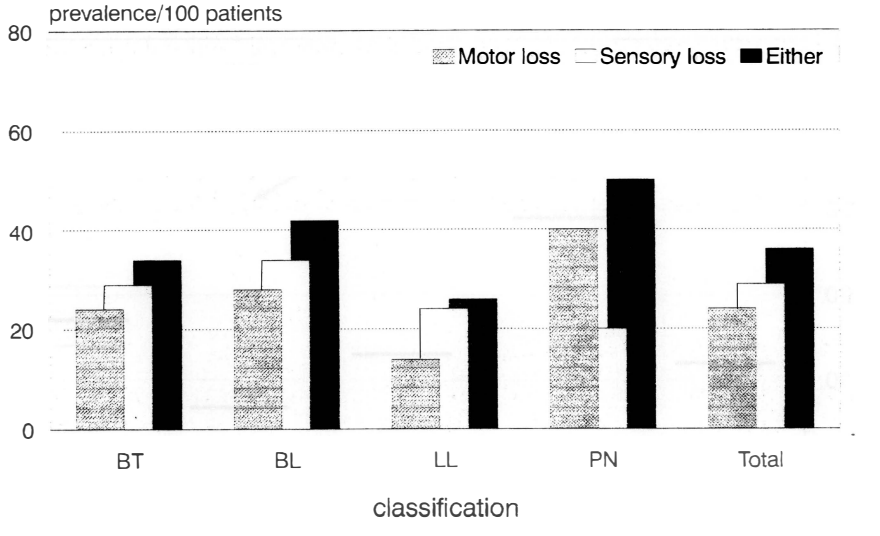

Figure 1. Prevalence of nerve function impairment at first registration ($n = 387$; TT and BB patients have been omitted). Either = motor and/or sensory impairment.

(1·4–3·7), $p = 0·0076$). The rate-difference between BL and LL patients was not significant at the 5% level (29 *vs* 13/100 PYAR, $p = 0·12$). Sensory impairment occurred more frequently than motor impairment (rate ratio 1·8 (1·2–2·7), $p = 0·0076$).

The prevalence of NFI for each separate nerve at the first examination is shown in Table 3. The posterior tibial nerve was the most frequent affected nerve, if only sensibility is considered (21 *vs* 17% for the ulnar nerve). We did not assess the motor function of the posterior tibial nerve (intrinsic muscles of the foot) on a regular basis, but subjectively it seems that the secondary effects of posterior tibial motor weakness or paralysis, namely clawtoes and loss of foot arches, are also very common.

Table 2. Incidence rates of nerve function impairment in 335 previously untreated patients at Green Pastures Hospital. The mean follow-up time was 21 months

	Motor impairment		Sensory impairment		Either	
Classification	Incident cases	Rates[a] (95% CI)[b]	Incident cases	Rates (95% CI)	Incident cases	Rates (95% CI)
TT	0		0		0	
BT	14/170	5·1 (3·0–8·7)	28/182	10 (7·1–1·15)	34/182	12 (8·9–17)
BB	1/4[c]		3/4[c]		3/4	
BL	14/106	12 (6·9–20)	27/106	22 (15–33)	35/106	29 (21–40)
LL	4/31	10 (3·8–27)	2/31	5·1 (1·3–21)	5/31	13 (5·3–31)
PN	1/10	6·7 (0·9–47)	1/10	6·7 (0·9–47)	1/10	6·7 (0·9–47)
Total	34/335	7·5 (5·4–10)	61/335	13 (10–17)	78/335	17 (14–21)

[a] Incidence rates per 100 person years at risk; [b] 95% confidence interval; [c] the numbers in the BB group were too small to calculate any meaningful rates.

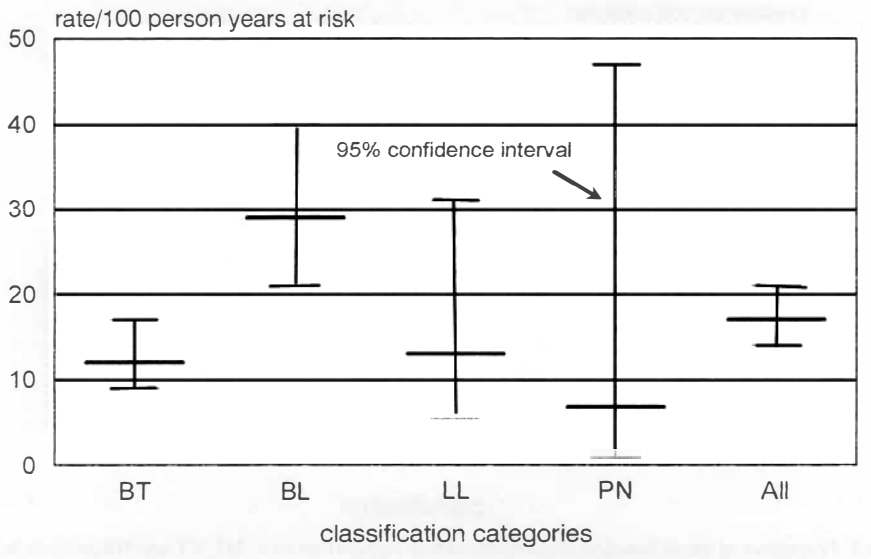

Figure 2. Incidence rates of nerve function impairment in 335 leprosy patients (PN, pure neuritic leprosy). TT cases (2) and BB cases (4) were omitted because no meaningful rates could be calculated.

In 3/792 median nerves (0·4%) and 16/792 ulnar nerves (2·0%) only motor function impairment could be detected (data not shown), and 7 median nerves (0·9%) and 16 ulnar nerves (2·0%) had sensory impairment only.

Figure 3 illustrates the prevalence of impairment in individual nerves at registration.

TIME OF ONSET

Table 4 shows the distribution of patients with nerve function impairment according to the time of onset of the impairment. All together 152/396 (39%) of patients required

Table 3. Prevalence at first registration of nerve function impairment in individual nerves. The numbers in the table refer to patients rather than nerves

	Motor impairment				Sensory impairment			
Nerve	One side only (%)	Both (%)	Total	Prevalence (%)[a]	One side only (%)	Both (%)	Total	Prevalence (%)
Facial	11 (2·8)	11 (2·8)	22	5·6 (3·3–7·8)				
Ulnar	54 (14)	27 (6·8)	81	20 (16–24)	39 (9·8)	30 (7·6)	69	17 (14–21)
Median	7 (1·8)	8 (2)	15	3·8 (1·9–5·7)	22 (5·6)	13 (3·3)	35	8·8 (6·0–12)
Radial	4 (1·0)	0	4	1·0 (0·03–2)				
Lat. Popliteal	16 (4)	3 (0·8)	19	4·8 (2·7–6·9)				
Posterior Tibial					35 (8·8)	50 (13)	85	21 (17–26)

Data on the sensory function of the lateral popliteal nerve and the motor function of the posterior tibial nerve were not collected. [a] Prevalence per 100 patients + 95% confidence interval.

Table 4. Number of patients in different 'onset of nerve function impairment' categories

Category of NFI	Number	%
None	181	46
Old[a]	63	16
Recent[b]	74	19
Acquired[c]	78	20
Total	396	100

[a] Onset >6 months ago at the time of registration; [b] onset <6 months ago at the time of registration; [c] nerve function impairment detected during or after treatment that was not present at the time of registration.

steroid treatment for nerve function impairment during or after their antileprosy treatment.

RISK FACTORS

Among the patients developing new NFI after the start of antileprosy treatment, no significant difference in risk was found between those on MDT and those on DDS. Table 5 summarizes the significance of individual risk factors in relation to the incidence of nerve impairment. There was no association between incidence of NFI and age of registration, sex, PGL-1 antibody titre or bacteriological index of the patient.

Table 5. Risk factors for nerve function impairment occurring after the start of antileprosy treatment among 335 new patients in Green Pastures Hospital

Risk factor	Category of patients	Rate ratio[a] (95% CI)[b]	*p*-value
Sex	all	1·1 (0·63–1·8)	0·79
Treatment (MDT vs. DDS)[c]	all	0·56 (0·27–1·1)	0·11
Extent of clinical disease:			
>10 skin lesions	all	3·2 (1·4–7·1)[d]	0·0044
>3 nerves enlarged	all	3·3 (1·4–8·0)[d]	0·0082
>2 body areas involved	all	5·0 (1·5–17)	0·0091
	B[e]	6·6 (1·6–29)	0·011
bacteriological index	all	1·6 (0·85–2·9)	0·11
PGL-1	B[e]	0·92 (0·51–1·7)	0·77

[a] Rate ratio adjusted for the simultaneous influence of age, sex, treatment, bacteriological index, phenolic glycolipid-1 antibody (PGL-1) titre and body area count; [b] 95% confidence interval; [c] multidrug therapy versus dapsone monotherapy; [d] rate ratio adjusted for the simultaneous influence of age, sex, treatment, bacteriological index, and PGL-1 titre; [e] borderline patients; [f] PGL-1 titre (> 0·199 = positive).

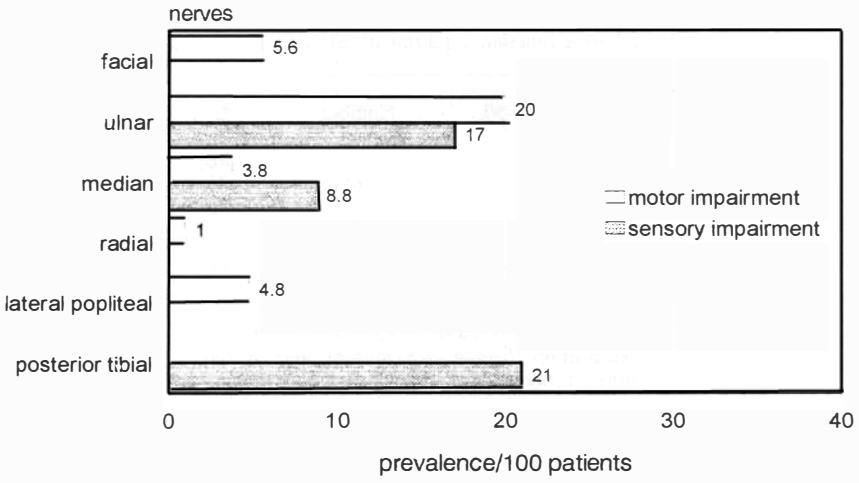

Figure 3. Prevalence of impairment at first registration in individual nerves in 396 new leprosy patients in Green Pastures Hospital. Data on the sensory function of the lateral popliteal nerve and the motor function of the posterior tibial nerve were not collected.

Unfortunately, data on pregnancy and lactation were not systematically recorded and therefore valid analysis of these risk factors was not possible.

The extent of clinical disease expressed as the number of body areas (out of 9) with primary or secondary signs of leprosy,[31] was a highly significant risk factor for developing neural impairment. The rate ratio of NFI for patients with >2 body areas involved in the disease ('extensive disease') compared to those with 2 or less was 5·0 (1·5–17, $p = 0{\cdot}0091$), i.e. the risk of developing impairment for patients with >2 body areas involved was 5 times higher than the risk for patients with only 1 or 2 body areas involved. Using skin lesion counts and taking 10 lesions as the cut-off point, the rate ratio was 3·2 (1·4–7·1, $p = 0{\cdot}0044$) for patients with 'extensive' disease. These rate ratios are illustrated in Figure 4.

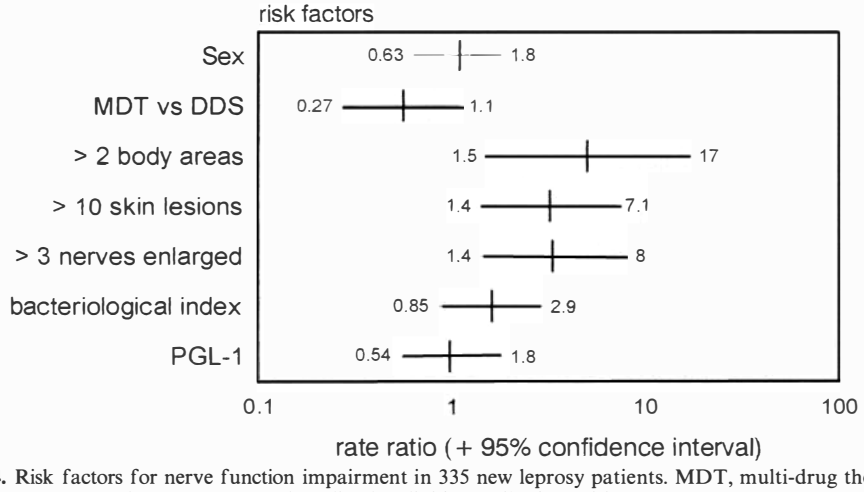

Figure 4. Risk factors for nerve function impairment in 335 new leprosy patients. MDT, multi-drug therapy; DDS, dapsone monotherapy; PGL-1, phenolic glycolipid-1 antibody positive.

Discussion

The peripheral neuropathy of leprosy has been neurologically classified by several investigators as a 'mononeuritis multiplex',[36–38] because there is a widespread, bilateral, but not homogeneous or systemic neuropathy involving both the sensory and motor fibre systems. A part of the nerve may show extensive destruction, while a nearby section of the same nerve may have a histopathologically normal appearance.[19,20] The neuropathy begins very early in the disease process and progresses to a considerable extent with destruction of Schwann cells and segmental demyelination, as well as extensive regeneration and re-myelination, even before the immune system becomes involved.[15,16,39] Once the immune response is initiated, inflammatory processes with destruction through granuloma formation, intraneural oedema and ischaemia dominate the pathophysiological picture.[1,22,26] It is clear from the available pathological evidence that extensive neuropathy is already present before the patient notices any signs and symptoms of nerve function impairment. The NFI discussed below is therefore only the 'tip of the iceberg' of the peripheral neuropathy of leprosy. Concerning our data in this study, it should be born in mind that our nerve function assessment instruments were crude, particularly for sensibility testing, and that, therefore, the true prevalence and incidence in these patients is likely to be higher than reported here.

Table 6. Comparison of publications on the prevalence of sensory nerve function impairment in leprosy

Author (new or treated patients, or mixed)	Type of patients	Testing methods	Nerves examined	Prevalence of nerve function impairment by classification (%)					
				TT	BT	BB	BL	LL	Overall
Brunel *et al.*[62] (treated)	25 Tuberculoid 18 Borderline 57 Lepromatous	2PD[a]	all ulnar median ulnar + median	20	15			65	54 21 6 71
Dorairaj *et al.*[42] (mixed)	100 in-patients (IP) 100 village patients (VP)	TST (mf)[b]	post.tib.						IP 78 VP 63
Becx-Bleumink & Berhe[10] (treated)	161 field patients with recent (<6 months) NFI	TST (bp)	SNFI[c] ulnar median post.tib.						49 44 36 68
Bell-Krotoski[6] (treated)	221 community-based hospital outpatients (CBP)	TST (mf)	CBP(S)	55	50	50	75	75	67
Brown *et al.*[41] (treated)	35 hospital outpatients 3 TT, 13 BT, 2 BB, 11 BL, 6 LL	TST (mf) SNC[c]	ulnar, TST SNC median, TST SNC radial, TST SNC						29 54 13 29 29 37
van Brakel & Khawas (new)	Hospital outpatients (new) 2 TT, 202 BT, 7 BB, 133 BL, 42 LL, 10 PN	TST (mf)	SNFI ulnar(S) median(S) post.tib (S)	0	29	0	34	24	29 17 8·8 21

[a] 2PD, 2-point discrimination (static); [b] mf, monofilament: 1 or more graded nylon monofilaments; bp, ballpoint pen; [c] SNFI, sensory nerve function impairment; [d] SNC, sensory nerve conduction testing (including velocity, amplitude and latency).

Table 7. Comparison of publications on prevalence of motor nerve function impairment in leprosy

Author (new or old patients, or mixed)	Type of patients	Testing methods	Nerves examined	Prevalence of nerve function impairment by classification (%)					
				TT	BT	BB	BL	LL	Overall
Magora *et al.*[63] (new?)	20 Indeterminate 8 Tuberculoid 8 Dimorphous 67 Lepromatous	MCV[a]	ulnar, 206[b] median, 77 radial, 46 lat.pop, 108						26 13 6·5 16
Becz-Bleumink & Berhe[10] (treated)	161 field patients with recent (< 6 months NFI)	VMT (s)[c]	MNFI facial ulnar median lat.pop						23 29 39 15 11
Bell-Krotoski[6] (treated)	221 community-based hospital outpatients (CBP)	VMT (l)	CBP	55	60	65	70	70	65
Brown *et al.*[41] (treated)	35 hospital outpatients 3 TT, 13 BT, 2 BB, 11 BL, 6 LL	VMT (l) MNC[d]	ulnar, VMT MNC median, VMT MNC radial, VMT						30 37 13 20 10
van Brakel & Khawas (new)	Hospital patients (new) 2 TT, 202 BT, 7 BB, 133 BL, 42 LL, 10 PN	VMT (l)	MNFI facial ulnar median radial lat.pop	0	24	0	28	14	24 5·6 20 3·8 1·0 4·8

[a] MCV, motor nerve conduction velocity testing; [b] the numbers refer to the number of nerves tested; [c] l, 'long' VMT, using 0–5 MRC scale; s, 'short' VMT, using only the categories 'strong', 'weak' and 'paralysed; [d] MNC, motor nerve conduction testing (including velocity, amplitude and latency).

THE PREVALENCE AND INCIDENCE OF NERVE FUNCTION IMPAIRMENT

The published studies of an epidemiological nature on the occurrence of NFI in leprosy that deal with bigger numbers of patients are summarized in Tables 6 and 7. There is considerable variance between the results due to differences in methods of testing, criteria for selection of patients (often not mentioned), etc.

The prevalence of ulnar, median, lateral popliteal and posterior tibial impairment found by Becx-Bleumink & Berhe[10] was understandably higher than in the present study since they report on a select group of treated patients with nerve function impairment. Overall motor impairment prevalence in the former study was 23% *vs* 24% in ours. These similar results may be explained by the fact that our study used a more detailed VMT, detecting more motor impairment than the short field VMT used in the Ethiopian study. Srinivasan *et al.*[40] found 46·7% motor impairment in 373 ulnar nerves.

Brown *et al.*, testing with graded nylon monofilaments, reported a prevalence of sensory impairment of 29% for ulnar and 13% for median nerves.[41] This is appreciably more than in our study, probably due to the fact that Brown *et al.* used graded monofilaments, which are much more sensitive than the single filament we used. Dorairaj *et al.* found 63% posterior tibial impairment among village patients,[42] which is very similar to the 68% found by Becx-Bleumink.

The incidence of neural impairment was higher in BL patients than in BT patients. This may be due to the increased risk of reversal reactions among BL patients that has

been observed in Ethiopian patients and also in ours.[10,43] We are not aware of any other studies reporting the incidence rates of neural impairment, so no direct comparisons could be made.

RISK FACTORS

One of the most significant findings of this study is that extensive clinical disease, expressed as 'number of body areas involved' or as a count of skin or nerve lesions, carries a much higher risk of developing nerve function impairment than limited disease. For NFI occurring after the start of antileprosy treatment this risk was increased up to 5 times. This means that new patients with extensive disease (> 2/9 body areas involved, and/or > 10 skin leasions and/or > 3 nerves enlarged) should be given appropriate health education, encouraging them to come back for examination immediately should any signs or symptoms of NFI or neuritis occur. Their nerve function should be carefully monitored at every clinic visit.

NERVE FUNCTION ASSESSMENT

Our ability to detect peripheral neuropathy obviously depends on the sensitivity of the instruments used during the NFA. In Nepal many field staff believed until recently that motor function was more important than sensibility, so if any assessment was carried out, it was only a crude field VMT. The importance of sensibility was well-illustrated by Moberg[44] when he called touch sensibility or 'tactile gnosis' the 'eyes of the hands'. Without it the hands are 'blind' and therefore severely disabled, and prone to trophic ulceration. The current results underline the importance of the testing of sensibility as the incidence of sensory impairment was almost twice as high as the incidence of motor impairment. Sensory testing in the field is usually done with the 'ballpen test', as recommended by Jean Watson.[45] This test and the field VMT certainly brought a great improvement to many field programmes where no NFA was done at all, but these tests as well as our 10-g and 75-g monofilaments are not sensitive enough to detect early NFI.

There are 3 areas which are of particular importance in the assessment of nerve function in leprosy:

Early detection of NFI

This is based on the assumption that early detection will lead to improved treatment prognosis. It has been shown that motor and sensory nerve conduction velocity measurements are able to pick up NFI before it becomes clinically evident.[7,46] Brown *et al.* found up to twice as much neural impairment with nerve conduction testing as with manual tests of sensibility and motor function.[41] Other modern advanced techniques that have been reported to be sensitive in diagnosing NFI in leprosy include radio-isotopic scintillography in a gamma camera,[3] vibrometry,[47] and the use of a laser Doppler flow meter.[48] A range of simple but useful neurological tests is available that could be used even under field conditions.[49]

Many of our patients who had 'normal' sensibility when measured with the previously used 10-g monofilament already had advanced impairment of touch sensibility when tested with the graded Semmes–Weinstein monofilaments, where the

force for 'normal' is 200 mg (data not shown). The use of graded nylon monofilaments has been found to be a sensitive and repeatable method to detect early nerve damage and to monitor the response of NFI to treatment.[49–52] It would greatly facilitate comparison of study results if the filaments and testing technique used would be standardized. A detailed description of the 'state of the art' of this testing method was given by Bell-Krotoski.[53]

Although epidemiological evidence is lacking it seems reasonable, on the basis of the histopathological evidence,[54] to believe that autonomic function and temperature discrimination, mediated by small, unmyelinated fibres, may be affected first. Reliable and repeatable testing of these modalities remains difficult, but has become possible with electronic instruments.[48,55] These instruments could also be of help for the so important testing of validity and reliability of NFA instruments.[56]

Protective sensibility

Although detection of early NFI is very important from the point of view of treatment/prevention, it is of great practical importance to know whether a patient has residual protective sensibility in hands or feet. Discussion of what constitutes protective sensibility is beyond the scope of this paper. The level of residual protective sensibility, expressed as touch sensibility thresholds, has been found to be 2 g in the hand,[57] and about 10 g in the foot.[47,58]

The patient's point of view

From a patient's point of view there are three conditions affecting the quality of life that are of major importance. The presence or absence of uncomfortable symptoms, like paraesthesia and shooting pains, physical deformities, and the (dis-)ability to function normally. If such adverse conditions can be cured or prevented, or at least minimized, the patient will be satisfied with his treatment. Therefore, the prevention of impairments and disabilities should be a priority of treatment. Effective antibacterial treatment is essential, but several investigators[10,59–61] have suggested that powerful bactericidal therapy might increase the risk of severe reactions and NFI. The current study revealed no differences in the risk of developing NFI between patients on MDT and those on dapsone monotherapy. However, caution is necessary. New and even stronger anti-bacterial drug combinations, which do not contain clofazimine, should be carefully monitored for incidence of NFI compared with other standard regimens. More data on the epidemiology of nerve function impairment and reactions in leprosy under current treatment regimens are therefore urgently needed.

