# LEPROSY REVIEW

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#### Leprosy Review

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

#### LEPRA

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# **Editor's Choice**

This issue opens with two complementary studies by medical students looking at sensory of the foot and the development of plantar ulcers. Mitchell tested healthy skin adjacent to ulcers to determine the level of protective sensation. In this small study, being able to perceive the 10 g monofilament protected against the development of ulceration whereas perception of a 30 g monofilament did not give protection. Feenstra *et al.* tested a larger Ethiopian group all of whom were unable to detect the 10 g monofilament. In this group, the 10 g monofilament was the most sensitive test, but only 43% of feet with this level of sensory loss developed ulcers. Other tests such as vibrometry or examination of functional anatomy were not more sensitive. The encouraging implication of this finding is that patients can protect their feet and stop ulceration. We shall soon be reporting the findings of the self care groups in Ethiopia, this being one social intervention aimed at reducing ulceration.

Meima *et al.* report on the dynamics of impairment. They have used the Eye-Hand-Foot scores to track the disability level of a cohort of patients. Being impaired at entry was the most important predictor of future impairment. In this cohort of the MB patients 56% had impairments at the start of their treatment and 43% improved or recovered whilst 13% worsened and 21% of those without impairments worsened at release from treatment. The post treatment follow-up was only 24–48 months but this and the succeeding years may be critically important, patients may still experience late reactions and they may deteriorate with secondary impairments (ulcers and tissue loss). Planning and funding services for these treated patients is a major challenge now.

Margaret Hogeweg, in her editorial on blindness in leprosy, highlights the importance of cataract and the importance of ensuring that patients are screened and referred for cataract surgery. There should be no barriers for ex-leprosy patients to receiving surgery.

After the special issue on the Leprosy Elimination campaigns [Lepr Rev 70(4) Dec 1999], it is good to have some follow-up. One worry about the LECS was that the treatment completion rates would be low as the campaign enthusiasm waned. Fortunately this has not happened in Nigeria where the completion rates have been 96%, an astounding result anywhere. Defaulters remain a problem in Mozambique, as detailed by Griffiths and Ready, where the leprosy control programme is being rebuilt after the unrest. In 1993, 60% patients were defaulting, although this has now fallen to 23% defaulters tend to default early. Thus early defaulters should be focussed on rather than hoping that they will return later.

The *M. leprae* genome has now been published and to celebrate this we shall be devoting the December 2001 issue to exploring the genome and looking at the possibilities this offers to leprosy research and control.

Diana NJ Lockwood

# **Call for Papers**

# INTEGRATION OF LEPROSY CONTROL WITH PRIMARY HEALTH CARE

Papers are sought for a special issue of *Leprosy Review* on the topic of integration of leprosy control with primary health care.

Leprosy has traditionally been managed by specialized vertical services in most endemic countries. However, with declining prevalence and shortened treatment, it is increasingly argued that general health care staff could, and should, be able to manage leprosy without a significant increase in their workload. Integration will strengthen the ongoing decentralization processes within the health services. Successful integration of leprosy services will be an important demonstration of operational capability to achieve similar goals in other disease specific campaigns. But what will it mean for the quality of care of people affected by leprosy and for leprosy workers?

The June 2002 issue will focus on Integration, setting out the theory and practice on how effective and sustainable leprosy control can be achieved through its integration with the work of the general or primary health care system. We are eager to publish as much data as possible in this special 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 by **December 2001** at the latest and will go through the usual peer review process.

Lepr Rev (2001) 72, 139-142

# Editorial

# CATARACT: THE MAIN CAUSE OF BLINDNESS IN LEPROSY

World-wide in year 2000 there were approximately 20 million people blind from age-related cataract.<sup>1</sup> Cataract is estimated to be responsible for at least 40%, and often more, of all blindness. [Blindness is defined as a visual acuity (VA) of less than finger counting at 3 m (<3/60) with the better eye; and severe visual impairment as a VA of less than finger counting at 6 m (<6/60) with the better eye.]

Cataract blindness is increasing, due to population growth and increasing longevity, combined with insufficient eye care services. Surveys have shown that 0.7-1% of the population in developing countries suffer from blindness, of which 40-80% is due to cataract. Cataract blindness increases dramatically above the age of 50 years, and in developing countries, lens opacification seems to start about 10 years earlier than in industrialized countries. In India alone, 8.4 million people are thought to be blind or severely visually impaired from cataract.

Blinding eye complications, specifically due to leprosy, have become relatively uncommon since the introduction of multidrug therapy (MDT) for leprosy and with earlier detection of disease. Thus age-related cataract is now the single most important cause of blindness, even amongst leprosy patients. Courtright<sup>2</sup> in 1997 estimated a total of 350,000-400,000leprosy patients suffering from blindness, of which about half was due to non-leprosy causes, mainly cataract. In a multicentre study of 844 blind eyes in leprosy patients, nearly half of the blindness was directly or indirectly related to cataract,<sup>3</sup> and in a retrospective study among 678 patients in Uganda<sup>4</sup> 1.3% were found to be blind, of which nearly half was directly related to leprosy. Cataract was the most common cause of blindness. In Nepal, among 260 newly diagnosed and untreated leprosy patients, 47 (18%) had some lens opacity or were aphakic, making it the most common eye lesion seen,<sup>5</sup> and in a recent 11-year follow-up study from Korea,<sup>6</sup> 87% of incident cases of blindness were due to cataract.

In addition to age-related cataract, steroid-induced cataracts may occur in leprosy patients on long-term steroids for recurrent reactions. Steroid treatment to prevent permanent nerve damage has priority and should continue in spite of cataract formation. Vision loss from cataract is reversible by surgery at a later stage. Secondary cataract may also develop in recurrent or chronic uveitis. In multibacillary (MB) patients with pinpoint pupils, centrally located, even small, lens opacities have a great impact on visual acuity. Age-related and secondary cataract due to steroids or chronic uveitis tend to become bilateral, and MB patients seem more prone to develop cataract than paucibacillary (PB) patients.<sup>7</sup>

Typically, patients with cataract are elderly and give a history of gradual and painless loss

of vision. Mature cataract presents as a gray-white opacity behind the pupil. Immature but visually disturbing cataract, in particular posterior subcapsular cataract, cannot be diagnosed so easily, but can be recognized by obscuration of the red reflex observed with a direct ophthalmoscope. Assessment of visual acuity and pupillary reaction are essential. Impaired visual acuity with a 'grayish' pupil in an elderly person is not always due to cataract. Retinal and optic nerve diseases as well as chronic glaucoma and changes in refraction may be the cause of gradual loss of vision. It is important that leprosy staff recognize visual impairment in elderly patients on MDT and in elderly RFT patients in 'care after cure' programmes.

The only treatment for cataract is surgery. Indications for cataract surgery will vary with the setting. In leprosy, disability grade 2 is defined as 'cannot count fingers at a distance of 6 m (<6/60)'. This is the level of severe visual impairment. A visual acuity of <6/60 with the better eye is thus a definite indication for referral to the eye care services for diagnosis and if cataract is confirmed, cataract extraction. Referral alone, however, may not be sufficient, and transport and subsidy for surgery may need to be provided in order for the patient to obtain treatment.

Cataract surgery has undergone significant developments in recent years. An array of different techniques is now available, from simple, low tech ICCE with aphakic spectacles; to ECCE, with or without artificial lens implantation (IOL); to small incision, sutureless techniques of lens removal with IOL; and finally high-tech and costly phako-emulsification. All lead to sight restoration, if performed well. Cataract surgery with IOL implantation has definite advantages. The quality of vision is better and it avoids the problem of lost or broken aphakic spectacles and the optical problems of correction of unilateral aphakia. With modern implant surgery the requirement of the cataract to be 'mature' is no longer necessary. IOL surgery is of extra advantage for leprosy patients, who may have collapsed noses that will not easily hold heavy spectacles, or severely damaged hands, which cannot handle spectacles. If IOL surgery is not possible for whatever reason, then good quality aphakic spectacles (S+10) should be provided at the time of discharge, as an integral part of the treatment.

The great majority of cataracts in leprosy patients are age related and in such patients the result of cataract surgery with IOL is assumed to be equal to surgery in non-leprosy patients. Intra-ocular involvement due to leprosy may be seen in elderly patients with long-standing MB disease. Small, distorted and non-dilating pupils, iris atrophy, posterior synechiae, anterior staphyloma, possibly complicated by corneal anaesthesia and corneal scarring from exposure keratitis, will make cataract surgery more challenging and the prognosis more guarded. A history of uveitis is associated with more intra-and postoperative complications, and the risks and benefits of surgery in such patients need to be considered. Experienced surgeons should operate on patients with complicated cataract and postoperative control with intensive steroid treatment may be necessary.

Patients with complicated cataract comprise not more than 5-10% of all leprosy cataracts, although this percentage depends on the setting, being less in a general leprosy programme, and more in a leprosy settlement where patients have a long history of disease and severe disabilities. No prospective studies have been published on the results of cataract surgery with IOL in patients, with or without intra-ocular involvement. Such studies, with a follow-up of at least 1 year, are needed.<sup>8</sup>

Eyes with lagophthalmos and lower lid laxity are more prone to chronic conjunctivitis. Patients with nose collapse may have blocked lacrimal sacs and chronic discharge. Any infection carries a risk of causing postoperative endophthalmitis, a disastrous complication of intra-ocular surgery. Such conditions must therefore be treated before cataract extraction can be undertaken. Eyes with active uveitis should be deferred until the inflammation is under control. Leprosy patients with anaesthetic limbs and blind from cataract cannot avoid trauma and wounds, and are therefore prone to develop ulcers. Surgeons may be reluctant to operate on such patients, because of fear for infection. They are thus in a vicious circle – they receive injuries because they cannot see, and because they have injuries, they cannot be operated on to improve their vision. Surgeons should be encouraged to operate once the wounds are 'clean' and granulating. Ideally, smear positive MB patients should be treated with MDT before cataract surgery, and any immune mediated reactions should be controlled first.

Where surgical facilities are available, there may be other barriers that have to be overcome before patients will accept cataract surgery. These can be summarized as: A, Awareness; B, 'bad services'; C, cost; and D, distance.

- A. Patients or caregivers may not be aware of the possibility to restore eyesight in cases of cataract, or may consider themselves 'too old'. Health care staff may not be aware of poor vision in their patients.
- B. The outcome of surgery or general care may have been disappointing in previous patients, and this will discourage new patients.
- C. Costs are a major constraint, not only for surgery, medicines, admission and cost of food, but also because of travel cost and loss of income for the escort.
- D. Distance to a surgical facility and lack of transport, and the unfamiliar environment in the city, may be significant barriers.

For leprosy patients, in addition, there is the stigma, which makes access to general health facilities often more difficult. Some eye departments are not willing to admit manifest leprosy patients. Cataract surgery for blind or severely visually impaired leprosy patients is an essential part of the prevention of disability. Leprosy programmes should therefore establish a collaborative agreement with the nearest eye-care unit for referral and surgery of such patients.

Severely disabled patients often cluster in leprosy settlements and are therefore easily accessible. Often little can be done, but cataract blindness can be cured. Programmes responsible for such patients can arrange for annual eye screening and surgery for those with visual loss due to cataract and other treatable conditions, such as severe lagophthalmos with exposure keratitis. Surgery in age-related cataract, in otherwise unaffected eyes, should preferably be with IOL implantation, provided that the expertise and necessary infrastructure are available. Surgery can be offered at the leprosy institution or settlements.

In conclusion, cataract has become the commonest cause of blindness in leprosy. Leprosy patients may experience the additional barrier of stigma and difficult access to the eye care services. The prevalence of cataract blindness among leprosy patients may therefore be higher then in the general population. Specific groups, such as those living in settlements, should be targeted for annual screening with arrangement for surgery. Otherwise, cataract surgery for leprosy patients should be part of regular POD services and preferably performed through the general eye care services.

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# The threshold for protective sensation that prevents neuropathic ulceration on the plantar aspect of the foot: a study of leprosy patients in a rural community in India

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Summary The protective sensation threshold is an important concept in the prevention of plantar ulceration in leprosy patients. Previous studies have suggested that skin with sensory nerve damage on the plantar aspect of the foot which can still detect the 5.07 Semmes-Weinstein monofilament ( $\sim 10$  g) is highly unlikely to develop ulceration. While the threshold is thought to be less than the 6.10 filament  $(\sim 75 \text{ g})$ , no work just testing adjacent to current ulcers has been undertaken to assess this more accurately. This is important, as it has been shown that a significant proportion of healthy individuals who wear sandals or go barefoot in India may fail to detect this 5.07 filament in at least some areas of the sole, especially in older age groups, and in certain cases the 5.46 filament ( $\sim$ 30 g) is the lightest detected. In an attempt to address this problem, a cross-sectional study on 26 current plantar ulcers in male adults with stable neuropathy due to leprosy was carried out in the rural town of Salur, India. It was confirmed that the ability to detect the 5.07 filament ( $\sim 10$  g) did prevent the development of ulceration while in contrast the ability to detect the 5.46filament ( $\sim 30$  g) did not. This suggests that the threshold for protective sensation lies between these two filaments. An approach is suggested which may help to differentiate feet genuinely at risk of ulceration from those merely unable to detect the 5.07 filament on account of thickened skin callus or advancing age.

#### Introduction

Ulceration on the plantar aspect of the foot is a frequent complication of neuropathy due to leprosy.<sup>1–3</sup> It is important for clinicians to know when nerve damage has progressed to the point where the skin is at risk of developing ulceration, if subjected to certain insults such as shear stresses from walking. Protective sensation is a term which has been used to describe the level at which the sensibility threshold of the skin to light touch stimuli is still sufficient to prevent the formation of ulcers.<sup>4–6</sup> Any further impairment in sensibility beyond this level

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means that there is insufficient sensory awareness in the skin to detect the insults which have the potential to lead to significant tissue damage and subsequent ulceration.

While a number of techniques have been used to assess sensibility to light touch stimuli in the skin,<sup>7-9</sup> Semmes-Weinstein graded nylon monofilaments are known to be a sensitive, reproducible and practical method.<sup>10-12</sup> These filaments have be used in apparently healthy skin adjacent to ulceration to determine the sensibility in that skin. In criticizing this method, it could be argued that only testing at the ulcer site itself would give the true sensibility, but this is clearly not possible once the ulcer has developed, nor after healing, when thickened scar tissue together with the potential for neurological improvement will complicate interpretation of results. The ideal approach, a large prospective study with frequent testing of locations across the sole to determine sensibility prior to the formation of any ulcers, has yet to be undertaken. However, it has been shown in a cross-sectional study testing adjacent to ulcers that skin which is able to detect the 5.07 filament ( $\sim 10$  g) is highly unlikely to develop plantar ulceration while skin able to detect the 6.10 filament ( $\sim$ 75 g) is still at risk of ulceration.<sup>4</sup> It is believed that the threshold of protective sensation for the plantar aspect of the foot must therefore lie somewhere between 10 g and 75 g, but no studies specifically testing skin adjacent to current ulcers have used a filament between these two to clarify the level further. In many populations this is not actually necessary as the 5.07 filament is suitable for screening for sensory impairment, since it is usually detected by all healthy individuals in communities where shoes are worn.<sup>4,13</sup> However, recent work in the rural community of Salur in India has shown that a significant proportion of healthy individuals who go barefoot or wear sandals produce thickened callus on the sole of the foot so that certain parts of the sole are unable to detect the 5.07 filament.<sup>14</sup> Similar findings have been noted in Ethiopia,<sup>15</sup> so this is clearly not a local phenomenon. Furthermore, it is now known that sensibility thresholds in feet actually increase with age due to physiological deterioration in nerve function, so that many older individuals can no longer feel the 5.07 filament.<sup>14,16</sup> At Salur all individuals were, however, able to detect the 5.46 filament ( $\sim$ 30 g) at all locations.

In light of these findings, it is necessary to determine if a filament can be identified that will differentiate those at risk of plantar ulceration from those with a higher sensibility threshold merely due to thickened callus or the normal ageing process. As the 5.46 filament lies between the previously used 5.07 and 6.10 filaments, it is interesting to see if it would be a suitable tool. The ability to identify the population at risk would allow more effective targeting of resources, so that only those with sufficient neuropathy to be at risk of complications need receive the extra measures available to minimize the formation of ulcers. While it is appreciated that not all developing regions can afford Semmes-Weinstein monofilaments at present, it is possible that the money saved by better targeting of existing resources may cover the cost of widespread use.

#### **Materials and methods**

All adult male leprosy patients released from treatment between 1983 and 1988 in the town of Salur, Andhra Pradesh State, India were identified. Those from the town who experienced longstanding stable plantar sensory impairment at the time of this study were asked to take part. They were identified as having sensory impairment by present or past plantar ulceration or failure in previous sensation testing using the ball-point pen technique. One hundred percent of these individuals complied, making a patient group of 54 individuals. In an area

characterized by monsoon and dry seasons, it might be expected that plantar sensation would vary as the skin becomes softened in the wet months and slowly hardens afterwards.<sup>17</sup> In consequence, a study on the same individuals might yield differing results depending on the season. Again, high temperatures and humidity are thought to alter the properties of the Semmes-Weinstein nylon monofilaments so that they buckle more easily than in cooler, dryer climates, and exert less force.<sup>18</sup> For ease of comparison with other research, it should be noted that the work was undertaken during the months of November and December, at the end of the monsoon, with high humidity and temperatures typically between 20° and 30°C.

The Semmes-Weinstein monofilaments were tested on a Sartorius L2200P top-loading balance to confirm their accuracy. Each filament was tested five times by applying perpendicularly to the balance until bowing, using a technique described elsewhere,<sup>11,18</sup> and the mean force calculated. The diameters were also checked using a binocular light microscope linked by a video camera to an RGB software package and compared with past work. The filament index numbers ( $\log_{10} \times$  force required to bow the filament) were then confirmed by consulting past research.<sup>11,18</sup> The mean force exerted by the filament of index 4·56 was 3·1 g, by the 5·07 was 8·0 g, by the 5·46 was 29·5 g and by the 6·45 was 203 g. It is well known that monofilaments do not exert exactly the same force in practice as recorded by any of the manufacturers, as they are not made to exacting standards<sup>19</sup> to make them more affordable. Variation tends to become more obvious as the index numbers become larger, and so the filaments thicker. The values listed here are comparable with past studies of the forces exerted by these nylon monofilaments.<sup>11,18</sup> In consequence, here we refer to the monofilament by its index number rather than by an estimation of the force it exerts.

All the patients were examined by the same clinician to avoid inter-observer variation. Sensory function was assessed on the apparently healthy skin immediately surrounding each ulcer. Skin with scarring, excess callus, granulation tissue or necrosis was avoided. The tests, outlined in detail elsewhere,<sup>11,18</sup> took place in quiet surroundings and were explained to each participant who then looked away from his feet. Each of the Semmes-Weinstein monofilaments with index 4.56, 5.07, 5.46 and 6.45 was applied in a concealed and random manner.

#### Results

Of the 54 individuals in this patient group, 18 (33%) had current plantar ulceration, 26 (48%) had no current ulcers but had done in the past and the remaining 10 (19%) had never had ulcers. Those with current ulceration were entered into the study. Details of their footwear use, class of occupation and age are shown in Table 1. Twenty-six ulcers were noted on the 18 individuals, each with both feet remaining (Figure 1). Sensation in apparently normal skin immediately adjacent to these ulcers was tested with the range of monofilaments. No individual was able to feel either the filaments with index of 4.56 or 5.07 in the surrounding skin. However, the 5.46 was felt around seven ulcers (27%) and in those unable to feel this, the 6.45 was noted around four ulcers (15%). The skin surrounding the remaining 15 ulcers was unable to detect any of the filaments (Table 2).

#### Discussion

In this community protective sensation was shown to be present where skin could detect a 5.07 monofilament in 100% of cases. Past research that tested skin adjacent to current ulcers

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Age range (years)	30-39	40–49	50–59	60–69	
	6 (33%)	6 (33%)	2 (11%)	4 (23%)	
Occupation	Light work (office or shop) 12 (67%)		Heavy work (labourer or farm 6 (33%)		
<i>Use of footwear</i> At work At home	None 6 (33%) 14 (78%)	Sandals 3 (17%) 0 (0%)	<i>MCR</i> 8 (44%) 4 (22%)	Shoes 1 (6%) 0 (0%)	

**Table 1.** Summary of the study population for age, occupation and footwear (n = 18)

has also found skin able to detect the 5.07 filament to be free from ulceration.<sup>4</sup> This agreement between research in the developed and developing world suggests that it may be related to the anatomy and neurophysiology of the skin over the human foot and be independent of environmental factors. In some past studies of protective sensation, the site of sensory testing remained identical regardless of the location of ulceration<sup>5</sup> and an individual with an ulcer at one site may have had normal sensation at the location where sensation was actually tested. The design of the study presented here has ensured that it is the



**Figure 1.** Location of current ulcers (n = 26)

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	Lightest filament detected							
	4.56	5.07	5.46	6.45	None			
No. of ulcers $(n = 26)$	0	0	7 (27%)	4 (15%)	15 (58%)			

Table 2. Best sensation in skin surrounding current ulcers

apparently healthy skin immediately adjacent to the ulcer which is tested, allowing a more representative assessment of sensibility of the skin in the area of the ulcer. Other research has tested sensation at the site of ulcers but also amalgamated data from tests at the site of ulcer scars, where previous ulcers have healed.<sup>6</sup> This means that the data have to viewed with caution, as there is no way of knowing if sensibility at the time of testing is the same as when the ulcer originally formed. It is quite possible that the nerve damage may have either progressed or healed with treatment since the ulcer was present, so that it is impossible to determine from this data the degree of sensation loss required before an ulcer can develop.

In this study, ulcers were noted in areas of callus skin able to sense the 5.46 filament ( $\sim$ 30 g). Previous work has determined that skin able to detect the 6.10 filament ( $\sim$ 75 g) but not the 5.07 ( $\sim$ 10 g) is at risk of developing ulceration but no work just testing adjacent to current ulcers has been performed to determine more exactly where the level of protective sensation actually lies. For this population, we have found that the threshold of protective sensation lies between the force applied by the 5.07 and 5.46 filaments. In populations where everyone can feel the 5.07 filament, especially where wearing shoes in common, then it seems reasonable to continue to use this filament as a tool to identify those at risk of developing plantar ulcers.

However, study of light touch sensibility thresholds in healthy individuals from some rural areas of India has shown that many of those who go barefoot or wear sandals for only part of the day are unable to detect the 5.07 filament, especially in older age groups.<sup>14</sup> They are, nevertheless, all able to detect the stiffer 5.46 filament. Similar research in Ethiopia has also demonstrated that the feet of many individuals are unable to detect the 5.07 filament,<sup>15</sup> so it is clearly not a localized phenomenon. This leaves the clinician managing the care of leprosy patients in some rural areas with a difficult dilemma. If all those who fail to detect the 5.07 filament are regarded as at risk of developing plantar ulcers, then it is likely that all those genuinely at risk of developing ulcers will have been identified, and can be managed appropriately. However, together with those genuinely at risk, a significant proportion of patients without nerve damage from leprosy may also be included if they are unable to detect the filament on account of thickened callous skin or normal age-dependent deterioration in sensibility threshold. It seems that testing using the 5.07 filament in this community would have very high sensitivity but only low specificity. While this might be the safest approach, it would flood clinicians with extra patients to assess, when so many clinics and hospitals are already overstretched. An alternative would be to use the 5.46 filament. This is felt by all individuals of all ages in all areas of the foot, so that it would ensure that no normal feet were included in the at risk group. Unfortunately, using this filament would mean that a proportion of patients who are at genuine risk of developing plantar ulceration would not be identified, 27% in this study. In consequence, the 5.46 filament would have very high specificity but only moderate sensitivity.

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A further interesting finding was that leprosy patients may develop plantar ulceration in skin only able to detect the 5.46 filament while healthy controls never do, even in areas of the foot with apparently the same sensibility threshold. One possible explanation is that the thickened, keratinized sole of a hard working, healthy foot impairs the ability of sensory receptors to detect fine touch stimuli such as the lighter monofilaments. However, deeper in the sole there remains the normal number of functioning sensory receptors. It is known that shearing stresses responsible for much ulceration act not just on the skin surface, where monofilaments are applied, but also deeper in the dermis and between tissue planes.<sup>20</sup> It is reasonable to presume that these deeper receptors in healthy individuals would detect early tissue damage quickly and lead to appropriate action to reduce this insult to the foot, perhaps by resting or modifying walking style. Patients with neuropathy, however, may have impaired function in both the most superficial and also deeper receptors. In consequence they will not detect friction stresses in deeper tissues and trauma may result, often developing into an ulcer if appropriate measures are not taken. It seems that while Semmes-Weinstein monofilaments are a good test for light touch sensation, they do have limitations in their ability to assess protective sensation in the foot. The monofilaments are not designed to assess sensibility to shear stress in the foot and it is this insult which is believed to be responsible for the majority of plantar ulcers. In consequence, a patient who fails to detect the 5.07 filament may not actually be at risk of developing ulcers if they can still detect shear stress adequately.

In the absence of a cheap and easy to use method of testing sensibility to shear stress in the foot, an alternative method of differentiating between these two groups must be found. One approach to this is to use common sense in conjunction with clinical assessment and these suggested guidelines might be found useful.

