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Leprosy Review

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

LEPRA

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CALL FOR PAPERS

Papers wanted for special issue of *Leprosy Review* on the topic of SOCIO-ECONOMIC REHABILITATION

A recent ILEP Workshop held in Wurzburg, Germany, concentrated on the issue of Socio-Economic Rehabilitation. Issues discussed included Self-Stigmatization and Psychological Impact, Special Needs Groups, Gender Issues, Impact Assessment and Quality of Life. The **December 2000** issue of *Leprosy Review* will focus on SER, setting out current thinking and understanding on best practice in all the social and psychological aspects of leprosy. We are keen to publish as much data as possible in this issue and would like to encourage potential authors.

If you have data that you would like to publish in this Special Issue, please analyse it and write it up. Papers for this issue should be submitted to the *Leprosy Review* office by **1 February 2000 at the latest** and will go through the usual peer review process.

Diana N. J. Lockwood (Editor)

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Editor's Choice

This issue of Leprosy Review starts with reflections by Paul Fine on the implications of the recently reported leprosy vaccine trial in S India. This trial has confirmed findings from elsewhere that BCG protects against leprosy and also showed that this effect was enhanced by the addition of either *M. leprae* or the ICRC bacillus. This finding with ICRC bacillus is particularly interesting, since it is a dead organism and one would not have predicted that a dead mycobacterium would enhance protection. Professor Fine notes that the results of this trial put down several challenges to both the leprosy and tuberculosis communities. In this issue we are also publishing a case control study from central India showing that BCG gives significant protection against leprosy (72% for multibacillary and 45% for paucibaillary disease, respectively). Clearly vaccines still have much to contribute to disease control.

June Nash is a newcomer to the Leprosy review editorial board so she was put straight to work and has contributed a review article on teaching that anyone who does any teaching will find useful.

We have two articles from Nigeria. The first is a piece of qualitative research looking at the expressed needs of ex-patients living in leprosy settlements. The range of expressed needs is interesting but I have been particularly struck by the gender differences. Women put their families first and wanted to be able to pay their children's school fees whilst the men rated their farming needs top. The authors also note that there are development-based opportunities in these settlements that could involve the whole village and not just people with leprosy. 'Ghosts' are apparently common in Nigerian public life, taking their place on payrolls and presumably not drawing ghostly pay! In the Letters section, an audit is reported which showed that there were 1411 non-existent cases in 321 Nigerian clinics. This is clearly cause for concern because 'ghosts' may produce severe imbalances in resource allocation.

We continue to cover rehabilitation and publish a questionnaire that has been used in Nepal to assess activities and I hope it will be useful in assessing rehabilitation needs. Surgery for facial deformities can be an important part of rehabilitation and we have the last of the surgery series in this issue. I would like to thank all the surgeons who have educated us about appropriate surgery and particularly thank Dr Dinkar Palande for editing the series.

We have another new column in this issue, 'Your questions answered'. In this column, questions from field workers will be passed on to experts for them to answer. Dr Patricia Rose has very kindly started the first column and I hope that questions will come in from the field.

We are also planning another Special issue. This one will focus on Socio-economic rehabilitation and will be published in December 2000. A separate announcement appears in this issue for contributions on this important and topical issue, and I hope it will produce a flurry of papers.

Diana N.J. Lockwood (Editor)

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EDITORIAL

South Indian leprosy vaccine trial: important lessons for mycobacterial immunology

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Between January 1991 and July 1993, 171,400 individuals living in Chingleput District, South India, were recruited into a major leprosy vaccine trial organized by the Indian Council for Medical Research. The participants were randomized to receive a placebo, a plain BCG vaccine, a combination of BCG plus killed leprosy bacilli, or else a killed environmental mycobacterial vaccine: either 'Mycobacterium W', or 'Mycobacterium ICRC'. Eighty-five percent of these individuals were examined for leprosy between August 1993 and February 1995 and 75% were examined between January 1997 and September 1998. The codes were broken in December 1998, and revealed that each of the vaccines had provided significant protection over the interval between 4 and 8 years after vaccination: 65.5% for the ICRC bacillus, 64% for combined BCG and killed *Mycobacterium leprae*, 34% for BCG alone and 25·7% for the W bacillus.[1] These figures, and the data behind them, include several findings of considerable importance for research on mycobacterial immunology and vaccines.

In the first follow-up survey (up to 4 years after vaccination), the incidence of leprosy was higher among each of the active vaccine groups, compared to the placebo recipients. Though these differences were not individually statistically significant, the result is consistent with similar patterns seen in the initial follow up in a leprosy vaccine trial in Burma,[2] and a tuberculosis vaccine trial in South India.[3,4] This finding provides important further evidence that antigenic challenge can accelerate progression to mycobacterial disease among individuals either incubating infection at time of vaccination (most likely) or infected very soon after vaccination (less likely explanation). The fact that the negative effect was greater for older (>14 years of age) than younger individuals for recipients of BCG, BCG plus killed *M. leprae* and *Mycobacterium W* (this age effect was statistically significant for BCG plus killed *M. leprae*) is consistent with the prior infection interpretation.

In the second follow-up (4–8 years after vaccination), there was significantly less leprosy in each of the active vaccine groups, compared to the controls. The finding of greater protection with the combination BCG plus killed *M. leprae* than with BCG alone is in contrast to findings in Venezuela[5] and Malawi,[6] as is the relatively low protection associated with BCG alone. These differences may be added to the long catalogue of variable efficacy results associated with BCG vaccine against leprosy and tuberculosis.[7] The finding of greater protection with the ICRC than with the W bacillus is ironic, given that the latter vaccine was

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licensed for therapeutic use in India 1 year ago. It is of interest that this protection appeared to be independent of age.[1]

The observation of highest efficacy attributable to killed ICRC bacillus vaccine has important implications. First is the fact that this protection was induced by a killed vaccine, which is in contrast a view, held widely among mycobacterial vaccinologists, that living vaccines such as BCG are likely to be better than killed vaccines in inducing protective responses. The finding is particularly opportune today, given that much research is devoted to development of new tuberculosis vaccines which might be used in populations with high prevalence of HIV, and thus where live vaccines are likely to be contraindicated. Second is the obvious need to clarify the identity and antigenic nature of the ICRC bacillus, which may explain its appreciable effect on leprosy. This organism has a complicated history, having been isolated originally from leprosy lesions (its isolation was once claimed to be the first successful *in vitro* culture of *M. leprae*), but later work indicated that it was a relative of *M. avium*.[8] If so, this could be of interest, as we now know that *M. avium* and *M. leprae* share certain antigens (e.g. the 18 kD[9]). Third, the published report notes that recipients of the ICRC vaccine had a far higher incidence of 'fluctuant lymphadenitis' compared to recipients of the other vaccines. The pathogenesis of these 'reactions' is of interest (could it be related to prior exposure to a related environmental mycobacterium?), and their association with the most effective vaccine may itself tell us something of the mechanism of the protective immune response.

There are several features of the trial that make interpretation difficult. The authors do not present overall efficacy, combining the two surveys, though this is critical to judging the overall public health utility of these vaccines. In addition, 17·4% of the trial population had scar evidence of previous BCG vaccination at time of recruitment into this trial. The authors chose to adhere strictly to protocol, and have not separated these individuals (who in effect had received repeat vaccination in the trial) in the analyses. The proportion of individuals with prior scarring was inversely related to age; thus it may be that protection in unvaccinated individuals actually declined with age, as has been observed in several other trials,[2,10,11] but that this trend is masked by the fact that many younger individuals had already been vaccinated at recruitment. It would not be surprising if the vaccines were less effective in previously vaccinated individuals than in those who had never been vaccinated before. Furthermore, all vaccinations were done in the evenings, avoiding exposure of vaccines to sunlight. This was a clever precaution, given the known sensitivity of BCG and of dermal Langerhans cells to light. However, the absence of a 'daytime control', and the fact that no other trial has used this procedure, makes it impossible to tell if the differences observed between this trial and, for example, the trials of BCG plus killed *M. leprae* in Venezuela and Malawi, are attributable to evening vaccination or to some other factor. Furthermore, it poses a difficulty in considering the programmatic implementation of the findings, as few vaccination programmes in the world are able to deliver vaccines only in the evening.

Students of mycobacterial vaccines get used to surprises, and this trial is no exception. The investigators are to be commended for the careful implementation of a very major task, and for having contributed importantly to our understanding of mycobacterial immunity. Beyond that, the research community should now seize three major challenges inherent in these results. First, the recognition of protection by a killed organism needs to modify if not replace the dogmatic statements favouring live mycobacterial vaccines in the immunological canon. Second is the need to clarify the nature of the ICRC organism. This should be a straightforward task, given available technology and the current activity in mycobacterial

genomics (e.g. the completed and imminent sequencing *M. tuberculosis*[12] and *M. leprae*, respectively). Third, there is a very powerful argument to introduce systematic tuberculosis ascertainment as soon as possible into this trial population. This was omitted in the original protocol, perhaps because of disappointment with the negative results of a large BCG trial against tuberculosis conducted earlier in the same region.[3] However, this population provides an immediate test of the efficacy of four different mycobacterial vaccines against tuberculosis, including two environmental mycobacteria. To neglect this opportunity would be most unfortunate. Funding for such work should have high priority among agencies supporting tuberculosis research.

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Scientific Commentary

THE US–JAPAN JOINT LEPROSY RESEARCH PROGRAM MEETING, SAN FRANCISCO, JUNE 28–30, 1999

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The US–Japan Cooperative Medical Sciences Program was founded in the 1960s by the then-President of the United States and the Prime Minister of Japan and, since then, has had the highest political support from both governments. Leprosy was among the first disease entities named as part of the overall program, and the US and Japanese leprosy research panels and their guests have met in the alternating countries every year for the past 34 years (in 1995, the separate leprosy and tuberculosis panels were amalgamated). These meetings of the joint US–Japan panels in the form of scientific conferences have become a highlight of the annual leprosy research agenda. Some of the major fundamental research developments in leprosy over the past 30 years have been first reported at this conference. These include: the early development of the drug regimens leading to present-day MDT and ROM; the early development of the mouse footpad; the recognition of sylvian leprosy in the armadillo and the development of this model of leprosy and, later, the Mangabey monkey model; the original work on the extension of hybridoma technology to leprosy and the development of banks of monoclonal antibodies; the first research on the application of genetic recombinant technology to *Mycobacterium leprae* and the production of 15–20 recombinant protein antigens; the discovery of the heat-shock proteins and of PGL-I, and the synthesis of corresponding neoglycoproteins and the development of ELISA systems; the major developments in the definition of the genome and proteome of *M. leprae*; all major developments in defining the cellular immune response in leprosy; the application of thalidomide to leprosy reactions and elucidation of its action mechanism etc.

The 34th US–Japan Leprosy Research Conference was held in San Francisco in conjunction with the US–Japan Tuberculosis Research Conference, June 28–30, 1999. Some of the highlights are as follows.

A. Rambukkana (Rockefeller University, New York, USA) described the latest chapter in his important work on the molecular basis of the interaction between the Schwann cell and *M. leprae.* Previously, he had described how the G domain of the laminin α_2 chain in the basal lamina that surrounds the Schwann cell-axon unit serves as an initial neural target for *M. leprae*. This time, he addressed the nature of the *M. leprae* surface molecules that bind

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to α_2 laminin. By using human α_2 laminins as a probe, a major 28 kDa protein in the *M. leprae* cell wall fraction was identified. Immunofluorescence and immunoelectron microscopy on intact *M. leprae*, using monoclonal antibodies against the recombinant protein, demonstrated that the protein is surface-exposed. Also, the recombinant protein was shown to bind avidly to α_2 laminins, the recombinant G domain of the laminin–α_2 chain, and the native peripheral nerve laminin. Thus, these data suggest that this 28 kDa protein functions as a critical surface adhesin that facilitates the entry of *M. leprae* into Schwann cells.

In subsequent discussion of this work, it was revealed that Dr Cristina Pessolani (Fio-Cruz, Rio de Janeiro) had also described a 28 kDa protein as a key bacterial ligand in *M. leprae*–Schwann cell interaction and had shown that this is a member of the histone-like protein family. It thus seems that the protein described by Dr Rambukkana is this HLP.

Dr Takeshi Yamada and colleagues (Nagasaki University, Japan) have also focused on this protein from a different perspective. They have been investigating the molecular basis of the slow growth of *M. leprae* and other mycobacteria and identified a 28 kDa protein (which they called MDPI) as the most abundant protein in *M. bovis* BCG. The protein was highly polymerized and localized in the nucleoid, 50S ribosomal subunit and cell surface. It interfered with replication, transcription and translation in *E. coli* cell-free systems, and was capable of transforming *E. coli* to slow growth. Sequence analysis also indicated a member of the HLP family. Thus, the 28 kDa HLP is apparently a major player in the pathogenesis and physiology of *M. leprae*. Its immunogenicity and diagnostic potential should now be examined.

Efforts to 'cultivate' *M. leprae* continue, but this time through genetic augmentation of the organism, a sensible plan in light of a genome that is small and very defective in gene density. Drs Scott G. Franzblau (GWL Hansen's Disease Center, Baton Rouge, LA, USA) and William R. Jacobs (Albert Einstein College of Medicine, New York, USA) have used a combination of freshly harvested, viable nude mouse-propagated *M. leprae* and a modified D29 mycobacteriophage vector to achieve phage infection of *M. leprae* and foreign gene expression. Therefore, the key preliminary work has been achieved as a prelude to constructing a shuttle cosmid vector, carrying DNA libraries from slow growing cultivable mycobacteria and capable of stable expression of foreign DNA in *M. leprae*, allowing, in future, perhaps, *in vitro* growth competence.

Widespread resistance to dapsone in the 1970s was the catalyst for the development of multiple drug therapy (MDT) for the treatment of leprosy. However, to date, researchers have not been successful in characterizing the molecular basis of dapsone resistance. Two laboratories have now conducted crucial preliminary experiments (Dr Y. Kashiwabara, Leprosy Research Center, Tokyo, Japan, and Dr Diana Williams, GWL Hansen's Disease Center). An analysis by others of sulphonamide resistance in *E. coli* has shown an association with dihydropteroate synthase (DHPS), a key enzyme in the folate biosynthetic pathway, encoded by the *folp* gene. Dr Williams has shown that *M. leprae* possesses two *folp* homologs (*folP1* and *folP2*). DDS resistance was not associated with mutations in *folP2* from two high-level DDS-resistant strains of *M. leprae*. However, mutations were observed within a highly conserved region of *folP1* in two of these high-level DDS-resistant *M. leprae* clinical isolates. In addition, this *folP1* homolog has been shown to encode a functional DHPS which itself is highly sensitive to DDS. These new data thus support early predictions that DDS resistance in *M. leprae* is associated with alterations in folate metabolism and that one possible mechanism of resistance is due to mutations in *folP1*.

Resistance to fluoroquinolones is becoming widespread, at a time when ofloxacin, one of the fluoroquinolones, is being used more and more frequently in the form of ROM (rifampin, ofloxacin, and minocycline) in leprosy control programs. Dr Y. Kashiwabara has determined the sequences of the QRDR (quinolone resistance determining region) of *gyrA* (the gene encoding the A subunit of gyrase, the site of action of the fluoroquinolones) in 13 clinical isolates of *M. leprae*, and demonstrated that eight of them showed mutations in this region. Importantly, five of the eight also showed mutations in the *rpoB* gene (the gene encoding the B subunit of RNA polymerase, the site of action of the rifamycins), suggesting that exposure to one or the other of the two drugs can lead to resistance to both, a new worry as we develop alternative drug regimens for leprosy.

The type of molecular epidemiology that is now being applied to *M. tuberculosis* isolates and tuberculosis in general has not been possible with leprosy, because *M. leprae* is devoid of the type of variable but relatively stable genetic polymorphism associated with the IS6110 insertion sequences in the *M. tuberculosis* chromosome. If other forms of DNA polymorphism could be identified in the *M. leprae* genome, the lessons that could be derived from its application would be profound in terms of tracking sources of infection, examining the relationship between non-symptomatic carriage of *M. leprae* and disease, probing the possibility of environmental sources of *M. leprae*, and differentiating between reactivation and new infection. Dr Y. Kashiwabara has now found some evidence of such polymorphism, albeit limited. The sequences of the *rpoT* gene from many *M. leprae* isolates were compared, allowing the classification of isolates into two broad categories. One group had three tandem repeats of a six-base-pair (AGATCG) sequence, and the other group had four tandem repeats. Isolates from Japan and Korea had the four-tandem repeat profile, whereas isolates from South-East Asian and Latin American countries had the three-repeat pattern, indicating that this genetic characteristic could be used to trace the origins of infections and the evolution of disease.

The role of various cytokines and different T-cell subsets in leprosy pathogenesis and immunity to leprosy has long been a favorite topic of US–Japan participants. The curious balance between acquired resistance and pathogenesis is seen in granulomatous infiltration, a consequence of the marshalling of the acquired response to essentially contain bacilli, but with pathological sequelae. In the hands of Dr Linda Adams (GWL Hansen's Disease Center), mice genetically incapable of producing a functional inducible NO synthase (iNOS) showed markedly enhanced granuloma formation, and these types of granulomas were composed primarily of $CD4^+$ cells and multinucleated giant cells. Thus, iNOS has an unexpected role in leprosy granulomatosis. Among the newer cytokines to be involved in the leprosy immune response are IL-12 and IL-10. According to Dr Robert Modlin (University of California, Los Angeles, CA, USA), some key lipoprotein ligands of *M. leprae* bind to the toll-like receptors in macrophages, evoking the dual response of NO production and IL-12 evocation, two new major players in counteracting infection. We have long been very conscious of the role of IFN-γ in the type-1 protective immune response in leprosy. Apparently, part of the mechanism of this effect is to up-regulate type-1 cytokine expression and down-regulate IL-10, one of the type-2 cytokines (Drs Y. Fukutomi and M. Matsuoka, Leprosy Research Center, Tokyo, Japan). The newest players in these events are the chemokines. *M. leprae* induces elevated levels of MCP-I, MIP-1α, and MIP-1β expression, and it is now believed that chemokines will prove to be important in regulating granuloma formation and other immune responses in leprosy (Dr Linda Adams).

Preliminary results were also reported by Dr T.P. Gillis (GWL Hansen's Disease Center)

on the application of DNA vaccines to an animal model of leprosy. A recombinant construct of the antigen 85A injected intradermally proved to be the most promising with strong IgG1 and Ig2a antibody responses and increased IFN-γ and IL-2 production. However, protection studies in the mouse footpad infection model were disappointing.

With the amalgamation of the US–Japan Leprosy and Tuberculosis Panels in 1995, a fear of leprosy research workers within the US–Japan Cooperative Medical Sciences Program was that leprosy research would be engulfed by the tuberculosis research juggernaut. This fear has proved to be unfounded. Basic research in leprosy is thriving, notably in Japan, where the Leprosy Research Center has been incorporated into the prestigious, well-endowed National Institute of Infectious Diseases. The formal combination of both panels is clearly benefiting leprosy research.

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Learning materials: their use and evaluation

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Introduction

The training role within leprosy programmes is becoming increasingly important as integration takes place. Over the years, countries and individuals have developed their own materials, so that there is a plethora of material available. TALMilep and INFOLEP, joint projects of the International Federation of Anti-leprosy Associations (ILEP) try to keep field workers up to date with what is available and maintain some quality control.[1] For many end users of the materials the questions of selection, quality and appropriateness still remain. Many health workers are just grateful to have any learning material at all, so clinics may be festooned with attractive but unintelligible glossy posters and bookshelves filled with unopened high-powered technical tomes. The indiscriminate use of learning materials also means that students with glazed eyes sit through videos that are difficult to translate into their work situations, and patients with numbed minds endure slide shows and illustrated lectures on the nature of leprosy that do not answer their questions. We need to be as discerning and selective in our use of learning materials as we are in our use of drugs to avoid learning-resistance and allergy.

Why use learning materials?

Learning materials are an aid to the learning process. They should not be for the benefit of the instructor or something that must be used all the time. They must facilitate the students' learning. They should:

- Arouse and maintain interest.
- Simplify instruction.
- Aid retention.
- Stimulate active thinking.
- Accelerate learning as more senses are involved.[2]

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Learning materials and adult learning

Adult learning is different from that of children. In order to evaluate and use learning materials properly, we need to understand a little about the theory of learning. Education and learning are different, education emphasizes the educator, whilst learning emphasizes the person in whom the change is expected to occur. Learning can be defined as the process of gaining knowledge and/or expertise. It is this change of behaviour and gaining of skills and knowledge that we particularly need to achieve in leprosy training and health education. Six core principles have been identified in the practice of adult learning;[3] these are:

- Learner's need to know.
- Self concept of the learner.
- Prior experience of the learner.
- Readiness to learn.
- Orientation to learning.
- Motivation to learn.

These are perspectives that come directly from the learner, and we need to take them into consideration in our teaching and use of learning materials if we want to have effective adult learning.

Health workers, particularly general health workers, do not need to know everything about leprosy, they are too busy to be interested in theory for theory's sake but they generally learn better if they are taught the why, what and how. You need to consider whom the person is that you are teaching; this is particularly true for health promotion. Ask these questions: How will they best learn? Do they like to find out for themselves? Will they learn better as partners in the process? Adults are not blank sheets. They have resources of experience and come complete with mental models and belief systems that need to be taken into account and built upon. They are ready to learn when the learning is life related, or helps them to develop new skills. They like to learn in context and in a problem centred way rather than with just theory. Their motivation for learning may be based on the intrinsic value of the learning but they will also want to consider the personal payoff for the learning.

This means that learning materials must have the following characteristics; they must be:

- Practical.
- Relevant to the learner's situation.
- Building upon existing knowledge.
- Problem centred.
- Logical.
- Clear.
- Rewarding.

They should be interactive and participatory, so that learners can easily apply the learning to their context and situations. This is particularly true for PHC workers in developing countries. In my experience of asking learners around the world how they learn, passive methods such as reading rate very low for most PHC workers. They learn much more by trying and doing. This means that the clarity and logical plan of written

materials becomes much more important. Study guides and exercises should also be used with text books and manuals.[4] Research has also shown that the age of the learner may influence learning preferences.[5] One of the possibilities that we should also not overlook is to include participant involvement in the development of learning materials. This can be particularly empowering in health education. The materials produced are reflective of the people, locale and the language and therefore are powerful models that people can identify with.[6]

Learning and memory

Three kinds of memory have been identified,[7] visual, auditory and kinaesthetic. Visual learners find it easy to take in information through visual media, charts and diagrams. Auditory learners take in their information through the spoken word, and kinaesthetic learners need to get physically involved; they enjoy trying things out and experimenting. In practice, most people use a combination of all three types of memory, but they generally dominate in one style and express a preference for one other. It is also helpful to look at the traditional learning methods used to see the cultural preferences for learning. Learning materials can be used interactively to develop the three kinds of memory strengths. This means making sure that there are good visuals in the material or asking the learners to make diagrams of the information, encourage the learners to read the words out, discuss the materials and summarize information. Physical involvement can include underlining, filling in sections of the material and practical assignments. Much has been written about the percent retention versus method of input, the accepted statistics are found in Figure 1. This again points to the need to be interactive in our use of learning materials. The 'banking' method of education, where students passively receive the teacher's wealth, has been criticized by Freire.[8] Participatory and interactive use of learning materials are keys to the educational process, particularly in health education where learning cannot be separated from action.

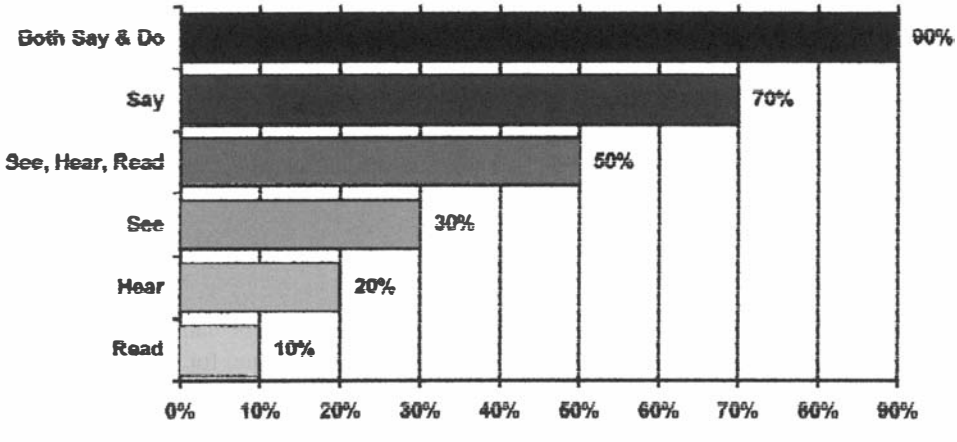

Figure 1. Percent retention versus method of input.

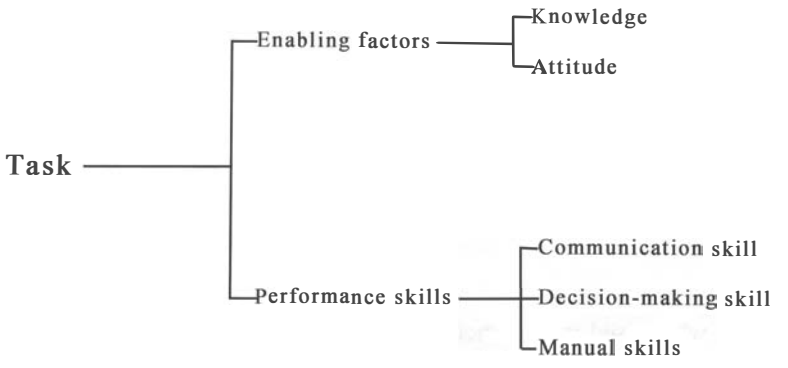

Figure 2. Task analysis model (Abbatt and McMahon).

Types of learning

Three distinct types of learning need to be considered when teaching and using learning materials. These are skills, attitude and knowledge. Although these are interlinked, learning materials often concentrate on providing knowledge learning and neglect the attitude and skills learning. It is quite helpful to break down health tasks into knowledge, attitude and skills. Abbatt[9] breaks this down further into knowledge, attitude and performance skills. This model is helpful for teaching health workers, since it helps the teacher to include all the learning necessary for performance and competency in each of the tasks. It is also helpful to consider learning materials under the same headings, so that we do not overload health workers with knowledge based materials but also use materials to help the learner consider his attitudes and learn performance skills (Figure 2).

Table 1 gives some idea of learning materials and their use in the different types of learning. Written materials are primarily knowledge based, they can address some attitude issues but their success in this may relate to the culture of the people who read them. People who are influenced by the power of the written word will be more likely to

Table 1. Learning materials and Abbatt's learning model (J. Nash, 1999)

Learning material	Knowledge	Attitude	Communication skills	Decision making skills	Manual skills
Video	Fair	Good	Good	Excellent	Fair
Leaflets	Excellent	Fair	Poor	Poor	Poor
Self learning books	Excellent	Fair	Poor	Poor	Poor
Books	Excellent	Fair	Poor	Poor	Poor
Posters	Excellent	Good	Poor	Fair	Poor
Teaching charts	Excellent	Good	Poor	Good	Poor
Check lists	Fair	Poor	Good	Poor	Good
Slides	Excellent	Poor	Poor	Excellent	Fair
CD ROMS	Good	Fair	Poor	Excellent	Fair
Simulation games	Fair	Excellent	Excellent	Excellent	Fair
PBL packages	Good	Fair	Good	Excellent	Poor
Video camera	Poor	Good	Excellent	Poor	Fair

change their attitudes than those who do not value the written word as much as seeing and doing.

Static visual materials (slides, posters, teaching charts) are also good for imparting knowledge, but may be used interactively to promote decision making skills by showing them and then asking questions to the learners or using them as illustrations in a problem centred approach. They may also help to influence attitudes, but we need to be aware that attitudes can be influenced for both good and ill when using visuals. Slides of badly disfigured patients or negative images can increase stigma even although they may be medically 'interesting'.

Animated visual material such as videos and films should not be used primarily for knowledge, but when used in conjunction with discussions in an interactive way can help change attitudes and promote decision making.

Interactive materials such as using video cameras, CD ROMs and problem based materials are more likely to help learners to gain skills, particularly in the area of decision making. This is one of the strengths of problem-centred learning programmes in which the learning is interactive and solving the problem is the focus of the learning process.[10]

Manual skills are particularly difficult to teach with learning materials and whilst animated visuals may help, there is no substitute for demonstration and practice.

It will be obvious from the above that the quality of materials is important if they are to achieve any of the learning objectives. Poor materials may not even be able to help the learner gain knowledge, let alone the more difficult learning attributes of skills and attitudes.

As well as using materials properly, it is important to evaluate them for quality and effectiveness. This is particularly true when developing materials.

What makes good learning material?

User-friendly written learning materials need to contain the right material in a logical and well presented form. They should be at the level of the learners and clear in their language and style. Several criteria have been developed to measure user friendliness. They look at simplicity of language, clarity of expression, logical sequence, page layout, pictures, style of writing and availability.[11,12] Clarity of language is important, particularly where materials are developed for use in a second language. Clarity is generally measured by looking at sentence length, use of active verbs, abstract ideas, and technical jargon. Many modern word processors do this automatically. The Cloze test is specific for assessing if the language is understandable to the target group. A test group is given a sample of the material with every 'nth' word or randomly selected words deleted from the text. The group is then asked to supply the missing words. This test has been used in several Asian and African languages, as well as English.

Visual materials also need testing. Sociological and educational differences have a large effect on picture understanding,[13] and since materials are often developed by the urban educated elite for the rural illiterate poor, there can be serious communication gaps. Pictures should be shown to the target audience and a series of simple questions asked such as: What is happening in this picture? What is this? Can you tell me what this diagram is saying? The same evaluation can be applied to animated visual materials such as videos. Viewers should be asked to summarize the message; to say which sections they like the best and why; and

which sections they found confusing. Again the test viewers should be drawn from the proposed target audience rather than a group of trainers or 'experts'.

The pre-testing of materials is very important not only to avert expensive disasters, but also to make sure that the goal of the material is achieved. The material should be pre-tested for acceptability of the idea, and comprehension of the individual pictures and whole message. The test should be carried out on several different people depending on the target audience and users.[14] It is also helpful to pre-test the use of the materials. Test the difference between interactive and passive use with different but matched groups.

Long-term outcome and impact assessment is particularly important to evaluate community health learning materials. To evaluate the material, it must have a clear goal and message. The evaluation must measure whether change has taken place and look at the attitudes that have changed, since the target group has been exposed to the media. The evaluation will thus be dependent on some baseline data about beliefs and practices prior to the health education. KAP studies can help measure general success, but the relationship between increased knowledge and a change in attitudes is often difficult to ascertain and may only apply to schoolchildren as in Tanzania.[15]

Conclusion

Learning materials should be seen as a dynamic part of the learning process and not just something given out to learners with no follow-up or input from the teacher or facilitator. The principles of adult learning should be incorporated into their development and use, so that they are practical, problem oriented and relevant to the learners' situation and learning needs. A variety of learning materials should be used to encourage learning for knowledge, attitudes and skills. Written materials may not be the most appropriate, particularly for health education programmes, other media should be considered and used. The participatory approach to the use of learning materials will not only improve retention of the learning but also increase the attitude and performance skills learning.

Testing of any learning material is necessary to see whether it is valid and effective. Both written and visual materials need to be tested and evaluated. Clear, logical well-set-out materials encourage learning and will enhance the teaching programme.

Learning materials are tools and as such are dependent upon their user. When used in an interactive and participatory approach they can facilitate effective learning, but when badly produced, and poorly used they may be worse than useless, since they can confuse or misinform.

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Antibody-based enzyme-linked immunosorbent assay for determination of anti-PGL-I specific circulating immune complex in leprosy patients

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Summary A serological study was performed in 122 individuals: 75 leprosy patients and 47 healthy controls. The ELISA test was performed for IgG and IgM using the glycolipid PGL-I antigen from *Mycobacterium leprae*. Circulating immune complexes (CIC) were isolated by PEG 6000 precipitation method and after dissociation with an acid solution, the IgG and IgM specific against PGL-I were tested with the ELISA test. The multibacillary patients had high levels of antibodies, compared with paucibacillary patients and controls. The antibodies isolated from the CIC presented a similar spectrum spectral distribution as the serology. A positive correlation between the levels of free and CIC bound antibodies was observed. In contrast with tuberculosis patients, specific antibodies present in CIC were not responsible for false-negative results found in some multibacillary patients' serology, since no or very low levels of specific antibodies were found in PEG precipitated serum of these patients. No relation was observed with specific antibody levels detected in CIC during leprosy reactions.

Introduction

When the body establishes contact with a foreign substance, an immune response may occur. Two types of specific response can be observed: the cell-mediated and the humoral immune responses. Mycobacteria can stimulate antibody production directed specifically against mycobacterial antigens. A specific antigen PGL-I (phenolic glycolipid I) from *Mycobacterium leprae* has been described by Brennan and Barrow,[1] and has been used for serodiagnosis

Part of this study has been presented at the 57th Meeting—The Society for Investigative Dermatology and European Society for Dermatological Research (May 1996, Washington)

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in leprosy. High levels of immunoglobulin G and M (IgG and IgM) against PGL-I have been detected in multibacillary patients, and some authors reported higher IgM than IgG.[2–4]

However, a small proportion of multibacillary patients (BL and LL) have low levels of anti-PGL-I antibodies, as do most paucibacillary (BT and TT) patients. In tuberculosis, some authors recently found that the negativity of serological tests in patients with confirmed tuberculosis was due to specific immune complexes in the serum.[5–8] We postulated that specific antibodies present within circulating immune complexes (CIC) would not be detected by the enzyme-linked immunosorbent assay (ELISA) test for PGL-I, and this could explain the false-negative reactions found in some paucibacillary and multibacillary patients sera before and during treatment.

Elevated CIC levels have been reported in leprosy patients[9,10] and deposition or *in situ* formation is thought to be a precipitating factor for the development of the erythema nodosum leprosum (ENL).[11] It is argued that some CIC are not eliminated and persist in the circulation, causing a hypersensitivity reaction, resulting in immune complexe (IC) disease, especially when they are deposited in blood vessel walls and peripheral tissues causing inflammation.[12] The polyethylene glycol (PEG) precipitation test for CIC was performed to show the presence of specific anti-PGL-I antibody in the precipitates, and to verify if there is any relationship between the specific CIC levels and the presence of leprosy reaction (reversal reaction or erythema nodosum leprosum), as the real role of the specific CIC in the leprosy reaction is not certain.

Materials and methods

SERA

Seventy-five sera from patients with leprosy [13 lepromatous lepromatous (LL), 26 borderline lepromatous (BL), 3 borderline boderline (BB), 16 borderline tuberculoid (BT), 14 tuberculoid tuberculoid (TT) and 3 indeterminate] were obtained from the Department of Dermatology, UNIFESP-Escola Paulista de Medicina, São Paulo, Brazil. Their ages ranged from 14 to 63 years, and 39 female and 36 male patients were included. The diagnosis was made by clinical, bacteriological (slit skin smears), histopathological and immunological (Mitsuda reaction) features. The cases were classified according to the Ridley-Jopling classification.[13] Operational classification of leprosy (World Health Organization, 1988) patients according to their type of treatment was gathered: LL and BL patients as multibacillary leprosy and BT and TT as paucibacillary leprosy. This classification was used in this report because the humoral response seems to corroborate such operational view. All sera were collected from patients before treatment, except from five who were treated for less than 1 year. Thirteen patients had type 1 reaction (reversal) and four patients type 2 reaction (ENL). Two to four samples of serial sera were collected from seven patients with leprosy reaction ($n = 19$ sera). The interval between each collected sample was 15 days; these patients have been treated with prednisolone and/or thalidomide. In addition, sera from 47 normal blood donors from the same hospital in São Paulo, Brazil were included as controls. Their ages ranged from 18 to 57 years; 16 females and 31 males.

ANTIGEN

The natural PGL-I of *Mycobacterium leprae* was used. The methods for isolation, purification and characterization were reported previously.[1]

ELISA PROCEDURE

An enzyme-linked immunosorbent assay (ELISA) was performed, using the method described by Cruaud *et al.*[14] for glycolipid mycobacterial antigens. Polystyrene microtitre plates purchased from COSTAR (USA) were coated with PGL-I (250 ng/well). For coating, the indicated amounts of antigen in 25 μ of *n*-hexane were placed in the wells, and the solutions were left to dry overnight at 37°C. To ascertain the absence of nonspecific adsorption, one well treated with 25 μl of *n*-hexane without antigen was included for each test. The storage of sera were at −20°C, until the serology was performed. The sera were diluted 1/250 in PBS (phosphate buffer saline) containing 0·5% of porcine gelatin (Sigma, USA). After saturation by PBS containing 0·5% of porcine gelatin (overnight at 4°C), the plates were washed with PBS without Tween (Micro plate washer LP 35, Diagnostics Pasteur, France) and 100 μl of diluted sera was incubated at 37°C during 90 or 180 min for IgG or IgM determination, respectively. After washings, the conjugates with appropriate dilution were allowed to react for 2 h at 37°C; the conjugates were goat antihuman IgM (anti μ)/beta-galactosidase (Biosys, France). After washing, the appropriate substrate, 2-nitrophenyl-beta-D-galactopyranoside (Merck, Germany) was added, and the plates were incubated at 37°C for 30 min. To correlate the data, three known tested sera having low, medium and high levels of antibodies were used as standards. They were included in each plate, and PBS was used as the control (zero point activity). The color developed was read at 405 nm, using an automatic spectrophotometer (LP 400, Sanofi-Diagnostics Pasteur, France). After reading, for each plate, a curve was drawn using the zero and standard values after calculation of the slope and the correlation coefficient (cc). If these data were not satisfactory (slope too low, cc below 98%...), the plate was rejected and the assay was repeated. The values of tested sera were corrected as follows: first, the difference between absorbance of serum and the nonspecific absorption was calculated. Then, the data were calculated to establish the corrected $\Delta 405$ values by using the curve of the standards.

PEG PRECIPITATION

The PEG 6000 (polyethylene glycol 6000, Prolabo, Paris, France) precipitation test for CIC (circulating immune complexes) precipitation was performed according to the method described previously by Louzir *et al.*,[15] developed from the original technique by Ohlson and Zetterstrand.[16] The sera were diluted 1/1 with PBS (pH 7.4) without Tween. To 200 μl of diluted serum, 200 μl of 5% PEG 6000 in 150 mM NaCl, 20 mM potassium phosphate buffer (pH 7·4) was added. The mixture was incubated overnight at 4°C. The precipitates were collected by centrifugation (1550 *g*, 20 min, 4°C) (CR 4.11, Jouan, France), washed twice with 2·5% PEG 6000 in buffer described below and then were dissolved in 100 μl of 150 mM NaCl, 20 mM potassium phosphate buffer (pH 7·5) 10 mM ethylene diamine tetraacetic acid [EDTA (Sigma, France)] by incubation for 30 min at 37°C. To 100 μl of the solubilized CIC solution, 50 μl of cold 0·2 M HCl-glycine (pH 2·8) was added and incubated at 4°C for 15 min. This solution was neutralized with 25μl of 1 M K_2HPO_4 (pH 9·0) and then diluted 1/20 by adding 1825 μl of PBS containing 0·5% of porcine gelatin without Tween. This solution was tested for ELISA within 30 minutes. The main difference between the CIC precipitation test and the current ELISA serology was the dilution factor for CIC 1/20, and for the sera, 1/250.

SUPERNATANT ANALYSIS

After the overnight serum incubation at 4°C with 2·5% PEG solution and first centrifugation, 40 μl of the supernatant (corresponding volume of 10 μl of serum) were diluted in 2·5 ml of PBS with 0·5% of porcine gelatin, and distributed in the ELISA plates. The final dilution corresponded to an equivalent 1/250 serum dilution. For some sera ($n = 24$), a double PEG precipitation was performed. The first supernatants were re-precipitated, repeating the same technique for PEG precipitation. The precipitate was analysed to verify if some CIC remained in the supernatant after this first PEG precipitation. The second supernatant obtained from the re-precipitation was tested for ELISA in following proceeding: 160 μl of the second supernatant was diluted in 2·34 ml PBS containing 0·5% porcine gelatin (a final serum dilution of 1/250), and tested for ELISA. It allowed us to determine whether the antibody activity remained after two PEG precipitations.

STATISTICAL ANALYSIS

The ANOVA (Analysis of Variance) and Kruskal-Wallis non-parametric test were performed for statistical analysis of the antibodies levels in respect to the different forms of leprosy and the control group. A box plot graphic was developed to represent the 10, 25, 50 (median), 75 and 90 percentiles of serology repartition results of each leprosy forms and control group, analyzing the IgG and IgM anti-PGL-I levels. The scattergraphs were used to represent the correlation of antibodies levels in leprosy patients and for all these statistical analysis the correlation coefficient was calculated. The contingency tables were analysed by the χ^2 test, using a significant P-value of <5%.

Results

INDIVIDUALS AND MEAN ANTIBODY LEVELS AGAINST PGL-I IN SERUM

The initial assessment was performed by ELISA, using PGL-I as antigen, on all whole serum before PEG precipitation. As expected, higher IgG and IgM antibodies levels were observed (Figure 1) in the serum of LL and BB leprosy patients as compared with those of BT and TT patients. A significant difference ($P < 0·05$) in IgG and IgM levels was found between healthy controls and multibacillary (LL + BL) patients. Mean levels were also significantly higher ($P < 0·05$) in multibacillary (LL + BL) patients than in paucibacillary patients (BT + TT). The corrected $\Delta 405$ optical density value corresponding to the 95 percentiles of all healthy subjects was taken as the normal upper limit for each immunoglobulin class (Table 1). Using this definition, we obtained a specificity of 95% for IgG and IgM classes. The sensitivity was 74·0% and 57·1% for IgG and IgM classes, respectively for the leprosy patients considered as a whole group. However, when the leprosy group was subclassified into two groups, the multibacillary and the paucibacillary, the sensitivity was 97·4% and 92·3% for IgG and IgM classes in the multibacillary group and 45·2% and 19·3% for IgG and IgM classes for the paucibacillary group. LL and BL leprosy patients were significantly ($P < 0·001$) more positive than BT and TT patients for both immunoglobulin classes. The presence of specific IgG and IgM antibody against PGL-I in dissociated CIC was tested in the same sera after the PEG precipitation.