The data in this paper refer to a self-selected group of hospital outpatients who are likely to be at higher risk of NFI than the whole leprosy 'patient population' which they are a part of. The prevalence and incidence figures can, therefore, only be generalized to referral centres and not to field programmes. The risk indicators should be valid even under field conditions, although confirmation of this is needed. Whatever the true rates in the population, it is evident that neural impairment is a frequent complication of leprosy, even after effective antileprosy treatment has been initiated. Regular assessment of nerve function should be a regular part of the management of every leprosy patient, particularly of those identified to be at increased risk.

Conclusions

With the nerve function assessment instruments used in this study about 33% of our patients were found to have sensory and/or motor impairment at first examination.

An additional 78 (20%) developed severe NFI during or after their antileprosy treatment in a mean follow-up period of 21-months. NFI is thus not an infrequent complication affecting patients on regular antileprosy treatment.

Risk of developing nerve function impairment was increased in patients who had more extensive clinical disease (> 2/9 body areas involved or > 10 skin lesions).

Further epidemiological studies on peripheral neuropathy in leprosy, validation of NFA instruments, and trials and improved protocols for the treatment and prevention of NFI are urgently needed.

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References

[1] Ridley DS, Job CK. The pathology of leprosy. In: Hastings RC (ed) *Leprosy*. Edinburgh: Churchill Livingstone, 1985.

[2] Antia NH. Some newer approaches to the study of nerve damage in leprosy. In: *Proceedings*, XII International Leprosy Congress. New Delhi, 1984: 435–8.

[3] Charosky CB, Gatti JC, Cardama JE. Neuropathies in Hansen's disease. *Int J Lepr*, 1983; **51:** 576–86.

[4] Naafs B. Leprosy Reactions. *Quad Coop San*, 1992; **12:** 67–72.

[5] McLeod JG. Peripheral nerve lesions. *Med Int*, 1992; **5** (18): 4191–7.

[6] Bell-Krotoski JA. A study of peripheral nerve involvement underlying physical disability of the hand in a Hansen's disease population. *J. Hand Ther*, 1992; **5:** 133–42.

[7] McLeod JG, Hargrave JC, Walsh JC, Booth GC, Gye RS, Barron A. Nerve conduction studies in leprosy. *Int J Lepr*, 1975; **43:** 21–31.

[8] Duncan ME, Pearson JMH. Neuritis in pregnancy and lactation. *Int J Lepr*, 1982; **50:** 31–8.

[9] Becx-Bleumink M, Berhe D, 'T Mannetje W. The management of nerve damage in the leprosy control services. *Lepr Rev*, 1990; **61:** 1–11.

[10] Becx-Bleumink M, Berhe D. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the Leprosy Control Program of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Ethiopia. *Int J Lepr*, 1992; **60:** 173–84.

[11] Weddell G, Jamison D, Palmer E. Recent investigations into the sensory and neurohistological changes in leprosy. In: *Leprosy in Theory and Practice*. Cochrane RG (ed). Bristol: John Wright & Sons, Ltd, 1959: 96–113.

[12] Boddingius J. Ultra-structural changes in blood vessels of peripheral nerves in leprosy patients (tuberculoid and borderline-tuberculoid). *Acta Neuropath*, 1976; **35:** 159–81.

[13] Boddingius J. Ultra-structural changes in blood vessels of peripheral nerves in leprosy patients (Borderline, Borderline-lepromatous, Lepromatous). *Acta Neuropath*, 1977; **40:** 21–39.

[14] Boddingius J. Ultra-structural and histophysiological studies on the blood nerve barrier and perineural barrier in leprosy neuropathy. *Acta Neuropath*, 1984; **64:** 282–96.

[15] Anita 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.
[16] Shetty VP, Mehta LN, Irani PF, Antia NH. Study of the evolution of nerve damage in leprosy: part I—lesions of the index branch of the radial cutaneous nerve in early leprosy. *Lepr Ind*, 1980; **52:** 5–18.
[17] Shetty VP, Vidyasagar PB, Antia NH. Study of the evolution of nerve damage in leprosy: part III—sciatic nerve lesions in mice inoculated with *M. leprae* with nerve conduction velocity correlates. *Lepr Ind*, 1980; **52:** 26–47.
[18] Vidyasagar PB, Damle PS, Antia NH. A study of the sciatic nerve compound action potential *in vitro* in normal and *M. leprae* infected mice. *Lepr Ind*, 1981; **53:** 537–54.
[19] Dastur DK, Pandya SS, Antia NH. Nerves in the arm in leprosy. *Int J Lepr*, 1970; **38:** 30.
[20] Dastur DK. Pathology and pathogenesis of predilective sites of nerve damage in leprous neuritis. Nerves in the arm and the face. *Neurosurg Rev*, 1983; **6:** 139–52.
[21] Chopra JS, Kaur S, Murthy JMK, Radhakrishnan K, Kumar B. Clinical, electrophysiological and teased fibre study of peripheral nerves in leprosy. *Ind J Med Res*, 1983; **77:** 713–21.
[22] Job CK. Nerve damage in leprosy. *Int J Lepr*, 1989; **57:** 532–9.
[23] Sabin TD, Ebner JD. Patterns of sensory loss in lepromatous leprosy. *Int J Lepr*, 1969; **37:** 239–48.
[24] Sabin TD. Temperature-linked sensory loss. A unique pattern in leprosy. *Arch Neurol*, 1969; **20:** 257–62.
[25] Swift TR. Peripheral nerve involvement in leprosy: quantitative histologic aspects. *Acta Neuropath*, 1974; **29:** 1–8.
[26] Pearson JMH, Ross WF. Nerve involvement in leprosy— pathology, differential diagnosis and principles of management. *Lepr Rev*, 1975; **46:** 199–212.
[27] Naafs B, Pearson JMH, Baar AJM. A follow-up study of nerve lesions in leprosy during and after reaction using motor nerve conduction velocity. *Int J Lepr*, 1976; **44:** 188–97.
[28] Notermans NC, Wokke JHJ, Jennekens FGI. Clinical work-up of the patient with a polyneuropathy. In: de Jong JMBV (ed), *Handbook of Clinical Neurology*. Elseviers Scientific Publishers B.V., 1991.
[29] *A Guide to Leprosy Control*. 2nd edition. WHO, 1988.
[30] World Health Organisation. *International classification of impairments, disabilities and handicaps*. Geneva: WHO, 1980.
[31] 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.
[32] Medical Research Council War Memorandum. *Aids to the investigation of peripheral nerve injuries*. (Memo no. 7), 2nd ed, London: HMSO, 1962.
[33] Brandsma W. Basic nerve function assessment in leprosy patients. *Lepr Rev*, 1981; **52:** 161–70.
[34] Armitage P, Berry G. *Statistical Methods in Medical Research*. 2nd ed. Oxford: Blackwell Scientific Publications, 1987: 121–4.
[35] 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.
[36] Verghese M, Ittimani KV, Satyanaran KR, Mathai R, Bhakthaviriam C. A study of the conduction velocity of the motor fibres of the ulnar and median nerves in leprosy. *Int J Lepr*, 1970; **38:** 271.
[37] Tzourio C, Henry P, Boucher P, Parent M, Millan J, Métral S. Lèpre lépromateuse: arguments clinique et électrophysiologiques en faveur d'une multinévrite axonale. *Act Lepr*, 1989; **7** (1): 51–6.
[38] Jennekens FGI, Jennekens-Schinkel. A. Neurological examination of patients suffering from leprosy: is it worthwhile? *Lepr Rev*, 1992; **63:** 269–76.
[39] Antia NH. Leprosy—a disease of the Schwann cell. *Lepr Ind*, 1982; **54:** 599–604.
[40] Srinivasan H, Namasivayam PR. Does entrapment neuropathy contribute to nerve damage in leprosy? *Ind J Med Res*, 1971; **59:** 1385–91.
[41] Brown RB, Kovindha A, Wathanadilokkokol U, Piefer A, Smith T, Kraft GH. Clinical assessment of early leprous neuropathy with electrophysiological correlation. Paper presented at the 14th International Leprosy Congress, Orlando, Florida, 1993. (Abstract no. 35 in 'Abstracts').
[42] Dorairaj A, Reddy R, Jesudasan K. An evaluation of the Semmes–Weinstein 6.10 monofilament compared with 6 nylon in leprosy patients. *Ind J Lepr*, 1988; **60:** 413–7.
[43] van Brakel WH, Lucas SB, Khawas IB. Reactions in leprosy: an epidemiological study of 386 patients in West Nepal. *Lepr Rev*, 1994; **65,** 190–203
[44] Moberg E. Objective methods of determining functional value of sensibility in the hand. *J Bone Jt Surg (UK)*, 1958; **40:** 454–66.
[45] Watson JM. *Essential action to minimise disability in leprosy patients*. The Leprosy Mission International. Stanley L. Hunt (Printers) Ltd, 1988.
[46] Hackett ER, Shipley DE, Livengood R. Motor nerve conduction velocity studies of the ulnar nerve in patients with leprosy. *Int J Lepr*, 1968; **36:** 282.
[47] Hammond CJ, Klenerman P. Protective sensation in the foot in leprosy. *Lepr Rev*, 1988; **59:** 347–54.

[48] Abbot NC, Beck JS, Samson PD, Butlin CR, Brown RA, Forster A, Grange JM, Cree IA. Impairment of fingertip vasomotor reflexes in leprosy patients and apparently healthy contacts. *Int J Lepr*, 1991; **59:** 537–47.
[49] Pearson JMH. The evaluation of nerve damage in leprosy. *Lepr Rev*, 1982; **53:** 119–30.
[50] 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 it's correlation with electrophysiologicic study. *Int J Lepr*, 1975; **43:** 256–64.
[51] Naafs B, Dagne T. Sensory testing: a sensitive method in the follow-up of nerve involvement. *Int J Lepr*, 1977; **45:** 364–8.
[52] Bell-Krotoski JA, Tomancik E. The repeatability of testing with Semmes–Weinstein Monofilaments. *J Hand Surg*, 1987; **12A:** 155–61.
[53] 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.
[54] Antia NH, Shetty VP, Mehta LN. Study of the evolution of nerve damage in leprosy: part IV—an assessment. *Lepr Ind*, 1980; **52:** 48–52.
[55] 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.
[56] Ewing Fess E. The need for reliability and validity testing in hand assessment instruments. *J Hand Surg*, 1986; **11A:** 621–3.
[57] Bell-Krotoski JA. "Pocket" filaments and specifications for the Semmes–Weinstein Monofilaments. *J Hand Ther*, 1990; Jan–Mar: 26–31.
[58] Birke JA, Sims DS. Plantar sensory threshold in the ulcerative foot. *Lepr Rev*, 1986; **57:** 261–7.
[59] Steenbergen GJ, Pfaltzgraff RE. Treatment of neuritis in borderline leprosy—a pilot trial. *Lepr Rev*, 1975; **46:** 115–8.
[60] Parkhe SM, Smith WCS, Samson PD, Solomon M. Sudden paralysis associated with multi-drug therapy—a cautionary tale. *Quad Coop San*, **9:** 380 (abstracts of the 13th International Leprosy Congress '88).
[61] Groenen G, Janssens L, Kayembe T, Nollet E, Coussens L, Pattyn SR. Prospective study on the relationship between intensive bactericidal therapy and leprosy reactions. *Int J Lepr*, 1986; **54:** 236–44.
[62] Brunel W, Schecter WP, Schecter G. Hand deformity and sensory loss due to Hansen's disease in American Samoa.
[63] Magora A, Sheskin J, Sagher F, Gonen B. The condition of the peripheral nerve in leprosy under various forms of treatment. *Int J Lepr*, 1970; **38:** 149–63.

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The role of antiperipheral nerve antibodies in nerve damage in leprosy¶

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Summary The objective of this study was to determine the role of antineural antibodies in leprosy. Indirect ELISA using antigen prepared from normal human peripheral nerves was carried out on the sera from 100 leprosy patients and 18 normal controls. In total, 9% of the patients had demonstrable levels of IgG antineural antibodies and 11% had demonstrable levels of IgM antibodies. There was no correlation with the type of leprosy, bacteriological index, treatment taken, the presence of a reactional state, the presence of enlarged nerves or active neuritis.

Introduction

The role of antineural antibodies in leprosy directed against peripheral nervous system components is, to date, inconclusive and controversial. There is always some degree of nerve damage throughout the whole spectrum of the disease. However, it has not always been possible to elucidate the exact pathogenesis of nerve damage in cases with neuropathies, keeping in perspective the available information on the subject.[2,4,7,8,14] Hence, it is postulated that an autoimmune mechanism may be responsible in leprosy either as a primary process leading to nerve damage, or as a secondary process perpetuating an already existing nerve damage.[17]

Materials and methods

STUDY SUBJECTS

Keeping in perspective the results obtained from previous studies, which ranged from 0

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Table 1. Duration of the disease in all leprosy patients tested

Type of leprosy	Total no. of cases	Cases with disease duration < 1 yr	Cases with disease duration 1–4 yr	Cases with disease duration > 4 yr
LL	43	5	25	13
BL	18	1	12	5
BB	3	2	0	1
BT	34	10	20	4
TT	2	1	1	0
Total	100	19	58	23

through 4·1, 13, 22, 23·86, 25, 25·6, 40, 47 to 100%, the average (31%) was taken as the anticipated population proportion having antineural antibodies. The sample size required for this anticipated population proportion was calculated using a 95% confidence interval and a precision of 9 percentage points. The minimum sample size was found to be 100, when calculated according to the formula:

$$\frac{n = Z_{\alpha}^{z} \times p \times (1 - p)}{d^2}$$

where n is the sample size, z is the standard normal curve value at $1 - \alpha/2$, $100(1 - \alpha)$ is the confidence interval, p is the anticipated population proportion and d is the percentage point. Thus serum from 100 leprosy patients were studied. Representative samples from the entire spectrum of the disease were collected and tested. The patients were classified according to the Ridley–Jopling classification of leprosy.[15]

There were 43 patients with lepromatous leprosy (LL), 18 with borderline lepromatous (BL) leprosy, 3 with borderline (BB) leprosy, 34 with borderline tuberculoid (BT) leprosy and 2 with polar tuberculoid (TT) leprosy. Out of the total 100 patients, 35 were cases in reaction, 20 with Type I and 15 with Type II reaction. The duration of the disease in the patients ranged from 4 months to 11 years. Duration of the disease in all cases at the time of collection of serum samples for the study is shown in Table 1. In all, 52 of the patients had enlarged peripheral nerves, of whom 19 had signs of active neuritis, as detailed in Table 2. The patients were aged between 14 and 60 years and 61 patients had bacteriological indices (BI) ranging between 0 and 2+, 30 had BI > 2+; the BI of 9 patients were not known, and 67 patients were on multidrug therapy for leprosy.

Table 2. Leprosy patients with clinical evidence of nerve involvement

Type of leprosy	Total no. of cases	Cases with nerve enlargement	Cases with active neuritis
LL	43	17	6
BL	18	14	5
BB	3	1	0
BT	34	18	7
TT	2	2	1
Total	100	52	19

Table 3. Control sera used in the study

Type of sera	No. of sera
I Normal healthy controls	18
II Controls with neurological deficiencies due to causes other than leprosy:	
a Gullian–Barré syndrome	2
b Abortive Gullian–Barré syndrome	1
c Diabetic neuropathy	4
d Motor neuron disease	3
e Paraparesis	2
f Polio	1
g Anterior horn cell disease (other than polio)	1
h Crush injury	1
Alcohol induced sensory motor neuropathy	1
j Neurofibromatosis	1
k Viral encephalitis with sensory deficiency	1
l Post-diphtheritic bilateral VI nerve palsy with left VII nerve palsy	1
m Neuropathy due to unknown aetiology	4
Total	41

The remaining patients had not received any treatment for leprosy. Control sera were included in the study. There were normal healthy controls as well as controls with neurological deficits due to causes other than leprosy, as detailed in Table 3.

ANTIGEN PREPARATION

Normal human nerves were taken at autopsy within 1 hr of death and teased. They were treated with warm acetone (37°C) and petroleum ether and then homogenized and sonicated. The protein content was 1·2 mg/ml, calculated by Lowry's method.[9] The major bands migrated at 15–22 kDa and 25–27 kDa.

ELISA

Indirect ELISA using 60 ng of antigen per well (after checker board titration) was carried out using U-bottomed polystyrene Nunc Immunoplates. Briefly, the coated plates were kept overnight at 37°C in a moist chamber and washed next morning 3 times with PBS-T. Blocking was done with 3% BSA in PBS-T. The sera was diluted at 1 : 400 and the plates were incubated at 37°C for 1 hr in a moist chamber and washed with PBS-T. To test for IgG type of antibodies, 50 μl of antihuman IgG conjugated with HRPO (Lupin) at a dilution of 1 : 1000 in PBS-T per well was used. In order to test for IgM antibodies, 50 μl of antihuman IgM conjugated with HRPO at a dilution of 1 : 1000 in PBS-T per well was used. Plates were incubated at 37°C in a moist chamber for 1 hr and washed with PBS-T. Orthophenylene diamine (Sigma) with 30% hydrogen peroxide was used as a substrate. The reaction was stopped using 7% sulphuric acid. The optical density was read after 10–20 min using 492 nm filter in a Titertek Multiscan plus ELISA reader from

Table 4. Details of cases with demonstrable levels of IgG antibody

Type of leprosy	A/S	Duration of disease	BI	Nerve enlargement	Active neuritis	Whether on treatment
LL	33/M	2 yr	3+	+	+	–
LL	45/M	10 yr	2+	–	–	+
LL	40/M	8 months	3+	–	–	+
LL	28/M	1 yr	5+	–	–	+
BL	22/F	Relapsed 1 yr ago	Not known	+	+	+
BT	30/F	3 yr	–ve	+	+	+
BT	65/M	1 yr	–ve	+	–	+
BT	25/M	2 yr	–ve	–	–	+
BT	25/F	1 yr	–ve	+	–	–

Flow Laboratories. All assays were done in triplicate. The cut-off values for sero reactivity were determined by adding 2 SD to the mean absorbance of the healthy controls who had no apparent neurological damage.

Results

Out of 18 normal controls, one (5·6%) had significant levels of antineural antibodies of the IgM type and none had significant levels of antineural antibodies of the IgG type. Out of the neurological diseases other than leprosy, the sera obtained from the 2 Guillian–Barré syndrome sufferers had significant levels of antineural antibodies of the IgG type, whereas none of sera from the other diseases had any significant levels of these antibodies.

In total, 9 leprosy patients (9%) had significant levels of IgG antibodies and 11 patients (11%) had significant levels of IgM antineural antibodies. They formed 2 largely nonoverlapping groups with only 2 patients positive for both isotypes. The clinical and bacteriological details of these 2 groups are given in Tables 4 and 5. The optical density values obtained with ELISA for the sera of leprosy patients and normal controls are

Table 5. Details of cases with demonstrable levels of IgM antibody

Type of leprosy	A/S	Duration of disease	BI	Nerve enlargement	Active neuritis	Whether on treatment
LL	60/M	Relapsed 5 yr ago	1+	+	–	+
LL	35/M	Relapsed 2 yr ago	1+	+	–	+
LL	33/M	2 yr	3+	+	+	+
LL	45/M	6 yr	4+	–	–	+
LL	45/M	10 yr	2+	–	–	+
LL	45/M	11 yr	3+	+	–	+
BT	35/M	13 yr	–ve	+	–	–
BT	45/M	4 month	–ve	+	–	+
BT	30/M	6 yr	–ve	+	–	+
BT	40/M	2 yr	–ve	–	–	–
BT	50/M	4 month	–ve	–	–	–

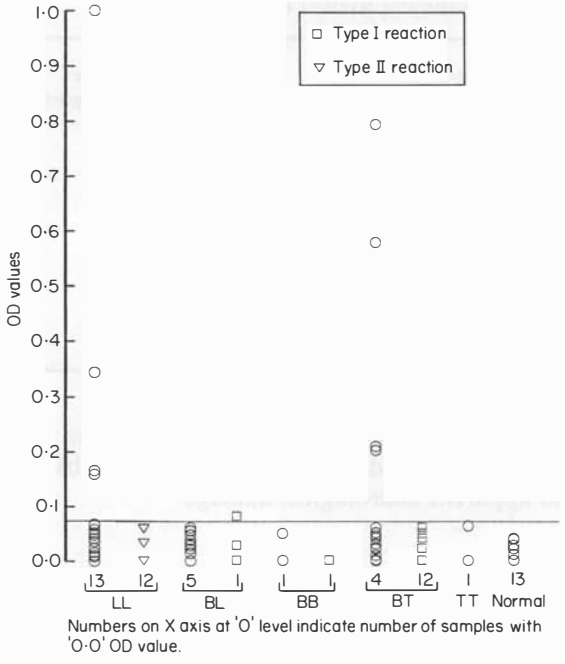

Figure 1. Optical density values with antigen derived from normal nerve using antiIgG.

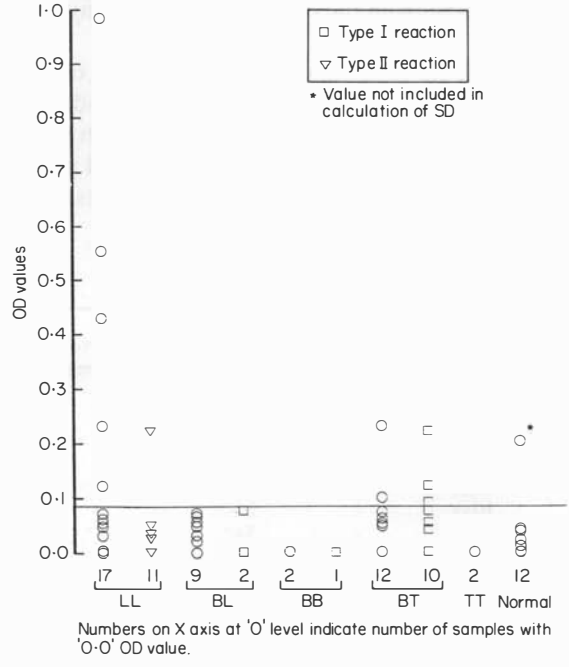

Figure 2. Optical density values with antigen derived from normal nerve using antiIgM.