- 1. All those patients who can detect the 5.07 filament appear to be safe from developing plantar ulcers.
- 2. All those patients who fail to detect the 5.46 filament should definitely be regarded as at risk of ulceration.
- 3. Those who cannot detect the 5.07 filament but can detect the 5.46 filament should be suspected of being at risk of plantar ulcers if:
  - a) they regularly wear shoes;
  - b) or they have impaired sensation compared with the same area on the other foot;
  - c) or have deteriorating sensation even if still able to detect the 5.46 filament.
- 4. If the sensation threshold for callous skin remains stable, comparable with the same location on the other foot and ≤5.46 filament, this may well be normal for them if they do not wear shoes or are of advancing age. This does not necessarily imply that they are at risk of ulceration.

Using this guide may help workers in rural developing world communities to differentiate those patients genuinely at risk from plantar ulceration from those who fail the 5.07 filament test due to thickened callus or advancing age. This study has not been designed to identify which sites on the foot to test, but rather which filament to use in testing and how to interpret the results. There is great variability in the locations tested on the sole of the foot, from a thorough 11 or 12 site approach.<sup>14,21,22</sup> to a less time consuming technique of as few as perhaps three to five sites.<sup>5,23,24</sup> However, it has yet to be determined in a prospective trial just which locations need to be tested in order to safely identify early sensory impairment. While one is awaited it might be prudent to test all those sites known to develop ulcers and to do this does require an 11 or 12 location technique.

An impartial prospective study of sufficient size in a comparable rural area would be useful firstly to confirm if these findings are a local phenomenon or representative of the wider population, secondly to assess the effectiveness of these suggested guidelines and thirdly to identify which locations on the foot to test. If that study were to validate the findings presented here, then companies manufacturing the Semmes-Weinstein monofilaments might choose to include the 5.46 filament in one of their standard sets and so allow its application in those communities in which shoes are rarely worn.

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# Can people affected by leprosy at risk of developing plantar ulcers be identified? A field study from central Ethiopia

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*Summary* In the ALERT leprosy control programme, 75 people affected by leprosy, in three different geographical areas, were investigated. Each person was documented as having anaesthesia to the 10 g monofilament. The study sought to determine why some people developed ulcers whilst others did not. According to the records, 43 had an ulcer during the last 5 years but 32 had never had an ulcer. In order to examine protective sensation on the sole of the foot, various sensory modalities were tested and the functional anatomy of the foot was examined. The results showed, as may be expected, that it is not possible to define a specific threshold for protective sensation that could be applied to all cases. Some people with only slightly diminished sensation developed ulcers, while many others with almost complete anaesthesia remained ulcer-free. In these rural communities, being a farmer reduced the risk of developing an ulcer, but no other demographic features were significant. Graded monofilaments were found to be the most appropriate test, with loss of sensation at any of five points tested being a 'positive' result. The 10 g filament was the most sensitive, but only 43% of feet identified by this test actually developed an ulcer. As people with partial loss of sensation were excluded from this study, this figure may be lower under programme conditions. The 50 g and 100 g filaments decrease the number of feet identified as at risk, but increase the percentage which actually develop an ulcer, to 46% and 49%, respectively. An appropriate test for selecting those for special programmes which may have a limited capacity, for example the provision of subsidized footwear or involvement in self-care groups, would be a 100 g filament, which would detect 86% of those feet likely to develop an ulcer, while reducing the number of those selected who are not at great risk. Vibrometry was found to be no better than graded filaments and an examination of functional anatomy did not help in identifying those at risk.

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#### Introduction

Plantar ulcers are well recognized as a major cause of disability in leprosy. Ulcers are the result of deformity and/or loss of protective sensation and are caused by repetitive moderate stress, direct trauma, pressure, burns and walking on infected feet.<sup>1</sup>

The presence of protective sensation allows an individual to minimize injury. There are many sensory modalities involved in this mechanism, including the cortical interpretation of these modalities and the resultant response. There is therefore much individual variation in what constitutes protective sensation.<sup>2</sup>

The characteristics of protective sensation and the relationship between it and the development of plantar ulcers are unclear. Birke and Sims suggest that the use of graded monofilaments is the most appropriate method of establishing a sensory threshold in the foot. They examined 132 plantar ulcer sites and concluded that the 10 g filament would identify all these sites and therefore indicate loss of protective sensation.<sup>3</sup>

Malavuja *et al.* compared feet of leprosy patients with and without ulcers and found that while there were no ulcers at points with 'normal' sensation (able to feel a 2 g filament), the majority (83%) of sites with 'complete anaesthesia' (unable to feel an 85 g filament) also had no ulcers.<sup>4</sup> Others have shown that having an abnormal anatomy due to paralyses of intrinsic and/or extrinsic muscles of the foot is a risk factor for plantar ulceration.<sup>5</sup> The influence of socioeconomic circumstances is also likely to be important in determining who is at greater risk of developing an ulcer.<sup>6</sup>

Various methods of testing the different sensory modalities in the foot have been developed, many of them being too cumbersome for use in the field and general health clinics. Light touch sensation is widely studied, using graded monofilaments. Two-point discrimination may be used for the hand, but is unsuitable for the foot.<sup>7</sup> Vibration sense can be measured using a vibrometer, or less precisely with a tuning fork.<sup>8</sup> Pain sensation can be assessed with a pinprick, but this could not now become a routine test because of the risk of transmitting HIV.

Patients with diabetes are also at risk of developing plantar ulcers due to loss of protective sensation. The 10 g nylon monofilament is becoming a standard screening tool in diabetic clinics to identify those at risk of ulceration.<sup>9,10</sup> While loss of protective sensation occurs in both leprosy and diabetes, the socio-economic setting of the two diseases is very different. The search for better management of diabetic complications is mainly taking place in the developed world, while leprosy is a problem most common in developing countries. The characteristics of a screening test for loss of protective sensation must relate to the circumstances in which it will be used. In diabetes, clinicians require a sensitive test that will not miss cases likely to ulcerate; the number of false positives selected by the test is unimportant, as the resources are available to provide for all. The 10 g monofilament seems to be an ideal test in this setting, being simple, reproducible and valid.<sup>10</sup>

The current situation regarding plantar ulceration in leprosy is, however, very different. In many countries, subsidized protective footwear is beginning to be made available (usually with an increasing proportion of the cost charged to patients) and other initiatives, such as self-care groups, are being developed, all within the context of limited resources.<sup>6</sup> What is needed in this situation is a screening test which will reduce the number of false positive results and enable resources to be targeted at those with a high risk of plantar ulceration.

ALERT has had a footwear programme for some years and has used the 10 g monofilament as the criterion for the provision of footwear. Anyone with one or more points of loss of sensation is eligible for footwear. Results have been gratifying,<sup>6</sup> but it is noted that many people who have never had an ulcer and seem to have a low risk of developing one, are being given subsidized footwear, because they qualify on the grounds of anaesthesia to the 10 g monofilament. This study was therefore set up to look for a screening test which would be more selective than the 10 g monofilament, but which would not miss many cases likely to ulcerate.

#### **Materials and methods**

Leprosy patients were selected from self-care groups in central Ethiopia, located near three towns: Sheshemane, Mukadima and Wolkite. Inclusion criteria were: age over 15 years, a history of leprosy of more than 5 years, complete loss of sensation to the 10 g monofilament on at least one foot and no more than a minimal amount of tissue loss on either foot. Seventy-five patients meeting these criteria were identified.

Demographic and other relevant information was recorded. The positions of ulcers, scars and cracks were noted, and the presence of sweating and clawing of the toes was recorded. Previous medical records were also examined for evidence of ulceration.

Touch, pain and vibration sense were each examined at five points (big toe, 1st metatarsal head, 5th metatarsal head, 5th metatarsal base and the heel). These are pressure points and risk positions for developing ulcers. If there was an ulcer at any point, the nearest area of intact skin was tested.

Touch sensation was tested using 10, 50, 100 and 300 g monofilaments. Vibration sense was tested with a bio-thesiometer, with a range of 0-50 V ( $0-25 \cdot 5$  microns of motion), at a frequency of 120 Hz; a tuning fork with a frequency of 256 Hz was used for comparison. A portable generator was used to provide power for the vibrometer.

The range of movement of the ankle joint (dorsi- and plantarflexion) and subtalar joint (inversion and eversion) was classified into three categories (hypermobile, normal or restricted). Proprioception sense at the ankle joint was examined clinically by asking the patient (first with eyes open, then with eyes covered) whether the foot was being moved up or down. The range of extension of the big toe was measured and the strength of dorsiflexion of the foot was assessed.

The walking pattern was inspected in the following order: heel first, lateral side, fore foot and big toe push-off. The pattern was described as abnormal if one or more phase was absent. The length and symmetry of the stride were inspected. The position of the tendoachilles attachment to the calcaneus was inspected in a natural standing position and was classified into five categories (severe supination, mild supination, normal, mild pronation, severe pronation). For the analysis severe supination or pronation were taken to be abnormal, while mild supination or pronation were included in the normal group. Footprints of both feet were taken during a natural walking pattern, using a Berkemann Harris Mat.

The data were analysed using Epi Info v6.

#### Results

Of the 75 patients, 32 had never had an ulcer and 43 had had a documented ulcer in the previous 5 years. Amongst the 43 patients with ulcers, there were 51 feet with ulcers or a

	Those without ulcers	Those with ulcers, now or in the past 5 years
Number	32	43
Male	17	32
Female	15	11
Farmers	25	23
Non-farmers	7	20
Age <50	18	26
Age >50	14	17
Area of residence		
Shashamene	19	24
Mukadima	5	12
Wolkite	8	7

**Table 1.** Baseline characteristics (n = 75)

recorded history of ulceration. Table 1 shows the characteristics of the study population. For none of these factors was the difference significant, except for occupation, with non-farmers having an increased risk of developing an ulcer [OR: 3.1 (95% CI: 1.0-10.0).]

Table 2 shows the results of sensation testing at each point using different methods. In those with ulcers, 51 points had ulcers at some time in the last 5 years (there are 43 patients and eight have an ulcer on both feet); if there was more than one ulcer on a foot, only the larger one was used for this exercise. Amongst those without ulcers, 320 points never had an ulcer (five points per foot  $\times$  32 patients).

Various criteria could be utilized as a screening test to identify those patients most at risk of developing an ulcer. Interventions could be designed for patients identified by these means. Table 3 examines potential tests in terms of their ability to identify those at risk, taking individual feet as the unit for testing. For each test, the result would be 'positive' if the person is unable to feel it at one or more of the five points on the foot being

<i>Touch</i> Filament Ulcer Non-ulcer	10 g 2 22	5	50g 8	100 3 72	) g 3	300 g 5 50	No 33 76	ne felt	Total 51 320			
Vibrometry Volts (microns) Ulcer Non-ulcer	5 (0·25) 0 2	10 (1·0) 0 8	15 (2·2) 0 11	20 (4·0) 1 19	25 (6·4) 2 31	30 (9·2) 3 29	35 (12·5) 1 27	40 (16·4) 7 29	45 (20·8) 3 20	50 (25·5) 9 46	None felt 25 98	Total 51 320
Tuning fork Felt Ulcer Non-ulcer	Yes 14 145	No 37 175	Total 51 320									

Table 2. Analysis by pressure point (n = 371). For touch and vibrometry, the site is categorized under the lowest reading that could be felt

Test	Number of feet with a 'positive' result $(n = 115)$	Numb 'posit develop	Number (%) of 'positive' feet developing ulcers		
10 g	112	48	(43)		
50 g	100	46	(46)		
100 g	90	44	(49)		
300 g	74	40	(54)		
Tuning fork (TF)	103	48	(47)		
Vibrometry 30 V	105	48	(46)		
Vibrometry 40 V	96	43	(45)		
Vibrometry 50 V	75	37	(49)		

**Table 3.** The performance of possible screening tests for identifying those at risk of plantar ulceration. If any of five pressure points on the sole of the foot cannot feel the stimulus, the test is 'positive'

tested—a 'positive' test would indicate an increased risk of developing an ulcer. The number of feet testing 'positive' is given, followed by the number (and percentage) of feet which developed ulcers. The percentage with ulcers rises with the heavier, or less sensitive filaments.

When the function of the foot as a whole was analysed, two groups were considered: the 51 feet with recent ulcers and the 64 feet with no history of ulcers. Table 4 shows the results of this analysis.

While the stride was not different between the two groups, an abnormal walking pattern was associated with the development of ulcers, although it is unclear whether the abnormalities seen are causative or have developed as a result of the ulceration. The most common abnormality of walking pattern was the absence of a normal push-off from the big toe.

The prints from the Harris mat were examined, but the quality was generally rather poor for technical reasons. Of the 29 ulcer points with a reasonable footprint, only 15 (52%) had pressure points seen on the print and of the 27 feet which had never had an ulcer, 10 (37%) pressure points were identified.

During the course of the study, it was found that it was difficult to make reliable

	Non-ul	cer group	Ulcer	011	
	Normal	Abnormal	Normal	Abnormal	(95% CI)
Ankle: range of movement: dorsiflexion	55	9	36	15	NS
Ankle: range of movement: plantarflexion	47	17	41	10	NS
Ankle proprioception	59	5	49	2	NS
Position of the tendo-achilles	60	4	47	4	NS
Eversion of sub-talar joint	37	27	27	24	NS
Inversion of sub-talar joint	47	17	29	22	NS
Extension of the big toe	44	20	26	25	NS
Walking pattern	38	26	20	31	2·27 (1·0–5·16)

**Table 4.** Function of the foot as a whole in cases and controls (n = 51 + 64 = 115)

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assessments of sweating and the intrinsic muscles of the foot. These items were therefore omitted from the analysis.

#### Discussion

In terms of sensation, light touch, using graded monofilaments, was the most valuable test in making a distinction between the ulcer and non-ulcer group. It is not possible, however, to make a firm statement about people at risk of getting ulcers. As can be seen in Table 2, two patients who felt the 10 g filament at a certain point have developed ulcers at that point and many patients unable to feel the 300 g filament have not developed any ulcers.

Vibrometry was found to be no better than graded monofilaments in identifying those at risk and it is much more difficult to use because of the need for electricity. The tuning fork gave similar results to vibrometry at an amplitude of 30-40 V. The Harris mat did not perform as well as the other tests and requires considerable skill both in carrying out the test and interpreting the results. In this group of patients without significant tissue loss or deformity, examination of the anatomy and function of the foot was unable to identify patients at risk.

Table 3 shows the results of using the worst result of all five points tested on each foot as the test result for that foot. It should be noted that one of the inclusion criteria for this study was complete loss of sensation to the 10 g monofilament on at least one foot. In fact, only 11 of the 64 feet without ulcers had any points that could feel the 10 g monofilament. In the routine programme, many patients have incomplete loss of sensation, but are currently eligible to receive protective footwear if there is any degree of sensory loss as measured by the 10 g monofilament. Thus under programme conditions, the figures in Table 3 for the 10 g test may be somewhat different, with a rather smaller percentage of those identified as at risk actually developing ulcers.

Various interventions are being developed to assist people affected by leprosy to protect themselves from further damage, including the provision of protective footwear and the formation of self-care groups. The cost of keeping all the patients with sole sensory loss supplied with free or subsidized footwear is likely to be prohibitive,<sup>11</sup> as is the cost of setting up and facilitating self-care groups. In addition to cost, the logistic difficulties involved in dealing with large numbers of patients may make a programme impossible to implement. A method of more accurately targeting such support would be valuable in many programmes.

The 10 g filament will identify almost all cases at risk of developing an ulcer and a certain number of false positive cases as well. A more appropriate test, at least in the initial phase of a footwear programme, would be the 100 g monofilament, which will identify 86% of patients needing special care, but fewer of those without ulceration. Obviously if such a criterion were to be used for any particular intervention, patients who are known to have had an ulcer would also be included, whatever their test results.

In conclusion, this study confirms the view of others that nylon monofilaments are the most appropriate means of testing for protective sensation.<sup>3,10</sup> Other methods of testing, such as vibrometry and assessment of the functional anatomy of the foot, are no more discriminating. The 10 g monofilament is a sensitive test and should be used in situations where all those identified by the screening process can be managed effectively, but this study shows that it will select many people who do not appear to be at risk of plantar ulceration. In programmes with limited resources and large numbers of patients, the 100 g monofilament

would be a more selective test that would reduce the numbers of false positives while retaining a high degree of sensitivity.

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# Dynamics of impairment during and after treatment: the AMFES cohort

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Summary This study investigates the dynamics of impairment during and after multidrug therapy treatment for the patient cohort of the prospective ALERT MDT Field Evaluation Study (AMFES). The impairment status was compared at intake, at release from treatment (rft), and at the time of the latest survey between 24 and 48 months after release from treatment (follow-up). The eye-hand-foot impairment score (EHF score), which is the sum of the WHO impairment grades of the eyes, hands, and feet, was used as tool for comparison. In all, 433 out of the 592 patients (224 PB and 209 MB) completed treatment in time and were assessed at release from treatment. The risk of getting impaired was 4% for the 113 PB and 21% for the 91 MB patients who were initially free from impairment. Out of the 111 initially impaired PB patients, 41% recovered or improved and 13% worsened in EHF score. For the 118 initially impaired MB patients, these figures were: recovery or improvement 43% and worsening 13%. Three hundred and twenty-three out of the 433 patients (158 PB and 165 MB) had a follow-up examination in between the next 24-48 months after rft. The risks of impairment at follow-up were 6% for the 79 PB and 18% for the 77 MB patients without impairment at rft. Out of the 79 PB patients with impairment at rft, 35% recovered or improved and 28% worsened. For the 88 impaired MB patients, these figures were: recovery or improvement 26% and worsening 27%. Patients showed a tendency to compensate EHF score improvement before rft by worsening after rft and vice versa. The first main conclusion is that the impairment status at intake was by far the most important determinant for future impairment. The second one is that the dynamics of impairment were less favourable after rft than before. Little is known about the long-term fate of leprosy patients with irreversible nerve damage and the associated risk of developing severe secondary impairment. Especially in this era of the leprosy elimination goal, we should give this accumulating patient group due attention in research and health policy agendas.

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#### Introduction

Newly detected leprosy patients may or may not present with impairments. During and after multidrug therapy (MDT), new impairments may develop, and existing impairments may worsen, remain stable or improve. Many studies have addressed the presence of impairments in newly detected patients.<sup>1–7</sup> Less attention has been paid to the dynamics of impairment during and especially after MDT treatment. One study addressed patients in Malawi;<sup>8</sup> other studies were conducted in Asian countries.<sup>3,5,9,10</sup> The percentage of newly detected patients presenting with impairment varied considerably across these studies. Whereas worsening of impairment at release from MDT already had impairment at registration. In only one of these studies,<sup>5</sup> the impairment dynamics were evaluated during a follow-up period that extended well beyond release from treatment.

All studies employed WHO disability grades. The use of the term 'disability' is however questionable. According to the International Classification of Impairments, Disabilities and Handicaps (ICIDH),<sup>11</sup> disability refers to inability to perform activities due to impairment. Impairment is defined as 'any loss or abnormality of psychological, physiological, or anatomical structure or function'. Under ICIDH, the WHO grades do not reflect disability but impairment.<sup>10</sup> Following earlier publications,<sup>7,9,10</sup> this paper will therefore use the term 'WHO impairment grade' instead of 'WHO disability grade'. In the generally known 1988 WHO system,<sup>12</sup> grades are assigned to each eye, hand and foot using a scale with three possible outcomes (0, 1, 2). The maximum of these six grades, the 'maximum WHO impairment grade', specifies the patient's overall score. The 1988 WHO system has again been updated in 1998 by re-defining the grades for the eyes.<sup>13</sup>

The maximum WHO impairment grade recognizes both first onset of impairment and total recovery of existing impairment. Otherwise, its sensitivity to improvement or worsening of impairments is limited. This is of concern because from patient registration onwards, the performance of the services of a leprosy control programme is expressed in changes in impairment and disability. Accordingly, the 1988 maximum WHO impairment grade has primarily been applied to compare impairment profiles of newly detected patients across countries.<sup>14</sup> De Rijk *et al.* introduced an alternative summary score,<sup>15</sup> which uses the sum instead of the maximum of the individual grades for eyes, hands and feet. Further study<sup>10</sup> of impairment dynamics promoted the so-called Eye-Hand-Foot impairment score (EHF score), as demonstrating a higher sensitivity in registering change than the maximum WHO grade. The EHF score has also been suggested as tool for evaluating the effectiveness of steroid programmes.<sup>16</sup> The EHF score and the maximum WHO impairment grade share the advantage that their components – the individual grades for eyes, hands and feet – are routinely recorded in leprosy control programmes.

In this paper, the EHF score is applied to investigate the severity and evolution of impairment over time for the cohort of the ALERT MDT Field Evaluation Study (AMFES). Comparisons are made between EHF scores at intake, at release from treatment, and at the latest survey examination between 24 and 48 months after release from treatment. Objectives and interim results of the AMFES study, which is conducted within a routine leprosy control programme in central Ethiopia, were described before by de Rijk *et al.*<sup>15,17</sup>

#### **Materials and methods**

Methods of enrolment, diagnosis, administration of fixed-duration MDT and case holding in AMFES have previously been specified<sup>15</sup> and reviewed<sup>18</sup>. The present study involves all enrolled newly detected patients except those who had errors in enrolment procedures or in diagnosis.

Recorded patient characteristics include age, sex, clinical classification and bacteriological index (BI). The type of treatment (PB or MB) was chosen on the basis of clinical classification and skin smears. For clinical classification, the simplified system for field workers recommended by Jopling<sup>19</sup> was used. It should be recognized that many patients correctly diagnosed as PB in the present study would be classified as MB if presently used criteria focussing on number of skin lesions or number of body areas affected had been applied.<sup>13</sup>

AMFES patients were scheduled for examination at intake, while on MDT, at release from treatment, at 3 and 6 months after release from treatment (rft) and thereafter at intervals of 6 months. Examination involved the recording of the WHO impairment grades for the eyes, hands and feet according to the 1988 WHO grade definitions.<sup>12</sup> The maximum WHO impairment grade and the sum of these six impairment grades for the eyes, hands and feet -EHF score (ranging from 0 to 12) – follow directly. This paper investigates the dynamics of impairment by comparing the EHF scores at three different points in time: intake, release from treatment, and the time of the latest survey conducted between 24 and 48 months after release from treatment. A considerable number of patients did not complete treatment, and some patients did complete treatment in due time but were not examined at release from treatment. Patients who did complete treatment and who were examined at release from treatment are referred to as 'rft patients'. Those among the 'rft patients' who in addition had a survey examination between 24 and 48 months after release from treatment are in this study denoted as 'follow-up' patients. Unless indicated otherwise, the term 'worsening' will refer to any increase in EHF score (this includes onset of impairment in previously unimpaired patients). 'Improvement' refers to a decrease in EHF score, while 'recovery' indicates that the EHF score has decreased to zero from a previously positive score.

In the data analysis, statistical significance refers to the 5% level. Frequency distributions were compared using the Chi-square test. The data analysis was carried out in SPSS.

#### Results

A total of 603 new patients were enrolled in the AMFES project. Out of these, 11 patients were excluded from the present data analysis because of either incorrect enrolment procedures or incorrect diagnosis. The resulting study cohort consists of 292 PB and 300 MB patients.

#### THE COHORT OVER TIME

Out of the 592 patients, 454 patients completed treatment in time. The treatment completion rates were higher for PB than for MB patients (PB: 242/292, or 83%, against MB: 212/300, or 71%, P < 0.001). Thirteen patients died before they could be released from treatment, 104 did not complete treatment and were lost to follow-up, and 21 did not complete treatment in due

time but were seen later. Twenty-one patients completed treatment in time but were not examined by the leprosy control supervisor (LCS) at the end of treatment. So, 433 (224 PB and 209 MB) patients completed treatment in time and were examined by the LCS at release from treatment.

The 433 rft patients differed from the other 159 patients in the cohort in several respects. Summarizing, the rft group included more children (PB: 22% against 7%, P < 0.01; MB: 11% against 5%, P = 0.1). As compared to the non-rft group, the MB rft patients more often had high BI values (BI  $\ge$  3; 75% against 63%, P < 0.05) and less often had EHF scores of 3 or more (28% against 41%, P < 0.05). The percentage with EHF score 3 or more was 25% for both PB rft and non-rft patients.

Out of the 433 rft patients, 323 patients had a follow-up examination between 24 and 48 months after rft (158/224 PB, or 71%, against 165/209 MB, or 79%; P < 0.05). In comparing these 'follow-up' patients with the 110 rft patients without follow-up (66 PB and 44 MB), again differences are observed. Females were under-represented in the follow-up group of PB rft patients (37% against 52%, P = 0.05). The age distributions of the PB rft patients with and without follow-up also differed significantly. In the follow-up group, children were over-represented (25% against 15%) and young adults (ages 15–29 years) were under-represented (30% against 52%). In MB patients, the percentages of females were similar (31% against 30%), whereas children and young adults together were over-represented in the follow-up did not differ significantly from the rft patients without follow-up in percentage with BI 3 or more (MB patients only), percentage with EHF-score 3 or more (PB: 27% against 20%, MB: 28% against 25%) and percentages improving (including recovery) and worsening in EHF score between intake and rft.