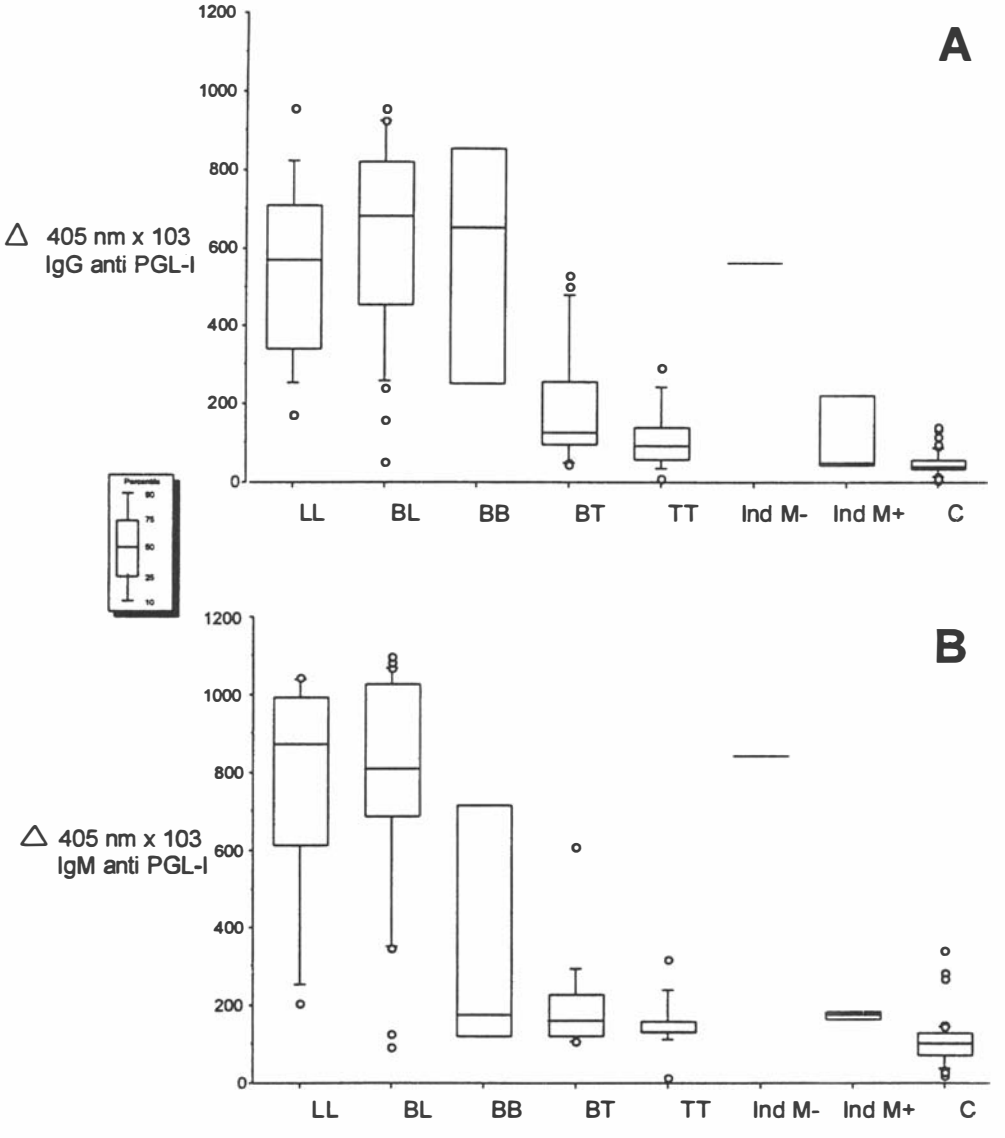

Figure 1. Distribution of antibodies levels anti-PGL-I IgG (**A**) and IgM (**B**) in whole sera according to the different forms of leprosy: 13 lepromatous lepromatous (LL), 26 borderline lepromatous (BL), 3 borderline borderline (BB), 16 borderline tuberculoid (BT), 14 tuberculoid tuberculoid (TT), one indeterminate with negative Mitsuda's reaction (Ind M−), 2 indeterminate with positive Mitsuda's reaction (Ind M+) patients and 47 healthy controls (C).

DEMONSTRATION OF SPECIFIC ANTIBODY AGAINST PGL-I IN IMMUNE COMPLEXES

All collected sera were subjected to PEG precipitation, the CIC were dissociated and the liberated IgG and IgM immunoglobulin classes were assayed by ELISA using the PGL-I antigen. Figure 2 illustrates the distribution of the individual IgG and IgM antibody levels after PEG precipitation in respect to the different forms of leprosy and control group. As

Table 1. Repartition of positive results for each group of leprosy patients. The cut-off point is defined as the corrected Δ405 optical density value corresponding to the 95 percentiles of all healthy subjects is taken as the normal upper limit in each immunoglobulin class. Using this definition, the specificity is 95%

	Free immunoglobulins			CIC complexed immunoglobulins			Both free and CIC complexed Immunoglobulins		
Groups	IgG pos. (%)	IgM pos. (%)	Both pos. (%)	IgG pos. (%)	IgM pos. (%)	Both pos. (%)	IgG pos. (%)	IgM pos. (%)	Both pos. (%)
LL ($n = 13$)	13 (100)	12 (92·3)	13 (100)	11 (84·6)	10 (76·9)	11 (84·6)	13 (100)	12 (92·3)	13 (100)
BL ($n = 26$)	25 (96·2)	24 (92·3)	26 (96·2)	20 (74·0)	23 (85·2)	23 (85·2)	26 (96·3)	25 (92·6)	26 (96·3)
BB ($n = 3$)	3 (100)	1 (33·3)	3 (100)	2 (66·7)	1 (33·3)	2 (66·7)	3 (100)	1 (33·3)	3 (100)
BT ($n = 16$)	8 (50·0)	4 (25·0)	8 (50·0)	2 (12·5)	2 (12·5)	4 (25·0)	10 (62·5)	6 (37·5)	10 (62·5)
TT ($n = 14$)	6 (42·9)	2 (13·3)	6 (40·0)	2 (13·3)	2 (13·3)	2 (13·3)	6 (40·0)	3 (20·0)	6 (40·0)
Ind. Mit + ($n = 2$)	1 (50·0)	0 (0)	1 (33·3)	0 (0)	1 (33·3)	1 (33·3)	1 (33·3)	1 (33·3)	2 (66·7)
Ind. Mit − ($n = 1$)	1 (100)	1 (100)	1 (100)	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)	1(100)

already shown in Figure 1, higher IgG and IgM antibody levels were observed in CIC of BL + LL forms as compared with BT, TT and controls. The spectral distributions appeared to be similar, when the antibody titers were compared with those obtained with the whole serum before CIC precipitation. The difference between the BL + LL and the BT + TT form was more evident for IgM.

RELATION BETWEEN ANTI-PGL-I FREE IMMUNOGLOBULINS AND SPECIFIC ANTIBODIES CONTAINED IN CIC

As shown in Figure 3, individual sera with high titers of free IgM antibodies also had high titers of the same antibody isolated from CIC. Although the dilution was not the same for serology and CIC precipitation, a positive correlation was observed in patients between the free antibodies and those isolated from CIC ($r = 0{\cdot}885$; $P < 0{\cdot}01$). Comparing leprosy patients with and without reaction, no significant difference on IgM isolated from CIC was noticed.

SUPERNATANT ANALYSIS

The analysis of the remained individual supernatants tested by the same ELISA method showed similar results in comparison with serology ($r = 0{\cdot}983$, $P < 0{\cdot}01$). No difference of free immunoglobulins levels was observed before and after PEG precipitation on the studied sera (Figure 4) indicating that free immunoglobulins were not coprecipitated by PEG. When the supernatant was re-precipitated by PEG, using the same technique, the precipitate obtained had very low or no antibody activity. The second supernatant had almost the same activity when compared with the first supernatant or serology (data not shown).

OCCURRENCE OF CIC AND FREE ANTIBODIES IN TYPE 1 AND TYPE 2 REACTIONS

A difference between patients with or without reaction (type 1 and 2) in relation to the specific antibodies levels, was not observed in all tested sera. The same analysis was also

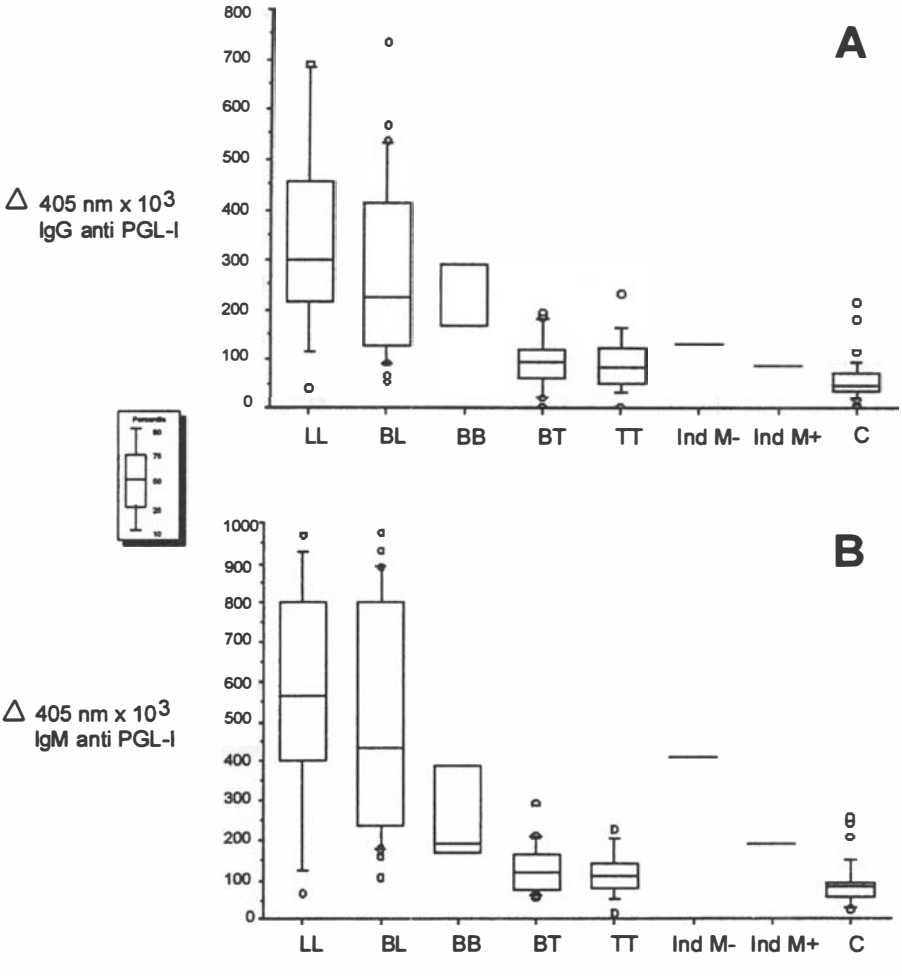

Figure 2. Distribution of dissociated anti-PGL-I IgG (**A**) and IgM (**B**) from polyethylene glycol 6000 precipitated circulating immune complexes according to the different forms of leprosy: 13 lepromatous lepromatous (LL), 26 borderline lepromatous (BL), 3 borderline borderline (BB), 16 borderline tuberculoid (BT), 14 tuberculoid tuberculoid (TT), one indeterminate with negative Mitsuda's reaction (Ind M−), 2 indeterminate with positive Mitsuda's reaction (ind M+) patients and 47 healthy controls (C).

valid for antibodies isolated from CIC. No significant difference ($\chi^2 = 0{\cdot}171$, $P > 0{\cdot}05$) was observed comparing patients with or without leprosy reactions for anti-PGL-I antibodies isolated from CIC (Table 2). The cut-off-point for this analysis was 0·253 (Δ405) (mean value plus three standard deviations of obtained titres in the control group). Using this analysis separately for reaction type 1 and 2, we found the same results. There are no significant differences in patients with reaction type 1 ($\chi^2 = 0{\cdot}263$, $P > 0{\cdot}05$) or in patients with reaction type 2 ($\chi^2 = 0{\cdot}107$, $P > 0{\cdot}05$), compared to patients without leprosy reaction, although the number of patients with leprosy reaction was small.

Nine patients with BT form had reaction type 1 and among them, eight patients had negative IgM titres of anti-PGL-I isolated from CIC. Four patients with BL form had reaction type 2, and 3 of them had positive titres for IgM anti-PGL-I isolated from CIC.

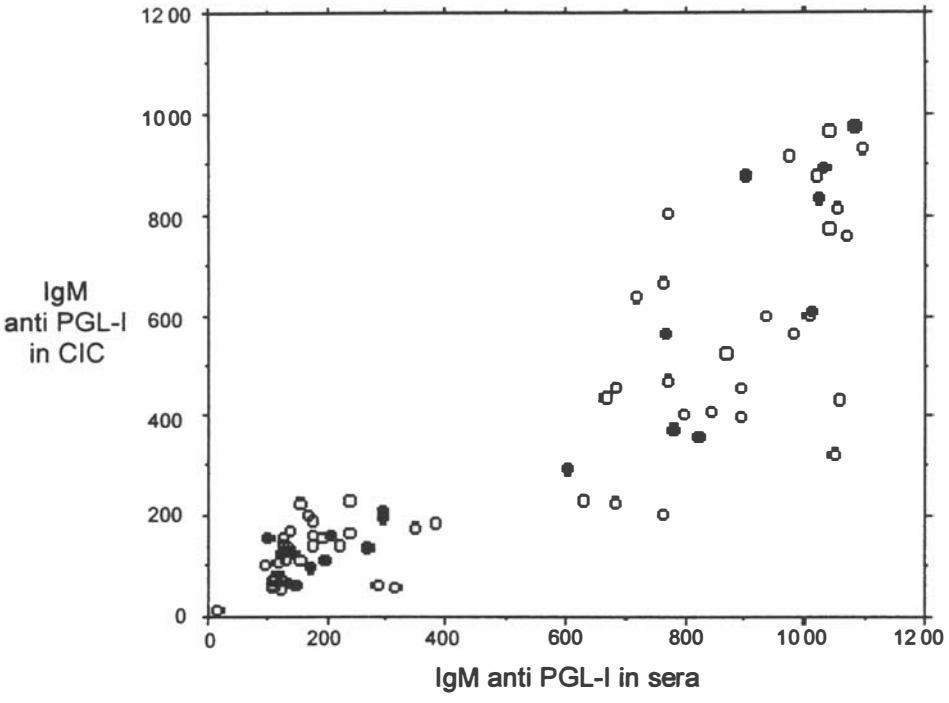

Figure 3. Scattergraphs showing individual paired IgM levels against PGL-I obtained by ELISA ($\Delta 405\,nm \times 10^3$) in sera and circulating immune complexes of leprosy patients. Open circles for patients without reaction and closed circles for patients with reactions ($r = 0{\cdot}885$, $P \leq 0{\cdot}01$).

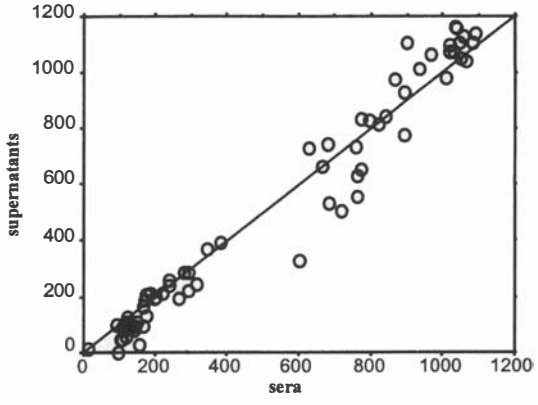

Figure 4. Scattergraphs showing individual paired IgM levels against PGL-I obtained by ELISA ($405\,nm \times 10^3$) in whole sera and in polyethylene glycol 600 treated supernatants ($r = 0{\cdot}983$, $P \leq 0{\cdot}01$).

Table 2. Comparison of positive or negative results of anti-PGL-I IgM antibodies isolated from circulating immune complexes in leprosy patients with or without reactions (type 1 or type 2)

	Positive	Negative	Total
Without reaction	9	44	53
Reaction type 1 or type 2	6	11	17
Total	15	55	70

$\chi^2 = 0{\cdot}171$, $P > 0{\cdot}05$.

Serial sera were collected during leprosy reaction, but there was no oscillation of the serology titres (data not shown).

Discussion

The specific PGL-I antigen from *Mycobacterium leprae* had been largely used for serological studies in leprosy diagnosis, although it is not used routinely. As shown in this report, almost all multibacillary leprosy patients (LL and BL) have high levels of IgG and IgM against PGL-I.[2–4] In the present work, leprosy sera for PGL-I serology were tested by ELISA and the results are in agreement with our previous work.[14,17] High antibody titres were observed in the multibacillary group (LL and BL) compared with low titres in the paucibacillary group (BT and TT) and controls. The specific IgM antibodies against PGL-I had higher titres while IgG presented low titres in the sera and in the PEG 6000 precipitates from CIC. In the present study, almost all the patients studied had not received specific leprosy treatment and, the attention was focused on IgM, as the majority of the studies in leprosy concern this immunoglobulin.

The IgG and IgM antibody against PGL-I isolated from CIC by PEG precipitation test had the same spectral distribution observed in serological studies by ELISA, that extends our previous observation.[17]

The present data comparing the frequency of specific antibody present in the whole serum with that in dissociated CIC, do not confirm our hypothesis since leprosy patients with low antibody levels in serum also have low antibody titres measured by ELISA in CIC. Other factors for the false-negativity in the multibacillary patients must be investigated, such as concomitant acquired immunosuppression. Among the three typical multibacillary leprosy patients, whose serological and CIC analysis were negative, one of them was co-infected with human immunodeficiency virus (HIV). Another explanation for the low antibody levels is that perhaps sero-positivity is related to high systemic and skin bacterial load. Perhaps exclusive high cutaneous bacterial load does not produce high levels of antibodies. We also observed two patients with a negative bacterial index and high positivity for serology, the histopathology and Mitsuda reaction, suggesting the multibacillary form. In these cases, perhaps the systemic bacterial load correlated with the high antibody titres, but not with the skin bacterial load.

The levels of specific free antibodies and isolated antibodies from the CIC were correlated, and the presence of CIC did not modify these antibodies levels as detected by

ELISA using the glycolipid PGL-I antigen. The CIC precipitation method by PEG does not increase the sensitivity of the ELISA test (Table 1). This is in sharp contrast with the results described by Bhattacharya *et al.*,[18] studying CIC by PEG precipitation method in tuberculosis. They presented data comparing the frequency of antibody with that of immune complexes. Circulating immune complexes were less frequently observed in their control subjects. However, the data presented by Bhattacharya *et al.*[18] did not give any assessment of the antigenic components of *Mycobacterium tuberculosis* in the immune complexes.

The CIC isolation by the 2·5% PEG precipitation is very efficient. The supernatant after the first precipitation had similar antibody levels as was found in serology analysis, so PEG used in this condition did not precipitate the free immunoglobulins present in the sera. Submitting this supernatant to another re-precipitation by PEG, very low or no antibody was found in the second precipitate, it demonstrated that all CIC have been effectively detected in the first precipitation. The supernatant resulted after the second precipitation showed almost the same antibody against PGL-I.

Analysing the levels of specific antibodies in sera and in CIC, we did not find any difference between patients with or without reaction (reversal reaction and ENL). Some authors have demonstrated that levels of free specific antibodies were not increased in reactional forms.[19,20] Separate analysis of different leprosy reactions did not show any difference in patients with reaction type 1 or 2, comparing to patients without leprosy reaction.

Patients with reaction type 1 presented a spectral results according to leprosy form. Paucilbacillary patients (BT) presented low levels of antibodies in sera and in CIC and; multibacillary patients (BL), high anti-PGL-I titres. These findings show that high levels of specific antibody, free or binding to CIC, is not related to leprosy reaction type 1, but to leprosy form.

Unfortunately, this study did not include a large number of patients with reaction type 2, as we analysed patients before the introduction of specific treatment. Most patients have ENL during the treatment, and we could not include patients with a long period of treatment, as these patients would have low levels of anti-PGL-I. In our previous work,[17] we have not found statistically significant difference, comparing patients with and without type 2 reaction, during specific treatment. Some authors reported that there is a decrease of antibodies during ENL and an increase after this reaction. This antibody level variation could be due to residual deposition of antibodies or immune complexes.[3,21]

In this report, we were testing only the specific CIC containing PGL-I antigens and anti-PGL-I antibodies. Such specific CIC did not seem to be involved in leprosy reaction. Other antigen or antibody could be involved, since Ramanathan *et al.*[10] reported different results. These authors measured CIC by PEG precipitation, and found a high titre of total CIC precipitates in all the patients who presented with a leprosy reaction. They also found that although BT and LL patients had elevated CIC titres, this increase was much less, compared to BT with reaction and ENL, respectively.

A deficiency in any of the complement components could be responsible for the lack of dissolution of immune aggregates in plasma, and thus further precipitate them in various tissues during the inflammatory processes.[11,22] According to our findings, we can conclude that leprosy patients, mainly BL + LL forms, produce specific CIC and their presence in peripheral circulation are not related to leprosy reactions. However, we are not able to conclude if the peripheral specific CIC reflect part of the immune complexes that are deposited in the tissues and if they have an important immunological role.

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Immunohistochemical detection of PGL-1, LAM, 30 kD and 65 kD antigens in leprosy infected paraffin preserved skin and nerve sections

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Summary A panel of lipid, carbohydrate and protein antibodies were optimized for use in detecting *M. leprae* antigens in paraffin embedded material. Skin and nerve biopsies from 13 patients across the leprosy spectrum were studied. All antibodies detected antigen in tissues with a BI >1. Phenolic-glycolipid was not detected in bacteriologically negative tissue but lipoarabinomanan (LAM) and protein antigens were detected. Staining with LAM was strongest and gave least background. The transfer of this immunohistochemical technique to paraffin embedded material will allow examination of tissue with better morphology and from clinics without access to tissue freezing facilities.

Introduction

The paucity of *M. leprae* bacilli in tuberculoid leprosy disease spectrum in leprosy poses diagnostic difficulties histologically. One potential solution to this problem is to use antibodies against *M. leprae* antigens in immunohistochemical techniques to detect individual antigens rather than bacilli. *M. leprae* has protein, lipid and carbohydrate antigens. The lipid and carbohydrate antigens are found in the *M. leprae* cell wall. Phenolic glycolipid is unique to *M. leprae*, lipoarabinomannan is a soluble polysaccharide and is present in other mycobacteria. *M. leprae* has numerous protein antigens; the 65 kDa is a heat shock protein and 30 kDa is a secreted antigen. Immunohistochemical studies have been done on leprosy infected tissue using anti-BCG monoclonals[1,2] and monoclonal antibodies (mAbs) directed against phenolicglycolipid-1 (PGL-1),[3–5] lipoarabinomannan (LAM)[6,5] and different protein epitopes of *M. leprae*[3,6–10,14] to detect these antigens. Most of these studies were performed on skin biopsies; only three workers have reported results of staining nerve biopsies for

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leprosy antigens.[1,3,4] Few studies have been performed on paraffin embedded material in which tissue morphology is better preserved. Wang *et al.*[5] have demonstrated PGL-1 and LAM-B in paraffin preserved leprosy material, but *M. leprae* protein epitopes have not been demonstrated in paraffin preserved leprosy specimens. In this study, a panel of mAbs was used for an immunohistochemical analysis of paraffin embedded nerve and skin biopsies. Intensity and differential staining patterns were analysed and compared with bacillary load and macrophage numbers.

Materials and methods

MATERIAL

Tissue specimens from 13 leprosy patients were obtained from the Hospital for Tropical Diseases (London) and the Dhoolpet Leprosy Research Centre (Hyderabad, India). Patients had been classified clinically and histologically using the Ridley–Jopling classification. Bacillary indices were counted at the London School of Hygiene and Tropical Medicine using the Ridley logarithmic scale. The group comprised two TT, four BT, three BL and four LL cases. In five cases nerve biopsy material was also available (one BT, one BL and three LL cases). Control skin sections were taken from psoriasis (as a control for skin inflammation) and leishmaniasis (granulomatous skin control) cases (Departments of Dermatology and Pathology, Academical Medical Centre, University of Amsterdam, The Netherlands) and normal skin and nerve (post mortem) tissue (University College Hospitals, London, UK). All material was paraffin embedded and 5 μm sections were cut.

IMMUNOHISTOCHEMICAL STAINING

Routine staining procedures (Dako) for immunohistochemistry of paraffin-embedded tissue sections were followed. Sections were incubated for 20 min in normal goat serum to block non-specific staining. The antibodies DZ-1 (PGL-1) and F26-7 (LAM) (Amsterdam) were diluted in a pre-evaluated dilution of 1:250 in PBS (phosphate buffered saline) and applied to the sections for 1 h, at room temperature. Pre-treatment in a trypsin-chymotrypsin bath for 15 min, at 37°C was required for sections stained with the antibodies 3A8 (30 kD) and F67-2 (65 kD). These antibodies were used at an optimal dilution of 1:75 and 1:1000 in PBS, respectively, with an overnight incubation at 4°C. The macrophage marker PG-M1 (Dako Cat

Table 1. Description of monoclonal antibodies used in this study: immunoglobulin class and specificity

mAbs	Ig class	Specificity	Source
DZ-1	IgG1	PGL-1	
F26-7	IgM	LAM	A. H. J. Kolk[12]
3A8	IgG1	30 kDa protein	P. K. Das[9,10,13]
F67.2	IgG1	65 kDa protein	A. H. J. Kolk[12,14]

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[2]Department of Pathology, Academical Medical Centre, University of Amsterdam, The Netherlands and J Bennedsen, Statens Seruminstitut, Copenhagen, Denmark.

Table 2. Description of other mAbs tested and their *M. leprae* protein epitope specificity

mAb	Specificity	Dilutions tested in PBS	Ref
A2h11	30 kD	1:5, 1:10, 1:20, 1:40	10, 15, 16
Rb2	30 kD	1:5, 1:10, 1:20, 1:40	10, 15, 16
A3e2	30 kD	1:50, 1:100, 1:500, 1:1000	16
A4g4	30 kD	1:50, 1:100, 1:500, 1:1000	10, 16
Pe12	30 kD	1:50, 1:100	10, 15, 16
A3c12	26/27 kD	1:250, 1:500, 1:1000	10, 16
Ne5	65 kD	1:50, 1:100	17
Nd4	65 kD	1:50, 1:100	17

No M0876) specific for CD68 was diluted 1 in 50 and applied for 1 h at room temperature. The sections were subsequently incubated with biotinylated rabbit anti-mouse immunoglobulin (Dako Cat. No. E413) diluted 1:200 in PBS + 10% human AB serum for 30 min and finally incubated with streptABComplex/HRP (Dako No. K377) for 30 min. The peroxidase reaction was visualized using 3,3′ diaminobenzidine tetrahydrochloride (DAB Sigmafast) for 5–10 min at room temperature and the sections were counterstained with haematoxylin. The specificity of the antibody staining was checked by omitting the primary antibody in at least one section from each patient.

Table 3. Staining intensity patterns of *M. leprae* monoclonal antibodies

Pat. no.	Classif.	Treatment status	BI	Antigen staining				Macrophages CD68
				PGL-1	LAM	30 kD	65 kD	
1.	TT	Untr	0	–	+	2+	+	2+
2.	TT act	Untr	0	–	+/–	+	2+	+
3.	BT	DDS/6 m	0	–	+/–	2+	3+	3+
4.	BT	DDS/1 m	0	–	+	+	2+	2+
5.	BT	Untr	0	+	+	2+	+	2+
6. A skin	BT	DDS/24 m	1+	+	+	+	2+	+
B nerve	BT	DDS/24 m	1+	–	+/–	–	+	+
7. A skin	BT/BL	MDT/irr	1+	+/–	+	+	+	+
B nerve	BT/BL	MDT/irr	2+	+	2+	–	+	2+
8.	BL	Untr	3+	+	+	+	+	nd
9.	BL act	DDS	3+	2+	2+	2+	+	2+
10. A skin	LL	DDS/12 m/MDT/23 m	2+	+	2+	2+	+	2+
B nerve	LL	DDS/12 m/MDT/23 m	3+	2+	2+	–	+/–	2+
11.	LL rel	unknown	3+	2+	3+	3+	+	4+
12. A skin	LL	DDS/irr	4+	2+	3+	3+	3+	3+
B nerve	LL	DDS/irr	5+	3+	4+	–	2+	4+
13. A skin	LL	DDS/2 m	5+	3+	3+	2+	2+	3+
B nerve	LL	DDS/2 m	3+	2+	2+	–	2+	2+
Leishmaniasis				–	–	–	–	nd
Psoriasis				–	–	–	+/–	nd
Normal skin				–	–	–	–	nd
Normal nerve				–	+/–	–	–	+/–

Patient 8 was in reversal reaction.

Grading of antigen staining: – negative, +/– weak, + fair, 2+ moderate, 3+ strong, 4+ very strong.

TT tuberculoid, BT borderline tuberculoid, BL borderline lepromatous and LL lepromatous leprosy.

Pat. no. patient number, *Class.* classification, *BI* bacillary index, *Untr* untreated, *DDS* dapsone, *m* month, *MDT* multidrug treatment, *irr* irregular, *nd* not done, *act* active, *rel* relapse.

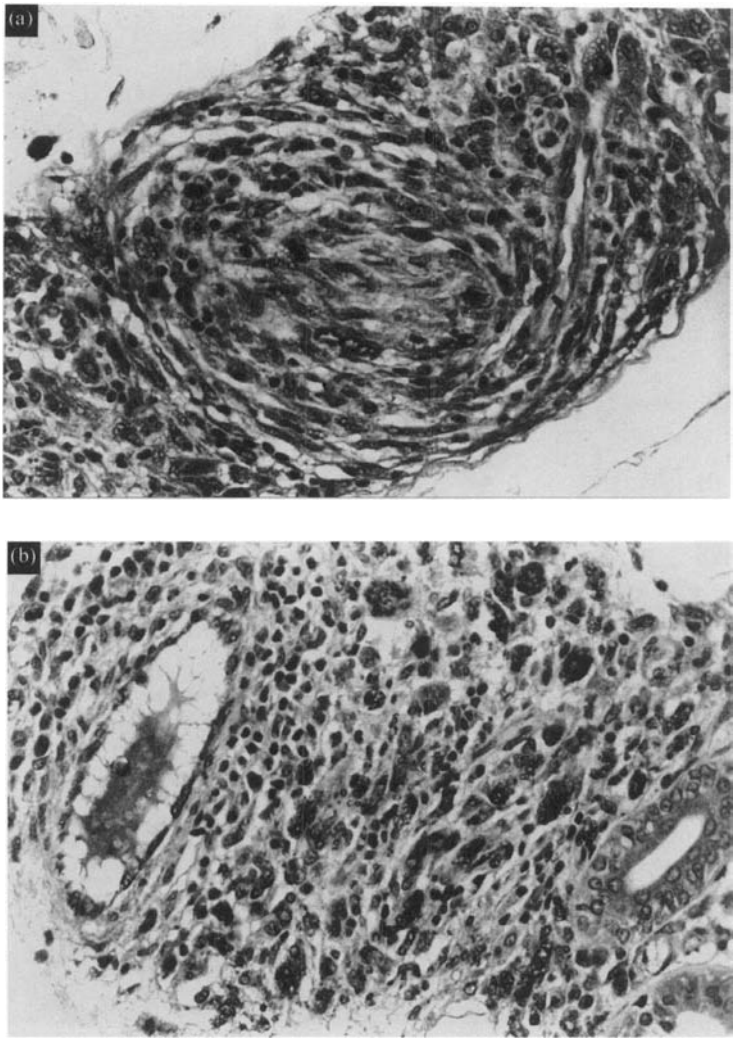

Figure 1. Staining patterns in LL patient (12) skin. All magnification ×400. (A) PGL staining, intracellular staining in macrophage. (B) LAM staining, strong vesicular staining in foamy macrophages. (C) 65 kDa (3A8) staining, cell surface staining is present. (D) Macrophage (CD68) marker.

Results

The characteristics of the four mAbs used in this study are listed in Table 1. At the start of the study, eight other mAbs (Table 2) were also tested on paraffin preserved material. However, no positive antigenic staining was found using dilutions around the optimal dilution for use on frozen material and following the above protocol.

Staining intensity patterns of the four *M. leprae* mAbs used in this study (directed against PGL-1, LAM, 30 kD and 65 kD) are shown in Table 3, together with data on bacillary index, CD68 positivity patterns and patient details. For grading purposes numbers of positively

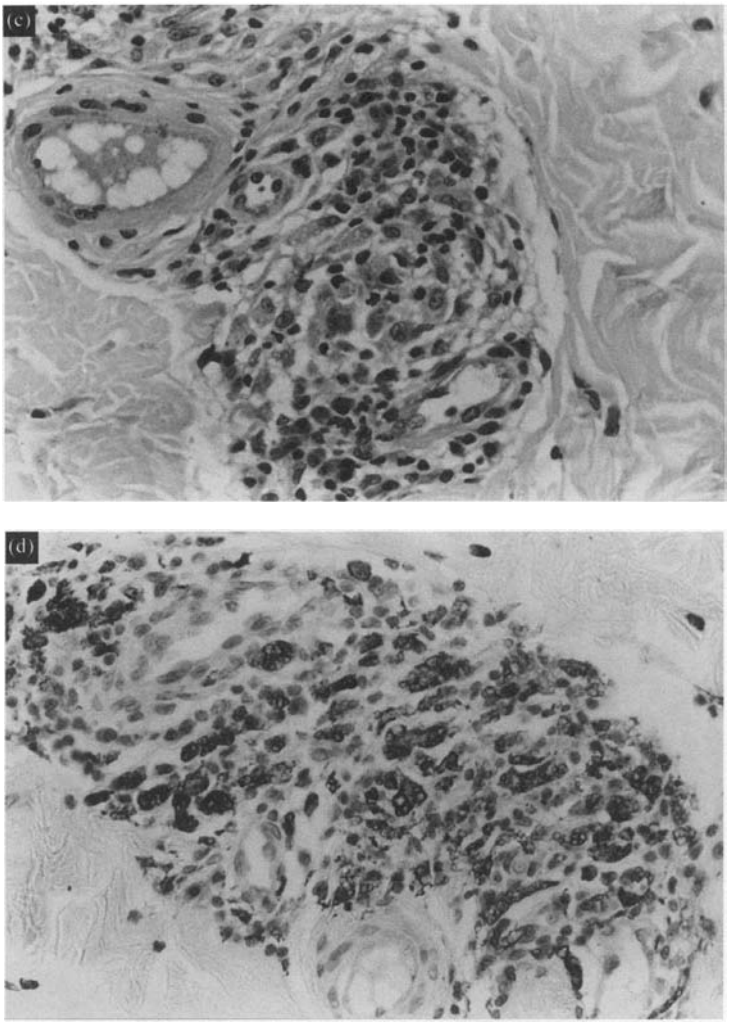

Figure 1. continued

stained infiltrating cells were counted semi-quantitatively by two observers. PGL-1 and LAM positive staining was found to be lowest at the tuberculoid pole and strongest at the lepromatous pole. Control samples were negative for antibody staining except for some 65 kD positivity in occasional subepidermal macrophages (identified by morphology) in psoriasis skin. In post mortem normal nerve tissue, a weak diffuse staining pattern was found within Schwann cells when staining for LAM.

SKIN

Both the PGL-1 and LAM antibodies gave intracellular granular staining in infiltrating macrophages and a clear vesicular staining pattern in foamy macrophages, although the latter

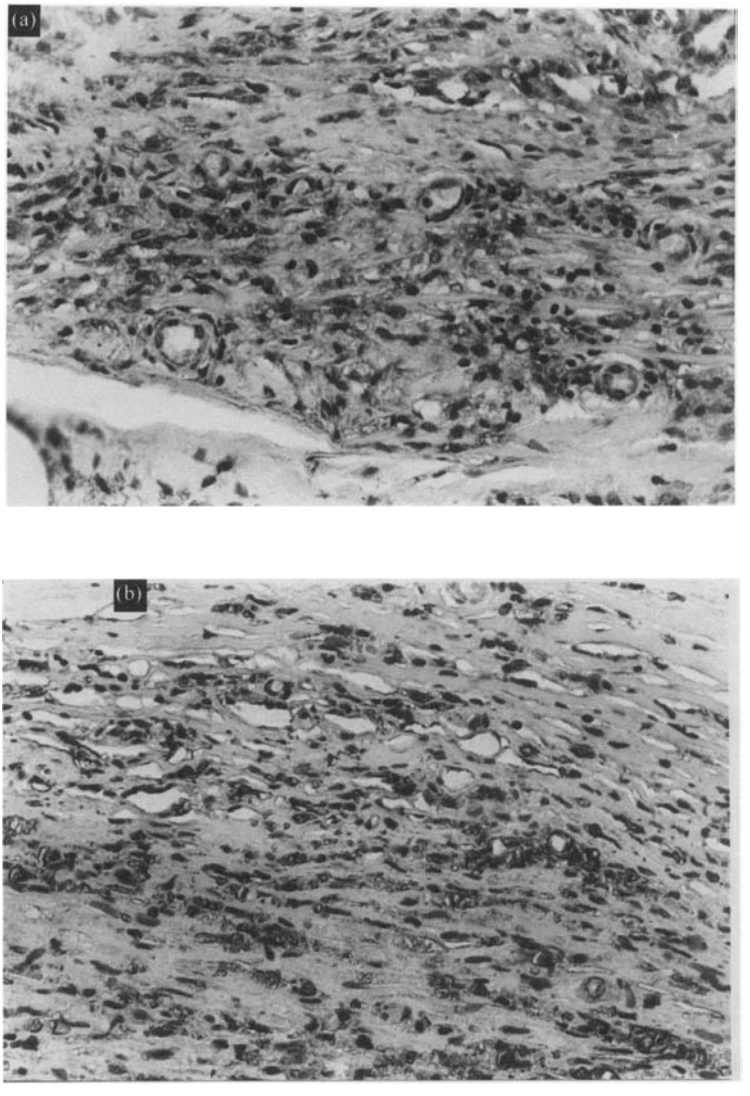

Figure 2. Staining patterns in LL (12) patient nerve. All magnification ×400. (A) PGL staining. (B) LAM staining in presumed Schwann cells. (C) 65 kDa (F67-2), weak cell surface staining. (D) Macrophage (CD68) infiltration in nerve.

pattern is mainly seen with LAM antibody staining (Figures 1A and B). With the PGL-1 antibody a weak diffuse staining was present in granulomata, this was not seen with LAM antibody staining. Occasionally some Langerhans cells stained positively with both the PGL-1 and LAM antibodies. With the 30 kD and 65 kD antibodies, staining of infiltrating cells was seen principally on cell membrane and nuclei with cytoplasm staining weakly (for 30 kD see Figure 1C). The intensity of the staining with the protein antibodies paralleled the macrophage infiltrate in the lesions. A diffuse granular staining observed within granulomas

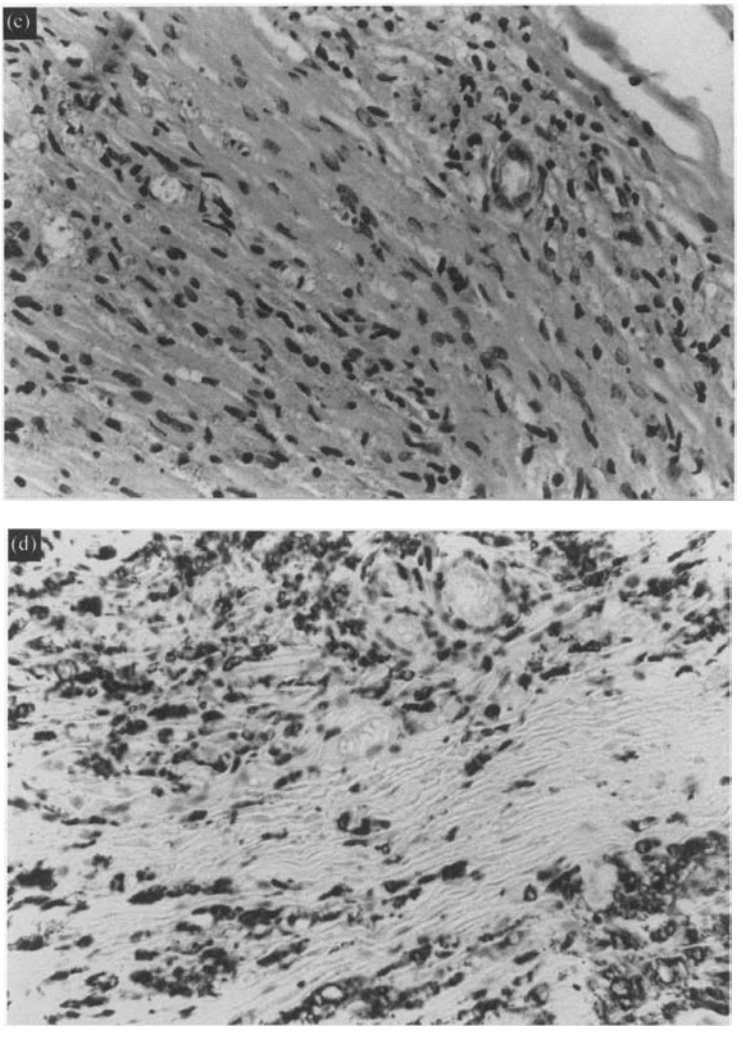

Figure 2. continued

was also seen with 30 kD, occasional background staining was present. The results of staining with 30 kD and 65 kD mAbs in skin suggested a parallel between the number of macrophages present and the intensity of staining.

NERVE

The 30 kD antigen could not be demonstrated in leprosy infected nerve tissue using the 3A8 antibody. For the other antigens the staining intensity paralleled the bacterial load and macrophage infiltrate (Figure 2D). In PGL-1 antibody stained samples PGL-1 was detected in infiltrating cells, mainly macrophages, in both granular and vesicular patterns (Figure 2A). The LAM antibody shows the same pattern, again staining foamy macrophages and with

considerably less background staining than the PGL-1 antibody (Figure 2B). The 65 kD mAb showed staining in infiltrating cells, but principally on the membranes and nuclei of those cells (Figure 2C). No identifiable bacteria were stained with the mAbs used in these skin and nerve sections. For both skin and nerve, positive staining was confined to areas where macrophages are found abundantly (Figures 1A–D).

In all infected skin tissue samples positive staining was also occasionally found in cells of the following cell lineages: melanocytes, vascular and sweat gland endothelial cells, hair follicles, and arrector pili muscle fibres. We have observed this epiphenomenon previously.

Discussion

In this study we have identified four mAbs that detect *M. leprae* antigens in paraffin embedded material. Using paraffin embedded material rather than frozen sections has the advantages that the morphology is much better preserved and specimens can be transported from remote areas for paraffin embedding.

The diagnosis of tuberculoid leprosy may be difficult when there are few granulomata, no definite nerve infiltration and no detectable acid fast bacilli. In such cases an antibody which stained antigen positive when Fite–Faraco staining was negative would be useful. In our study the LAM antibody would fulfil some of these criteria, because although both the PGL-1 and LAM antibody staining intensity correlated with the acid fast bacilli load the LAM antibody also stained positively in Fite–Faraco negative tissues whilst PGL-1 staining was negative at the tuberculoid pole. With the PGL-1 antibody (DZ-1) used here, four of the five TT/BT patients with a BI 0 had no detectable PGL-1, whether or not they had been treated. This contrasts with the work of Narayanan *et al.*[3] and Wang *et al.*,[5] who demonstrated the presence of PGL-1 antigens in bacteriologically negative tissue. The staining for LAM antigens was strongest and clearest, with less background than with the protein and lipid antibodies. One problem with the LAM antibody was that the normal nerve also stained positively with this antibody. This phenomenon has also been reported by Shetty *et al.*[4] and there may be cross reactive epitopes for LAM and nerve tissue. However, further work would be needed in a prospective study comprising patients with leprosy and other skin conditions to determine the sensitivity and specificity of this antibody.