Table 6. Comparison of the various clinical and laboratory attributes of leprosy with the prevalence of significant levels of antineural antibodies of the IgG type

	LL ($n = 43$)		BL ($n = 18$)		BB ($n = 3$)		BT ($n = 34$)		TT ($n = 2$)	
	+	−	+	−	+	−	+	−	+	−
	4	39	1	17	0	3	4	30	4	2
No. of cases with active neuritis	1	5	1	4	−	0	1	6	−	1
No. of cases with nerve enlargement	1	16	1	17	−	1	3	15	−	2
No. of cases with reaction	0	15	0	2	−	1	0	20	−	0
No. of cases on treatment	3	30	1	14	−	0	3	15	−	1
No. of cases with BI: 0 − 2+	1	22	0	6	−	2	4	25	−	1
No. of cases with BI: > 2+	3	17	0	10	−	0	0	0	−	0
No. of cases with BI: Not known	0	0	1	1	−	1	0	5	−	1
No. of cases with duration of dis.*: < 1 yr	1	4	0	1	−	2	0	10	−	1
No. of cases with duration of dis.*: 1 − 4 yr	2	23	1R	11	−	0	4	16	−	1
No. of cases with duration of dis.*: > 4 yr	1	12	0	5	−	1	0	4	−	0

+, No. of cases with significant levels of antineural antibodies; −, No. of cases without any significant levels of antineural antibodies; dis.*, disease; R, relapsed case.

shown in Figures 1 and 2. A comparison of the clinical and laboratory attributes of leprosy with the prevalence of significant levels of antineural antibodies of IgG and IgM was done. The details are given in Tables 6 and 7.

Using the χ^2-test, there was no significant association ($P > 0{\cdot}05$) between the type of leprosy, the BI and the presence of significant levels of antineural antibodies of the IgG or IgM type; nor was there any significant association ($P > 0{\cdot}05$) between the treatment taken and the presence of detectable levels of antineural antibodies. Using Fisher's exact test, there was no significant association between the presence of detectable levels of antineural antibodies and nerve enlargement, active neuritis and duration of the disease.

Table 7. Comparison of the various clinical and laboratory attributes of leprosy with the prevalence of significant levels of antineural antibodies of the IgM type

	LL ($n = 43$)		BL ($n = 18$)		BB ($n = 3$)		BT ($n = 34$)		TT ($n = 2$)	
	+	−	+	−	+	−	+	−	+	−
	6	37	0	18	0	3	5	29	0	2
No. of cases with active neuritis	1	5	−	5	−	0	0	7	−	1
No. of cases with nerve enlargement	4	13	−	14	−	1	3	15	−	2
No. of cases with reaction	1	14	−	0	−	0	3	2	−	0
No. of cases on treatment	6	27	−	15	−	0	2	16	−	1
No. of cases with BI: 0 − 2+	3	20	−	6	−	2	4	25	−	1
No. of cases with BI: > 2+	3	17	−	10	−	0	0	0	−	0
No. of cases with BI: Not known	0	0	−	2	−	1	0	5	−	1
No. of cases with duration of dis.*: < 1 yr	0	5	−	1	−	2	2	8	−	1
No. of cases with duration of dis.*: 1 − 4 yr	2 (1 + R)	23	−	12	−	0	1	19	−	1
No. of cases with duration of dis.*: > 4 yr	4 (3 + R)	9	−	15	−	1	2	2	−	0

+, No. of cases with significant levels of antineural antibodies; −, No. of cases without any significant levels of antineural antibodies; dis.*, disease; R, relapsed case.

Discussion

The results obtained after ELISA showed that 9% had significant levels of IgG antineural antibody and 11% had significant levels of IgM antibody. None of the normal controls had detectable levels of the IgG type of antineural antibodies, but 1 control (5·6%) had significant levels of IgM type of antineural antibody. There was no significant association with the type of leprosy, BI, treatment received, presence of nerve enlargement or active neuritis and the duration of disease.

Most of the patients with significant levels of antineural antibodies belonged to either the LL or BT group, but considering the fact that a large number of patients who were included in the study belonged to these 2 groups, in comparison with the other groups this was quite predictable.

Of the other neurological diseases tested for antineural antibodies, the sera from the 2 Gullian–Barré syndrome sufferers had significant levels of antineural antibodies of the IgG type and none of the others had significant levels. This was expected because the Gullian–Barré syndrome has a documented autoimmune pathogenesis. Thus these 2 sera have acted as positive controls for the ELISA test.

Similar to the results obtained in our study, Chujor *et al.*[3] have reported 4·1% of the leprosy patients and 5·6% of the normal sera positive for antineural IgG antibodies. Ghaswala *et al.*[6] were not able to demonstrate any antibodies in their series as the optical density values of patients' sera were within those of normal controls. Thomas & Mukherjee,[16] on the other hand, have shown 100% positivity in all of their 258 sera tested. None of their normal controls were positive. Such variation in results are difficult to explain. The 100% positivity shown by this group[16,11,12] has not been substantiated by any of the studies carried out so far.[3,5,6,10,13,18]

Benjamin *et al.*,[1] using immunoblot and antigen prepared from intermediate filament derived from human spinal cord, showed a high positivity of antineural antibodies (47%) in leprosy patients, but the positivity in normal controls was also high, ranging from 20% in American subjects to 41·6% in Ethiopians. Eustis Turf *et al.*[5] used indirect immunofluorescence and found 40% positivity in leprosy patients. Our study gave a 9% level of significant IgG antibodies in leprosy patients.

This variation in results is probably due to different kinds of antigens used. In the studies where human peripheral nerve antigen has been used,[3,11,12,16] the type of proteins predominating in the preparation were probably different. The major protein in experiments by Chujor *et al.*[3] was PNS myelin protein Po with 28 kDa mol. wt, whereas, in the antigen prepared by Thomas & Mukherjee[16] there was a major band in the 40–70 kDa mol. wt. The SDS–PAGE protein analysis of the antigen used in this study showed bands migrating at about 15–22 kDa and 25–27 kDa.

Other studies using animal nerve as antigen have found varying percentages of positivity. Wright & Hirst,[18] using rat sciatic nerve, found 25% positivity, but 22·2% of normal controls were also positive. Mshana *et al.*[10] used bovine sciatic nerve myelin basic protein and found 13% positive and Om Parkash *et al.*[13] used rabbit nerve and found 22% positive. However, we have used human peripheral nerve as the source of antigen. This might explain the differences in these results and the results obtained by us.

In our study the number of leprosy patients with significant levels of IgM antineural antibodies (11%) were more than those with detectable levels of IgG antibodies (9%).

Patients with significant levels of IgM antibodies belonged only to the LL and BT group. However, again considering the fact that a large number of patients who were included in the study belonged to these 2 groups in comparison with the other groups, this was quite predictable. Thomas & Mukherjee[16] tested only 35 patients with antihuman IgM conjugates. They obtained IgM antibody titres in the range of 0·14 to 0·67 OD. We have also obtained values in a similar range, with only 1 lepromatous leprosy patient having a high value of 0·984 OD. Chujor *et al.*[3] also characterized antineural antibodies with respect to immunoglobulin classes and found that the antibodies they detected belonged mainly to the IgG and IgM class. However, Benjamins *et al.*,[1] using intermediate filament fraction of the human spinal cord as an antigen, were not able to detect any IgM antibodies using the immunoblot technique. Others[5,6,13,18] did not study the sera for antineural antibodies of the IgM type. IgM antibodies are the earliest antibodies to appear. However, in our study, there was no significant association between the presence of IgM antibodies and a recent onset of the disease. We looked for such an association because IgM antibodies are usually associated with the early stages of any infection.

Conclusions

This study is not able to demonstrate any statistically significant levels of antineural antibodies associated with any type of leprosy, or any specific feature of the disease ($P > 0{\cdot}05$). It cannot be said with any certainty that an autoimmune pathogenesis exists for neuropathy in leprosy. However, further studies will be required to confirm this assumption.

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References

[1] Benjamins JA, Callahan RE, Runft D, Gerras G, Lefford MJ. Antineural antibodies in leprosy sera: further characterisation of antigens. *J Neuroimmunol*, 1989; **21:** 125–35.

[2] Boddingius J. Mechanisms of nerve damage in leprosy. In David Humber (Ed). *Immunological aspects of Leprosy, Tuberculosis and Leishmaniasis*, Excerpta Medica, Oxford. 1981, pp. 64–73.

[3] Chujor SNC, Regele H, Bernheimer H, Levis W, Schwerer B. Serum antibodies against peripheral nervous system antigens in leprosy. *Int J Lepr* 1991; **59:** 590–6.

[4] Dastur DK, Mohan JR, Shah JS. Ultrastructure of nerves in tuberculoid leprosy. *Neurol (India)*, 1972; **20:** 89–99.

[5] Eustis Turf EP, Benjamins JA, Lefford MJ. Characterisation of the antineural antibodies in the sera of leprosy patients. *J Neuroimmunol*, 1986; **10:** 313–30.

[6] Ghaswala PS, Mistry NF, Antia NH. Serum antibodies of normals and leprosy patients show equal binding to peripheral nerve. (Letter to the Editor). *Int J Lepr*, 1989; **57, 3:** 690–2.

[7] Job CK. Pathology of peripheral nerve lesions in lepromatous leprosy. A light and electron microscopic study. *J Neurol Sci*, 1971; **29:** 423–41.

[8] Job CK, Desikan KV. Pathologic changes and their distribution in lepromatous leprosy. *Int J Lepr*, 1968; **36:** 257–70.
[9] Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with Folin phenol reagent. *J Biol Chem*, 1952; **193:** 265–75.
[10] Mshana RN, Harboe M, Stones GL, Hughes RAC, Kadlubowski M, Belehu A. Immune response to bovine neural antigens in leprosy patients. 1. Absence of antibodies to an isolated myelin protein. *Int J Lepr*, 1983; **51, 1:** 33–40.
[11] Mukherjee R, Itty BM, Yadava A, Kharat I, Talwar GP. Characteristics of Antineural antibodies in leprosy patients. Po 317—Abstracts of Congress papers. *Int J Lepr*, 1989; **57, 1:** 359.
[12] Mukherjee R, Thomas BM, Vemuri N, Talwar GP. Nerve antigen based serological tests for the diagnosis and prognosis of leprosy. *Trop Med Parasitol*, 1990; **41:** 357–8.
[13] Parkash O, Srrevasta, Sengupta U. An attempt to demonstrate antinerve antibodies in leprosy sera using rabbit nerve as an antigen. Letter to Editor. *Int J Lepr*, 1990; **58, 1:** 129–30.
[14] Ridley DS, Job CK. The pathology of leprosy. In *Leprosy*. Hastings (Ed). Churchill Livingstone, New York. 1985, pp. 100.
[15] Ridley DS, Jopling WH. Classification of leprosy according to immunity—a five group system. *Int J Lepr*, 1966; **34:** 255–73.
[16] Thomas BM, Mukherjee R. Antineural antibodies in sera of leprosy patients. *Clin Immunol Immunopathol*, 1990; **57:** 420–9.
[17] Wright DJM. Auto antibodies in leprosy. Letter to Editor, *Lancet*, 1973; **ii:** 40.
[18] Wright DJM, Hirst RA. Neural auto antibodies in leprosy. *Lepr Rev*, 1975; **46:** 157–67.

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Eye disease in newly diagnosed leprosy patients in eastern Nepal

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Summary To determine the magnitude of eye lesions in newly diagnosed leprosy patients we examined their eyes.

The Eastern Leprosy Control Project was supported by The Netherlands Leprosy Relief Association; we used the regional clinic in Biratnagar and 5 mobile clinics in surrounding districts as our survey area.

All patients who presented at the clinics over 10 weeks, diagnosed as having untreated leprosy were included.

Of the 260 examined patients 97 (37·3%, 95% confidence interval 28·3–40·3%) had an eye lesion; 12/260 patients (4·6%, 95% confidence interval 2·0–7·2%) had sight-threatening lesions (lagophthalmos, iris involvement, corneal anaesthesia), directly related to leprosy; 46 (17·7%) patients were diagnosed as having some degree of cataract; 2 patients were aphakic; 3 patients (1·2%) were blind according to the WHO definition.

In this series of new and untreated leprosy patients many eye lesions found are not relevant or leprosy related. There were 9 new patients with lagophthalmos, some too longstanding to treat with steroids. We found 3 patients with iris involvement. The figures we found for eye lesions, sight-threatening lesions and blindness are low when compared to other studies. The number of patients with any grade of cataract is high. The average total of leprosy patients who were blind can be compared with the average total who are blind in the general population.

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Introduction

Involvement of the eye in leprosy is well known and several prevalence studies have been carried out among different populations, but mainly within leprosy institutions.[1–9] As far as we know no studies have been done on the eye problems which exist at the moment the patient is diagnosed. This assessment of the starting condition is important in order to study the effect of MDT treatment on the development of leprosy related eye complications.[8,10] The most important leprosy-related sight-threatening lesions are lagophthalmos and iris involvement. Lagophthalmos is caused by the involvement of the facial nerve in the disease process, either by direct invasion of the nerve by *Mycobacterium leprae* or due to a Type 1 leprosy reaction (reversal reaction) in the nerve. The complications of lagophthalmos which cause blindness are damage to the exposed cornea with consequent ulcers and opacities. Corneal anaesthesia occurs either in combination with lagophthalmos or as a result of invasion and atrophy of the corneal nerves. Iris involvement also arises from different mechanisms; there is either direct invasion of the anterior eye and secondary atrophy or reaction to an antigen load that causes iridocyclitis in Type 2 leprosy reaction (ENL). Blindness may result subsequently from a miotic pupil, secondary cataract and secondary glaucoma.

This study has been done in eastern Nepal. The setting is described elsewhere.[11]

Patients and methods

Between September and November 1992 (10 weeks) we examined all new patients who presented at the clinics and were diagnosed as having leprosy.

After recording a registration number, age, sex, type of leprosy, duration of disease, district and presenting symptom the eyes were examined.

Visual acuity (VA) was tested with the Snellens E-chart and if necessary with finger counting. Pinhole examination was done when VA $< 9/12$. Facial patches were drawn.

Eye examination was carried out in a semidark area. We closely examined lids, brows, conjunctiva, sclera and the lacrimal system with focal illumination. We looked for lagophthalmos by measuring the gap at mild and strong closure and by testing the strength of the orbicularis oculi muscle.

The cornea was checked with a lighted loupe (magnification $7\times$) for opacities and pannus; the iris for signs of iridocyclitis, iris atrophy or iris pearls. Pupil size was measured with a transparent measure and shape and reaction to light noted down. The corneal sensitivity was tested with cottonwool. The eye was then stained with fluorescein to look for punctate staining. All patients' pupils were dilated with tropicamide and cataract grading was done using direct ophthalmoscopy.[12] Any eye history was noted down. All data were recorded on a proforma adapted from that proposed by ffytche.[13]

Results

POPULATION

We saw 260 newly-diagnosed leprosy patients. The mean age was 34·5 years. There were 88 females and 170 males. In all, 41% of the patients suffered from the TT or BT type of

Table 1. Eye-problems in 260 new leprosy patients

Eye brows		
Madarosis		
lateral	20*	19 MB, 9 PB
total	6*	
Eye lid		
Lagophthalmos (1 eye)	9*	3BL, 4BT+, 2PNL
Nodules	1*	LL
Chalazion	3	BT+, TT
Ptosis	1	BT
Blepharospasm	1	PNL
Blepharochalasis	1	LL
Blepharitis	1	BT+
Trichiasis	1*	BT+
Conjunctiva and sclera		
Conjunctivitis	1	BT+
Scleral leproma	2*	LL, BL
Pterygium		
1 eye	21	7MB, 22PB
2 eyes	6	
Cornea		
Corneal opacity	11	4MB, 7PB
Corneal sensitivity reduced	1	PNL
Iris		
Iridocyclitis (acute)	1*	BL
Irispearls	1*	LL
Synechiae		
ant (traumatical)	1	TT
post	1*	BL
Irreg. pupil shape	1	BT+
Different pupil size L & R	5	1MB, 4PB
Lens		
Cataract		
1 eye	7	
2 eyes	38	
Aphakia	2	
Total	144 (in 97 patients: 37·3%)	
Sight threatening	13 (in 13 patients: 5·0%)	

* Leprosy related.

leprosy which was treated with a 6-month multidrug regimen, and 59% suffered from the BT+, BB, BL, LL and PNL type of leprosy and were treated with a 24-month regimen. BT+ is defined in Nepal as having patches and/or nerves involved in at least 3 body areas.[14] The mean duration of disease, according to the patients, was 22·8 months. The population is described more extensively elsewhere.[11]

EYE LESIONS

In 97 patients (37·7%) we found 1 or more of the eye problems listed below in Table 1. Visual acuity of all 520 eyes is given in Table 2. Aphakic eyes were tested with spherical

Table 2. Visual acuity in 520 eyes/best eye in 260 patients

	Eyes	Patients
6/18 or better (normal)	471 (90·6)*	244 (93·8)
6/24–6/36 (impaired)	22 (4·2)	6 (2·3)
6/60–3/60 (severely impaired)	19 (3·7)	7 (2·7)
Less than 3/60 (blind)	8 (1·6)	3 (1·2)
Total	520	260

* Numbers in parentheses are percentages.

+10 correction. Sight-threatening lesions (lagophthalmos, iris involvement and corneal insensitivity) were found in 12 patients (4·6%). Some of the eye-problems of Table 1 will now be described more extensively.

LAGOPHTHALMOS ($n = 9$)

Lagophthalmos was defined as a consistent gap on mild closure with muscle weakness of the orbicularis oculi. In all, 3 patients had multibacillary leprosy (BL) and the other 6 had paucibacillary leprosy (PNL and BT+). Only 1 of the lagophthalmos patients had reduced vision (6/18 both eyes), but this was caused by cataract. The other 8 patients had good vision (6/6). There were no other eye lesions apart from a slight conjunctivitis in 1 eye, and 3 patients had a severe lagophthalmos with a gap on strong closure. The duration of lagophthalmos according to the patient was less than 2 months in 4 patients, more than 2 years in 2 patients and 3 patients did not know they had lagophthalmos. These results are summarized in Table 3.

IRIS INVOLVEMENT ($n = 3$)

Of the 3 patients, 1 (male, 35 years, BB, duration of disease 96 months) had a slight pain in the left eye with pericorneal redness, a small pupil with sluggish reaction to light and only slight dilation with tropicamide. Vision was 6/6 in both eyes but was subjectively decreased in the affected eye, another (male, 30 years, BL, duration of disease 18 months) had old posterior synechiae in both eyes but had no signs of active iridocyclitis (VA both eyes 6/36), and patient 3 (male, 35 years, BL, duration of disease 48 months) had an atrophic iris of the left eye (VA left 6/12, right 6/18), but no active signs of iridocyclitis.

CORNEAL HYPAESTHESIA ($n = 1$)

There was 1 patient (PNL) with unilateral reduced sensitivity which was probably not leprosy related (accident).

CORNEAL OPACITY ($n = 11$)

Of the 11, 1 patient had a severe leprous keratitis in both eyes in the upper outer quadrant with a vision of 6/18 in both eyes, and the rest had opacities which were not leprosy related; most of them were only small nebular lesions.

Table 3. Lagophthalmos in 9 new leprosy patients

No.	Age	Type	Dur. lepr. (m)	Dur. lag. (m)	Gap mild closure (mm)	Gap strong closure (mm)	Remarks
1	26	BL	2	1	2	0	
2	36	BL	2	2	2	0	
3	60	BL	12	?	2	0	in reaction, start steroids
4	8	BT+	84	42	5	3	patch
5	20	BT+	60	?	2	0	patch in reaction, start st.
6	35	BT+	2	2	5	2	patch, start steroids
7	55	BT+	12	?	1	0	
8	19	PNL	48	24	5	3	patch
9	28	PNL	2	2	2	0	start steroids

All patients were male, only unilateral lagophthalmos.
dur. lepr.: duration of leprosy in months.
dur. lag.: duration of lagophthalmos in months.

CATARACT/APHAKIA ($n=47$)

Of the 47 patients, 38 had cataracts in both eyes and 7 in 1 eye. The severity of the cataracts in these 83 eyes is given in Table 4.

We did not find a correlation between cataract and classification in this series of new untreated and relatively young patients. The percentage of patients with cataracts (more than 1/2) was 7·0% in the paucibacillary group and 5·0% in the multibacillary group. There was 1 patient with 1 aphakic eye and 1 with 2 aphakic eyes after cataract extraction.

MADAROSIS ($n=26$)

In 6 patients there was a complete madarosis and in 20 patients a lateral madarosis. In 5 of the 26 cases lateral madarosis was found in paucibacillary patients (probably as a normal variant).

Table 4. Cataract grading (520 eyes)

Grade	No.	%
0 no cataract	434	(83·5)
1 spot	26	(5·0)
2 <1/2	25	(4·8)
3 >1/2	25	(4·8)
4 complete	8	(1·5)
5 aphakia	3	(0·6)
Total	520	(100·0)

BLINDNESS (n= 3)

According to the WHO definition blindness is defined as a VA in the better eye of less than 3/60. There were 3 blind patients found. There were 2 more patients with 1 blind eye. All were caused by cataract.

Discussion

In his article about methodology Courtright pointed out the major shortcomings in methodology of surveys on ocular complications in leprosy.[4] Although some of these were also unavoidable in our survey (clinic based, sequentially sampled population) we tried to avoid the others as much as possible.

Eye lesions of some kind were found in 37% of the newly diagnosed patients (95% confidence interval 28·3–40·3%). This is much lower than the figure found in Nepalese leprosy institutions: 69·8%, 74·2% and 57·3%.[5–7] Courtright mentioned in his critical survey 'ocular complications' in 1–91% (!).[4]

Leprosy related 'eye problems' including madarosis but excluding cataract were found in 15·4% (95% confidence interval 10·9–19·9%) of the patients. Without madarosis the figure is 6·9% (95% confidence interval 3·8–10·0%). ffytche found 'significant ocular involvement' (excluding cataract) in 21·9% in a series of surveys.[9] In South India 24% of eye lesions were diagnosed as being due to leprosy in outpatients in a big institution.[1] It is difficult to compare these figures but it seems that leprosy-related eye problems are less in new patients than in patients under treatment or after treatment. In the present study sight-threatening lesions (lagophthalmos, iris involvement and corneal anaesthesia) were found in 4·6% (95% confidence interval 2·0–7·2%) compared with 24·3% by ffytche and 8·22% in South India.[1,2] In institutions this figure is also high but cannot be compared.