#### IMPAIRMENT AT INTAKE

Table 1 gives details of impairments at intake. About half of the patients had no impairment. Five percent of both PB and MB patients had just one extremity or eye affected with WHO grade 1 (EHF score 1). Thirty-three percent of PB and 39% of MB patients had EHF scores ranging from 2 to 4. The percentages with EHF score 5 or more were 11% for PB and 12% for MB. Between PB and MB, no significant differences were observed in percentage with any impairment (PB: 50%, MB: 56%) and with WHO grade 2 impairment (PB: 26%, MB: 21%). PB patients with EHF scores ranging from 2 to 4 more often had at least one extremity or eye affected with WHO grade 2 than MB patients (PB: 45%, MB: 21%, P = 0.001). All patients with EHF score 5 or more had at least one extremity or eye with grade 2 impairment. Further analysis showed that, with two exceptions for both PB and MB, they all had at least four extremities affected (for this analysis both eyes are included with the hands and feet to give a total of six 'extremities'). The large majority of the group of all impaired patients had at least two extremities affected (PB: 76%, MB: 87%). 5/224(2%) PB patients and 3/209(1.4%) MB patients had eye impairment: all these patients, except for one PB patient, had only grade 1 eye impairment. After re-examining patients with eye problems, data on eyes were corrected to refer to eye impairment that is due to leprosy only. Eye impairment figures earlier presented by de Rijk et al.<sup>15</sup> were therefore higher. Overall, the distribution of EHF scores did not differ significantly between PB and MB patients.

Table 1. Comparison between maximum WHO impairment grade and eye-hand-foot (EHF) score at intake for patients who completed treatment and who were assessed for impairment grades of eyes, hands and feet at release from treatment ('rft patients')

	EHF score									
Maximum WHO grade	0	1	2	3	4	5	6	7+	Total	Percentage (%)
PB patients										
0	113								113	50
1		11	29	6	6				52	23
2			16	11	7	4	11	10	59	26
Total	113	11	45	17	13	4	11	10	224	
Percentage (%)	50	5	20	8	6	2	5	4		100
MB patients										
0	91								91	44
1		10	45	11	9				75	36
2			5	5	7	10	11	5	43	21
Total	91	10	50	16	16	10	11	5	209	
Percentage (%)	44	5	24	8	8	5	5	2		100

## PB rft patients



# PB follow-up patients



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**Table 2.** Relation between changes in eye-hand-foot (EHF) score between intake and treatment completion ('intake  $\rightarrow$  rft') and between treatment completion and latest assessment between 24 and 48 months after treatment completion ('rft  $\rightarrow$  follow-up') for patients who completed treatment and were assessed for impairment grades at release from treatment and in the post-treatment period (percentages of all patients in brackets). In the table, 'improvement' refers to any gain and 'worsening' to any loss in EHF score

	Change in EHF score (rft $\rightarrow$ follow-up)									
Change in EHF score (intake $\rightarrow$ rft)	Improvement (%)	No change (%)	Worsening (%)	Total (%)						
PB patients										
Improvement	8 (5)	16 (10)	12 (8)	36 (23)						
No change	12 (8)	84 (53)	13 (8)	109 (69)						
Worsening	8 (5)	3 (2)	2 (1)	13 (8)						
Total	28 (18)	103 (65)	27 (17)	158 (100)						
MB patients										
Improvement	2 (1)	20 (12)	20 (12)	42 (25)						
No change	10 (6)	72 (44)	14 (8)	96 (58)						
Worsening	11 (7)	12 (7)	4 (2)	27 (16)						
Total	23 (14)	104 (63)	38 (23)	165 (100)						

#### DYNAMICS OF IMPAIRMENT IN PB PATIENTS

Figure 1 summarizes changes in impairment over time for the PB patients. Four of 113 (4%) patients free from impairment at intake had impairment at rft. At the same time, 15/111 (14%) initially impaired patients recovered from their impairment. These changes imply that the vast majority of patients with impairment at rft (96 out of 100) already had impairment at intake. Overall, improvement including recovery was more common than worsening (which includes onset of impairment, 46 versus 18 patients). Nearly half of the initially impaired patients (46%) did not change in EHF score.

Between rft and follow-up, the numbers of patients improving or recovering and worsening were very similar with 28 and 27. Having impairment at rft is by far the most important determinant for having impairment at follow-up: 69/74 (93%) of those with impairment at follow-up were already impaired at rft.

Table 2 shows the relation between changes in EHF score in the two consecutive time intervals. A tendency for compensating changes is most noteworthy. Out of those who improved or recovered during treatment, 33% (12/36) worsened in EHF score after rft, compared to 12% (15/122) for those who stayed the same or worsened during treatment (P < 0.005). Similarly, 62% (8/13) of patients who worsened during treatment improved or recovered after rft, versus only 14% (20/145) of the others (P < 0.001).

EHF score change does not necessarily reflect a patient's impairment dynamics well because improvement in one extremity or eye may coincide with worsening in another. Between intake and rft, this actually happened in three patients (the EHF score did not change

**Figure 1.** Changes over time in impairment status as measured by the eye-hand-foot (EHF) score for PB patients who completed treatment and whose impairment grades were assessed at release from treatment ('PB rft patients'), and for PB rft patients who in addition were assessed for impairment grades between 24 and 48 months after release from treatment ('PB follow-up patients').

## **MB rft patients**



## **MB** follow-up patients



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in one and improved in two of them). Further analysis revealed the same phenomenon in seven patients after rft. One of them worsened, two did not change and four improved in EHF score. These opposite changes imply that 35% (28/79) of the already impaired follow-up patients worsened in at least one eye or extremity during follow-up, against 28% (22/79) who worsened in EHF score.

Further analysis revealed the maximum change in EHF score between intake and rft to be three points: one rft patient worsened, and two rft patients improved by three points. The change was at least two points in 33% of all worsening patients, and in 16/39 (41%) of improving patients with an initial EHF score of 2 or more (including eight recoveries). Between rft and follow-up, two patients worsened, and four patients improved by three points or more. The change between rft and follow-up was at least two points in 41% of all worsening patients, and in 15/25 (60%) of improving patients with an EHF score of 2 or more at rft (including seven recoveries). Overall, no important changes occurred over time in the distribution of EHF scores for PB patients as a group; the differences between intake, rft and follow-up were not statistically significant for the rft patients, nor for the follow-up group (EHF score categorization used: 0, 1, 2, 3-4, 5-6, 7-12).

#### DYNAMICS OF IMPAIRMENT IN MB PATIENTS

The EHF score changes for the MB patients are summarized in Figure 2. In the MB group, recovery of existing impairment (23 patients) between intake and rft is largely compensated by first onset of impairment (19 patients). Still, the vast majority of patients with impairment at rft were also already impaired at intake (95/114, or 83%, against 96% for PB). Improvement plus recovery again occurred more often than worsening (51 versus 34 patients). Over 40% of initially impaired patients (44%) did not change in EHF score.

Between rft and follow-up, less patients improved than worsened in EHF score (23 versus 38 patients). In comparison to earlier change, impaired patients less often improved or recovered (23/88, or 26% against 51/118, or 43%, before rft) and about twice as often worsened (24/88, or 27%, against 15/118, or 13%). Again, presence of impairment at rft is by far the most important determinant for later impairment: 76/90 (84%, against 93% for PB) patients with impairment at follow-up also had impairment at rft.

A tendency for compensating changes similar to that for PB patients is observed (Table 2). Out of those who improved or recovered during treatment, 48% (20/42) worsened in EHF score after rft, compared to 15% (18/123) for those who stayed the same or worsened during treatment (P < 0.001). Also, 41% (11/27) of patients who worsened during treatment improved or recovered after rft, versus only 9% (12/138) of the others (P < 0.001).

WHO impairment grades of extremities and eyes also simultaneously changed in opposite directions in MB patients. Out of the nine patients who experienced this before rft, three improved in EHF score and six maintained their score. Because 13% (15/118) of the patients with impairment at intake worsened in EHF score, this implies that 20% (24/118) of them worsened in at least one eye, hand or foot. After rft, only two MB patients experienced

**Figure 2.** Changes over time in impairment status as measured by the eye-hand-foot (EHF) score for MB patients who completed treatment and whose impairment grades were assessed at release from treatment ('MB rft patients'), and for MB rft patients who in addition were assessed for impairment grades between 24 and 48 months after release from treatment ('MB follow-up patients').

simultaneous improvement and worsening (one worsened and two of them did not change in EHF score).

Further analysis also demonstrated notable changes in the MB patients. Between intake and rft, six rft patients worsened, and eight rft patients improved by three EHF points or more. The total change was at least two points in 47% of all worsening patients, and in 33/47 (70%) of improving patients with an initial EHF score of 2 or more (including 19 recoveries). Between rft and follow-up, six patients worsened, and one patient improved by 3 points or more. The total change between rft and follow-up was at least two points in 34% of all worsening patients, and in 10/20 (50%) of improving patients with an EHF score of 2 or more at rft (including nine recoveries). Statistically significant differences in the EHF score distributions over time were not observed for the MB patients.

#### Discussion

The present study confirms the earlier indication that the AMFES cohort is severely affected by impairment and disability.<sup>7</sup> Many patients were impaired at intake, frequently with WHO grade 2 and usually with multiple extremities involved. More than 10% of both PB and MB patients had EHF scores of 5 or more. Such scores imply very extensive nerve involvement.

#### DYNAMICS OF IMPAIRMENT OVER TIME

The dynamics of impairment over time were illustrated by comparing EHF scores between intake and rft, and between rft and follow-up survey. Only a minority of patients with impairment at intake recovered completely. Impairment at the previous assessment was the most important determinant for impairment at the next. The dynamics of impairment were less favourable after rft than before. The risk of becoming impaired was both before and after rft significantly lower for PB than MB patients without previous impairment. During both periods, more than half of the impaired PB and MB patients changed in EHF score. A tendency towards compensation of EHF score improvement before rft by worsening after rft and vice versa was observed. Overall, the EHF score distributions of the PB and MB groups hardly changed over time.

Although the differences in the EHF score distributions at the different assessments were not statistically significant, the dynamics of impairment after rft deserve special attention. Compared with the treatment period, both PB and MB patients with impairment showed further worsening of their EHF score after rft twice as often. The EHF score measures both primary and secondary impairments. The development of primary impairments (sensory loss and muscle weakness) relates to active neuritis, which although it occurs, is much less common after rft than before.<sup>20</sup> The worsening of the EHF score after rft is therefore likely to be due to increasing secondary impairment (wounds, ulcers and tissue loss), although the AMFES database does not contain this information in detail. This is in accordance with the suggestion from a study from Thailand that with longer periods after rft, changes in impairment status will more and more be due to new/increased tissue damage (e.g. wounds, bone loss) than to increases in NFI.<sup>5</sup>

Drop-out rates in our study were considerable. The greatest number of losses occurred at the time of the overthrowing of the former Ethiopian government in 1991.<sup>18</sup> Probably, the longer duration of MB treatment contributes to the lower treatment completion rates in MB as

compared to PB patients (71% versus 83%). In contrast, follow-up of rft patients was more successful in the MB group (79% examination versus 71% for PB). The drops-outs before and after rft differed from the other patients in several respects. Significant differences in EHF score change before rft were not observed between patients who did and did not drop out after rft. It must be noted that patients who experience complications may at times both be more prone (need for extra care) and less prone (due to loss of confidence in the programme, or hiding because of stigma) to complete treatment and to present at follow-up examinations.

Studies that address change in impairment over time<sup>3,5,8-10</sup> are difficult to compare because of differences in case definitions, treatment durations and scoring systems for impairment. Still, all these studies found that clear majorities of patients with impairment at rft already had impairment at registration. One study also addressed change after rft.<sup>5</sup> In contrast to our study, the risks of worsening after rft were lower (but still significant) than before for MB patients and similar for PB patients. The EHF score was only utilized in two studies from Nepal.<sup>9,10</sup> Both studies addressed the same group of MB patients at diagnosis and examination after two years of MDT. The percentage with impairment at diagnosis (44%) was identical to our MB group. Although the percentage of patients with EHF scores of seven or more was higher in the Nepal group (6% versus 2%), the EHF score distributions at diagnosis were overall rather similar. Differences in the EHF score dynamics between the Nepal study and our study (usually rft was also 2 years later than intake) were observed, but a consistent pattern was not observed.

The dynamics of the EHF score after rft are worrisome. In addition, little is known about the long-term fate of leprosy patients who have irreversible nerve damage. The years of life lost to disability in this patient group, which accumulates over periods of many years, represents the real burden of leprosy disease. More insight into the size of this group, in the health related problems that they experience, in the care and support that they judge appropriate and in the associated resource requirements is urgently required. This patient group should get the attention in health policy agendas that it is entitled to.

#### REFLECTION ON THE USE OF THE EHF SCORE

We chose the EHF score as the evaluation tool for the present study. The EHF score gives a more detailed picture of the impairment status than the maximum WHO grade. In one of the two papers from Nepal, van Brakel *et al.*<sup>10</sup> showed the EHF score to be much more sensitive than the maximum WHO impairment grade: 37% of patients who changed in EHF score did not change in maximum WHO grade. Further analysis showed this difference to be more pronounced in our study.

We agree with van Brakel that the EHF score is not a perfect impairment indicator: it remains a simple sum of the WHO impairment grades of the extremities and eyes. A point of criticism with respect to summary scores such as the EHF score is that they are unable to discriminate between a major change in one component and minor changes in several components. But for the WHO grades for extremities and eyes that make up the EHF score, van Brakel *et al.*<sup>10</sup> stated that 'a change of one point at any site usually constitutes a major change in impairment status'. In extremities that improved in WHO impairment grade upon corticosteroid treatment, Broekhuis *et al.*<sup>16</sup> showed the changes in sensory testing (ST) and voluntary muscle testing (VMT) to be important. Nevertheless, the EHF score may mask simultaneous changes of extremities and eyes in opposite directions. The frequency with which this happened in our study group is however not alarming.

The reliability of the EHF score has not yet been established. To our knowledge, the retrospective study by Broekhuis *et al.*<sup>16</sup> is the only study that investigated the reliability question. They indicated the hand-foot impairment score (sum of the WHO grades for extremities: HF score) to be a promising device for the evaluation of the effectiveness of corticosteroid treatment at programme level. They also demonstrated that the EHF score is not a suitable device for supporting individual patient management.

Unfortunately, it is not possible to validate the EHF score on the basis of the AMFES cohort. The main reasons for this are lack of detailed information on secondary impairment and the fact that the monitoring of AMFES patients was less close after rft. Compared with other scoring systems, the EHF score has some important advantages. It is simple, reproducible, and information on its components (the WHO impairment grades for extremities) is already routinely collected in many control programmes.<sup>16</sup> Although we acknowledged a number of deficiencies in the EHF score, we are convinced that they are outweighed by the practical usefulness of the EHF score. Following van Brakel<sup>10</sup> and Broekhuis,<sup>16</sup> we therefore strongly recommend initiation of prospective validation studies of the EHF score as tool for the evaluation of activities at programme level.

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# Fine needle aspiration cytology (FNAC) of nerves in leprosy

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Summary Leprosy is primarily a disease of the peripheral nerves and a technique that is simpler than nerve biopsy is required to evaluate nerve involvement, especially in pure neuritic (PN) leprosy. This study was designed to evaluate the role of FNAC of the nerve in the diagnosis and classification of leprosy. A prospective study was carried out on 25 patients with clinically active leprosy and at least one thickened peripheral sensory nerve. Nerve aspirates were evaluated by May-Grunwald-Giemsa and Fite's staining. Lepromin test, slit skin smears (SSS), skin biopsies (except PN cases) and nerve biopsies were performed and compared with FNAC. FNAC of nerve from 23 cases (92%) yielded diagnostic aspirates. Acid fast bacilli were observed in six cases by FNAC. FNAC and nerve pathology were equally comparable with the other parameters evaluated. Based on the results, cytological criteria were developed for interpreting nerve aspirates and the cases were classified as paucibacillary (18), BB (2), BL (2), LL (1) and non-diagnostic (2). All PN cases showed diagnostic paucibacillary type cytology. FNAC of the nerve yields diagnostic aspirates in leprosy comparable with nerve pathology and the proposed cytological criteria may be useful in classification of nerve aspirates.

#### Introduction

Although leprosy is primarily a disease of the peripheral nerves, the main criteria for diagnosis and classification are related to skin parameters such as slit skin smears (SSS) and skin biopsies.<sup>1–3</sup> Several studies have shown discrepancies between skin and nerve histopathology, with a higher bacterial load in the peripheral nerves when compared to the skin.<sup>4–8</sup> In addition, pure neuritic (PN) leprosy, which involves the nerves alone without any skin changes, is a definite entity recognized in the Indian classification of leprosy.<sup>9</sup> The diagnosis of this form of leprosy can be confirmed only by a nerve biopsy.<sup>2</sup>

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Hence, a technique that is simpler than nerve biopsy is required to evaluate nerve involvement, especially in pure neuritic leprosy. Cytology is widely accepted as a diagnostic procedure for a large variety of malignant and inflammatory lesions.<sup>10</sup> Fine needle aspiration cytology (FNAC) of skin lesions and lymph nodes has already been shown to be useful in the diagnosis and classification of leprosy.<sup>10,11</sup> Theuvenet *et al.*<sup>12</sup> and Jayaseelan *et al.*<sup>13</sup> have shown that FNAC of the nerve could yield adequate material for the diagnosis of pure neuritic leprosy. This study was designed to evaluate the role of FNAC of the peripheral sensory nerve in the diagnosis and classification of leprosy by comparing the aspirate with nerve pathology by biopsy.

#### **Materials and methods**

Twenty-five consecutive patients with a clinical diagnosis of leprosy and having at least one thickened peripheral sensory nerve were included in the study. Informed consent for performing FNAC and biopsy of the nerves was obtained from all the patients. The study population included patients attending the leprosy clinic of our department and those referred from other specialities of our institute with features of peripheral nerve involvement.

Slit-skin smears for acid-fast bacilli (AFB) from lesional skin, ear lobules and normal skin and lepromin test (lepromin-A) were done in all the cases. Skin biopsies were obtained from the suggestive lesions (except pure neuritic cases).

Fine needle aspiration was done from the peripheral sensory cutaneous nerves, viz. radial cutaneous nerve (15), cutaneous nerves of forearm (5), sural nerve (4) and superficial peroneal nerve (1). A disposable 10 ml plastic syringe fitted with a 21G needle was used. We used a 'hand held' method rather than a syringe holder to create negative pressure. The nerve was fixed between the thumb and the index finger of one hand, and with the other, the needle was inserted into the nerve as parallel to the nerve as possible and aspiration was performed by creating negative pressure. Sensory function and tenderness of the aspirated nerve were assessed clinically on the day of aspiration and 1 week after the procedure. Nerve biopsies were taken in all the cases from the same nerve 1 week after the FNAC procedure.

The biopsies were studied in haematoxylin and eosin (H&E) stained sections, and modified Fite–Faraco staining was used to evaluate the bacteriological index (BI) according to the Ridley's logarithmic scale.<sup>1</sup> The histological criteria as described by Ridley<sup>14</sup> for skin biopsies and Ridley and Ridley<sup>15</sup> for nerve biopsies were used to classify the cases along the Ridley–Jopling classification. The smears for cytology were air dried and cytological assessment was done by May–Grunwald–Giemsa (MGG) staining and AFB status assessed by modified Fite's staining.

#### Results

The age of our patients ranged from 21 to 59 years (mean 38 years), with 20 men and five women. The duration of the presenting clinical feature ranged from 2 weeks to 4 years. Based on the clinical criteria according to Ridley–Jopling classification<sup>3</sup> and using the criteria of

**Table 1.** Correlation of nerve pathology and nerve cytology. I = indeterminate, NS = non-specific, Ep = epithelioid cell, Lc = lymphocyte, Ma = macrophage, PMN = neutrophil, GC = giant cell, AFB = acid fast bacilli, GA = good aspirate

		Nerve cytology													
	Granuloma				Ep		Lc		Ma		PMN		GC	AFB	
Nerve pathology	+	1	Ep	Ma	++	+	++	+	++	+	++	+	+	GA	+
TT(2)	2		2	4	2	-	-	2	_	-	_	_	_	2	2
BT(14)	6	8	6	_	6	8	7	7	_	-	_	5	4	14	2
BB(2)	1	1	-	1	1	1	-	2	1	1	-	-	-	2	1
BL(2)		2	_	-	-	-	2		_	2	<u></u>	1	_	2	2
LL(2)	_	2	-	-	-	-	-	2	1	-	-	-	-	1	1
I(2)		2	-	-	-	1	1	1	_	-	-	1	-	1	
NS(1)	1	_	1	_	1	_	1	_	_	-		_	1	1	-

the Indian classification of leprosy for pure neuritic leprosy,<sup>9</sup> we classified our cases clinically as BT (12), BB (1), BL (2), LL (2) and pure neuritic (8).

#### CYTOLOGY OF NERVE ASPIRATES

Out of the 25 cases, good aspirates with adequate cellularity enabling classification along the Ridley–Jopling classification were obtained in 23 cases (92%). AFB were obtained in six cases (24%) by nerve aspiration which correlated with nerve biopsy, except in one LL case, which was negative for AFB by cytology (Table 1).

A cohesive collection of epithelioid cells or macrophages in the cytological smear was defined as a granuloma (Figure 1). The granulomas observed were epithelioid (9) and macrophage (1). Collections of lymphocytes alone were observed in two cases. By comparing the cellular features and BI of nerve aspirates with the histopathology and BI of nerve



Figure 1. Cohesive epithelioid cell granuloma in a case of pure neuritic leprosy (FNAC nerve, MGG stain × 250).



Figure 2. Lymphocytes in a case of tuberculoid leprosy (FNAC nerve, MGG stain×250).

biopsies (Table 1) a set of criteria was devised for interpreting the cytology of nerve aspirates as follows.

#### Paucibacillary (PB) pole (consisting of indeterminate, TT and BT)

- Good cellular aspirate
- Cohesive epithelioid cell granuloma or lymphocytic cell collection (Figures 1 and 2).
- Predominantly epithelioid cells with predominant to moderate number of lymphocytes (Figures 1 and 3)



Figure 3. Lymphocytes, epitheliod cells, nerve fibre in a case of tuberculoid leprosy (FNAC nerve, MGG stain  $\times$  500).

- Occasional giant cells and neutrophils
- BI = zero to 1+

#### Borderline borderline (BB)

- Fair cellular aspirate
- Mixed cellularity of predominantly non-foamy macrophages, moderate number of epithelioid cells and lymphocytes.
- Macrophage granuloma
- BI = 2 + to 3 +

#### Borderline lepromatous (BL)

- Fair cellular aspirate
- Predominantly lymphocytes and moderate number of foamy macrophages
- BI = 4 + to 5 +

#### Lepromatous leprosy (LL)

- Fair to poor cellular aspirate
- Predominantly foamy macrophages and few lymphocytes
- BI = 6 +

Based on the proposed criteria, cytological classification of the 23 cases with good aspirate was: PB (18), BB (2), BL (2) and LL (1). In two cases the aspirate was non-diagnostic. No cases with nerve abscesses were observed in the study. However, caseous necrosis was observed in three cases both in nerve histopathology and FNAC.

#### PURE NEURITIC CASES

By nerve biopsy, the cases in our study were classified as TT (2), BT (5), and indeterminate (1). All the eight cases of pure neuritic leprosy yielded adequate aspirates showing PB type cytology. Epithelioid cell granulomas were observed in three cases and a BI of 1 + was seen in one case.

#### CORRELATION OF NERVE PATHOLOGY AND CYTOLOGY

Classification of cases by nerve biopsy and nerve cytology was comparable in 22 cases (88% concordance). One case with LL pathology in the nerve biopsy yielded a non-specific aspirate and another case with indeterminate type of pathology showed a diagnostic PB type cytology (Tables 1 and 2).

Among the non-pure neuritic cases, concordance between clinical diagnosis and nerve cytology was seen in 14 cases (82.4%) and concordance between skin biopsy and nerve cytology was seen in 12 cases (70.6%). The concordance percentages between clinical diagnosis and nerve biopsy and that between skin biopsy and nerve biopsy were also 82.4 and 70.6%, respectively.

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Table 2. Grading across Ridley–Jopling classification (excluding pure neuritic cases). I = indeterminate, NS = non-specific

	Ι	TT	BT	BB	BL	LL	NS
Clinical diagnosis	_	_	12	1	2	2	_
Skin pathology	2	1	8	1	2	2	1
Nerve pathology	1		9	2	2	2	1
Nerve cytology	10			2	2	1	2

#### BACTERIOLOGICAL INDEX (EXCLUDING PURE NEURITIC CASES)

Four cases showed BI of 3+ to 6+ by SSS, skin biopsy and nerve biopsy, but one was negative by FNAC. In cases with BI of 1+ to 2+, nerve biopsy and FNAC were positive for AFB in two cases, while skin biopsy was positive in only one of these and SSS was negative in both (Table 3).

#### COMPLICATIONS OF FNAC OF THE NERVE

Tenderness at the aspiration site was observed in 13 cases immediately after the procedure, but none of them had tenderness 7 days after aspiration. None of the patients had significant increase in sensory loss of region supplied by the aspirated nerve 7 days after the procedure.