In patients 6 and 10, who had both received many months of treatment (Table 3), staining for all antigens was still positive. This is in accordance with other workers who have found long term persistence of mycobacterial antigens in skin and nerve.[4,11]

The nerve sections used in this study could only be analysed for PGL-1, LAM and 65 kD staining, since the mAb against 30 kD (3A8) did not produce any positive staining in these sections. For PGL-1 and LAM, positive staining in nerve material when compared with staining in the corresponding skin correlated directly with the AFB load. Only PGL-1 showed an overall higher intensity staining in nerve material (three out of five cases), supporting the statement that mycobacterial antigen load is usually higher in nerve when compared with skin from the same patient.[4,11]

Using a panel of antibodies on paraffin embedded material permits future work assessing the amount and location of the different *M. leprae* carbohydrate, lipid and protein antigens in leprosy lesions. Defining *M. leprae* antigens in leprosy, in different disease types and at different sites may extend our understanding of the pathology of leprosy and may thus lead to new diagnostic and therapeutic modalities.

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Presence of *M. leprae* in tissues in slit skin smear negative multibacillary (MB) patients after WHO-MBR

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Summary This study looked for *M. leprae* in the lymph node, nerve and skin of multibacillary (MB) leprosy patients who become slit skin smear negative after the completion of WHO-MBR. Twenty-five WHO-MBR-treated multibacillary leprosy patients were studied; borderline lepromatous (BL) leprosy ($n = 11$) and lepromatous (LL) leprosy ($n = 14$)). Fifteen patients had reaction (erythema nodosum leprosum 11, upgrading reaction 4) either at presentation or during therapy. All patients attained slit skin smear negativity after WHO-MBR (range 24–39 months. Sixteen (64%) patients with multibacillary leprosy showed fragmented bacilli in skin and nerve biopsy or lymph node aspirates after WHO-MBR. Lymph node aspirates alone revealed *M. leprae* in seven patients, followed by nerve in two and skin in one patient. Four cases showed *M. leprae* at all sites followed by nerve and skin or lymph node in one case each. A pretreatment bacteriological index (BI) of 4+ or more was significantly associated with the presence of *M. leprae* at the end of treatment. Also, significantly more lymph node aspirates contained *M. leprae* in comparison with nerve or skin biopsies. All seven cases in whom treatment was extended beyond 24 months showed *M. leprae* in tissues even after attaining slit smear negativity. In conclusion, *M. leprae* persist in tissues after 2 years of WHO-MBR and patients with an initial BI of 4+ or more need to be closely followed up after stopping MDT.

Introduction

The aims of therapy in leprosy are to interrupt the transmission of infection and to eliminate all viable *M. leprae* from the body as rapidly as possible. Ever after treatment with monotherapy and multidrug therapy regimens, bacilli linger in protected sites like Schwann cells, perineural cells, smooth muscle, cells of blood vessel walls, erector pili of the skin and

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dartos tunica of the scrotum. Rarely, Kupffer cells in the liver and macrophages in the lymph nodes, bone marrow and spleen may also harbour *M. leprae*. These persisting bacilli survive in the host despite adequate antimicrobial treatment.[1–3] The study of persisters is important because persistence of bacilli is one of the major reasons for relapses in leprosy following both monotherapy and multidrug therapy, irrespective of the regimen used and the duration of treatment. The WHO study group on chemotherapy or leprosy has recommended stoppage of MDT after 24 months in all multibacillary cases irrespective of slit skin smear status.[4] This needs to be critically evaluated if persisters are present. This study was carried out to document *M. leprae* in the lymph nodes, nerves and skin in multibacillary leprosy patients who become slit skin smear (SSS) negative after the completion of 24 months or more of WHO recommended multibacillary regime (WHO-MBR).

Materials and methods

Twenty-five multibacillary (MB) patients attending the leprosy clinic of Department of Dermatology, Venereology who had become SSS negative after treatment with WHO-MBR for 24 doses or more were recruited for the present study. SSS from five sites (both ear lobes and three skin lesions) and a skin biopsy was carried out in all patients before and after treatment. In addition, nerve (radial cutaneous/sural) biopsy and fine needle aspiration cytology of inguinal or femoral lymph nodes were carried out after treatment as described previously.[5,6]

Sections from the skin and nerve were stained with haematoxylin and eosin stain and evidence of active leprosy was looked for. The above were also stained with Ziehl–Neelsen stain and studied for presence of *M. leprae*. Smears from lymph node aspirates were similarly studied. Two observers independently assessed for persisting bacilli and looked for any solid staining bacilli. Percentage, mean and Student's *t*-test were used for statistical analysis.

Results

PATIENTS

Of the 25 patients 17 were males and eight females. The age range was 16–72 (mean age 39 years). Duration of the disease ranged from 1 month to 7 years (mean duration 24 months). There were 14 lepromatous leprosy (LL) and 11 borderline (BL) lepromatous patients. Fifteen (60%) patients (nine males and six females) had reaction either at presentation or during the course of their treatment. Three of the four patients with type 1 reaction and all the 11 patients with type 2 reaction required systemic prednisolone. Two patients also received colchicine and pentoxyphyline besides prednisolone. All patients showed regression of lesions at the end of therapy.

PRE- AND POST-TREATMENT SLIT SKIN SMEAR

All patients were SSS positive prior to instituting WHO-MBR and 15 had BI 4+. Eighteen patients attained slit skin smear negativity at 24 months, three patients at 30 months and the remaining four attained smear negativity after 30 months (range 31–39 months).

HISTOPATHOLOGY FINDINGS

Skin

The study of pre- and post-treatment biopsies showed resolution of granulomas at the end of treatment. All biopsies showed atrophy of epidermis, paucity of skin appendages and increased collagenization of dermis. Mild perivascular and periappendageal lymphocytic infiltrate was noticed in all patients and scanty foam cells in 15 (60%) patients. Six (24%) patients showed *M. leprae*.

Nerve

All nerve biopsies showed fibrosis and varying amount of lymphocytic infiltrate around the vessels and in the nerve tissues. Scanty foam cells in perivascular locations were seen in 20 (80%) biopsies. *M. leprae* were present in eight (32%) biopsies both in Schwann cells and in foam cells.

Table 1. Clinical profile of patients treated with WHO-MBR and presence of *M. leprae* in tissues after MDT

Subject no.	Age/ Sex	Diagnosis	BI	MI	Duration of disease	Reaction type	Drugs required	Duration of		*M. leprae* in	
								MDT	LN	Nerve	Skin
1	43/F	LL	5	2%	2y	II	P+C	49m	+	+	+
2	48/F	LL	4	5%	2y	II	P	38m	+	–	–
3	35/F	LL	4	4%	6y	II	P	24m	+	+	+
4	17/F	LL	4	2%	1·5m	II	P	24m	NP	–	–
5	22/M	BL	4	2%	1y	I	–	24m	+	+	–
6	27/F	LL	4	1%	5m	II	P	24m	NP	–	–
7	25/M	LL	4	1%	1y	II	P	30m	+	–	–
8	35/F	BL	4	1%	3y	–	–	24m	–	+	–
9	58/F	LL	4	1%	6m	–	–	46m	–	–	+
10	40/M	LL	4	1%	2y	II	P	26m	+	–	–
11	28/M	LL	4	0%	2m	II	P+C	44m	+	+	+
12	30/F	LL	4	0%	1·5y	II	P+PF	28m	+	+	+
13	40/M	LL	4	0%	1y	II	P	24m	NP	–	–
14	40/M	BL	4	0%	2y	I	P	24m	NP	+	–
15	70/M	LL	4	0%	5y	II	P	24m	+	–	–
16	33/M	LL	2	0%	7y	–	–	24m	–	–	–
17	72/M	BL	1	0%	10d	–	–	24m	NP	–	–
18	55/M	BL	1	0%	2m	–	–	24m	–	+	+
19	16/M	BL	1	0%	2y	–	–	24m	+	–	–
20	56/M	BL	1	0%	1·5y	–	–	24m	NP	–	–
21	46/M	BL	1	0%	1y	–	–	24m	+	–	–
22	34/M	BL	1	0%	4y	–	P	24m	NP	–	–
23	60/M	BL	1	0%	3y	–	–	24m	+	–	–
24	21/M	LL	1	0%	4y	–	–	24m	NP	–	–
25	38/F	BL	1	0%	1·5y	I	P	24m	NP	–	–

y = year, m = month, dis = disease, d = day, P = prednisolone, C = colchicine, PF = pentoxiphyline, NP = not possible, LN = lymph node.

Table 2. Presence of *M. leprae* at different sites after WHO-MBR

Tissue	No. studied	No. positive for *M. leprae*
Lymph node	16	12[a]
Nerve	25	8[a]
Skin	25	6[b]

[a] Lymph node versus nerve, $P = 0{\cdot}02$.
[b] Lymph nodes versus skin, $P = 0{\cdot}004$.

CYTOLOGY FINDINGS

Lymph node

Fine needle aspiration cytology in lymph nodes was possible in 16 of the 25 patients. Reactive lymphoid cells were seen in all patients and foamy macrophages in eight (50%) patients. *M. leprae* were seen in 12 (75%) aspirates both within and outside the macrophages. All aspirates with foamy macrophages showed *M. leprae*.

The clinical profile and presence of *M. leprae* in nerve and skin biopsies and lymph node aspirates is summarized in Table 1.

PRESENCE OF LEPRA BACILLI AFTER WHO-MBR

Sixteen (64%) WHO-MBR-treated patients showed fragmented bacilli in tissues. Lymph node aspirates alone revealed *M. leprae* in seven patients followed by nerve in two patients and skin in one patient. Four cases showed bacilli at all the sites followed by nerve and skin or lymph node in one case each. The presence of bacilli in lymph nodes was significantly higher than in nerve ($P = 0{\cdot}02$) and skin ($P = 0{\cdot}004$) (Table 2). *M. leprae* were present in lymph nodes when nerve and skin biopsies were negative in seven and eight patients, respectively. *M. leprae* were also more frequent in nerves compared to skin, but this was not statistically significant (Table 2).

A significant correlation ($P < 0{\cdot}05$) was found between the bacillary presence after

Table 3. Pretreatment slit skin smear in patients with presence of lepra bacilli after WHO-MBR

Pretreatment BI	No. studied	No. of patients with *M. leprae* after WHO-MBR			Total no. with *M. leprae* in tissues
		Lymph node	Nerve	Skin	
4+ to 6+	15	9	7	5	12*
1+ to 3+	10	3	1	1	4*

* P value <0·05.

WHO-MBR and pretreatment bacteriological index (BI) of 4+ and above (Table 3). *M. leprae* were detected in tissues of all seven patients who received WHO-MBR for more than 24 months for attaining slit smear negativity (Table 1).

All the four patients with multiple site (i.e. lymph node, nerve and skin) positivity had lepromatous leprosy and severe type 2 reaction which required systemic prednisolone. All had BI of 4+ or more at the beginning of treatment. Three (75%) of these patients were females and all were below 50 years of age.

Discussion

The long-term efficacy of any therapeutic regimen in leprosy is assessed by its relapse rate. Job[7] proposed various reasons for relapse, namely persisting bacilli, drug resistant *M. leprae*, reinfection, misdiagnosis of multibacillary cases treated as paucibacillary and inadequate therapy or non-compliance. Amongst these reasons, bacterial persistence plays a significant role in the causation of relapses.[8]

Various workers have demonstrated viable *M. leprae* in various human tissues after both monotherapy and multi-drug therapy irrespective of drug regimen and duration of therapy. Katotch *et al.*[9] found persisting bacilli in 16% of highly bacilliferous (BI 4+ to 6+) BL/LL patients after 2 years of modified WHO regimen. This figure fell to 5% with continuation of treatment for another year, i.e. at 3 years. No viable bacilli were found after 36–45 months of treatment. In contrast, using immunosuppressed mice, Shetty *et al.*[10] found viable bacilli in 12 (46%) out of 26 patients after 24 months or more of WHO-MBR. Persisters were demonstrated twice as frequently in nerve (46%) compared to skin (23%). Similar results reported by other workers.[11,12]

Sivaprasad *et al.*[13] found *M. leprae* in 9/11 (81·9%) skin biopsies and all the 11 lymph node biopsies after 5 years of dapsone monotherapy supplemented with 2 years of multidrug therapy. Also, it was found that *M. leprae* disappeared from the skin lesions much earlier than from the draining lymph nodes. The author therefore suggested that *M. leprae* persist in the macrophages of the regional lymph nodes much longer than in the skin. Similar observations were made in the present study. Despite the limitation of not studying viability of *M. leprae*, our study shows the presence of *M. leprae* at different sites even after attaining slit skin smear negativity. Finding of *M. leprae* in lymph nodes, nerve and skin are not surprising because they are known sites for persisters. However, it has been shown that fragmented bacilli may be viable[14] and therefore may cause relapse. Moreover, there are reports of relapse in patients with high initial BI (4+ or more).[7] In this group of patients, one needs to be cautious in stopping MBR at the end of 2 years despite BI continuing to fall even after stopping treatment and results are comparable in both groups when treatment is stopped at 2 years or continued.[15] The Marchoux chemotherapy study group[8] has suggested that treatment should not be stopped in patients with BI of 2+ or more at the end of 2 years of therapy. The current recommendation of stopping WHO-MBR at the end of 1 year even in highly bacilliferous patients (BI 4+ or more) who show clinical improvement needs to be evaluated in view of the above findings.

The role of corticosteroids in the presence of *M. leprae* in tissue after 24 months or more of WHO-MBR could not be confirmed as the association did not attain statistical significance. Moreover, the majority of such patients had a high initial BI and severe disease.

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Protective effect of Bacillus Calmette Guerin (BCG) against leprosy: a population-based case-control study in Nagpur, India

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Summary A population-based pair-matched case-control study was carried out in an urban community, Nagpur, India, to estimate the effectiveness of BCG vaccination in the prevention of leprosy. The study included 212 cases of leprosy (diagnosed by WHO criteria), below the age of 35 years, detected during a leprosy survey conducted by the Government of Maharashtra over a population of 20,03,325. Each case was pair-matched with one neighbourhood control for age, sex and socioeconomic status. A significant protective association between BCG and leprosy was observed (OR = 0·40, 95% CI = 0·23–0·68). The overall vaccine effectiveness (VE) was estimated to be 60% (95% CI = 32–77). The BCG effectiveness against multibacillary and paucibacillary leprosy was 72% (95% CI = 35–88) and 45% (95% CI = 3–73), respectively. Vaccine was more effective during the first decade of life, among females and in lower socioeconomic strata. The overall prevented fraction was 39% (95% CI = 16–58). In conclusion, this first ever population-based case control study performed in Central India, identified a beneficial role of BCG vaccination in prevention of leprosy in study population.

Introduction

Seven large controlled trials[1–7] have been conducted to assess the protective effect of BCG vaccination against leprosy. The efficacy observed for the vaccine in these studies has varied

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from approximately 20% in Myanmar (Burma)[3] to 80% in Uganda.[6] During the last few years, the effectiveness of BCG was also studied by several case-control studies[8–16] which provided consistent results with the prospective trials when considering all forms of leprosy (leprosy per se). However, there is a wide variation of efficacy and effectiveness reported from the different parts of the world.[1–16] Although different results are reported in literature, findings of three studies[4,7,14] added to the evidence that BCG vaccine affords greater protection against leprosy than against tuberculosis.

Of the total seven controlled trials[1–7] and nine case control studies,[8–16] evaluating role of BCG in prevention of leprosy carried out around the world, two trials,[1,7] and one case control study[13] are reported from India. The 1997 figures from WHO suggested that 70% of the world's leprosy patients are from India. With this background, the current case-control study was performed to estimate the effectiveness of BCG vaccination against leprosy in urban population of Nagpur city in Central India.

Materials and methods

BACKGROUND[17]

The Government of India started the National Tuberculosis Control Programme (NTCP) in 1962. The programme identified, districts as the working units where primary prevention, early detection, chemotherapy and case holding were the major activities. One of the primary prevention measures to which a lot of emphasis was given was BCG vaccination. During initial phase of the programme BCG was administered to a broader age range; however, since the implementation of the Expanded Programme of Immunization (EPI) in 1978 emphasis was given to BCG vaccination of infants. The BCG vaccine prepared from Danish 1331 strain in Guindy, Madras is used in a dose of 0·1 ml intradermally (0·05 ml dose for newborns). The vaccine is given without prior testing with purified protein derivatives.

STUDY SETTING AND POPULATION

The current population-based pair-matched case control study was carried out in urban population of Nagpur City, Maharashtra State, India. As a part of the National Leprosy Eradication Programme, a house to house cross sectional survey was performed by Government of Maharashtra over 20,03,325 urban population to detect hidden cases of leprosy and estimate overall prevalence, during January to March, 1998. This survey was conducted under direct supervision of Assistant Director Health Services (Leprosy) Govt of Maharashtra and involved undergraduate students from the local Medical College and urban leprosy workers. Provisional diagnosis done by surveyors was later cross checked and confirmed by leprologists. The list and detailed addresses of leprosy cases were then obtained from concerned authorities for the current study purpose.

Study investigators along with urban leprosy workers performed home visits to recruit cases and neighborhood controls. The study included 212 cases of leprosy (diagnosed by WHO criteria).[18] As suggested by WHO,[18] an individual was regarded having leprosy if he or she showed one of the following cardinal signs: hypopigmented or reddish skin lesion(s) with definite loss of sensation; damage to the peripheral nerves, as demonstrated by loss of sensation and weakness of the muscles of hands, feet or face; positive skin smears. When skin smears were not available or not dependable, more than five skin lesions were classified as

multibacillary and skin lesions up to five were considered as paucibacillary leprosy. When skin smears were available and dependable, smear negative was considered as paucibacillary and smear positive as multibacillary leprosy. Nerve damage involving only one nerve trunk was considered as paucibacillary and involvement of many nerve trunks was considered as multibacillary leprosy. Diagnosis and classification was performed by leprologists. All the study subjects (including the cases) were below the age of 35 years, to take into account those born since the beginning of the NTCP in 1962. Each case was pair-matched with one neighbourhood control for age (within 1 year of the age of the case), sex and socioeconomic status (SES). For selection of a control, the immediate neighbourhood of a case was contacted and age, sex and SES was recorded. If the chosen neighbourhood could not be matched, the subject was excluded and the same procedure repeated for the next neighbourhood. Socio-economic status was recorded using the modified Kuppuswamy scale[19] of socioeconomic status classification, using occupation, education and per capita income as parameters. This is a 5-point scale, with class I representing the highest socioeconomic status (upper) and class V representing the lowest (lower). Class II, III and IV are represented by upper middle, lower middle and upper lower socioeconomic status, respectively.

MEASUREMENT OF EXPOSURE TO BCG

Evidence of BCG vaccination was determined by direct observation of a BCG scar at insertion of deltoid; immunization records if available and information from study subjects or parents in case of children. Cases or controls with missing data about BCG vaccination were excluded from the study. The measurement of exposure was thus carried out as per the guidelines given by Smith.[20]

STATISTICAL ANALYSIS

Odds ratios for the matched design were calculated as described by Greenberg and Ibrahim.[21] The method described by Schlesselman[22] was used for calculating 95% confidence intervals for the odds ratios. McNemar's χ^2 test was also used. Subgroup analysis for matching variables was carried out separately. The effectiveness of BCG vaccination was calculated by the formula (1-OR) $\times$ 100% where OR is the estimated odds ratio. The proportion of potential new cases that were prevented, the 'Prevented Fraction' was determined according to the method of Miettinen.[23] The statistical analysis was done by using the MINITAB statistical package and dedicated Turbo C routines.

Results

A total of 400 cases (including active old cases) were recognized in leprosy survey. Prevalence of leprosy was estimated to be 2 per 10,000 in Nagpur urban population. Of these, 215 cases were aged less than 35 years. Three cases, who had missing records or uncertain about BCG vaccination, were not included. Hence the current study could include 212 cases of leprosy. Table 1 describes the subjects by the study characteristics. The majority of the cases were males aged 10–20 years and from the upper lower and lower middle classes of Kupuswamy's socioeconomic status scale. Because of small number of study subjects in other strata, classes I, II and III are merged to form one group and classes IV and V formed

Table 1. Distribution of subjects by study characteristics

Factors	Cases $n = 212$ (%)	Controls $n = 212$ (%)
Age (years)		
<10	34 (16·04)	34 (16·04)
10–20	114 (53·77)	114 (53·77)
>20	64 (30·19)	64 (30·19)
Sex		
Male	124 (58·49)	124 (58·49)
Female	88 (41·51)	88 (41·51)
Socioeconomic status		
Upper	12 (05·66)	12 (05·66)
Upper middle	27 (12·74)	27 (12·74)
Lower middle	76 (35·85)	76 (35·85)
Upper lower	92 (43·40)	92 (43·40)
Lower	5 (02·35)	5 (02·35)
Exposure to BCG	92 (43·40)	120 (56·60)

another group. The prevalence of exposure was 43·40% and 56·60% in cases and controls respectively. The study included 135 (63·68%) cases of paucibacillary leprosy and 77 (36·32%) cases of multibacillary leprosy.

Table 2 describes subgroup analysis of paired data. The significant protective association (OR = 0·40, 95% CI = 0·24–0·69) between BCG and leprosy is seen from this table. The subgroup analysis revealed that the odds ratios were lower in the less than 10 years age group and in females, but these were not significantly different from the other groups. The different socioeconomic strata also did not differ significantly from each other with respect to the estimated odds ratios. The estimates of odds ratios were lower for multibacillary leprosy as compared to paucibacillary leprosy, but this difference too was not statistically significant. The vaccine effectiveness and prevented fraction were maximum for females, multibacillary

Table 2. Subgroup analysis of paired data

Groups	Odds ratio	95% CI	McNemar's Chi-square	*P* value
All pairs	0·40	0·24–0·69	11·87	<0·001
Type of leprosy				
Multibacillary	0·28	0·12–0·65	10·12	<0·001
Paucibacillary	0·55	0·27–0·97	2·94	>0·05
Age (years)				
<10	0·20	0·04–0·91	5·33	<0·05
10–20	0·41	0·20–0·86	5·76	<0·05
>20	0·54	0·22–1·35	1·80	>0·05
Sex				
Male	0·50	0·25–0·99	4·00	<0·05
Female	0·30	0·13–0·71	8·53	<0·01
Socioeconomic status				
Upper middle & lower middle	0·44	0·22–0·89	5·44	<0·05
Upper lower & lower	0·36	0·16–0·82	6·53	<0·01

Table 3. Estimates of BCG effectiveness and prevented fraction calculated from odds ratios

	BCG effectiveness		Prevented fraction	
Groups	%	95% CI	%	95% CI
All pairs	60	31–76	39	16–58
Type of leprosy				
Multibacillary	72	35–88	38	11–63
Paucibacillary	45	3–73	31	2–60
Age (years)				
<10	80	9–96	60	4–81
10–20	59	14–80	38	7–64
>20	46	−35–79	29	−14–63
Sex				
Male	50	1–75	30	1–56
Female	70	29–87	51	16–75
Socioeconomic status				
Upper middle & lower middle	56	11–78	36	5–62
Upper lower & lower	64	18–84	42	9–69

leprosy, lower socioeconomic group and subjects in the age group of less than 10 years (Table 3). The BCG effectiveness and prevented fraction for whole study group were calculated to be 60% (31–76) and 39% (16–58), respectively.

Discussion

The rationale for the use of BCG for prevention of leprosy was based on the postulate by Fernandez[24] of a protective effect of such vaccination. This postulate was supported by the observation that when household controls of leprosy patients were vaccinated repeatedly with BCG, the Mitsuda reaction became positive.[25] This observation was later confirmed by several workers and led to a series of studies to evaluate the protective efficacy of BCG against leprosy.[26] So far, seven controlled trials[1–7] have been conducted to assess the role of BCG in prevention of leprosy, which included two trials from India.[1,7] Since Smith[20] recommended the use of case-control design to evaluate the effectiveness of BCG against tuberculosis, investigators shifted their choice of design to case control studies.[8–16] Although this design has obvious advantages (quicker, cheaper, free from ethical considerations), it has a major weakness: susceptible for biases.[21] The prospective studies are supposed to provide results without bias. The case-control study may not have control over these inherent biases. This methodological issue has also been attributed to the differences in the vaccine estimates measured by different study designs. This may be the reason why the results differ in a case-control study and a prospective study in South India in two adjacent districts. In spite of the well understood limitations of case-control design, it has been widely used and so far nine case-control studies of BCG vaccination and leprosy are reported world wide. Age, sex, socioeconomic parameters and area of residence have conventionally been considered as the confounding factors. Most of the case control studies have therefore used these as matching factors. The current study also have used these variables as matching factors. Selection of

neighbourhood controls and use of socioeconomic status as a matching variable appears to have created a good balance between cases and controls with respect to many of the socioeconomic parameters which could have had a bearing on the chance of receiving BCG, on the one hand, or the risk of disease detection on the other.

The crude criteria of exposure classification have been used in this study, which could have resulted in misclassification to a certain extent. However, this bias is quite small if 90% of vaccinations leave scars and around 70% of the population is vaccinated.[20] Nevertheless, this possibility is unlikely to alter the results of this study. However, it cannot be overlooked that the reported sensitivity of scar reading (the proportion of vaccinated individuals who develop a recognizable scar) has been reported to vary from 98·9% in South India, as assessed 4 years afterwards, to 60% among Swedish children 14 years after having been vaccinated at birth.[27] Moreover, the specificity of scar reading (the proportion of individuals who have no evidence of a BCG-like scar among those who have never been vaccinated) is more problematic to measure, since it is difficult to confirm a negative vaccination history.[27] Additionally, selective susceptibility in individuals in whom the BCG scars disappeared for leprosy particularly of the MB form cannot be ruled out. In this case, higher estimates of vaccine effectiveness for MB leprosy can be attributed to this phenomenon. In this respect, vaccine efficacy studies based upon scar evidence of vaccination should consider the effect of this bias on vaccine efficacy. In some circumstances, it may be possible to validate scar information against documentary evidence of vaccination.

The present study demonstrated 27% statistically non-significant excess protective effectiveness of BCG against multibacillary leprosy as compared to paucibacillary leprosy. A few earlier studies[10,11] have reported higher estimates of BCG effectiveness against multibacillary leprosy as compared to paucibacillary leprosy, which has significant public health implications because multibacillary disease is thought to be a major source for the spread of *M. leprae* in the community. Thus in general the findings of the present study are consistent with the theory that BCG vaccination brings about a shift in the immune response to a higher level of cell mediated immunity, and thereby offers protection especially against the more severe multibacillary form of the disease.[10,13] When this phenomenon is operative, case control studies on the protective effect of BCG vaccination on paucibacillary leprosy suggest that there is no or less effect when, in fact, there is an important effect; BCG shifting of the potential multibacillary patients in the direction of the clinically less severe paucibacillary form.

The present study recognized that the protective effect of BCG vaccination in the age group less than 10 years was higher than in the 10–20 years and more than 20 years age groups. The policy of BCG immunization during infancy is followed in India. Hence, the age of a vaccinated individual approximates the years since vaccination. It is logical to believe that as the time since vaccination advances, immunity decreases. Hence, this may be the reason for the decline in effectiveness of BCG as the age advances in the present study. Earlier studies have indicated that the protective efficacy of BCG vaccine increases with the interval of time since vaccination.[14–16] However, another study from India[13] observed that with advancing age, BCG effectiveness declines in females. The current study demonstrated 20% excess protective effectiveness of BCG vaccination in females as compared to males. This finding is in agreement with earlier reports.[12–14] The only case control study carried out in India,[13] investigating the relationship between leprosy and BCG, has also reported higher estimates of BCG vaccination in females. However, few case referent studies[11–16] have reported an excess protective effectiveness of BCG vaccination in

males. Although vaccine effectiveness in this study was 8% higher in upper lower and lower socioeconomic strata, it was non-significant and could be because of chance.

The present study showed 60% (31–76) vaccine effectiveness and 39% (16–58) prevented fraction with the use of BCG vaccination in the prevention of leprosy. This finding is in agreement with earlier studies,[8,10,14,15] which evaluated the role of BCG in prevention of leprosy in other parts of the world. Earlier controlled trials[1–7] and case control studies[8–16] have demonstrated the efficacy and effectiveness of BCG in the range of 20–81%. The estimate of vaccine effectiveness (60%) observed in this study is relatively closer to the upper estimate of this range. Moreover the proportion of potential new cases that were prevented, the 'prevented fraction' was calculated to be 39% (16–58), i.e. the vaccination programme prevented 39 of every 100 cases that would have occurred in its absence. The findings of this study thus indicated that BCG vaccination was effective against leprosy in Central India. This finding is encouraging for prevention of a disease that has been more prevalent in this country as compared to other parts of the world. However, an earlier case control study performed in this country, in South India,[13] has reported relatively low estimates of BCG vaccine effectiveness in the prevention of leprosy. Hence, with this background and fortified by the fact that vaccine efficacy/effectiveness seems to be dependent more on geography and environmental factors than on vaccine strain, further studies should be carried out to evaluate the role of BCG in prevention of leprosy in different parts of the country.

Conventionally, BCG vaccination is practised worldwide for prevention of tuberculosis. Its effectiveness against leprosy is the additional advantage. Even though it is moderately effective against both these mycobacterial diseases, it has a beneficial role, particularly in countries like India, where both these diseases are widely prevalent. As observed in the current study, its role in prevention of MB leprosy as compared to PB leprosy has definite public health implications. Additionally, the findings of the present study, that, as the age advances BCG effectiveness declines, which is supported by other studies also, call for a public health recommendation on thinking of a booster dose of BCG at the appropriate age.

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What would make your life better? A needs analysis of leprosy settlements in the middle belt region of Nigeria

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Summary A needs analysis using rural appraisal and matrix ranking techniques was done in six leprosy communities in the middle belt region of Nigeria. Asked 'what would make their life better?' whole village groups were made to list, prioritize and rank their expressed needs by voting in a matrix table drawn on the ground. Out of a total of 504 votes, 31% was for health care or drugs for their general ailments, 23·6% for money and less than 10% for other needs that ranged from water, trade and housing to love and, least, mobility aids. Health care was prioritized in all communities but got the highest votes in three communities, money got the highest in the only two communities where it was prioritized and water in one. The need ranked the highest in each settlement seemed to be a reflection of its peculiar socio-economic situation. Apart from the similar priorities of health care and money, men's differing priorities were water, housing, clothes and assistance with farming, and women's, school fees for children, family, trade and food. These reflect their different traditional roles. Considering the variety of needs we think that there is no one solution to rehabilitation in the Nigerian context, but the situation and context of individual settlements should be considered, looking at general health care, income generation or loans schemes, schooling and water supply.

Introduction

Leprosy settlements in Nigeria are the results of cured leprosy patients being unable to return home due to external or self-stigma. The settlements are associated with old leprosaria, some of which are now closed. During the dapsone era, many patients were kept in hospital compounds so that they could receive regular treatment. Over the years some of the settlements developed into villages, with people affected by leprosy settling

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there and farming. Some people have lived in them for over 40 years. With the present focus of most national leprosy control programmes being elimination of leprosy, little attention, if any, is being paid to the plight of these ex-patients living in leprosy communities. The Leprosy Mission International (TLMI) has prioritized development of leprosy communities through partnership with persons affected by leprosy.[1] It was decided that a needs assessment should be done to investigate the help needed by the leprosy settlements in assisted programmes in Nigeria. The analysis was done without committing TLMI to anything and bearing in mind the policy of the Nigerian government to close leprosy settlements and resettle persons affected by leprosy in their own home communities.

The aim of the needs analysis was to gain an overview of the situation in leprosy communities in order to develop a sustainable rehabilitation programme. The programme should seek both to meet the needs and where possible, encourage re-integration. This paper summarizes the situation of leprosy communities in three States, Niger, Kogi and Kwara States, describes the role of leprosy hospitals more from the viewpoint of settlers, and lists and ranks the expressed needs in settlements. Also investigated were their opinions about returning home and what they would need to achieve this.

Materials and methods

The needs analysis used qualitative and rural appraisal methods to investigate, list and rank the expressed needs of people affected by leprosy living in seven leprosy communities in three contiguous States in the middle belt region of Nigeria. The situation of the leprosy communities was reviewed using existing quantitative data, direct observation and comments from the villagers. Semi-structured group interviews were used to find out the villagers' view of the role of the existing leprosy hospitals adjoining the settlements.

In each settlement, villagers were gathered into one big group of 12–47 people with men and women seated separately. After our own introduction, they were asked to introduce themselves and say how long they had been in the settlement. The main research question '*What would make your life better?*' was then asked. The question was asked to individuals and then four or five priorities were given from the larger list. Men were asked to give three and women two. These five were then put into a matrix table drawn on the ground with articles from around the village representing the choices given. For example, if water was a choice, then a bowl of water was put into the square. If health care, then some drugs were in the square. The villagers were then given two sticks to vote with. Men and women were asked to vote separately.

Initially, the matrix had two columns, one for improving their family life and the second for improving their status. This was an attempt to look at stigma. However, the second column was not used, so we used a ranking matrix with first and second choice. At the end of the matrix ranking, the villagers were asked whether they could go home, and then what they would need to do to be able to return home. The final question asked about the settlers' views on the role of the adjoining leprosy hospital. After the group session, some quantitative data was collected using a structured checklist regarding the social and economic situation of the settlements. Interpreters were used to ask the questions and the translated answers were recorded. A diary of each visit was made, noting observations about the village structure and the people affected by leprosy.

Results

The needs analysis was done in August 1997 in six leprosy communities. These include Kuta and Tunga-Minna in Niger State, Ochadamu and Oyi-River in Kogi State, and Okegbala and Elehin in Kwara State. Three communities, each with a leprosy hospital, had more than one settlement—Chanchaga (2), Ochadamu (2) and Okegbala (3). Two communities, Kuta and Oyi-River, were beside now-closed leprosy institutions. Tunga-Minna is an urban community with people affected by leprosy living in a section of a city. Three communities including Tunga-Minna, Kuta and Elehin were now recognized as bone-fide integrated communities with people affected by leprosy and non-leprosy affected people living side by side.

SITUATION OF THE LEPROSY COMMUNITIES

Apart from Elchin and Tunga-Minna, the five communities were situated within a range of 1–15 km from the nearest town. The number of houses in each settlement ranged from 5 to 47 and all six communities had a population of 624 people, with an average of five persons affected by leprosy living in each house. Each house had up to two to four rooms or huts. The settlements that had grown out of leprosaria had houses built by the settlers themselves, made of local materials, and matched those of the surrounding non-leprosy villages. The buildings in the hospital-based settlements were built by the hospital and were dormitory-like with males and females living separately. In virtually all communities, the population has been decreasing in the last 10 years. Subsistence farming was the main occupation, but the land belonged either to the hospital or the local government. Begging was another major occupation in two communities, Tunga-Minna (urban) and Okegbala. Most appeared to have a good variety of crops, though the distance to their farms was variable and some had to walk long distances to their fields. In two groups, there were business activities: palm oil and petty trading.

Each settlement had a chief or leader, often one of the older, more disabled men. Most of the people affected by leprosy had been in the settlement for more than 20 years. The shortest time spent was 2 years and the highest more than 50 years. Some had gone home and returned. There was a mix of people in all settlements, though the majority seemed to be middle-aged or above and visibly disabled. The disability status for the various age groups was not assessed. Wells and streams were the most common source of water. In some, the streams were far and seasonal and the wells could be very deep. Only the urban communities in Minna had a borehole or tap. Source of light was mainly the bush lamp. One had a generator and the urban community enjoyed the electricity supply in the city. In four out of the six communities, settlers had to walk the 1–15 km to the nearest town to shop or grind their produce. Apart from those living close to leprosy hospitals, there was no easy access to a health facility.

PRIORITY RANKING OF NEEDS

A total of 252 people, 115 men and 137 women, voted in the matrix priority ranking of their needs in all six communities. The matrix table in Table 1 shows the ranking of the list of all priorities given. It shows that the majority of the villagers (31% of 504 votes cast) needed health care. Health care was followed by money with 23·6%, but unlike health care, which was prioritized in all settlements, money was prioritized in only two communities. The

Table 1. Matrix table showing the priority ranking of needs in six leprosy communities in the middle-belt region of Nigeria

List of priorities	Kuta	Ochadamu	Oyi-River	Okegbala	Elehin	Tunga	Total	Ranking
Health care	12	2	35	63	10	34	156	1
Money	X	13	X	106	X	X	119	2
Water	18	X	24	1	X	X	43	3
Trade	X	X	X	14	9	18	41	4
House	X	X	X	37	X	X	37	5
School fees	X	X	22	12	X	2	36	6
Food	2	5	X	X	3	19	29	7
Grinding mill	X	X	9	X	X	X	9	8
Light	X	X	X	7	X	X	7	9
Handwork	X	1	4	X	X	X	5	10
Clinic repairs	5	X	X	X	X	X	5	10
Clothes	X	4	X	X	X	X	4	11
Footwear	X	1	X	X	X	3	4	11
Fertilizer	3	X	X	X	X	X	3	12
Family/love	X	3	X	X	X	X	3	12
Assist farming	X	X	X	X	2	X	2	13
Mobility	X	1	X	X	X	X	1	14
Total	40	30	94	240	24	76	504	

priorities that received less than 10% but more than 1% of votes each were, in descending order, water, trade, housing, school fees, food, grinding mill, and electricity. Other priorities with less than 1% of votes each were handwork, clinic repairs, clothes, footwear, fertilizer, family, assistance with farming and, lastly, mobility aids. Table 2 shows the highest priorities of the individual communities, and revealed health care as the highest priority and first choice in three out of the six communities and as second choice in two. Money was the highest first choice in the two communities where it was mentioned. Trade was a highest first choice in one community only and water, a highest priority as a second choice in two communities. Clothes and food were the other highest priorities as second choice in another two communities.

Table 2. The highest-ranking priorities of the individual leprosy communities in the middle belt region of Nigeria

Community	1st choice	2nd choice	No. of voters
Kuta	Health care (55%)	Water (65%)	20
Ochadamu	Money (67%)	Food (27%) Clothes (27%)	15
Oyi-River	Health care (55%)	Water (36%)	47
Okegbala	Money (68%)	Health care (43%)	120
Elehin	Trade (50%)	Health care (50%)	12
Tunga	Health care (66%)	Food (39%)	38
Total			252

Table 3. Priority ranking of needs by men and women in leprosy communities in the middle-belt of Nigeria

	Men $n = 115$			Females $n = 137$		
List of priorities	Votes	%	Ranking	Votes	%	Ranking
Health care	73	32%	1	83	30%	1
Money	50	22%	2	69	25%	2
Water	26	11%	3	17	6%	5
Trade	17	7%	5	24	9%	4
House	21	9%	4	16	6%	6
School fees	11	5%	6	25	9%	3
Food	13	6%	5	16	6%	6
Grinding mill	2	0·9%	9	7	3%	7
Light	0	0%	11	7	3%	7
Handwork	4	2%	7	1	0·4%	9
Clinic repairs	2	0·9%	9	3	1%	8
Clothes	4	2%	7	X	X	X
Footwear	1	0·4%	10	3	1%	8
Fertilizer	3	1%	8	0	0%	10
Family/love	X	X	X	3	1%	8
Assist farming	2	0·9%	9	0	0%	10
Mobility	1	0·4%	10	X	X	X
Total	230	100%		274	100%	

Table 3 compares the choices of all the men and women. The first and second ranked priorities of men and women were the same—first, health care and second, money. The order of the other priorities is different for the two sexes. For instance, the third, fourth and fifth priorities for men were water, housing and trade, while for women these were school fees for children's education, trade and water. In Figure 1, it is seen that more men than women

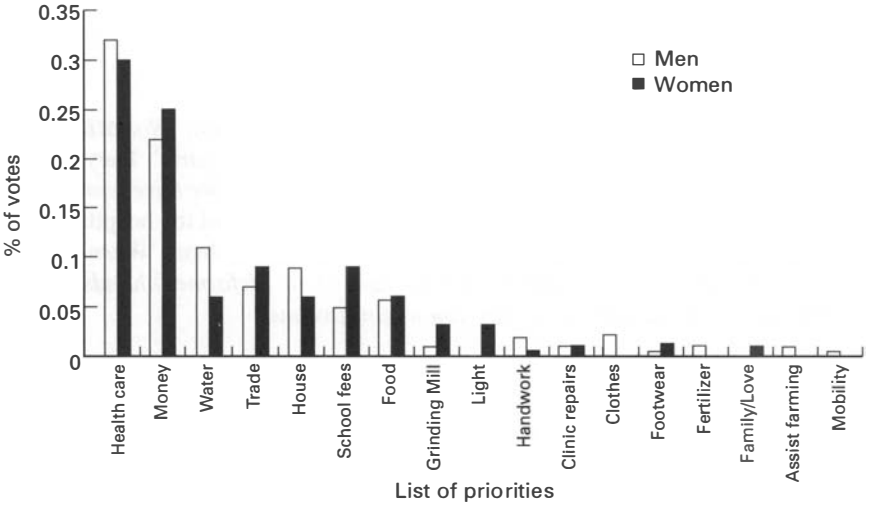

Figure 1. Comparison of choice of priority needs by men and women in leprosy communities in the middle-belt region of Nigeria.

Table 4. Highest-ranking priorities of men and women in the leprosy communities in the middle-belt region of Nigeria

	Men			Women		
Community	1st choice	2nd choice	*n*	1st choice	2nd choice	*n*
Kuta	Health care (55%)	Water (55%)	11	Health care (56%)	Water (78%)	9
Ochadamu	Money (71%)	Clothes (57%)	7	Money (63%)	Food (38%)	8
Oyi-River	Health care (68%)	Water (50%)	28	School fees (42%)	Grinding mill (37%)	19
Okegbala	Money (73%)	Health care (42%)	45	Money (65%)	Health care (43%)	75
Elehin	Trade (50%)	Health care (50%)	6	Health care (50%) Trade (50%)	Health care (50%)	6
Tunga-Minna	Health care (50%)	Health care (33%) Food (33%) Trade (33%)	18	Health care (80%)	Food (45%)	20
Total			115			137

n = Number of voters.

wanted health care, water, house, and handwork. More women wanted money, trade, school fees, grinding mill and footwear. Only men wanted clothes, fertilizer for their farms, assistance with farming and means of mobility whilst only women wanted light (electricity) and family or love. Table 4 shows that the highest-ranking first and second choices of both men and women were the same in all but two communities. In those two communities, men wanted clothes and water while women wanted food and grinding mills.

REASONS FOR THE FIRST CHOICES

Health care

When asked what they meant by health care, the villagers replied, '*Not MDT* (multi-drug therapy) *but drugs for other diseases: we need general health care*.' They said this was largely because of stigma. *'If we go to ordinary clinics they tell us we have leprosy and do not attend to us!'* Those close to the leprosy hospitals said they wanted the hospitals to be better equipped to provide them with general health services. For one of them, '*When I am healthy, I can do many other things. Now I cannot farm because of my (deformed) hands.*' For another, '*When I am healthy, I can use the money you might give me.*'

Money

It was found that money was the top priority in the settlements that were not so functional as villages—those still dependent on their attached hospitals or where begging was a main occupation. When the settlers were asked why they had made money their first choice, a variety of answers was given to identify exactly what they meant by money. Some were asking for loans to develop income generation and others wanted more of a regular pension.