We found cataracts in 17·7% (95% confidence interval 12·0–23·4%); cataracts with an absent red light reflex and a poor vision of less than 6/60 were found in 2·7%. ffytche found cataracts (defined as either aphakia or visible lens opacities or an absent red reflex with VA < 6/36) in 17·2%.[9] In leprosaria in Nepal 8·2% of the eyes were found to have a VA of < 6/60 as a result of cataract. The average age was 59·8 years. Cataract in that series was seen more commonly among lepromatous patients, as a result of iridocyclitis.[15] In Nepal there is cataract in 2·8% of the general population; in the terai 4·17%.[16]

We found blindness in 3 patients, i.e. 1·2% (95% confidence interval 0–2·6%). ffytche found blindness in 5% or 7% (VA < 6/60) (depending on the definition of blindness);[9] in South India there was blindness in 0·8% and in Nepalese institutions in 6·0% and 2·4%.[1,5,7] In another study in a Nepalese institution 12·7% of the eyes were blind (VA < 6/60).[6] According to an epidemiological survey on blindness in Nepal the overall figure for Nepal is 0·84% and for the Eastern and Central terai regions more than 1%.[16] If we take the age distribution into account we find in the prevalence per age group mentioned in the survey in Nepal a predicted prevalence of 2·9%; corrected for age the number we found (1·2%) is low. Courtright mentioned in his survey 0–50% (!).[4] In our study all lagophthalmos patients and all patients with iris involvement were male. We have no explanation for this finding.

The mean age of patients is not mentioned in many studies but most probably our patients are younger than patients in resettlement villages or leprosaria.

Ideally populations should be compared using age, sex, type of disease, systemic treatment and duration of disease. Unfortunately this is often not possible.

Conclusions

The first conclusion of this study is that eye problems in newly diagnosed patients do exist. Lagophthalmos and iridocyclitis are potentially treatable and should be detected early.

The second conclusion is that the figure for blindness in newly diagnosed patients is relatively low (1·2%) and can be compared with the figure in the general population, although this must be corrected for age and sex, and the numbers are small. This means that eye complications in new patients have not yet damaged the vision severely.

The figure we found for eye lesions is much lower than the figure found in other studies, mainly because the research carried out up to now was not done in newly diagnosed patients. The patients studied in previous research were older, had suffered from leprosy longer, and there was a big selection bias because the most disabled patients tend to end up in institutions. The figure we found for cataract is relatively high. This is probably because we used a sensitive method. Because of the lack of correlation with classification the cataract in this relatively young population does not seem to be leprosy related.

Our results stress the importance of a good eye examination both in new cases and in cases under treatment.[17] The examination we carried out can be done without using any high technology equipment like a slit lamp, although some patients with early iris changes may be missed. Competent field workers can and should perform this examination almost everywhere (perhaps with the exception of the tropicamide).

Iridocyclitis should be treated with local corticosteroids and atropine, and any lagophthalmos which had developed or progressed during the previous 6 months should be treated with oral steroids.[18]

Detection of poor eye sight or blindness in leprosy is of extra importance because the patient may already be disabled by sensory loss.

Careful documentation of any eye complications at the start of treatment is necessary as it forms the baseline for further assessment, and also enables the effect of MDT to be seen on the incidence of new eye complications. It would be interesting to examine the same group of patients after treatment and after, for example 5 years.

References

[1] Soshamma G, Suryawanshi N. Eye lesions in leprosy. *Lepr Rev*, 1989; **60:** 33–8.
[2] ffytche, TJ. Residual sight threatening lesions in leprosy patients completing multidrug therapy and sulphone monotherapy. *Lepr Rev*, 1991; **62:** 35–43.
[3] ffytche, TJ. The American Peace Corps Survey of the ocular complications of leprosy in South Korea: an evaluation and appraisal. *Lepr Rev*, 1984; **55:** 239–46.
[4] Courtright PD. Defining the magnitude of ocular complications from leprosy, problems of methodology. *Int J Lepr*, 1988; **56:** 566–73
[5] Brandt F, Malla OK. Ocular findings in leprous patients. A report of a survey in Malunga/Nepal. *Albrecht von Graefes Arch Klin Ophthalmol*, 1981; **217:** 27–34.
[6] Malla OK, Brandt F, Anten JGF. Ocular findings in leprosy patients in an institution in Nepal (Khokana). *Br J Ophthalmol*, 1981; **65:** 226–30.

[7] Brandt F, Kist P, Wos J. Augenbefunde bei Lepra, Ergebnisse einer Studie im Green-Pastures Leprosy-Hospital Pokhara/Nepal. *Klin Mbl Augenheilk*, 1981; **178:** 55–8 (German).
[8] Rajan MA. Eye in multidrug therapy. *Ind J Lepr*, 1990; **62:** 33–8.
[9] ffytche T. Blindness in leprosy—a forgotten complication. *Australian and New Zealand Journal of Ophthalmology*, 1989; **17:** 257–60.
[10] Editorial. Ocular complications in leprosy. *Lancet*, 1992; **340:** 642–3.
[11] Schipper A, Lubbers WJ, Hogeweg M, Soldenhoff R de. Disabilities of hands, feet and eyes in newly diagnosed leprosy patients in Eastern Nepal. *Lepr Rev*, 1994; **65:** 239–47.
[12] Mehra V, Minassian DC. A rapid method of grading cataract in epidemiological studies and eye surveys. *Br J Ophth*, 1988; **72:** 801–3.
[13] ffytche TJ. A computer form to aid in the collection of data on the ocular complications of leprosy. *Lepr Rev*, 1983; **54:** 271–81
[14] 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:** 231–46.
[15] Brandt F, Kampile A, Malla OK, Pokhrel RP, Wos J. Blindness from cataract formation in leprosy. *Dev Ophthal*, 1983; **7:** 1–12.
[16] Brilliant LB, Pokhrel RP, Grasset NC *et al.* Epidemiology of blindness in Nepal. *Bull WHO,* 1985; **63(2):** 375–86.
[17] Courtright PD, Lewallen S. Considerations in the integration of eye care into leprosy care services. *Lepr Rev*, 1992; **63:** 73–7.
[18] Kiran KU, Hogeweg M, Suneetha S. Treatment of recent facial nerve damage with lagophthalmos, using a semistandardized steroid regimen. *Lepr Rev*, 1991; **62:** 150–4.

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Disabilities of hands, feet and eyes in newly diagnosed leprosy patients in eastern Nepal

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Summary The objective of the study was to determine the magnitude of hand/feet/eye disabilities in newly diagnosed leprosy patients by examining all newly diagnosed leprosy patients who presented at the Eastern Leprosy Control Project (supported by The Netherlands Leprosy Relief Association), made up of a regional clinic in Biratnagar and 5 mobile clinics in surrounding districts.

The study comprised of all new and previously untreated patients who presented at the clinics over a 10-week period who were diagnosed as leprosy sufferers.

Of the 260 leprosy patients examined 12 (4·6%) had sight-threatening lesions (lagophthalmos, iris involvement, corneal anaesthesia); 3 patients were blind due to cataract; 96/260 patients (37·0%, 95% confidence interval 35·0–43·0%) had 1 or more disabilities of their hands and/or feet. The most frequently found disabilities were sensory loss of the hands and feet, claw hand and plantar ulcers. According to the WHO disability grading 60% had no disabilities, 19% had grade 1 and 21% had grade 2 disability.

Disability assessment is very important not only to evaluate the effectiveness of the control programme but also for the patient, whose most important worry is the stigmatizing deformities leprosy patients suffer. The earlier detection of sensory loss might reduce these secondary deformities.

Introduction

Leprosy patients are the same as everybody else in that they need their hands, feet and eyes in order to cope with daily living. Unfortunately, many patients still present to a clinic already suffering from limb damage in a disease which now can be well treated and

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even cured. The 2 most important leprosy-related sight-threatening lesions are lagophthalmos and iridocyclitis.[1]

Disabilities occur because of the direct involvement of peripheral nerves which cause sensory loss and/or motor paralysis. Secondary deformities can also develop, e.g. contracture, ulcers and absorption of digits. With early detection many of these problems can be prevented.

According to the International Classification of Impairment, Disabilities and Handicaps (ICIDH), disability is defined as: 'any restriction or lack of ability (resulting from an impairment) to perform an activity in the manner considered normal.'[2] Sensory loss, by this definition, is an impairment, but for practical reasons we have used the term disability. The Eastern Leprosy Control Project (ELCP) is a joint project of the Nepalese Government with the Netherlands Leprosy Relief Association. The project covers 6 districts in the eastern terai (lowlands) of Nepal. An increasing number of patients come from India. From previous data and a subjective impression we presumed there would be more disabilities in the Indian patients.

The main clinic of the ELCP is in Biratnagar. There are 5 mobile clinics in the surrounding districts where the central staff goes once every month. In addition to these clinics there are 72 health posts where multidrug therapy (MDT) is provided for that area. District leprosy workers are responsible for supervising the resident multipurpose staff in these health posts.

Patients and methods

For 10 weeks between September and November 1992 we saw all new diagnosed leprosy patients who presented at the clinics.

After recording a registration number, age, sex, type of leprosy, duration of disease, district and presenting symptom, the eyes were examined.

Hands and feet were checked for deformities: clawing, drop foot, absorption, ankylosis, contracture and the presence of ulcers. The degree of deformity was measured and noted down. Voluntary muscle testing and sensory testing was then done by the physiotherapy technician, who also tested the following muscles: abductor digiti minimi, abductor pollicis, wrist extensors and dorsiflexors of the foot. For sensory testing a nylon filament was used on the hands and feet to test protective sensibility. Sensory loss was defined as missing more than 1 point of 12 test points on the hand and of 13 test points on the foot.

Disability grading was done according to the WHO 2 point scale (Table 1).[3]

Results

POPULATION

We examined 260 newly diagnosed leprosy patients; 219 in the main clinic in Biratnagar and 41 in the mobile clinics. There were 88 females and 170 males (sex ratio 1 : 9). The mean age was 34·5 years (females 32·9 and males 35·3 years). The patients from India tended to be older than the Nepalese patients (mean age 36 (India) and 32 (Nepal) years, statistically significant, 2-tailed t-test, $p < 0{\cdot}05$).

Table 1. WHO disability grading 2-point scale

Hands and feet:
Grade
0: no anaesthesia or visible deformity or damage.
1: anaesthesia, but no visible deformity or damage.
2: visible deformity or damage.
Eyes:
Grade
0: no eye problems due to leprosy, no evidence of visual loss.
1: eye problems due to the presence of leprosy, but vision not severely affected (VA $\geq$ 6/60).
2: severe visual impairment (VA < 6/60).

For age distribution see Figure 1.

Of the total population investigated 46·5% came from Nepal. In the main clinic in Biratnagar the percentage of Indian patients was 63·5%.

In total, 41% of the patients had tuberculoid leprosy (TT) or borderline–tuberculoid leprosy (BT) and these were treated with the 6-month WHO multidrug regimen. The other 59% had BT+, mid-borderline leprosy (BB), borderline–lepromatous leprosy (BL), lepromatous leprosy (LL) and pure neural leprosy (PNL) and were treated with a 24-month WHO regimen (Figure 2).

BT+ is defined in Nepal as having BT with at least 3 body areas involved.[4]

There is a significant difference in the distribution of leprosy type between females

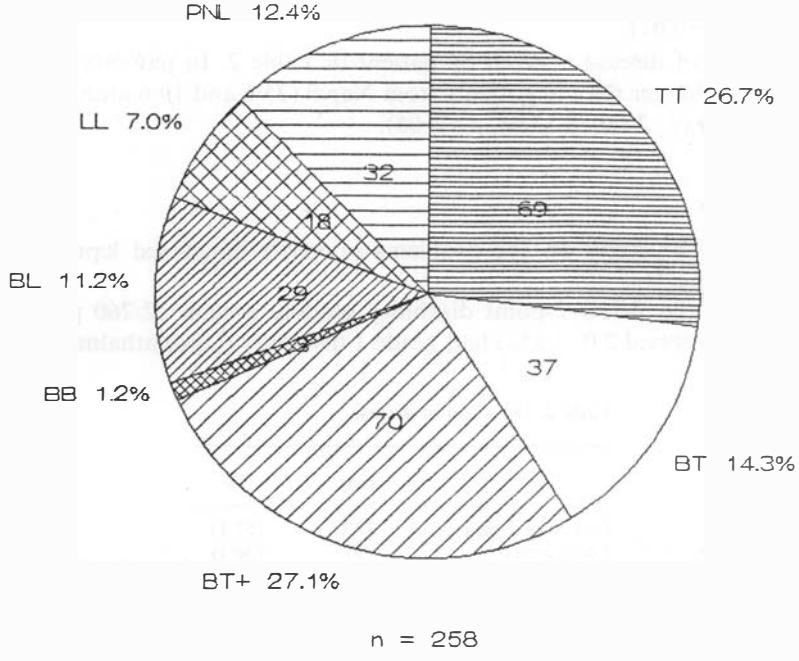

Figure 1. Age distribution.

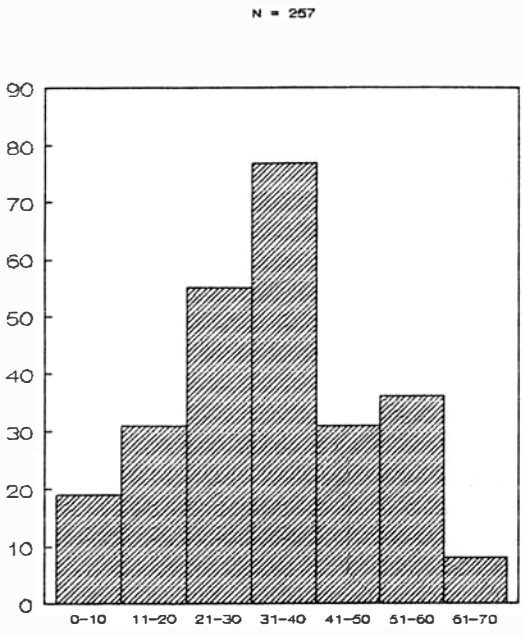

Figure 2. Type of leprosy. TT, tuberculoid; BT, borderline tuberculoid; BT+, borderline tuberculoid with 3 or more body parts involved, Nepalese definition;[4] BB, borderline; BL, borderline lepromatous; LL, lepromatous; PNL, pure neural leprosy.

and males, with 52% of females in the TT,BT group against 34% of males (statistically significant, χ^2, $p < 0{\cdot}01$).

The duration of disease is given by patient in Table 2. In patients from India the mean duration is longer than in patients from Nepal (25·6 and 19·6 months, statistically significant difference, 2-tailed t-test, $p < 0{\cdot}05$).

EYE-DISABILITIES

The outcome of the study on eye problems in newly diagnosed leprosy patients is presented elsewhere.[5]

According to the WHO 2-point disability grading system 12/260 patients (4·6%, 95% confidence interval 2·0–7·2%) had grade 1 disability (lapophthalmos, iris involve-

Table 2. Duration of disease

	No.	%
Less than 1 year	133	(51·1)
1 to 5 years	91	(35·1)
More than 5 years	14	(5·8)
Unknown	22	(8·5)
Total	260	(100.00)

Table 3. Disabilities (306 disabilities in 96 patients)

	Unilateral	Bilateral	Total (% of 260)
Hand			
Clawing	22	7	29 (11·0)*
Contracture	5	4	9 (3·5)
Ulcer	6		6 (2·3)
Absorption	11	3	14 (5·4)
Sensory loss	45	21	66 (25·0)
Foot			
Drop foot	5	1	6 (2·3)
Ulcer	16	6	22 (8·5)
Absorption	8	5	13 (5·0)
Sensory loss	22	36	58 (22·3)
Eye			
Lagophthalmos	9	—	9 (3·5)
Iris involvement	3	—	3 (1·2)

* Numbers in parentheses are percentages.

ment with VA $\geqslant$6/60). Grade 2 disability was found in 13/260 patients (5·0%, 95% confidence interval 2·3–7·7%) with VA < 6/60 in 1 or 2 eyes. All were caused by cataract. More patients had impaired vision caused by cataract but they are not included in grade 1 disability by the WHO standard.

DISABILITIES OF HANDS/FEET

No disability or muscle weakness was found in 60% of patients. Only muscle weakness, without sensory loss or other disabilities, was found in 3% of patients; 96 patients (36·9%, 95% confidence interval 30·9–42·9%) had 1 or more of the disabilities listed below in Table 3.

Table 4 shows the number of disabilities per patient. When there was only 1 disability this was most often sensory loss.

In total, 66 patients (26%, 95% confidence interval 20·6–31·4%) had 1 or more motor nerves involved (voluntary muscle testing score less than 5). The distribution in the 135 nerves concerned in these 66 patients is as follows: facial 7%, ulnar 51%, median 29%, radial 4% and peroneal 9%. The total number of nerves involved per patient is given in Table 5.

According to WHO disability grading 60% of patients had no disability, 19% had grade 1 and 21% had grade 2 disability. The mean age of these 3 groups is respectively 32, 39 and 36 years. The WHO disability grading does not seem to be higher in Indian patients (Table 6, no significant difference, χ^2, $p > 0{\cdot}1$).

Proportionally, 73% of females had no disability (WHO grade 0), against 53% of males. There were more disabilities (64%) in the multibacillary group of patients, against 27% with disablities in the paucibacillary group (Table 7, statistically significant, χ^2, $p < 0{\cdot}01$).

The disabilities listed in Table 3 will now be discussed more extensively.

CLAWING AND CONTRACTURES

There were 29 patients (11%) with 1 or 2 claw hands, giving 36 claw hands in all. In 18

Table 4. Number of disabilities

No. of disabilities	No. of patients	%
0	163	62·7
1	36	13·8
2	20	7·7
3	9	3·5
4	8	3·1
5	6	2·3
6	8	3·1
7	3	1·2
8	3	1·2
9	2	0·8
10	1	0·4
14	1	0·4
Total	260	100·0

Sum of above disabilities: absorption hand, absorption foot, clawing hand, contracture hand, ankylosis hand, ulcer hand, ulcer foot, sensory loss in hand, sensory loss in foot; each

patients (20 hands) there was only ulnar clawing, which did not exceed 60 degrees. In 11 patients (16 hands) there was ulnar/median clawing exceeding 70 degrees, of which 10 hands had contractures (7 patients), and 1 patient with only mild clawing also had a contracture.

ULCERS

The 6 hands with an ulcer all had partial or complete sensory loss—4 out of 6 were on the dorsum of the fingers. Of 26 feet with ulcers, 20 had complete sensory loss and 6 had partial sensory loss. Ulcers were most frequently on the metatarsal heads (Table 8).

Table 5. Number of muscles involved

No. of muscles involved	No of patients	%
0	198	76·2
1	30	11·5
2	18	6·9
3	4	1·5
4	4	1·5
5	4	1·5
6	2	0·8
Total	260	100·0

Sum of facialis, abductor digiti minimi, abductor pollicis, wrist extensors, dorsiflexors foot; each left or right. Max = 10.

Table 6. WHO disability grade by localization ($n = 247$)

WHO grade	India	Nepal	Total
0	80 (58·8)*	68 (61·3)	148 (59·9)
1	27 (19·9)	20 (18·1)	47 (19·0)
2	29 (21.3)	23 (20·8)	52 (21·1)
Total	136 (55·1)	111 (44·9)	247 (100·0)

Difference not significant, χ^2, $p > 0{\cdot}1$.
* Numbers in parentheses are percentages.

ABSORPTION

Of 17 hands (14 patients) with a shortening of the fingers 3 were caused by an accident unrelated to leprosy, 10 hands had only slight absorption (tips of fingers or one phalanx) and 4 had more severe absorption with more than 1 phalanx missing. Of 18 feet (13 patients) with absorption, 1 was caused by an accident. There were 10 feet with a slight absorption of toes and 8 with severe absorption.

SENSORY LOSS

There were 90 patients (36%) with sensory loss of hands and/or feet. Of the 66 patients (25%) with a sensory loss of hands (78 hands) there was in 25 hands a partial loss, in 38 hands a loss in the ulnar region and in 24 hands a complete sensory loss; 58 patients (22%) had sensory loss of feet (94 feet), 44 feet with partial and 50 feet with complete sensory loss.

DROP FOOT

Drop foot is defined as a voluntary muscle testing (VMT) score of 3 (or less) for the dorsiflexors if the foot can just be moved against gravity (or less). There were 6 patients with drop foot, 1 of them with bilateral drop foot. In 3 feet there was a complete paralysis.

Table 7. WHO grading in pauci- and multibacillary patients (missing 16)

WHO grade	PB	MB	Total
0	120 (73·2)*	28 (35·9)	148
1	21 (12·8)	21 (26·9)	42
2	23 (14·0)	29 (37·2)	52
Total	164 (100)	78 (100)	242

Difference statistically significant, χ^2, $p < 0{\cdot}01$.
* Numbers in parentheses are percentages.

Table 8. Ulcers on feet

	No.
Metatarsal heads	18
Dig. 1	3
Dig. 2–5	3
Heel	6
Midfoot	2
Dorsum/Lat malleolus	4

Discussion

We examined 260 new patients. The fact that we could not examine the new patients in the health posts might mean that our population has more complications than the mean leprosy population of eastern Nepal. We do not think this difference is significant in new patients when selection has not yet taken place.

The mean age of our patients was less than that in other studies,[6,7] which was to be expected because other studies have usually been done in resettlement villages or leprosaria.

DISABILITIES

Of our population 36·9% (95% confidence interval 30·9–42·9%) had 1 or more disabilities. A similar study in Nigeria recorded 38·8% in a hospital-based population.[6] Reports from Malawia and Tanzania give figures of 21·9% and 30·0%, also in new patients.[8] This lower figure is probably due to the higher prevalence of tuberculoid leprosy in Africa in comparison with Asia, while disabilities are found more frequently in lepromatous patients.[7] More male than female patients suffer from disabilities, as reported by others, perhaps because the percentage of men suffering from lepromatous disease is significantly higher.[6,7]

Sensory loss was the most common disability, accounting for 59·1% of the total number of disabilities. When only 1 disability was present this was most often sensory loss. This means that some of the secondary disabilities can be prevented with health education and regular check-ups.

Apart from sensory loss the most frequent disabilities were claw hand (11·8%) and plantar and palmar ulcers (11·2%). In Molai these were also the 3 most frequently found disabilities (sensory loss 35%, claw hand 13%, ulcers 17%).[6] The high figure of sensory loss in our study might be due to our definition of sensory loss.

Although we expected more disabilities in the patients coming from India, this could not be confirmed. Neither was there a greater percentage of patients with disabilities, nor more disabilities per patient. The self-history of disease according to the patient is not very reliable because of their subjective interpretation.

Conclusions

The importance of careful disability measuring at intake in a leprosy control programme

cannot be overestimated, because it is an indication of effectiveness. Also, from the patient's viewpoint, the deformity caused by leprosy is the part of the disease which affects his or her life most, because of the stigmatizing and disabling effect. Some of the early detected disabilities may still be suitable for treatment by steroids.

Because a high percentage of the disabilities is sensory loss in hands and feet, which can be the cause of secondary deformities, early detection and frequent monitoring of disabilities may prevent secondary deformities. Early detection and early treatment does not always mean secondary deformities can be prevented, but they can be minimized.[8]

References

[1] Editorial. Ocular complications in leprosy. *The Lancet*, 1992; **340:** 642–3.