#### Discussion

FNAC is widely accepted as a diagnostic procedure for several malignant and inflammatory lesions.<sup>10,13</sup> The procedure is simple and can be repeated a second or third time if needed. The efficacy of this procedure in Hansen's disease has, however, not been exploited fully, though, slit skin smears have been conventionally used in leprosy to assess the bacteriological and morphological indices. Also, Ziehl–Neelsen staining does not provide adequate morphological details of the cell types.<sup>10</sup> Singh *et al.*<sup>10</sup> have shown that MGG staining complemented Ziehl–Neelsen staining in skin smears and yielded information almost comparable to skin histopathology. Theuvenet *et al.*<sup>12</sup> and Jayaseelan *et al.*<sup>13</sup> have shown that adequate aspirates could be obtained from nerves aiding in the diagnosis of pure neuritic leprosy.

Table	3.	Bacteri	iological	index	(excluding	pure	neuritic	cases).	BI = 1	bacteriol	ogical
index,	SS	SS = slit	t skin sm	lear							

skin smear	Number of cases (%)								
BI	SSS	Skin biopsy	Nerve biopsy	FNAC					
0	13 (76.5)	12 (70.5)	11 (64.7)	12 (70.5)					
1+ to 2+	0	1 (5.9)	2 (11.8)	2 (11.8)					
3+ to 6+	4 (23.5)	4 (23.5)	4 (23.5)	3 (17.6)					
Total	17	17	17	17					

This is the only large series in which the cytological findings of nerve aspirates have been compared with the histopathology of the nerves and by analysing these, a set of criteria was devised to classify the cytological smears. Differentiation between indeterminate, TT and BT forms was difficult in cytological smears, which were grouped together as PB leprosy. In the PB pole, cohesive epithelioid cells and lymphocytes were observed. Towards the lepromatous pole, no cohesion of cells was observed. It was observed that the cellular characteristics were more useful in PB pole and BB type, and that the BI was more useful in the lepromatous pole.

The nerve aspirate was negative for AFB in one LL case with non-specific cytology. This may be explained by the associated fibrosis of the nerve in the lepromatous pole of the disease. In cases with lower BI (1+ to 2+), two cases showed AFB positivity in nerve aspirates but both were negative in slit skin smears. These two cases of BT leprosy would have been classified as PB by the WHO case definition,<sup>16</sup> whereas in fact, they were multibacillary by nerve cytology.

All the eight cases diagnosed as pure neuritic leprosy yielded diagnostic nerve aspirates and were classified as PB type of leprosy based on cytology with one of the cases showing AFB positivity. In the study by Theuvenet *et al.*,<sup>12</sup> seven of the 11 cases of suspected pure neuritic leprosy showed multiple AFB in the nerve aspirate. No cytological evaluation was done in that study. In the study by Jayaseelan *et al.*,<sup>13</sup> 18 of 27 cases were diagnosed as pure neuritic leprosy based on cytology of nerve aspirate but only three showed AFB positivity. Hence, we recommend the use of both cytological and AFB evaluation of the nerve aspirates. In both the previous studies published on FNAC of the nerve, aspiration of motor nerves was also done safely.<sup>12,13</sup> Though no iatrogenic sensory loss was noticed in the superficial sensory nerves, the use of FNAC on motor nerves requires caution and further standardization of the technique.

When nerve pathology and nerve cytology were separately compared with the clinical diagnosis and the skin pathology, equal concordance was observed. A nerve aspirate with cytology as described in the devised criteria or AFB positivity is diagnostic as seen by the 92% positive aspirates in this study. However, a negative aspirate does not entirely rule out leprosy. Hence FNAC, being a simpler, quicker and less invasive technique, can be attempted on the nerve before deciding on a nerve biopsy. This would be particularly useful when pure neuritic leprosy is suspected.

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# Response of *Mycobacterium habana* vaccine in patients with lepromatous leprosy and their household contacts. A pilot clinical study

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Summary Single dose vaccination was carried out with Mycobacterium habana vaccine, 31 lepromatous leprosy cases receiving  $1.5 \text{ mg} (1.5 \text{ mg}=6.27 \times 10^8 \text{ bacilli})$ and 36 household contacts randomly receiving 1.5, 2.0, 2.5 mg vaccine intradermally. Duration of study was 18 weeks. Vaccination induced lepromin conversion in 100% of lepromatous leprosy cases and lepromin negative household contacts and augmentation of lepromin reactivity in 100% of lepromin positive household contacts, which was stable for the 15 weeks duration of follow-up. The maximum augmentation in lepromin reactivity was obtained with 1.5 mg of vaccine, which is probably the supramaximal dose. Overall, post-vaccination, those without prior BCG vaccination scars showed higher mean values of lepromin augmentation. Local vaccination site changes included induration, ulceration, itching, pain and uncomplicated regional lymphadenopathy, all of which remitted spontaneously by 15 weeks. Systemic sideeffects noted were pyrexia, ENL and jaundice, and were seen with no greater frequency than that reported in other vaccine trials. Overall, systemic side-effects were easily controlled and were not accompanied by clinically detectable nerve or ocular damage. The safety profile investigations revealed an increase in the mean values of Hb%, RBC count and PCV in household contacts and of PCV in lepromatous patients, post-vaccination. Alterations in the liver function tests were also observed in patients of lepromatous leprosy. Thus, M. habana vaccine appears to be useful in stimulating specific CMI against *M. leprae* as evidenced by increased lepromin reactivity.

#### Introduction

Any vaccine potentially effective against *Mycobacterium leprae* should induce immune responsiveness to *M. leprae*. Various vaccine trials against leprosy have conclusively shown

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changes in disease subtype, reduction in bacteriological and morphological indices, and protection in contacts of leprosy patients, postvaccination.<sup>1-7</sup> The specific CMI against *M. leprae* and disease status correlate well with the degree of lepromin reactivity (delayed type hypersensitivity; DTH) of an individual.<sup>1,7-9</sup>

*Mycobacterium habana (M. simiae* serovar-1, TMC 5135), an atypical mycobacterium belonging to Runyan group I, was obtained from the TMC Collection Center, Saranac Lake, New York, USA. *M. habana* vaccine was treated by gamma-irradiation of the culture at 300 kRad from a <sup>60</sup>CO source. The immunoreactive fractions of the vaccine have been characterized by Chaturvedi *et al.*<sup>10</sup> *Mycobacterium habana* protects mice against infectious challenge with *Mycobacterium leprae*<sup>11-13</sup> and induces lepromin positivity in monkeys.<sup>14</sup> The vaccine generated sufficient delayed-type hypersensitivity responses in mice against *M. leprae.*<sup>15</sup> Various subunit components of *M. habana*, namely 65 kDa protein<sup>16</sup> and 23 kDa protein,<sup>17</sup> have been isolated and their putative role in immunity against *M. leprae* described. Thus, *M. habana* might prove to be useful as a potential vaccine against leprosy.

This study evaluated the efficacy (change in lepromin reactivity), safety and tolerance of M. habana vaccine in humans.

#### **Materials and methods**

The entire preclinical data<sup>18</sup> on *M. habana* vaccine was submitted to the Drugs Controller of India and permission to undertake this clinical study was obtained. The study was also cleared by the Institutional Ethics Committee and informed written consent was obtained from all the subjects before inclusion into the study. Total duration of study was 18 weeks.

#### SUBJECTS AND STUDY DESIGN

Thirty-one lepromatous leprosy (LL) cases and 36 household contacts (HC) were vaccinated. Another group of 10 household contacts were included as controls; they were repeatedly lepromin tested but received no vaccine. Subjects under 12 years, pregnant women, those with major illnesses, and those who were taking immune modulatory drugs, were excluded from the study.

Patients with typical clinical features of lepromatous leprosy, who were lepromin negative, had numerous bacilli in their slit skin smears/skin biopsies and had typical features of lepromatous leprosy on histopathology were included in the study, irrespective of their duration of treatment.

Individuals from families having at least one index case of lepromatous leprosy and who had been residing with the index case for at least 5 years were randomly included as household contacts for vaccination and as controls. They were included irrespective of their lepromin status.

#### FOLLOW-UP AND EVALUATION OF LL CASES AND HOUSEHOLD CONTACTS

After the initial pre-vaccination history and clinical examination (general and systemic) and initial lepromin test, the subject was vaccinated (day 0), and closely followed for changes in their clinical status thereafter. Changes at the site of vaccination were noted as size of induration, ulceration, pain, itching, discharge and regional lymphadenopathy. LL cases were

assessed for their subjective feeling of well being and systemic reactions like pyrexia and erythema nodosum leprosum (ENL). Change in lepromin reactivity was read at +6 and +15 weeks post-vaccination, i.e. 3 weeks after each lepromin injection. Safety profile investigations (Table 3) were done before vaccination and subsequently at +3 and +15 weeks after vaccination.

During the trial, standard WHO multidrug therapy for multibacillary leprosy was continued and any other concomitant medication was avoided as far as possible.

LL cases were evaluated clinically using a body chart, the body being divided into head and neck, both upper limbs, both lower limbs, chest and abdomen and back and buttocks. Patients were clinically examined for impairment of pain (pinprick), touch (wisp of cotton, tip of finger), temperature (test tubes with warm and cold water), vibration (128 Hz tuning fork) and reflexes in the distribution of the major nerves viz. great auricular, ulnar, median, lateral popliteal and posterior tibial nerves. Sensation was graded as normal, impaired (percent impairment from normal reference point) and absence of a particular modality. Corneal and conjunctival reflexes were tested. A detailed ophthalmic evaluation was performed. Motor system was examined for nutrition, power (Standard Medical Research Council Scale, grade 0-5), reflexes and tone. Electromyography, nerve conduction velocity (n = 12) and slit lamp examination were done wherever possible (few cases only).

Each household contact was thoroughly evaluated for evidence of leprosy and only those who were clinically free of the disease were included for vaccination or as controls. Evaluation included a history for skin lesions, anaesthetic patches or other sensory symptoms and detailed examination for skin lesions, thickened nerves and sensory system examination.

#### VACCINE

Single dose vaccination was done with *M. habana*, a whole cell killed vaccine provided by Central Drug Research Institute, Lucknow. Each millilitre of vaccine contained 15 mg of wet weight of bacilli  $(1.5 \text{ mg} = 6.27 \times 10^8 \text{ AFB} = 63.3 \,\mu\text{g}$  of protein). A single vaccine dose was injected intradermally into left upper deltoid region using calibrated tuberculin syringes. Local changes at vaccination site, systemic reactions and changes in lepromin reactivity were noted.

Contacts were randomly allocated to receive 1.5 (group I, n = 11), 2.0 (group II, n = 13) and 2.5 (group III, n = 12) mg vaccine, respectively, while lepromatous leprosy cases received 1.5 mg vaccine (group IV, n = 31). Controls (group V, n = 10) received consecutive doses of lepromin but no vaccine.

#### LEPROMIN

The lepromin (Mitsuda) test was performed using 0.1 ml of lepromin A, a suspension of killed *M. leprae*, obtained from GWL Hansen's Disease Centre, Carville, Louisiana, 70721, USA. Lepromin (0.1 ml) was injected intradermally at -3, +3 and +12 weeks (day 0 = day of vaccination) on the ventral surface of the right forearm at variable distances from each other and local response in the form of maximum diameter of nodule was read 3 weeks later. A response of 3 mm or greater was taken as a positive response.

#### BACTERIOLOGICAL INDICES (BI) AND HISTOPATHOLOGY

Slit skin smears were taken from six sites (two each from eyebrows, ear lobes and skin lesions). Slides were stained by the Ziehl-Neelsen method and BI was calculated according

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to Ridley logarithmic scale. Skin punch biopsies were obtained for all LL cases from skin lesions.

#### Results

Lepromatous leprosy cases with disease duration ranging from 6 months to 3 years and were on standard WHO regimens for multibacillary leprosy at the time of vaccination. Patients had characteristic skin lesions at the time of vaccination, ranging from asymmetrical to bilaterally symmetrical shiny or erythematous macules, nodules and plaques with normal or impaired sensation and normal hair growth. Nerve thickening was seen in 60% of the cases. Impaired sensation (loss/impairment of temperature, pain, sweating and touch with relative preservation of vibration and reflexes) in the distribution of ulnar, median and lateral popliteal nerves was noted in 20% of cases. No patient had facial nerve palsy, median nerve palsy, claw hand, foot drop, glove and stocking anesthesia or deformities. Disability grading (WHO) was grade 0 in 80% and grade 1 in the above-mentioned 20% of cases. Slit skin smears were performed in 24 of the 31 lepromatous leprosy patients, and revealed a median bacteriological index of  $5 \cdot 1$  (range =  $4 \cdot 8 - 6 \cdot 0$ ). Skin biopsy and histopathological examination were performed in all 31 LL cases, which showed the characteristic histology of lepromatous leprosy in all cases.

The age and sex distribution among cases and contacts are shown in Table 1. The age of contacts was significantly lower as compared to cases. The mean lepromin reaction in patients with lepromatous leprosy and various groups of household contacts is shown in Table 2.

#### LEPROMIN CONVERSION AND AUGMENTED LEPROMIN REACTIVITY

Single dose vaccination induced lepromin conversion in 100% of lepromatous leprosy cases and lepromin negative household contacts (one contact in group I, 2 contacts in group II, 1 contact in group III) and augmentation of lepromin reactivity in 100% of lepromin positive household contacts and was stable for the 15-week duration of follow-up. Post-lepromin scar formation was observed in 65% lepromatous leprosy cases and 72-77% of household contacts (Table 2). The maximum increment in lepromin reactivity occurred in the initial 6 weeks after vaccination, subsequent to which the response plateaued; but the increments in lepromin reactivity continued up to 15 weeks post-vaccination, when the follow-up was

Characteristic	Contacts $(n = 36)$	Cases $(n = 31)$
Age	I 24.2 ± 8.1*** II 29.2 ± 14.2*	38.4 ± 14.1
Sex	III $30 \pm 10.1*$ Male = 58.3% ( <i>n</i> = 21) Female = 41.6% ( <i>n</i> = 15)	Male = $64.5\%$ ( <i>n</i> = 20) Female = $35.4\%$ ( <i>n</i> = 11)

<b>Fable</b>	1.	Age	and	sex	distribution	of	lepromatous	leprosy	cases	and	contacts
mean	$\pm$	SD)									

\*P < 0.05.

\*\*P < 0.01.

\*\*\* P < 0.001.

		No. of	Dose of	Lepromin (M	litsuda) test (mea	$n \pm SD, mm$ )	Post-lepromin
Group	Clinical	subjects	(mg)	Initial	+6 weeks	+15 weeks	scar (15 weeks)*
I	HC	11	1.5	$7.0 \pm 2.7$	$11.7 \pm 2.5*$	13·7 ± 1·9*	72.2%
II	HC	13	2.0	$5.3 \pm 2.8$	$10.6 \pm 4.1*$	$11.9 \pm 3.7*$	76.9%
III	HC	12	2.5	$5.4 \pm 1.9$	$8.8 \pm 2.4*$	$9.3 \pm 3.4*$	75%
IV	LL	31	1.5	$1.2 \pm 1.4$	$7.3 \pm 3.3*$	$8.5 \pm 4.4*$	64.5%
V	Controls	10	_	$5.3 \pm 1.8$	$5.5 \pm 1.8$	$5.5 \pm 1.8$	-

Table 2. Effect of M. habana vaccination on lepromin (Mitsuda) reaction

HC = healthy household contact.

LL = lepromatous leprosy cases.

Controls underwent consecutive lepromin testing but did not receive the vaccine.

<sup>a</sup>Percentage of patients with post-lepromin scar.

\*P < 0.05.

terminated. Among the contacts of lepromatous leprosy cases, comparable degree of augmentation in lepromin reactivity post-vaccination was observed with 1.5 mg and 2.0 mg vaccine, while a lesser degree of augmentation was seen with 2.5 mg vaccine. In 15% of cases, the size of the first lepromin test increased up to 15 weeks post-vaccination. Overall, post-vaccination, those without BCG vaccination scars showed higher mean values of lepromin augmentation (Figure 1A–D). There was no relation between lepromin reactivity and the gender of the subject.

The control group of 10 household contacts of leprosy cases, of either sex, were given three lepromin injections consecutively (as per the schedule for those who received vaccination) but no vaccine. Initially, eight patients were lepromin positive (mean = 6 mm) and two were lepromin negative (<3 mm). The lepromin negative and six of the lepromin positive controls did not show any change in their consecutive lepromin reactivities. Two lepromin positive controls showed an increase of 1.0 mm in their subsequent lepromin reactivities (Table 2).

#### LOCAL SITE CHANGES

The administration of the vaccine did not produce any acute local reaction. The vaccine site remained quiescent for 7–8 days. Mild to moderate pain and tenderness started at the local site by 7–8 days post-vaccination in almost all cases and persisted for about 6 weeks. Induration started by days 10–12 and progressively increased till about day 16 and persisted thereafter for 7–8 weeks. The indurated area ulcerated by day 15–18 post-vaccination and started healing by 8–9 weeks (Figures 2, 3). Healing was usually complete by week 15 post-vaccination (Figure 4). An indurated nodule was formed in 100% of cases. Mean diameter of nodule among contacts was 18.5 mm (range = 15-23 mm) and among LL cases was 15.4 mm (range = 8-20 mm). However, there was no correlation between the degree of induration and lepromin reactivity.

Ulcers were formed in 100% of the cases and were punched out, with erythematous base and healthy looking granulation tissue. Mild serous or serosanguinous discharge was present. The mean diameter of ulcer among contacts was 7.5 mm (range = 4-10 mm) and among LL cases was 6.5 mm (range = 4.5-9.0 mm). The ulcer required no treatment in any case except local cleaning. The degree of ulceration and discomfort produced by vaccination was accepted by majority of subjects.



Figure 1. Lepromin reactivity (mean  $\pm$  SD) in BCG scar positive and negative contacts and lepromatous leprosy (LL) cases, initially and after vaccination with *Mycobacterium habana* vaccine. (A) Eleven contacts, 1.5 mg vaccine; (B) 13 contacts, 2.0 mg vaccine; (C) 12 contacts, 2.5 mg vaccine; (D) 31 LL cases, 1.5 mg vaccine. Greater increase in lepromin reactivity was seen among BCG scar negative individuals (B & D).



Figure 1. continued.

Regional lymphadenopathy, 0.5-1.5 cm non-tender, non-matted and non-suppurative, was observed in a small percentage of cases (n = 11/67), which resolved spontaneously.

#### SYSTEMIC REACTIONS

Some patients (n = 42/67; 19/31 LL cases, 23/36 contacts) developed mild to moderate pyrexia around days 3–4, which resolved in 7–10 days with antipyretics.

Twenty-six percent (n = 8/31) of the lepromatous leprosy cases developed ENL at 6–9 weeks post-vaccination. Of these, 25% (n = 2/8) had experienced previous episodes of ENL (ranging from one to three episodes). Patients developed mild to moderate pyrexia, aches,



Figure 2. Vaccination site changes (induration and ulceration) 3 weeks after M. habana vaccination.



Figure 3. Vaccination site changes (induration and ulceration) 9 weeks after M. habana vaccination.

arthralgias (but no arthritis) and an increase in the size and number of cutaneous lesions in the form of tender, erythematous macules, nodules and plaques. The nerves became more tender on palpation, reflexes were exaggerated almost universally; however, there was no clinically manifest increase in or new development of hypoaesthesia or anaesthesia. There was no



Figure 4. Vaccination site changes (healed scar) 15 weeks after M. habana vaccination.

**Table 3.** Mean values of safety profile investigations initially and after vaccination with *M. habana* vaccine in lepromatous leprosy cases (LL) and household contacts (HC) (mean  $\pm$  SD)

Investigation	Group	Initial	+3 weeks	+15 weeks
Hb %	HC	$11.8 \pm 1.7$	$11.0 \pm 1.7$	$12.2 \pm 1.4$
	LL	$11.0 \pm 1.8$	$12.5 \pm 1.1*$	$11.7 \pm 1.7$
TLC (per mm <sup>3</sup> )	HC	$7431.4 \pm 38.7$	$7758.1 \pm 2018.3$	$7297 \pm 894.2$
	LL	$7520 \pm 1452$	$7170.6 \pm 932.5$	$7384.2 \pm 2018.3$
Platelets (per mm <sup>3</sup> )	HC	$2.6 \pm 0.4$	$2.7 \pm 0.3$	$2.7 \pm 0.2$
	LL	$2.6 \pm 0.2$	$2.7 \pm 0.4$	$2.7 \pm 0.2$
RBC (per mm <sup>3</sup> )	HC	$3.9 \pm 0.4$	$3.7 \pm 0.5$	$3.9 \pm 0.4$
	LL	$3.4 \pm 0.5$	$4.1 \pm 0.3*$	$3.8 \pm 0.5$
ESR (mm 1st h)	HC	$9.5 \pm 6.3$	$10.4 \pm 6.1$	$9.6 \pm 4.5$
	LL	$9.6 \pm 5.6$	$8.70 \pm 6.9$	$10.0 \pm 5.3$
PCV (cc%)	HC	$36.5 \pm 5.5$	$33.6 \pm 5.0$	$38.2 \pm 5.6$
	LL	$34.8 \pm 4.6$	$38.4 \pm 3.6**$	$36.3 \pm 4.5**$
Blood urea (mmol/l)	HC	$8.6 \pm 2.8$	$9.8 \pm 4.3$	$8.3 \pm 1.4$
	LL	$8.7 \pm 2.6$	$8.6 \pm 3.1$	$9.4 \pm 2.0$
Serum creatinine (µmol/l)	HC	$70.7 \pm 8.8$	$70.7 \pm 8.8$	$70.7 \pm 8.8$
	LL	$79.5 \pm 8.8$	$61.8 \pm 8.8$	$79.5 \pm 8.8$
Random blood sugar (mmol/l)	HC	$5.3 \pm 2.7$	$5.2 \pm 1.2$	$5.6 \pm 1.4$
	LL	$5.0 \pm 1.5$	$5.7 \pm 3.0$	$5.1 \pm 1.0$
Serum bilirubin ( $\mu$ mol/l)	HC	$13.6 \pm 3.4$	$13.6 \pm 3.4$	$13.6 \pm 3.4$
	LL	$15.3 \pm 8.5$	$13.6 \pm 3.4$	$17.1 \pm 13.6$
SGOT (IU/l)	HC	$24 \cdot 1 \pm 6 \cdot 1$	$24.7 \pm 8.4$	$25.9 \pm 14.4$
	LL	$23 \cdot 7 \pm 4 \cdot 9$	$25.6 \pm 9.9$	$29.7 \pm 8.9*$
SGPT (IU/I)	HC	$33.3 \pm 21.8$	$30.7 \pm 18.1$	$31.5 \pm 20.4$
	LL	$35.9 \pm 26.5$	$27.4 \pm 12.1$	$40.2 \pm 35.3$
Serum alkaline	HC	$113 \pm 63 \\ 97 \pm 35$	$99 \pm 52$	99 ± 46
phosphatase (IU/I)	LL		112 ± 46	116 ± 49*
Serum protein (g/l)	HC	$82 \pm 8$	79 ± 7	82 ± 10
	LL	79 $\pm 6$	76 ± 5*	77 ± 6*
Serum albumin (g/l)	HC	$45 \pm 4$	$44 \pm 4$	$46 \pm 3$
	LL	$44 \pm 4$	$46 \pm 3$	$42 \pm 4$
Serum uric acid (µmol/l)	HC	$404.4 \pm 118.9$	$422.3 \pm 83.2$	$404.4 \pm 95.1$
	LL	$386.6 \pm 65.4$	$446.1 \pm 190.3$	$422.3 \pm 89.2$
Serum cholesterol (mmol/l)	HC	$3.8 \pm 0.9$	$3.5 \pm 0.9$	$3.6 \pm 0.8$
	LL	$3.5 \pm 0.8$	$4.2 \pm 0.8$	$3.5 \pm 0.4$
Serum triglyceride (mmol/l)	HC	$1.7 \pm 0.8$	$1.5 \pm 0.7$	$1.4 \pm 0.5$
	LL	$1.9 \pm 1.2$	$1.9 \pm 0.8$	$1.7 \pm 0.7$
Serum HDL (mmol/l)	HC	$0.9 \pm 0.2$	$0.9 \pm 0.1$	$0.9 \pm 0.1$
	LL	$0.9 \pm 0.1$	$0.9 \pm 0.1$	$0.9 \pm 0.1$

\*P < 0.05.

 $^{**P}<0{\cdot}01.$ 

\*\*\**P* <0.001.

Hb, haemoglobin; TLC, total leukocyte count; RBC, red blood cell count; ESR, erythrocyte sedimentation rate; PCV, packed cell volume.

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weakness or paralysis of muscle groups and no muscle wasting. These episodes were not associated with any organomegaly, cardiac or pulmonary abnormalities. There was no rhinitis, epistaxis or epididymo-orchitis. There was no swelling, discharge, or pain in the eye. Corneal reflexes were intact in all the patients. The episodes of ENL were easily controlled with antipyretics and non-steroidal anti-inflammatory drugs, requiring cortico-steroids in only two cases. Duration of ENL was 3–4 weeks except in two cases where it lasted for 7–8 weeks. Overall, the systemic side effects were easily controlled and were not accompanied clinically by organ, nerve, or ocular damage.