The older ones and the more disabled who could not trade wanted money for food. When asked whether they wanted money or an occupation, the persons affected by leprosy replied, '*We have no hands and feet, how can we work?*' Some groups felt that money would solve all their problems since it could be used in so many ways: '*We can use it to buy anything we want. Any one who has money can use it for anything. If I have money, I will buy food, also to build my house, in fact, everything I want!*' Linking money with rehabilitation, one woman said, '*The machine for sewing that I want to buy can be bought with money*,' and a man, '*Money will buy tools for my children.*'

Others

Water was a high priority second choice in two settlements. One was an isolated village where a deep and almost dry well was the only source of water. The other community gets water from a distant stream. Clothes and love were priorities in a particular community where male and females live in two separate dormitories. Food as a specific need was a high priority in communities with more of the very old and disabled persons who could neither farm nor walk to beg. This was the case especially in the urban community.

FACTORS THAT PREVENT RESETTLEMENT AT HOME

All settlers were informed of the government return home policy. There were many reasons why they felt they could not return home. These included the leprosy stigma and disabilities, family problems, care at home, employment and no housing.

Stigma and disabilities

Many believed that because of their disabilities, they would not be received back home or cared for. They said, '*We are happy to return but it is others who won't accept us. Even when we are begging, the people drop the money into our hands without touching us!*' '*Ulcers don't go, people at home will not look after them.*' Many settlers did not want to return home because they were deformed by leprosy. They were cured, but continued to have problems and felt no-one would look after them at home. For some it was the shame of their disabilities. Some of them said, '*I do not want to go home, I am ashamed of my foot which is only half now. Here I can farm, feed, and look after myself.*' '*Frequent ulcers prevent me from going home. I cannot do anything because of my hands. I prefer to die here!*'

Family and care

For some people affected by leprosy, the problem was their isolation and lack of family and care at home. '*No family at home, so I have given myself to the Mission—I can't go anywhere!*' Others felt their children would be better off in the settlement. Some were staying to care for their disabled partners. One said, '*If I go home I cannot look after my children who have no work. Here I farm.*' And another, '*My husband has no eyes, he has no legs, I am staying to care for him!*' For some, the issue was food. They would not find food to eat, if they went home. Some had tried to return but found rejection or lack of care. For one very old man, '*I have tried to go home but my people do not want me. There is no one to look after me. While I am here, I am cared for.*'

Employment

Some of the younger and fit looking people stayed in the settlements because there was no chance to get work elsewhere. For a young healthy looking man with an ulcer, '*I have not had help to get a job. God has already helped me with my foot, but I don't have a job.*' His father said, '*I was unable to find money to buy tools so that he can start his job.*' To buttress this point, one said, '*If I have the health and the money to trade at home, I can go tomorrow!*'

Housing

One group was actually keen to return home but did not have housing. They felt if they could have houses, then they would return home. '*I have wanted to leave here for a long time, but I don't have money to build a house.*'

ROLE OF THE LEPROSY HOSPITALS

The majority of settlers wanted health care provision from the leprosy hospitals. Provision and renewal of artificial limbs were also expected. Other broader expectations were farmland, water, electricity and food. '*The hospital should feed us, give us light, water and drugs,*' they said. '*They should provide food for those who are admitted.*'

Discussion

Leprosy settlements in Nigeria are dying communities. This was evident from the age structure of the population of settlers that was observed. It was older than expected for the structure in Nigeria where almost half (48%) of the population are children less than 15 years.[2,3] The population of settlements is apparently declining. There has also been social integration and urbanization of some settlements, where persons affected by leprosy live alongside people not affected by leprosy. This may occur through the process of time. It may also result from the positive influence of the government's 'go-home' policy.

Housing in the settlements appeared similar to the ones in non-leprosy communities in the same socio-economic setting. With the paucity of basic social amenities, leprosy communities are definitely not self-sufficient. The few available amenities are not always within easy reach of the settlers. The daily long walks to streams, shops, mills and farms mean that living in settlements could encourage formation and worsening of disabilities. The settlements at present therefore provide little or no prospect for disability prevention. Driven by self-stigmatization and fear of rejection by the wider society, new settlement admissions of persons affected by leprosy are likely to fall into a vicious rejection-stigma-disability cycle. This cycle may have caused many old settlers to be rejected by their communities and prefer a permanent stay in the settlements despite the apparent difficulties and isolation. Waxler[4] has noted similar self-stigmatization linked to fear and rejection.

All communities in the region saw their need of care for their multifarious health problems as a prime priority. The other popular expressed needs of these leprosy communities are money and water, where it is a major problem. They also need financial assistance for trading, education of children and housing. The priority need ranked the highest in each community seemed to be a reflection of its particular socio-economic situation. Where the

communities were more like villages and less dependent on the adjoining leprosy hospital, their needs were more community-oriented, such as health care and water. The more dependent and beggarly communities seem to have money as their overriding need. The sex differences observed in the choice of priorities reflect the traditional roles of men and women in the Nigerian society. Men need better health in order to work on the farms for which they also require fertilizer and assistance. The women, being traders and food providers, need money for their families. The women's concern for school fees shows their care for their children's future although it is unlikely that they were asking for 'leprosy' schools.

The findings of the needs analysis were initially surprising, especially the unexpected emphasis on health care in all settlements. The variety of needs expressed showed clearly the value of this study approach. There is therefore no single solution to rehabilitation in the Nigerian context. Each community needs to be looked at individually, taking into account the particular situation and context. The group in the dormitory-like settlements seemed to be quite hopeless and depressed. For them money was the only way out, particularly if they were old and severely disabled. This indicates that community and social care is important. For such dependent communities, loans for income generation were seen to be a great need. This was also true in a settlement where people were prepared to go home if they could be made independent. The younger and less disabled, given money for trade, would more readily be rehabilitated and reintegrated back to their home communities than the older ones who have resided in the settlements for decades. They are therefore more likely to benefit from a community based rehabilitation programme. Any programme issuing pensions to people affected by leprosy has a poor prospect of sustainability and would continue to create dependency and self-stigma. It will directly provide welfare for settlers, who are old, grossly disabled and cannot help themselves, but it cannot be described as a rehabilitation programme.

The issue of settlers returning home is complex. It seems unlikely that people who have lived in a leprosy community for 20 years or more will be able to resettle in their home villages, particularly if they no longer had family or support there. Some have tried to go back but failed. It was evident that stigma and dependency had played significant roles in preventing settlers from going back home, especially those who wanted to return. For the category of settlers who may never return, an appropriate and sustainable approach to meet their expressed needs should be considered. A policy enabling these long stay settlers to remain in their villages without attracting more people affected by leprosy needs to be developed. The focus of reintegration and rehabilitation could be on young newcomers of less than 5 years, who can still be saved from a disability-prone life in leprosy communities. An active effort should be made to discourage new admissions into the settlements before they enter the vicious disability-stigma-rejection cycle and before close ties with families at home are severed by long absence.

In conclusion, this study shows that we may have to change our approach to rehabilitation and take a more development-based approach, looking at health care provision, water supply and schooling in established leprosy communities. We ought to look at ways to make the more dependent communities less dependent on the founding leprosy institutions. Income generation schemes may also help people resettle at home, and perhaps these can be done through development agencies and be available to whole village groups rather than just people affected by leprosy. It is important that rehabilitation does not further isolate patients by making them different from their peers in the wider society. A fully integrated and holistic

health service is a dire need for persons affected by leprosy living in settlements. Where this is not possible in general health facilities, it may be met by integrating general services into the existing leprosy hospitals. Mobile consulting clinics from the hospitals to isolated leprosy villages should be considered where no other means of health care provision is feasible.

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Reliability of Semmes Weinstein monofilament and ballpoint sensory testing, and voluntary muscle testing in Bangladesh

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Summary The reliability of methods of testing nerve function is important, since diagnostic decision making is a direct function of the quality of the test. Three methods of nerve function testing were investigated at the Danish Bangladesh Leprosy Mission (DBLM) in north Bangladesh, and assessed for inter-observer reliability. The three methods were 1) ballpoint pen test (BPT) for sensory function; 2) graded Semmes Weinstein monofilament test (SWM) for sensory function and 3) voluntary muscle testing (VMT) for motor function. The weighted kappa (κ_w) statistic was used to express inter-observer reliability. Using this statistic, 0 represents agreement no better than random, and 1·0 complete agreement. κ_w values of $\geq$0·80 are reckoned to be adequate for monitoring and research. Fifty-three patients were tested, a Senior physiotechnician acting as 'gold standard' against whom four other staff physiotechnicians were assessed. All three testing methods were found to have minimal inter-observer variation, with the κ_w for inter-observer agreement using BPT being 0·86, the SWM 0·92, and VMT 0·94. It is concluded that in trained and experienced hands, all three methods are reliable and repeatable to a level allowing confident use of results obtained in monitoring and research.

Introduction

Routine assessment of nerve function in leprosy patients is essential for the early detection of nerve function impairment and its treatment.[1,2] Recently, van Brakel has drawn attention to the need for the measurements used to test nerve function to themselves be the subject of reliability testing.[3] It is empirically true that the results of any measurement cannot be better than the measure itself.

While there is general agreement about the use of the modified MRC scale for measuring muscle strength,[4,5] there is less agreement about the preferred method for sensory testing. Owen and Stratford[6] reviewed several commonly used methods and concluded that the WHO (ballpoint) test, cotton wool and pinprick were all cheap and easy to use but were not

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sensitive enough to be of practical value. They found monofilaments and the biothesiometer to be reliable pieces of equipment, but the latter are expensive and dependent on electricity.

Perhaps the two methods that are most commonly used for sensory testing are the Ballpoint Pen test (BPT) described by Jean Watson[7] and the Semmes Weinstein Monofilaments (SWM) test described by Judith Bell-Krotoski.[8] Both methods have their advocates and critics. The BPT is advocated on the grounds that is cheap and readily available, and criticised on the grounds that the force applied may vary considerably and therefore the results are likely to be unreliable.[6] Also, since it is a threshold (yes/no only) test, it relies on a count of the number of sites at which gross sensation is lost to provide an indication of the level of sensory loss. On the other hand, SWM testing is advocated on the grounds that the results are reliable, since the force required to bend the accurately manufactured monofilaments is relatively constant and repeatable,[9] and since they are a graded test they provide a quasi-quantitative estimate of sensory loss. The SWM test is sometimes criticized on the grounds that the monofilaments used less easily available, and too 'technical' and time-consuming for widespread use.

Lienhardt, Currie and Wheeler carried out inter-observer testing using BPT, SWM and voluntary muscle testing (VMT) in Ethiopia.[10] They found a 32–58% agreement using SWM with a weighted kappa (κ_w) statistic of 0·736–0·814, indicating good agreement ($\kappa_w \geq 0{\cdot}60$ indicates good agreement, see explanation in the Methods section of this paper[11]) but with wide confidence intervals. With the BPT the agreement was 71–84%, κ_w 0·604–0·793; and 79–98% agreement for the VMT (κ_w could not be determined for all tests). Van Brakel[3] in a similar kind of study assessed the reliability of SWM testing, moving touch sensibility and pinprick testing in Nepal. He found the intra-observer κ_w for SWM to be very good at 0·83–0·92, inter-tester κ_w agreement for moving touch sensibility 0·75–0·82, and the pinprick 0·54–0·82. He concluded that the SWM and moving touch sensibility tests were both suitable for reliable sensory testing.

This study was performed to check the reliability of a core team of physiotechnicians at the Danish Bangladesh Leprosy Mission (DBLM) in the use of the most common diagnostic tests for leprosy related nerve impairment. The reliability study was performed after training in the one new test, SWM, and after refresher training in the other two (BPT and VMT).

The results of the reliability testing were to be used as follows:

1. To help the project decide whether to change from BPT and SWM for routine use in sensory testing.
2. To give the project confidence in the use of these tests as outcome measures in research running at the project (Bangladesh Acute Nerve Damage Study BANDS, and Trials of Prevention of Disability, TRIPOD).

Method

The percentage of occasions on which direct agreement is obtained can be measured. This provides a simple useful indicator of the reliability of the test. The statistic of choice for measurement of reliability is the weighted kappa (κ_w). The use of weighting ensures that where operators disagree on the result, bigger disagreements have a bigger effect on the κ_w. κ_w ranges from 0 (agreement no better than random), to 1 (perfect agreement). A target of a κ_w of at least 0·60 (Altman – good agreement[11]) was believed at the outset to be achievable

immediately post-training for the SWM test. 'Good agreement' would be required for any test to be implementable. A κ_w higher than this ($\geq 0{\cdot}80$) would be desirable for monitoring and research work.

The DBLM project at Nilphamari used the BPT and VMT as components of their testing for nerve function impairment (see Appendix). Patients were treated with corticosteroids on the basis of a locally developed scoring method. This composite score was made up of one point for every point of lost sensation (as determined by the BPT), plus one point for every grade lost on the MRC scale of muscle strength. The composite score obtained was therefore made up of both sensory and motor loss in any of the nerves tested. Subjects whose composite score increased by 2 or more points within a 6-month period were treated for nerve function impairment.[12] Thus patients were treated on the basis of 2 or more points of sensory loss only, or 2 or more points of lost muscle strength only, or a combination of at least one point of sensory loss and 1 point of lost muscle strength. The Appendix gives details of testing procedures used.

For this project, a knowledge of the comparative reliability of the two types of sensitivity testing was important in choosing the best test for the project. For tests like the SWM and BPT, the reliability depends on the patient, the operator and on the equipment. This study examined inter-tester reliability only, assuming this to be the major source of test variability. The other potential sources of test variability are intra-tester and equipment reliability, but these were not tested in this study, since it was assumed that they would be at least as good as the inter-tester reliability.

SAMPLE SIZE

Fifty-three patients were each tested twice by a pair of operators. Four physiotechnicians were used in the study, as well as the senior physiotechnician against whom, as the gold standard, each operator's results were checked. Each pair of operators tested a minimum of 10 patients. Patients were tested with the two types of sensory test (SWM and BPT) in random order, and the VMT always performed during or after the sensory testing.

PATIENT SELECTION

Patients selected were known to have at least one nerve trunk impaired. The target was to test a selection of all grades of impairment within the sensory and motor testing scales. The patients were selected from among hospital inpatients at the DBLM hospitals in Nilphamari and Rangpur, and at some outpatient clinics. In order to maximize the number of patients available, some patients with missing limbs were included, but a total of 304 nerves were tested. One patient declined further testing after BPT, resulting in only 300 nerves being tested using SWMs.

TRAINING

For the SWM test, $2\frac{1}{2}$ days of training were given by one author, AMA, to all testers. The procedure was written in training notes. A set of six graded Semmes Weinstein monofilaments was used. These filaments were obtained from Carville, USA and were designed to bend slightly when forces of 70 mg, 200 mg, 2 g, 4 g, 10 g and 300 g are respectively applied. The filaments were individually touched on the skin until they bent slightly, and then withdrawn. The patients were asked to point to where they felt the stimulus applied. If the

filament was not felt, the next thickest one was used until a level was found where a filament could be felt. Details of filaments used on the hands and feet are given in the Appendix.

For BPT and VMT a short 1-h refresher training was given by the senior physiotechnician to ensure that all staff were familiar with the test criteria. DBLM has used BPT and VMT for 5 years regularly on all patients both in clinic and inpatient situations, so staff are very experienced (see Appendix for details of tests). All testers participated in the testing of some pilot patients, to ensure they were confident in the study procedure and recording of results.

TESTING

Patients were selected by the testers themselves, asked for their consent and cooperation and brought to the test site. They were allocated a study number and tested by the testers in the order given in the randomization. Pairs of testers took turns to test and observe the study, each tester testing three to five patients on one occasion, watching for some sessions, then testing a further block of patients later on.

Each test was performed with the tester blind to previous results. At the end of each block of testing (morning, afternoon) any results showing unusually large discrepancies were discussed, along with possible methods for improving testing technique. Although such feedback was given the data obtained were still included, unchanged.

DATA RECORDING

Test results were recorded on forms separate from the patient record. A new form was used for each tester for each patient, to ensure that blinding occurred. Patient details (age, sex, registration number etc.) were also recorded.

DATA HANDLING

Since the data for the several points of the hand and foot are not independent, only two points for each hand and one for each foot (corresponding to the three nerves being tested) were used in calculations. The chosen sites were the first and fifth metacarpal heads and the first metatarsal head. All data was entered into an Epi Info database and exported to Stata software for the calculation of κ_w.

PATIENT TREATMENT

Where sensory loss was found by the BPT, or motor loss which had not previously been recorded on the patient card, the patient was asked to describe the duration of the impairment. The standard DBLM criteria for prednisolone prescription were used, and patients who met these criteria were referred for treatment.

Results

SENSORY AGREEMENT

Tables 1 and 2 show the agreement between the senior physiotherapist and all staff members for BPT and SWM tests. Table 3 shows the absolute agreement and κ_w for these two tests, and Table 4 the absolute agreement and κ_w by testing pair.

Table 1. Agreement between senior physiotechnician and other physiotechnicians using the ballpen test (BPT)

	Other Physios			
Senior physio	0	1	2	Total
0	85	3	14	102
1	1	2	3	6
2	1	4	191	196
Total	87	9	208	304

0 = Ballpen not felt (complete anaesthesia).
1 = Ballpen felt uncertainty (partial anaesthesia).
2 = Ballpen felt normally (normal sensation).

Table 2. Agreement between senior physiotechnician and other physiotechnicians using the Semmes Weinstein monofilaments

	Other physiotechnicians						
Senior physio	0	1	2	3	4	5	Total
0	81	2	4	1	1	0	89
1	5	6	7	1	0	1	20
2	0	4	7	2	3	2	18
3	1	1	4	16	10	3	35
4	0	1	1	7	20	8	37
5	0	0	0	5	11	85	101
Total	87	14	23	32	45	99	300

The numbers 0–5 indicate levels that the at which the different monofilaments were felt.

Different sets of filaments were used for hands and feet. Details are given in the Appendix.

Table 3. Absolute agreement and weighted kappa (κ_w) with confidence intervals, for the ballpoint and Semmes Weinstein tests

Test	*n*	Absolute agreement	Agreement within 1 grade	κ_w	95% CI
BPT	304	91%	95%	0·86	0·75–0·97
SWM	300	72%	92%	0·92	≥0·80

Table 4. Absolute agreement and κ_w by testing pair for the ballpoint and Semmes Weinstein tests

Test	Testers	*n*	Absolute agreement	Agreement within 1 grade	κ_w	95% CI
BPT	A	69	93%	94%	0·89	≥0·65
	B	68	91%	97%	0·89	≥0·65
	C	87	95%	98%	0·92	≥0·70
	D	80	86%	90%	0·77	0·66–0·88
SWM	A	69	78%	96%	0·96	≥0·70
	B	68	71%	96%	0·95	≥0·70
	C	83	65%	83%	0·87	≥0·65
	D	80	74%	88%	0·90	≥0·65

Table 5. Agreement and κ_w for the individual muscles in the VMT

Test	*n*	Absolute agreement	Agreement within 1 grade	κ_w	95% CI
Tight eye closure	105	90%	96%	0·80	0·62–0·98
Little finger abduction	101	86%	98%	0·94	≥0·72
Thumb abduction	102	90%	98%	0·94	≥0·72
Wrist extension	103	98%	100%	–	–
Dorsiflexion of foot	95	98%	99%	0·89	≥0·67
Eversion of foot	94	98%	100%	0·88	≥0·67
All tests except eye	495	93%	98%	0·94	≥0·84

MOTOR TESTING

Table 5 shows the percentage agreement and κ_w for the individual muscles tested in the VMT. The muscles tested did not cover the full range of the possible grades, therefore in some cases κ_w is not calculable. Table 6 shows the agreement by tester.

Discussion

These data suggest that both sensory tests and the VMT can be performed by this team of testers to an excellent standard of reliability, using a sample of patients similar to the

Table 6. Absolute agreement by tester for the VMT

Tester	*n*	Absolute agreement	Agreement within 1 grade	κ_w	95% CI
A	110	95%	98%	0·94	≥0·73
B	109	91%	99%	0·93	≥0·73
C	144	92%	98%	0·89	≥0·72
D	132	92%	99%	0·95	≥0·77

population they normally test. The BPT showed a κ_w for inter-observer agreement of 0·86, with the weakest operator having an individual κ_w of 0·77. This is an encouraging result, indicating that not only can the BPT be performed to a high degree of reliability, but that in DBLM itself it is a reliable and repeatable test. The reliability of the monofilament was found to be even higher, with a κ_w for inter-observer agreement of 0·92, the weakest tester's individual κ_w being 0·87. This result is excellent, and staff could be expected to improve still further in reliability and specificity with more experience. While both methods of testing were found to be reliable, it can be expected that SWM testing will be more consistently reliable since the force applied by each monofilament is limited by bending. However, whilst inter-observer reliability was good for both methods, the 5-point SWM testing method provides richer data than the BPT since it gives a semi-quantitative assessment of sensory loss.

The reliability of motor testing was also found to be very good. The κ_w for inter-observer agreement was overall 0·94, excluding eye strength testing, and the poorest individual tester's result was 0·89.

In terms of the first aim of testing as described in the introduction, the project decided to switch over to SWM testing as a routine for sensory testing. It also enables data from DBLM to be comparable with data from other projects using SWMs.

Secondly, the exercise boosted the project's confidence in all three methods of testing. This lends weight to the results from the Bangladesh Acute Nerve Damage Study.

Whilst this study indicates that high levels of reliability can be obtained from the three nerve function testing methods in common use, it must be emphasized that this followed a long period of experience with BPT sensory and VMT methods, and $2\frac{1}{2}$ days of training for SWM testing. Such levels of reliability may not be found amongst workers with less experience and training.

In conclusion, ballpoint pen and Semmes Weinstein Monofilament sensory testing techniques for assessing sensory function, and standard voluntary muscle testing for motor function testing are reliable test methods in trained hands. Results obtained may be used with confidence for monitoring and research.

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Appendix

Details of motor and sensory testing used in the study.

a Modified 5-point MRC scale for muscle strength scoring[4,5]

Hands and feet	MRC grade	Eyes
Full ROM[1], full resistance	5	Normal muscle strength
Full ROM, reduced resistance	4	Closes, stays closed against some resistance
Full ROM, no resistance	3	Closes, no resistance[2] (may be gap)
Reduced ROM, some joint movement	2	Gap on strong closure[2]
Flicker only	1	Flicker only
Full paralysis	0	Complete paralysis

[1]ROM: Range Of Movement.
[2]In addition, lid gap in mm is measured and recorded.

b Movements/muscles tested

Nerve	Movement	Muscle/muscle group
Ulnar	Little finger abduction	Abductor digiti minimi
Median	Thumb abduction	Abductor pollicis brevis
Radial	Wrist extension	Wrist extensors
Lateral popliteal	Foot dorsiflexion	Foot dorsiflexors
Facial	Close eyes	Orbicularis oculi

c Ballpoint pen testing technique

The skin is gently dented using an upright, ordinary ballpoint pen to create a dimple of approximately 1 cm across. The subject is asked to point to the place where he feels the sensation, whenever he feels a touch. Accurate pointing to within approximately 3 cm of the point touched is taken to indicate *normal sensation*. Some sensation, but inability to point to within 3 cm is taken as *partial anaesthesia*. Inability to feel anything is taken as *complete anaesthesia.*

d Filaments used in sensory testing of hands and feet

Filaments used for palms of hands*	Filaments used for soles of feet*	Level of sensation (see Table 2)
(No filament felt)	(No filament felt)	0
300 g	300 g	1
4 g	10 g	2
2 g	4 g	3
200 mg	2 g	4
70 mg	200 mg	5

*The weights given indicate the force at which the monofilament will bend.

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A scale to assess activities of daily living in persons affected by leprosy

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Summary The aim of this study was to develop a scale for identifying disability among people in the rural areas of developing countries. The studies were carried out in the Green Pastures Hospital and the leprosy field programme of the Western Region of Nepal. With the help of staff experienced in working with people with disability, a 68-question questionnaire was made, based on the International Classification of Impairments, Activities and Participation (ICIDH-2). A survey was carried out of 269 people affected by leprosy who had impairments, as well as a sample of those who were unimpaired. The survey results were used to develop the questionnaire into a scale, using standard scale development methods. This included checking of criterion validity, discrimination and reliability and stability using weighted kappa statistics. Of the 68 questions, 38 were included in the second draft of the instrument. Eight questions were added to identify difficulty in relationships, about the use of aids and about occupation and employment. The sum score of the scale against the expert score gave a Spearman correlation coefficient of 0·72. Intra- and inter-interviewer reliability coefficients were 0·77 (95% CI 0·73–0·81) and 0·61 (95% CI 0·56–0·67), respectively. The stability test gave an overall kappa of 0·76 (95% CI 0·70–0·82). Four questions with particularly poor results were omitted from the final draft of the instrument. An interview-based instrument was developed for identifying limitations in activities of daily living (disability) in people living in a rural setting in a developing country—the Green Pastures Activity Scale (GPAS). The scale performed well during validity and reliability testing. It consists of 34 activity questions, five relationship questions, and three questions on the use of aids, occupation and employment.

Introduction

Leprosy often causes impairment of autonomic, sensory and motor nerve function.[1–3] This in

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turn leads to secondary impairments or deformities of the eyes, face, hands and feet.[4,5] Too often these become irreversible before the affected person receives appropriate treatment. Impairments and deformities (visible impairments) may cause limitation of activities of daily living (disability) and adverse social reactions (restriction of participation).

The International Classification of Impairments, Activities and Participation (ICIDH-2):[6] defined impairment as 'a loss or abnormality of body structure or of a physiological or psychological function, e.g. loss of a limb, loss of vision'.

Activity is defined as 'the nature and extent of functioning at the level of the person, e.g. taking care of oneself, maintaining a job' In the field of rehabilitation, limitation of activities is commonly called 'disability'.

Participation is 'the nature and extent of a person's involvement in life situations in relation to Impairment, Activities, Health Conditions and Contextual Factors, e.g. participation in community activities, obtaining a driving license'. Restriction in participation was called 'handicap' in the first edition of the ICIDH.

As a result of fixed-duration multidrug therapy (MDT), the number of leprosy cases on treatment has decreased considerably in recent years.[7] Thus, attention is shifting to the needs of those 'cured' with MDT, but left with residual impairments, activity limitation or participation restrictions.[8] These cause long-term problems for the individual and place a demand on community resources. The global number of people with irreversible deformities due to leprosy is estimated to be between 1 and 2 million—up to twice the number of cases currently registered for MDT.[9]

Aware of the rehabilitation needs of people affected by leprosy, several authors have pointed out the advantages of applying the ICIDH concepts in leprosy.[8,10–12] The first edition of the ICIDH, published by the WHO in 1980, has been succeeded by the second edition, the ICIDH-2.[6] It is important that the outcome of rehabilitation be assessed in terms of disability and handicap.[13] The concepts described in the ICIDH(-2) may help in this.

Information on the impairment and activity status of people affected by leprosy may be used for: (i) decision making and management concerning (physical) rehabilitation of individual patients, (ii) assessing the effectiveness of a leprosy programme in preventing the development of (further) impairments and activity limitations, and treatment of pre-existing ones, and (iii) planning of resources needed for treatment and care of patients with impairments and activity limitations, before and after release from drug therapy.

No 'instrument' has been developed for identifying limitation in activities of daily living (ADL) suitable for use with people affected by leprosy in developing countries. Many disability scales are available in Western countries,[14–18] but none appeared suitable for use with people living under conditions common in rural areas of leprosy-endemic countries.

With increasing emphasis on rehabilitation, such a tool is needed to assess adequately the rehabilitation needs of those affected by leprosy and to evaluate the results of rehabilitation interventions. Using standard scale development techniques, we designed such an instrument: the Green Pastures Activity Scale (GPAS). This paper describes the development of the GPAS.

Materials and methods

The studies were carried out in the Green Pastures Hospital of the International Nepal Fellowship in Pokhara and in the leprosy field programme of the Western Region of Nepal.

STEPS IN THE SCALE DEVELOPMENT PROCESS

Standard procedures for scale development were used.[19] First, suggestions for activities of daily living to be included in the assessment were collected during a group consultation of Nepali staff members experienced in working with people with leprosy, or who had had leprosy themselves. Second, a questionnaire was drawn up in English, translated into Nepali and back translated to check the translation. The third step was pilot testing of the questionnaire on 26 subjects. Questions answered affirmatively (endorsed) less than 10% of the time or more than 90% were omitted. The remaining questionnaire was checked for face validity. Extensive validity and reliability testing was not done at this stage, because this instrument was only a precursor of the eventual activity assessment.

Fourthly, using this questionnaire, 269 people affected by leprosy who had impairments and a sample of unimpaired patients were surveyed. All subjects were interviewed about their common daily activities. As far as possible, the interview was conducted in the person's vernacular language, with interviewers of the same sex as the interviewees. They were asked to rank a list of activities on a scale of difficulty of performing them (never do this, same as before, some difficulty, much difficulty, only possible with help or impossible).

In the scale development process, the results of the survey were used for the fifth step. Questions with an endorsement of more than 20% on the 'don't do' category and questions where fewer than 15 people reported 'much difficulty' (or worse) with the activity were excluded. The remaining questions and a few additional ones, each with a five-point response scale, were rearranged into a new questionnaire, the first draft of our eventual scale. Using the method of Laman and Lankhorst,[20] an attempt was made to include an additional question for each activity to assess the perceived importance of that activity to the person concerned. The resulting questionnaire was again translated and back-translated to check the understanding of the wording.

The sixth step was the running of a series of pilot studies to check the criterion validity, discrimination, intra- and inter-interviewer reliability and stability of the draft scale. Criterion validity was checked by comparing the sum score of the scale with a sum of scores given by a panel of experienced staff in a sample of 37 patients. Using three groups of people with different severity of impairment, divided according to the 'maximum WHO disability grade method',[21] we checked the discriminative ability of the scale. Intra- and inter-interviewer reliability was assessed with paired interviews on 29 patients. Four different interviewers were involved. Stability over a period of a week was evaluated in a similar way.

The remaining steps in the GPAS development are checking for responsiveness to change and determining the optimal scoring and summary method.

STATISTICAL METHODS

The percentage 'endorsement' was used to quantify how many respondents gave a positive answer to a given question, or who indicated that they didn't do that particular activity.[19] Criterion validity between the sum scores of the draft scale and the expert score was quantified using the non-parametric Spearman rank correlation coefficient.[22] The chance-corrected percentage of agreement between occasions (intra-tester reliability and stability) and interviewers (inter-tester reliability) was calculated using Cohen's weighted kappa statistic (j_w) for categorical scales.[23] Kappa values are given with their 95% confidence intervals. The kappa value ranges from 0 (agreement no better than by chance alone) to 1

(perfect agreement). Values of 0·40 or less may be interpreted as poor agreement, 0·41–0·60 as 'moderate', 0·61–0·80 as 'good' and values above 0·80 as very good agreement.[24] The percentage direct agreement between occasions or interviewers is also given. The significance of the difference between two kappa values was tested with an appropriate z-test.[23]

Results

The group consultation resulted in a long list of possible activities to be questioned. After eliminating activities that were not common enough to be of use in an assessment instrument, a pilot questionnaire with 95 items was drawn up. The endorsement pilot study led to elimination of 24 items, leaving a survey questionnaire consisting of 68 questions (with three additional questions specific for men or women). These questions were based on the Activity domain of the ICIDH-2. The survey showed that severe limitation of activity was not uncommon among people affected by leprosy who had at least some clinically detectable impairment. The detailed results of this survey have been reported elsewhere.[25]

The results of the survey were used to refine the questionnaire further for validity and reliability testing as described under Materials and methods. Of the original 68 questions, 38 were included in pilot-2 draft of the instrument. Five questions were added to identify difficulty in relationships, one question about the use of aids and two about occupation and employment. These eight questions were added to collect relevant information, but were not intended to be part of the actual scale.

Figure 1 shows the correlation between the sum score of the activity scale and the expert sum score. The Spearman correlation coefficient was 0·72. Discrimination testing showed significant differences in GPAS sum score between people with WHO impairment grade 0 (no impairment) and grade 2 (visible deformity; results not shown). Table 1 shows the results of the reliability testing. Intra-interviewer reliability was good. The overall kappa for all questions pooled together was 0·77 (95%CI 0·73–0·81). The percentage direct agreement was 95·5%. As expected, inter-interviewer reliability was less good, with an overall kappa value

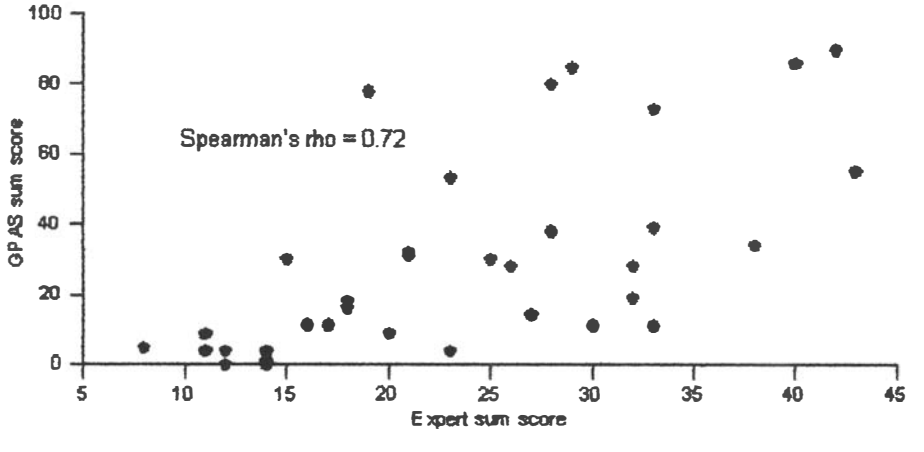

Figure 1. Correlation between the sum score of the Green Pastures Activity Scale and the expert sum score.

Table 1. Results of reliability testing of the pilot-2 draft of the Green Pastures Activity Scale

	Difficulty questions				Importance questions			
	n^a	k_w	95% CI[b]	% DA[c]	n	k_w	95% CI	% DA
Intra-tester agreement	1199	0·84	0·73–0·81	95·9	877	0·60	0·53–0·67	93·1
Inter-tester agreement	1235	0·61	0·56–0·67	92·7	918	0·36	0·30–0·42	85
Stability	1061	0·76	0·70–0·82	95·6	792	0·66	0·59–0·73	91·6

k_w = weighted kappa, [a]n = total number of questions included in the calculations, [b]95% confidence interval for k_w, [c]percentage direct agreement.

of 0·61 (95% CI 0·56–0·67). Direct agreement was still 92·7%. The stability test resulted in an overall kappa of 0·76 (95% CI 0·70–0·82), with direct agreement in 95·6% of questions.

The results were also analysed by interviewer, by question and by interviewee. One interviewer appeared to do less well than the others, with significant differences between the overall kappa values (data not shown). Four questions that gave particularly poor results (weighted kappa <0·40) were omitted from the final draft of the instrument.

The results of the reliability testing were much poorer for the 'importance questions' than for the 'difficulty questions' (see Table 1). Feedback from the interviewers suggested that many interviewees had difficulty understanding the concept of asking 'How important is it to you to . . .?' During the drafting and translating of the questionnaire, this problem had already been encountered. We tried rephrasing these questions and put the least misunderstood version in the pilot-2 scale. However, after reviewing the results of the reliability testing, we decided to omit these questions altogether, thereby shortening the questionnaire considerably.

The final draft of the instrument was named the 'Green Pastures Activity Scale' (GPAS). The English translation of the scale is shown in the Appendix.

Discussion

Irreversible impairments and deformities are the main causes of the complex of negative social reactions attached to leprosy, commonly known as 'stigma'.[26,27] Many investigators have studied the types of impairment occurring in leprosy and their prevalence, often using the term 'disabilities'[28–31] Others have described the management of impairments[4,5,32] and their incidence and associated risk factors.[33–36] However, few studies have addressed disability (activity limitation) as defined in the ICIDH.[6]

People with impaired sensation of the hands, weakness of muscles and deformities of hands and feet may have difficulty with many activities. However, in case management leprosy workers often do not consider the difficulties people experience in activities of daily life. Reconstructive surgery of hands, feet and face, in an attempt to replace lost muscle function, dates back to the pioneering work of Dr Paul Brand and others, more than 4 decades ago.[37,38] Nevertheless, a holistic approach to rehabilitation, including physical, psychological, spiritual and socioeconomic aspects, has been lacking.

In assessing the outcome of treatment or rehabilitation, measures of activity (disability) and social participation (handicap) are much more meaningful for the person involved and thus for clinical decision making.[39,40] However, ADL and participation (handicap) scales

used in Western countries are not appropriate to identify the problems experienced by people living in developing countries, particularly not those of people living in rural areas. We developed the Green Pastures Activity Scale (GPAS) in an attempt to provide a tool suited to this task, especially for use with people affected by leprosy. The GPAS is an interview-based instrument to identify difficulty experienced in activities of daily living. This will potentially allow the instrument to be used under field conditions as well as in referral centres. The structure of the scale is based on the 'Activity' concept of the ICIDH-2. Validity, discrimination and reliability testing in a series of pilot studies showed very acceptable results.

We included questions about perceived importance of the various activities in the questionnaire to subjectively weight reported disability.[20] However, the pilot testing showed that such questions were not sufficiently well understood to be reliable. They were therefore omitted from the final scale. Although interviewers were instructed in interview techniques for the GPAS, inter-interviewer reliability can perhaps be further improved through additional training. Responsiveness to change and the best way to summarize the scale into a single index are still under investigation. The GPAS will be made available for general use. An English copy of the scale and instructions for its use can be obtained from the corresponding author.

AN EXAMPLE

Mr S. is a 27-year-old self-employed tailor referred to the clinic for rehabilitation. He has extensive impairments on both hands: complete bilateral ulnar/median palmar anaesthesia and motor paralysis with mobile clawing of four fingers on his right hand. He also has a partial footdrop on the left. All impairments are over 3 years old. He has completed 24 months of MDT, but says he is unable to do his job, because he cannot thread or hold a needle anymore. The GPAS interview identified severe difficulty with mobility, because he lives in a hillside village and cannot lift his foot high enough when walking uphill. In addition, he reported severe limitations with activities requiring fine dexterity, scoring 'very difficult' on items like opening containers or bottles (13), cutting nails (24), using buttons, hooks or pins (28) or making knots (29).

He underwent surgical correction of his footdrop and claw hand, which resolved the walking limitation, but not the dexterity problem. Therefore, at his request, weaving training was arranged, followed by a micro-credit loan to buy a hand loom. This proved successful, as weaving requires less fine dexterity than tailoring.

Use of the GPAS forced the staff to take time to talk with Mr S. and to listen carefully to the difficulties he experienced, as opposed to what they assumed he might have, based on his impairments. They were then able to identify specific areas of activity limitation and offer problem-oriented interventions to help him reintegrate as a contributing member of his community.

CONCLUSIONS

An instrument was developed for identifying activity limitations in people living in rural areas of a developing country—the Green Pastures Activity Scale. The scale performed well during validity and reliability testing. The GPAS consists of 34 activity questions; in addition, five questions explore difficulty in relationships and three questions the use of aids, occupation and employment status.

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Appendix

Green Pastures Activity Scale

Name of the patient:
Card number:
Reason for assessment: Admission/Discharge/Home visit/Other:

Question	Something I have to do	Not difficult	A bit difficult	Very difficult	Something I can't do because of the disease
A. Walking					
1. For you, walking outside the house is					
2. For you, climbing stairs is					
3. For you, walking uphill is					
4. For you, walking downhill is					
B. Sitting and getting up					
5. For you, squatting is					
6. For you, sitting with crossed legs is					
7. For you, getting up is					
C. Seeing					
8. For you, recognizing people from far away is					
9. For you, seeing small things at a short distance (e.g. reading or putting a thread through a needle) is					
D. Preparing meals					
10. For you, cutting vegetables is					
11. For you, putting pots on the stove is					
12. For you, stirring food is					
13. For you, opening containers or bottles is					
E. Activities in the house					
14. For you, sweeping is					
15. For you, opening a door is					
F. Activities around the house or in the fields					
16. For you, opening a tap is					
17. For you, cutting grass or rice with an asi is					
18. For you, weeding grass or rice is					
19. For you, planting seedlings is					
26. For you, going to the toilet is					
27. For you, cleaning yourself after toilet is					
H. Dressing					
28. For you, using buttons, hooks or pins is					
29. For you making knots or tying laces (or bows) is					
30. For you, putting on shoes or sandals is					
31. For you, putting on clothes is					
I. Eating and drinking					
32. For you, eating with the hand is					
33. For you, drinking water from a container or glass is					
34. For you, peeling fruit is					

Question	No problems	Some problems	Many problems	To live separately	No such relation
J. Relations					
35. Because of leprosy, in the relationship with your spouse, do you have					
36. Because of leprosy, in the relationship with your children, do you have					
37. Because of leprosy, in the relationship with your family, do you have					
38. Because of leprosy, in the relationship with your neighbours, do you have					
39. Because of leprosy, in formal relationship (eg. employer or village head), do you have					

Question	Not necessary	Not difficult	Difficult	Very difficult
K. Assistive devices: Do you use (an) assistive device(s)? YES/NO If yes, which:				
40. For you, the use of a device(s) is				
L. Occupation: Do you have any difficulty in your job/daily work? YES/NO				
41. What is your occupation?				
42. Do you do it /daily/sometimes/rainy season/winter season/unemployed?				

Name of the interviewer Date of the interview:

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The stapedial reflex as a topographical marker of proximal involvement of the facial nerve in leprosy. A pilot study

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Summary This study aimed to determine the parameters necessary for a study of stapedial reflexes in leprosy patients to ascertain if the facial nerve is involved more proximally than the stylomastoid foramen. It involved leprosy patients with and without facial nerve involvement and non-leprosy controls. Clinical examination of the patients' ears, a tympanogram and audiogram to exclude conductive and sensorineural deafness, followed by the measurement of a stapedial reflex and the acoustic reflex threshold, were carried out. The number of absent reflexes and the acoustic reflex thresholds did not differ between the three groups of subjects. A definitive study would be logistically impossible. Suggestions are made as to more exact patient selection in order to demonstrate any stapedial reflex changes due to leprosy. The findings of this study do not suggest that facial nerve pathology extends proximally to the stylomastoid foramen, unless such proximal involvement is subclinical to the detection methods used.

Introduction

Leprosy is a disease that affects the skin, the peripheral nervous system and the upper respiratory tract.[1,2] Measurable peripheral neuropathy occurs in about one-third of leprosy cases.[3] Nerves most commonly involved are superficial dermal nerve twigs, cutaneous nerves, nerve trunks in the limbs and the trigeminal and facial cranial nerves.[4] Classical understanding of neuropathy in leprosy holds that there are 'sites of predilection' of nerve involvement. These sites are generally cool in temperature or where nerves are subject to stress from mechanical shearing near joints or points at which swollen nerves are compressed by osseo-ligamentous tunnels.[5–7] Recently, investigators have questioned whether nerve

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involvement is limited to these sites of predilection.[6,8] Turkof *et al.*[8,9] showed via intra-operative spinal root stimulation that lesions of the ulnar and median nerves were far more proximal than macroscopic nerve thickening suggested. In addition, the phenomenon of involuntary co-contraction of facial muscles after facial nerve palsy points to the proximal involvement of the facial nerve with mis-reinnervation. Many people with a recovered facial palsy from leprosy elevate their upper lip on gentle eye closure.[6,10,11] This implies that regenerating axons of the zygomatic branch now innervate the buccal branches because the latter had degenerated back as far as the main facial nerve trunk.[6] Does the leprous lesion extend even more proximally?