[2] Brandsma JW, Heerken YF, Lakerveld-Heyl, Mischer van Ravensberg CD. The international classification of impairments, disabilities and handicaps in leprosy control projects. *Lepr Rev*, 1992; **63:** 337–44.

[3] *WHO: a guide to leprosy control*. 2nd edition. World Health Organization. Geneva 1988.

[4] Brakel WH van, Soldenhoff R de, McDougall AC. The allocation of leprosy patients into paucibacillary and multibacillary groups for multi drug therapy, taking into account the number of body areas affected by skin, or skin and nerve lesions. *Lepr Rev*, 1992; **63:** 231–46.

[5] Lubbers WJ, Schipper A, Hogeweg M, Soldenhoff R de. Eye disease in newly diagnosed leprosy patients in Eastern Nepal. *Lepr Rev*, 1994; **65:** 231–38.

[6] Iyere BB. Leprosy deformities: experience in Molai Leprosy Hospital, Maiduguri, Nigeria. *Lepr Rev*, 1990; **61:** 171–9.

[7] Fine PEM. Leprosy, the epidemiology of a slow bacterium. *Epidemiologic Review*, 1982; **4:** 161–88.

[8] Watson JM. Disability control in a leprosy control programme (editorial). *Lepr Rev*, 1989; **60:** 169–77.

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Palatal palsy in a case of lepromatous leprosy

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Summary A male patient with lepromatous leprosy developed nasal regurgitation of food due to palatal palsy during Type 2 reaction. Early high-dose administration of corticosteroid achieved a prompt therapeutic response and he completely recovered from palatal palsy. The associated lagophthalmos, foot drop and ulnar paralysis persisted.

Introduction

Mycobacterium leprae commonly affects the sensory fibres of the peripheral nerves, although motor fibres are often affected. The trigeminal and facial nerves are also commonly affected, but as the involvement of other cranial nerves is uncommon,[1–6] we report a patient with lepromatous leprosy who developed a palatal palsy during Type 2 reaction.

Case report

A 45-year-old man (Figure 1) was diagnosed to have lepromatous leprosy on 3 March 1983 on clinical, bacteriological and histopathological features. His history and progress are summarized in Table 1.

Discussion

The central nervous system remains unaffected in leprosy, though the cranial nerves during a superficial course may be involved. In the patient reported here, two cranial nerves—the facial fibres of the cranial part of the eleventh nerve which travel in the

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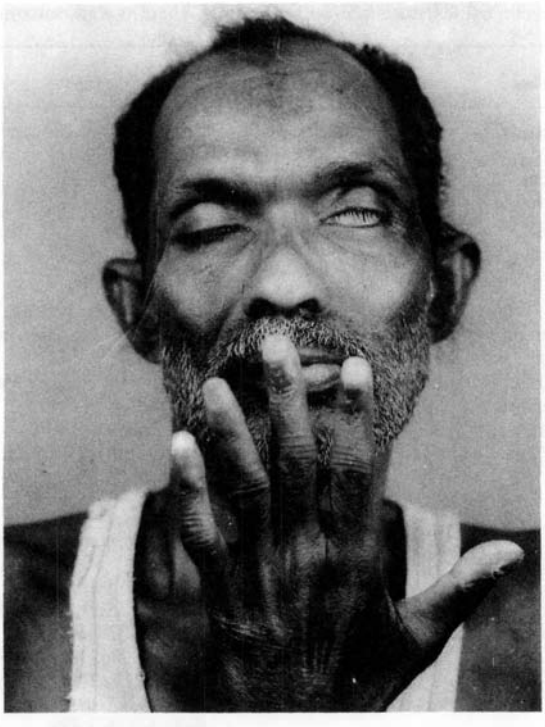

Figure 1. Note lagophthalmos of the left eye, the absence of nasolabial fold on the left side and clawing of the left hand.

vagus—were affected. Involvement of the zygomatic branch alone of the left facial nerve, resulting in lagophthalmos, and obliteration of the nasolabial fold suggested leprous aetiology for facial palsy in our patient. In most other conditions the facial nerve trunk, rather than its isolated branches, becomes affected, causing paralysis of all muscles of one-half of the face. The cranial nerves I, II, V, VII and VIII are affected in the patients reported by Katoch *et al.*[2] Involvement of the first and eighth cranial nerves has also been reported.[1,3–6]

Paralysis of the palate is unusual in leprosy. Its occurrence in association during a Type 2 reaction is of interest, especially as the severity of nerve involvement is usually greater in Type 1 reactions. Masashi and Schigenobu[8] reported bulbar palsy syndrome of leprosy in 6 patients with involvement of cranial nerves VII, IX, X and XI. They suggest an immunological mechanism as an aetiological factor. The most severe focus of inflammation was found in the nucleus ambiguus.[9] Leprous granulomata may occur in the palate in lepromatous patients.[10] The motor fibres derived from the nucleus ambiguus are distributed through the glossopharyngeal, vagus and cranial accessary nerves to the striated muscles of the palate, pharynx and larynx. With the exception of tensor palati, which is innervated by the mandibular division of the trigeminal nerve, muscles of the palate are supplied by fibres of the cranial part of the eleventh nerve which run in the vagus.[11] The normal CSF and isolated palatal palsy unassociated with

Table 1. Summary of the clinical features, laboratory findings, therapy and outcome

Date	Clinical features	Laboratory findings	Therapy	Outcome
3.3.83	Bilateral symmetrical multiple, shiny, ill-defined macules and plaques on face, trunk and limbs.	Slit-skin smears AFB. BI 6+, MI 68%. Skin biopsy features typical of LL leprosy. Routine blood and urine tests within normal limits.	Tab. dapsone 100 mg daily till 5.6.86.	Gradual clinical improvement with less infiltration of skin lesions. Gradual fall in MI to 42% on 6.6.86; BI 6+.
6.6.86	Type 2 reaction with fever, neuralgia and ENL lesions. Right and left ulnar and common peroneal nerves thickened and tender at elbow and popliteal fossa, respectively.	Slit-skin smears BI 6+ MI 42%. ESR 60 mm first hour, Blood TC 12,000 cells/c mm; VDRL negative, SGPT 40 IU/L. Chest X-ray normal.	Tab. dapsone 100 mg daily, Cap. Rifampicin 600 mg once a month, cap clofazimine 100 mg tid,[7] Tab Ibuprofen 400 mg tid till 23.6.86.	Type 2 reaction persisted till 20.8.1986.
24.6.88	Developed left lagophthalmos and obliteration of nasolabial fold on the left side. Ulnar clawing on the left side.	ESR 42 mm/first hour.	Tab. prednisolone 40 mg daily (24.6.86–24.7.86, 30 mg daily till 20.8.86, 25 mg daily till 20.10.86, 20 mg daily till 20.12.86, 15 mg daily till 28.2.87, 10 mg daily till 30.4.87, then 5 mg daily till 16.7.87). Dapsone, rifampicin and clofazimine continued. Clofazimine dose reduced to 200 mg daily on 20.10.86, and then 100 mg daily 16.7.87 onwards. It was further reduced to 100 mg on alternate days from 10.10.1987.	Gradual regression of Type 2 reaction, steroid withdrawn on 16.7.87. Persistent lagophthalmos and ulnar paralysis, BI 6+, MI 10%. Antileprosy drugs continued.

paralysis of the pharynx and larynx in our patient suggest involvement distal to the nucleus ambiguus. Palatal palsy in our patient was probably caused by the bilateral involvement of the peripheral motor fibres that supply the striated muscles of the soft palate. Nasal regurgitation of the food was caused by the failure of the paralysed soft palate to shut off the nasopharynx during swallowing. This might suggest either the involvement of all muscles or that the tensor is too weak to affect sufficient movement. For the same reason his voice acquired a nasal resonance.[12] This report emphasizes the need to also consider leprosy in the differential diagnoses of palatal palsy. It also stresses the importance of administering corticosteroid at the earliest evidence of palatal palsy, which if unilateral may be completely asymptomatic. Another question is also raised by the persistent ulnar paralysis and foot drop. The possibility of early release or constriction at the cubital tunnel and at the neck of the fibula combined with steroid therapy merits consideration.

Table 1. Continued

Date	Clinical features	Laboratory findings	Therapy	Outcome
9.5.88	Recurrence of Type 2 reaction with ENL lesions. Developed foot drop left side, nasal regurgitation of food and nasal resonance of voice. Complete palatal paralysis, with absent reflex. Pharyngeal reflex retained. Normal palatal sensations.	Slit-skin smears BI 5+ MI 4%. CSF—cells, proteins within normal limits. Blood sugar fasting 80 mg %.	Tab. prednisolone 80 mg daily for 1 month, 60 mg daily for 1 month, 40 mg daily for 1 month, 30 mg daily for 1 month, 20 mg daily for 1 month, 15 mg daily for 1 month, 10 mg daily for 2 months, 5 mg daily for 2 months and stopped on 7.3.89. Dapsone, rifampicin and clofazimine continued. Dose of clofazimine 300 mg daily for 3 months, then 200 mg daily for 3 months, then 100 mg daily till 7.3.89. Then 100 mg alternate days.	Complete recovery from palatal palsy when seen on 7.3.89. Foot drop, claw hand and lagophthalmos unchanged.
7.3.89	Skin lesions, regressed leaving atrophic macules. Foot drop, lagophthalmos and claw hand persist.	Slit-skin smears AFB 2+MI.O. Histology of the sural nerve; thickened perineurium, nerve parenchyma replaced by fibrosis and hyaline degeneration. Many granular AFB in Schwaan cells and perineurial cells. No granuloma or amyloid. Skin biopsy. No granuloma. Fibrosis and scanty lymphocytic infiltration in dermis.	Dapsone 100 mg daily rifampicin 600 mg once a month, clofazimine 100 mg alternate days + 300 mg once a month[7] till 10.10.89 when the slit-skin smears were negative.	Antileprosy drugs stopped on 10.10.89. Lagophthalmos, foot drop and claw hand persist. Patient is on follow up. No relapse of the disease.

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References

[1] El Arini F, Shehata MA, Abdel Zeid SA. Eighth cranial nerve affection in leprosy. *Int J Lepr*, 1970; **38:** 164–9.
[2] Katoch K, Ramu G, Sengupta U, Bharadwaj VP. Central nervous system involvement in leprosy. *Ind J Lepr*, 1984; **56:** 813–8.
[3] Singh TR, Agarwal SK, Bajaj AK, Singh RK, Singh MM. Evaluation of audiovestibular studies in leprosy. *Ind J Lepr*, 1984; **56:** 24–9.
[4] Chaturvedi VN, Rathi SS, Raizda RM, Jain SK. Olfaction in leprosy. *Ind J Lepr*, 1985; **57:** 814–19.

[5] Mann SBS, Kumar B, Yande R, Kaur S, Kaur I, Mehra YN. Eighth nerve evaluation in leprosy. *Ind J Lepr*, 1987; **59:** 20–5.
[6] Awasthi SK, Singh G, Dutta RK, Pahuja OP. Audiovestibular involvement in leprosy. *Ind J Lepr*, 1990; **62:** 429–34.
[7] WHO Study Group. Chemotherapy of Leprosy for Control Programmes. WHO Technical Report Series No. 675, WHO, Geneva, 1982.
[8] Masashi N, Schigenobu K. Bulbar palsy syndrome of leprosy due to cranial nerve involvement and its suppression. Abstracts of Twelfth Joint Leprosy Research Conference, Boston, 1977. *Int J Lepr*, 1978; **46:** 120–21.
[9] Norisuka S, Masashi N. Histopathological studies on leprotic bulbar palsy. Abstracts of Eighth Joint Leprosy Research Conference, San Fransisco, 1973. *Int J Lepr*, 1974; **42:** 123.
[10] Kumar B, Yande R, Kaur I, Mann SBS, Kaur S. Involvement of the palate and cheek in leprosy. *Ind J Lepr*, 1988; **60:** 280–4.
[11] Williams PL, Warwick R, Dyson M and Bannister HL, eds. *Gray's Anatomy*, 37th edition. Churchill Livingstone, Edinburgh, London, Melbourne and New York, 1989; p. 1290.
[12] Bannister R. *Brain's Clinical Neurology*, 4th edition. The English Language Book Society and Oxford University Press, London, 1973; p. 61.

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The predictive value of sensation testing in the development of neuropathic ulceration on the hands of leprosy patients

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Summary The early detection of the loss of protective sensation in leprosy patients is vital if neuropathic ulceration and subsequent disabilities are to be avoided. The aim of this study was to find protective value of sensory thresholds in the hands of leprosy patients.

Thresholds for touch-pressure, vibration and temperature were assessed in areas on leprosy-affected hands near ulcers or ulcer scars (LU-group), in areas without lesions (LN-group), and in controls (N-group). Semmes–Weinstein monofilaments were used for testing the touch-pressure threshold (PST), a biothesiometer for the vibration threshold (VST) and a Thermo Sensation Tester for the temperature threshold (TST).

The distribution of ulcers was about equal on palmar and dorsal aspects of the hands. In the LU-group there was a negative response to SWF of 2·0 g in all patients, while 74% could feel the 2·0 g in LN-areas and in N-areas 100% could detect the 2·0 g SWF. In the LU-group about 11% felt 8 V VST, in the LN-group about 60% and in the N-group 89%. Testing temperature sensation was given up prematurely because the results in controls were unsatisfactory.

Both palmar and dorsal sides of the hands should be tested for sensation. The thresholds for protective sensation are 2·0 g SWF and 8 V for vibration sense. It is recommended that Semmes–Weinstein monofilaments should always be used for early detection of loss of protective sensation.

Introduction

Nerve damage is a major problem in the treatment of leprosy patients and often results in an irreversible loss of sensation. The disabilities resulting from loss of sensation and trauma inevitably have a great impact on the patient's life. Leprosy patients with ulcers, or a history of ulcers, have clearly demonstrated the loss of protective sensation in that area on the hand. Areas without deformities, however, might already have lost their protective sensation without there being any visible signs of nerve damage (WHO-disability grading 1). These areas, therefore, might be at risk and need to be identified as

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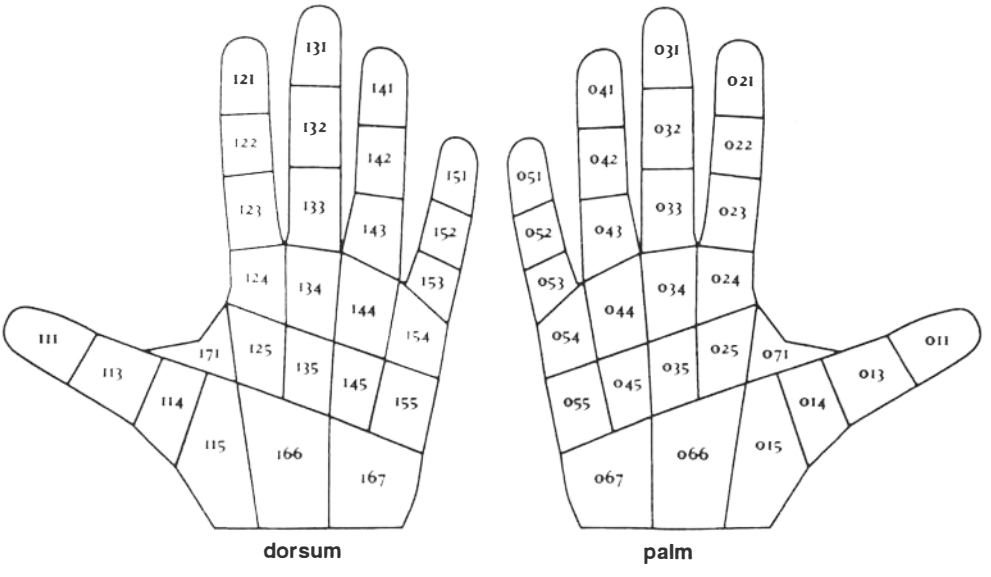

Figure 1. Chart designed according to Von Prince,[7] used for mapping the hand.

soon as possible. At first sight the choice for monitoring peripheral nerve function and protective sensation thresholds would be pain sensation testing, but for reasons of reproducibility and hygiene it was decided instead to measure touch-pressure, vibration and temperature sense. Semmes–Weinstein monofilaments (SWF) are reliable tools for testing light-touch sensation,[1] and have been used to detect nerve damage in the hand,[2] disability grading and follow-up of nerve recovery control.[3] SWF and the biothesiometer (for testing the vibration sense) have been used to measure protective sensation levels on the feet of leprosy[4,5] and diabetic[6] patients. Quite complicated instruments have been used in the past for measuring thermal sensibility and it was felt that the Thermo Sensation Tester could be used in estimating the thermal sensibility in the hand.

Materials and method

All the leprosy patients included in this study were registered at the McKean Rehabilitation Centre in Chiang Mai, Northern Thailand, which specializes in the treatment and rehabilitation of leprosy patients. The control subjects (nonleprosy) lived in the vicinity of the Centre or were patients attending a skin clinic in Chiang Mai. The exclusion criteria for both leprosy and control subjects were: diabetes mellitus, compression neuropathy of the upper extremity, drug or chemically induced neuropathy, and patients in reaction. Patients who could not complete the tests were also excluded. Name, age, sex, occupation and type of leprosy were recorded. Occupations were classified into three groups: heavy work, i.e. farming, labouring; mixed work, i.e. truck-driving, cleaning; and light work, i.e. teaching, office work and retired subjects. Absorptions, ulcers, cracks, blisters and scars on the hands were recorded in a drawing using a modified chart based on Von Prince's design[7] (Figure 1).

We selected 3 areas:

Areas on the dominant hand of a control subject (N-area)—5 points were tested on the palmar side: the distal area of the thumb, index and little finger and the proximal part of the thenar and hypothenar area, i.e. area 011, 021, 051, 015 and 067 on the chart. Controls were matched to the sex difference in leprosy (2 : 1).
Areas on the hands of leprosy patients with ulcers or a history of ulceration (LU-area). Tested points were on the perimeter of an ulcer, or other lesions, which were unquestionably of neuropathic origin. The number of areas tested on each patient was dependent on the number of lesions.
Areas without visible damage on the hands of leprosy patients (LN-area). Areas were always located distally on the digits and proximally on the palm of the hand; whenever possible, they were selected as in group 1.

A total of 150 subjects was tested, of whom 31 were controls (M : F = 21 : 10, mean age 36·6 years and age range 17–62 years), and 119 leprosy patients (M : F = 82 : 38, mean age 52·2 and age range 12–93 years).

All tests were carried out in a quiet room and all subjects were blindfolded. Each patient sat at a table with his/her hand resting comfortably on a pillow. Following an adequate explanation and demonstration of the methods of testing, the selected areas were tested. A set of 5 SWF was used: 0·5, 2·0, 5·5, 11·0 and 29·0 g (index number 3·61, 4·31, 4·74, 5·07 and 5·46, respectively) according to the technique described by Semmes & Weinstein.[8] Each SWF was applied 3 times to the respective area; 2 or 3 correct answers out of 3 tests was recorded as a positive score, and 1 or no correct answer as a negative score. The monofilaments were used randomly and the Pressure Sensation Threshold (PST) was determined by selecting the smallest SWF with a positive score. Care was taken that there were no movements of the tested hand when the SWF was applied in order to prevent any stimulation of the proprioceptive fibres.

The Vibratory Sensation Threshold (VST) was measured for all selected areas with the biothesiometer (model PVD, Bio-Medical Instrument Company, Newbury, Ohio, USA) with a fixed frequency of 120 Hz and a changing output of 0–50 V (the square voltage divided by 100 is the amplitude in micrometers). Subjects were tested following the technique described by Bloom *et al.*[9] Each selected area was tested 3 times from which the VST mean was calculated.

The Thermal Sensation Threshold (TST) was tested with a Thermo Sensation Tester, developed by the WHO.[10] Randomly the normal or the hot tip was placed on the respective areas. Subjects again responded verbally to the stimulus. Each selected area was tested 3 times with the hot tip; 2 or 3 correct answers was a positive score, and 1 or no correct answer a negative score.

Findings and results

The composition of the stratified areas is shown in Table 1.

DISTRIBUTION OF ULCERS

In 119 leprosy patients, 65 had a total of 151 ulcers, cracks, blisters and burn wounds. The type of lesion and the sex distribution are shown in Table 2.

Table 1. Area comparisons of all tested leprosy patients and controls

	N-areas ($n = 165$)	LN-areas ($n = 170$)	LU-areas ($n = 361$)
M:F	105:60	102:68	278:83
Mean age (yr)	36·6	49·3	52·1
Age range (yr)	17–62	25–79	12–92
Occupation ratio (h:m:l)	60:40:65	64:33:73	127:37:197

The lesions were on the palm in 48% and on the dorsal aspect in 52%. On the palm they were most frequently situated on the base of the hypothenar eminence (near the pisiform bone), on the tips of the thumb and index and on the proximal phalanx of the middle finger. On the dorsum the lesions were mostly located on the thumb, on the MCP of the index and on the midphalanx of the ring finger. The distribution of the lesions on the palm and dorsum is shown in Figure 2.

PST

The cumulative percentage of the PST for all areas of the LU-, LN- and N-groups is shown in Figure 3.

The type of occupation and PST in the N-group is shown in Table 3.

In the case of the N-group 13% of the areas revealed a PST higher than 0·5 g; the control subjects were able to detect the 2·0 g SWF in all areas.

VST

Of the areas tested in the N-group, 11% had a VST higher than 8 V, whilst in the LU-group 90% of the areas tested had a VST higher than 8 V. The cumulative frequency of the VST of the LU-, LN- and N-groups is shown in Figure 4.

TST

The TST of the areas tested in the N-group are presented in Table 4.