Two patients, both of whom had ENL, developed concomitant clinical jaundice 4 weeks post-vaccination. In both cases, patients had been taking MDT for more than 6 months. The jaundice was insidious in onset, associated with a prodrome of nausea, vomiting and malaise 1 week prior to clinical detection. Both the patients had 3–4 cm tender, soft hepatomegaly with no splenomegaly. Serum bilirubin (patient 1, 3·5 mg%; patient 2, 4·5 mg%), SGOT (patient 1, 150 IU/l; patient 2, 210 IU/l) and SGPT (patient 1, 450 IU/l; patient 2, 600 IU/l) were elevated with marginally raised serum alkaline phosphatase (patient 1, 140 IU/l; patient 2, 160 IU/l). Ultrasound revealed hepatomegaly with a mild decrease in echogenicity and contracted gallbladder in both the cases. Rifampicin, dapsone and clofazimine were stopped on account of possible hepatotoxicity. Viral markers for HBsAg and anti-HCV were negative. Both patients were conservatively managed and recovered completely by the end of 3 weeks after clinical detection, after which drug therapy was re-started, without subsequent re-appearance of jaundice till the end of follow-up.

There was complete absence of nerve palsies both among cases and contacts, post-vaccination and no new sensory or motor loss was detected in these patients.

One lepromatous patient presented with bilateral pitting pedal oedema 3 weeks after vaccination, non-commensurate with his serum protein and albumin status, which had resolved completely by the end of the study.

Two patients presented 4–6 weeks post-vaccination with papulonodular eruptions all over the body. No features suggestive of ENL were present. The rashes subsided on their own at final follow-up.

#### INVESTIGATIONS

There was an increase in the mean values of Hb%, RBC count and PCV in household contacts and of PCV in lepromatous patients, post-vaccination. Alterations in the liver function tests were also observed in patients of lepromatous leprosy (Table 3), especially in the two who developed clinical jaundice and ENL. Slit lamp examination could not be performed due to constraint of resources. Other patients who developed ENL had no proteinuria and the liver and renal function tests were unremarkable.

#### Discussion

Leprosy has a very long incubation period, and years of observation will therefore be required to measure the efficacy of a vaccine in terms of its capacity to lower incidence rates. As a first step, it is essential to show that a 'candidate' vaccine is able to induce *persistent* changes in immunity as evidenced by changes in the Mitsuda lepromin reaction. Available clinical, laboratory and experimental evidence clearly show that the late lepromin (Mitsuda) reaction is closely linked to the immune status of the host against *M. leprae*. Early work by Dharmendra and Chatterjee<sup>8</sup> has shown that lepromin-negative individuals in endemic areas run a very high risk of contracting the multibacillary forms of the disease.

One hundred percent lepromin conversion or augmentation, which was observed in the present study with a single dose of vaccine, has been rarely reported with administration of other vaccines.<sup>1–5,19</sup> In the present study, the maximum change in lepromin reactivity was observed in the first 6 weeks post-vaccination, after which the degree of rise, although continuing for 15 weeks, plateaued off. Further follow-up will be required to ascertain whether this gradual rise continues, stabilizes or steadily declines. The maximum increment in lepromin reactivity with other vaccines has been variably described from 1 month onwards; most have described peak values at 8-9 months post-vaccination with stability for 3-5 years of follow-up.

The present study has demonstrated that the maximum lepromin augmentation or conversion was obtained with the smallest dose of 1.5 mg vaccine. That 1.5 mg vaccine is probably the maximum tolerated dose and requires reduction is further suggested by the constellation of reduced responses with higher doses of 2.5 mg and higher incidence of ENL reaction.

The diminished responses seen with higher doses of vaccine can be explained by either suppression of immature B-cells by antigen excess or the suppression of cell mediated immunity by 'blocking' immune complexes.

The degree of lepromin conversion or augmentation in lepromin reactivity was consistently less among BCG scar positive individuals. This is contrary to other leprosy vaccine trials, which show a higher degree of augmentation among BCG vaccinated individuals.<sup>1</sup>

The phenomenon of augmentation in the nodule size of prevaccination lepromin after vaccination has also been reported by Deo *et al.*<sup>2</sup> and probably reflects continuing delayed reactivity at site of first lepromin test; the clearance of *M. leprae* is markedly retarded in lepromatous leprosy patients as shown by Convit *et al.*<sup>20</sup>

Sixty to 75% of all subjects in the present study developed post-lepromin scars, which have been proposed as indicators of stable changes in cell mediated immunity by Dharmendra<sup>9</sup> and Walters.<sup>21</sup>

A control group of unvaccinated, healthy household contacts who were repeatedly lepromin tested did not exhibit any change in subsequent lepromin reactivity, indicating that the conversion was not merely a consequence of the previous lepromin test and that lepromin did not act as a mini-vaccine. It has also been demonstrated that *M. leprae* bacilli (armadillo grown), at 4 times the concentration contained in lepromin, failed to induce lepromin conversion.<sup>22</sup> Household contacts were chosen as controls because they had a greater chance of reacting to lepromin as compared to LL cases who are anergic to lepromin (lepromin negative). Since repeated lepromin testing did not alter the lepromin reactivity of lepromin positive or lepromin negative household contacts, lepromin negative LL cases were not included as controls subsequently.

The local vaccination site changes observed with M. habana vaccination are similar to those observed with various other vaccines.<sup>2,4,6</sup> The large inducation and ulceration occurring in a number of vaccinated subjects may, by itself, not be considered as an unacceptable side effect of the vaccine, given that most people have accepted both BCG and smallpox vaccines. None of the local site changes bore any correlation with lepromin conversion in the present study.

Zaheer et al. observed type I upgrading reactions in 45.2% of their vaccinated

lepromatous leprosy cases.<sup>4</sup> We did not observe type I reactions during our study, which could be due to the short duration of our study or because only a single dose of vaccine was given in our trial as opposed to the other vaccine trials.<sup>4</sup>

Twenty-six percent of lepromatous leprosy patients in the present study developed type 2 reactions in variable time duration of 6-9 weeks post-vaccination. Development of ENL after vaccination has been described by Deo *et al.* with ICRC vaccine, to occur 3-4 weeks after vaccination in  $42\cdot2\%$  cases with high bacteriological index.<sup>2</sup> ENL after vaccination has also been described by Zaheer *et al.* with *Mycobacterium w* vaccine, to occur in  $56\cdot6\%$  of lepromatous leprosy cases, while unvaccinated patients taken as controls developed ENL in  $60\cdot2\%$  cases.<sup>4</sup>

Two cases of ENL in the present study developed jaundice; The jaundice could have been a result of concomitant viral hepatitis or due to ENL. Convit *et al.* have observed two cases of hepatitis with jaundice in borderline leprosy cases with reversal phenomenon post vaccination.<sup>6</sup>

Two lepromatous patients in the present study developed a papulonodular eruption 4-6 weeks after vaccination. This has been previously reported by Convit *et al.*,<sup>6</sup> who demonstrated tuberculoid histology of the papules. The rash was seen to subside on its own at subsequent follow-ups.

The changes in safety profile investigations did not reveal any abnormality that could directly be attributed to the vaccine except for changes in liver function tests in lepromatous leprosy cases which could also be due to concomitant multi drug therapy regimen or due to the nature of the disease itself.

Thus, *M. habana* vaccine appears to be useful in stimulating specific cell mediated immunity against *M. leprae* as evidenced by lepromin conversion or augmentation of reactivity observed in the present study. Further, the vaccine, by virtue of minimal, well tolerated side-effects and good acceptability among the trial population, may be deemed tolerable.

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## Treatment outcome and impact of leprosy elimination campaign in Sokoto and Zamfara states, Nigeria

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Summary A Leprosy Elimination Campaign (LEC) was implemented in 37 districts of Sokoto and Zamfara states, Nigeria from 13 August to 30 November 1998. The campaign utilized intensive community mobilization and training of local health personnel to detect hidden leprosy cases. During 8 weeks of case finding, 160,127 persons were screened; 353 new cases of leprosy were detected and placed on MDT; 236 (67%) of new cases detected were classified as MB, 64 cases (18%) suffered visible deformities and 24 patients (6.8%) were children. Follow-up in December 1999 of patients placed on MDT revealed 97% PB and 96% MB cure rates, respectively. Detection of cases in communities led some community leaders to ask for repeat surveys in their communities. Repeat surveys continue to yield new cases. The authors recommend that LECs be maintained for 3 years to accelerate leprosy elimination in the region. The cost effectiveness and impact of LEC in Sokoto-Zamfara are discussed.

#### Introduction

In 1995, the World Health Organization (WHO) introduced a new initiative, leprosy elimination campaigns (LECs), the purpose of which was to detect and treat hidden leprosy patients. Between 1995 and 1999, LECs have been carried out in 24 endemic countries,<sup>1</sup> including Nigeria. In July 1999, a WHO consultative meeting assessed, among other parameters, the impact of LECs.<sup>2</sup> A review of LECs in the 24 countries observed that >500,000 new cases had been detected by LECs. Apart from detecting new cases, some LECs were successful in promoting community awareness, reducing stigma, and improving the accessibility of multidrug therapy (MDT) and skills of general health workers for diagnosis and treatment. The meeting also observed, however, that case holding was weak in some LECs and defaulter rates were high, with low treatment completion rates.

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While reports describing the conduct of LECs are increasing,<sup>3,4</sup> these reports are limited to the objectives of LECs, activities carried out, problems encountered and the immediate gains of LECs namely; i) population covered, ii) health workers/volunteers trained, iii) active cases detected and put on MDT, and iv) new MDT clinics opened during the campaigns. However, reports of cure rates among new patients put on MDT during LECs are few. This paper presents treatment outcome of patients detected during LEC and discusses the cost effectiveness and impact of LEC in Sokoto-Zamfara states, Nigeria.

#### Background

Sokoto and Zamfara states situated in the Northwest corner of Nigeria, have a total area of about 68,000 km<sup>2</sup> and population of  $5.4 \times 10^6$  people (1991 census) living in 37 administrative districts (23 in Sokoto and 14 in Zamfara). Over 80% of the population are Hausa speaking, Moslem rural farmers. There are 625 health facilities in Sokoto-Zamfara region; 116 (18.6%) of these offer MDT services to leprosy patients.

Leprosy work in Sokoto-Zamfara started in 1938 when Sudan Interior Mission built a leprosarium in Sokoto town to cater for approximately 36,000 patients in old Sokoto province. Satellite dispensaries were established in the late 1940s to serve patients who lived far from the leprosarium. Between 1948 and 1992, the leprosy service in the region used dapsone monotherapy as the strategy for control. The introduction of MDT for treatment of leprosy in the region was delayed because Sokoto-Zamfara did not commence a statewide leprosy control programme until 1993 when The Leprosy Mission (TLM) was invited to support implementation of MDT services. Sokoto-Zamfara introduced MDT in October 1993 following a statewide case verification exercise when the registered prevalence was 7142 cases. There was a 96% reduction in registered cases following MDT implementation to only 273 cases in September 1998. Despite the drastic fall in prevalence, the annual new case detection averages 360 cases, and MB proportion and grade 2 disability rate among new cases remain high. Table 1 shows leprosy control indicators from 1993 to 2000.

The high MB proportion and grade 2 disability rate among new cases from 1993-1997 led to the suspicion of a large number of hidden cases in the region. A LEC was therefore proposed to verify above suspicion and to accelerate elimination activities by detecting hidden cases, and complement routine control activities.

Indicator	1993	1994	1995	1996	1997 Jan-Sept	1998 <sup>a</sup> (LEC)	1998 <sup>a</sup>	1999	2000
Registered prevalence	7142	2414	2240	647	519	273	_	266	255
New case detection	158	241	594	236	471	226	353	256	271
MB proportion (%)	65	52	44	52	75	73	67	78	93
Grade 2 disability (%)	34	15	6	11	31	20	18	16	14
Child proportion (%)	5	3	2	8	7	9	6.8	6	9

Table 1. Annual leprosy control indicators in Sokoto-Zamfara (1993–2000)

<sup>a</sup>1998 figures represent the periods January to September (before LEC) and during LEC respectively.

#### Materials and methods

Sokoto-Zamfara region was selected for LEC due to (i) high MB and grade 2 disability rates among new cases leading to the suspicion of a large number of hidden patients in the communities, (ii) easy accessibility of majority of communities and (iii) availability of MDT services in the region. A statewide LEC was conducted in the region from 13 August to 30 November 1998 to detect and treat hidden cases using intensive population mobilization (via radio, town criers, and WHO posters to increase awareness of leprosy) and task-oriented training of health staff. This campaign was described by Sofola, in a recent paper,<sup>5</sup> stating the objectives of and activities carried out during the campaign and immediate achievements of the campaign namely numbers of (i) villages/population covered, (ii) health workers/ volunteers trained, (iii) active cases detected and put on MDT, and (iv) new MDT clinics opened during the campaigns. Except for (iii) above, the foregoing is not repeated here.

Radio messages were broadcast at prime time twice a day for 8 weeks to emphasize curability of leprosy, availability of MDT at no cost to patients and duration of LEC. More than 5000 posters affixed conspicuously at health centres and public places displayed skin lesions of leprosy and invited persons with similar lesions to report to health facilities nearest to them for confirmation. Town criers announced venues and dates of surveys in communities. Announcements by town criers were done 2 days prior to surveys and continued daily throughout the duration of the surveys.

Skin surveys took place in health facilities in selected communities for 8 weeks (4 October to 30 November). Thirteen special teams conducted the screening. Each team comprised a Leprosy Supervisor (LS), a General Health Worker (GHW), and a Voluntary Village Health Worker (VVHW). To ensure quality control of diagnosis, (i) special teams were headed by LS with more than 5 years experience in leprosy control, and (ii) active leprosy cases and suspect cases referred by the teams were re-examined by a monitoring team, of two state leprosy control officers and a physiotherapist, with more than 7 years experience in leprosy control. Cases confirmed by the monitoring team were placed on MDT immediately. During the campaign, cure was defined as completion of fixed duration WHO-MDT.<sup>6</sup> PB patients were required to take six doses of PB.MDT blister calendar packs within 9 months. MB cases were to take 12 doses of MB.MDT blister calendar packs within 18 months before they were released from treatment (RFT). A review of all patients put on MDT was carried out 1 year after the LEC exercise (in December 1999) to assess the outcome of treatment.

#### Results

During 8 weeks of case finding, 160,127 people (107,285 males and 52,842 females) were examined; and 353 new leprosy cases were detected (a rate of 22 cases/10,000 population) as against 226 cases detected by routine control activities (a rate of 0.42/10,000 people, using  $5.4 \times 10^6$  total population) between January and September 1998. Furthermore, 108 suspect cases were referred by special teams for confirmation, 88 (81.5%) of which suffered fungal infection. The remaining 20 suspect cases (18.5%) had birthmarks, psoriasis or vitiligo. In addition, the monitoring team discovered 11 cases (3.1%) of over diagnosis of burnt-out MB leprosy and removed them from the register. The number of cases of under-diagnosis cannot be ascertained, as those patients were sent away without the diagnosis being made and no records of under-diagnosis were kept.

State	Population screened		New cases		Disability grade 2	<15 years
		PB	MB	Total		
Sokoto	56,117	86	141	227	37	12
Zamfara	104,010	31	95	126	27	12
Total	160,127	117	236	353	64	24

Table 2. LEC in Sokoto-Zamfara. New cases detected by classification, disability grade, and age

Table 2 shows 236 (67%) of the 353 leprosy cases were classified as MB, 24 cases (6.8%) were <15 years of age and 64 patients (18%) suffered visible deformities. Table 3 shows 227 (96%) of MB and 113 (97%) of PB patients completed fixed duration MDT; and four patients died. All 227 MB patients completed their course of MDT within 12 months and were released from treatment without the need to extend the period of treatment to 18 months. A total of US\$ 19,712 was spent on LEC in the 37 districts of the region. Table 4 shows comparison of cost of LEC with cost of routine case finding.

#### Discussion

The success of the multi-media campaign at prompting a positive health seeking behaviour in 160,127 people is noteworthy. Furthermore, the authors who were sceptical of detecting any more than 200 new cases through LEC, were surprised by the enthusiasm displayed by LS, GHW, VVHW and community leaders during the campaign and at the detection of 353 cases (22/10,000 population). The campaign therefore detected 127 (36%) more cases in 8 weeks than 226 cases (0.42/10,000) detected in 36 weeks by routine control activities. Even though it was difficult to ascertain the number of people reached or examined by routine control activities due to poor records, the authors infer from the foregoing that routine control activities are slow at increasing awareness about leprosy and could be reaching only a small proportion of the population. This may perhaps explain why patients hide in the community or report with visible deformity.

Tab	ole 3.	Post-LEC	treatment	outcome.	December	1999
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PB (%)	MB (%)
117 (100)	236 (100)
113 (96.6)	227 (96.2)
1 (0.85)	3 (1.3)
1 (0.85)	2 (0.85)
2 (1.7)	4 (1.7)
	PB (%) 117 (100) 113 (96.6) 1 (0.85) 1 (0.85) 2 (1.7)

<sup>a</sup>Two MB patients died of severe lepra reaction and one MB and one PB patient died of non-leprosy related causes.

	Amount spent on activity (US\$)					
Activities performed	Routine case finding	Through LEC				
Salaries	3252	11,120				
Training	1925	4830				
Travel	6655	1338				
Public enlightenment	1710	2067				
Administration	276	357				
Total	13,818	19,712				

Table 4. Comparison of cost of routine case finding with cost of LEC

#### BENEFITS OF LEC

In addition to promoting public awareness, this campaign combined (i) capacity building of GHW and VVHW to diagnose leprosy, (ii) mobilization of community and health services participation in LEC, (iii) screening of 160,127 people, and (iv) opening of new MDT clinics<sup>5</sup> into one co-ordinated activity in an effective manner and with important interactions.<sup>7</sup> These aforementioned activities are often conducted separately or at different times during routine control activities. Following community mobilization during LEC, awareness has been raised to the extent that active cases continue to report to clinics several months after LEC, claiming they were motivated by messages broadcast during LEC.

#### COST OF LEC COMPARED WITH ROUTINE CASE FINDING

The comparison of cost of routine activities with the cost of LEC is interpreted with caution, as it is difficult to ascertain the number of people reached or examined during routine (opportunistic) case finding. However, if number of cases detected is used as the basis of comparison, the cost of LEC screening was US\$19.712 and cost of routine screening in 1998 was US\$13,818. This means that LEC detected 353 cases at the cost of US\$56 per case while routine screening detected 226 cases at the cost of US\$61 per case.

#### COST-EFFECTIVENESS OF LEC

The main criteria for conducting LEC in the region (high MB and grade 2 disability rates among new cases and suspicion of hidden cases), led to intensive multi-media campaign, which encouraged persons with skin lesions to present for examination. The strategy of sensitizing the whole population while inviting only persons with skin lesions for examination made screening for new cases less cumbersome than house-to-house survey, which is often very expensive<sup>8</sup> and would have aimed at examining  $5.4 \times 10^6$  people in the region. The authors therefore consider the detection of 353 cases from 160,127 people (22/10,000 population) in 8 weeks cost-effective when compared with 226 cases detected from a population of  $5.4 \times 10^6$  (0.42/10,000) in 36 weeks by routine control activities. The benefits of LEC above are worth the cost especially as LEC was conducted as one activity within a short period. It would hence be justified to continue the media campaign to ensure that everyone learns about signs of leprosy and its cure.

#### TREATMENT OUTCOME

Though case holding was given high priority in this LEC, the high cure rates recorded above were a pleasant surprise to control staff, especially the authors, who perhaps did not expect cure rates higher than the known rates of 81% in MB and 92% in PB patients in the region (ILEP B report, 1998). This higher than expected cure rates could be attributed to (i) the commitment of LS and GHW to follow-up absentees, (ii) effective health information on compliance to treatment given to patients and (iii) patients' trust in the health service. The cure rates from LEC in Sokoto-Zamfara are higher than MB cure range of 30-89% and compare favourably with PB cure range of 65-100% from Indonesia, Nepal, and Philippines.<sup>9</sup>

#### IMPACT OF LEC

#### Follow-up LECs

The detection of 353 patients during LEC compared to 226 patients detected between January and September of the same year, 1998, confirms suspicion of hidden cases in the region and led to the adoption, in the year 2000, of modified LEC campaigns<sup>5</sup> in other north western states supported by TLM in the hope of detecting all hidden cases. To date, all five states have conducted mini-LECs in a total of 29 districts. Preliminary results show that mini-LECs detected 260 hidden cases within 5 days in 29 districts surveyed (Mini-LEC reports 2000; Abuja, Kebbi, Kogi, Kwara and Niger states). Three of the five states that implemented mini-LECs in 2000 plan to extend the exercise to more districts in 2001.

#### Increased community awareness and participation in leprosy control

Detection of cases in communities led some community leaders to ask for repeat surveys in their communities (Quarterly Statistical Report 1999, Zamfara state). Repeat surveys continue to yield new cases. Referrals of leprosy from communities to the health service are also increasing (Quarterly Statistical Report 1999, Sokoto state) proving that community awareness remains high. These repeat surveys may contribute to annual new case detection for 1999 and 2000 (256 and 271 cases, respectively) remaining higher than pre-LEC detection figure of 226 in 1998 (see Table 1), suggesting that though multi-media campaigns are effective, not every one has been reached and that there are active cases still hiding in the communities. The campaigns should be sustained to motivate hidden cases to continue to report for confirmation and treatment, if a declining trend in new case detection is to be seen in future.

In addition to strengthening routine activities in the field by training local health workers, detecting hidden cases and increasing awareness of leprosy in the community,<sup>5</sup> LEC in Sokoto-Zamfara resulted in improved cure rates among patients treated with MDT; and the adoption of mini-LECs in five neighbouring states. The authors recommend that LECs be maintained for at least 3 years, to accelerate leprosy elimination, since (i) LEC is cost effective in the region, (ii) repeat mini-LECs continue to yield cases, and (iii) annual new case detection figures of 1999 and 2000 remain higher than pre-LEC annual case detection of 1994, 1996 and 1998.

The authors agree with WHO that in assessing the performance of LECs, looking at case

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detection alone is insufficient. Attention should also to be given to improvement in MDT coverage, capacity building, increasing community awareness, and the review of cure rates, (which should be maintained at around 90-95% MDT completion)<sup>2</sup>.

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# Defaulting patterns in a provincial leprosy control programme in Northern Mozambique

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Summary Cohort-based multidrug therapy (MDT) completion rates are used to assess adherence to MDT. However this measure gives no information about when during the treatment period defaulting occurs. Two districts in Cabo Delgado province in Northern Mozambique were selected for evaluation of multibacillary patient defaulter data between 1993 and 1997 to examine when patients default during the treatment period. In all, 548 (59.2%) of 926 MB patients completed treatment and 378 (40.8%) defaulted between 1993 to 1997. The percentage of defaulters fell steadily from 59.8% in 1993 to 23.2% in 1997. Of the 378 defaulters 57.7% defaulted treatment within 6 months and 83.1% within 1 year of starting treatment. It was observed that patients tend to default early rather than late in the treatment period and that this pattern is maintained over time despite a fall in defaulter rates. Patients established early into a treatment routine were more likely to complete treatment. A comprehensive effort to improve and maintain leprosy control services will probably influence adherence more than any single, specific strategy, Shortening MDT treatment from 2 years to 1 year is unlikely to affect the defaulter rate.

#### Introduction

In December 1992, following the cessation of hostilities in Mozambique, the Provincial Tuberculosis/Leprosy Control Programme (Estratégia de Luta Anti-Tuberculose/Estratégia de Luta Anti-Lepra Provincial) of the Ministry of Health was restarted in Cabo Delgado Province, Northern Mozambique with technical, logistical and financial support from The Leprosy Mission International. The Provincial Tuberculosis/Leprosy Control Programme aimed to serve a population of 1,284,480 people in an area of 83,000 square kilometres.<sup>1</sup> Cabo Delgado remains one of the poorest provinces in the country, with lower literacy rates than the national average (18% adult literacy) and unreliable communication and supply systems. There was no telephone link from provincial to national capital. There was no rail

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connection, so re-supply of drugs could take months by ship. Sometimes this meant that drugs (including MDT) would run out altogether and health institutions were without some drugs for several months.

The Provincial Medical Directorate had 30% of staffing levels at health institutions recommended by the Ministry of Health's own guidelines. There was poor geographical coverage by the health system with populations of up to 30,000 people with no health facility within 80 km. Poor roads, minefields and banditry made travel hazardous. Only eight of 17 district health directorates had even one vehicle in 1992 and fuel was often not available. There was inadequate physical infrastructure at peripheral, district and provincial levels. Around one-third of health institutions had been destroyed during the civil war and so a health centre sometimes consisted of a table under a tree. Of those that were left most had not been maintained for more than 20 years or had lost doors, windows and roof to theft. Only three district health centres had electricity. Health centres up to and including some district heath centres consisted of pole and dagga huts with a very low level of lighting, comfort and hygiene. Drugs, equipment and patient files were often damaged by rain, termites or rats. Even pens were in short supply and leprosy notifications written in charcoal were received from some districts.

In December 1992 the leprosy control component of the combined Provincial Tuberculosis/Leprosy Control Programme was weak. The registered leprosy prevalence rate for the province was 33 per 10,000 population. Only 14% of the 3883 patients registered for treatment were on MDT, the remainder theoretically on dapsone monotherapy. There were 11 drug delivery points for the entire province. Supervision by provincial staff was infrequent only four districts were visited once each during 1992. The case detection rate was 2.2/10,000 population. For those on MDT, the provincial 1992 MB cohort had a treatment completion rate of  $20\cdot1\%$  (44 of 222 patients completed treatment).