Facial paralysis (present in 4–10% leprosy cases[6,10–12]) is thought to be due to bacterial invasion of the extracranial branches of the facial nerve by *M. leprae*.[13] It is not known whether the intracranial portion of the nerve is involved prior to its emergence from the stylomastoid foramen. Were it involved at this level, an ascending infection of the facial nerve would most likely be responsible. Alternatively, as leprosy is a disease involving the upper respiratory tract and its mucosa, there is a potential conduit for the *M. leprae* into the middle ear through the eustachian tube.

The stapedial reflex has been described as a topographical marker to help delineate the site of a lower motor neuron facial nerve palsy.[14] Absent acoustic reflexes or elevated thresholds have been reported in non-leprosy patients with unilateral facial nerve paralysis with a presumed viral aetiology,[15] so-called Bell's palsy. We predicted that if there were intracranial involvement of the facial nerve in leprosy, the acoustic reflexes would be elevated or absent in leprosy patients with facial nerve palsy, whereas they would be normal in people with leprosy but no facial palsy and normal in controls.

This pilot study was undertaken to assess the feasibility of setting up a study to test this hypothesis.

Materials and methods

The nerve to the stapedius muscle is the first branch of the facial nerve after the genu and the second last branch prior to the exit of the nerve from the cranium.[16] Unlike other intracranial branches of the facial nerve, its integrity is easily measured, via the multisynaptic acoustic reflex (Figure 1). This reflex is protective, occurring when the ear is exposed to loud sound. The afferent pathway is via the vestibulocochlear nerve and efferent nerve fibres are from the facial branch to the stapedius muscle. The afferent pathway synapses on both ipsilateral and contralateral nuclei in the brainstem; thus stimulation of one ear results in efferent activation in both ears. Upon stimulation, the stapedius muscle contracts, stiffening the stapedial tendon, which in turn limits the movement of the stapes and dampens the conductance of loud sounds from the middle to the inner ear. The acoustic reflex provides simple access to the proximal portion of the facial nerve. The reflex is determined by administering suprathreshold tones to the ear and measuring the change in compliance of the middle ear. For the ipsilateral reflex, the test signal and the response are measured in the same ear. A probe tip is inserted into the test ear, the right ear in the example in Figure 1. A microphone in the probe sends a series of pure tone signals at octave intervals from 250 to 4000 Hz into the right ear. The intensity of the signal is increased from 0 decibels hearing level (dB HL) until the same probe detects a change in volume of the external auditory canal. This is usually at 85–95 dB HL. The change in volume reflects the contraction of the stapedius muscle as it pulls on the ossicular

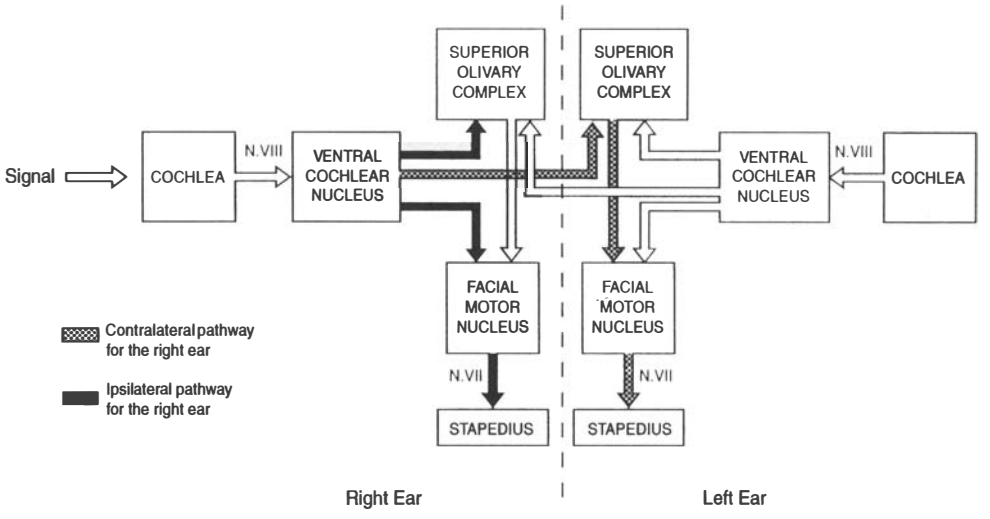

Figure 1. Schematic diagram of the neuronal pathways for ipsilateral and contralateral acoustic reflexes.

chain, displacing the tympanic membrane and thus changing the dimensions of the middle ear. The volume of the canal is a surrogate for the change in compliance of the tympanic membrane, the true reflection of the integrity of the stapedius muscle and its innervation. For the contralateral reflex of the right ear, pure tones are delivered to the right ear via a headphone and the probe tip measures the reflex contractions in the left ear. In this study ipsilateral and contralateral reflexes were taken from subjects if they had normal hearing and normal tympanograms in both ears.

Before testing the stapedial reflex as a topographical marker of a facial nerve lesion, it was important to delineate factors that could confound our results. In one study of audiovestibular status in persons affected by leprosy in India, 8% of subjects had absent or elevated reflexes, but no mention was made of facial nerve involvement or hearing impairment.[17] Hearing impairment from conductive (external or middle ear), cochlear or vestibulocochlear nerve pathology can result in absent reflexes or elevated reflex thresholds.[15] The prevalence of hearing impairment in the people of Nepal over 5 years of age is 17%.[18] There are reports of middle ear pathology and resultant conductive hearing loss in leprosy.[17,19] Cochlear deafness in leprosy has also been described.[20] The prevalence of hearing loss in the leprosy population has been reported to be as high as 44–82%;[17,19,20] this variability can be explained by differences in study sample size, selection and definition of hearing loss. Leprologists do not normally consider hearing loss to be a clinical issue; nevertheless, these studies suggest the leprosy population is more frequently hearing impaired than the normal population. We questioned whether we could obtain enough subjects from our leprosy population who had facial nerve palsy but were not hearing impaired. Reference data on normal acoustic reflex thresholds for Nepalis are unavailable. Western literature reports normal acoustic reflex thresholds between 80 and 90 dB HL (decibel hearing level) for activator signals 250, 500, 1000, 2000 and 4000 Hz.[15] Elevated or abnormal thresholds are considered by some to be above 95 dB HL for pure tones between 250 and 2000 Hz and above 100 dB HL for 4000 Hz,[15,21] while others state that abnormal

thresholds are those above 100 dB HL across all frequencies.[15] These studies do not mention the racial makeup of their subject groups. Nepalis may not share the same stapedial nerve reflex profile of the people in the reported studies. We therefore conducted a study which would: 1) document the yield of subjects who had leprosy and normal hearing, 2) provide some information on normal acoustic reflex thresholds in Nepalese controls and 3) test the use of the acoustic reflex as an indicator of proximal facial nerve pathology.

Subjects

Subjects with leprosy were recruited from the inpatient population at Green Pastures Hospital, a regional leprosy treatment facility in Pokhara, Nepal. Control subjects were recruited from visitors and the support staff at the Western Regional Hospital, Pokhara.

Subjects with facial nerve palsy were selected on the basis of voluntary muscle testing (VMT) and chart review. Severity of facial nerve palsy in all five extra cranial branches of the facial nerve was documented prior to audiometric testing. All subjects underwent screening for ear pathology by the participating otolaryngologist. Controls were admitted to the study only if both ears were healthy. Leprosy subjects were admitted to the study if they had at least one healthy ear. This was because the pool of subjects for leprosy patients was more limited and yet it was possible to obtain a portion of the acoustic reflex data with one ear only. The criteria for entering only one ear to the study were as follows. If there was a unilateral hearing loss and an abnormal tympanogram in one ear, but normal hearing and a normal tympanogram in the other ear, only an ipsilateral reflex from this 'good' ear was possible. If the first ear had a hearing loss but a normal tympanogram and the other ear had normal hearing and a normal tympanogram (good ear) then ipsilateral and contralateral reflexes were taken from the 'good ear'. The contralateral reflex only requires normal hearing in the ear receiving the pure tone signal and normal middle ear and facial nerve function in the opposite ear. Pure tone audiometry was carried out on each subject and the pure tone average obtained (the average of thresholds at 500, 1000 and 2000 Hz).

There is no universal definition of normal hearing. Jerger[22] defined normal hearing as pure tone thresholds at or below 20 dB HL between 500 and 8000 Hz, while most classification systems define hearing loss as thresholds greater than 25 dB HL.[23] Subjects were included if the tested ear had a pure tone average below 26 dB HL. Tympanograms and acoustic reflex thresholds were then obtained for qualifying ears. Ears were disqualified if they had abnormal tympanograms. Ipsilateral and contralateral reflexes were obtained for pure tone signals at 250, 500, 1000 and 2000 Hz. These stimuli produce acoustic reflex thresholds that do not change with age.[15]

Pure tone audiometry was conducted in a sound treated room that met American National Standards Institute (ANSI) standards for acceptable ambient noise levels as measured by a Breuel and Kjaer sound level meter.[24] Tympanometry and acoustic reflex testing was carried out on an Interacoustics AZ 26 Impedence Audiometer. Pure tone audiometry was conducted with an AC4 Kamplex Clinical Audiometer with Audiocups earphones. Both audiometers were certified as calibrated by an Interacoustics service technician prior to the study. The automatic mode was used for tympanometry and reflex testing, since the investigator conducting the audiometric tests could not be blinded to subject group. Increments of 1 dB were used for reflex testing. Reflex records were reviewed later by the otolaryngologist blinded to subject group.

Results

Seventeen subjects with facial palsy due to leprosy were recruited, eight (47%) of whom qualified with one or both ears normal. Of these eight subjects, 12 ears gave 12 valid ipsilateral reflex measurements and 11 valid contralateral measurement. Of those with leprosy alone, 49 people were recruited but only 17 subjects (35%) qualified, rendering 31 ipsilateral and 29 contralateral reflex measurements. Of the 62 controls recruited, 27 (44%) qualified with two healthy ears, that is 52 ears with 52 ipsilateral and 52 contralateral reflex measurements. All three groups were comparable in age and sex distribution (Tables 1 and 2). Seventy-one percent of the subjects were male and 29% female. Age ranged from 16 to 57 years. The median age was 37 years.

Of the 27 subjects who had leprosy, eight had lepromatous leprosy (LL), six had borderline lepromatous leprosy (BL), nine had borderline tuberculoid leprosy (BT) and two had borderline borderline leprosy (BB). The distribution of leprosy type between the leprosy subjects with and without facial nerve involvement is shown in Table 3. Leprosy subjects had a median history of 4 years and the range was from 0·5 to 40 years.

All the acoustic reflex and threshold results were analysed by a medical statistician and subjected to parametric and non parametric testing, but Chi-square and Kruskal–Wallis values are not presented, as the study was a pilot one and the sample size was inadequate for any definitive results or trends to be valid. The median pure tone average for each group is listed in Table 4. The median acoustic reflex thresholds did not appear to differ much between the three groups. However, there was a tendency for thresholds to be slightly lower in the facial palsy group (Table 5). Variances about the mean in the leprosy groups were large. Absent reflexes occurred in all subject groups but were not significantly absent in any one group.

Table 1. Sex distribution by subject group

	Leprosy and facial palsy	Leprosy only	Controls	Total
Female	1	4	10	15
Male	7	13	17	37
Totals	8	17	27	52

Table 2. Age distribution by subject group

Leprosy and facial palsy	Median age (years) range
Leprosy and facial palsy	42 (17–55)
Leprosy only	35 (16–57)
Controls	35 (16–57)

Table 3. Distribution of leprosy type between subject groups

Leprosy type	Leprosy and facial palsy	Leprosy only	Total
BT	4	5	9
BB	1	1	2
BL	2	4	6
LL	1	7	8
Total	8	17	25

Discussion

In this small pilot study, an absent reflex in leprosy patients with facial palsy was no more likely than in those with no facial nerve palsy or in those without leprosy. Furthermore, acoustic reflexes were not elevated in the facial nerve palsy group when compared to leprosy alone or to controls. Type of leprosy did not influence threshold values. While the numbers of reflexes in the groups were small and variances were large, the results were consistent across frequency and method (ipsilateral or contralateral stimulation). Even in ears rejected from the study, there was no difference in absent reflexes between the two leprosy groups and the qualifying controls, despite hearing loss. Due to the phenomenon of mis-reinnervation we presume that leprosy involves the facial nerve up to its main trunk.[6,10,11] The results from this study suggest that facial nerve pathology may end distal to the stylomastoid foramen. The warmer temperature within the temporal bone may not be hospitable to *M. leprae*.[25–27] However, in a previous study of biopsies of non-functioning facial nerve from leprosy patients with irreversible facial nerve palsies, we have established that there are large numbers of unmyelinated axons, often in regeneration clusters. This finding was evenly distributed throughout the facial nerve branches and between the fascicles. This was seen as possible evidence of proximal compression of the nerve trunk.[28] If this is the case, we thought we might find absent or elevated thresholds for stapedial reflexes in such patients. Recently a dermatologist in Brazil, managing 10 leprosy patients with an acute facial patch in reversal reaction with minimal or no facial nerve paralysis, used magnetic resonance imaging (MRI) to delineate the lesions more accurately. As an incidental finding, the intratemporal portion of the facial nerve on the facial patch involved side, was noted to be irregularly thickened. This was interpreted as oedema of the nerve and the patients started on steroids to prevent facial nerve palsy (personal communication, Jane Yamashita, Brazil). This supports our hypothesis of possible compression neuropathy in the facial nerve biopsies. This oedema could be in those extracranial fascicles of the facial nerve affected by leprosy, but not involving the intratemporal branches of the facial nerve. So whilst this pilot study did

Table 4. Median pure tone averages for each subject group (n = sample size of ears)

	Leprosy and facial palsy	Leprosy only	Controls
	($n = 12$)	($n = 31$)	($n = 52$)
Pure tone average, dB HL	17	15	12

Table 5. Median acoustic reflex thresholds for each stimulus frequency across subject groups (n = sample size of ears)

Hz	Ipsi 500	Ipsi 1000	Ipsi 2000	Contra 500	Contra 1000	Contra 2000
Leprosy and facial palsy	98·0 ($n = 12$)	98·0 ($n = 12$)	109·5 ($n = 12$)	101·0 ($n = 11$)	94·0 ($n = 11$)	97·0 ($n = 11$)
Leprosy only	102·0 ($n = 31$)	100·5 ($n = 30$)	110·0 ($n = 29$)	102·5 ($n = 30$)	97·0 ($n = 30$)	97·5 ($n = 30$)
Controls	103·0 ($n = 50$)	102·0 ($n = 52$)	110·0 ($n = 51$)	102·0 ($n = 51$)	99·0 ($n = 51$)	100·0 ($n = 49$)

not indicate a consistent intratemporal specific facial nerve deficit, it remains extremely likely that leprous neuropathology could cause an intratemporal compression neuropathy and thus be implicated in the more severe types of total facial nerve palsy.

Less than half the facial palsy subjects qualified for this study on the basis of abnormal external and middle ear anatomy, abnormal tympanometry or abnormal hearing. Our results are consistent with the 44% prevalence rate of hearing loss in persons affected by leprosy found by Mann *et al.*[20] Of the few studies of cochleo-vestibular function in leprosy patients some demonstrate a mild sensorineural hearing loss (of the order of 16–60 dB hearing loss) in 44–60% of lepromatous patients.[17,20] One recent small study showed no hearing loss in 19 lepromatous patients.[29] The former studies also suggest that it is the cochlear portion of the eighth nerve that is involved and not the vestibular apparatus.

Two recent studies of auditory brain stem evoked potentials in leprosy patients suggest a lesion between the cochlear and the lateral lemniscus in the auditory brain stem pathway.[29,30] We noted a difference of 10 dB between the ipsilateral and contralateral stapedial reflex thresholds at 2000 Hz. The difference, however, was that the ipsilateral threshold was 10 dB higher than the contralateral, whilst the expected finding would be no difference or a small (2–5 dB) higher contralateral threshold.[15] Again, the variance is large, so this may not be the correct interpretation. This finding provides no evidence to refute or support a lower midbrain leprous pathology.

Controls were excluded for abnormal tympanic membranes, abnormal tympanometry or hearing loss. The rejection rate for our controls was 56%. This is over 3 times the reported national average for hearing impairment.[18] We believe one reason for this was that when people who thought they might have a hearing problem found out about our study, they volunteered so that they could have quick and free access to testing.

While this was not a normative study on acoustic reflex thresholds in Nepalese people, the thresholds obtained were, in most cases, above normal values reported in the literature.[15,31] This may be related to the automatic testing mode used, as the stimulus tone may have been rising while the reflex was initiated and thus the reflex was given at a higher threshold than may have been recorded manually. Alternatively, it may reflect a racial or environmental effect of life in Nepal.

Testing of the stapedial branch of the facial nerve in leprosy has not been previously reported. The acoustic reflex test is a simple, non-invasive method for accessing this intratemporal branch of the facial nerve. The greater petrosal and chorda tympani branches, whilst amenable to quantifiable testing (Schirmer test, salivary flow test and electrogustometry),[1]

fail to differentiate between an intratemporal or an end organ aetiology for any abnormal findings in the case of leprosy. None of our patients reported aguesia, nor did we attempt to test for any taste loss. We have previously, seen two patients with catastrophic facial nerve palsy reporting diminished taste sensibility.

Little clinical attention is paid to hearing loss in leprosy, as it is presumed that leprosy does not affect cranial nerves intracranially.[20] Our results show mild deafness to be a problem in approximately 50% of persons affected by leprosy, whilst the prevalence of hearing impairment in the people of Nepal over 5 years of age is 17%.[18] We suggest that hearing assessment should be a standard component of intake assessment at our leprosy treatment centre.

In view of the small differences between the reflex thresholds in the three groups and the large variance of thresholds between patients, a definitive study would need to be very large. Given that no consistent large differences were found in this pilot study, the clinical value of a large study would also be unsure. We therefore suggest evaluating the acoustic reflex technique as a research tool in the following two situations.

- Test subjects with a trigeminal patch in reaction, or a recent new facial nerve palsy to determine whether there is involvement of the intratemporal facial nerve during this acute phase. This would be corroborative evidence of intratemporal compression.
- Test subjects prior to steroid treatment for reversal reactions resulting in facial palsy and compare the thresholds with those obtained after successful treatment.

Routine otological and audiometric testing would provide leprologists with further information about nerve involvement beyond the stylomastoid foramen and surgeons information with which to avoid incomplete neurolysis.

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Facial nerve pathology in leprosy: searching for the proximal extent of the lesion in facial nerve biopsies

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Summary A light and electron microscope study was made of resin embedded facial nerves in three cases of leprosy involving the facial nerve. The patients had irreversible facial nerve palsies and had requested facial reconstruction. No consistent pattern of nerve fibre damage was found. In one case the temporozygomatic was affected, but the cervical branch was normal, suggesting the damage begins distally. In two cases the loss of nerve fibres in the trunk and all branches was similar, and is likely to emanate from damage at a more proximal site. The presence of increased numbers of unmyelinated axons, often in clusters, is evidence of regeneration. These axons probably have the potential to develop into functional myelinated fibres provided that they can innervate a viable distal target such as a muscle graft. These regenerating axons are distal to the stylomastoid foramen suggesting that the most proximal level of involvement of the facial nerve could be intracranial. The finding of a more proximal level of nerve involvement, implies that the mis-reinnervation seen in partially recovered facial nerve palsies in leprosy, could be due to some regenerating axons being mis-directed at the level of the main trunk bifurcation.

Introduction

Leprosy is a disease of nerves; its pathogenesis is poorly understood. Of the facial nerve branches, the zygomatic branch is reported to be the most frequently affected by leprous infection.[1,2] Its branches pass through 'fibrous fascial tunnels'[3] and over the 'bony protuberance of the zygoma',[1] both probably contributing to its vulnerability. A further factor is its passage through the thin superficial tissue over the zygomatic bone, a region of lowered temperature.[2]

The zygomatic branch of the facial nerve is known to have interconnections of its more distal parts with those of the sensory maxillary division of the trigeminal nerve.[1,4] Dastur and Antia[1,3,5] pointed this out following studies correlating facial nerve involvement with

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sensory loss over the malar region, suggesting that leprous infection had spread to the motor nerve from a primary infection of the sensory nerve terminals of the trigeminal nerve.

The site at which the facial nerve is involved is not known, although it is assumed to be the distal zygomatic branch, since palsies are more frequent in the zygomatic region, and there is some histological evidence[1,5] to support this view. Although evidence for the particular susceptibility of the zygomatic branch is strong,[3,6–12] a recent study of patients with lagophthalmos[9] has shown that in over 80%, other facial muscles were involved, suggesting that, on clinical grounds, the zygomatic branch is not uniquely vulnerable.

The cervical branch of the facial nerve might be expected to be frequently involved as it innervates a very superficial panniculus carnosus muscle, the platysma, and is surrounded by cutaneous sensory nerves in the neck which are commonly enlarged. However, most leprologists do not regularly examine the action of the platysma as any functional deficit would be of little clinical relevance. Some believe the cervical branch never to be involved,[13] while we at Green Pastures Hospital have demonstrated it to be occasionally affected in those with a facial nerve palsy[14] and probably never as an isolated palsy.

Recent intra-operative electrodiagnostic studies have demonstrated proximal lesions in trunk nerves that appear to the naked eye to be normal. Subsequent intrafascicular neurolysis at this more proximal level has proved to be beneficial.[15,16]

The intention of this study was to establish by electron microscopy the most proximal level at which the facial nerve is affected by leprosy. The possibilities for the site of the irreversible part of the lesion are several: exclusive distal nerve branch disease with failed reinnervation: or more proximal disease but the fibro-osseous tunnels over the zygoma cause such severe compression and subsequent fibrosis preventing nerve regeneration beyond this level: or the irreversible damage could be more proximal, in the main trunk, stylomastoid foramen or middle ear. In our attempt to answer this, we carried out facial nerve biopsies on three selected patients in order to correlate if possible, the histological findings of electron microscopy of the facial nerve with the clinical picture of the patients facial nerve palsy.

Patients and methods

Leprosy patients requesting reconstruction of a facial deformity caused by a near total facial nerve palsy of more than 4 years (and so considered to be irreversible), were offered a static sling reconstruction for the mouth, and if clinically indicated, a temporalis muscle transfer for lagophthalmos. At the same time, they were asked if they would permit a dissection of the facial nerve for the purposes of a biopsy for medical research. Ethical permission for this study was obtained from the Hospital research resource committee, and the consent of each patient was given after full explanation by a Nepali staff member.

SURGERY

Under general anaesthetic, the main trunk of the facial nerve was located proximally and the nerve dissected by carrying out a superficial parotidectomy. Once the entire nerve was displayed, from the level of the sternomastoid foramen up to its distal branches entering the musculature of the face (Figure 1), non-functioning branches were biopsied. The patients had a static sling reconstruction of the angle of the mouth using fascia lata strips attached to the malar periosteum. A Johnston type temporalis muscle transfer was used for the lagophthalmos.[17,18]

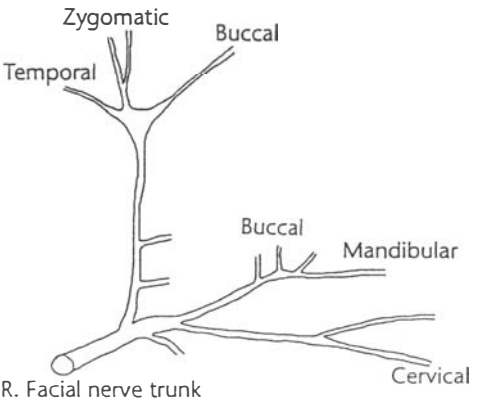

Figure 1. Line drawing of an example of an entire right facial nerve excised from the mastoid foramen to all the branches distal to the superficial parotid gland.

NERVE BIOPSY

Nerves were held carefully and fixed in 3% glutaraldehyde in 0·05 M cacodylate buffer and stored at 4°C.

Semithin and ultrathin sections were prepared for light and electron microscopy. Semithin sections were stained with methylene blue, Azure II and basic fuchsin[19] and *Mycobacterium leprae* bacilli when present, are readily visible staining a deep red. *M. leprae* also have a highly characteristic appearance by electron microscopy (EM). Quantitative methods have been described elsewhere[20] i.e. counting of myelinated fibres and measurement of their diameters, and counting of unmyelinated axons. Control data of the normal buccal branch of the facial nerve are taken from a quantitative study of the facial nerve regenerating through a graft.[21] Findings are summarized in Table 1.

Results

CASE 1

SDD; a 67-year-old male, first presented in 1962 with borderline lepromatous leprosy (BL). He had many small red raised skin lesions with sensory neuropathy of the feet. The right ulnar, lateral popliteal and left great auricular nerves were enlarged. He had a right facial nerve paresis with malar and corneal anaesthesia. Facial macules were in reversal reaction with a right lagophthalmos. He had a right temporalis muscle transfer in 1963. He presented in 1994 requesting reconstruction for his facial weakness. On examination he had a right facial nerve lower motor neuron (LMN) paresis. The angle of the mouth drooped, but he could control the lower lip, and pout weakly. He could not show his teeth, and only weakly hold his buccal pouch full of air. His platysma was normal with no paralysis. Transcutaneous electrical stimulation confirmed no function in the zygomatic and temporal branches of the facial nerve and weakness of the buccal and mandibular branches. At operation (April 1994), because the mandibular branch had some residual function, it was decided to give him a static facial sling but not to excise his entire facial nerve. The nerve was dissected from the main trunk to all five named branches. Excision biopsies of his *temporo-zygomatic* branch (2 cm),

Table 1. Qualitative and quantitative description of facial nerve biopsies in three leprosy patients with facial nerve palsies

		Fascicles			Myelinated fibres			Unmyelinated axons	Endoneurium			
Case	Nerve	No.	Area, mm^2	Fascicles affected	Density/ mm^2	Active degeneration	Regeneration	Density mm^2□	Collagen increased	Odema	Inflammatory cells	Comments
1	Temporo-zygomatic	1	0·12	1	5474	–	Few	81,252	Moderate	–	–	
	Cervical	4	0·13	4	6250	–	–	Normal for motor nerve	–	–	–	Normal motor nerve
	Great auricular	?		?	–	–	–		Totally collagenized	–	–	Nerve architecture destroyed
2	Facial nerve trunk	3	0·46	3	1048	V. occ	Few	54,646	Mild	–	V. occ.	
	Temporal	2	0·08	2	1705	–	V. few	Many*	Mild	–	–	
	Zygomatic	5	0·06	5	1304	–	V. few		Mild	–	–	
	Mandibular	1	0·06	1	2150	–	–	Many	Mild	–	–	
	Cervical	4	0·08	4	1180	–	V. few	Many	Mild	–	–	
	Buccal	7	0·34	5	5593	–	?	Many	Mild	–	–	
				2	743	–	V. few	Many	Mild	–	–	
3	Facial nerve trunk	4	1·05	4	209	Occ	V. few	23,653	–	Marked	Numerous	Fascicular area increased
	Temporo-zygomatic	3	0·86	3	255	Occ	V. few	Many	–	Marked	Numerous	"
	Mandibular	1	0·18	1	481	Occ	V. few	Many	–	Marked	Numerous	"
	Cervical	2	0·36	2	306	Occ	V. few	Many	–	Marked	Numerous	"
	Great auricular	8	0·66	8	2265	–	Many	Few	–	Marked	Numerous	

– = none or negative, * = in excess of normal, □ = range for normal motor (buccal) nerve = 15,666/mm^2 ± SD 5470 (n = 14).

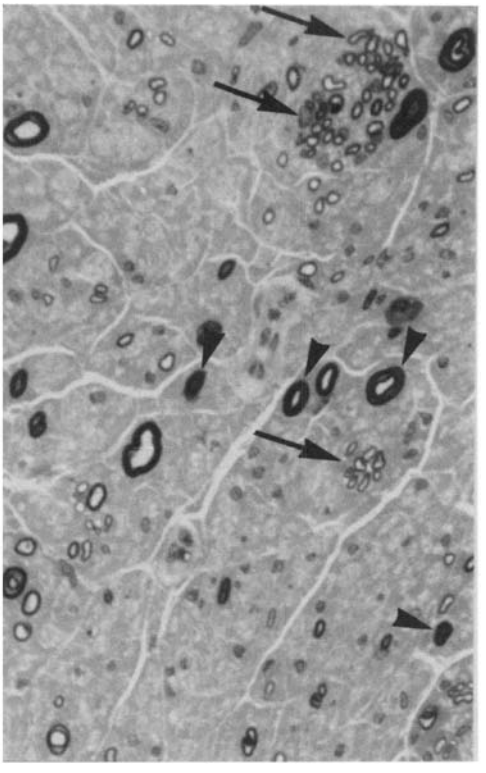

Figure 2. Case 1. Temporo-zygomatic branch of facial nerve. 1 μm resin section stained with methylene blue, basic fuchsin, azure II (MBA). There is a reduced density of myelinated fibres; clusters of small regenerating fibres are seen (arrows). A few 'original' myelinated fibres remain; some are very small and atrophic with axons small for myelin sheath thickness (arrowheads). ×600.

and of the (functioning) *cervical* branch (3 cm), together with a biopsy of his non-functioning *great auricular* nerve were taken.

Eighteen months after the operation the patient reported no paraesthesiae in the facial nerve, and no Tinel sign was elicited over the two biopsy sites.

Temporo-zygomatic branch

The 2 cm length of nerve was examined at proximal and distal ends. Proximally the nerve consisted of a single fascicle with myelinated fibres distributed in a highly collagenized endoneurium. There were a total of 630 myelinated fibres including a number of regeneration clusters (Figure 2). Some of the larger fibres appeared atrophic, with axons small relative to myelin sheath thickness. The distal end showed a generally similar appearance but more fibres showed axonal atrophy resulting in numbers of unusually small myelinated fibres of 2 μm or less. Electron microscopy showed many unmyelinated axons; their density was 81,252/mm^2 compared with a mean of 15,660/mm^2 $\pm$ SD 5470 in the normal buccal branch of the facial nerve. Many are therefore likely to be regenerating axons. There was no evidence of any ongoing pathology, no inflammatory cells, and no bacilli.

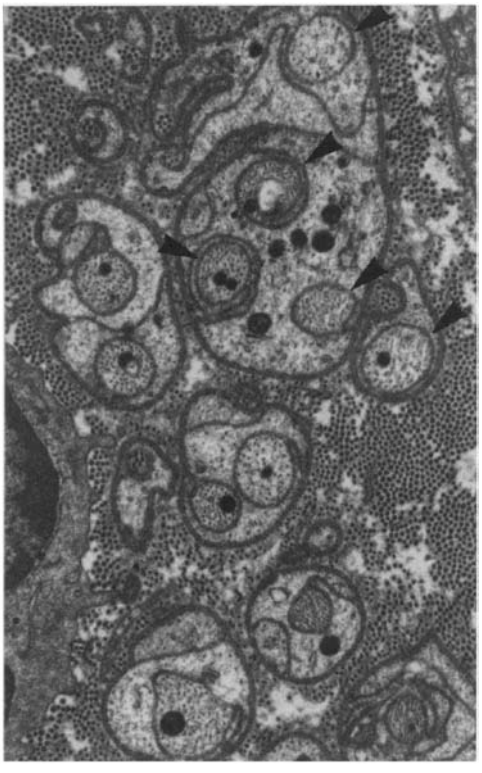

Figure 3. Case 2. Mandibular branch. Electron micrograph showing unmyelinated axons (arrowheads); it is not possible to distinguish regenerated from 'original' unmyelinated axons with certainty. ×10, 000.

Cervical branch

The 3 cm length of nerve at both proximal and distal ends was composed of four small fascicles each having the normal appearances of a motor nerve, with the majority of myelinated fibres of large size and few small myelinated and unmyelinated axons.

Great auricular nerve

A very collagenized piece of tissue with nothing in it resembling a nerve. A small group of cells (not bounded by perineurium) was identified by electron microscopy as mainly Schwann cells, most of which were denervated but with an occasional unmyelinated axon.

CASE 2

PS; a 46-year-old female, first presented in 1988 with borderline tuberculoid leprosy (BT). She had 4–10 hypopigmented and hypoaesthetic, dry macules with raised edges. She had enlarged right ulnar and left lateral popliteal nerves with dry and anaesthetic hands and feet, claw toes and bilateral feet ulcers. Skin smears were negative. She was treated with a course of multibacillary multi drug therapy (MB MDT). She presented again in 1992 with an

18-month history of a right facial palsy. She had a course of steroids, but with no improvement and was referred with a right lagophthalmos with a 6 mm palpebral gap and facial palsy.

In 1994, 4 years after the almost total facial palsy developed, there was minimal eyebrow lift, and minimal platysma function. There was no buccal continence for air and no lower lip continence for liquids.

The patient requested surgical correction of her deformity and consented to lose the minimal platysma activity that she had. This allowed us to include the partially functioning cervical branch of her facial nerve in the planned total facial nerve excisional biopsy. In 1994, her entire facial nerve was excised from mastoid foramen to all the branches distal to the superficial parotid gland. She had a temporalis muscle transfer to reconstruct her eye closure and a static sling for the lower lip palsy. Seventeen months after the surgery she continued to note paraesthesiae in the distribution of the right facial nerve. She had a Tinel sign over the proximal nerve stump.

Facial nerve trunk, temporal, zygomatic, mandibular and cervical branches

These all showed similar appearances. Only in the nerve trunk were there a few inflammatory cells, around epineurial blood vessels. In all nerves there was marked loss of myelinated fibres (Table 1) with densities varying from 1048–2150/mm^2. Some of the remaining fibres were atrophic; there were no regeneration clusters. Electron microscopy (EM) showed many bands of Büngner, i.e. denervated Schwann cell processes indicating earlier myelinated fibre degeneration. The numbers of unmyelinated axons (density 54,646/mm^2) were much greater than in a normal motor nerve (Figure 3) (see Table 1) and many are therefore assumed to be regenerating.

Buccal branch

A nerve made up of seven fascicles; five fascicles had a near normal density of myelinated fibres (Table 1) although with an abnormal fibre size distribution; compared with a control buccal nerve there was a shift to the left, with increased numbers of small fibres but fewer large fibres. Measurement of myelin sheath thickness showed many fibres to have inappropriately thin myelin sheaths, consistent with being regenerated.

EM of a fascicle well populated with myelinated fibres showed an occasional band of Büngner indicating earlier loss of a few myelinated fibres. Many unmyelinated axons were present. In a severely affected fascicle there were many bands of Büngner, and unmyelinated axons were numerous. The area of the parent facial nerve trunk was 0·46 mm^2 and it contained 477 myelinated fibres; the total number of myelinated fibres in all of the branches was 1707 in a total area of 0·62 mm^2; this disparity is discussed later.

CASE 3

MDP, a 64-year-old male, first presented in 1986 with multiple enlarged peripheral nerves, a new total left LMN facial nerve palsy and loss of sensation over the chin and left ear, associated with a fever. He had a swollen and red skin patch over the left mid-face. He had also lost some movement and sensation in his tongue. The tongue and skin sensory changes all reversed but the facial palsy remained. He was noticed to have a single hypoanaesthetic

patch on his back. There were no other cardinal signs of leprosy. A smear was negative and leprosy serology inconclusive. He was considered to be a case of multibacillary borderline tuberculoid leprosy (MB BT) in reversal reaction and treated with MDT for 24 months. His facial palsy recovered well after a course of steroids and he was left with a lagophthalmos and reduced corneal sensation. However, he returned in 1991 with a left facial nerve palsy again and this time it did not respond to steroids.

On examination in 1995, he was noted to have a complete left LMN facial nerve palsy with 6 mm lid gap, small corneal ulcer, previous medial tarsorraphy and normal trigeminal dermatome sensation. Clinically, there was a completely paretic left platysma.

At operation (1995), he had a complete dissection of the facial nerve for excision biopsy and a temporalis muscle transfer for lagophthalmos. The great auricular nerve was also biopsied.

Eight months later, he returned for a facial sling procedure (something that he had refused earlier) and he was noted to have a positive Tinel sign over his left facial nerve stump.

Facial nerve trunk

All four fascicles showed a similar appearance with marked endoneurial oedema causing the fascicular areas to be greatly increased in size (Table 1, compare sizes of branches with those of case 2); endoneurial collagen was not increased. There was marked loss of myelinated nerve fibres; the debris of many quite recently degenerated myelinated fibres still remained. The few myelinated fibres present were very small, occasionally in clusters, and were probably regenerating fibres. Each fascicle was infiltrated by inflammatory cells often grouped around endoneurial blood vessels. The cells were mononuclear (macrophages and lymphocytes), but no foam cells. No organisms were seen. No inflammatory cells were present in the epineurium, and the perineurium appeared normal. Electron microscopy showed bands of Büngner signifying earlier degeneration of myelinated fibres. The density of unmyelinated axons (Table 1) was somewhat greater than that of a normal motor nerve, presumably due to regeneration.

Temporal-frontal, zygomatic, cervical, buccal/mandibular branches

These had appearances generally similar to those of the nerve trunk.

Great auriciular nerve

This nerve consisted of eight fascicles, each with a moderate population (see Table 1) of thinly myelinated fibres, often in clusters and identified as regenerated fibres. EM confirmed the presence of regenerating myelinated fibres. Banding of Schwann cell processes associated with unmyelinated axons suggests loss of some of the 'original' unmyelinated axons. No bacilli were seen in any nerve by light or electron microscopy. A number of plasma-like cells often with a basal lamina, previously described in leprosy,[22] were observed.

Discussion

There is one previous paper in the literature documenting histology of the facial nerve in leprosy.[5] The study was of 11 facial nerves, where 10 had a biopsy of only the most peripheral

branches of non-functioning temporo-zygomatic branches (lagophthalmos), and one biopsy was of a whole, non-functioning facial nerve (F11). The histology was by light microscopy and found evidence of leprosy bacilli in only two of the 11 cases. The findings of fibrosis were severe in the orbicularis oculi nerve endings and less severe in the distal temporo-zygomatic branches. In the one total nerve biopsy, there was a well preserved trunk and proximal nerve with worsening fibrosis into the temporo-zygomatic branch. No acid-fast bacilli were found.

EXTENT OF FACIAL NERVE DAMAGE

There was a generally even distribution of pathology in the various facial nerve branches examined in case 3 (which showed evidence of severe and relatively recent myelinated fibre degeneration), and also in case 2 (with the exception of the buccal branch), with fibre loss at a later stage. These cases do not support the suggestion that the zygomatic branch is selectively involved. It seems likely that nerve fibre degeneration begins more proximally than at the levels examined here. We do not know whether there is more uniform involvement of other facial nerve branches in patients who only have lagophthalamos clinically. Proximal trunk involvement could be the explanation of Ranney's observation[11] of mis-reinnervation of the facial nerve in patients with a severe facial palsy that later recovers to a large extent. These patients have voluntary co-contractions of unrelated facial muscles and co-contractions associated with the reflex act of blinking (blink bursts) in muscles that do not normally contract in the blink reflex. The mechanism of mis-reinnervation could be regenerating axons in the proximal trunk entering the wrong branch at the main bifurcation or collateral sprouting from non-involved axons into adjacent empty myelin sheaths.[23]

The appearance of the buccal nerve is difficult to explain. It is the only nerve in which there are marked differences from one fascicle to another, some having very few, but others having many myelinated fibres. The origin of these myelinated fibres is puzzling, because their numbers are greater than those in the parent nerve trunk which seems to imply that some originate from another source. They do not have the size distribution of a normal motor nerve and are almost certainly regenerated fibres although none are in clusters, usually a recognized feature of regenerating myelinated fibres. Although within the normal range of total fascicular area for the buccal branch,[21] the number of fascicles in the nerve was greater than that seen normally, so the possibility that all fascicles do not derive from the parent facial nerve must be considered. Variations in the anatomy of the facial nerve have been described[24] and this patient may be one of the few (3%) in which the facial nerve has two main trunks, the minor (which may be missed) contributing to the buccal branch.

The cervical nerve appeared normal in case 1 and clinically, platysma function was normal. In case 2 the nerve showed similar marked pathological changes to those seen in its other facial nerve branches, and clinically there was minimal platysma function; the apparent sparing of this nerve[13] is not confirmed.

Palpable or macroscopic thickening of a nerve is an important indicator of nerve involvement in leprosy, but it should be noted that there was no evidence of nerve swelling in the cervical or any other of the affected nerves in case 2. Clearly, the condition of a nerve cannot be judged solely on external appearances.

EVIDENCE OF LEPROSY INFECTION

The absence of any evidence of leprous infection in case 1 and only minimal evidence of

inflammatory cell infiltration in the most proximal nerve examined in case 2 may reflect the late stage of the disease when the biopsies were taken. MDT treatment was begun 16 years ago in case 1 and 4 years ago in case 2. In case 3 the treatment began 9 years ago, but the patient presented with a new facial palsy just 4 years before this biopsy, and inflammatory cells remain, suggesting that this neuropathy is directly caused by leprosy, perhaps associated with a change in the patient's immunological status. No bacilli were seen nor were any identified in any of the nerves from other patients. In none of the cases was there evidence of thickening of the perineurium, a change frequently noted in lepromatous leprosy.[25]

In case 1, the two motor nerves examined showed very different appearances, the temporo-zygomatic nerve being markedly affected while the cervical nerve appeared normal. This would lend some support to Dastur's suggestion of zygomatic nerve involvement originating through the infection of sensory branches of the maxillary nerve. The temporo-zygomatic nerve contained over 600 myelinated fibres, many identified as regenerating. However, axonal atrophy was noted in many of these fibres, a change consistent with eventual loss of the distal target perhaps due to atrophy of the associated muscle (also exemplified in a permanent axotomy model[26]). The total destruction of the great auricular nerve is consistent with a severe leprous lesion.

In all motor nerves in cases 2 and 3 (with the exception of the buccal nerve in case 2) the pathology was generally evenly distributed both throughout the facial nerve branches and between the fascicles of these nerves. If there is any element of compression involved in the pathogenesis of the lesions, it would have to be operating at levels more proximal than those examined in this study.

REGENERATION

The presence of unmyelinated axons in excess of normal in affected motor nerves in cases 1, 2 and 3 was evidence of regeneration; however, there was little further maturation into myelinated fibres and when this occurred only a few, small fibres were seen. This somewhat resembles the appearance of nerves examined in a study of nerve grafts in facial palsy[21] in which large numbers of unmyelinated axons regenerated from a (motor) branch of the facial nerve into a nerve graft which was unconnected at its distal end. Myelinated fibres were few in number and invariably small in size. The appearances in the leprous nerves possibly reflect a similar situation of axons capable of regeneration, but failing to mature into myelinated fibres because of the absence of stimulus provided by a distal target. Presumably in the leprosy patients, there is atrophy of the associated muscles after long-term denervation. In the nerve graft study,[21] examination of grafts after distal connection to a grafted muscle (which became functional a few months later) showed large numbers of regenerated myelinated fibres of considerable size. This demonstrates that the unmyelinated axons have the potential to develop into myelinated fibres once they become functional. In the leprosy patients, it raises the possibility of a free gracilis muscle graft to the face for a patient with a complete irreversible facial palsy, with anastomosis of the gracilis nerve to the proximal facial nerve trunk.