When it became apparent that a remarkably high percentage (39%) of the areas in

Table 2. Type and sex-difference for all current lesions

	Female	Male	All
Blister	3	9	12
Burn	0	11	11
Crack	10	20	30
Ulcer	24	74	98
All	37	114	151

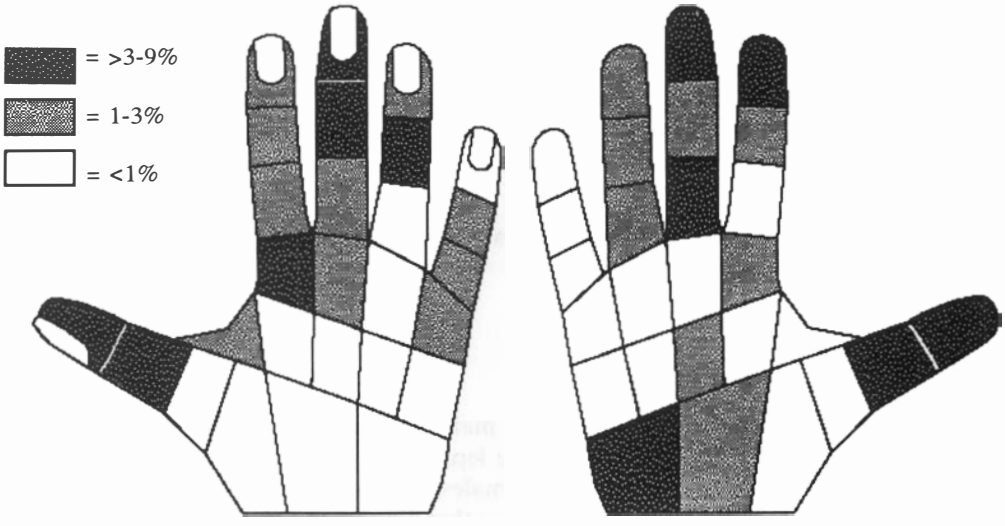

Figure 2. Distribution of lesions on the palm and dorsum of the leprosy-affected hand (expressed as percentage of all lesions).

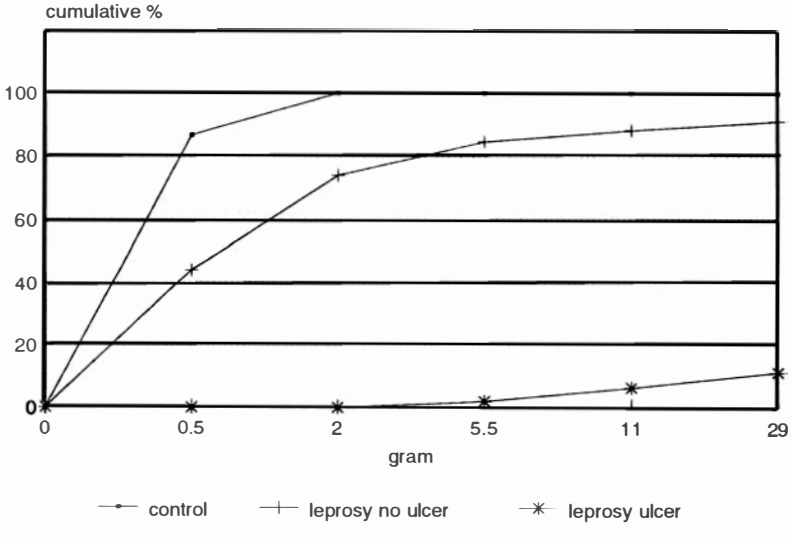

Figure 3. Cumulative percentage of pressure sensation thresholds of areas of the LU-, LN- and N-groups.

Table 3. PST for each type of occupation in the N-group

Weight (g)	Heavy occupation	Mixed occupation	Light occupation
0·5	48 (80)*	35 (88)	60 (92)
2·0	12 (20)	5 (12)	5 (8)
all	60 (100)	40 (100)	65 (100)

* Numbers in parentheses are percentages.

the N-group produced no response to the hot tip of the Thermo Sensation Tester, it was decided not to proceed with this test.

Discussion

It is known that leprosy is more common in male than in female adults (sex ratio 2 : 1 to 3 : 1)[11] which resembles the sex ratio of the leprosy patients in this study. In children there is less difference between males and females, suggesting that sociodomestic factors are quite important. There is no clear evidence that women in Thailand report leprosy or ulceration less than men because of social reasons. The controls in this study are matched to this sex difference.

Lesions were seen in 52% of areas on the dorsum of the hand. There seems to be no difference in the type of lesions between men and women (see Table 2). In preventative education, patients should certainly be taught to be alert to changes on palmar and dorsal side of the hands.

This study confirms the relation between decreased light-touch sensation and ulcers.

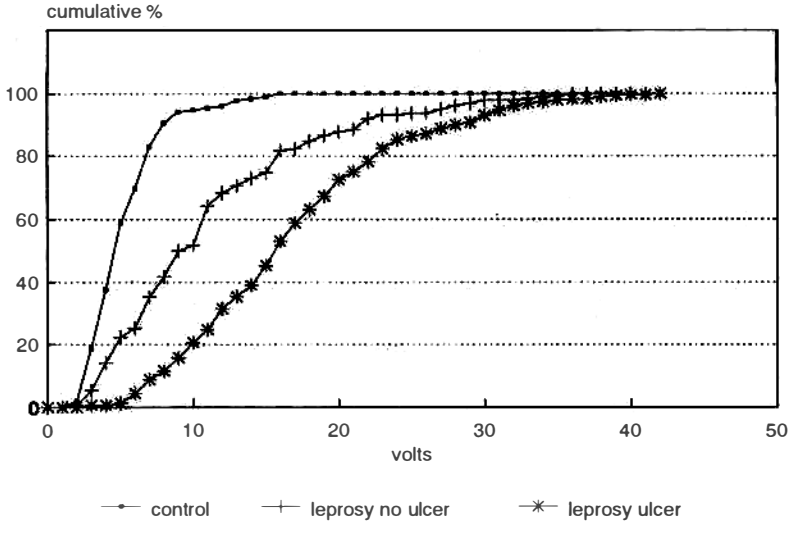

Figure 4. Cumulative percentage of vibration sensation thresholds of areas of the LU-, LN- and N-groups.

Table 4. Sensation of the hot tip of the Thermo Sensation Tester in the N-group

	Temp. sensation	No temp. sensation	All
Control subject areas	85 (61)*	55 (39)	140 (100)

* Numbers in parentheses are percentages.

In the N-group, subjects were able to feel the 2·0 g SWF in all areas, whilst the LU-group did not respond to the 2·0 g SWF in any area, so this cut-off point is accepted as the level of protective sensation. By applying this criterion it is possible to predict that 46 out of 170 tested areas in the LN-group are potentially at risk of developing ulcers. A follow-up study is needed to determine the predictability of this risk factor.

The present study demonstrated that SWF were easy for the examiner to use in practice and not too difficult for the subjects to understand. Questionable patients/subject responses were easily verifiable by the use of simple techniques, i.e. taking care to apply the stimulus randomly in time and place. It is recommended that touch pressure testing be incorporated into control programmes so that areas prone to ulceration can be monitored and treated accordingly.

The WHO recommendation to use a pencil for PST measurements is open to dispute, since it is almost impossible for staff to be able to control the pressure applied, i.e. 2·0 g. In the N-group, it was found that a surprising number of areas, especially on the hands of subjects with heavy occupations, were not responsive to the 0·5 g SWF (Table 3). This is possibly due to the number of callouses in those areas. According to Von Prince's scale, these areas should be classified as having 'diminished protective sensation'.[12] This study indicates that this scale needs to be reconsidered and possibly adjusted for use on subjects with mixed and heavy occupations.

A stimulus of 8 V cannot be detected in 11% of the areas tested in the N-group and in 90% of the LU-areas. The level of protective sensation is estimated at 8 V (0·66 μ). On the basis of this criterion it could be predicted that 69 out of 170 areas in the LN-group are at risk of neuropathic ulceration. Subjects tended to have more difficulty understanding the VST test, and the degree of guess-work is more difficult to assess than the PST test. According to Williams *et al.*'s[13] findings in VST testing, readings are inconsistent in 11% of the cases. In the light of these results and the added disadvantages of the biothesiometer (safety, repair, calibration, electricity dependency and costs of purchase)[14] it was concluded that this apparatus is inappropriate. The use of tuning forks might be considered.

It was assumed that the Thermo Sensation Tester would be useful in TST testing, but experience has shown that in the N-group there was a failure to distinguish the hot tip from the normal tip in a surprising 39% of the tested areas. The conclusion must be drawn, therefore, that the Thermo Sensation Tester is of little or no use in assessing hand nerve functions.

It must be acknowledged that loss of protective sensation is not the only factor of development in ulcers. Other factors include loss of autonomic (dryness) and motor-function (clawing), the way in which hands are used and the degree of care they receive. The prevention of diability is an attempt to improve hand-care in general and to adapt

tools to insensitive hands. These are essential elements of treatment, and they should be extended for subjects with areas at risk, and should be incorporated into the patient's general life in such a way that no new stigmas are created as a result.

Conclusion

Within the limitations of this study it is feasible to conclude that:
Distribution of lesions indicates a remarkable high percentage (52%) on the dorsum of the hand. The registration and monitoring of this occurrence should not be overlooked in the future.
The level of protective sensation in the hand is 2·0 g SWF. A prospective study is needed to determine the predictability of developing neuropathic ulceration or other lesions.
The Von Prince standard sensory threshold scale[7] needs to be adjusted.
Biothesiometry is both more complicated and less accurate than the SWF in distinguishing areas in control subjects from lesion areas in leprosy patients.
The newly-developed Thermo Sensation Tester is deemed inappropriate for measuring thermal sensibility thresholds on the hand.

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References

[1] Bell-Krotoski J, Tomancik E. The repeatability of testing with Semmes–Weinstein monofilaments. *J Hand Surg*, 1987; **12-A:** 155–61.
[2] Palande DD, Bowden REM. Early detection of damage to nerves in leprosy. *Lepr Rev*, 1992; **63:** 60–72.
[3] Naafs B, Dagne T. Sensory testing: a sensitive method in the follow-up of nerve involvement. *Int J Lepr*, 1977; **45:** 364–8.
[4] Birke JA, Sims DS. Plantar sensory threshold in the ulcerative foot. *Lepr Rev*, 1986; **57:** 261–7.
[5] Hammond CJ, Klenerman P. Protective sensation in the foot in leprosy. *Lepr Rev*, 1988; **59:** 347–54.
[6] Holewski JJ *et al*. Aesthesiometry: Quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. *J Rehab Res*, 1988; **25:** 1–10.
[7] Von Prince K, Butler B. Measuring sensory function of the hand in peripheral nerve injuries. *Am J Occ Ther*, 1967; **21:** 385–95.
[8] Semmes J, Weinstein S. *et al*. Somatosensory changes after penetrating brain wounds in man. Cambridge, 1960, Harvard University Press, pp. 4–11.
[9] Bloom S. *et al*. Use of a biothesiometer to measure individual vibration thresholds and their variation in 519 non-diabetic subjects. *Br Med J*, 1984; **288:** 1793–5.
[10] Srinivasan H, Stumpe B. Value of thermal sensibility testing in leprosy diagnosis in the field—field trial of a pocket device. *Lepr Rev*, 1989; **60:** 317–26.
[11] *Hunter's Tropical Medicine*, ed. G. T. Strickland, W. B. Saunders Company, Philadelphia, 7th edition, p. 485.

[12] Von Prince K, Butler B. Measuring sensory function of the hand in periferal nerve injuries. *Am J Occ Ther*, 1967; **21:** 385–95.
[13] Williams G. *et al*. Variability in vibration perception threshold among sites: a potential source of error in biothesiometry. *Brit Med J*, 1988; **269:** 233–5.
[14] Watts GF, Shaw KM, Long G. Warning on the use of the biothesiometer. *Daib Med*, 1986; **3:** 91.

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Measurement of pressure walking in footwear used in leprosy

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Summary Pressure measurements were made on 10 leprosy patients while walking barefoot and while using 6 sample shoes. The sample shoes, which represented footwear currently used worldwide in leprosy programmes, included: 1, a USA extradepth shoe without insole; 2, a USA extradepth shoe with insole; 3, a Chinese tennis shoe; 4, a Mozambique sandal; 5, a Bombay sandal; 6, a Bombay sandal with rigid sole; and 7, the patients' prescribed footwear. Peak pressure was significantly lower while walking in all footwear, except with the extradepth shoe without an insole, when compared to barefoot walking. Peak pressure was significantly lower walking in the Bombay sandals, the Chinese tennis shoe, the extradepth shoe with an insert and the patients' prescribed shoe when compared to the extradepth shoe without an insert. Regression analysis showed a significant inverse relationship between pressure and insole thickness ($P < 0{\cdot}001$, $R^2 = 0{\cdot}17$).

Introduction

Neuropathic plantar ulcerations usually result from repetitive stress on the foot.[1,2] Studies demonstrate that neuropathic plantar ulcerations develop over areas of high pressure associated with deformity or joint limitation.[3–5]

Footwear and insoles designed with soft elastic materials, moulded insoles and/or rigid rocker soles have been recommended to reduce pressure and prevent plantar ulceration in leprosy.[6–10] The effectiveness of these devices has been generally based on qualitative measurements using the Harris mat and Carville microcapsule socks.[11,12] Bauman *et al.*[13] demonstrated, using noncommercial pressure transducers, the effectiveness of soft material and a rigid rocker sole on reducing plantar pressure. Transducer systems, however, provide only limited measurement of plantar pressure and suffer from

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measurement errors due to sensor thickness, movement, and interaction of the foot/shoe interface on the transducer.[11,14] The recent development of commercially available inshoe pressure measurement systems (FSCAN, Tekscan Inc, Boston, MA and EMED, Novel USA, Minneapolis, MN) have provided the methodology to quantitatively evaluate footwear and insole designs. These systems utilize inshoe mats containing an array of sensors which measure pressure over the entire plantar surface of the foot. The FSCAN sensor mat, measuring 0·178 mm thick, should minimize measurement error resulting from interactions at the foot/sensor/shoe interface.

Rose *et al.*[15] found, using an early version of FSCAN (version 1.20), that the system was reliable when the same sensor was used for repeated tests of less than 12 walking trials. Variation was noted between sensors, and after 12 walking trials pressure measurements significantly decreased. The FSCAN manufacturer has developed new sensors designed to be resistent to failure, and the updated software (version 3.601) provides for sensor calibration before testing.

Patients with sensory loss and deformity are considered to be at high risk of ulceration.[16] High-risk patients should be provided with protective footwear as part of a foot deformity prevention programme. Demonstrating the effectiveness of protective footwear is a critical issue for prevention programmes.[14] Programme managers and clinicians need data to support the purchase and distribution of specific footwear designs. Footwear should be shown to be effective in reducing pressure, not harmful to the foot, acceptable to the patient, and cost-effective.

Method

This study evaluated the effectiveness of a sample of footwear currently used by leprosy sufferers. The footwear tested were selected by The Footwear Committee, The Leprosy Mission. Inshoe pressure measurements were made on 9 male and 1 female leprosy patients of the Gillis W. Long Hansen's Disease Center, Carville, LA. Measurements were made during walking using the FSCAN System (software version 3.601) and concurrently using the EMED Platform (Novel USA, Minneapolis, MN) during barefoot walking. The peak pressure for the patients' high risk area on the barefoot trial was used for comparisons (Figure 1). Measurements were made in the middle of a 20 foot walking trial. Each FSCAN sensor was calibrated before testing using a pneumatic calibration device (Novel USA, Minneapolis, MN). Measurement of a standard 500 KPa pressure was made before and after testing each subject. Speed of walking was measured using a photoelectric trigger (Model 49310, Radio Shack, Fort Worth, TX) and electronic counter (DC 503 Universal Counter, Tectronix, Inc, Beaverton, OR) to maintain a self-selected pace during each trial. The test conditions (Figure 2) for each subject included:

1 barefoot;
2 extra depth shoe (P. W. Minor Shoes, USA) with a poron insole;
3 extra depth shoe (P. W. Minor Shoes, USA) without an insole;
4 tennis shoe (commercial, China) with 2 microcellular rubber insoles;
5 sandal (handmade, Mozambique) with a microcellular insole;
6 sandal (commercial, Bombay) with a microcellular rubber insole;

7 sandal (commercial, Bombay) with a microcellular rubber insole and metal stave for rigidity; and
8 the patients' prescribed footwear (not standardized)

Test conditions were randomized by lottery. The mean of 4 steps of walking were used to analyse pressure during walking. Statistical analysis was made using an analysis of variance for repeated measures. A Duncan's test was used for comparisons between test conditions. A Pearson correlation and a paired *t*-test were used to compare concurrent validity of FSCAN and EMED measurements barefoot. A paired *t*-test was used for comparison of the standard 500 KPa load before and after testing to determine if there was a systematic source of measurement error.

Footwear were compared for the following design characteristics: insole thickness, insole firmness, toespring height, heel height, sole firmness, and sole stiffness (Table 1). A

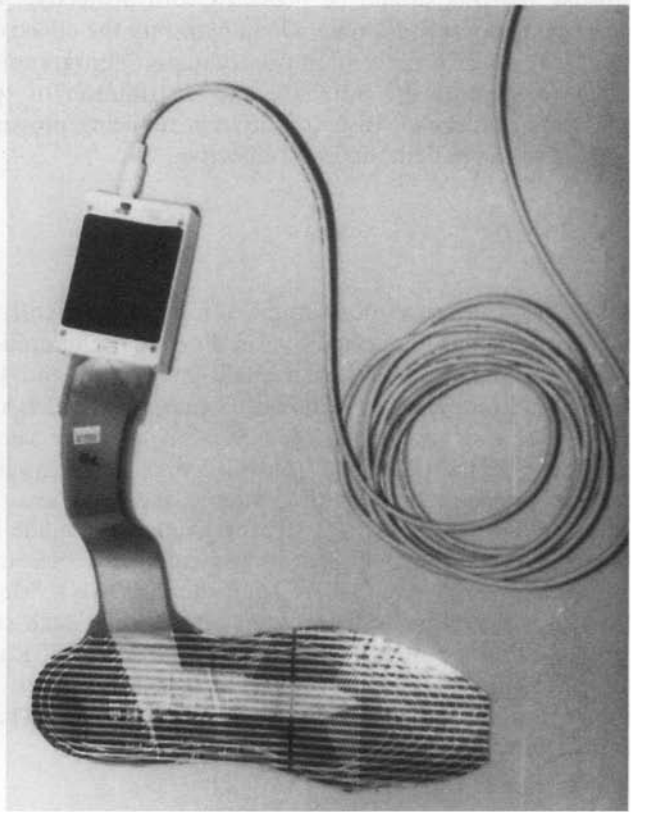

Figure 1(a)

Figure 1. (a) FSCAN inshoe pressure sensor and cuff unit; (b) 3-dimensional FSCAN recording barefoot shows the great toe to be the high risk area in this patient; (c) numerical mapping for the same step barefoot shows the peak pressure to be 1620 KPa; (d) 3-dimensional recording on the same individual walking in the Bombay sandal shows a significant reduction in peak pressure at great toe; (e) numerical mapping for the same step in the Bombay sandal shows the peak pressure at the great toe to be 688 KPa.

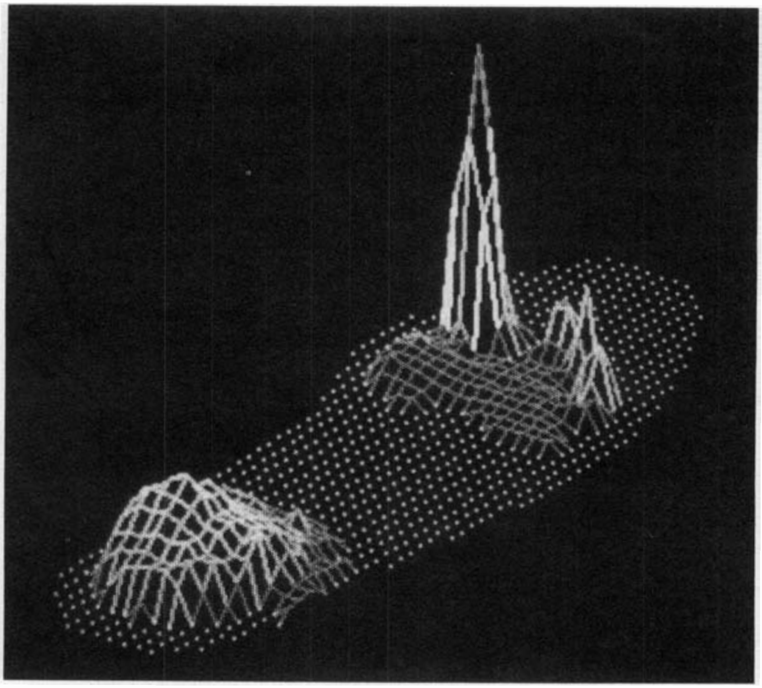

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Figure 1(b) and (c)

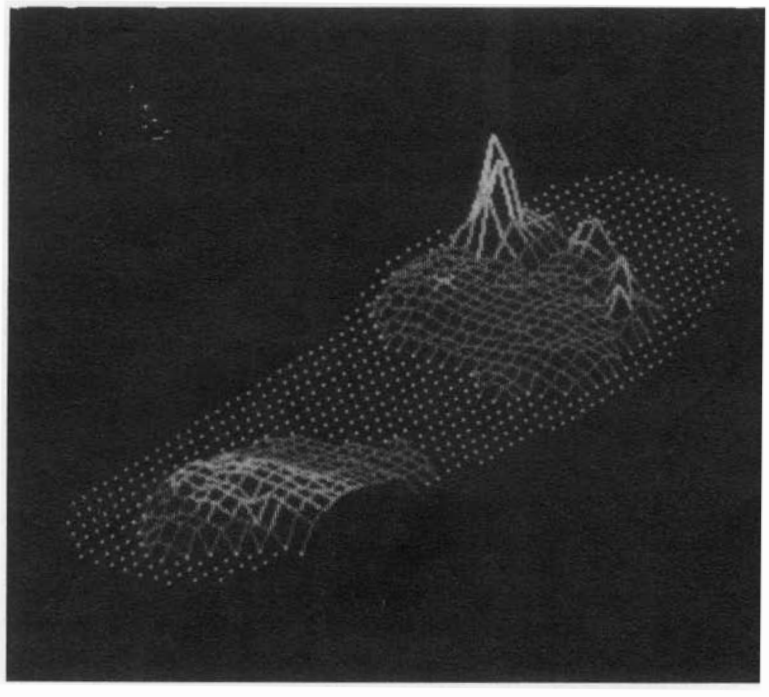

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Figure 1(d) and (e)

Figure 2. Footwear used for testing: (left to right) the Chinese tennis shoe, the Bombay sandal, the Mozambique sandal, the USA extradepth shoe.

durometer (type O, Rex Gauge Co, Glenview, IL) was used to measure insole and sole firmness in degrees shore. A cantilever straingauge (GWLHDC, Carville, LA) was used to measure sole stiffness in mm gm torque (Figure 3). Regression analysis was used to show the relationship between foot pressure and footwear characteristics.

Results

Analysis of variance showed a significant difference in peak pressure between various walking conditions ($p < 0{\cdot}0001$). Duncan's multiple range test showed that all footwear conditions, except the extradepth shoe without an insole, had significantly lower peak pressures when compared to barefoot walking (Table 2). The Bombay sandal, the Chinese tennis shoe, the extradepth shoe with an insert and the patients' prescribed shoe had significantly lower peak pressures compared to the extradepth shoe without an

Table 1. Characteristics of sample footwear

Footwear tested	Toespring height (mm)	Heel height (mm)	Insole thickness (mm)	Insole firmness (Durometer)	Outsole firmness (Durometer)	Sole stiffness (gm mm)
Bombay sandal	14*	9	10	33	68	780
Bombay sandal with rigid stave	14*	9	10	26	68	2000
Chinese tennis shoe	10	0	14 (2 at 7 mm)	35	72	940
Mozambique sandal	19*	10	5	22	73	730
P. W. minor shoe with insole	11	17	7	21	66	1630
P. W. minor shoe without insole	11	17	0	80	66	1630

* Measurements variable.