Improvement of the leprosy control component of the Provincial Tuberculosis/Leprosy Control Programme began in 1993. Six District Tuberculosis/Leprosy Control Programme (DTBLCO) supervisors were selected each year and sent to a 6-week national tuberculosis/ leprosy (TB/L) training course. They were then based one in each of 17 district administrative centres. Regular supervisory visiting (at least once in every 6 months for every district) was initiated and a standardized supervision report form was in use by late 1996 together with regular in-service training. Reserve MDT stocks were created at provincial and district levels.

In 1995, 57 peripheral health post staff and 120 village health workers were trained to assist in TB/L control. This allowed the opening of a further 123 treatment points beyond the 17 district health centres. From 1995 DTBLCO supervisors were supplied with motorbikes, which allowed regular visiting, technical support and logistical re-supply of peripheral health centres. Blister calendar packs of MDT were introduced to simplify the handling and distribution of drugs. Funding was made available for each DTBLCO supervisor's activities, based on an annual work plan drawn up by each district. All interventions were concentrated on improving the quality of service offered.

The provincial leprosy service was adjudged to have improved during the period under study; during December 1997, the percentage of patients on MDT had risen from 14% to 100%, the leprosy case detection rate had risen from 2.2/10,000 to 4.7/10,000 and the provincial leprosy prevalence rate had fallen from 33/10,000 to 10/10,000 through review and removal of patients who no longer required chemotherapy.

The treatment completion rate for the 1996 multibacillary (MB) cohort at provincial level was assessed in September 1999 (by which time it was possible to determine an entire cohort

outcome) and had risen from 20.1% to 73.7% (590 of 801 patients completed treatment). All districts were supervised, restocked with drugs and notified statistics at regular intervals.

This study had two main objectives: (i) to discover at what point MB patients default during MDT treatment and (ii) if improvements in the leprosy control programme had an effect on the number of doses patients received before defaulting.

#### Materials and methods

Chiúre and Namuno districts were selected because they had stable leprosy control programmes between 1993 and 1997. Relatively reliable registration and patient records were available. Chiúre's population in 1997 was 189,100 inhabitants and Namuno's was 137,275 inhabitants.<sup>1</sup> Both districts are land-locked with the vast majority of the population involved in the subsistence farming of cassava and maize, and growing cashew nuts and cotton for cash income.

Chiúre and Namuno districts were visited in October and November 1999 and all records available were reviewed with the DTBLCO supervisors. All patients classified as MB (i.e. more than five skin lesions) who entered the leprosy control programme in Chiúre and Namuno districts between January 1993 and December 1997 were taken. Treatment registers were examined and the number of supervised monthly doses taken before defaulting recorded for each MB defaulter. An MB defaulter was defined as a patient diagnosed with leprosy and classified as being multibacillary who had failed to take 24 supervised monthly doses in a total period of 36 months.<sup>2</sup> This definition remained constant from 1993 to 1997. From mid-1999 onwards, the National Tuberculosis/Leprosy Control Programme reduced the treatment period for MB cases from 24 supervised monthly doses to 12 supervised monthly doses so the last cohort studied was the 1997 MB cohort. All patients in these two districts had a defined outcome before the change in policy took effect despite the fact that the cohort was only due to be evaluated in January 2000.

To simplify the presentation of the data the number of doses taken were divided into eight 3-month periods. Each defaulting patient was assigned to a period depending on the number of supervised monthly doses he/she had received before defaulting.

#### **Results**

A total of 930 MB patient records were available. Four patients either died or were transferred before completing treatment and were excluded from the study. The DTBLCO supervisor's records showed that 548 (59.2%) of 926 MB patients completed treatment and 378 (40.8%) defaulted during the period 1993 to 1997.

Table 1 shows the numbers of patients in each district defaulting over the time span of the study period against the total number of patients entering the programme. This shows a steady fall in the percentage of defaulters between 1993 and 1997.

Table 2 shows the distribution of the numbers of patients by doses taken before defaulting in each dosage category. Most patients defaulted early in the treatment period rather than later. This pattern was sustained year by year throughout the period under review. Of 378 defaulters 57.7% defaulted treatment within 6 months and 83.1% within 1 year of starting treatment. Figure 1 shows this information.

District	1993		1994			1995		1996		1997			Total					
	DF	%	DF&TTC C	DF	%	DF&TTC C	DF	%	DF&TTC C	DF	%	DF&TTC C	DF	%	DF&TTC C	DF	%	DF&TTO
Chiúre	45	57.0	79	53	64.6	82	63	54.8	115	56	38.1	147	29	26.4	110	246	46.2	533
Namuno Total Province	53 98 287	62·4 59·8 62·3	85 164 461	15 68 172	39·5 56·7 57·0	38 120 302	29 92 162	28·7 42·6 44·0	101 216 368	18 74 172	22·2 32·5 22·6	81 228 762	17 46 N/A	19·3 23·2 N/A	88 198 N/A	132 378 793	33·6 40·8 41·9	393 926 1893

 Table 1. Number of patients defaulting in Chiúre and Namuno districts 1993–1997

DF = defaulter, TTC = treatment complete, N/A = not available.

Doses	1993	1994	1995	1996	1997	Total defaulters	% of total
1-3	29	24	26	27	12	118	31.2
4-6	25	16	14	27	18	100	26.5
7–9	14	5	11	13	12	55	14.6
10-12	15	4	13	6	3	41	10.8
13-15	9	3	13	1	1	27	7.1
16-18	3	6	11	0	0	20	5.3
19-21	3	10	4	0	0	17	4.5
22-23	0	0	0	0	0	0	0
Total	98	68	92	74	46	378	

**Table 2.** Distribution of number of patients by doses taken before defaulting in Chiúre and Namuno districts –1993–1997

#### Discussion

We thought that the distribution of the number of patients defaulting plotted against the number of supervised monthly doses taken before defaulting would have a Gaussian distribution. Few patients would default early, few would default late but the bulk of patients would default in the middle of the treatment period. We predicted that improvements in the leprosy control programme would result in more patients taking mores doses of MDT before defaulting. Unfortunately, it was not possible to compare defaulter rates in Cabo Delgado province with other provinces as they simply reported the annual total number of defaulters and did not break these figures down by classification or by entry cohort.<sup>2</sup>

We believed the package of interventions undertaken in this leprosy control programme should have caused a consistent reduction in the number of patients defaulting annually



Figure 1. Distribution of number of patients by doses taken before defaulting in Namuno and Chiure between 1993 and 1997.

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despite a rise in the detection rate increasing the new MB caseload. However, instead of a gradual increase in the number of supervised monthly doses taken before defaulting, resulting in a progressive rise in patients who actually completed their treatment period, it would seem from our data that an improved service resulted in a reduced proportion of defaulters but did not change the pattern of defaulting from the programme. Once patients were established in a treatment routine, they were likely to complete. If a good treatment routine was not established within the first few visits patients were much more likely to default. A study in Nepal<sup>3</sup> reached the same conclusion.

'To complete treatment is usually an independent choice of patients'.<sup>4</sup> But for a successful treatment outcome, there needs to be input from both health service provider and client seeking care. In Mozambique at the outset of the study period, the ability to complete treatment was probably more often determined by the low quality of the leprosy service rather than patient choice. For example, after 4 months without drugs in one district in 1993, it is hardly surprising that all leprosy patients there defaulted. A few contacts with an inadequate leprosy service was probably enough to discourage most patients from returning.

On questioning DTBLCO supervisors about the initial high defaulter rate in Cabo Delgado, the explanation consistently given was what might be termed the 'bad patient' hypothesis. The patients were variously described as lazy, ignorant and not interested in their own health, despite the fact that all patients had come seeking help in the first place as case finding was entirely passive. However, as staff were trained, were motivated by regular supervision and meetings and were re-supplied with drugs, they saw the defaulter rate fall despite the fact that there was no attempt at mass health education or improving community awareness of leprosy and duration of leprosy treatment. We observed that over time the 'bad patient' hypothesis was less frequently offered by staff as an explanation for defaulting.

Directly observed treatment for tuberculosis has been associated with substantial improvements in rates of adherence in some countries.<sup>4</sup> However, a study in Pakistan showed no advantage of directly observed treatment over self-administered or family observed treatment.<sup>5</sup> However, both papers showed improvement in adherence rates as a result of a comprehensive effort to improve tuberculosis services – improved service accessibility, increased availability of drugs, changes in drug regimens, staff training, increased supervision of staff – rather than one specific strategy.

With trained, motivated, accessible staff with the means to treat, defaulter rates decreased probably because more patients were established early into a regular pattern of treatment and so an increased proportion each year completed. However, the defaulter rate did not fall to zero and patients tended to default early rather than late. This suggests that a good quality control programme may impact on the early establishment of a regular treatment routine but then patient factors determine the final establishment of a treatment routine. The leprosy service may or may not be able to influence these patient factors. Heynders et al.<sup>3</sup> suggest targeting patients who miss several monthly supervised doses early in treatment with a letter or home visit. This has been shown to be effective in reducing defaulting in other settings. But in a human-resource poor environment, where travel is time-consuming and patients widespread, it is possible that time spent away from the health centre by leprosy control staff following up irregular attenders will adversely affect the treatment outcome for patients coming to the health centre. Perhaps peer help (preferably volunteer) as animators would be more useful, particularly in the collective village setting. Clear, structured health education guidelines for health staff together with a take-home leaflet for patients, appropriate to a population with low literacy skills, would be two further strategies to examine. Due to the

complex nature of non-adherence, probably a combination of strategies will be found to work best.

The recent introduction of a 12-dose fixed duration regime for MB patients in Cabo Delgado province will probably have only a minor effect on improving the defaulter rate further. Improving and maintaining the quality of a leprosy control service is more likely to keep defaulter rates low than the reduction of the length of treatment from 2 years to 1 year. Since the default rate has changed but the default pattern has remained constant, further research would be justified in looking at factors influencing why those patients that default continue to do so early despite an improved leprosy control service.

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## Should nutritional status evaluation be included in the initial needs assessment of leprosy patients with disability prior to socio-economic

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Summary Because of the large numbers of leprosy patients with disability and the limited resources available, it is important that socio-economic rehabilitation (SER) is targeted towards those who are most in need. Towards this purpose, current assessments of leprosy patients prior to initiating SER include the evaluation of income, assets and household possessions. Conspicuously absent is the nutritional assessment of the patient. In the absence of weight loss associated with illness, population studies indicate that undernutrition reflects poor socio-economic conditions. In this study of 151 cured leprosy patients with disability, 57% of the patients were found to be undernourished using body mass index (kg/m<sup>2</sup>) derived from body weight and height, and 10% of the patients were severely undernourished (grade III). Undernutrition in the patients was poorly though significantly correlated with personal income (r = 0.18, P < 0.05). Total household income, reported amount of money spent on food and estimated cereal intakes were not correlated with the BMI of the patient, possibly due to reporting bias and other methodological issues. We propose the inclusion of nutritional status evaluation by anthropometry as part of the initial screening of leprosy patients prior to instituting SER. We believe that this simple and objective evaluation can add to the assessment of 'threat' of economic deprivation or actual economic 'dislocation', and thus help in the prioritization of leprosy patients for SER.

#### Introduction

While considerable efforts have been made to reduce the development of disability in leprosy patients, there are still a large number of cured leprosy patients with residual deformity.<sup>1</sup> In

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India, for instance, it is estimated that there are 1 million individuals with disabilities attributable to past and present leprosy.<sup>1</sup> The leprosy patient with deformity has unique sociocultural problems. These include, among others, a lower acceptance in the community<sup>2,3</sup> and lower incomes.<sup>3,4</sup>

One of the tasks undertaken by personnel working with leprosy patients is the socioeconomic rehabilitation (SER) of leprosy patients with disability. This has, in fact, been listed as a priority area for leprosy programme planners.<sup>5</sup> In a situation where economic resources are limited, and the numbers of people with disability are large,<sup>6</sup> the process of rehabilitation needs to be targeted to those most in need. In this context, it has been suggested that in assessing rehabilitation needs, simple counts of those with impairments will not suffice.<sup>7</sup> Indeed, people with impairments (even deformity) are not necessarily in need of rehabilitation.<sup>5</sup> It has now been suggested that (i) individuals with physical disability whose social and economic life is under threat, or (ii) already economically dislocated patients, should be the primary targets of SER.<sup>8</sup> Gopal, based on a large survey in India, estimated these numbers to be 2.5 and 9% of the total leprosy population, respectively.<sup>9</sup> The challenge in the first instance, clearly, is to identify these individuals. In order to do this, it is recommended that initial screening of disabled individuals should include an assessment of financial status, including employment history, earnings, assets and liabilities before the disease as well as an assessment of employment and economic impact of leprosy.<sup>8</sup> Some of these indicators, however, are subjective and can possibly have a reporting bias. It is our contention that the objective evaluation of nutritional status in disabled leprosy patients can help separate out those who are economically deprived from those who are not, and can add valuable information to the initial needs assessment aimed at identifying individuals most in need of SER.

This paper explores, in part, the theoretical construct outlined in Figure 1 which illustrates the possible links of nutritional status with other economic indices, some of which are used in the initial needs assessment of leprosy patients with disability. In so doing, we propose that nutritional status evaluation using simple anthropometric measures be included as part of the needs assessment of leprosy patients with disability.

#### Materials and methods

This analysis is based on 151 cured, adult leprosy patients with residual disability. This data set is a sub-sample of a larger study reported earlier,<sup>3</sup> and includes all the leprosy patients with disability of that study. Fifty-two of the leprosy patients were women. This sample of cured leprosy patients comprised 12% of the total number of living leprosy patients with deformity registered at the Emmaus Swiss Leprosy Project in Palamaner, South India, the site where the study was conducted.

The details of the sampling strategy have been described earlier.<sup>3</sup> Briefly, patients were motivated to attend the mobile leprosy clinic services, during which a nutritional assessment was performed by a trained nutritionist accompanying the clinic team. The nutritional assessment included basic anthropometry at the clinic site. In addition, paramedical workers also filled in a questionnaire during home visits prior to the clinic. This questionnaire related to the detailed evaluation of deformity status and the purchase of food staples. The extent of disability was assessed using the method of Bechelli and Dominguez.<sup>10</sup> The cereal energy intake of the index case was assessed by applying appropriate consumption units to the

household cereal supply.<sup>11</sup> The anthropometric assessment included height and weight of all subjects. Nutritional status was determined using body mass index (BMI: weight in kg/ height<sup>2</sup> in m) cut-offs described earlier.<sup>12,13</sup> Thus, well nourished subjects had BMIs of >18.5. Chronic undernutrition of varying grades was identified as follows: grade I = BMI 17–18.5, grade II = 16 to <17, grade III = BMI <16.

All data are presented as mean  $\pm$  standard deviation (SD). In order to facilitate analysis, leprosy patients were divided into four groups (well nourished, and three grades of undernutrition). A comparison of parameters in these four groups was done using a one-way analysis of variance (ANOVA). The null hypothesis was rejected at P < 0.05.

#### Results

Table 1 summarizes the characteristics of the cured leprosy patients with residual deformity classified into four nutritional groups. The age of the patient, the extent and duration of disability, and the prevalence of unemployment were similar in all nutritional groups. The total household income of leprosy patients with grade III undernutrition was 70% of that of well-nourished leprosy patients (not statistically significant), and was explained almost entirely by the loss of earnings in the index case. Despite the  $\sim$ 30% lower total income in the households of patients with grade III undernutrition, the amount of money reportedly spent on food was comparable across all groups. The cereal-based daily energy intake of leprosy patients with grade III undernutrition was >20% lower than patients who were well nourished, although this difference was not statistically significant.

When the data of all groups were pooled, the income of the leprosy patient was, significantly, albeit poorly correlated with the BMI of the leprosy patient (r = 0.18, P = 0.03).

Well nourished	Undernourished Grade 1	Grade II	Grade III	<i>P</i> -value
65	47	23	15	
$20.8 \pm 0.4$	$17.8 \pm 0.4$	$16.6 \pm 0.3$	$15.1 \pm 0.5$	0.000
$41.4 \pm 7.9$	41.5 ± 7.9	42.4 ± 6.2	38.6 ± 8.1	0.503
$1.92 \pm 1.18$	$1.9 \pm 1.19$	$1.96 \pm 1.0$	$1.77 \pm 1.0$	0.962
$10.3 \pm 6.6$	11.9 ± 8.0	$10.1 \pm 7.1$	11.9 ± 6.4	0.548
21 (32.3%)	17 (36.2%)	12 (52.1%)	4 (26.7%)	Chi square: NS
239.9 ± 136.3	249.2 ± 192.6	213.9 ± 145.9	$170.0 \pm 93.2$	0.354
88.8 ± 101.2	80.7 ± 128.2	40.4 ± 75.7	28.8 ± 43.1	0.105
$123.3 \pm 56.6$	$102.6 \pm 55.1$	99.9 ± 70.1	$113.3 \pm 46.4$	0.199
2202.9 ± 752.1	2131.0 ± 811.2	2105.9 ± 756.9	1697.1 ± 762.8	0.160
	Well nourished 65 $20.8 \pm 0.4$ $41.4 \pm 7.9$ $1.92 \pm 1.18$ $10.3 \pm 6.6$ 21 (32.3%) $239.9 \pm 136.3$ $88.8 \pm 101.2$ $123.3 \pm 56.6$ $2202.9 \pm 752.1$	Well nourishedUndernourished Grade 1 $65$ $47$ $20.8 \pm 0.4$ $17.8 \pm 0.4$ $41.4 \pm 7.9$ $41.5 \pm 7.9$ $1.92 \pm 1.18$ $1.9 \pm 1.19$ $10.3 \pm 6.6$ $11.9 \pm 8.0$ $21$ ( $32.3\%$ ) $17$ ( $36.2\%$ ) $239.9 \pm 136.3$ $249.2 \pm 192.6$ $88.8 \pm 101.2$ $80.7 \pm 128.2$ $123.3 \pm 56.6$ $102.6 \pm 55.1$ $2202.9 \pm 752.1$ $2131.0 \pm 811.2$	Well nourished Grade 1Undernourished Grade 1Grade II $65$ $47$ $23$ $20.8 \pm 0.4$ $17.8 \pm 0.4$ $16.6 \pm 0.3$ $41.4 \pm 7.9$ $41.5 \pm 7.9$ $42.4 \pm 6.2$ $1.92 \pm 1.18$ $1.9 \pm 1.19$ $1.96 \pm 1.0$ $10.3 \pm 6.6$ $11.9 \pm 8.0$ $10.1 \pm 7.1$ $21$ ( $32.3\%$ ) $17$ ( $36.2\%$ ) $12$ ( $52.1\%$ ) $239.9 \pm 136.3$ $249.2 \pm 192.6$ $213.9 \pm 145.9$ $88.8 \pm 101.2$ $80.7 \pm 128.2$ $40.4 \pm 75.7$ $123.3 \pm 56.6$ $102.6 \pm 55.1$ $99.9 \pm 70.1$ $2202.9 \pm 752.1$ $2131.0 \pm 811.2$ $2105.9 \pm 756.9$	Well nourished Grade 1Undernourished Grade 1Grade IIGrade III $65$ $20.8 \pm 0.4$ $41.4 \pm 7.9$ $47$ $41.5 \pm 7.9$ $23$ $42.4 \pm 6.2$ $15$ $42.4 \pm 6.2$ $1.92 \pm 1.18$ $10.3 \pm 6.6$ $1.9 \pm 1.19$ $11.9 \pm 8.0$ $1.96 \pm 1.0$ $10.1 \pm 7.1$ $1.77 \pm 1.0$ $11.9 \pm 6.4$ $21$ (32.3%) $17$ (36.2%) $12$ (52.1%) $4$ (26.7%) $239.9 \pm 136.3$ $88.8 \pm 101.2$ $249.2 \pm 192.6$ $80.7 \pm 128.2$ $213.9 \pm 145.9$ $40.4 \pm 75.7$ $170.0 \pm 93.2$ $28.8 \pm 43.1$ $123.3 \pm 56.6$ $102.6 \pm 55.1$ $2131.0 \pm 811.2$ $99.9 \pm 70.1$ $2105.9 \pm 756.9$ $1697.1 \pm 762.8$

Table 1. Characteristics of index cases with deformity

All mean  $\pm$  SD, statistical analysis using one-way ANOVA.

The extent of disability, total household income and reported food expenditure were all not significantly correlated with the extent of undernutrition in the index case.

#### Discussion

There is considerable literature on the principles involved in the successful implementation of community based rehabilitation programmes.<sup>16</sup> There are few data, however, on the methods of prioritization of disabled individuals for rehabilitation interventions. Historically, early reports of effective community based rehabilitation focused more on the positive changes in individuals who were rehabilitated, rather than the process involved in the choice of these individuals.<sup>17</sup> Towards the latter part of the 1990s there have been calls for more accurate methods to assess the global needs in relation to rehabilitation,<sup>5,9</sup> culminating in comprehensive guidelines.<sup>8</sup>

The data of this study demonstrate the simplicity with which nutritional status can be assessed anthropometrically. Fifty-seven percent of the leprosy patients with residual disability had some degree of undernutrition. In approximately 10% of patients, the extent of undernutrition was severe (grade III). The only significant correlate of undernutrition in the individual with disability was personal income. Reported household income, amount of money spent on food, and estimated cereal intake were not correlated with the BMI of the individual, although the mean value of all these parameters was lower (NS) in leprosy patients with grade III undernutrition as compared to those who were well nourished.

As mentioned earlier, it has been suggested that those with physical disability whose social and economic life are under threat or already dislocated should be seen as the primary targets for SER.<sup>8</sup> The issue then is to quantify the 'threat' or 'dislocation'. Personal and household income, possessions and assets are all obvious measures and have been advocated in the initial needs assessment of leprosy patients with disability.<sup>8</sup> Some of these, however, like income and amount of money spent on food, are subject to reporting bias and are difficult to verify in situations where individuals are self employed, where employment may be intermittent, and where food procurement is variable, and dependent on variable financial situations. This may account for the poor correlation between nutritional status and other economic indicators in our study. It is our contention, based on a large body of data,<sup>13</sup> that in the absence of disease, undernutrition is reflective of a poor economic status and should be included as part of the needs assessment of disabled leprosy patients being evaluated for SER. Furthermore, undernutrition in the index case also reflects an increased household vulnerability as evidenced by the increased burden of undernutrition in these households.<sup>3</sup> Figure 1 outlines the natural process that links nutritional status to primary measures of economic status like income. While some measures of nutrition are cumbersome and fraught with methodological issues; the estimation of food intake, for instance,<sup>18</sup> the advantages of nutritional status assessment by anthropometry are that it is objective, and simple to perform, requiring no more than the measurement of height and weight in adults.

The title of this paper poses a question: should nutritional status evaluation be included in the initial needs evaluation of leprosy patients? Based on the data of this study, we believe it should. The data clearly demonstrates that within a group of disabled leprosy patients, simple anthropometry allows the categorization of subjects along a nutritional spectrum. Grade 1 undernutrition in the presence of other lowered economic indicators like income is likely to represent economic 'threat', while grade III undernutrition is more likely to represent



Figure 1. Flow chart indicating potential parameters that can be used to assess nutritional vulnerability as economic indices, and the specific role of anthropometry.

economic 'dislocation'. We accordingly propose that heights and weights of disabled adult leprosy patients, be routinely recorded as a part of the initial assessment of patients prior to SER. The presence and extent of undernutrition can be assessed using the cut-offs in this paper, and delineated earlier.<sup>12,13</sup>

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## FURTHER EDUCATION SERIES

# The biology of HIV infection

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Summary This article reviews the cell and molecular biology of human immunodeficiency virus (HIV), emphasizing the features that lead to opportunistic infection by organisms such as mycobacteria. Mycobacteria, especially M. avium complex and M. tuberculosis infections, are closely associated with HIV disease. HIV is a very small retrovirus and its high mutation rate leads to extremely variable viral populations, both within and between individuals. It is coated with glycoprotein 120 (gp120), which it uses to bind to and infect a range of CD4+ leukocytes, depending on the co-receptor specificity. T cell-tropic HIV strains tend to use the CXCR-4 chemokine receptor, while macrophage-tropic strains tend to use the CCR-5 chemokine receptor. Immunosuppression is induced in a number of ways. As well as frank depletion of virus-infected T cells, antigen-specific T cell clones can be selectively deleted by mechanisms such as defective antigen presentation by HIV-infected macrophages (activation-induced cell death). Changes in cytokine production in HIV infection are also proposed. All this leads to falling T cell counts, B cell dysregulation and macrophage dysfunction. Opportunistic infections exploit this immunosuppressed environment. Certain infections are prevalent, reflecting factors such as environmental exposure to pathogens, poor mucosal defences and subcellular interactions between HIV and, e.g. viral or mycobacterial infections. Opportunistic infection exacerbates immune destruction by HIV, producing a vicious cycle that is ultimately fatal.