A previous morphological study of facial nerves injured during surgery (and examined before faciohypoglossal anstomosis) showed that although some endoneurial fibrosis had occurred this was not sufficient to prevent regeneration even after facial palsy of up to 7 years duration.[27] In the present study, endoneurial fibrosis was seen at its most extreme with total loss of great auricular nerve architecture in case 1, and to a much milder degree in the

temporo-zygomatic branch of the same patient; however, in other nerves the extent of fibrosis was probably not sufficient to compromise regeneration.

Clinically, a Tinel sign was elicited over biopsy sites in cases 2 and 3, suggesting the presence of regenerating axons in a neuroma.

The situation in sensory (great auricular) nerves is different. In case 1, there was total destruction of the great auricular nerve, an appearance consistent with a severe leprous lesion; in case 3, there was regeneration of myelinated fibres, suggesting successful distal connection with sensory targets presumably in the skin.

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CASE REPORT

Lepromatous lymphadenopathy and concomitant tuberculous axillary lymphadenitis with sinus. A case report

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Summary A 25-year-old male patient with florid lepromatous leprosy presented with right axillary lymphadenopathy and a discharging sinus. He also had scabies with chronic right otitis media. Histopathological examination of the lymph node revealed lepromatous lymphadenitis coexisting with tuberculosis. This unusual combination of two different clinical entities is recorded in this case report.

Introduction

Tuberculosis and leprosy are two different clinical entities but share similarities in morphology of the causative organism. However, coexistence of both diseases in the same patient has been recorded only occasionally. Sharma[1] studied 40 lymph node biopsies of leprosy patients of whom one case showed characteristic features of tuberculous infection. Desikan and Job[2] found tuberculous lymphadenitis in six of 22 autopsied lepromatous cases. Although generalized lymphadenopathy in lepromatous leprosy is a common feature, concomitant tuberculous infection of the same gland is rare. One such case is reported here.

Case report

A 25-year-old male reported with thickened ear lobes and an enlarged right axillary lymph node which had broken down and had been discharging necrotic material for $1\frac{1}{2}$ months. He had also a history of skin rash for 10 days, epistaxes for 1 month and pus discharge from the right ear for 3 months. On examination, the patient had a papular rash all over the body more on the finger webs, the axillae and groins. Ear lobes were thickened and succulent with nodules in the margins. There were partial loss of eyebrows. He had multiple thickened cutaneous nerves with grade one deformity. Cardiovascular, respiratory and gastrointestinal

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systems were clinical normal. Inguinal lymphnodes were enlarged but not tender. The right axillary lymph nodes were enlarged on both sides and matted together (Figure 1a). A discharging sinus arising from the enlarged lymph nodes was seen (Figure 1b). On palpation, the swelling was tender. A clinical diagnosis of lepromatous leprosy with tuberculous axillary

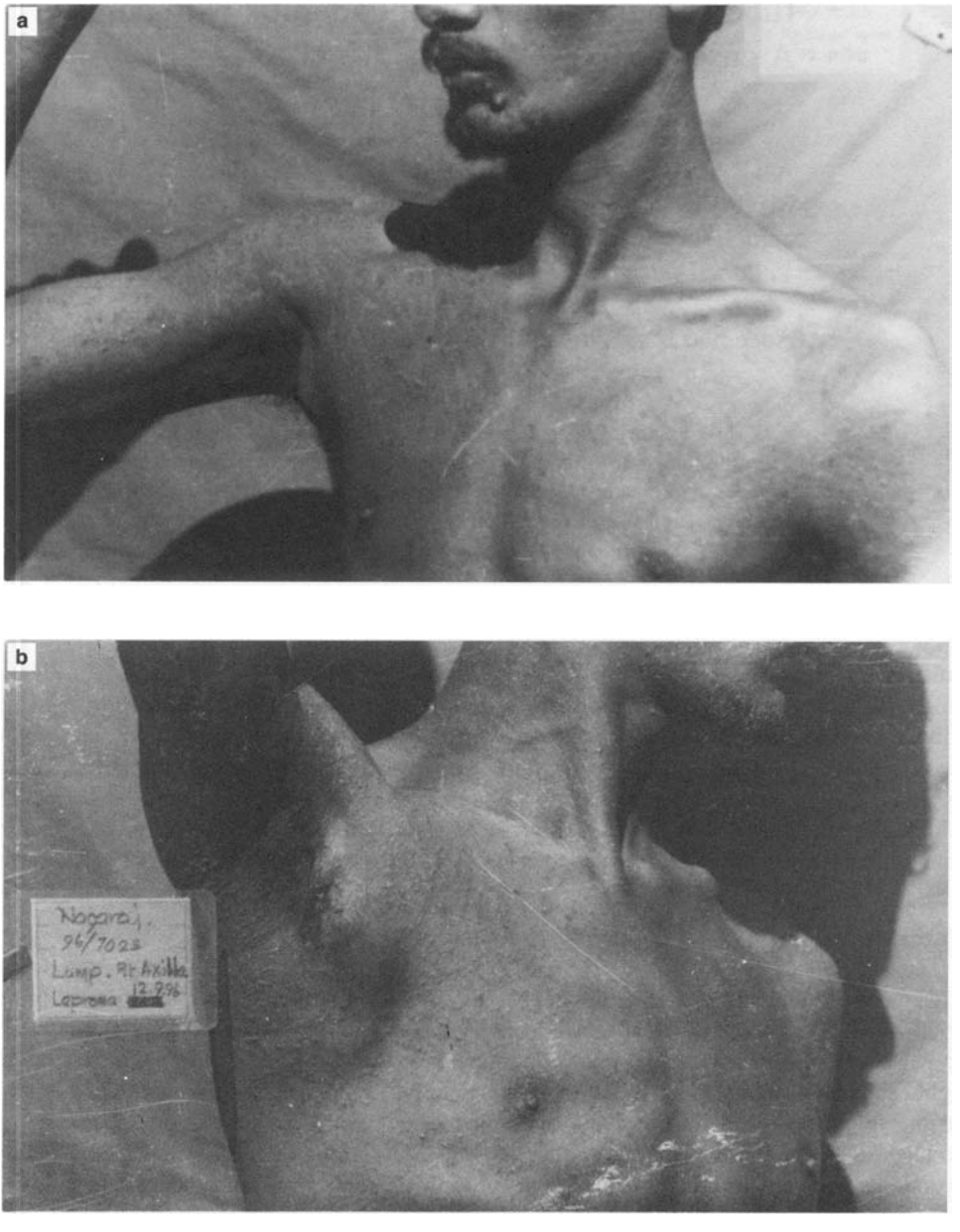

Figure 1. a Clinical photograph showing right axillary lymphadenopathy and thickened ear lob. **b** Clinical photograph showing right axillary lymphadenitis with discharging sinus.

lymphadenitis, scabies and chronic otitis media of the right ear was made and the patient was started on anti-leprosy treatment consisting of rifampicin, clofazimine and dapsone.

Routine blood, urine and stool examinations were normal. Malarial parasite and microfilaria were absent. Chest X-ray was normal. Mantoux test was recorded at 17 mm. Lepromin was negative. ELISA test for HIV infection was negative. Skin smears showed a bacteriological index (BI) of 4·20. Routine culture of the pus obtained from the right ear showed heavy growth of *Morganella morganii* and scanty growth of diphtheroids. The pus from the axillary sinus grew *Staphylococcus aureus*. Ziehl–Neelsen stain failed to show acid fast bacilli (AFB) from pus from the ear and from the axilla. One week of treatment with antibiotics reduced the size of the gland and the pus discharge from the ear. Scabies was treated with benzyl benzoate topical application. Biopsy of the right ear lobe was performed and was fixed in 10% neutral formalin for histopathological examination and for drug sensitivity studies using the mouse foot pad technique. The draining lymph node with the discharging sinus was surgically excised. Cut surface of the nodes showed extensive areas of caseous necrosis. Two months later, another group of matted glands from the same site was excised. A part of the specimen obtained was fixed in 10% neutral formalin and was examined histopathologically. The other portion was processed for mouse foot pad inoculation for the growth of *M. leprae* and for culture in Lowenstein–Jensen (LJ) media for *M. tuberculosis*.

Histopathological examination

SKIN FROM EAR LOBE

The epidermis was atrophic. In the dermis there were focal areas of foamy macrophages. Dermal

Figure 2. Photo-micrograph showing lymph node structure with scattered collections of epithelioid cells and foci of foamy macrophages (H&E ×40).

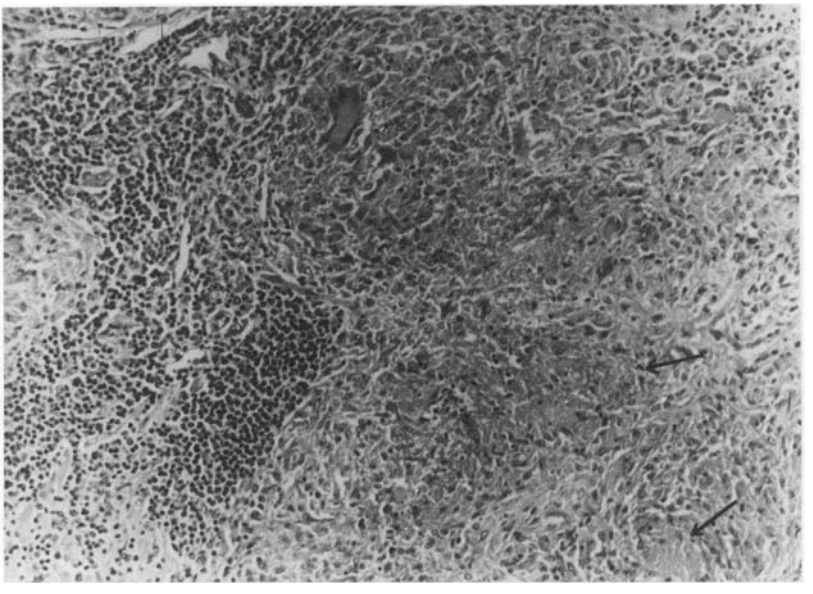

Figure 3. Photo-micrograph showing tuberculoid granuloma composed of epithelioid cells, a Langerhans giant cell and foci of caseous necrosis (H&E ×200).

nerves were surrounded by macrophages. Acid-fast stain showed numerous bacilli inside macrophages and nerves. They were predominantly granular and beaded. A histopathological diagnosis of lepromatous leprosy was made.

Mouse foot pad studies from the skin specimen showed organisms resistant to rifampicin

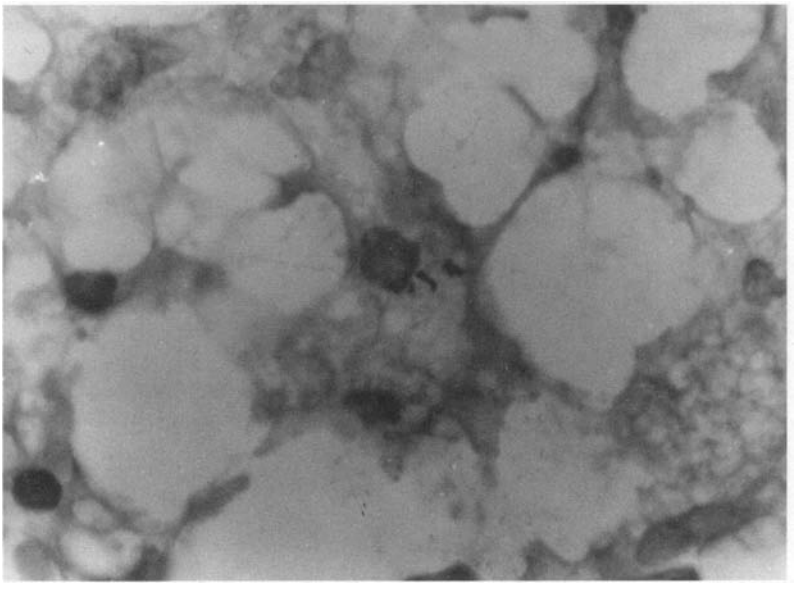

Figure 4. Photo-micrograph showing foam cells containing intracellular acid fast organisms (modified Fite ×1000).

at 0·03% concentration in the diet but sensitive at 0·01% concentration. The Lowenstein–Jensen media did not grow *M. tuberculosis.*

LYMPH NODE

The normal architecture of the lymph node was replaced by many focal and confluent granulomas composed of epithelioid cells surrounded by lymphocytes and Langerhans giant cells. There were extensive areas of caseous necrosis (Figure 3). In addition, there were clumps of foamy macrophages and macrophages with pink granular cytoplasm. These sheets of foamy macrophages were in close association with epithelioid cell granulomas (Figure 2). The capsule of the lymph node was thickened and fibrosed. Acid-fast stain showed clumps of AFB inside foamy macrophages (Figure 4). With the above histological features, a diagnosis of tuberculosis in a lepromatous lymphnode was made.

Discussion

This patient had matted lymph nodes in the right axilla which on histological examination showed epithelioid cell granulomas with caseous necrosis. There was also a sinus draining pus and necrotic material in the axilla. The histological diagnosis of tuberculosis lymphadenitis was based on these findings. In addition, in the same lymph node there were sheets of foamy macrophages packed with AFB. With the history and clinical picture of lepromatous leprosy, and the lymph node showing sheets of foamy macrophages packed with AFB, a diagnosis of lepromatous lymphadenitis was made. It is possible that the *M. tuberculosis* was not grown in LJ media, as the patient had already had rifampicin therapy for a period of 3 months as anti-leprosy treatment, when the lymph node biopsy was done. The patient also had chronic otitis media and scabies.

Lepromatous leprosy in association with pulmonary tuberculosis has been reported earlier.[2,4] In an autopsy study it had been shown that tuberculosis is the common case of death in leprosy patients.[3] In addition, tuberculosis of the hip joint,[5] skin,[6] carpal bones of the hand[7] and larynx[8] have been over-recorded in the literature. In clinical practice, unless careful history, clinical examination and necessary investigations are carried out in every patient, associated diseases can be easily missed. Leprosy workers should adopt an holistic multi-disciplinary approach in treating tropical disease[9] and concomitant diseases like tuberculosis should always be borne in mind and alternative treatment strategies, where appropriate, should be co-opted.

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FURTHER EDUCATION

Surgery of less common conditions in leprosy

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Introduction

The uncommon conditions in leprosy requiring surgical correction are either the direct result of the disease or secondary to nerve paralysis. They usually occur in the later stages of leprosy and are uncommon today, thanks to early treatment of leprosy by multidrug therapy (MDT). However, in areas where treatment has only started recently, there is a backlog of such deformities needing correction. These conditions are:

Primary deformities: these are directly due to the disease.

1. On the face: megalobules, nasal perforation, depression of nose, and loss of eyebrows.
2. In the extremities: contractures of fingers and toes.

Secondary deformities: these are usually secondary to trunk nerve paralysis.

1. Lagopthalmos.
2. Facial paralysis.
3. Wrist-drop.
4. Triple paralysis of the hand.
5. Neuro-arthropathies (e.g. carpal disintegration in the wrist and tarsal disintegration in the foot).
6. Gynaecomastia is secondary to involvement of the testis.

All these are disabling conditions that may not occur if early treatment of leprosy is instituted and many of them can be reversed by proper treatment. Early and effective institution of MDT is the best way of prevention of these deformities.

How are these caused?

PRIMARY DEFORMITIES

These occur by direct involvement of the soft tissues, particularly the skin and the mucosa, by

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leprosy granuloma. Resolution of the granuloma in the skin leads to loss of collagen substrate. The skin becomes lax, causing facial wrinkles and elongation of the ear lobules. The integumental structures such as hair follicles and sweat glands are also destroyed in this process. Loss of eyebrows is one result. Perforation of the nose and depression of nose is due to the loss of the inner lining, loss of the nasal cartilage and secondary infection. Direct involvement of the skin and later of other soft tissues in reactional states of lepromatous leprosy results in severe contractures of the fingers and toes.

SECONDARY DEFORMITIES

These are secondary to involvement of a specific organ or area. Lepromatous infiltration of the testis causes testicular atrophy. The resulting excess of female hormones may lead to gynaecomastia, i.e. enlargement of the breast seen in male leprosy patients. Uncommon trunk nerve involvement, e.g. of the facial nerve outside the skull, of the radial nerve in the arm or forearm, median nerve near the elbow, or of all the three nerves innervating the hand, leads to the corresponding paralytic deformities. Involvement of the nerves supplying the joints of the hand or the foot leads to neurotrophic arthropathies.

Prevention

Prevention is by early treatment of leprosy and appropriate action in the early stages of the deformity. Treatment must begin before the soft tissue changes set in. During reactions, the affected parts should be kept clean, aseptic and at rest. The nose is kept clean by saline washes and this also prevents secondary infection. The affected hands, fingers and feet and toes are appropriately splinted in their correct positions, to prevent contractures and external injury. Anti-inflammatory and immunosuppressive drugs and drugs providing symptomatic relief can prevent many of these deformities.

Though these conditions are uncommon, for an individual patient they are of immense importance, being disabling and ugly. Thus, every medical or paramedical person working in leprosy should know of these conditions, that these can be treated surgically and where and when to refer them for surgery. With the exception of lagopthalmos, which if not urgently treated may lead to damage to the eye and even blindness, all other conditions are surgically treated after the reactions subside and the disease is well controlled.

Early diagnosis and MDT has reduced the occurrence of deformities, especially in the lepromatous spectrum.

Deformities can occur:

1. Following resolution of the lepromatous granulomata.
2. Due to loss of hair follicles and laxity of skin resulting from loss of elastic and collagen tissue.
3. Secondary to involvement of the nerves.
4. Due to the loss of testicular function following leprous involvement.

Though these deformities are uncommon, for the patient they are a cause of social isolation and their surgical correction is of immense importance.

Surgical treatment

The treatment of all these conditions is through well-established methods of plastic and reconstructive surgery.

Surgery for the depressed nose

1 Before the development of the saddle nose, there is a period when infiltration of nasal mucosa by *Mycobacterium leprae* leads to nasal stuffiness, congestion and discharge. As the disease progresses, there is ulceration of the inner nasal lining that may lead to perforation or external nasal fistula.
2 The cartilaginous part of the nasal septum receives its nourishment from this lining. Repeated nasal ulceration leads to destruction of the septal cartilage and ultimate collapse of the nasal bridge, leading to the deformity. The loss of nasal spine of the maxilla inferiorly also contributes to the deformity. The process of ulceration can be arrested in the earlier stages by health care and medication. Established deformity can be effectively corrected by reconstructive surgery.
3 The causation of the deformity can be easily understood if the nose is likened to a single pole tent with the nasal septum as the central support and skin and the mucoperiosteum as outer and inner linings, respectively.

Surgical reconstruction of the nose requires understanding of three important factors in the causation of the deformity.

1. Except in those cases of external nasal fistula, there is no loss of the external skin of the nose; it simply telescopes in and becomes tethered to the underlying bone.
2. There is loss of internal lining of the nose (mucoperiosteum) due to repeated ulceration, leading to contracture and scarring.
3. There is loss of cartilaginous central nasal support. It must be reconstructed with the help of a bone graft or a synthetic support. Thus in any reconstruction, dissection of the tethered skin, providing adequate internal lining of skin and providing internal support are important prerequisites for a good result (Figure 1).

Development of saddle nose is a slow process and is totally preventable in the early stages. Integrity of the nose depends on the cartilaginous central support and the inner lining and outer skin. If either is damaged, the nose is deformed.

Reconstruction is based on:

1 Providing a central support, usually by a bone graft or a prosthesis and,
2 Restoring the internal lining by skin grafting.

The post-nasal inlay operation provides complete nasal cosmetic restoration.

Surgery for lagopthalmos

The condition is due to involvement of the facial nerve and subsequent paralysis of the muscles supplying the eyelids. The usual signs and symptoms are:

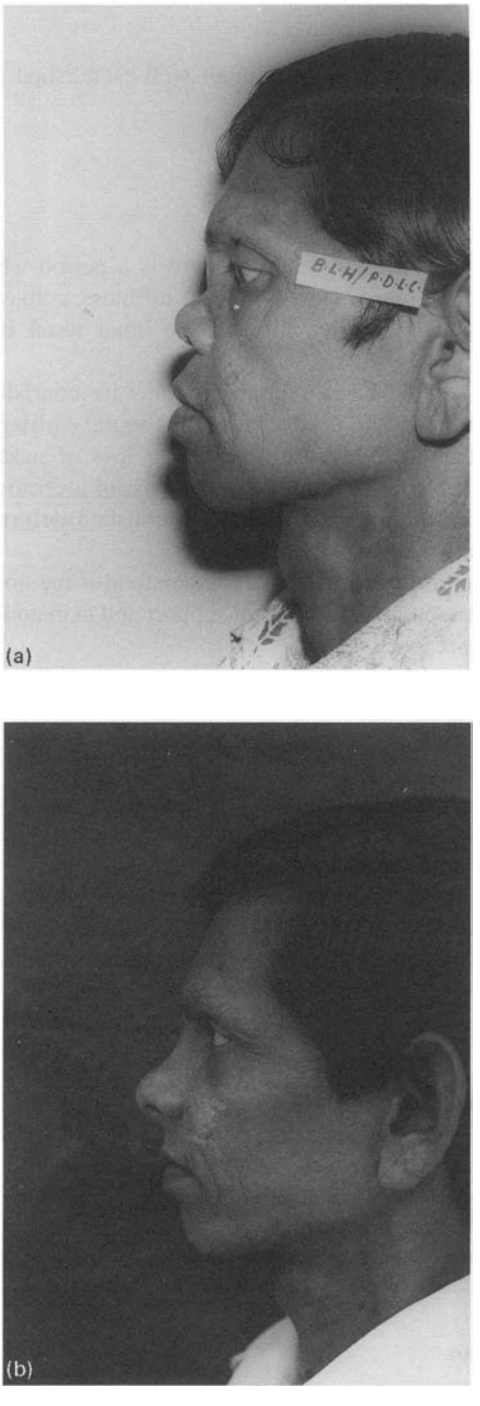

Figure 1. Facial appearance (a) before and (b) after correction of nasal deformity.

1. Inability to close the eye fully voluntarily; there is an appreciable gap on tight voluntary closure.
2. The eye remains half-open during sleep.
3. There is watering and dryness of the eyes.
4. The eye looks bigger than the other eye

Prevention is by detecting early onset of paralysis of the ocular muscles. The patient complains of excessive watering of the eyes and notices a sluggish response of eyelid closure to any external stimulus. Appropriate measures instituted early can prevent this deformity. These consist of medication to reduce the nerve inflammation and oedema, supportive vitamins for nerve recovery, physical exercises and electrical stimulation. Dark glasses are given to protect the eyes from exposure keratitis and subsequent blindness and tear substitutes to prevent dryness.

INDICATIONS FOR SURGERY

After 6 months, if attempts at treatment fail, surgical intervention is mandatory. In an established case, absence of any protective measures to protect the anaesthetic eye warrants surgery on an emergency basis.

The common procedures are tarsorrhaphy and temporalis transfer.

Passive permanent reduction of palpebral fissure by medial or lateral tarsorraphy is one solution. This is a static procedure, a simple operation that can be learnt by an inexperienced surgeon.

Active eyelid closure with the help of a temporalis muscle sling operation is a dynamic procedure. The Gillie's operation and its Johnson's variation are the two common methods. In the latter, instead of temporalis fascia, a free graft of fascia lata or palmaris longus is used to extend a partially detached tendon of the temporalis muscle. Postoperative care, especially only soft food for 3 weeks and training for integration of the transfer, is essential for achieving a good result (Figure 2).

Paralysis of the eyelids is a slow process and responds very well to the conservative line of treatment, if diagnosed early.

Surgical correction of lagopthalmos is mandatory to protect the eye from danger of repeated keratitis and consequent total blindness.

A simple static procedure like tarsorraphy can be done by any qualified eye surgeon. The temporalis sling operation, a dynamic procedure for the closure of the eyelids, requires a trained reconstructive surgeon.

Loss of eyebrows, sagging of facial skin and megalolobule

SURGICAL CORRECTION OF LOSS OF EYEBROWS

This is done by using one of the following three methods: a direct free graft from behind the ear or scalp, a temporal artery flap, and direct hair implantation, e.g. by multiple punch grafts. All methods can yield excellent result. Care must be taken regarding the patient's preference and aesthetics (Figure 3).

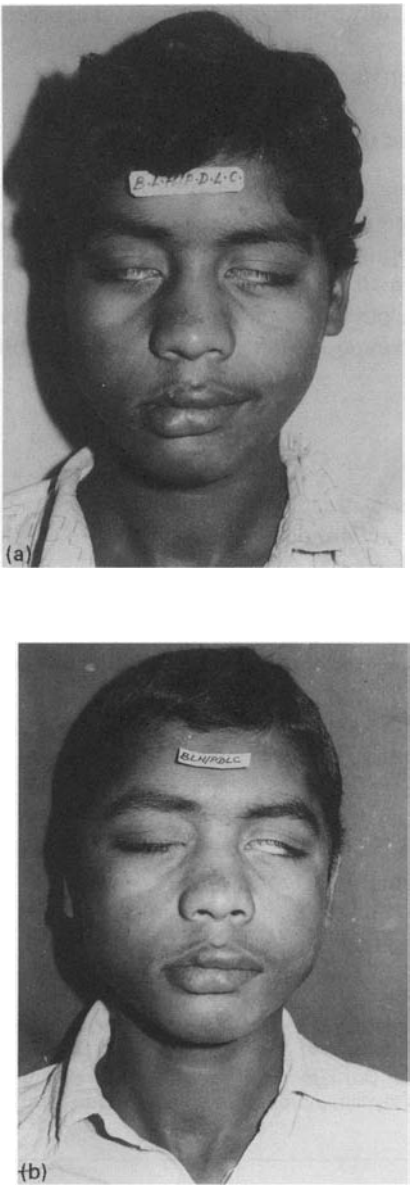

Figure 2. (a) Pre- and (b) postoperative appearance after a temporalis transfer operation using the Johnson method.

FACE-LIFT OPERATIONS

The facial skin is sometimes affected in lepromatous leprosy by the disease process. Atrophy of tissues subsequent to granulomatous infiltration causes sagging of skin. Though the deformity does not cause any functional loss, the patient's appearance prevents them being

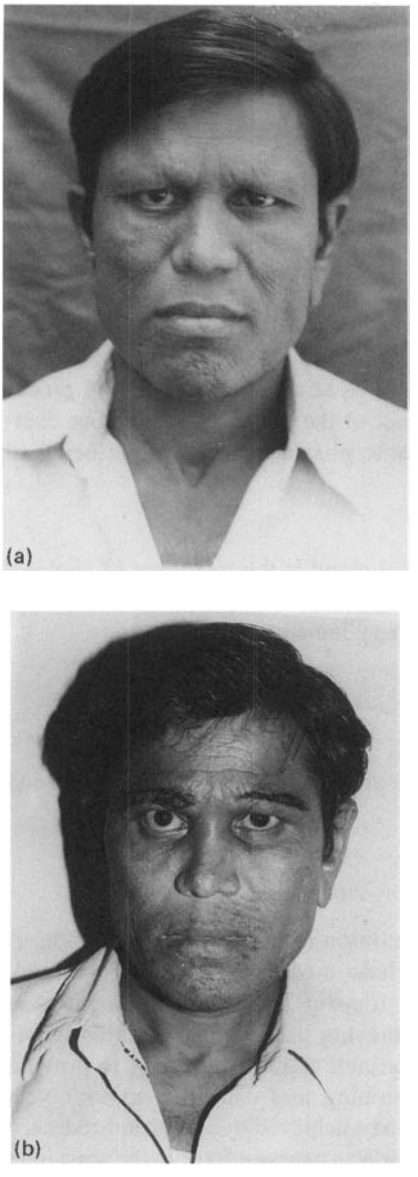

Figure 3. Surgical correction of loss of eyebrows. (a) Before and (b) after surgery.

accepted in society. Thus facial reconstruction is of prime importance and is the first step in the rehabilitation process in these patients.

When the disease is active, granulomatous infiltration causes distension of the skin and destruction of the collagen infrastructure, which is responsible for the toughness of the skin and its elasticity. Resolution of the granulomata with effective drug therapy leaves loose sagging skin without collagen support, and the patient's facial skin is furrowed with lax skin

folds. Thus there is redundant facial skin mainly around the nose, chin and in the upper neck, and also in the posterior part of the face. Surgery aims at excision of the redundant skin and re-tensioning the skin so as to remove the wrinkling. This is done through careful skin incisions, which are hidden and planned in the hairline, and great care is taken to preserve and not to damage the delicate facial nerve branches supplying the facial muscles. When there is total involvement of skin, a classical face-lift operation is required. More commonly, anterior or circumoral face-lift is sufficient.

MEGALOLOBULE

The process that disfigures the face is responsible for the deformity of the ears. The skin of the pinna and the lobule becomes lax. Excision of the redundant skin and trimming followed by refashioning is required and is a straightforward simple procedure. The skin incisions are placed on the posterior aspect of the pinna, thus avoiding over- or under-correction. These operations enable the patient to mix in society without being stigmatized.

GYNAECOMASTIA

Excision of the hypertrophied gland is the treatment of choice. This can be done in smaller glands by a circumareolar cosmetic incision, which leaves little scar. Larger glands are excised through a submammary incision.

Nerve lesions

Appropriate tendon transfers are used to treat the paralytic conditions. Only the triple nerve paralysis is described here.

TRIPLE NERVE PARALYSIS OF THE HAND

This extremely disabling condition is fortunately uncommon. Almost all the muscles in the forearm are affected. Only those muscles supplied by the median nerve in the forearm are spared, and can be used for transfer. With very few options remaining for reconstruction, priority is now more on achieving a functionally stable wrist first, then to provide finger extension, to provide an opposable thumb and lastly, to provide claw finger correction. The whole process is time consuming and can take up to 1 year, but the results are fairly satisfactory. Wrist stability can be achieved by a wrist arthrodesis in 15–20 degrees dorsiflexion, or by a tendon transfer to provide an extensor force at the wrist joint, usually done by transferring the pronator teres muscle. Reconstitution of finger extensors is done by transferring flexor carpi radialis. Opponens replacement is accomplished by transferring the ring finger superficial to the short abductor insertion on the thumb. Claw finger correction is done either by a superficial flexor transfer or by capsulorraphy of the maetacarpo-phalangeal joints.

Neuroarthopathy

Involvement of the nerve supply of joints together with minor injuries causes this condition and is more common in the feet, involving the mid-tarsal joints. The treatment is by rest and

the use of a special orthotic device as such as patellar tendon bearing orthosis, which must be used for a long period before stabilization occurs. In some cases, operations for correction of deformity and stabilization are required. These must be followed by appropriate orthotic devices to prevent direct weight bearing on these joints.

Claw toes

This condition, though not uncommon, is commonly neglected and hence is mentioned here. Claw toes are due to paralysis of the intrinsic muscles of the foot. This is the result of the involvement of the posterior tibial nerve or its branches and causes the hyperextension of the toes at the metacarpophalangeal joint and flexion at the interphalangeal joint. This leads to excessive pressures on the tips of the toes while walking and metacarpophalangeal joint hyperextension, which exposes the metatarsal head to the shearing forces leading to ulceration. Its treatment can significantly reduce the incidence of plantar ulceration under the metatarsal heads. Correction is by transfer of the toe flexors to the extensors. In this operation, the flexor digitorum longus tendon of each toe is detached from its insertion, brought out onto the dorsum of the toe, and sutured to the extensor expansion. The foot is immobilized for 3 weeks, after which the patient is prescribed MCR footwear.

It should be emphasized again that all these conditions, though uncommon, are still found even in areas where leprosy has a low prevalence. For the patient, the correction of these deformities is of major importance. Patients should have access to facilities where these corrections can be done.

Acknowledgement

The photographs in this article are of patients operated on in the Dr Bandorawalla Leprosy Hospital, Khondwa, Pune, India.

Lepr Rev (1999) **70,** 360

Your questions answered

In response to feedback from our subscribers, we are introducing a new section in Leprosy Review *in which questions on leprosy-related problems will be answered by experts in the field. This first question is answered by Dr Patricia Rose.*

Question: A man attended our rural leprosy clinic 10 months ago with swollen ear lobes and the nodular lesions of lepromatous leprosy. Nerve trunks were enlarged but not tender; slit skin smears were positive. The patient was started on MB MDT and for the first 4 months of treatment progress was uneventful with steady improvement in his clinical condition. The patient then began to experience severe ENL with painful nerves and typical skin rash. We tried to control the ENL by adding 40 mg prednisolone daily to his MDT and reducing by 5 mg a fortnight. Although the initial response was satisfactory, it proved impossible to reduce the dosage of prednisolone below 25 mg daily without a recurrence of ENL. Nothing but a return to a higher dosage of prednisolone relieved the patient's nerve pain. At the moment, our patient seems to be trapped on a see-saw, rocking in and out of ENL every few months, according to the prednisolone dosage. The ENL is becoming increasingly difficult to control and we are afraid that our patient is liable to both nerve damage and steroid side-effects. What can we do to ensure control of the ENL without incurring steroid damage or fixation?

Answer: ENL is best regarded as an illness spanning 4 or 5 years with the potential to cause severe nerve damage. Unfortunately, prednisolone, though relieving nerve pain, does not cure the illness and if given continuously is associated with a plethora of dangerous side-effects. The most useful drug at present available for field use is clofazamine but because this takes about 10 days to be effective, it is useful to give prednisolone at the same time for a short course, reducing the dosage by 10 mg a fortnight from 40 mg daily. Clofazamine is maintained at 300 mg daily until prednisolone has been withdrawn and the patient has been free of ENL for a month while on clofazamine alone (with MDT but without steroids). Only then can the clofazamine be reduced by 100 mg a month, provided always that the patient remains free of ENL. It is important that the patient understands that ENL is a long-standing illness and that attacks will undoubtedly recur but that, with adequate and prompt treatment, the severity of the illness can be controlled and attacks will become less frequent and less severe with time. It is also important to check regularly for nerve damage and to ensure that the patient knows how to contact the programme out of clinic hours so that treatment of ENL can be initiated as soon as an attack occurs. The patient should not have to wait for a clinic day in order to receive treatment.

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Lepr Rev (1999) **70,** 361–369

Letters to the Editor

Are there 'ghost' leprosy patients in Nigeria? An audit of the point prevalence of leprosy at 30 September 1996 in seven States

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Accepted for publication 5 July 1999

How much do statistical reports of national leprosy control programs reflect the actual number of leprosy patients registered in clinics? An audit of the point prevalence at the end of September 1996 in seven States of Nigeria revealed that up to two out of every five reported cases did not exist. The proportions of 'ghost' cases in the individual States suggest that the level of over-reporting of prevalence statistics by leprosy control programs could be very high and could have significant economic concerns.

The registered prevalence of 14,309 cases reported by the World Health Organization (WHO) for Nigeria is 2% of the total global prevalence of leprosy.[1,2] The global figures of leprosy prevalence come from national statistical reports, which in turn are products of reports submitted by sub-national levels of the national leprosy control programme using standardized health information systems.[3]

A situational analysis of the leprosy control programs in seven States of Nigeria in April 1996 suggested a possible over-reporting by programme managers at the State or regional level of the national programme.[4] A prevalence audit was then done at the end of the third quarter of 1996 to verify the actual prevalence and determine the level of discrepancy between the reported and the actual registered figures. The States audited included Akwa Ibom in the southeast; Kwara, Kogi and Abuja (FCT) in the middle belt; and Niger, Kebbi and Sokoto in the northwest.

The audit was a descriptive cross-sectional review of records of all leprosy clinics in the seven States at the end of September 1996. Individual patient charts and clinic registers were examined, using a structured checklist to collect data on clinical and personal variables of registered patients.

The actual numbers of patients registered in the clinics and the exact numbers of doses of MDT (multidrug therapy) received by the end of September 1996 were counted directly from the registers before they were confirmed from the individual patient charts. Only the data of patients still on MDT were recorded in the checklists. In the analysis, the figures from all clinics in each State were summed up to determine the actual prevalence of leprosy in each State. The actual prevalence figures in each State were then compared with the figures reported in the quarterly statistical reports for the end of the third quarter of 1996.

The audit exercise reviewed 321 clinics in the seven States. There was a mean of seven patients per clinic (one PB and six MB), and a mode of zero to four patients per clinic. There was an actual total of 2276 (PB 358, MB 1918) patients at the end of September (prevalence rate, 1.3 per 10,000 population) in the seven States. Compared with the reported prevalence of 3586 (PB 950, MB 2636) cases (2.0 per 10,000), there was a total discrepancy of 1310 cases. In all, 592 (45.2%) and 718 (54.8%) of the discrepant cases were PB and MB, respectively. Out of the total reported for each classification, the discrepant cases were 62.3% and 27.2% for the total PB and MB cases, respectively. The observed differences between actual and reported prevalence figures in the seven States were statistically significant ($P < 0.05$).

The total 1310 discrepant cases actually include 1411 non-existent but reported cases and 101 unreported cases. The unreported cases were in only one project. The 1411 cases (39.3%) of the total reported prevalence were therefore the 'ghost cases' not found in the clinic registers but reported in the statistical reports of the projects. The range of proportions of 'ghost cases' in individual states was from 20.6% to 67.8%.

Reporting of 'ghosts' is common in Nigerian media.[5,6] A Local Government Council found in a staff audit in 1998 that 33% of the 1800 workers on its pay-roll did not exist and subsequently reduced its council's salary bill by 28%.[6] 'Ghost' leprosy patients are a similar phenomenon. Although the usual problem in reporting of disease occurrence is under-reporting,[7] the possibility of 'artifacts' in reports of leprosy prevalence has been mentioned in some texts.[8]

The discrepancies found by this leprosy prevalence audit confirm that reported statistics do not always agree with the actual registered figures. PB cases are more likely to be over-reported than MB. The proportions of 'ghost' cases in the individual States suggest that the level of statistical over-reporting in the national leprosy control programme as a whole could be high.

The significant over-reporting as proved by this audit is a cause for concern. It confirms that the actual prevalence figure for the whole country could be much less than is reported by the national authorities and WHO. The main concern in over-reporting which could be a purposeful act by leprosy supervisors and managers who prepare reports from clinic records is economic, particularly its likely effect on allocation of programme resources. It could easily lead to over-allocation of resources that are based on the number of patients in the clinics, e.g. MDT drugs. So, planning at national and global levels usually based on district and regional statistical reports[3,8] are flawed where fictitious reporting is practised. Therefore, routine audit of clinic records and actual case reviews could make an immense positive contribution to the global effort towards achieving elimination of leprosy by the year 2000.

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EXTRA DEPTH SHOES MADE ON SPECIAL LAST

Editor,

A Letter to the Editor in *Leprosy Review*[1] highlighted the use of deepened canvas footwear. This aroused our interest to place an order for a similar type of shoes with one of the shoe manufacturing company in China. The first consignment of 100 pairs of deep canvas boots received was used amongst patients from September 1991. Proving to be protective and comfortable, they earned a good reputation. Due to difficulties in the procurement of deepened canvas shoes, a special wooden last was designed so that similar types of shoes could be made. Since early 1992, we have been regularly using shoes made on the specially designed last, for patients with badly deformed feet who need special footwear.

Indications for use

1. A severely distorted foot, with loss of bone, padding, skin or balance.
2. Disparate feet which cannot be fitted with sandals or other kind of ready-made shoe.
3. Unmatched foot length—to give matching shoes to avoid stigma.
4. Other conditions: this type of shoe is also used to improve or correct walking pattern (gait) by using different types of orthosis for realignment of the foot and leg.

Advantages

The use of this new technique saves plaster of Paris (POP) work, and a cost equivalent to NRs 300/- (5 US dollars) per pair, and consumes 50% less time. Different foot orthoses can be incorporated, removed, replaced or adjusted at any time. The shoe has increased acceptability due to its attractive commercial design. Matching shoes for badly deformed feet are a help to avoid stigma. The wooden shoe last can be used again and again, for ages. Ready-made shoes can be made available for issue in the hospital or field. Leather shoes are also strong, firm, and appropriate for hilly or cold countries like Nepal and Bhutan.

Disadvantages

The shoes are more expensive than canvas ones. Frequent care of footwear is required. Deterioration of leather may cause ulceration of skin. Such shoes are not available elsewhere, so the patient incurs expense travelling to the hospital for replacements. If the stock of ready made footwear runs out, then a replacement is not possible immediately. This type of shoe is not suitable for field work during the monsoon.

Production

The wooden shoe last is made by a local carpenter by adding 10 mm thickness underneath (Figure 1). Below the line, 10 mm extra space has been added to give the room for thick microcellular rubber (shown underneath) inside.

The six lasts used are numbers 3–8 (i.e. normal Nepali shoes sizes). The technique of making the shoe is similar to making an ordinary shoe, except for leaving 1·5 cm on the upper leather side to meet the extra depth of the wooden last. When the shoe is ready, it looks perfectly normal and gives enough

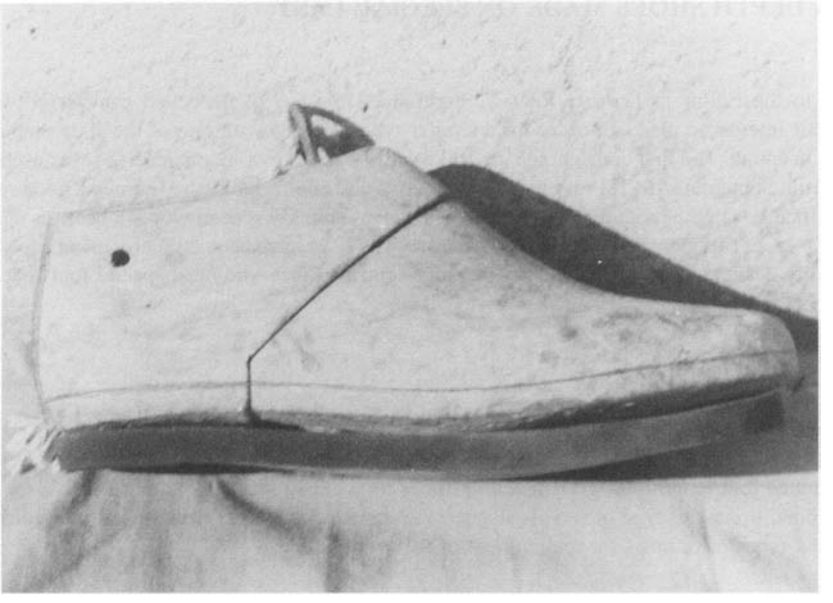

Figure 1. Extra space is provided for microcellular rubber interior.

room inside (Figures 2 and 3) to accommodate the desired foot orthosis. If additional build-up is desired to reduce pressure on certain areas, the last can be temporarily built up (with a piece of cork or rubber or leather, which is later removed when unwanted), without jeopardizing the original shape of the last.

Over 200 pairs of shoes have been produced and used for patients since 1992, as an alternative to the conventional moulded boot made on a POP cast. This technique proved to provide sufficient space to

Figure 2. Appearance of finished shoe.

Figure 3. Provision of different foot orthoses.

accommodate various foot orthoses into the shoe to create a comfortable environment for the foot. Perfectly normal-looking shapes and attractive designs of the shoes have increased their acceptability amongst users, and encouraged them to build up a positive attitude which helps to give mental as well as physical protection to the patient. Relatively speaking, the shoe is cheap to produce.