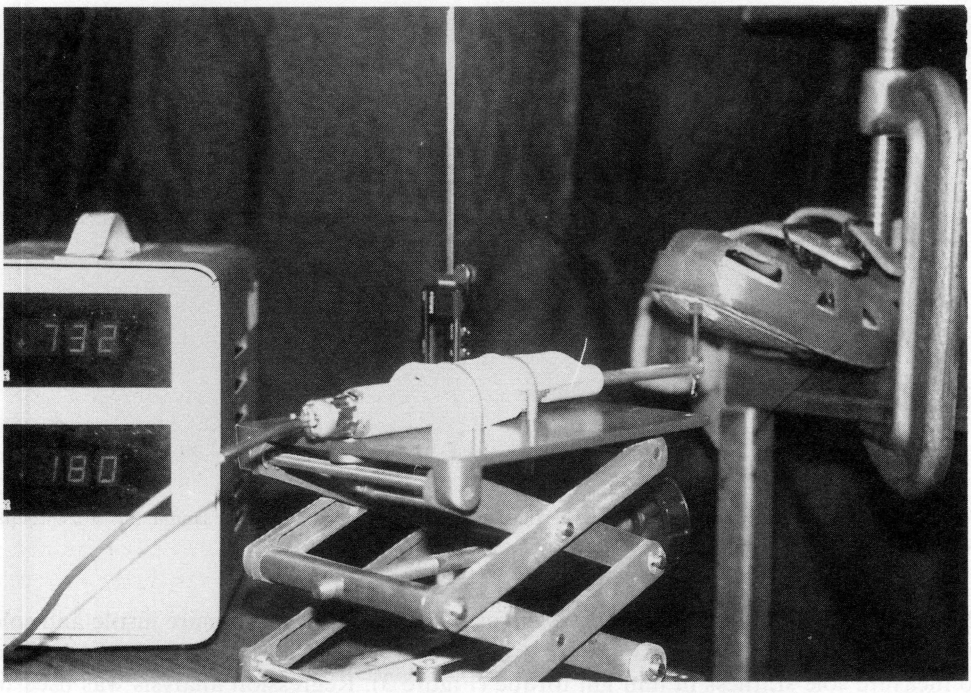

Figure 3. Cantilever straingauge used to measure sole stiffness.

insert. The Chinese tennis shoe and the Bombay sandal without a stave had significantly lower peak pressure than the Mozambique and extradepth shoe without an insole. The patients' prescribed shoe had significantly lower peak pressures than the Mozambique sandal and the extradepth shoe with an insole.

Regression analysis showed a significant inverse relationship between peak pressure and insole thickness ($p < 0{\cdot}001$, $R^2 = 0{\cdot}17$). A significant relationship was not found for the shoe characteristics of insole firmness, toespring height, heel height, sole firmness, or sole stiffness.

Table 2. Comparison of mean peak walking pressures ($n = 10$)*

Footwear tested	Mean (kPa)	Comparison of means†
Barefoot	1194·4	a
P. W. minor without insole	985·5	a, b
Mozambique	840·7	b, c
P. W. minor with insole	645·2	c, d
Bombay with stave	594·3	c, d, e
Chinese	549·2	d, e
Bombay without stave	508·5	d, e
Patients prescribed	359·5	e

* Peak pressures for patients' high risk area on the barefoot trial.
† a > b > c > d > e; $p < 0{\cdot}05$.

There was a small but significant difference between the initial and the final 500 KPa standard pressure test ($p < 0{\cdot}0265$). Initial mean pressure was $463{\cdot}9 \pm 25{\cdot}1$ KPa and the final pressure was $430{\cdot}6 \pm 45{\cdot}9$ KPa. This represents a 7% loss in pressure after 7 trials of walking 20 feet.

There was a significant correlation between FSCAN and EMED barefoot measurements ($r = 0{\cdot}85$, $p < 0{\cdot}0018$). Mean FSCAN barefoot measurements ($1199{\cdot}4 \pm 617{\cdot}7$ KPa, range 295·0–2330·0 KPa) were significantly higher ($p < 0{\cdot}0607$) than mean EMED barefoot measurements ($943{\cdot}0 \pm 330{\cdot}5$ KPa, range 280·0–1280·0 KPa).

Discussion

These results demonstrate that all the footwear tested were effective in reducing peak walking pressure, apart from the extradepth shoe without an insole. Based on regression analysis, a thick insole was the footwear feature which was most significantly associated with lower pressures. Weak relationships were also found for insole firmness and heel height. Rose *et al.*[15] also found heel height was positively related to foot pressure in normal subjects. This study was not designed to show strong relationships between pressure and shoe characteristics, because the footwear tested did not vary greatly for the traits tested. In particular, all the footwear tested had soft insoles except for the extradepth shoe without an insole.

This study investigated whether a stiff *versus* flexible sole footwear is more effective in reducing pressure. Regression analysis showed no significant relationship between sole stiffness and peak pressure. Peak pressure was not significantly different walking in the Bombay sandal with and without a rigid stave fit beneath the insole. Future studies should be designed to determine the relationship between plantar pressure and shoe characteristics in leprosy patients.

The most effective footwear in this study were the patients' prescribed footwear. The patients' footwear were not standardized, and included cases with moulded insoles and rocker soled shoes. Moulded insoles and rocker sole modifications may more effectively reduce pressure than the flat soft insoles which characterized the footwear sampled in this study. Shoes with flat insoles are easy and inexpensive to produce and ideal for prevention programmes. Further studies are needed to compare the effectiveness of flat soft insoles, moulded insoles, and rocker soles in reducing foot pressure in patients with leprosy.

This study supports the findings of Rose *et al.* that a reduction in pressure is expected during the continual use of FSCAN sensors. FSCAN sensors should not be used under conditions which require long repeated walking trials, since pressure readings are related to use. Research using the FSCAN should randomly assign treatments so that a systematic error is not caused by the testing order.

The concurrent validity between FSCAN and EMED peak pressure measurements was shown to be good. Peak pressure walking barefoot was higher using the FSCAN when compared to the EMED System, and 2 subjects had readings at the maximum testing range on the barefoot trial for the EMED system. The maximum reading for the EMED system is 1270 KPa and peak pressure was probably underestimated in these cases. Differences in barefoot pressure measured by both systems may have resulted from limitations in the method of calibration of the FSCAN sensors. The EMED system

provides for calibration of individual transducers within the platform. The FSCAN system provides for the calibration of the entire sensor but not the individual sensels. However, we have not found sensels to vary greatly from each other after calibration. In this study, FSCAN sensors were calibrated cold while walking measurements were made within a warm shoe interior. Cold sensor calibration, however, would have resulted in an underestimation of pressure measurements inside the shoe. Errors due to limitations in calibration of the FSCAN system may be minimized by utilizing a repeated measures research design where the same sensor is used for all treatment trials on a given subject, and absolute pressure measurements are less important.

FSCAN peak pressure barefoot measurements exceeded 700 KPa on 8 patients and 1380 KPa on 3 patients. Cavanagh and Ulbrecht[17] determined, using a piezoelectric pressure mat, that a 750 KPa pressure was the threshold for injury in the neuropathic foot. The finding of high peak pressures in this leprosy population is consistent with previous studies on diabetic patients, which have found high foot pressures associated with neuropathy and plantar ulceration.[3,4,18] Studies have not determined a risk level for high pressure in the neuropathic foot using the EMED and FSCAN systems.

Conclusions

Within the limitations of this study it is possible to conclude the following:

The sample footwear used by leprosy programmes for prevention of foot ulcers were effective in reducing plantar pressure.

2 There was a significant inverse relationship between pressure and insole thickness ($p < 0{\cdot}001$, $R^2 = 0{\cdot}17$).

3 The relative accuracy of the FSCAN inshoe pressure system was shown to be good within the limited testing conditions.

References

[1] Hall DC, Brand PW. The etiology of the neuropathic ulcer. *J Am Podiatry Assoc*, 1979; **69:** 173–7.

[2] Brand PW. The insensitive foot (including leprosy). In: *Disorders of the Foot* Jahss M (ed). Philadelphia: W. B. Saunders, 1982; 1266–86.

[3] Ctercteko GC, Dhanendran M, Hutton WC, Le Quesne LP. Vertical forces acting on the feet of diabetic patients with neuropathic ulceration. *Br J Surg*, 1981; **68:** 608–14.

[4] Veves A, Fernando DJS, Walewiski P, Bouton AJM. A study of plantar pressures in a diabetic clinic population. *The Foot*, 1991; **35:** 89–91.

[5] Fernando DJS, Masson EA, Veves A, Boulton AJM. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care*, 1991; **14:** 8–11.

[6] Fritschi EP. *Surgical Reconstruction and Rehabilitation in Leprosy*. The Directory for Southern Asia Leprosy Mission, New Delhi, 1986; 227–44.

[7] Ross WF. Footwear and the prevention of plantar ulcers. *Lepr Rev*, 1962; **33:** 202.

[8] Ward D. Footwear in leprosy. *Lepr Rev*, 1962; **33:** 94–105.

[9] Enna CD, Brand PW, Reed JK, Welch D. Orthotic care of the denervated foot in Hansen's disease. *Orthot Prosthet*, 1976; **30:** 33-00.

[10] Hampton GS. Therapeutic footwear for the insensitive foot. *Phys Ther*, 1979; **59:** 23.

[11] Shipley DE, Miner KM. The role of physical therapy in foot problems. In: *Surgical Rehabilitation in Leprosy*, McDowell F, Enna CD (eds). Baltimore: Williams & Wilkins Co, 1974; 301–12.

[12] Shipley DE. Clinical evaluation and care of the insensitive foot. *Phys Ther*, 1979; **59:** 13.

[13] Bauman JH, Girling J, Brand PW. Plantar pressures and trophic ulceration. *J Bone Joint Surg*, 1963; **45B:** 652–73.

[14] Cavanagh PR, Hewitt FG, Perry JE. In-shoe plantar pressure measurement: A review. *The Foot*, 1992; **2:** 185–94.
[15] Rose NE, Feiwell LA, Cracchiolo A. A method for measuring foot pressures using a high resolution, computerized insole sensor: the effect of heel wedges on plantar pressure distribution and center of force. *Foot & Ankle*, 1992; **13:** 263–70.
[16] Birke JA, Sims DS. The insensitive foot. In: *Physical Therapy of the Foot and Ankle*, Hunt GC (ed). New York: Churchill Livingstone. 1988; 133–68.
[17] Cavanagh PR, Ulbrecht JS. Plantar pressure in the diabetic foot. In: *The Foot in Diabetes*, Sammarco GJ (ed). Philadelphia: Lea & Febiger. 1991; 54–70.
[18] Boulton AJM, Hardisty CA, Betts RP, Franks CI, Worth RC, Ward JD, Duckworth T. Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy. *Diabetes Care*, 1983; **6:** 26–33.

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Transmission of health information on leprosy from children to their families in an urban centre

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Summary A health education study utilizing a homework assignment was carried out in a private secondary school in Bangalore, South India, to determine whether health information about leprosy would be transferred from children to their families. After a pre-test questionnaire on knowledge and attitude about leprosy was administered to 3 Standard VII classes and their family members, a different comprehensive health education session was given to each class: (i) leprosy plus a homework assignment; (ii) leprosy alone; and (iii) tuberculosis alone. A post-test questionnaire was administered to all participants 1 month later.

Of the 118 children and 229 family members who entered the study, almost 80% of the participants completed it. The children in the leprosy-educated groups showed significant improvement in knowledge compared with controls, but no change in their attitude towards leprosy. Although post-test responses of household members showed modest improvement in knowledge about leprosy, attitudes remained the same or worsened. The homework assignment did not appear to improve the transmission of health information to household members.

This study showed that the knowledge level of family members in South India could be improved modestly by educating their children about leprosy. However, attitudes towards leprosy were unaffected or worsened.

Introduction

In 1990 Premkumar and his colleagues reported on a controlled study in a rural area of South India which was designed to determine whether health information given to schoolchildren would influence the knowledge and attitudes of their families about leprosy.[1] Although significant improvement in knowledge about leprosy was detected in

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the educated children, no transmission of information to their family members was detected. Also, the attitudes of children who had been educated about leprosy appeared to be adversely affected by the health education session.

The present study was an extension of the initial study with several important differences. The study population was larger and came from an urban centre. In addition, a homework assignment was added in order to encourage children to discuss with their families health information acquired in the classroom.

PATIENTS AND METHODS

In 1990 a health education study was carried out in a private secondary school in Bangalore, Karnataka, S. India. Children attending the school were drawn from middle-class families living in Bangalore (70% of the male household heads were officers, clerks, professional persons or skilled labourers, more than 80% of these individuals had matriculated from secondary school, and the majority had post-secondary school education).

There were 700 children in the school which had classes from Standard I to X. A Standard VII class (aged 11–13) was chosen for the investigation. Males made up 50% of the classes. Approximately 85% of the children came from Christian families, with the remainder from Hindu and Muslim.

During the first part of the study, the knowledge and attitude of 3 classrooms of children and their family members concerning leprosy was tested by means of a standardized questionnaire which was administered in English by a health care worker. The 32 questions either required a yes/no response or were the open-ended type for which the evaluator filled in the response. This pre-test questionnaire did not focus specifically on leprosy but contained a number of questions about tuberculosis and AIDS. It tested attitudes and several areas of knowledge about leprosy such as the aetiology of leprosy, its curability, contagiousness and recognition. In addition to knowledge acquisition as a means to determine transfer of information from children to their families, we questioned household members about their familiarity with leprosy and where that knowledge was acquired.

The participants were not informed about the purpose of the study or what might be expected of them in the future—1 month after the pre-test questionnaire was administered, the 3 Standard VII classes received a comprehensive educational session. Class (A) learned about leprosy and was given a homework assignment on the subject which they were specifically asked to discuss with their family members. Class (B) received the identical educational session on leprosy but was not given a homework assignment. Class (C) was given a comprehensive educational session on tuberculosis.

The children and their family members were re-tested with the identical questionnaire (post-test) 1 month after the educational sessions, and in the same fashion as at the start of the study.

As noted in Table 1, there were no significant differences between the 3 classes of children and their families with respect to age, gender, education level and occupation: 41 of 45 children in a class were enrolled in group A, 36 of 50 in another class were enrolled in Group B and 27 of 44 children in a 3rd class were enrolled in group C. Students not enrolled in each class were those who were absent on the day that the pre-test questionnaire was administered. The mean age of the children in groups A, B and C

Table 1. Demographic characteristics of the household members of the 3 groups of children who completed this study

Characteristics	Educational session		
	Leprosy plus homework (A) ($n = 76$)	Leprosy alone (B) ($n = 73$)	Tuberculosis (C) ($n = 80$)
Mean age (years):	37·2 ± 9·53	39·1 ± 10·4	37·3 ± 8·9
Sex:			
M	40 (53)	36 (50)	37 (46)
F	36 (47)	37 (50)	43 (54)
Education:			
literate	5 (6)	5 (6)	3 (4)
primary	1 (1)	3 (4)	1 (1)
secondary	5 (6)	10 (13)	11 (15)
matriculate	12 (15)	23 (29)	19 (26)
P.U.C./technical diploma	18 (24)	17 (21)	18 (25)
graduate/prof. degree	26 (36)	18 (22)	15 (21)
post-graduate/prof. degree	9 (12)	4 (5)	5 (8)
Occupation:			
housewife	22 (30)	30 (38)	22 (32)
student	2 (3)	4 (5)	3 (4)
manager	7 (10)	1 (1)	4 (6)
officer	7 (10)	4 (5)	6 (9)
clerk	7 (10)	8 (10)	9 (13)
professional	16 (22)	10 (12)	13 (19)
skilled labourer	7 (10)	8 (10)	8 (11)
unskilled labourer	1 (1)	2 (2)	0 (0)
agricultural worker	0 (0)	0 (0)	0 (0)
shop/factory owner	3 (4)	7 (9)	4 (6)
other		6 (8)	

was 12·2, 12·8 and 12·5 years, respectively. The gender ratio and religious composition were similar for both groups. Statistical analysis was carried out by the Wilxocon signed rank test and χ^2 analysis.

Results

In total, 118 of 139 children (85%) in the 3 classes and 229 of the 269 family members (85%) entered the study. Of those who were entered, 89 of the children and 183 of the adults completed the study with a compliance of 75% and 80% for children and adults, respectively. Overall, 93 of 139 (67%) family units completed the study. Family unit compliance was 69% in group A, 60% in group B and 72% in group C. The family members and students who entered, but did not complete the study were unavailable for follow-up or refused to take part in the second half of the study.

In the analysis of the results of the pre-test questionnaire no significant differences were found in knowledge level or attitude concerning leprosy between the study groups of children or their families except that the 2 groups of children who were taught about leprosy feared the disease more than the control children at the start of the study.

Table 2. Knowledge level of schoolchildren and their families about leprosy

Sample questions	% Response					
	Children			Families		
	A	B	C	A	B	C
1 Cause of leprosy: germs/sneezing						
pre:	15	24	24	14	18	38
post:	72*	58*	57*	58*	49*	37
heredity						
pre:	46	63	64	57	60	70
post:	16*†	61	38*	61	31*	44*
sexual transmission						
pre:	34†	56	70	50	68	52
post:	36†	49	64	55†	48*†	76*
2 Can leprosy be acquired by touching? (no)						
pre:	52	66	60	46	40	54
post:	48	63	66	42	54	69
3 Who spreads leprosy? (infectious persons only)						
pre:	18	26	36	50	25	27
post:	73*†	52*†	30	81*†	53*	39
4 How to detect leprosy? (% of 14 signs/symptoms identified)						
pre	31	29	26	27	31	34
post:	32	44*	45*	37	36	46
5 Can leprosy be cured? (yes)						
pre:	93	89	94	75	82	71
post:	100	100	92	90	82	89

+, * $p < 0{\cdot}05$ χ^2 analysis: *, (pre-test *vs* post-test within the group); †, (result *vs* control group C).
( ), correct response

In the evaluation of the post-test questionnaire responses, children in groups A and B (those educated about leprosy) showed significant improvement in knowledge in 2 and 3 of the 5 areas tested, respectively. In group B, knowledge improved in all but 1 area. On the other hand, the control group of children (C) showed significant improvement in 2 areas only and no tendency to improvement in other areas. Compared with group C, the post-test knowledge level of those who had been educated about leprosy was statistically significantly improved in 2 areas (the aetiology and transmission of leprosy). In spite of improvement in their knowledge base, the attitudes of the children were basically unchanged. In fact, in Group A there was a tendency towards a worsening of attitudes since after the health education session, fewer of these children were willing to employ persons who had been successfully treated for leprosy or invite them to eat in their homes. This change in attitude did not reach statistical significance.

An analysis of the post-test responses of household members in all 3 groups showed that there was improvement in knowledge concerning leprosy. Statistically significant improvement in knowledge of the aetiology of leprosy was noted in all 3 groups and about transmission groups A and B. However, there was a trend to improvement in knowledge in at least 2 other areas in both A and C household members. With 2 exceptions, there were no significant differences in the post-test responses between the

Table 3. Attitudes of school children and their families about leprosy

Questions	% Response					
	Children			Families		
	A	B	C	A	B	C
1 Leprosy feared most (Yes, compared with TB, cancer and AIDS)						
pre:	12†	7†	39	4	4	3
post:	0†	11†	27	1	3	3
2 Leprosy like other diseases (yes)						
pre:	30	48	30	33	34	30
post:	52	55	40	54*	57*	45
3 Would you offer food in your home to a person with leprosy? (yes)						
pre:	45	37	36	62	59	51
post:	27	40	30	35	63	64
4 Would you employ a person who had been successfully treated for leprosy (yes)						
pre:	48	55	61	47	38	52
post:	36	52	55	39	47	49

*, † $p < 0{\cdot}05$ χ^2 analysis: *, (pre-test *vs* post-test within the group); †, (result *vs* control group C).

leprosy-educated groups and controls. Overall, among family members there was no significant change in attitude except in group A families who, like their children, showed a worsening of attitude about employing and sharing food with a person who had been successfully treated for leprosy.

When we enquired from family members whether they had received information about leprosy from their children, 55% of group A, 63% of group B and 42% of group C indicated that their child had brought home information from school approximately 1 month before the follow-up questionnaire was administered. In all, 16% of the family members of group A, 22% of group B and 32% of group C said that they had not received this information. The remaining household members could not recall whether they had or had not received information about leprosy from their children.

Discussion

In order to ascertain whether health information might be imparted from schoolchildren to their families, we first had to assess whether or not the children gained in knowledge from the health education session. We did detect significant improvement in knowledge among those educated about leprosy and a modest improvement in the controls. The change in the control group likely occurred because of a sharing of information from the leprosy educated groups. Alternatively, the questionnaire itself may have stimulated the group C students to learn more about the subject from other sources and to share this knowledge with their families. Although we could have chosen our control group from a

different institution, we wanted to ensure that the 3 groups were comparable in all respects and therefore carried out the study in 1 school. In retrospect, it might have been wiser to go with the former option.

As noted in our previous study, in spite of an increase in knowledge on the subject, the students' attitude towards leprosy did not change and, in the case of group A students, appears to have worsened. However, unlike the results in our previous study, students did not admit to fearing the disease more after the health education session. They just did not want to have personal contact with a person with leprosy even if that person had been treated successfully.

It was interesting to note that this same attitudinal change was seen only in the families of group A students. We considered several possible explanations for these disturbing findings. First, it is well-known that change in knowledge does not in itself guarantee a change in attitude. This finding emphasizes the need for a more in-depth discussion by health educators of cultural taboos and irrational fears concerning leprosy. 'Booster doses' of health education might also help to affect an attitude change. With centuries of stigma to overcome, it may be too much to expect a single health education session to affect attitudinal changes towards leprosy.

It might have been postulated that since group A had the homework assignment to discuss with their families, pre-existing prejudice towards persons with leprosy by family members might have accounted for the worsening attitudes of group A students. However, the results of the pre-test questionnaire did not show group A family members to be more negative than the other groups towards persons with leprosy.