#### Abbreviations

HIV	human immunodeficiency virus
AIDS	acquired immunodeficiency syndrome
MAC	Mycobacterium avium complex
CD4	cluster of differentiation antigen 4
HLA	human leukocyte antigen
RNA	ribonucleic acid

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deoxyribonucleic acid
T cell receptor
tumour necrosis factor $\alpha$
HIV glycoprotein 120
antigen presenting cell
major histocompatibility antigen
macrophage tropic HIV strains
T cell tropic HIV strains
cerebrospinal fluid
regulated on activation, normal T expressed and secreted chemokines
macrophage inflammatory protein $1\alpha$
chemokines containing a cysteine-any amino acid-cysteine motif
CXC chemokine receptor
HIV strains that bind to CXCR-4
chemokines containing two adjacent cysteine molecules
CC chemokine receptor
HIV strains that bind to CCR-5
HIV strains that bind to both CXCR-4 and CCR-5
non-syncytium inducing HIV strains
activation-induced cell death
interleukin-10
T helper subset 1
immunoglobulin G
mycobacterial lipoarabinomannan
avirulent strain of M. tb
virulent strain of M. tb

## Introduction

There are more than 30 million people living with human immunodeficiency virus (HIV) worldwide.<sup>1</sup> As the immune system is progressively compromised and HIV infection develops into clinical acquired immunodeficiency syndrome (AIDS), many opportunistic infections are encountered, including some important mycobacteria.

*Mycobacterium avium* complex (MAC) is ubiquitous in the environment and commonly causes serious opportunistic disseminated infection in AIDS patients who have low circulating CD4 T cell counts (<50 cells/ml).<sup>2</sup>

*Mycobacterium tuberculosis* (*M.tb*) is also a frequent cause of morbidity and mortality in HIV-infected patients. With a third of the world latently infected with TB, especially in non-industrialized countries, much of the HIV-related TB is due to reactivation of dormant bacilli, often in the earlier stages of HIV disease (CD4 counts of >300 cells/ml). Primary infection is also a problem, especially in patients with low CD4 cell counts, and, alarmingly, nosocomial outbreaks (including with multidrug resistant strains) have occurred in healthcare settings.<sup>3,4</sup> There is a less well documented association between leprosy and HIV, but the two diseases coexist geographically and co-infection does occur.<sup>5–8</sup>

It is clear then that health professionals and researchers involved with mycobacteria need a working understanding of HIV disease. This article in the series aims to review and give an

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update on the biology of HIV, highlighting the cellular events behind the clinical association between HIV and opportunistic infections such as mycobacteria.

#### The HIV virus – structure and replication

The structure of the HIV viruses helps us understand why they mutate so much and how they infect and multiply in particular cell types.

HIV-1 and HIV-2 are retroviruses, and are impressively small, simple viruses. The genome is a mere 9.8 kilobases, coding for just a dozen proteins. The core and matrix of viral proteins are surrounded by a lipid envelope, which is derived from the host cell as the virus particle buds off the cell. It can contain host cellular proteins such as HLA and these help to mask the virus from the immune system. The envelope is also studded with viral envelope glycoproteins, which are crucial in infectivity and immunogenicity, as we shall see below. HIV-2 is about 55% sequence divergent from HIV-1 and is serologically distinct, mostly due to differences in the envelope glycoprotein.<sup>9</sup>

HIV uses the envelope protein gp120 to bind to cellular receptors (CD4 and a coreceptor) and fuse with target cells, particularly T cells and macrophages (about which much more later). Once inside the host cell, the viral genome and reverse transcriptase are unpacked and the RNA is reverse transcribed into DNA (see Figure 1). Reverse transcriptase is relatively error-prone, so viral variants are continually produced. This variability underlies many of the features of HIV infection (see next section). The transcribed DNA is then transported to the nucleus and randomly integrated into the host genome, and new viral copies are made by hijacking the host's cellular machinery (see Figure 1). This process requires the cell to be activated [e.g. via the T cell receptor (TCR)<sup>10</sup> or via the cytokine tumour necrosis factor- $\alpha$  (TNF- $\alpha$ )],<sup>9</sup> so we can immediately see that activation of the immune response stimulates virus production. This leaves the host in an impossible situation; in attempting to eliminate the virus (or other opportunistic infections), it can actually trigger further virus production.

#### **HIV diversity**

HIV has a very high mutation rate, giving rise to hugely variable viral populations, both within an individual and between individuals.

Variation is most prevalent and important in the major immunogenic envelope protein gp120, where there are several hypervariable regions. Within an individual, the virus can change over time and in different locations within the body. Between individuals, strains can vary by around 10% of their total sequence and by as much as 40% of amino acid sequences in gp120. This has led to the classification of global HIV-1 strains into 11 subtypes (A–J and O), also called clades.<sup>9</sup>

As well as making life difficult for epidemiologists, there are at least two major biological implications of gp120 diversity. Firstly, the constantly changing viral antigens means the immune system is always a step behind and is less able to mount an effective response. On a larger scale, this also means the medical community is struggling to find an effective vaccine. Secondly, because gp120 is used to bind to host cells, infectivity of the virus changes between strains and over time within an individual, as described below.



**Figure 1.** Schematic representation of HIV entry, disassembly, replication and release from susceptible cell (lymphocyte or macrophage). (1) HIV binds to cell surface via receptors (CD4 molecule and coreceptors). (2) Viral uncoating in cytoplasm. (3) RNA viral genome transcribed to DNA copy-reverse transcriptase (RT) enzyme.\* (4) DNA copy integrates into host cell genome in cell nucleus via integrase enzyme. (5) Following cell activation viral DNA is translated to RNA copies in cytoplasm. (6) Viral peptide chains translated from cytoplasmic viral RNA. (7) HIV proteinase cleaves functional viral proteins from polypeptides.\*\* (8) Virion assembly. (9) Viral release from cell surface – cell lysis. \*RT inhibitors act here. \*\*Proteinase inhibitors act here. (Reproduced with permission from Davidson's Principles and Practice of Medicine, 18th edition, Harcourt Brace, 1999.)

#### **Receptors for HIV**

We now know that CD4 is the major cellular receptor for HIV and that there is also a family of minor coreceptors, which determine the cell types that different HIV strains infect.

It was quite early in HIV research, in 1984, that CD4 was shown to be the major cellular receptor for the virus, binding directly to gp120.<sup>11,12</sup> CD4 is present at high levels on most T cells and also at lower levels on many antigen-presenting cells (APCs), such as macrophages. It associates with the T cell receptor complex during antigen presentation, binding with MHC class II proteins on the antigen presenting cell and acting as a co-stimulatory molecule.

However, the cellular distribution of CD4 went most, but, crucially, not all the way, to explaining the cellular range of susceptibility to the HIV virus. It was found that some viral isolates were tropic for T cells (T-tropic), especially those that had been passaged in T cell lines in the laboratory). Others were tropic for macrophages (M-tropic). Isolates from patients in early stages of the disease tend to be M-tropic, T-tropic strains appearing in more advanced disease. M-tropic strains are also more able to infect neural cells – patients succumbing to AIDS-related dementia tend to have M-tropic strains of the virus in their brain and CSF.<sup>9</sup>

Then in 1995, Cocchi *et al.*<sup>13</sup> showed that infection of cells by M-tropic isolates was inhibited by a group of chemokines known as RANTES (regulated on activation, normal T expressed and secreted), MIP-1 $\alpha$  (macrophage inflammatory protein 1 $\alpha$ ) and MIP-1 $\tilde{\beta}$  This prompted a publishing frenzy in 1996 when the second receptor was shown, by molecularly engineered expression, to be various members of a chemokine receptor family.<sup>14–17</sup> It is the viral gp120 that also binds to these chemokine receptors.<sup>18,19</sup>

At least 10 different chemokine/HIV receptors have now been identified, but the names, classification and specificity can appear confusing. Put simply, there are two groups. CXC chemokines (containing cysteine–any amino acid–cysteine) mostly attract neutrophils and the receptors are designated CXCR. Laboratory-adapted HIV strains, grown for many passages in T cell lines and which can only infect T cells (and are often able to induce syncytium formation in host cells), use only CXCR-4 as the coreceptor, so these strains are also referred to as X4 tropic. Conversely, CC chemokines (containing two adjacent cysteine residues) attract both monocytes and lymphocytes and the receptors are designated CCR. Macrophage-tropic HIV strains (including most primary isolates from patients) use the CCR-5 receptor, are therefore referred to as R5 tropic and are usually non-syncytium-inducing (NSI). To confuse matters further, there are also HIV strains (mostly patient isolates of primary T cell strains), which are able to use both CCR-5 and CXCR-4, referred to as R5X4 tropic. This classification should be considered as an approximation of reality.<sup>10,20</sup>

There is a fascinating clinical observation relating to all this molecular coreceptor wizardry. There are two known mutations of the CCR-5 gene in humans, both of which result in failure of the functional receptor to appear on the cell surface. People carrying two mutant copies of the CCR-5 gene have a protective advantage against HIV infection, and those with one copy of the mutant gene follow a long-term non-progressive disease course.<sup>21,22</sup> About 1-3% of European-descended populations are protected from HIV infection because they carry two mutant copies of the CCR-5 gene (CCR-5 del32) and 14% carry one copy. They do not suffer any obvious ill-effects from lacking this chemokine receptor. It is speculated that the mutation became fixed in the population during the fourteenth century, when it might have conferred some protection during the bubonic plague epidemic.

Knowing now how HIV gets into different cell types and that a mutant receptor for HIV is

sufficient to prevent HIV infection gives researchers some hope for designing drugs that inhibit HIV entry into cells.

#### **HIV-induced immunosuppression**

Among the paradoxes of HIV research have been the facts that a) not enough virus is produced in the asymptomatic phase of the infection to cause the direct death of the vast number of T cells that are ultimately destroyed, and b) immune dysfunction is apparent even before T cell counts have dropped significantly. It is now becoming clear that HIV's effects on the immune system are far more extensive than mere depletion of virally infected T cells; the disruption involves a variety of cell types, both infected and bystanders, plus cytokines and other soluble molecules.

Gp120 is the prime suspect in immune disruption, both on the viral surface and as soluble, extracellular protein (see Figure 2). When it binds to CD4 and chemokine receptors on T cells or antigen presenting cells, it can block binding of the normal ligands and therefore interferes with normal antigen presentation and normal chemokine signalling, and, it can lead to internalization of the receptors and therefore loss of surface receptors. Gp120, either free or when presented on the surface of antigen presenting cells, can also cause inappropriate activation of intracellular signalling pathways. This can lead to anergy or even



**Figure 2.** HIV-1 interactions with APC cell surface receptors. HIV-1 and its shed surface protein gp120 are able to interact with a number of receptor molecules on APC. The gp120 protein has binding sites for CD4 and chemokine receptors such as CCR5. It can also interact with Fc or complement receptors via anti-HIV-1 antibodies. Outcomes of HIV-1 proteins binding to APC receptors include infection of the cell by HIV-1 (a process that can be enhanced by antibodies to HIV-1, antibody-enhanced infection), and phagocytosis of receptor complexes bound to soluble gp120, leading to the loss of receptors, such as CD4, and possible entry of the receptor/gp120 complex into antigen processing pathways. It should be noted that all of the HIV-1 receptors are linked to intracellular signalling pathways that can be activated on binding HIV-1 or gp120 and that this can lead to disruption of the cell's function. CKR, chemokine receptor. [Reproduced with permission from Hewson T, Lone N, Moore M *et al.*, Interactions of HIV-1 with antigen-presenting cells, *Immunology and Cell Biology*, 1999; 77: 289–303 (http://www.blackwell-science.com/icb).]

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activation-induced cell death (AICD, a form of apoptosis) being induced instead of cell stimulation, and is probably a major mechanism by which the functional depletion of T cells seen in HIV disease occurs.<sup>10,20,23</sup> These kinds of antigen-specific mechanisms can explain how significant damage can be wreaked in the immune system even before the wholesale collapse in T cell numbers; crucial T cell clones that are needed to combat HIV and other concurrent infections are being selectively wiped out instead of being stimulated.

In addition to blatant T cell death and functional depletion, the immune system can also be unbalanced by changes in cytokine production in HIV infection. HIV infection of APCs modulates production of interferon, interleukin (IL)-10 and IL-12, which can induce a switch of T cell phenotypes from T helper (Th-1, associated with cell-mediated immune responses) to Th-2 (associated with humoral responses). This switch in dominant T cell subsets has been reported in patients as their disease progresses, but the hypothesis is probably rather simplistic.<sup>10</sup>

The loss of T cell clones and the proposed shift in cytokine profile from Th-1 to Th-2 also compromises other, effector arms of the immune system. B cell dysregulation leads to spontaneous polyclonal proliferation and IgG secretion, but an impaired response to *de novo* antigens.<sup>24</sup> Macrophage function, including phagocytosis and intracellular killing of bacteria, is impaired both by the change in cytokine profile and by the fact that macrophages themselves are infected by HIV. This is of particular relevance to mycobacteria, which live inside macrophages.

#### **Course of HIV infection**

Armed with the basic biological evidence described above, we can now suggest explanations for the course of HIV infection.

The (typically M-tropic) virus usually enters an individual by infecting macrophages, dendritic cells and other CD4+ cells in mucosal tissue. The virus is passed on to systemic activated T cells and a period of acute infection develops, where virus replication is high and can be easily detected in the blood and lymph nodes. An initial antiviral immune response then causes viral titres to drop drastically and a persistent state is established, which can continue for years. During this time there is a low level of viral production (when new variants will be continually produced), kept in temporary check by the immune system. However, there is a slow, persistent decline in CD4+ lymphocytes. Eventually, more virulent viral strains (often T-tropic, syncytium inducing) emerge, which leads to a second high level of viraemia. This is usually coupled with a decline in T cell count to below 300 cells/ $\mu$ l, and is the point at which opportunistic infections manifest themselves.<sup>9</sup>

#### **Opportunistic infection in HIV-infected patients**

Viruses, fungi, bacteria and parasites all exploit the immunosuppressed environment of patients with AIDS, often leading to disseminated disease. The likelihood of opportunistic infection depends both upon the degree of immune dysfunction and on the environment in which the individual lives (and has lived, for those infections that are reactivated).

The most common viral infections in HIV patients are those of the herpes family. Such viruses can also enhance HIV production, not only by induction of cytokines, but also directly

by transactivating factors within co-infected cells. Other viruses include ones associated with neoplasms, such as human papilloma virus. The B cell polyclonal activation induced by HIV is favourable for Epstein–Barr virus proliferation and can promote B-cell lymphomas.<sup>9</sup>

The likelihood of developing opportunistic fungal and parasitic infections in HIV depends largely on the geographical location of the patient and therefore their exposure to the pathogen. For example, exposure to *Cryptococcus neoformans* is universal (though particularly in Africa), whereas histoplasmosis occurs mainly in the United States of America.<sup>24</sup> Toxoplasmosis and leishmaniasis are good examples of protozoal infections exacerbated or reactivated by HIV.

Bacteria thrive in the face of impaired antibody production and macrophage dysfunction induced by HIV. Poor mucosal defences encourage a range of enteric infections, such as *Salmonella* and *Shigella*, which can lead to bacteraemia. Since mycobacteria prefer to live inside macrophages, it is obvious that they will benefit from impaired macrophage function. *M. avium*, in particular, thrives and leads to disseminated disease, mostly when T cell counts are very low. It is perhaps surprising that *M. leprae* is not more of a problem in HIV. Slow multiplication rate of *M. leprae* means it cannot quickly colonize an immunocompromised host. There are only very few reports of some degree of association between HIV and leprosy<sup>7</sup> and of HIV altering the clinical course of leprosy cases.<sup>5</sup>

Tuberculosis, on the other hand is remarkable because it can be reactivated somewhat earlier in HIV infection. This is either because it is a more virulent pathogen or because of involvement of more specific mechanisms, such as functional depletion of antigen-specific T cell clones which were holding latent infection in check. The proposed Th-1/Th-2 switch would also facilitate the proliferation of mycobacteria (which are controlled more effectively by a Th1-mediated response). The question of whether there is a more specific relationship, on a cellular level, between mycobacteria and HIV infection, has been addressed by a few researchers. MAC replication is enhanced by HIV co-infection of cell cultures *in vitro*, although the mechanism behind this has not been elucidated.<sup>25–27</sup> Conversely, lipoarabinomannan (LAM) from *M.tb* H37Ra (although less so for LAM from virulent *M.tb* strains) has been shown to stimulate HIV replication in macrophage cell lines both directly via NF- $\alpha$ B and via TNF- $\alpha$  production.<sup>28,29</sup> So we can see how HIV can facilitate HIV survival.

The terminal phase of HIV disease is therefore a vicious cycle of viral production, destruction of immune cells, repeated opportunistic infection and further immune dysfunction, from which the body cannot by itself escape.

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## Letter to the Editor

#### COMPARATIVE VALUE OF ACTIVE AND PASSIVE SURVEILLANCE OVER TIME IN TREATED LEPROSY PATIENTS, IN THE PREVENTION OF FURTHER DISABILITY

#### Editor,

Van Brakel *et al.* have recently made a strong case for using the EHF score (Eye-Hand-Foot score) as a means of monitoring changes in impairment status in individuals or groups of people over time. It would provide at least a crude measure of the effectiveness of prevention of impairment activities.<sup>1</sup> It is a simple score, the components of which are already collected in most leprosy control programmes.

At ALERT, the WHO Impairment Grades have been recorded for each eye, hand and foot at regular intervals for all patients on treatment and the EHF score can therefore be calculated by summation for each patient at various points after diagnosis. Some preliminary results of using the EHF score over time were reported at the International Leprosy Congress in Beijing and we would like to point out some of the most relevant findings.

Many leprosy control programmes, including ALERT, have previously had a policy of active surveillance after release from treatment (RFT) in order to detect possible relapses as early as possible. Patients were given an annual appointment for review and were actively sought if they failed to attend.

With multiple drug treatment (MDT), relapses have been extremely rare, so it is no longer deemed cost-effective to have active follow-up. Patients are now advised to report back to the health unit each year, or at any time if they develop any health problem, especially any sign of recurrence or worsening of their leprosy. This is termed passive surveillance and no action is taken if the patients do not attend.

A disadvantage of the change from active to passive surveillance is that the opportunity for early detection of reactions and neuritis (especially silent neuritis) is lessened and this may become more important with shorter treatment courses.

At ALERT, a cohort of patients in an MDT evaluation study is being followed up actively, while all others are followed passively. This situation gave us the opportunity to assess whether active surveillance of patients after RFT prevents further disability, as compared with passive surveillance.

#### Methods

The study compared two groups of patients, both of whom were released from treatment 5 years ago. In all, 223 patients in the ALERT MDT Field Evaluation Study (AMFES) were seen every 6 months under a scheme of active surveillance. Another 184 patients in another supervisory area formed a cohort that was not followed actively.

The study was carried out in central Ethiopia. All patients in specified areas released from treatment during the period 1990–1992 were included in the study.

The AMFES patient data are already collected routinely and computerized. The non-AMFES patients were traced for assessment of impairment status. During the assessment the following procedures were carried out: VMT, ST, noting the presence of ulcers and other damage, allocation of impairment grading according to the WHO guidelines of 1988.<sup>2</sup>

Follow-up year	1	2	3	4	5	Never
Patient attendances	22	18	16	13	4	66

**Table 1.** Numbers of patients attending in each year after RFT (n = 116)

The findings of the review were recorded with basic patient information and impairment status at start and RFT. EHF scores were calculated for status at start, RFT and the 5-year review.

#### Results

Sixty-eight (37%) of the 184 patients in the passive surveillance cohort could not be traced because of a change of address or death. One hundred and sixteen patients in this group were therefore assessed; 63 (54%) were multibacillary. Table 1 shows how often these patients had attended for review on a voluntary basis.

Of the 223 patients actively followed up, 108 (48%) were multibacillary. The difference in classification was not significant. There was no significant difference between the groups in their impairment status at the start of treatment or in the change in status before RFT, as illustrated in Table 2. This was expected, as both groups were treated in exactly the same way until RFT.

Table 3 shows the change in status, assessed by the change in EHF score, during the 5 years after RFT.

Odds ratio for deterioration when no active surveillance was carried out (adjusted for age, sex and classification, by multiple logistic regression analysis): 1.9 (95% CI: 1.2-3.3; P < 0.01).

#### Discussion

Under the passive surveillance system, 116 patients were supposed to attend their clinic every year for 5 years to be checked for VMT, ST and disability grading, but very few patients came for follow-up.

The number of attendances is more than 116, because some patients came more than once, while 66 (56.9%) did not attend during the 5-year period; they were seen at the end of the 5 years as part of this study. Thus while passive surveillance is reasonable in theory, in practice many patients did not attend voluntarily for follow-up examinations. In Ethiopia, the distances people have to travel to their nearest clinic may be large and this may partially explain the low voluntary attendance rate.

In this study, active surveillance, which is expensive, only slightly reduces further disability. We suggest that more effort should be put into educating and supporting patients before they are released from treatment, so that they understand that further damage may occur, how to recognize it and what steps to take if it occurs.

The main conclusion from this study is that the EHF score is a useful method of assessing any such intervention, whose main purpose is to prevent further impairment. It has previously been used to assess

	Deteriorated (%)	Same (%)	Better (%)
Passive surveillance $(n = 116)$	19 (16)	70 (60)	27 (23)
Active surveillance $(n = 223)$	26 (12)	143 (64)	54 (24)

Table 2. Change in status between diagnosis and RFT

Table 3. Change in status after 5 years surveillance

	Deteriorated (%)	Same (%)	Better (%)
Passive surveillance $(n = 116)$	43 (37)	59 (51)	14 (12)
Active surveillance $(n = 223)$	52 (23)	138 (62)	33 (15)

change between the start of treatment and RFT.<sup>1,3</sup> It is a simple indicator, which can be used to measure the level of impairment in groups of patients over time.

All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) PO Box 165 Addis Ababa Ethiopia (e.mail: psaunderson@leprosy.org) ALEMU GEBRE-YESUS PAUL SAUNDERSON

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# Obituary

#### DR SUSHILA NAYAR

Dr Sushila Nayar died on 3rd January 2001 at the age of 87 years. Dr Nayar was born in 1914 in the Gujarat district of Punjab. She graduated from Punjab University and completed her studies at Johns Hopkins University in the USA. She worked for some time as Registrar and Assistant Professor at Lady Hardings Medical College and was Chief Medical Officer at Faridabad. Later, she was Professor of Community Medicine in Mahatma Ghandi Institute of Medical Sciences at Sevagram, which was founded by her in 1969. Dr Nayar was also a member of several national institutions concerned with women's problems and the handicapped, and was the author of several books.

Following the founding of the Mahatma Ghandi Institute of Medical Sciences, Dr Nayar and her colleague, Dr R. V. Wardekar, treated many patients with leprosy. She became deeply involved in the problems of these patients, and remained so for the rest of her life. In 1946, Dr Nayar was instrumental in blocking a bill for compulsory sterilization of leprosy patients.

Dr Nayar and her colleagues established the Gandhi Memorial Leprosy Foundation in 1951, and the Foundation conducted trials of chemotherapy in leprosy in 10 endemic states in India. The National Leprosy Programme in India was based on the results of these early trials.

Dr Nayar's contribution to the field of leprosy was extensive, and she will be remembered for her initiative in bringing the care of leprosy patients from the close confinement of leper colonies into the wider community.

> (Condensed from a longer article written by Dr S. P. Tare, National Leprosy Organisation, India)

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# **Teaching Materials and Services**

# International course on Rehabilitation and Prevention of Impairment and Disability (RPOID) Management and Skills module

For many years now a much needed and very successful international course on Rehabilitation and Prevention of Impairments and Disabilities (RPOID) has been conducted in Pokhara, Nepal. The international faculty are very experienced in clinical leprosy and the rehabilitation of persons affected by leprosy.

#### RPOID MANAGEMENT COURSE

The next RPOID Management course will aim at teaching concepts in rehabilitation and POID, approaches to rehabilitation, rehabilitation and POID management, including monitoring and evaluation of activities in these areas. The course will be based on the concepts and terminology used in the International Classification of Functioning, Disability and Health (ICIDH-2) published by the WHO.

For a limited number of participants, an opportunity will be offered for additional in-service training during the week(s) following the management course. The participants will be assigned on a one-to-one basis to a tutor who will guide them through a self-learning programme.

Available topics include institutional rehabilitation, CBR, expanding the services of a leprosy hospital to serve people with other rehabilitation needs, agricultural rehabilitation, statistics and information systems, footwear, prosthesis and orthoses, physiotherapy and occupational therapy. These placements will be available strictly by arrangement prior to the course only.

Dates: February 4–17, 2002 (2 weeks) (+optional week(s) if pre-arranged) Target group: Managers of rehabilitation and/or POID programmes, senior hospital staff, senior leprosy control staff and doctors and therapists with managerial responsibilities for RPOID activities. Venue: The Green Pastures Training Centre in Pokhara, Nepal Course fees: \$175 per week (including board & lodging)

#### RPOID SKILLS COURSE

The RPOID Skills course aims at RPOID-related assessments, such as nerve function assessment, psychosocial assessment, ADL assessment, impairment assessment and socio-economic assessment, treatment and rehabilitation interventions. This course will therefore concentrate on skills acquisition. Through optional workshops the second course will offer the opportunity to study certain topics in more depth. The course will include a 1-week field trip to practice the learned skills in a real programme setting.