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USE OF PREDNISOLONE BLISTER PACKS IN THE FIELD

Editor,

The leprosy control programme of the All Africa Leprosy, Tuberculosis & Rehabilitation Training Centre (ALERT) has been treating leprosy reactions with corticosteroids at the field level for over 10 years. Over 150 cases of leprosy reactions (both type 1 and type 2) are diagnosed and receive treatment every year. We have tried to improve the ways in which steroids are given out and monitored.[1]

During this time, prednisolone tablets of 5 mg have been used. Although our 70 field staff are well trained and experienced, handling the loose tablets is time consuming and miscalculations have been observed on occasions. It is unknown how often the patients made errors in taking the tablets at home.

Blister strips have been used for many years for oral contraceptive pills and for multiple drug therapy (MDT) in leprosy; they are beginning to be used for the treatment of tuberculosis in some programmes.[2] It has generally been difficult, however, to demonstrate any direct medical benefits from their use, for example, increased patient compliance; the reasons for their introduction have mainly been operational and logistic, rather than therapeutic.[3,4] Recently, improved patient compliance and other operational benefits have been demonstrated using blister-packs for the treatment of malaria in South-East Asia.[5]

In 1998 with the help of the Netherlands Leprosy Relief (NLR), prednisolone blister strips were provided for use in the ALERT field programme. Each blister strip has 14 tablets of the same strength, but different blister strips have different strength tablets according to a colour code; the patient always takes one tablet a day, but the dose decreases according to a fixed schedule.

We have interviewed most of our leprosy field workers and some patients, and the following advantages were mentioned:

- Easy handling of the drug both by the health workers and the patients.
- Patients find it easy to follow the instructions and remember the daily dose.
- Tapering of the dose is easy; the blister strips are marked with different colours to indicate the dose and it is simple for the patients to shift from one dose to the next. Patients from further away need not come to the health unit for instruction to reduce the dose every 2 weeks.
- Easy monitoring of the utilization of the drugs by the patient. Patients are requested to come back with each empty pack.
- The loose tablets were sometimes damaged after dispensing, but this complaint is rare with the blister packs.
- Expiry dates are easily checked.

The Ethiopian National Guidelines indicate that for paucibacillary cases, the dose is reduced every 2 weeks through the following doses: 40 mg, 30 mg, 20 mg, 15 mg, 10 mg and 5 mg. The course lasts for 12 weeks and corresponds to one box of six blister strips. For multibacillary cases each stage lasts for 28 days, so that two blister strips of each strength are needed. This caused some confusion initially.

While the cost of the blister strips is slightly more than the loose drugs, the advantages mentioned above are considered to be well worth it. On the other hand, the blister packs could be further improved by adding a calendar on the back of the strip, which would serve as a reminder for the patients, as found on the blister packs of MDT.

The ALERT leprosy programme is in the process of being integrated into the basic health services. This entails the management of reaction cases by less experienced general health staff and it is anticipated that the blister strips will make it easier for them to do this correctly.

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MULTIDRUG THERAPY: REPLY TO LETTERS

Editor,

Exactly 1 year after publication of my Editorial, 'Why multidrug therapy for multibacillary leprosy can be shortened to 12 months,[1] in *Leprosy Review*, two 'Letters to the Editor'[2,3] related to my Editorial appeared in the June 1999 issue. I would like to reply to these letters.

It is correct that, as Mr Lynch[2] has pointed out, an article of which I was a co-author proposed prolonging the duration of MDT for those MB patients who had an average BI $\geq$ 4·0 before MDT.[4] This proposal was based on our observation that the risk of relapse was closely correlated with the bacterial load of the patient, and was significantly greater among patients with BI $\geq$ 4·0 before MDT or $\geq$ 3·0 at the end of MDT.[4] The proposal was logical, but we knew that it was not feasible. On the other hand, Mr Lynch completely ignored our alternative proposal, which was also presented in the same article. We concluded that, from an operational point of view, it is not necessary to introduce a lengthy duration of MDT for a small number of special cases;[4] we thought that MB patients with an initial average BI $\geq$ 4·0 are relatively few, that, in the great majority of relapses, the patients' organisms would remain susceptible to rifampicin and clofazimine, and that tremendous efforts to upgrade the quality of skin-smear services for detecting patients with a BI $\geq$ 4·0, would be required. For these reasons, my colleagues and I did not recommend prolonged duration of MDT for patients with an initial high BI in an article[5] published separately.

Although I continue to believe that the potential risk of relapse is higher among patients with an initial BI $\geq$ 4·0, I have no reason to challenge the low relapse rates reported by control programmes.[6] In fact, we attributed the low relapse rates to the small proportion of patients with BI $\geq$ 4·0 in the field.[4]

With respect to the WHO/CTD/LEP/94.1 document,[6] because the average duration of follow-up was relatively short at the time this document was published in 1994, it was, of course, necessary to emphasize the need to interpret the findings with 'great caution'.[4] However, by the time I prepared my Editorial 4 years later, no significant increase in the relapse rate had been observed. Was it not then reasonable to quote the document as one of the references demonstrating a low relapse rate from routine control programmes?

Various adjectives, e.g. 'relatively few',[4,5] 'rare'[7] and 'relatively scarce',[1] have been employed to emphasize the fact that patients with a high initial average BI are few. Both Mr Lynch and Dr Van Brakel disagreed with this assessment. Mr Lynch[2] stated that, among the MB cases registered in the Dhanusha District, almost 10% had a BI $\geq$ 4·0. However, there is a difference between registered cases and previously untreated cases. If he were to demonstrate that 10% of the newly detected and previously untreated MB cases in the Dhanusha District have an average BI $\geq$ 4·0, I would certainly agree with Mr Lynch that such a frequency is not 'relatively scarce' or 'rare'; in this case, the adjective 'relatively few' appears more appropriate.

Dr Van Brakel also stated[3] that high smear positive (HSP) patients are not rare, but his definition of high smear positivity is > 3 +, a value approximately 10% of our cut-off point, $\geq$4·0. It is not possible to compare the numbers of patients at risk employing two so different criteria.

Because of the lack of evidence showing that 12 months of MDT is as efficacious as the standard

24-month regimen for HSP MB cases, Dr Van Brakel considered that it is unethical to treat such patients with the shortened regimen, and proposed to continue treating all MB patients with the 24-month regimen.[3] Many of us heard the same criticism when MDT was first introduced in the early 1980s, and again, when the fixed duration, 24-month regimen was recommended in the early 1990s.

I am pleased to learn that our report of the correlation between high relapse rate and high initial BI of patients[4] caught the attention of Mr Lynch and Dr Van Brakel and their colleagues in Nepal, and was a source of concern to them. However, if our observation was valid, even the 24-month regimen may be too short to prevent relapse among MB patients with high initial BI;[4] should this be the case, is it 'ethical' to propose continuing the 24-month regimen for all MB patients? I am disappointed that, 4 years after it was reported, the correlation between relapse rate and bacterial load has yet to be confirmed or denied by other investigators. Because they are dealing with a significant number of MB patients with high initial BI, both Mr Lynch and Dr Van Brakel could provide valuable information regarding this issue.

Shortened MDT regimen may be associated with higher relapse rate, and one of the objectives of chemotherapy research is to identify the shortened possible duration of treatment without significantly compromising its efficacy. After the publication of the Seventh Report[7] of the WHO Expert Committee on Leprosy, in terms of duration of treatment, there are two alternative regimens for MB patients, either 12 or 24 months. For individual national leprosy programme, the final choice of the regimen is the responsibility of the national authorities, particularly the programme managers. To avoid unnecessary confusion in the field, whenever possible the two MB regimens should not be employed simultaneously in the same programme. Whatever the regimen being implemented, detection and treatment of relapse is always part of the daily activities of the national programme, and should be incorporated in the training, case-holding, supervision and monitoring. On the other hand, relapse is almost unavoidable after treating hundreds and thousands of patients with MDT. All of us should fully accept the few relapses that may occur from patients with a high initial BI and treat those patients who do relapse with a further course of MDT,[1] and there is no reason to exaggerate the consequence of relapse in leprosy.

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[7] WHO Expert Committee on Leprosy. Seventh Report. *WHO Technical Report Series, No. 874*. Geneva: World Health Organization, 1998.

Erratum

In the original Letter to the Editor 'Proposal regarding MB MBT', by W. H. Van Brakel (*Leprosy Review* 1999; **70**: 70–72), an error was made when drafting the text. We apologize for this error, and for any confusion caused, and reproduce here the correct version of the two paragraphs affected.

'Dr Lynch draws attention to the Institut Marchoux Study, which reported on the increased rate of relapse even with the previous 24-month regimen. In addition to the possible increased risk of relapse, highly smear positive patients are likely to have a much increased risk of ENL (or type 2) reaction once the clofazimine component of MDT has been withdrawn. We have also observed this after the introduction of the current 24-dose fixed-duration treatment. Before the introduction of clofazimine, the cumulative incidence of ENL was up to 25% in BL and 50% in LL patients. Thanks to clofazimine these percentages have now been more than halved. It is well known that such reactions can lead to irreversible nerve damage, blindness and other severe impairments.

The argument put forward in some WHO publications in favour of reducing the duration of MDT for all MB patients has been that highly smear positive (HSP) patients are nowadays rare. There are three flaws to this argument. First, relapse from leprosy is not like relapse from other infectious diseases, such as amoebic dysentery or even malaria. Each leprosy relapse could spell social disaster for the person involved and also for their whole family. Second, the success of the MDT campaign is partly due to the trust that has been built up in the 'community', that leprosy can be cured. Often new cases present because they have heard that leprosy can be cured from others who have (had) the disease. An increased frequency of relapses could jeopardize this trust. Third, and most importantly, MB patients are most likely to relapse with multibacillary disease. It may take years in individual cases before the diagnosis of relapse is made. All the time they may be a source of infection in the community, creating a new pool of infection at a time when the battle against leprosy might otherwise have been in its final stage'

Lepr Rev (1999) **70,** 370–383

Teaching Materials and Services

The Robert Cochrane Fund for Leprosy

The Fund, in memory of the great leprologist Robert Cochrane, is administered by the Royal Society of Tropical Medicine and Hygiene. It is to be used to finance up to three travel Fellowships each year, to a maximum value of £1000 each. The Fund will support travel for:

Leprosy workers who need to obtain practical training in field work or in research

Experienced leprologists to provide practical training in a developing country

There is no restriction on the country of origin or destination providing the above requirements are fulfilled.

Application forms are available from the Society and completed forms must be received by the Society at least 6 months ahead of the proposed visit. All applications must be sponsored by a suitable representative of the applicant's employer or study centre, and agreed by the host organization. A two-page report on the travel/study should be submitted to the Society within 1 month of the recipient's return.

Apply: The Secretary, Robert Cochrane Fund for Leprosy, Manson House, 26 Portland Place, London W1N 4EY, United Kingdom. Tel: 0171 580 2127; Fax: 0171 436 1389.

Training courses at ALERT in 2000

January 10–February 11
Prevention and management of disabilities

Target group: physiotherapists, occupational therapists, podiatrists as well as experienced leprosy workers involved in POD. Emphasis on both patient care (early detection of nerve deterioration, health promotion, problem solving) and programme management (POD management, home based care and rehabilitation).

March 6–March 17
Introduction to leprosy for physicians

Highly recommended for the participants in the following 'Management of Combined Programmes' course who need to refresh their knowledge of clinical leprosy. The course can also be taken on its own by physicians responsible for diagnosis, treatment and care of patients with leprosy in either a hospital or a control programme setting.

March 20–April 14
Management of combined leprosy and tuberculosis control programmes for physicians

Target group: experienced physicians responsible for managing a leprosy and TB control programme at

the regional level or above. Emphasis on programme management: needs analysis, action plan, implementation of activities, supervision, evaluation, management of POD. A brief review of the essentials of TB is included, but leprosy expertise is a prerequisite. Participants lacking the latter should also take the preceding 'Introduction to leprosy' course.

May 29–June 16
Essentials of leprosy and tuberculosis for administrative and programme support staff

Target group: administrative and managerial staff without a medical background, working in leprosy and TB programmes and donor agencies. Objectives: to gain a better understanding of the two diseases, to communicate more effectively with the medical staff, and to contribute more efficiently in decision making and priority setting.

September 4–October 13
Essentials of leprosy and tuberculosis for physicians

Target group: physicians with limited experience in either leprosy or TB. Emphasis on clinical aspects of leprosy and TB, individual patient care and its application in the context of a combined programme, with an introduction to health promotion and managerial issues, paying special attention to POD and supervision.

November 6–November 17
Introduction to leprosy for senior field staff

Highly recommended for the participants in the following 'Management of Combined Programmes' course who need to refresh their knowledge of clinical leprosy. The course can also be taken on its own.

November 20–December 15
Management of combined leprosy and tuberculosis control programmes for senior field staff

Target group: experienced nurses, paramedical workers or supervisors responsible for leprosy and TB control at the district (or equivalent) level. Emphasis on planning, implementation, supervision and evaluation of control activities, with special attention for POD, health promotion and support functions. A brief review of the essentials of TB is included, but leprosy expertise is a prerequisite. Participants lacking the latter should also take the preceding 'Introduction to leprosy' course.

In-service training

In-service training, tailor made to the individual trainee's needs and interest, can be arranged in surgery, physiotherapy, dermatology ophthalmology, laboratory etc.

For further information, please contact: ALERT Training Division, PO Box 165, Addis Ababa, Ethiopia, Tel: +251 1 711524 or +251 1 712792; Fax: +251 1 711199 or +251 1 711390; e-mail: ahri@telecom.net.et

TALMilep: Teaching and Learning Materials on Leprosy

TALMilep is an Action Group of ILEP—the International Federation of Anti-Leprosy Associations which produces and supplies teaching materials on leprosy and related subjects free or at low-cost.

Leprosy: A Bryceson and R. E. Pfaltzgraff (1989)—a readable reference book for medical students, general practitioners and physicians. £2·00.

Essentials of Leprosy: Dr Leo Yoder (1996)—this booklet contains information on leprosy care and treatment suitable for a range of health workers. FREE.

A Guide for Eliminating Leprosy as a Public Health Problem (1997), WHO—a pocket guide to diagnosis and management. FREE.

Leprosy for Field Staff: Alison Summers (1993)—this excellent book is aimed at health workers in specialized leprosy programmes or general health workers who see leprosy on a regular basis. FREE.

Atlas of Leprosy: Guinto *et al.*, Sasakawa (1997)—this book of colour photographs is most suitable for use in areas such as East Asia where leprosy is seen in lighter skins. FREE.

Leprosy in Africans: Jacyk (1986)*—an booklet containing colour photographs with short notes in English and French. Arabic translation available on request. A popular and practical reference guide for health workers. FREE.

Care of the Eye in Hansen's Disease: M. Brand (1993)*—outlines the management of eye complications in leprosy for ophthalmologists and other health workers. FREE.

Insensitive feet: P. Brand (1994)—a good background to the problems of insensitive feet. FREE.

Prevention of disabilities in patients with leprosy a practical guide: H. Srinivasan (WHO 1993)—for those involved in patient assessment, treatment and teaching self-care to people with leprosy. Price (for use in developing countries) £9.50.

Essential action to minimise disability in leprosy patients: J. Watson (1994)*—an excellent book with clear text and illustrations written for general health workers caring for people with leprosy. FREE.

Leprosy Surgery for General Hospital: H. Srinivasan, WHO. FREE (for use in developing countries).

Guide to health education in leprosy: P. J. Neville (1993)—contains messages for patient education. FREE.

Don't treat me like I have leprosy: Frist—a book about the history of leprosy and the importance of social issues. FREE.

Tuberculosis Guide for low-income countries: IUALTD—FREE.

*Also available in French.

All of these can be ordered directly from TALMilep. A more detailed list of books can be obtained from TALMilep. TALMilep is currently reviewing and updating the materials it supplies as a result some titles may be replaced by new or revised publications.

TALMilep also distributes a catalogue of training courses and a video catalogue which reviews leprosy related videos and gives information on how to order them.

For people developing health training materials locally for leprosy in general, combined or specialist programmes, TALMilep can help by sharing information on what has been produced elsewhere and can provide technical and editorial advice.

INFOLEP, TALMilep's sister organization, provides a leprosy information service and bibliography through mail and the world wide web (http://infolep.antenna.nl). It is based at the offices of the Netherlands Leprosy Relief (NLR).

For further information and to order books, please contact: The Teaching and Learning Materials Co-ordinator, ILEP, 234 Blythe Road, London W14 0HJ, United Kingdom. Tel: +44 171 602 6925; Fax: +44 171 371 1621; e-mail: ilep@ilep.org.uk; Website http://www.oneworld.org/ilep

Keele University, UK: International Health Management Teaching Programme

Embarking upon a formal management education and development programme can be a rewarding and valuable experience: but only if you choose a programme that is right for you! **The Centre for Health Planning and Management at Keele University** is a postgraduate research, education and training institute specializing in the planning and management of the health and related sectors, and editorial office of the widely respected **International Journal of Health Planning and Management**. After close consultation with national governments, non-governmental and donor agencies, and prospective applicants, we have designed a number of programmes designed to meet the management needs of experienced health professionals working in the health-related sectors of the developing world.

Our programmes range from short-term management workshops, to full-time Masters and Doctoral Programmes, of one year or longer. Cutting across the boundaries of specific professional interests, they appeal to cadres as diverse as: doctors, administrators, nurses, planners, pharmacists, university faculty, aid administrators, and programme managers. Indeed, they are relevant to all whose present or intended careers are likely to incorporate a significant management component. They offer an advanced scheme of study designed to develop the management potential, analytical powers, and problem-solving skills of experienced professionals working in, or for, the health and health-related sectors of developing countries.

Typically, participants are drawn from: ministries of health, education, population, nutrition, or social welfare; educational establishments or research institutes; planning units at national, regional or local levels; national planning or economic development agencies, with responsibility for health or related sectors; and health related non-governmental, voluntary or external agencies or programmes.

Our flagship programme is the ***Master of Business Administration*** (MBA) in ***Health, Population and Nutrition*** in Developing countries. A 1-year full-time programme, it comprises five taught courses in: Health Planning and Management; Health Economics and Financial Management; Marketing and Community Participation in Health; Human Resource Management; and, Health Information and Management Science. Participants also complete a management project which takes the form of a research dissertation. The latter provides the opportunity for participants to put into practice the concepts, methods and techniques acquired on the earlier part of the programme.

A new Masters programme was launched in 1996 in response to an increasing need for human resource specialists within ministries of health. The 1-year full-time ***Master of Arts*** MA (***Human Resources in Health***) comprises five taught courses and similar dissertation requirements to that of the MBA. The taught courses are: Health Planning and Management; Health Economics and Financial Management; Human Resource Management; Human Resource Planning Techniques; and, Workforce Management and Mobilization.

For those not meeting the entry requirements of our MBA/MA Programmes, we offer a 9-month ***Diploma Programme***, with opportunities for successful students to later transfer to the MBA/MA Programmes. We also offer a number of 1-month management ***workshops*** for those unwilling or unable to embark upon a longer full-time programme. Indeed, where appropriate, we are able to develop customised development programmes for individual or groups of managers. Invitations are also invited from suitably qualified candidates wishing to register for higher degrees by research and/or instruction (i.e. Mphil, PhD).

The Centre is part of the University's School of Management and Economics, and has an academic faculty of some 40 staff (full-time, part-time, and associate). The Centre's own ***Graduate School*** currently has some 200 students registered on its taught courses and for higher research degrees in health services' management. A truly international atmosphere is guaranteed, with students from over 20 developing countries registering on our various programmes this year. The opportunity that this affords for a sharing of management insights and experience, and for the development of professional and social links, is seen as a valuable part of the learning experience.

The Centre's teaching faculty has extensive relevant experience of working for, and in, developing countries, thereby helping us to keep abreast of important developments and management issues. Centre faculty regularly undertakes research, training, management consultancy and advisory missions for national governments, international development agencies, and research and educational foundations. In the past 4 years, Centre faculty has undertaken over 30 assignments in the developing world alone.

For further details, or application forms for any of our programmes, write to: The International Programme Director, Centre for Health Planning and Management, Darwin Building, Keele University, Keele, Staffordshire, ST5 5BG, England. Tel: +44 1782 583 191; Fax: +44 1782 711 737; e-mail: hma07@keele.ac.uk

How to set up a village library

This publication from the *Rajiv Gandhi Foundation* is distributed from *Books for Change* (details below). The Preface reads as follows:

How to Set up a Village Library–a Training Manual is intended to serve as a guide for trainers of Rajiv Gandhi Foundation (RGF) village librarians as well as a reference document for village librarians, village library supervisors and officials of organizations currently implementing the project or interested in implementing similar programmes. However, the contents are to be treated as guidelines and not strict rules.

The introduction continues: Village libraries have been opened in hundreds of villages in different parts of the country by the Rajiv Gandhi Foundation (RGF) in partnership with field-based organizations. The main objective of this project is to provide suitable reading material to the villagers at their doorstep so that they can continue to be literate and have access to useful information as well as recreational material.

The libraries are called 'Rajiv Gandhi Village Library'. They are lending libraries and not reading rooms. Non-availability of adequate space for the latter in a village is a major reason for this. The concept of a reading room has also been discouraged to keep the library accessible to women by ensuring that it does not become a 'gossip-centre' for men.

The library has approximately 400 books on diverse topics which are of interest and use to the local population. Two newspapers also come to the library daily. The books and newspapers are both in the local language.

The library is housed in a room or building invariably provided by the community. The basic furniture and the initial stationery are provided by RGF or the local partner. A local person (preferably a women) operates the library for a few hours every day depending upon the convenience of the community. This person is imparted a brief training by RGF before the library begins functioning. She/he is given a small honorarium for her/his services.

On payment of a very nominal membership fee, villagers can register as members of the library and have access to the books. A bank account is opened in a nearby bank/post office and all money received as fees or donations etc., is deposited in the account.

The policy decisions regarding the day-to-day functioning of the library are taken by a Village Library Committee (VLC).

For logistical, administrative and supervisory convenience, the libraries are normally set up in clusters of at least ten villages, which are close to each other geographically.

There are two other programmes that are linked to the TGF village libraries:

One is the 'Skills Training Programme' for which RGF provides training support for upgradation of existing skills and practices of villagers, specially women, who are members of the library, with the idea of enhancing their income earning capacity.

The other is the 'Rural Publishing Programme' under which the knowledge and experiences

from villages are documented by the rural authors. These are then published and disseminated by RGF.

Further information: Books for Change, 3 Rest House Road, P.B. No: 5406, Bangalore-560 001, India. Tel: (080) 5586682/5586583/5586704; Fax: (080) 5586284.

WHO: 'Blue trunk' libraries (Bibliothèques bleues)

A recent issue of *LIAISON* Newsletter of the WHO Office of Library and Health Literature Services Volume 9, Number 3, November 1998 describes this initiative as follows:

A dearth of health information

Many university libraries in developing countries suffer from a shortage of medical books and journals. Very often the only ones available are several decades old and covered with a thick layer of dust because, for good reason, no one consults them. Often the only useful information in these libraries is a collection of theses which, in contrast, are frequently consulted and copied. Without a budget, libraries have no books or journals, but they do have readers. The thirst for knowledge is very real, even though in comparison with other needs it is often wrongly judged as superfluous.

Outside the major cities, the situation is even gloomier. Health professionals who wish to keep up to date have scant resources. Books are rare in health centres or hospitals. Those university libraries which do have some information resources often lack the means, for a multitude of reasons, of disseminating the information they possess: a limited supply of paper for the photocopiers, unreliable postal services, lack of personnel or ignorance of needs. Lastly, university libraries frequently have no mandate to carry out this task as they are directed by the Ministry of Education, whereas health centres are directed by the Ministry of Health, responsibility and communications being therefore strictly compartmentalized.

There is nothing new about the idea of reaching out and setting up health libraries in districts: trials have been more or less successful in Malawi, Tanzania and Uganda. The Blue Trunk Libraries project, however, differs in both its philosophy and scale.

The background

The Blue Trunk Libraries project is based on several observations:

- In its technical cooperation activities, WHO has given priority to developing district health services. Improving community health services depends to a great extent on training and on updating the knowledge of health personnel.
- Following this policy, WHO and a number of other publishers (more often English speaking than French speaking) have produced numerous manuals intended for district health centres. Unfortunately, the works in question often reach only a few ministries and lucky individuals whose names happen to be on the right distribution list.
- The work of librarians in many countries is hampered by lack of funds and resources, and by the low status of their profession. In addition, their activity is limited to the university or institution where they work. It is out of the question, for the reasons cited above, to imagine they might provide services to remote health centres.
- Lastly, district health workers as a whole rarely have access to books, so that reading as a means of acquiring information is not among their habits or work patterns.

The basic approach adopted by the Blue Trunk Libraries is to include the skills and know-how of librarians in a ready-to-use documentation module, appropriate for health districts. It focuses on disseminating the information contained in the Blue Trunk library within the health community, using a

local person training specially for the task. The Blue Trunk library does not replace continuing education. Its mission is rather to provide validated information to support training activities, health promotion and community information in peripheral health centres.

What are Blue Trunk libraries?

The Blue Trunk library is a collection of one hundred or so books on medicine and public health, together with three or four subscriptions to medical journals. The collection, which is organized according to major subjects, has been developed by the Library of the World Health Organization for installation in district health centres as a means of compensating for the lack of up-to-date medical and health information. In order to make it easier to transport and store, the collection has been packed into a blue metal trunk fitted with two shelves on which the cardboard boxes containing the books are arranged.

Among the works chosen, priority has been given to practical manuals (especially those published by WHO) offering an easily accessible solution to the medical, public health and management problems medical staff may have to face. Differing levels of education among district medical staff have also been taken into account. The same topic may be addressed in different publications from a different point of view: that of the physician, the nurse, the nursing auxiliary or health worker. The collection, which has been deliberately kept small, is not exhaustive. Other suitable local material is available at district level and should be added. The WHO publications in the collection are updated by the provision of new editions. The price of each module for Africa is US$ 2000. This includes the books and periodicals, transport and delivery, and training for the person responsible for the Blue Trunk library in the district. A procedure for keeping WHO publications up to date has been established, together with monitoring and evaluation of the operation of the Blue Trunk libraries locally by a national coordinator, with the support of the Office of the WHO Representative.

The material specifications for the initial installation of the Blue Trunk library are minimal. It must be placed in clean premises that are accessible to all the district health staff, subject to some supervision to ensure that the collection remains as complete as possible.

For people unable to read or who are not familiar with French or English, the Blue Trunk library can be used to create simple educational material in the form of drawings, pictograms, pictures and diagrams. Health professionals in the field are best placed to translate and adapt theoretical knowledge to local conditions and to the culture of the populations with whom they deal.

Further information: Mrs Edith Certain, WHO Library, 1211 Geneva 27, Switzerland. E-mail: certain@who.ch

CD-ROMs on topics in international health

A comprehensive resource for health care professionals, students and researchers in developed and developing countries, the 'Topics in International Health' series of interactive CD-ROMs now includes eight titles, and more are to follow.

Distance learning does not come much more distant than this. Working at the Wellcome Trust's Tropical Medicine Resource (TMR) in London, a team of science writers, working with expert advisers, has produced a series of aids to learning that have been enthusiastically taken up by research and training organizations in 75 countries. Within the slim and sparkling form of a compact disk, each package contains the potential to bring to the people who need it most the equivalent of a well-trained teacher equipped with a comprehensive bank of text and visual material. Over 2000 disks have already been sold, benefiting thousands worldwide.

Each title in the 'Topics in International Health' series tackles a single health problem that is common in developing countries. The first four, launched in April 1998, cover malaria, trachoma,

sexually transmitted diseases and sickle cell disease. These were swiftly followed by four more on tuberculosis, leprosy, schistosomiasis and diarrhoeal diseases. Further additions, on HIV/AIDS, nutrition and leishmaniasis are due in late 1999. Each takes the form of a set of illustrated tutorials on topics such as aetiology and transmission, prevention and control, diagnosis, and treatment, followed by self-assessment tests. The illustrations include not only photographs and diagrams, but animated graphics and video clips. An impressive feature of the disks is a searchable database of up to 1000 high-quality images, drawn from the TMR's own vast collection and from other sources. A detailed glossary of terms used in the tutorials and image descriptions is also included, to help those who are beginners in medical terminology or for whom English is not the first language.

The series is distributed with the help of CAB International, a not-for-profit intergovernmental organization whose Information for Development Programme aims to make health and agricultural information more readily accessible in the developing world. CABI is targeting other organizations worldwide both to help introduce the CD-ROMS into universities, hospitals and research organizations, and to obtain sponsorship to minimize the costs to those who have most need of training. This has already led to the CD-ROMs' integration into international disease control programmes. The International Trachoma Initiative, based in New York and supported by the pharmaceutical company Pfizer and the Edna McConnell Clark Foundation, has bought 50 copies of the trachoma disk. According to Program Director Jeff Mecaskey, 'The CD-ROM will enable our partners—whether they work in Vietnam or Vienna—to develop a common body of knowledge tailored to their own specific needs'. More recently, Netherlands Leprosy Relief has bought 125 copies of the leprosy and TB disks, and a training organization affiliated with Johns Hopkins University in Baltimore, Maryland, has bought 50 disks for use in their learning centres in Nepal, Bolivia, Indonesia and Haiti.

The Wellcome Trust and CABI have kept the price of the disks deliberately low for customers from developing countries. Some have voiced fears that there are not enough PCs with CD-ROM drives available in these countries for the disks to be useful. Chris Coyer, who heads the TMR, argues that this view is out of date. 'Many developing nations are catching up on hardware provision, and cultural attitudes to computers are changing' he says.

One satisfied customer is Eunice Sendikadiwa, Deputy University Librarian at the Makerere Medical School in Kampala, Uganda, who has responded with great enthusiasm to the appearance of the disks. The library at Makerere has two computer stations equipped with CD-ROM drives, which she plans to use to help students reinforce their lectures with interactive training materials—including 'Topics in International Health'.

Current and planned CD-ROMS

Disks currently available: Leprosy; Schistosomiasis; Diarrhoeal diseases; Tuberculosis; Malaria; Trachoma; Sexually transmitted diseases; Sickle cell disease.

Disks in preparation: HIV/AIDS; Leishmaniasis; Nutrition.

Price and ordering information can be found at: www.cabi.org/catalog/cdrom/tih/price.htm or contact CABI directly:

CAB International, Wallingford, Oxon OX10 8DE, UK. Tel: +44(0)1491 832111; Fax: +44(0)1491 826090; E-mail: publishing@cabi.org.

For customers in North America: CAB International, 198 Madison Avenue, New York, NY10016-4314, USA. Tel: 212 726 6490/6491; or Toll-free: 800 528 4841; Fax: 212 686 7993; E-mail: cabi-nao@cabi.org.

London School of Hygiene and Tropical Medicine: Short Study Programmes, 1998–99

A 40-page booklet from the LSHTM describes the short study programmes—Teaching Units and Short

Courses—available at the LSHTM. The activities of the three main Departments are described as follows:

1. *Department of epidemiology and population health*

The Department of Epidemiology & Population Health focuses on issues of major public health or social importance, with a strong emphasis on the relevance to public health and social policy. Research contributes to the development of evidence-based medicine by feeding directly into the database of scientific evidence underlying this. The department encompasses the largest group of epidemiologists, statisticians and medical demographers in Europe, together with nutritionists, social scientists and public health practitioners. There is considerable expertise in the analysis of routinely collected statistics, the conduct and analysis of observational studies, clinical trials and large-scale field studies and in the design and evaluation of interventions.

2. *Department of infections and tropical diseases*

This is a new Department, created in 1997 to exploit and develop the School's unique multi-disciplinary research base which ranges from molecular sciences through to field implementation. The mission of the Department is to employ basic, applied, clinical and epidemiological techniques to improve health internationally by performing high quality research on major infectious diseases, and to be a national and international resource for the study of established and emerging infectious diseases.

3. *Department of public health and policy*

The Department of Public Health & Policy applies health, social and management sciences to important policy issues in public health and health services. It is concerned with understanding patterns and causes of disease; effectiveness and cost-effectiveness of interventions; organization, quality, management, financing and production of health services; disease prevention and health promotion; and the processes and development of health policy.

Full details are given of 13 short courses and 42 Teaching Unit Profiles.

Further information: The Registry, London School of Hygiene & Tropical Medicine, 50 Bedford Square, London, WC1B 3DP, UK. Tel: +44(0)171 299 4648; Fax: +44(0)171 323 0638; e-mail: registry@lshtm.ac.uk; Internet: http://www.lshtm.ac.uk/prospectus.

IAL Symposium on Therapy—Dermatologist's View

The Indian Association of Leprologists Maharashtra Branch (IAL-MB) in collaboration with Poona District Leprosy Committee (PDLC), IAL central, Bombay Leprosy Project (BLP) and Government of Maharashtra conducted a symposium at BJ Medical College, Pune on 28 February 1999. Eighty practising and teaching dermatologists in addition to leprologists and District Leprosy Officers (DLO) participated.

This symposium on 'Therapy of Leprosy' was organized to have interaction between leprologists, programme managers and practising dermatologists of Pune so as to arrive at some consensus on the current treatment regimens recommended by WHO and NLEP. This was considered necessary because the practising dermatologists treat about 10–15% of the leprosy patients in the cities. However they do not follow the national guidelines while treating patients but decide on the classification, treatment regimen and duration of treatment on individual patient to patient basis.

Major General M. A. Tutakne, Dean, Armed Force Medical College, chaired the symposium. Dr A. S. Naik, Prof and Head, Dermatology Department, BJ Medical College, reviewed WHO and Government of

India recommendations on 12 months MDT for MB leprosy and ROM single dose for single skin lesion (SSL) PB leprosy.

Dr R. Ganapati, Director, BLP who traced the evolution of short course treatment for leprosy and described his experiences in current regimens recommended by the WHO/NLEP. He asserted that long term follow-up of patients of FDT 24 and 12 should be undertaken if we want to observe relapses before doubting the efficacy of FDT 12. He presented long-term observations of 74 cases (FDT 24+ FDT 12) whose BI was more than 3+ and who were also followed up for more than 5 years. No relapse were reported.

Dr M. B. Gharapure narrated the reservations of practising dermatologists on classification and duration of treatment recommended recently which are good for a mass programme but not for individual patients attending dermatologists clinic who are concerned about their clinical problems. He cited an example of one relapse case after WHO PB-MDT who is likely to sue a dermatologist in the court. He also pointed out that his questionnaire study of 92 dermatologists of Pune and surrounding districts showed that 80–90% off them did not accept FDT-24 and PB MDT-6. They managed 4627 cases in their clinics successfully on an individual patient basis specially those cases reporting with clinical problems such as reactions, active skin lesions etc. after starting treatment with NLEP staff.

Dr W. S. Bhatki, Medical Superintendent, Acworth Municipal Leprosy Hospital, gave an immunological background of cure specially in SSL-PB leprosy and explained how a single dose of ROM is adequate to kill bacteria. The residual patch will be taken care by the body system for which chemotherapy is not required.

Dr D. Poricha, IAL Secretary (Central), drew the attention of participants to the fact that in the game of single dose treatment of SSL-PB we will be losing sight of potential smear positive single lesion cases as skin smears are not practised. The programme people should be cautious about it.

The following views were expressed by the dermatologists Drs D. J. Patil, A. H. Patki, D. G. Jogaikar, Deepak Kulkarni, M. Y. Honap and Ben Naffs.

1 The nerve histology should be considered for classification as some studies have shown viable bacilli in the nerves even after long term treatment.
2 Dermatologists have to treat patients adequately only to prevent relapses and hold on them.
3 As SSL-PB leprosy may harbour millions of viable bacilli (as per the Katoch report), a single dose of ROM will not be adequate.
4 As viable bacillary load is very high in LL cases, FDT 24 or 12 is not adequate to eliminate all the viable bacilli.
5 Absence of dapsone increases the incidence of reaction.

No consensus could be arrived at the end of this session, the subject is kept opened for further interaction.

Mr S. S. Naik, while presenting a summary of the workshop, highlighted the 15th International Leprosy Congress, Beijing 1998, passed a resolution to work towards a 'World Without Leprosy'. The main thrust was on chemotherapy, elimination and rehabilitation. This workshop was planned accordingly to accelerate the activities in that direction.

The participants appreciated both Dr V. H. Jadhav and Dr D. G. Jogaiker for organizing this symposium so successfully.

(This symposium was sponsored by The Leprosy Mission, New Delhi, American Leprosy Mission, Damien Foundation and Indian Leprosy Foundation.)

Dr C. R. Revankar, Hon. Secretary, IAL-MB

IAL Workshop on further strategies for leprosy elimination in Maharashtra

The Indian Association of Leprologists Maharashtra Branch (IAL-MB) in collaboration Poona District

Leprosy Committee (PDLC), IAL central, Bombay Leprosy Project (BLP) and Government of Maharashtra conducted a workshop at BJ Medical College, Pune on 27 February 1999. In all, 135 delegates consisting of leprologists, District Leprosy Officers (DLO), practising dermatologists and postgraduate students participated.

The workshop discussed the strategies for Leprosy Elimination with special reference to case detection and treatment in difficult population groups and areas specially in Maharashtra state. Selected DLOs were invited to present their survey findings among fishermen, hotel and restaurant boys, construction workers, stone cutters and nomads who are generally not examined routinely or missed by the leprosy workers.

Dr J. A. Ponniah, President of IAL Central, chaired the first session. In this session, Dr Jal Mehta, Honorary President of PDLC (paper was read by Dr V. H. Jadhav) and Dr C. S. Walter, Director, The Leprosy Mission, New Delhi, discussed various steps involved in institutional rehabilitation and community participation in leprosy elimination, respectively. Dr M. D. Gupte, Director, Institute for Research in Medical Statistics, Chennai presented an account of a recently completed field trial of Leprosy vaccine which showed that both ICRC and BCG + HKML vaccines gave 65% protection rate against leprosy. Dr Ben Naffs, Dermato-Venereologist of Tropical and Import Dermatology, Netherlands shared his experience on immunopathology and treatment of reactions including nerve damage.

The second session was chaired by Dr P. B. Joshi. Dr C. R. Revankar, Deputy Director BLP, reviewed WHO-supported SAPEL and LEC projects in different countries, including India. While describing LEC in India, he pointed out that states like Bihar, Orissa, Uttar Pradesh and Madhya Pradesh detected 322,193 (82%) cases out of 416,301 new cases identified during campaign indicating a high rate of hidden prevalence in these states calling for intensification of case finding activities.

Dr V. P. Bhardwaj, Consultant Leprologist of NLEP shared his experiences with reference to case detection and treatment in difficult hilly areas such as Chamoli of Uttar Pradesh. In this, a SAPEL project was taken up and 13 new patients could be given MDT through community volunteers.

Drs S. V. Dinni (Thane), M. G. Singh (Raigad) and Amar Thakur (Yavatmal), all DLOs, examined 41,568 individuals belonging to special groups such as hotel boys, fishermen, labourers, stone cutters etc. by innovative methods. Such efforts unearthed 43 new cases (7 MB) who would have remained undetected. The detection rate was 103 per 100,000 population which is abnormally high as compared to current new case detection rate at national level. As some of the patients were from Northern Indian states like Bihar, Uttar Pradesh and Madhya Pradesh, it was stressed that programme managers at District level specially in cities should constantly identify such groups and examine to identify new cases and give them short course chemotherapy wherever necessary as these patients may not be available even for 12 months MDT.

The third session was chaired by Dr A. C. Parikh, president of IAL-MB. Mr Uday Thakar of Kustha Rog Nivaran Samiti, (paper presented by Mr S. S. Naik) presented his observations on RO-28 days treatment (rifampicin and ofloxacin combination) in MB cases in hilly areas of Panvel. All the patients were showing good response. This study showed that the RO regimen could be practised in difficult situations where patients are not available for longer duration treatment.

DLOs Dr B. R. Chavan, Kolhapur, Dr Bansode, Nagpur, Dr M. S. Pimpalgaokar, Bhandra, B. B. Munde, Parabhani Dr B. P. Betal, Wardha and Dr P. S. Bhusari, Chandrapur, described various innovative methods for case detection such as involvement of non-allopathy students, teachers, community volunteers etc.

The fourth session was chaired by Dr P. V. Joshi, Dr D. D. Palande from Pandicherry described methods of early identification of nerve damage and management in the field. Mr V. N. Kulkarni, Physiotherapist. Kondawa Leprosy Hospital presented on the approaches for disability care in the hospital.

(This workshop was sponsored by The Leprosy Mission, New Delhi, American Leprosy Mission, Damien Foundation and Indian Leprosy Foundation).

Dr C. R. Revankar, Honorary Secretary, IAL-MB

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News and Notes

Variations in the *NRAMP1* gene and susceptibility to tuberculosis in West Africans

This is the title of a paper published in the *New England Journal of Medicine* by Bellamy R *et al*., Volume 338, Number 10, March 5, 1998, pages 640–44. The *Abstract* reads as follows:

Background Genetic factors may affect the susceptibility to tuberculosis, but no specific genes governing susceptibility have been identified. In mice, natural resistance to infection with some mycobacteria is influenced by the gene for natural-resistance-associated macrophage protein 1 (*Nramp1*), but the role of the human homologue of this gene, *NRAMP1*, in tuberculosis is unknown. We typed polymorphisms in *NRAMP1* in a case–control study of tuberculosis in the Gambia, West Africa.

Methods Sequence-specific oligonucleotide hybridization and microsatellite analysis were used to type *NRAMP1* polymorphisms in 410 adults (mean age, 34·7 years) with smear-positive pulmonary tuberculosis and 417 ethnically matched, healthy controls. Patients with human immunodeficiency virus infection were excluded.

Results Four *NRAMP1* polymorphisms were each significantly associated with tuberculosis. Subjects who were heterozygous for two *NRAMP1* polymorphisms in intron 4 and the 3′ untranslated region of the gene were particularly overrepresented among those with tuberculosis, as compared with those with the most common *NRAMP1* genotype (odds ratio 4·07; 95 percent confidence interval, 1·86–9·12; chi-square = 14·58; $P < 0·001$).

Conclusions Genetic variation in *NRAMP1* affects susceptibility to tuberculosis in West Africans.

—and the final paragraph of the *Discussion:*

The association of *NRAMP1* variation with a major infectious disease provides support for the strategy of mapping and identifying genes for resistance to infectious disease in mice and then testing their homologues as candidate genes for susceptibility to related infections in humans. Further analysis of the mechanism of action of *NRAMP1* and its genetic variants may lead to new approaches to controlling tuberculosis, which kills more people than any other disease caused by an infectious pathogen.

Report of WHO/TDR Scientific Working Group on the Utilization of Genomic Information for Tropical Disease Drug and Vaccine Discovery, Geneva, 18–20 February 1998

This Report (TDR/GENOMICS/98.1) deals with the impact of genomics on the future of drug and vaccine discovery in tropical disease.