The more disturbing finding was the definite trend for group A family members, like their children, to reject persons with leprosy to a greater extent after the health education session. Perhaps discussions about leprosy awoke old prejudices or fears. Alternatively, it is possible, but unlikely, that during the session with students in group A, the health educator inadvertently enhanced the pupils' fear of leprosy which was then transferred to their families. Since both of our studies employing different health educators for students and families of very different backgrounds showed very similar results we are convinced that our findings reflect a definite failure of a single health education session to alter attitudes towards leprosy. We feel that more research needs to be done on ways in which knowledge of leprosy can be used to affect a change in the age-old prejudices about the disease in endemic areas.

In contrast to our previous study, there was definite transfer of health information on leprosy from children to their families. This was confirmed by the proportion of household members who could recall having received information on leprosy from their children during the study period. It was interesting to note that in the present study more than 50% of family members of the students educated on leprosy recalled learning about the subject from their children compared with only 8% in our previous study. This difference is probably explained by the fact that our previous study was carried out in a rural population of lower socioeconomic status compared with a well-educated middle class population in our present study. Intuitively, one might expect more communication to occur between student and parent in the latter population. However, in spite of the study design which was geared to maximize knowledge transfer among group A students, we did not find that the homework assignment offered a significant advantage over a standard health education session.

The results of out study in South India demonstrate that by educating urban, middle

class children about leprosy, the knowledge level and perhaps the attitudes of their families concerning leprosy can be influenced. Although our study showed that health education did not uniformly generate positive attitudes towards leprosy, a single session may not have been sufficient. It is likely that ongoing, continuous health education is needed in order to reinforce concepts and influence attitudes. More studies of this type are needed, particularly to assess the optimal types of educational activities which are most likely to affect attitudinal changes both in students and their families.

Reference

[1] Premkumar R, Keystone JS, Christina M, Jesudasan K. Transmission of health information on leprosy from children to their families: another approach to health education. *Lepr Rev*, 1991; **62:** 58–64.

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Dapsone agranulocytosis in a leprosy patient

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Summary Dapsone-induced agranulocytosis is a rare adverse effect. There are various reports of agranulocytosis in patients treated with dapsone for malaria prophylaxis and other dermatological diseases. However, this adverse reaction in leprosy is not often encountered. We describe agranulocytosis in a young patient who was taking dapsone (100 mg) for borderline–tuberculoid leprosy in a rural environment.

Introduction

Since the drug was first introduced in 1941, 73 cases of dapsone-induced agranulocytosis have been reported, including our case.[1] Dapsone agranulocytosis has been described in the chemoprophylaxis of malaria,[2,3] dermatitis herpetiformis,[4–6] granuloma annulare,[7] 'dermatitis',[8] and recently in leukocytoclastic vasculitis.[9]

There have not been many studies on agranulocytosis in patients being treated with dapsone for leprosy. Available literature reveals only 3 case reports[10–12] of dapsone associated agranulocytosis in leprosy patients. We report a case of dapsone agranulocytosis in a young female who was taking dapsone (100 mg) unsupervised for borderline–tuberculoid leprosy in a rural environment.

Case history

A 25-year-old female presented with a high grade fever, with chills, vomiting and weakness, which had lasted 2 weeks—a physical examination revealed a toxic, ill looking, febrile (39°C) patient with a pulse rate of 120/min. She was pale, had multiple shallow ulcers over the tongue and the buccal mucosa. There were a few purpuric spots over the body, and she also suffered from hepatosplenomegaly. All other systems were normal.

The patient had hypopigmented anaesthetic macules over the dorsum of the left foot with poorly differentiated margins. The left popliteal nerve was thickened and tender.

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She had been diagnosed as having borderline–tuberculoid leprosy 8 weeks before her admission and was started on dapsone (100 mg daily). She had discontinued the drug when she commenced the fever.

Investigations on admission showed the following values: Hb-7·1 g/dl, leucocyte count $0{\cdot}6\times10^9$/l. A differential count revealed occasional lymphocytes with an absence of polymorphs. Platelets were adequate. The blood smear showed normochromia and poikilocytosis with few macrocytes. Malarial parasites, sickled RBCs, and G_6PD deficiency were not present. Bone marrow tap from manubrium sterni revealed hypocellular marrow with absent myeloid series. Megakaryocytes and erythropoiesis were normal.

Biochemical parameters were blood urea 47·1 mmol/l, serum creatinine 167·7 μmol/l, serum bilirubin 109 μmol/l (conjugated 49·6 μmol/l, unconjugated 59·8 μmol/l), AST 88 μ/l and ALT 80 μ/l. Venous blood cultures grew *Pseudomonas aeruginosa*. A skiagram of the chest was normal. The patient remained critically ill for about 15 days. She was managed with barrier nursing, cephotaxime and gentamicin, metronidiazole and blood transfusion. On the 15th day, she started showing an improvement; the total leucocyte count improved to 2×10^9/l which steadily rose to 33×10^9/l on the 26th day, indicating a leukaemoid reaction during the recovery phase.[8] She was discharged on the 31st day, after a complete recovery. The total leucocyte count was 12×10^9/l; the differential was polymorphs 72%, lymphocytes 21%, and eosinophils 3%. Repeat bone marrow aspiration showed hypercellularity with increased early granulopoiesis, normal erythropoiesis and megakaryocytosis.

Discussion

Dapsone agranulocytosis is a rare complication. In 1970 Ognibe[3] reported agranulocytosis in 16 US soldiers in Vietnam who were on 25 mg dapsone as chemoprophylaxis for malaria. Friman *et al.*[2] reported the incidence as 1 : 10,000 to 1 : 20,000 in US soldiers who were on chemoprophylaxis for malaria with maloprim. In 17 years (1972–1988) only 7 cases of agranulocytosis associated with the use of dapsone for dermatitis herpetiformis were reported by Hornsten *et al.*[5] Recently it has been reported in a patient with granuloma annulare[7] and leukocytoclastic vasculitis.[9] In only 9 of 72 cases of agranulocytosis was dapsone the only medication taken.[5–8,10–12] Our patient was taking dapsone as the sole therapy.

Why is this complication so rare in leprosy? Obviously the dapsone dose has no relation to this adversity. There has been only 3 cases of dapsone-induced agranulocytosis reported in patients treated for leprosy,[10–12] although millions of patients are treated each year. Furthermore, the daily dose (25 mg) given to the US soldiers who developed agranulocytosis is lower than the daily dose (50–100 mg) given to most leprosy patients.[3] The reaction is purely idiosyncratic rather than dose-dependent and is observed in immunologically hyper-responsive conditions. It is possible that the risk is linked to the type of disease treated, rather than the dose. Hornsten *et al.*[5] suggest that there is an interaction between the drug and the patient's immune system. Dermatitis herpetiformis and granuloma annulare are autoimmune diseases characterized by immunologic hyper-responsiveness[13] and there we found agranulocytosis to occur. Leprosy is a disease in which immunologic reactivity[14] in some aspects is compromised

and agranulocytosis is rare. Borderline–tuberculoid leprosy, being more immunologically responsive, is susceptible to have agranulocytosis.

It would seem wise to keep any new leprosy patient under close observation after initiating treatment, since reactions to dapsone commonly occur in the first weeks to months of taking dapsone. Patients should be advised to report immediately if they develop fever, chill and sore throat as these could be due to Leucopenia, which may progress to agranulocytosis. It is wise to monitor haemoglobin or haematocrit levels and obtain white cell counts weekly during the first 2 months of therapy.

In managing patients the drug should be stopped and cultures of blood, sputum and throat should be taken. The common organisms which causes sepsis in these patients are pseudomonas *E. coli*, *Proteus* and *Staphylococcus aureus*. Initial treatment with aminoglycosides, cephalosporins and metronidazole are recommended. Barrier nursing and good oral hygiene are also advised.

Finally, although leprosy can be managed by nonspecialists in a rural environment, a careful and cautious observation on drug toxicity and reaction should be carried out.

References

[1] Weinstein L. Drugs used in chemotherapy of tuberculosis and leprosy in the basis of therapeutics. Goodman LS, Gilman A (eds). Macmillan, New York, 1975; p. 1216.

[2] Friman G, Nystrom K, Rosander C, Jonsella G, Bijorkman A, Lekas G, Svendsrup B. Agranulocytosis associated with malaria prophylaxis with Maloprim. *Br Med J*, 1983, **286:** 1244–5.

[3] Ognibe AJ. Agranulocytosis due to dapsone. *Ann Intern Med*, 1970, **73:** 521–4.

[4] McKenna WB, Chamber AC. Agranulocytosis following dapsone therapy. *Br Med J*, 1958, **1:** 324–5.

[5] Hornsten, P. Keisu M, Wiholm BE. The incidence of agranulocytosis during treatment of dermatitis herpetiformis with dapsone as reported in Sweden, 1972 through 1988. *Arch Dermatol*, 1990, **126:** 919–22.

[6] Lahuerla-Palacios JJ, Gomes Pedroja JF, Montalhan MA *et al*. Proliferation of Fg D_k plasma cells after agranulocytosis induced by dapsone. *Br Med J*, 1986; **290:** 282–3.

[7] Potter MN *et al*. Agranulocytosis caused by dapsone therapy for granuloma annulare. *J Am Acad Dermatol*, 1989; **20(1):** 87–8.

[8] Levine PH, Weintraub LR. Pseudoleukemia during recovery from dapsone induced agranulocytosis. *Ann Int Med*, 1968; **60:** 1060–5.

[9] George R Woodbury Jr, Walter Fried, James O Ertle, Frederick D Malkenson. Dapsone associated agranulocytosis and severe anaemia in patient with leukocytoclastic vasculitis. *J Am Acad Dermatol*, 1993; **28:** 781–3.

[10] Brass P. Fatal dapsone agranulocytosis in Malanesian. *Lepr Rev*, 1986; **57:** 63–6.

[11] Figueiredo MS, Pinto BO, Zago MA. Dapsone induced hemolytic anaemia and agranulocytosis in a patient with normal glucose-6-phosphate dehydrogenase activity. *Acta Haematol*, 1989; **82:** 144–5.

[12] Leiker D. The mononucleosis syndrome in leprosy patients treated with sulfones. *Int J Lepr*, 1956; **24:** 402–5.

[13] Uetrecht JP. Idiosyncratic drug reactions: Possible role of reactive metabolites generated by leucocytes. *Pharm Res*, 1989; **6:** 268–73.

[14] Gill HK, Godal T. Deficiency of cell mediated immunity in leprosy. *Prog Allergy*, 1986; **37:** 377–90.

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Letters to the Editor

CONCOMITANT OCCURRENCE OF LEPROSY, CUTANEOUS TUBERCULOSIS AND PULMONARY TUBERCULOSIS—A CASE REPORT

Sir,

We report a leprosy patient also suffering from both cutaneous and pulmonary tuberculosis, a concomitant occurrence that has not previously been reported in the literature available to us. We report here a case of such rare combination. Though both the diseases are caused by mycobacteriae, no true antagonism exists to stop coexistence.

The concomitant occurrence of leprosy and pulmonary tuberculosis has been well documented in the literature,[1,2] but the association of leprosy and cutaneous tuberculosis has rarely been reported.[3,4,5]

A 23-year-old male presented complaining of an erythematous lesion around the left orbit that

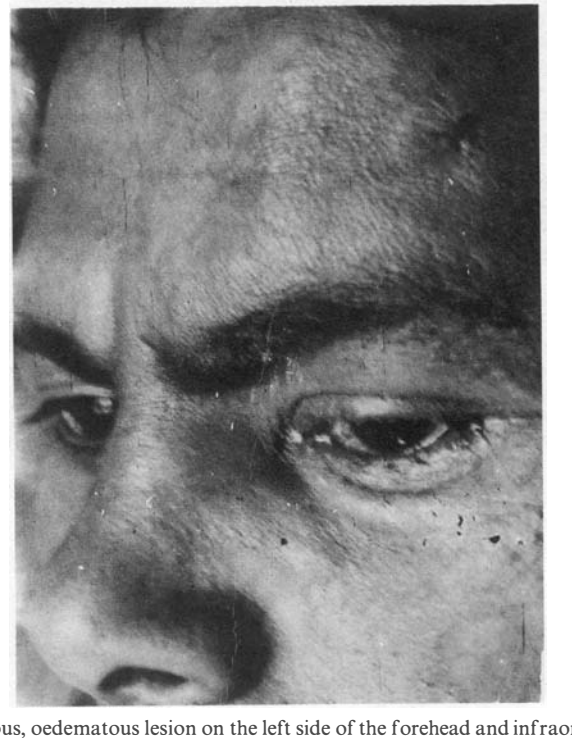

Figure 1. An erythematous, oedematous lesion on the left side of the forehead and infraorbital area, that almost encircles the orbit.

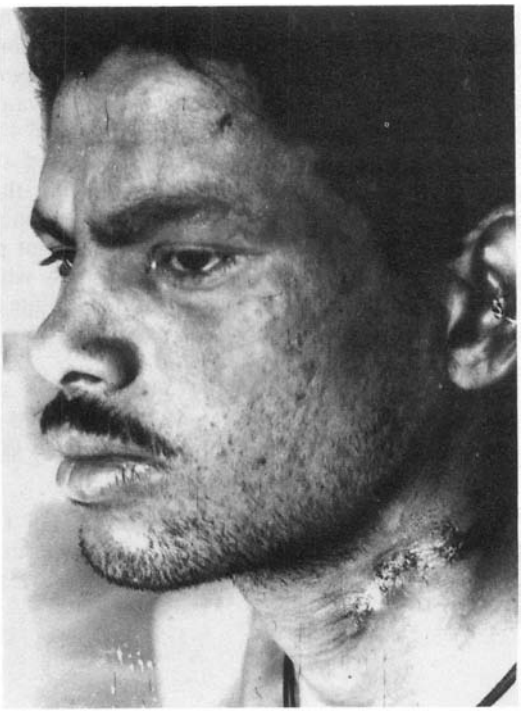

Figure 2. Multiple ulcers in linear fashion with undermined edges and marginal hyperpigmentation on the left side of the neck.

had continued for 1 month and multiple ulcerations with a discharge of pus on the left side of the neck for 15 days; ulcerations followed rupturing of the swelling in the neck. The swelling was of $1\frac{1}{2}$-months' duration, mildly painful and was gradually increasing in size.

There was a history of a rise of temperature each evening and of significant weight loss. He had not been treated for leprosy and/or tuberculosis.

Cutaneous examination revealed a well-defined erythematous plaque around the left orbit (Figure 1). There were multiple ulcers in linear fashion over the left side of the neck with undermined edges and hyperpigmented borders (Figure 2). There was no BCG scar on the left deltoid region.

A neurological examination revealed loss of touch and pain over the periorbital plaque. There was a weakness of the left orbicularis oculi muscle with epiphora suggestive of lagophthalmos due to involvement of the zygomatic branch of the facial nerve. No peripheral nerve thickening was observed. Respiratory system examination revealed crepitations in the right infraclavicular, axillary and interscapular regions. Mild hepatomegaly without splenomegaly was also detected.

Routine haematological and urine examinations were within normal limits except for raised ESR (40 mm/1st hour). Sputum smear was positive for *Mycobacterium tuberculosis* by ZN stain. A tuberculin test was negative. A chest X-ray revealed a cavity in the right apical region and miliary mottling in the midzones and basal zones on both sides of the lungs were suggestive of pulmonary miliary tuberculosis. Slit skin smears from both ear lobes and periorbital lesions were negative for AFB.

Clinically, we diagnosed the case as TT Hansen's disease in Type I reaction with scrofuloderma and miliary tuberculosis. Biopsy for HPE was done from the periorbital region and a lesion suspected as scrofuloderma from the neck. H&E stained sections confirmed our diagnosis of TT Hansen's disease in type I reaction from the periorbital lesion and scrofuloderma from the neck lesion.

The patient was treated with dapsone 100 mg per day, rifampicin 600 mg per day, INH 300 mg per day and pyrazinamide 750 mg twice daily. A topical application of steroid cream for periorbital lesion and administration of chloroquine reduced the severity of Type I lepra reaction.

The reported incidence of tuberculosis in leprosy patients in India varies from 2·5 to 7·7%.[6] A study in South Africa by Gatner[7] revealed pulmonary tuberculosis in 13·4% leprosy patients. Both Nigam[1] and Gatner[7] found that pulmonary tuberculosis occurred throughout the leprosy spectrum. This view was contested by Singh[6] who suggested that the association could be fortuitous or that it may actually reflect common environmental denominators.

The immunological defect in leprosy is quite specific and does not predispose to any other mycobacterial infection.[8] In this context, the association of leprosy with both pulmonary and cutaneous tuberculosis may be incidental as clinically there is no absolute antagonism between the two infections. Host resistance may be very poor thus paving the way for coexistence of dual mycobacterial diseases.

Management of the present case requires daily administration of rifampicin to avoid development of resistance to M. tuberculosis, and topical steroids and chloroquine to manage the type I lepra reaction, instead of oral/parenteral steroids, as they may exacerbate the pulmonary tuberculosis.

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References

[1] Nigam P, Dubey AL, Dayal SG et al. The association of leprosy and pulmonary tuberculosis. *Lepr India*, 1979; 51: 65–73.
[2] Kumar B, Kaur S, Kataria S, Roy SN. Concomitant occurrence of leprosy and tuberculosis—a clinical, bacteriological and radiological evaluation. *Lepr India*, 1982; **54:** 671–6.
[3] Ganapati R, Deshpande DH, Chulawalla RG. Some interesting disease combinations—report on two cases. *Lepr India*, 1976; **48:** 428.
[4] Patki AH, Jadhav VH, Mehta JM. Leprosy and multicentric lupus vulgaris. *Ind J Lepr*, 1990; **62:** 368–70.
[5] Pinto J, Pai GS, Kamath N. Cutaneous tuberculosis with leprosy. *Ind J Dermatol Venereol and Leprol*, 1991; **57:** 303–4.
[6] Singh M, Kaur S, Kumar B et al. The associated diseases with leprosy. *Ind J Lepr*, 1987; **59:** 315–21.
[7] Gatner EMS, Glatthaaar E, Imkamp FMJH, Kok SH. Association of tuberculosis and leprosy in South Africa. *Lepr Rev*, 1980; **51:** 5–10.
[8] Ridley DS. *Pathogenesis of leprosy and related diseases.* London: Wright, 1956.

NEED FOR PERIPHERAL NERVE EXAMINATION DURING LEPROSY CASE-DETECTION SURVEYS

Sir,

The main thrust of leprosy control/elimination programmes is based on the early detection of leprosy cases, but during leprosy surveys, peripheral nerve examination is often neglected. Though the proportion of pure neuritic leprosy is much less, these are the cases who run the risk of disability if not treated at an early stage.

At the SLR & T Centre, it has been routine practice to review the previous clinical status whenever a new case is detected (clinical status at previous survey).

A 28-year-old patient reported to the clinic at Gudiyatham town on 19 April 1993 with numbness of both hands and fissures on his hands and feet. There was no record of clinical findings. A skin smear for AFB and a urine test for sugar were carried out and were negative.

A total population survey was carried out in his village on 24 April 1993. According to the survey records, this person was examined and declared as healthy, i.e. no signs of leprosy, by the paramedical worker.

The patient voluntarily reported again to a roadwise leprosy clinic on 5 July 1993. This time he had detailed screening and was found to have enlarged peripheral nerves (both great auricular, left ulnar, both radial cutaneous and left sural) and weakness of muscles supplied by the left ulnar nerve. He had sensory loss over all 4 extremities. A skin smear was negative for AFB. A histopathological examination of the left sural nerve revealed borderline lepromatous leprosy neuritis. He was started on MDT–MB and steroids.

Therefore, it is important to examine peripheral nerves during surveys and at clinics. This will enable us to detect not only PN leprosy patients more quickly, before they develop disability, but also other MB cases where skin lesions are not apparent.

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Teaching Materials and Services

ALERT Training Calendar, 1995

In 1995, ALERT proposes to organize the following training courses:

Dates	Course title	Recommended for
Jan 9–Feb 17	Prevention and management of disabilities	qualified physiotherapists, and paramedical workers in a leprosy programme with a minimum experience of 2 years in a disability prevention capacity
Feb 20–Mar 31	Leprosy and tuberculosis control	physicians, and senior staff familiar with the clinical aspects of leprosy or TB (preferably both), who will be in charge of managing a combined leprosy and TB control programme
Apr 3–Apr 14	Information, education and communication	staff in charge of health education (of the community and of the individual patient) in a leprosy and/or TB control programme
Apr 17–Jun 9	Training of trainers	trainers, and staff in charge of organizing training programmes for leprosy and TB workers. Participants should be familiar with leprosy or TB (preferably both), and preference will be given to applicants who have participated in a formal leprosy and TB course in the past
Jul 7–Jul 28	Essentials of leprosy for nonmedical staff	administrators, planners, managers and other staff without a medical background, who are unfamiliar with the common leprosy terminology when dealing with medical technical staff, either in the context of a field programme or of a donor agency
Jul 31–Aug 12	Social rehabilitation	staff dealing with the socioeconomic problems of leprosy patients
Aug 21–Sep 1	Tropical dermatology	physicians with dermatological experience
Sep 4–Oct 14	Essentials of leprosy for medical staff	physicians without leprosy experience, who are going to work in a leprosy project (either hospital based or in a control programme)
Oct 16–Oct 20	The eye in leprosy	physicians and experienced paramedical workers responsible for managing leprosy patients
Oct 23–Dec 15	Supervision of a district leprosy control programme	experienced leprosy workers who will be in charge of the supervision of a leprosy control programme at the district (or comparable) level

If you are interested in any of these courses, or if you want more information please write to: International Administrative Coordinator, Division of Training, ALERT, P.O. Box 165, Addis Ababa, Ethiopia. Fax: +251-1-711199; Telephone +251-1-712792 (International Administrative Coordinator), +251-1-711524 (Director of Training).

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News and Notes

International Symposium on Aetiology and Pathogenesis of Infectious Diseases, Dakar, Senegal, April 1995

The Symposium, dedicated to the memory of Louis Pasteur, will focus on Host–Microorganism relationships (parasites, mycobacteria, bacteria and viruses). The range of infectious diseases chosen will not be exhaustive, but rather limited to the major infectious plagues threatening the planet's population, especially in Africa, at the end of the 20th century. This is the case of malaria, tuberculosis and AIDS, and also of organ specific pathologies (central nervous system, digestive tract, liver), whatever the aetiologic agent implicated. The programme will include Special Lectures describing the lessons to be learned for the future from a historical perspective, 6 specialized Plenary Sessions, each associated with a Workshop on the same theme, and Poster Sessions: 1 Tuberculosis; 2 Viral hepatites; 3 Parasitic diseases; 4 Infections of the central nervous system; 5 Enteric diseases; and 6 AIDS.

The Symposium is to be held between 10 and 13 April 1995. For further details write to: Dr J.-P. Digoutte, Institut Pasteur de Dakar, 36 Avenue Pasteur, BP 220, Dakar, Senegal. Tel: 221 23 98 83; Fax: 221 23 87 72.