The *Introduction* reads as follows:

The availability of complete microbial genomic sequence data offers unique opportunities to improve our understanding of the basic biology of these organisms. Eighteen microbial genomes have been completed and approximately another 40 are in the process of being sequenced. For human pathogens

such as those of interest to TDR it also opens up the opportunity to identify weaknesses that leave them open to chemotherapeutic or immunological attack, i.e. it offers unique possibilities for the discovery of new drugs and vaccines. The major target diseases of TDR are:

- Malaria
- Leishmaniasis
- African trypanosomiasis
- Chagas' disease
- Onchocerciasis
- Lymphatic filariasis
- Schistosomiasis

It is expected that the complete genomic sequence of the most significant of the human malarial parasites, *P. falciparum*, will be available by 2002. In addition, sequencing of many other pathogens of interest to TDR is under way, in part sponsored by TDR.

Many pharmaceutical companies have utilized genomic information from human pathogens for the discovery of drug targets and potential vaccine antigens, but very few, if any, are engaged in drug or vaccine discovery research for the diseases of interest to TDR. It is therefore imperative that, where possible, public sector organizations and academic scientists interested in tropical diseases interact and learn from these industrial endeavours and try and apply them to tropical diseases.

In addition, post-genomic tools are being rapidly developed for organisms, such as yeast and *C. elegans*, which are of scientific interest. Here too, tropical disease scientists can learn and develop appropriate tools for their pathogens.

TDR has recently reorganized its structure to enable it to approach the funding of drug discovery and vaccine discovery in a more focused way. It is also further developing its capacity to develop and register products, preferably with private sector partners, and so realise the full potential of any scientific discoveries that are made. Key to the future efficient use of TDR funds will be an appropriate and efficient funding of functional genomic research, often in collaboration with other agencies.

It was with these thoughts in mind that this meeting was organized. Concurrent with these needs, and integral to the philosophy and process of TDR funding, emphasis was also laid on the need to ensure that adequate opportunity and assistance is provided to developing country scientists and institutions to participate in these new technological developments. Ultimately, the best way to ensure the sustainable discovery and development of tropical disease products is to develop the capacity and resources for their resolution in the populations that are afflicted by these diseases.

The *Conclusions* (page 21) were:

The following conclusions from the round table discussion require action and deserve highlighting:

i) There is a continuing need to promote genomic sequencing efforts.
   - It was proposed that a small task force, in consultation with relevant agencies, should decide on an optimum malaria species for further genome sequencing projects
   - TDR may consider the stimulation of *Anopheles* genomics/EST projects

ii) There is a need for TDR, together with other agencies, to promote the appropriate curatorship of genomic sequence information and its annotation.

iii) There is a need for TDR, together with other agencies, to create repositories of reagents to assist functional genomics research.

iv) There is a need for TDR to actively promote activities in functional genomics.
   - Genomic approaches that require large-scale concerted efforts involving many labs (e.g. large scale knockouts) should be pre-discussed extensively between appropriate scientists and agencies to ensure their optimal implementation. *P. falciparum* may be an important starting point for these discussions and full use should be made of the experiences of the yeast and *C. elegans* scientific communities in this regard

v) There is a need for TDR to fund the development of new and improved technologies that will facilitate functional genomics research in its target diseases.

vi) Within TDR there is a need for functional genomic research to be coordinated effectively between the genome and pathogenesis committees of Strategic Research (TDS) and the drug and vaccine discovery committees of Product R&D (TDP).

vii) There is a continuing need to engage with industry where possible and appropriate to maximise the translation of genomics research into appropriate product R&D.
- Further efforts will be made by TDR to improve funding and support to projects that show particular promise for the future development of products (drugs and/or vaccines) for its target diseases.

viii) There is a need for appropriate training and institutional strengthening in disease endemic countries in functional genomics, especially bioinformatics.
- TDR undertook to make a major commitment in the training of DEC scientists in post-genomic technologies, particularly bioinformatics. Training and institutional strengthening will form an integral part of all its post-genomic activities.

ix) TDR should investigate the potential role it has to play in promoting partnerships between scientists and institutions in the bioinformatics field.

Genetic basis for susceptibility to mycobacteria

The following appeared on page 1027 of the *British Medical Journal*, Volume 318, 17 April 1999:

New research has suggested that there is a genetic reason why some people are more susceptible to infections with non-tuberculous mycobacteria.

Researchers at INSERM, in Paris, investigated disseminated non-tuberculosis mycobacterial infection, in which otherwise healthy individuals develop overwhelming infections with mycobacteria that normally are not virulent (*Nature Genetics* 1999;21:370–8). *Mycobacterium tuberculosis* and *M. leprae*—the organisms that cause tuberculosis and leprosy—are the most pathogenic mycobacteria, but most bacteria in the class are relatively harmless. Rare individuals develop disseminated infections with normally non-virulent non-tuberculous mycobacteria. Some develop fatal infections after vaccination with Bacille-Calmette-Guérin (BCG).

The researchers studied 18 people from 12 unrelated families with idiopathic reactions to vaccination with BCG or disseminated non-tuberculous mycobacterial infection. Previous investigations had shown that the receptor for interferon gamma—a cytokine with a central role in combatting infections—was implicated. The researchers found homozygous mutations in the DNA regions encoding for the interferon receptor.

Wellcome Trust (UK) and drug giants fund gene marker database

The following is taken from page 1093 of the *British Medical Journal*, volume 318, 24 April 1999:

A 2-year, £28 m ($44·8 m) initiative to create a high quality map of genetic markers, which will be available to everyone without charge, has been launched by the Wellcome Trust together with a group of leading pharmaceutical companies and academic centres.

The collaborative effort, called the SNP Consortium, will seek to identify and analyse single nucleotide polymorphisms involved in disease processes so that safer and more effective drugs can be developed.

Single nucleotide polymorphisms, sometimes called 'snips', are common variations that occur in human DNA. Scientists believe that the 'snips' can help pinpoint the subtle genetic differences that predispose some people to disease and underlie the variability in individual responses to drugs.

'A large, high density and high quality single nucleotide polymorphism map will be of great utility

to the medical research community, as it will help answer questions about genetic factors that contribute to disease susceptibility and response to treatment, and [will] suggest directions for future investigation,' said Arthur Holden, chairman and chief executive officer of the consortium.

'The members of the consortium believe that free and unrestricted access to this powerful tool will benefit scientific inquiry in industry, government, academic, and independent laboratories,' he added.

The consortium intends to identify up to 300,000 'snips' and map at least 150,000 of them so that they can then be used in association studies. Single nucleotide polymorphism patterns from a target population—such as patients who have a particular disease or who respond poorly to a particular drug—would be compared with patterns from unaffected populations to find genetic variations shared only by the affected group.

From these association studies disease specific genes might be identified, and novel therapeutic avenues and even tailor made treatments might be expected to evolve.

Using DNA from a diversified, representative panel of anonymous volunteers, sequence information from the publicly funded Human Genome Project, and advanced sequencing and mapping technologies, scientists from the academic centres will identify and map the polymorphisms. The laboratories involved include: the Whitehead Institute in Cambridge, Massachusetts; the Washington University School of Medicine in St Louis, Missouri; the Stanford Human Genome Center, in Palo Alto, California; Cold Spring Harbor Laboratory, New York state and the Wellcome Trust's Sanger Centre, in Cambridge, United Kingdom.

Cold Spring Harbor Laboratory will use computerized methods to organize, analyse and manage the resulting single nucleotide polymorphism database, and will also distribute the information contained in the database.

N-Acetyl transferase (NAT) activity in *M. tuberculosis* and isoniazid resistance

A recent publication in the *Journal of Bacteriology*, Feb. 1999, volume **181**, Number 4, p. 1343–1347 by Mark Payton *et al.* carries the following summary:

Arylamine *N*-acetyltransferases (NATs) are found in many eukaryotic organisms, including humans, and have previously been identified in the prokaryote *Salmonella typhimurium.* NATs from many sources acetylate the antitubercular drug isoniazid and so inactivate it. *nat* genes were cloned from *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, and expressed in *Escherichia coli* and *M. smegmatis.* The induced *M. smegmatis* NAT catalyzes the acetylation of isoniazid. A monospecific antiserum raised against pure NAT from *S. typhimurium* recognizes NAT from *M. smegmatis* and cross-reacts with recombinant NAT from *M. tuberculosis.* Overexpression of mycobacterial *nat* genes in *E. coli* results in predominantly insoluble recombinant protein; however, with *M. smegmatis* as the host using the vector pACE-1, NAT proteins from *M. tuberculosis* and *M. smegmatis* are soluble. *M. smegmatis* transformants induced to express the *M. tuberculosis nat* gene in culture demonstrated a threefold higher resistance to isoniazid. We propose that NAT in mycobacteria could have a role in acetylating, and hence inactivating, isoniazid.

Under the heading '*Tuberculosis Treatment Technology*', a less technical account of this potentially important discovery appeared in *ISIS Innovation News*, Edition 26, Winter 1998, page 10:

Research in Oxford University's Department of Pharmacology has resulted in the discovery that Mycobacterium tuberculosis has the enzyme **N***-acetyl transferase (NAT). Because of the interaction between NAT and isoniazid, a major tuberculosis therapeutic, novel insights into tuberculosis treatment have resulted.*

Background

The incidence of tuberculosis is increasing. Currently TB accounts for >2 million deaths worldwide

each year. The prevalence of drug-resistant strains of *M. tuberculosis* are the core of the problem, in particular strains resistant to the major anti-TB drugs: isoniazid, rifampin, pyrazinamide and ethambutol.

Resistance to isoniazid has been partially (≈70%) explained by changes in metabolic oxidation or reduction processes in resistant strains. However, no effective therapy currently exists to combat these genetic variations. The discovery of NAT activity in the bacterium may account for some of the isoniazid resistant events as acetylation interferes with isoniazid action.

Using proteins or peptides related to *M. tuberculosis* NAT should enable novel enzyme inhibitors to be identified using a combinatorial chemistry approach.

Applications arising from the Oxford Tuberculosis work

The Oxford Technology, which includes; sequence data of the new NAT, polyclonal antibodies capable of identifying *M. tuberculosis* NAT at very low concentrations and systems for expressing Mycobacterial NATs in a number of hosts, will enable both drug screening and drug development programmes. An immediate application is the ability to screen for and test compounds that reinstate isoniazid sensitivity to otherwise resistant strains of *M. tuberculosis.*

The Oxford Invention

Discovery of *M. tuberculosis*' latent ability to produce functional NAT together with development of associated molecular biology tools creates a new drug discovery opportunity.

Commercialization

This fundamental discovery is the subject of a patent application. Companies interested in product developments arising from the tuberculosis research are invited to contact Isis Innovation to discuss how they could interact with Oxford to utilize this technology.

Combinations to combat resistance

The following article appeared in *TDR news*, February 1999:

In our last issue, reference was made to an initiative to combat antimalarial drug resistance (*TDRnews*, 1998, 57: 7). Since activities under the initiative began in July 1998, three studies have been conducted and completed: a pharmacokinetic interaction study, a pilot clinical study, and a double-blinded clinical study of a combination of sulphadoxine/pyrimethamine + artesunate. Studies with chloroquine or amodiaquine are about to start; and a meta-analysis is planned for late 1999—as soon as data on the over 4000 patients to be enrolled in the various studies become available.

Upon completion of this first 'proof-of-principle' phase, the intention is to select combinations of drugs to be tested in large, longitudinal population-based studies. Centres interested in carrying out community-based studies to test the hypothesis that antimalarial drug combinations can delay or contain the emergence of resistance should contact: Dr P. Olliaro, Manager, Working Group on Research on Drug Resistance and Policies, E-mail: olliarop@who.int; tel: (+41) 22 791 3734; fax: (+41) 22 791 4854.

Molecular targets for filariases drug discovery

The following article appeared in *TDR news*, February 1999:

Studies on the genome and biochemistry of *Onchocerca volvulus*, *Wuchereria bancrofti* and *Brugia*

malayi have led to the identification of a myriad of enzymes, receptors, and metabolic pathways as potential targets for chemotherapy. Modern drug discovery relies more on molecular targets such as these than it does on random screening.

Molecular targets in filarial diseases were the subject of a meeting of researchers from both public and private sectors (universities, institutes and biological laboratories) in Africa, America, Australia and Europe held in WHO/HQ in November 1998. The challenge was to identify potential chemotherapeutic targets and novel strategies from among all the candidates. There were 21 presentations that addressed, in this context, the stage of parasite life cycle, biological processes, and the specificity and uniqueness of possible targets as well as the availability of infrastructures (crystallography, genomics, proteomics, etc.) that could facilitate the drug discovery process.

TDR filarial drug discovery is now becoming more targeted. It is aimed at discovering new macrofilaricides, discovering anthelmintics which sterilize adult female worms, and identifying new microfilaricides to combat any emergence of ivermectin resistance. It includes work on existing drugs such as antibiotics, antifungals and anti-parasitic agents, whose spectra of activity seem likely to be extendable.

Calls for grant proposals for filarial drug discovery research have already been sent out and the first grants will be disbursed by mid-1999 through the Drug Discovery Research Steering Committee which meets in Geneva, April 26–30. The closing date is February 28. Anybody interested in this area should contact:

Janis Lazdins, Manager Filariasis R&D, E-mail: lazdinsj@who.int; tel: (+41) 22 791 3818/2111; fax: (+41) 22 791 4854; or Rob Ridley, Manager, Steering Committee on Drugs Discovery Research; E-mail: ridleyr@who.int; tel: (+41) 22 791 3884; fax: (+41) 22 791 4854.

SPIN online

This is a free abstract service for anyone with an interest in science policy. *SPIN* (*Science Policy Information News*) is published weekly by the Unit for Policy Research in Science and Medicine (PRISM) at the Wellcome Trust.

SPIN is a collection of article abstracts with relevance to biomedical science policy. Issues covered include UK research policy, funding, employment and research ethics.

The articles are abstracted from a large number of relevant medical and scientific journals as well as other publications concerned with higher education and research issues, ranging from *BMJ* (*British Medical Journal*) and the *Lancet* to the *THES* (*Times Higher Education Supplement*) and *The Guardian.*

SPIN is a popular publication with scientific researchers and policy makers in both the UK and abroad.

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WHO: the new structure

The following is taken from *TDR News* (UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases), No 58, February 1999, pages 1 and (conclusion) 12:

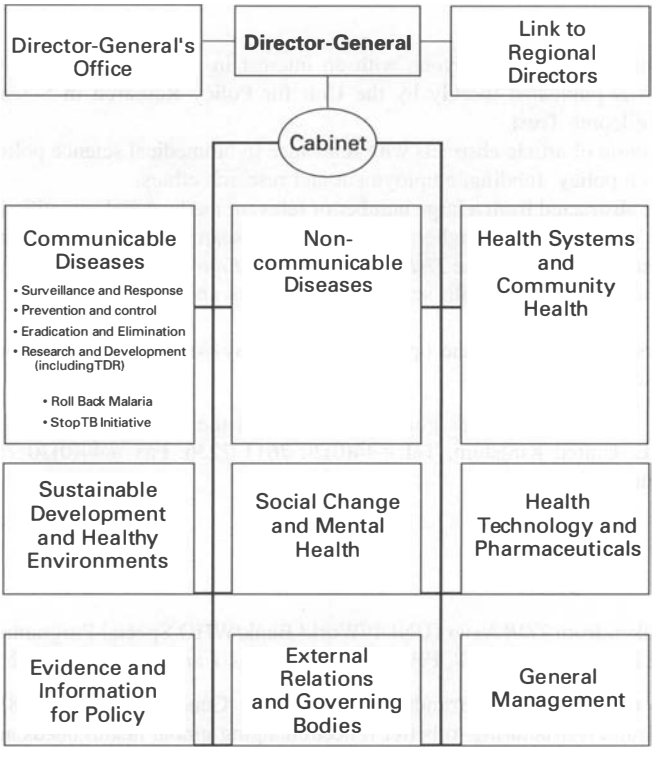
Since the advent of Gro Harlem Brundtland as Director General in July 1998, WHO has been undergoing a profound restructuring to better reflect changing global health needs and priorities.

Dr Brundtland has also been championing the role of the private sector as another vital player in the changing response to meet the world's health needs, especially in technology development and provision of health services. 'We need open and constructive relations with the private sector and industry, knowing where our roles differ and where they may complement each other' said Dr Brundtland.

Apart from the private sector, Dr Brundtland is also reaching out to NGOs, whose influence 'goes beyond that of any official body'. She is also intent on making a difference from grassroots level (combatting disease, premature death and disability) to policy-making level, and has established a separate function on Evidence for Health Policy— 'WHO will speak out for health, back its case with solid evidence and thereby be a better advocate for health towards a broader audience of decision-makers', she says.

Although still a 'Special Programme', and an entity independent of WHO, TDR is now managed administratively along with several other programmes in a 'cluster' concerned with Communicable Diseases (CDS), headed by David Heymann, former director of the Division of Emerging and other Communicable Diseases Surveillance and Control. The CDS cluster has four departments, of which one is 'Research and Development including TDR', and Carlos Morel is Director of this Department. This means that, for the first time, the WHO structure as a whole has a R&D section. Joining us in CDS are the erstwhile WHO programmes on Control of Tropical Diseases, the Action Programme for the Elimination of Leprosy, the Global Tuberculosis Programme, the Division of Emerging and other Communicable Diseases Surveillance and Control, and the WHO project known as Roll Back Malaria.

But what does this mean for TDR? How integrated will TDR become in the new WHO? Will TDR eventually lose its status as a Special Programme? Will TDR broaden its disease portfolio? Will TDR's established good contacts and working practices with industrial partners serve as a guide for improved



collaboration with the private sector? As yet, these questions and others remain unanswered. Answering them will involve TDR's governing bodies—the Standing Committee, the Scientific and Technical Advisory Committee, and the Joint Coordinating Board, as well as the scientific and donor communities.

As to Dr Brundtland's emphasis on the private sector, a number of initiatives in which TDR is involved are already taking off.

Periodicals and serials published by the World Health Organization

Bulletin of the World Health Organization

The International Journal of Public Health

Presents original research findings selected on the basis of their immediate or potential relevance to problems of human health. Although editorial scope includes all topics relevant to international public health, priority is given to research that advances understanding of health problems in the developing world.

Beginning in 1999, the journal's traditional editorial scope has been expanded to include papers of direct practical relevance to public health policy and practice. By placing scientific findings together with policy-relevant discussions, WHO aims to help ensure that decisions and practices affecting human health are based on the best scientific evidence available. The *Bulletin* now appears, in its expanded format, in monthly issues.

ISSN 0043-9686; monthly
1999 (Vol. 77): Sw.fr. 200·–/US $160·00

International Digest of Health Legislation

The only periodical that allows readers to follow worldwide developments in laws and regulations designed to protect public health and the human environment. Scope includes any new or amended legal text, whether national or international, that has a bearing on health protection or medical care. In recent years, the *Digest* has become a key reference to new AIDS legislation enacted throughout the world.

ISSN 0020-6563; quarterly
1999 (Vol. 50): Sw.fr. 230·–/US $184·00

Weekly Epidemiological Record

An essential instrument for the collation and dissemination of epidemiological data useful in disease surveillance and control on a global level. Priority is given to data on diseases known to threaten international health. The *WER* also serves as a medium for conveying technical and practical experiences relevant to WHO-sponsored programmes such as those for the control of tuberculosis, the elimination of leprosy, the expansion of immunization coverage, and the eradication of poliomyelitis and guinea-worm disease. Data on AIDS include updates on the global number of cases.

Weekly issues can now be accessed electronically at the following address: http://www.who.int/wer/

ISSN 0049-8114; weekly
1999 (74th year): Sw.fr. 230·–/US $184·00

WHO Drug Information

Communicates drug information that is either developed and issued by WHO or transmitted to WHO by

research and regulatory agencies throughout the world. News briefs, which may number more than 50 items per issue, serve to alert manufacturers and prescribers to:

— newly detected side effects
— dangerous drug combinations
— drugs considered contraindicated in certain patient groups
— amendments in product information
— changes in treatment of choice for specific disorders

The Journal also includes regular presentation of newly recommended International Nonproprietary Names (INN) for Pharmaceutical Substances.

ISSN 1010-9609; quarterly
1999 (Vol. 13): Sw.fr. 75·–/US $60·00

WHO Technical Report Series

Since the inception of the World Health Organization in 1948, the *WHO Technical Report Series* has served as a mechanism for collecting the views of international experts on technical issues crucial to the improvement of human health. Each volume in the series, which has released close to 900 titles, records the consensus reached by a group of experts commissioned to advise the world's scientific and medical communities on the best way to tackle a selected health or medical problem.

ISSN 0512-3054; approximately 10 volumes in 1999
1999: Sw.fr. 132·–/US $106·00

Environmental Health Criteria Series

This series was launched in 1976 in response to concern over the risks to human health and the environment posed by the growing number of chemicals on the market and in the environment. In planning the series, the aim was to give national authorities all the information needed to understand the specific hazards posed by a chemical and then devise appropriate protective measures, whether for the health of workers, the safety of the general public, or the survival of the environment.

In keeping with this aim, volumes in the series issue authoritative conclusions about human and environmental risks based on a study of virtually everything ever written about a selected industrial chemical. To date, over 200 chemicals and other environmental contaminants have been critically assessed.

ISSN 0250-863X; approximately 12 volumes in 1999
1999: Sw.fr. 242·00/US $194·00

Further information: WHO, Marketing and Dissemination, CH-1211, Geneva 27, Switzerland. Tel +41 22791 2476. E-mail: publications@who.ch

Eliminating world poverty: new strategy from the Department for International Development, UK

The following is extracted from *International Health Matters* (details below) Issue 3, December 1998, page 3:

The Department for International Development (DFID) replaced the Overseas Development Administration (ODA) following Britain's general election in May 1997. Unlike ODA, DFID is a separate

government department, independent of the Foreign and Commonwealth Office. DFID is headed by a Cabinet minister, Clare Short, who is Secretary of State for International Development.

In November 1997, the Government published a major policy document (a White Paper) on international development, under the title *Eliminating World Poverty: a challenge for the 21st Century* (available from Her Majesty's Stationery Office, or from DFID's Web site at http://www.dfid.gov.uk). This White Paper commits DFID to the goal of eliminating poverty in poorer countries—that is, the developing countries of Africa, Asia, Latin America and the Caribbean, and the countries of Central and Eastern Europe and Central Asia that are now undergoing economic and political transition.

DFID is working with partners toward the internationally agreed development target of a 50% reduction in the proportion of people living in extreme poverty by 2015.

Improving health is a key component of poverty elimination, not only because poverty increases the risk of ill-health, but also because illness tends to impede poor people's escape from poverty. DFID is committed to meeting three international development targets for health and population by 2015:

- a two-thirds reduction in the mortality of infants and children under 5 years,
- a 75% reduction in maternal mortality,
- access to reproductive health services for all individuals of appropriate ages.

In order to use scarce resources in a way that gives the greatest benefits to poor people, DFID wants to discover and test new interventions; to find out which ones work best; to identify the most cost-effective measures for different settings; and to determine the most equitable ways to deliver them. Health policy makers, health care practitioners and the public all need reliable evidence concerning the feasibility, effectiveness and equity implications of different strategies for disease prevention and control, and of different approaches to the organisation, financing and management of health care systems. DFID helps make the necessary knowledge available and accessible by:

(i) promoting a pro-poor international health research agenda in its dialogue with other UK and international funders of health research,
(ii) supporting a range of knowledge-related activities.

In July 1998, DFID's Health and Population Knowledge Strategy was revised to reflect the policy changes set out in the White Paper. DFID's Health and Population knowledge priorities and channels for the support of knowledge activities are detailed in the Health and Population Knowledge Strategy Paper for 1998–2001, which is available on request from: Knowledge Section, Health and Population Division, DFID, Room V217, 94 Victoria St, London SW1E 5JL, UK. E-mail: T-Burdett@dfid.gtnet.gov.uk.

International Health Matters is a digest of information about research funded by the Health and Population Division of the UK Government's Department for International Development (DFID). Each issue reports both completed and ongoing research on a particular subject, and also includes details of other projects funded by the Health and Population Division. *International Health Matters* is published twice a year.

Editor: Robert Cole, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA. Tel: +44(0)151 708 9393. Fax: +44(0)151 707 1702. E-mail: rcole@liv.ac.uk.

Rapid health assessment protocols for emergencies

1999, vi + 97 pages (available in English; French and Spanish in preparation) ISBN 92 4 154515 1. Sw.fr. 31·–/US $27·90. In developing countries: Sw.fr. 21·70, Order no. 1150463

This book provides a collection of 10 protocols for conducting rapid health assessments in the

immediate aftermath of different types of emergencies. Noting the vital importance of rapid and accurate information in the earliest stage of an emergency, the protocols respond to the urgent need for common standardized technical tools for assessing damage, gauging health risks, and gathering the information immediately needed by decision-makers at the national and international level.

The protocols were prepared by WHO in collaboration with a large number of international agencies and experts with broad experience in the field of emergency management. Although all protocols follow a common format, each is specific to the circumstances, potential hazards, and immediate information needs that characterize a distinct type of emergency. Emphasis is placed on the exact information needed, the best sources of data and methods for rapid collection, and the specific questions that need to be answered in order to draw initial conclusions and direct immediate actions. Although the advantages of using experienced assessments teams are stressed, the book also explains how the protocols can be used to train general health workers as part of emergency preparedness.

The book opens with an introductory protocol covering the aims and methods, responsibilities, complexities, and inherent difficulties of rapid health assessments. Addressed to health authorities as well as assessment teams, the chapter also includes abundant advice on preparedness for emergencies. Details range from the comparative need for speed in different types of emergencies, through a suggested format for presenting the results of assessments, to a list of common logistic, organizational, and technical errors. Advice on the best working practices, including ways to avoid being an 'emergency tourist', is also provided.

Against this background, the additional nine protocols are presented according to a common format which covers the purpose of the assessment, preparedness, the steps to follow during the assessment, assessing the impact on health, assessing local response capacity and immediate needs, and presenting results. A general protocol on epidemics of infectious origin is followed by protocols specific to meningitis outbreaks, outbreaks of viral haemorrhagic fever, including yellow fever, and outbreaks of acute diarrhoeal disease, with information specific to dysentery and cholera.

Sudden-impact natural disasters are covered in the next protocol, which includes a day-by-day list of information priorities for different stages of the disaster. A protocol dealing with sudden population displacements offers guidelines for conducting rapid health assessments in all emergencies caused by sudden displacement of refugees or population groups within a country. Included are a sample checklist for rapid assessments and a sample form for weekly reports on morbidity and mortality. Subsequent protocols deal with the special situations of nutritional emergencies and chemical emergencies, including those caused by food contaminated with chemicals or toxins. The final protocol addresses the difficult task of conducting assessments in complex emergencies in which the cause of the emergency, as well as the assistance to the afflicted, is complicated by intense levels of political considerations. The protocol includes a form which has recently been used for rapid health assessment at local level in Bosnia and Herzegovnia.

The book concludes with a brief summary of survey techniques, followed by a tabular presentation of reference values for assessing needs, hazards, and logistic requirements in developing countries.

Two LECS in Bangladesh and Nepal

Bangladesh and Nepal are two Asian countries which are embarking on National Leprosy Elimination Campaigns in order to further the drive towards elimination within the target year of 2000.

Bangladesh has already reduced the estimated prevalence from about 13 cases per 10,000 population in 1991 to the current level of 3·3 per 10,000, and the caseload has fallen from 136,000 in 1991 to an estimated 40,000. There is every hope that the country will achieve the elimination goal. Nepal had a registered prevalence of 6·2 per 10,000 in 1996 and had brought this down to 5·3 per 10,000 2 years later, but the new case detection rate has remained at a high level of 3 to 4 cases per 10,000 for the last 3 years.

Bangladesh has planned a large-scale LEC between 7 and 12 February this year, drawing on the

resources of all available general health staff, NGO workers, local leaders, schoolteachers and volunteers from the communities affected. These were expected to total around 47,500. Imams and priests were being recruited or at least asked to mention the salient facts about leprosy during their weekly discourses in the 50,000 mosques of the country.

As many as possible of these 'human resources' were being given some degree of training or orientation. Extensive use was to be made of the meda, both electronic and print. Television 'spots' were being broadcast at prime time, twice a day over a period of 30 days, while radio jingles conveyed appropriate messages and special press conferences were arranged. A total of half a million flyers were being printed, underlining that leprosy *is* curable, thanks to MDT.

Nepal's Nationwide LEC (NLEC) was planned for 31 January to 5 February in 27 hyper-endemic districts with the main objective of detecting all existing cases, including the backlog of 'cases of consequence.' Besides generating community awareness and widespread support for leprosy elimination activities, there was to be a high degree of capacity building among health workers to undertake assigned tasks during and beyond the NLEC. A deliberate effort will be made to bring MDT services—including initiating appropriate WHO-MDT regimens for MB and PB cases and single-dose ROM for single-lesion PB cases—as near to the patients as possible.

Around 1300 general health service personnel were to have a 1-day training course, and 14,000 voluntary health workers would also receive training. Orientation was offered to members of Village Development Committees.

Many thousands of posters, pamphlets and stickers were being prepared as well as announcements in newspapers. BBC-MPM (the London-based Marshall Plan of the Mind sponsored by the BBC) was helping the Nepalese government to arrange television advertisements, radio spots, drama productions for both TV and radio, and radio question-and-answer sessions. Street dramas and anti-leprosy rallies all formed part of the campaign. Every household in all villages and municipalities in the districts were to be visited by around 6600 two-member teams to look for suspected signs and symptoms of leprosy cases, and every case detected was being assured of a cure through MDT. Altogether 10·7 million population were being covered by this NLEC.

Reproduced from *LEP NEWS*, March 1999

Research Awards in Tropical Medicine for Young Investigators, 1999–2000: The Wellcome Trust, UK

The Trust encourages young science, medical and veterinary graduates from the UK/Republic of Ireland and abroad to pursue research in tropical medicine by providing opportunities for training and for undertaking research projects in the tropical countries of the world. Studies on all aspects of health and disease in the tropics including both infectious and non-infectious human diseases in developing countries are encouraged, together with research relating to veterinary problems in these regions. Cancer and AIDS/HIV-related studies relevant to tropical regions are acceptable.

Fellowships in Tropical Medicine

Research fellowships provide for research into diseases of developing countries. Fellows will normally carry out the majority of their research project abroad.

Advanced training fellowships provide an opportunity for individuals to train in scientific skills that will enhance their ability to carry out research in the field of tropical medicine. Fellows will be expected to undertake research training in a discipline that differs from their previous experience. A period of training may be spent in an appropriate overseas laboratory.

These awards are open to postdoctoral basic scientists and to veterinary graduates with a minimum of 2 years' research experience. Candidates should be graduates of a UK/Republic of Ireland university,

or be overseas graduates who have worked for at least 3 years in a UK/Republic of Ireland university, hospital or research institute. Awards are usually for 3 years and are tenable in a UK/Republic of Ireland university.

The closing date for submission of full applications to the Trust for the coming year is **4 October 1999**. Interviews will be held in February 2000.

Research Development Awards

These awards are to enable young clinical (medical or veterinary) and non-clinical researchers from developing countries to establish a programme of research within their home institution with the continued collaboration and support of a UK/Republic of Ireland sponsor. The candidate must have recently completed PhD training or held a research fellowship in the UK or Republic of Ireland. Research proposals should address issues of health and disease that are of regional significance in the country concerned.

All applicants must hold a full-time established post in an appropriate university or research institute in a developing country. Awards are tenable for a maximum period of 3 years. The Trust will provide funds for research and equipment within the applicant's home institution, some assistance towards research costs in the UK/Republic of Ireland and funds for exchange visits.

Applications are considered three times a year and the closing dates for submission of full applications for the next year will be **16 November 1998, 14 February 2000 and 31 July 200**.

Enquiries should be directed to: **The Grants Section (Tropical), The Wellcome Trust, 183 Euston Road, London, NW1 2BE, UK. Tel: +44(0)20 7611 8409/8641. Fax: +44(0)20 7611 7288. E-mail: tropical@welcome.ac.uk**

Further details of this and other schemes that may be relevant to individuals, especially medical and veterinary graduates, with an interest in tropical medicine are available upon request from the Trust and can be found at **www.wellcome.ac.uk.**

NB: *Applicants may not apply for more than one Trust fellowship scheme at any one time.*

Publications from Healthlink Worldwide (formerly AHRTAG)

Healthlink Worldwide (formerly AHRTAG) publishes newsletters, resource lists, manuals and briefing papers containing practical information for health and development workers.

Healthlink Worldwide's four newsletters—*AIDS Action, CBR News, Child Health Dialogue* and *Health Action*—are published in over 20 regional editions, reaching an estimated two million readers worldwide.

Single copies of most of Healthlink Worldwide's publications are FREE to individuals and indigenous organizations in developing countries.

NEW PUBLICATIONS

Caring with Confidence

Practical information about preventing and treating HIV infection in young children.

We Can Play and Move

Ideas for play activities that help disabled children to move and balance.

For details of these and other publications, please contact: Publications Administrator (TC), Healthlink

Worldwide, 29–35 Farringdon Road, London EC1M 3JB, UK. Tel: +44 171 242 0606. Fax: +44 171 242 0041. E-mail: publications@healthlink.org.uk. Or visit the Healthlink Worldwide website: http://www.healthlink.org.uk

Health Promotion in Developing Countries: University of London

- Do you want to develop your career in community health education and health promotion?
- Do you have experience working in a developing country?
- Do you have a professional qualification but not a first degree?
- Do you want to study by distance learning?

IF THE ANSWER IS 'YES'—then we have a new module which has been especially prepared for you. This module is called 'Concepts and Determinants of Health and Models of Health Promotion'.

What is the module about?

- This course provides a comprehensive introduction to the theory of health promotion in the context of international development. It is essentially educational and is planned for practitioners concerned with health promotion in developing countries.
- It aims to equip participants with the understanding needed to plan health promotion programmes and services.
- The distance learning package includes participatory learning materials, a reader and a text book. It comprises 8 Units:

1. **Concepts and models of health**
2. **Determinants of health**
3. **Inequalities in health**
4. **Understanding human behaviour**
5. **Concepts and models of health promotion**
6. **How adults learn**
7. **The ethics of health promotion**
8. **Communication for health**

- The course is assessed by a 4000 word essay.

How much does the course cost?

Overseas students—£750 (20 credits). Home/EU students—£495 (20 credits).

When can I start?

You can start whenever you want to but you must complete the assessment for the module within a maximum of 12 months from the time you start the module.

How can I use this course to gain a qualification?

- You can use it as part of the access route to the internal MA degree in Education and International Development: Health Promotion. (MA EID/HP)
- You can use it as part of an internal Certificate in Primary Health Care, Education and Development.
- You can also use it as part of the MA EID/HP degree if you already have a first degree.

Contact The Student Programmes Office, Institute of Education, University of London, 20 Bedford

Way, London, WC1H OAL, UK. Tel: +44 171 612 6102 or 6104. Fax: +44 171 612 6097. e-mail: Liaison@ioe.ac.uk

The St Francis Leprosy Guild, UK

The St Francis Leprosy Guild held its Annual General Meeting in May 1998. Accumulated funds totalling £283,900 were allocated to leprosy workers in Angola, Bangladesh, Bolivia, Brasil, Cameroon, Egypt, Ethiopia, Ghana, India, Indonesia, Jamaica, Kenya, Korea, Madagascar, Mozambique, Myanmar, Nigeria, Pakistan, Papua New Guinea, Philippines, Sri Lanka, Sudan, Tanzania, Thailand, Uganda, Vietnam, Zaire, Zambia and Zimbabwe.

The Guild aims to help *cure* people who suffer from leprosy (Hansen's Disease), to *rehabilitate* into the community those who have been cured wherever possible and when necessary to give residential *support* to those whose disabilities require it.

Further information: St Francis Leprosy Guild, 26 Inglis Road, Ealing, London W5 3RL. Tel: 0181-992 0799. Fax: 0181 752 0119

Dr S. K. Noordeen meets with Pune dermatologists

Dr Noordeen, former Director, Action Programme for Elimination of Leprosy, WHO, Geneva met a group of senior teaching and practising dermatologists of Pune on 9th June 1999 in an advocacy meeting organized by the Indian Association of Leprologists, Maharashtra State Branch, Bombay Leprosy Project, Hind Kusht Nivaran Sangh, and RRE Society. The main objective of this advocacy meeting was to clarify controversies and doubts about current treatment regimens for leprosy raised by the practising dermatologists. Dr Noordeen while interacting with the participants clarified the following issues.

1. The current strategy for leprosy elimination of WHO is to reach MDT to all leprosy patients to achieve leprosy elimination by the end of this century. To achieve this target, WHO simplified treatment and diagnostic technologies to suit the health workers even in the most difficult situations. The treatment strategy has been designed for a public health programme.
2. So far, more than 10 million patients have been cured in 121 endemic countries with a very low relapse rate of 0·1% annually which is much lower than for other diseases and acceptable in a public health programme. This has built up confidence in the current treatment strategy.
3. Public health treatment strategy is to eliminate all viable *M. leprae*, including drug resistant mutants with powerful drugs and allow the body to heal residual skin lesions. Any addition of drugs by the physicians after the minimum course of treatment will not be of any use either to hasten the clearance of bacterial debris or healing of skin lesions.
4. The current treatment regimens have been recommended based on WHO prospective multicentre double blind trials and retrospective data analysis of drop out patients from MDT. Both these studies have shown that 12 months MDT in MB leprosy is quite adequate as compared to 24 months MDT. The concern about high relapse rate among high BI cases reported by certain studies is limited to those studies only. Even with reduction in duration of MDT in MB leprosy one cannot expect a high relapse rate. Similarly, ROM single dose treatment in single skin lesion-PB (SSL-PB) leprosy has been evaluated in a WHO double blind controlled study and found to be as effective as 6 months MDT. As SSL-PB leprosy patients have lesser number of bacilli as compared to PB leprosy with two to five lesions, the risk of relapse rate is also likely to be very low. In a country like India, where SSL-PB leprosy is very high, this regimen would be quite suitable to save manpower and resources. As such self-healing rate is also very high in such cases.
5. There is a concern about high risk of relapse in MB leprosy patients, as their nerves are likely to

harbour higher proportion of bacilli. However we have no knowledge about viable proportions in the nerves. The risk of relapse rate is acceptably on the lower side in MB leprosy.

6. A large majority of reported new cases are backlog-hidden prevalence and not incidence cases. It is difficult to assess the incidence rate at this stage. Currently India contributes more than 60% of the global caseload. In all probability India may not be able to reach the target of leprosy elimination by the turn of this century.

Dr Noorden expressed his satisfaction over increasing interest shown by the dermatologists over a period of time in different countries. However he pointed out that only about 10–15% of leprosy patients are handled by dermatologists as compared to about 80–90% of TB patients by the private physicians. Of course, dermatologists will be dominating the field of leprosy in years to come.

Dr C. R. Revanker
Honorary Secretary, IAL-MB

Immunotherapy with *Mycobacterium vaccae*

The following summary is taken from a paper submitted to the *Lancet*, July 10, 1999 by the Durban Immunotherapy Trial Group. The commentary is by Dr Lee B. Reichman, and is taken from the same issue.

Summary

Mycobacterium vaccae, an environmental saprophyte, has immunogenic properties that enhance the host immune response. Immunotherapy with *M. vaccae* has been suggested to shorten short-course antituberculosis chemotherapy. We tested the hypothesis that the addition of *M.* vaccae to standard short-course antituberculosis chemotherapy would decrease the time to achieve a negative sputum culture. Patients with newly diagnosed tuberculosis were randomly assigned an injection of saline (placebo) or *M vaccae* on day 8. All patients received antituberculosis chemotherapy with rifampicin, isoniazid, pyrazinamide, and ethambutol. Sputum samples were checked by microscopy and culture every week for the first 8 weeks and monthly until the end of chemotherapy at 6 months. The primary outcome was the time to a negative sputum culture in the first 8 weeks. Intention-to-treat analysis was used and time to sputum clearance was assessed by log-rank test and Cox's proportional-hazards regression. A total of 172 patients received *M. vaccae* and 175 patients received placebo. At 8 weeks, 70 patients in the *M. vaccae* group and 65 patients in the placebo group had a negative culture; there was no difference between groups in the time to a negative culture ($P = 0.83$). There was no interaction between HIV status and treatment. *M. vaccae* immunotherapy was concluded to have no benefit when added to standard antituberculosis chemotherapy.

Commentary

Whither *Mycobacterium vaccae?*

Tuberculosis used to be feared and respected, but more recently it has also been taken for granted and even ignored. The paradox that this preventable, curable disease remains, of any single infection, the greatest killer is difficult to understand and impossible to accept.

Few diseases have been as extensively studied. The most reliable information on treatment became available after the introduction of randomized controlled trials (RCTs), the first of which on tuberculosis was published 50 years ago and related to the use of streptomycin.

The history of tuberculosis is one of disappointment – of therapeutic measures that, in many instances, were fads. Many were sincere, some were misguided – for example, horseback riding, sea voyages, blood letting, blistering, purging, starving, vomiting, cupping, leeches, counter-irritants, strict bed rest, lung-collapse therapy, phrenic crush, thoracoplasty, pneumoperitoneum, and plombage with paraffin, oil, bone fragments, or Lucite spheres.

The introduction of antibiotics with specific effects on tubercle bacilli led to great celebration (patients dancing in the aisles at New York's Seaview Hospital) but RCTs from the UK Medical Research Council, US Armed Forces, Veterans Administration Hospitals, US Public Health Service, and now the US Centers for Disease Control's Tuberculosis Trials Consortium have shown the strengths and weaknesses of new drugs and rhythms of administration.

Why RCTs are so critical for tuberculosis was stated in a leading article with the first RCT in 1948: 'In few infections is it so difficult to assess the results of treatment as in pulmonary tuberculosis, with its varied clinical picture and unpredictable course. Remarkable recoveries can take place with no treatment except rest in bed'.

It is against this background that the *Mycobacterium vaccae* story has lamentably come to a close. Lamentably, because *M. vaccae* immunotherapy was far more plausible and intellectually promising than some of the bizarre interventions mentioned above. *M. vaccae* was expected to be successful because the hosts' own immune response had long been suspected to be an effective 'cure' for tuberculosis, and several studies have yielded positive results and been widely publicized.

However, for ultimate proof, *M. vaccae* immunotherapy still had to be tested in an RCT. The conclusion, from the RCT of the Durban Immunotherapy Trial Group published in today's *Lancet*, is inescapable – *M. vaccae* has virtually no effect, positive or negative, on tuberculosis.

Two questions remain. First, why is there the discrepancy between past reports and this definitive one? The most likely explanation is that the earlier studies may well have had design problems resulting in biased observations that were obviated by an RCT.

The more important question is what the next step is. A few years ago in an unprecedented pronouncement, the WHO declared tuberculosis to be a 'global health emergency', the only disease ever so designated. Since then there has been an increase in the prevalence of multiple-drug-resistant tuberculosis (MDRFB) and its transmission worldwide, and MDRTB propagation, especially in Russian prisons with failure of the WHO retreatment regimen, has been reported.

The Durban study shows that a plausible therapy for tuberculosis has been lost. But the finding is an urgent reminder to health-care workers and policymakers of the seriousness of the global tuberculosis situation. The findings should once again underscore the necessity of addressing the crisis immediately, not only by expanding WHO's DOTS strategy, but also with a major research effort to find an effective vaccine and new, better, less toxic drugs and routes of administration, and most importantly the political will and commitment to bring all this about.

Instructions to Authors

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