#### Dates: April 29 to May 24 2002 (4 weeks)

*Target group*: Physiotherapists, occupational therapists, physiotherapy technicians, social workers and field staff with responsibility for the assessment, treatment and/or rehabilitation of people needing RPOID interventions.

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*Teaching/learning methods*: Lectures, group discussion, group assignments, individual assignments, practical work in small groups, problem-based learning, self-study, presentations, and simulation exercises. The teaching medium is English. Because of the complicated nature of the subject, fluency in both spoken and written English is required. Experience in leprosy work will be an advantage, but is not essential.

Venue: The Green Pastures Training Centre in Pokhara, Nepal.

Course fees: \$175 per week (including board & lodging)

#### FURTHER INFORMATION

Detailed information can be obtained from: The Training Officer, GPTC, PO Box 28, Pokhara 33701 Nepal (Tel: +977-61-24562, Fax +977-61-20430, e-mail: gptc@inf.org.np))

#### **Ophthalmic Course, Karigiri, India. February 2001**

The 16th annual 5-day ophthalmic teaching module was held at the Schieffelin Leprosy Research and Training Centre, Karigiri from the 5th to 10th of March 2001. The course, which received sponsorship from Lepra and The Leprosy Mission, was designed to give instruction to medical officers on the detection, prevention and management of the ocular complications of leprosy by means of a series of lectures and clinical and surgical demonstrations, augmented by videos and a field trip. Teaching included formal didactic presentations on the basic anatomy, physiology and pathology of the eye with a special emphasis on leprosy: in addition there were lectures on the pathogenesis and treatment of corneal ulcers, lagophthalmos, ocular inflammation, rehabilitation, epidemiology and the global aspects of blindness in the disease.

Preference was given to problem-based clinical instruction concentrating on the identification of sight-threatening complications of the disease, their prevention and management.

The course was attended by 15 participants working in India, and was organised by Dr Sheena Koshy of Karigiri, with the assistance of members of the Staff of the Centre. Mr Timothy ffytche from Moorfields and the Hospital for Tropical Diseases, London and Dr. Kirsteen Thompson from Glasgow were invited as a members of the Faculty.

The Director of Karigiri, Dr P. S. S. Sundar Rao, is to be thanked for his continued support for this important and popular contribution to teaching.

#### London School of Hygiene & Tropical Medicine

The London School of Hygiene & Tropical Medicine was founded by Sir Patrick Manson in 1899. An institute of state medicine, to be called the School of Hygiene, was recommended in 1921, and a united School was established in 1924. The new London School of Hygiene & Tropical Medicine was opened in its present building in Keppel Street, a gift from the Rockefeller Foundation, in 1929. At that time, the term 'hygiene' was not restricted to its current meaning of 'cleanliness' or 'sanitary science', but was used in the wider sense of the establishment and maintenance of health—now more usually described as 'public health'.

The London School of Hygiene & Tropical Medicine is the University's major resource for postgraduate teaching and research in public health and tropical medicine, as well as the leading postgraduate medical institution in these subjects in Europe. It has international standing with a staff that has unique multidisciplinary and international experience. The School trains future senior academics, researchers, policy-makers and practitioners in the international medical and public health community worldwide.

The mission of the School is to contribute to the improvement of health worldwide through the pursuit of excellence in research, postgraduate teaching, advanced training and consultancy in international public health and tropical medicine. As Britain's national school of public health, the

School's mission is to make a major contribution to the improvement of the health of the British public. As a major academic centre for public health in Europe, the School's mission is to play a leadership role in regard to public health research and teaching throughout Europe. As the premier institution worldwide in the field of tropical medicine and public health, the School's mission is to continue to advance and promote these subjects and maintain its position as an international centre of excellence.

The diversity of LSHTM's students is exceptional. The 750 Internal students come from 95 countries, and staff come from 35 nations. School alumni are now working in more than 140 countries; many former students hold prominent positions in health ministries, universities and international organisations throughout the world.

For further information about the London School of Hygiene & Tropical Medicine please refer to the following website: http://www.lshtm.ac.uk/prospectus

#### Tropical Medicine Research Awards for scientists from developing countries; The Wellcome Trust, London, UK

The Wellcome Trust has a long-standing interest in tropical medicine research and offers a number of awards to encourage the development of sustainable research expertise to address diseases of particular significance in tropical and developing countries. Studies of infectious or noncommunicable diseases are equally acceptable.

#### Research Training Fellowship for Scientists from Tropical and Developing Countries

These awards are intended to provide training and research experience for applicants from tropical and developing countries. The training can take place at international centres of excellence in any country of the developing world, in the UK or the Republic of Ireland, but a substantial period of research should be undertaken in the applicant's home country.

#### Eligibility

Applications are invited from postdoctoral basic scientists, medical, dental or veterinary graduates of up to 6 years' post-qualification research experience who are nationals of developing countries. Applications may be considered in exceptional circumstances from those who are educated to first degree or Master's level, who are able to demonstrate substantive potential for research and operational leadership and who have research experience equivalent to a PhD, as evidenced by their publication record. Applicants will wish to become independent research scientists through high quality research into diseases of regional significance to their home country.

#### Funding

Awards will be for a maximum of 4 years, nonrenewable, and will include a stipend/salary appropriate to the countries in which the candidates will be studying/working as well as project dedicated costs and travel expenses. Consideration may also be given to the expense of attending a course leading to a recognized qualification in a discipline relevant to the fellowship research programme.

#### Research Development Awards in Tropical Medicine

These awards are to enable clinical (medical, veterinary or dental) and non-clinical researchers from developing countries to return to their home institution and establish a programme of research with continued collaboration and support of a UK sponsor.

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#### Eligibility

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.

#### Funding

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 and funds for exchange visits.

Applicants for each of these awards are accepted throughout the year. Further information on the awards, including details of the application procedure can be obtained from the Wellcome Trust website: www.wellcome.ac.uk/international or from:

The Tropical Medicine Programe The Wellcome Trust 183 Euston Road London NW1 2BE, UK Tel +44 (0)20 7611 8409 Fax +44(0)20 7611 7288 E-mail: tropical@wellcome.ac.uk

NB: Applicants may not apply for more than one Trust fellowship scheme at any one time.

#### A new Atlas of Leprosy

The *Atlas of Leprosy* was first published in English in 1981 and revised in 1983. In response to widespread and continuing demand, it was reprinted on 10 occasions between 1984 and 1997, with distribution to virtually all leprosy-endemic countries worldwide. Chinese, Spanish, French and Arabic translations were published in 1986; Portuguese and Indonesian in 1990. In total 38,000 copies of the English edition have been printed and an additional 23,000 copies in the translations.

The original aim was to provide high quality colour pictures as an aid to recognition and diagnosis. This new *Atlas of Leprosy* maintains this objective, whilst incorporating some changes in contents and format. The original Atlas contained a section on histopathology of leprosy, which has been removed. Almost all the photographs, originally from the Philippines, have been replaced with patients from India and South East Asia, since about 75% of the remaining world problem of leprosy is found in those areas.

In the face of diminishing prevalence in most parts of the world, opportunities to see leprosy patients and acquire clinical skills, including observation, will diminish. With the inevitable change from specialized leprosy programmes to integration with general health services, it will become more important to supply peripheral health care workers with appropriate information, including written and illustrated material on the diagnosis and treatment of leprosy.

It is hoped that this new *Atlas of Leprosy* will contribute not only to the Strategic Plan, 2000–2005 for the Final Push towards the Elimination of Leprosy, recently published by the World Health Organisation (CDS/CPE/CEE/2000.1), but also to our continued efforts, for many years beyond the year 2005, until we reach A World Without Leprosy.

#### Scholarship Guidelines for the Dick Rees' Memorial Fund

In honour of the late Dick Rees, Lepra has decided to set up a training fund for those working in the field of leprosy. This fund will incorporate monies donated in his memory. Dick Rees was a leading researcher in the field of leprosy over a period of 25 years. He began his medical research career working on TB at the National Institute for Medical Research at Mill Hill, London but gradually switched to research into leprosy. One of his major contributions to the effective treatment and cure of leprosy was his demonstration of primary and secondary drug resistance to existing drug treatments. This lead to the development of multi-drug therapy by WHO in the early 1980s. He was made chairperson of Lepra's (The British Leprosy Relief Association) Medical Advisory Board in 1963 and was appointed Head of the Medical Research Council's Laboratory for Leprosy Research in 1969. Here he developed a source of live *M. leprae* bacteria by setting up a colony of infected armadillo. It is from this source that the latest research on the genome sequencing of the leprosy bacillus has been derived. Last October Dick Rees died at the age of 81. His scientific abilities and commitment to the cause of leprosy will be missed by all in the field of leprosy, particularly those working at Lepra and WHO. Even after his retirement in 1982 he continued to work for both organisations, influencing and inspiring many to bring about a world without leprosy.

#### CIRCULATION OF GUIDELINES

This set of guidelines will be made available to all ILEP members and Leprosy Training Institutions. It will be advertised in *Leprosy Review, International Journal of Leprosy, Indian Journal of Leprosy, CBR* Journals and on the Internet. The target group for the scholarship are leprosy workers in the field who have had limited training opportunities.

#### APPLICATION PROCESS

#### Amount available

 $\pounds 20,000$  will be available each year. This may be split between a number of candidates. Selection will be based on the merit of the applications; making the best use of this limited amount of funding. Each award will be sufficient to cover the costs of the training selected, the travel and living costs for the duration of the training and where justified, additional costs to facilitate access.

#### Scholarship criteria

- Candidates should preferably be working in countries where leprosy is endemic.
- The training selected should enhance their ability to contribute to the field of leprosy.
- Candidates should have a commitment from their employer that they will release them for the duration of the training and keep their job open for them on their return.
- Candidates agree to any bond arrangements stipulated by their employer.
- The training selected normally should be no longer than 6 months.
- The training selected normally should be at the closest venue that offers the level of training, qualification and recognition sought by the candidate.
- The selected candidates will produce a report at the end of the training to indicate its value in relation to their expectations as outlined in their application.

#### Equal opportunities

Consideration will be given to those who have justified additional costs which would facilitate their participation in their preferred training (for example child care costs).

#### APPLICATION DETAILS

Applications should include:

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- 1. CV of candidate
- 2. Details of the training or course selected:
  - Description of training, or course name.
  - Objectives, i.e. knowledge and practical skills to be gained by end of training, or course content.
  - Venue.
  - Pre-requisite training or qualifications.
  - Cost of training.
  - Estimated cost of travel/accommodation and living expenses and where necessary, justified additional costs to facilitate access.
  - Duration.
- 3. Covering letter from candidate indicating: their career goals and how the training selected will enhance their ability to contribute to the field of leprosy and thirdly, why they should be considered for the award.
- 4. A letter of recommendation from their current employer, indicating their willingness to release the candidate if they are selected for the award and agree to keep the job open for the candidate and stipulate any bond arrangements they would like to make.
- 5. A reference from another employer or tutor.
- 6. A letter of invitation or acceptance from the host of the training or course.

Prospective candidates for the award should apply in writing to: Doug Soutar, Lepra, Fairfax House, Causton Road, Colchester CO1 1PU, UK (Fax: +44 1206 762151; e-mail: Doug\_Soutar@lepra.org.uk)

#### TIMING

Applications with all the above attachments can be sent to Lepra at any time throughout the year. All applications will be assessed at the end of February each year. Successful candidates will be notified within 3 weeks of their selection for the award.

#### Technical Guide: Sputum Examination for Tuberculosis by Direct Microscopy in Low Income Countries. Fifth edition 2000

Copies of this Guide, now in its Fifth Edition, are now available, free of charge in reasonable numbers, from the International Union Against Tuberculosis and Lung Diseases, 68 boulevard Saint Michel, 75006, Paris, France. The Preface, by Dr Adalbert Laszlo, Ottawa, Canada, reads as follows:

A technical guide for sputum smear microscopy, based on one initiated in 1969 by Dr J. Holm, the then Director of the International Union against Tuberculosis, was first published in 1978 by the IUAT as the *Technical Guide for Sputum Examination for Tuberculosis by Direct Microscopy*. The guide was included in the third and fourth editions of the IUATLD's *Tuberculosis Guide for Low Income Countries*. It was designed to be a simple reference standard for the collection, storage and transport of sputum specimens and for the examination of sputum smears by direct microscopy. It was meant to address the needs of health care workers in low income, high prevalence countries which represent the bulk of the global tuberculosis caseload.

More than 20 years have elapsed since its first publication, and the guide has remained unchanged throughout that time. Today, tuberculosis is one of the main causes of death from a single infectious agent among adults in low income countries, where it remains a major public health problem. The basic tool for TB diagnostic services, i.e. sputum smear microscopy, has not changed in its technical details in spite of major advances in modern diagnostic technologies. However, the context in which it is applied, the National Tuberculosis Programme, has been refined to a considerable extent in the last 2 decades.

The field use of the guide over the years has revealed omissions and inaccuracies that needed to be addressed. Furthermore, biosafety and quality assurance aspects of sputum smear microscopy were not

sufficiently well covered in the previous edition. It was therefore felt that the IUATLD Technical Guide needed revision so it could better reflect its public health essence and keep up to date with modern TB control strategies. This document was carefully revised by members of the *Bacteriology and Immunology Section* of the IUATLD, by directors of the *WHO/IUATLD Supranational TB Reference Laboratory Network* and by other distinguished professionals in the field of tuberculosis control.

#### WHO. The 'Blue Trunk' Library Project

At a recent meeting of the *Health Information Forum* (HIF) of INASP-Health hosted by the *British Medical Association* in London, Irene Bertrand of the *WHO Library and Information Networks for Knowledge* organised an exhibition of the Blue Trunk Libraries, a 'WHO project for health districts'. A summary of the present situation and progress reads:

The Blue Trunk Library project was developed by the WHO Library to provide basic health and medical information to district health teams in developing countries. Each 'ready-to-use' mini-library consists of 100 books on medicine and public health together with three journal subscriptions and is contained in blue metal trunks to ensure easy transportation and protection. This project is funded at country level, by international organizations, aid agencies and NGOs.

Approximately 833 Blue Trunk Libraries have already been ordered and dispatched to 34 countries in the world and 300 BTL 'keepers' in health district centres have been trained.

One year after the project was launched, an evaluation showed that the Blue Trunk Library did respond to a basic need by district health personnel and that they had a positive impact on the delivery of health services.

Price: US\$ 2000

**Contact:** Edith Certain, Library and Information Networks for Knowledge, World Health Organization, 1211 Geneva 27, Switzerland. Tel: +41 22 791 20 61. Fax: +41 22 791 41 50. Email: certaine@who.int

The cost is obviously considerable and the idea would not work without careful attention to preliminary training on the use of these books and journals and the identification of a reliable 'keeper'. Nevertheless, there is already evidence that the Blue Trunk concept, originally developed as 'bibliothèques bleues' for French-speaking countries in Africa, is 'delivering the goods', at least to district level, better than anything previously attempted. A 'Red Malaria Trunk' is under development in Southern Africa.

#### **Biology of Disease Vectors Course**

The following article appears in the February 2001 issue of TDR News:

Since its inception in 1991, the training course on the Biology of Disease Vectors (BDV) has been supported annually by TDR in partnership with, and under the leadership of, the MacArthur Network on the Biology of Parasite Vectors. The Howard Hughes Medical Institute has also become a co-sponsor.

The BDV course trains highest quality students in molecular, genetic and quantitative approaches to the study of disease-transmitting insects. The course's main objectives are to 1) train a new generation of vector biologists and provide current medical entomologists with a foundation of modern molecular techniques; 2) recruit molecular biologists from other research areas into the field of vector biology; 3) establish a global network of scientists to facilitate collaborative investigations and to enhance progress in the field.

Initially, the course was taught at the Colorado State University in the USA. More recently, it has been hosted in a variety of international venues (Greece, Mali, Brazil and the Czech Republic) to provide easier access for students from regions where vector-borne diseases are endemic.

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The course is advertised internationally and attracts hundreds of applicants each year, of which approximately 35 outstanding students are selected. The students come from around the globe, including a significant number from countries where vector-transmitted diseases are a major problem. Students are typically advanced Ph.D. students, postdoctoral fellows, and established investigators aiming to increase their skills in vector biology or redirecting their careers from other areas. Some 40% of participants are women. As a rule, 20 world-renowned scientists from leading institutions are chosen to give the lectures and supervise the laboratory work.

The BDV course has been an extraordinary success. Small class size and global expert teachers provide an unparalleled learning and networking experience. International collaborations are established and continue to grow. Course evaluations have been overwhelmingly positive. Recommendation from former students and faculty is the primary driving force for new applications. Graduates from the early courses are already emerging as leaders in the field of vector borne diseases, and a number of them have been chosen to teach in more resent courses. The BDV course is helping to train a new generation of vector biologists, who are already playing leading roles in improving the health of millions of people.

#### Tuberculosis: Manual for Medical Students (Tuberculose: Manuel pour les Etudiants en Médecine). WHO and the International Union Against Tuberculosis and Lung Disease

Those who have long advocated the production and use of a manual or textbook on tuberculosis of medical students may be surprised to learn that an excellent one exists—though in French only. It is a paperback of 149 pages, written by Nadia Ait-Khaled and Donald Enarson, published by the World Health Organisation and the International Union Against Tuberculosis and Lung Disease (IUATLD): WHO/CDS/TB/99.272. Although written mainly for medical students, the Preface indicates that it is also suitable for medical practitioners. The Acknowledgements list colleagues who have contributed to the text and content, nearly all of whom come from French-speaking Africa—Côte d'Ivoire, Guinea, Algeria, Bénin, Sénégal, and Morocco. The three main divisions of this valuable publication are entitled—Basics/fundamentals, Individual approach to tuberculosis and community approach to tuberculosis.

We have no information on the extent to which this has been distributed to French-speaking medical schools, including both teachers and students, or on any plans which may exist to translate into English or other languages. Current information on the active involvement of medical schools in improved teaching of their students seems to indicate that there is much room for improvement, despite the encouragement given, for example, in 'Tuberculosis Control and Medical Schools' (WHO/TB/98.236. English) and other publications from WHO and IUATLD.

#### **INASP-Health, Oxford, UK**

INASP-Health is a UK-based organization working to improve access to reliable information for healthcare workers in developing and transitional countries.

The programme was launched in April 1996 in response to multisectoral demands to strengthen the effectiveness of health information activities worldwide. It focuses specifically on providing a range of services to promote cross-sectoral cooperation, analysis, and advocacy among those working to improve health information access. INASP-Health promotes 'access to reliable information for healthcare workers' as a key development issue, as potentially the most cost-effective approach to sustainable improvement in healthcare in developing countries.

The INASP-Health programme provides an advisory and referral service for health information activities and publishes the INASP-Health Directory—a reference and networking tool for

organizations, North and South, working to increase the availability of appropriate, reliable, low-cost information in developing countries and countries in transition.

The Health Information Forum (HIF) was launched as an activity of the INASP-Health programme in March 1998 in response to requests for a neutral focal point in the UK for dialogue and exchange of experience and ideas among organizations involved in improving access to reliable information for healthcare workers. HIF is the only activity of its kind worldwide and has rapidly gained international recognition. The workshops have been highly popular, drawing increasing numbers of participants with successive meetings. They have engaged support and participation from the British Medical Association, Royal College of Physicians, and the World Health Organization, among others; and have attracted distinguished guest speakers from international agencies and developing countries.

The HIF-net at WHO is an email discussion for people worldwide who want to improve access to reliable information for health care workers which, currently (early 2001) is proving to be extremely successful. Further information: majordomo@who.int. Further information on the INASP-Health Programme generally: Dr Neil Paenham-Walsh, 27 Park End Street, Oxford OX1 1HU, England. Email: INASP\_Health@compuserve.com

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# News and Notes

#### African Medical and Research Foundation (AMREF)

The African Medical and Research Foundation (AMREF) is Africa's largest indigenous health charity. Based in Nairobi, Kenya, AMREF employs 500 people, 97% of them African. It supports communities in their own efforts to improve their health and well being. It also runs comprehensive training courses for health professionals at all levels and a unique laboratory support programme. AMREF is also the parent organisation of the Flying Doctors' Service.

AMREF UK is one of 11 international offices in Europe and North America that raise funds to support the charity's work in Africa. AMREF's total annual budget is over  $\pounds 10.5$  million, to which AMREF UK contributes over  $\pounds 1$  million.

AMREF News is published by the UK office of the African Medical and Research Foundation. AMREF 4 Grosvenor Place, London SW1X 7HJ Telephone: +44 (0)20 7201 6070 Fax: +44 (0)20 7201 6170

E-mail: amref.uk@amref.org

web sites: www.amref.org and www.passporteastafrica.com

#### BBC World Service Trust: leprosy media campaign in India

From *Connect*, the Newsletter of the International Federation of Anti-Leprosy Associations (ILEP), No 1, Autumn 2000:

The BBC World Service Trust is nearing the end of its 12-month leprosy media campaign in India. The India project is phase two of their 5-country media campaign for leprosy. The Nepal phase was completed in 1999. The campaign aims to transform health programming into dynamic entertaining media that engages audiences in matters of crucial importance to them. The project also aims to make sustainable changes to programme design, build technical capacity and skills, and generate momentum around health issues. Working in partnership with local media companies Doordarshan TV and All India Radio, the BBC project has used the cultural sensitivity skills, and imagination of local programme makers. Project output included:

- 27 TV spots and 146 radio spots in 20 languages
- 13 TV dramas
- 53 radio dramas
- Total of 808 TV and 5545 radio broadcasts
- For media dark areas—2175 song and drama performances, 5455 video van screenings and 150 000 posters

Following an independent survey of audience responses commissioned by the BBC, results have been encouraging. Two important successes of the campaign have been highlighted. 176 000 patients have come forward for treatment, and there has been a real impact on attitudes to leprosy. Radio and TV spots

were seen by 48% of the total population in the five targeted states (Bihar, Madhya Pradesh, Orissa, Uttar Pradesh, West Bengal), representing 224 million people. Of these, 79% correctly recalled one or more messages.

As the Indian phase of the campaign comes to an end, an independent evaluation survey will now take place, while the Brazil, Ethiopia and Indonesia campaigns are being prepared. If you would like more information on this campaign or the preparation of future campaigns in this project, please contact the BBC Health Projects Director, Mr. Roy Head at roy.head@bbc.co.uk

#### New publication and leprosy organization from India

We were delighted to receive Vol 1 No 1, January 2001 of the *Bulletin of the Leprosy Elimination Alliance* (LEA) which includes the following information:

Welcome to the *Bulletin of the Leprosy Elimination Alliance!* It will be out every 3 months, and will be available free of charge to everyone who wishes to fight and eliminate leprosy. Through this bulletin, the LEA hopes to communicate with a large number of leprosy workers, and help them—and learn from them—in fighting the disease, especially in India.

The Bulletin will carry news, reportage, analysis and in-depth reviews of various facets of leprosy and the war against it. We promise facts and figures and revealing charts and maps. We will also go beyond the cold statistics to carry warm personality accounts of and interviews with men and women who are at the forefront of the eliminate-leprosy campaign. We will talk about current trends and developments, and update old information. We will discuss specific issues. We will focus in-depth on what's going on at particular locations—in India and abroad.

We appeal to leprosy workers to use the Bulletin as their forum for highlighting operational and technical problems in the war against leprosy. Tell us about your experiences, your views, give us your ideas and insights.

Our approach at all times will be positive and constructive. We will not shun controversy.

But in presenting and analysing controversial issues, we will make clear the distinction between fact and opinion. You will have your own opinions—please feel free to air them in our 'Readers write' column.

We reserve the right to abridge and edit any article before publication. The Editor's decision in this respect will be final. Please address all correspondence to Editor, Bulletin of the Leprosy Elimination Alliance at:

1-A, K. V. Valencia, 57, First Main Road, Gandhinagar, Chennai-600 020, India. Phone: (044) 4456337 Fax: (044) 4456338 E-mail: noordeen@eth.net

A word about the Leprosy Ellimination Alliance (LEA). It was launched in Chennai in August 2000, with Dr S K Noordseen, formerly Director of the Action Programme for Elimination of Leprosy at the World Health Organization headquarters in Geneva as its Chairman.

The main objectives of the organization are (a) to promote the cause of leprosy elimination (b) to promote exchange of information and ideas on leprosy elimination among leprosy workers and others (c) to monitor progress towards leprosy elimination and assist towards development of better strategies and methods to achieve the goal in collaboration with other interested parties and (d) to produce and distribute among leprosy workers and others interested, publications on leprosy elimination.

The *Bulletin of the Leprosy Elimination Alliance* plays an important awareness and networking role in the drive to eliminate leprosy.

#### Veterinary Laboratories Agency, UK: research on M. bovis

The following is taken from the Annual Review 1999/00: Working for Animal Health of the Veterinary Laboratories Agency, New Haw, Addlestone, Surrey KT15 3NB, United Kingdom, www.maff.gov.uk/ vla:

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#### BOVINE TUBERCULOSIS

#### Sequencing the Mycobacterium bovis genome

A collaborative project between VLA, the Sanger Centre and Institut Pasteur, jointly funded by MAFF\* and the Wellcome Trust, was initiated to sequence the *M. bovis* genome. The project represents a highly cost-effective approach to supporting the MAFF initiative on *M. bovis* vaccine development. Sequencing has started and a database of assembled sequences greater than 1 kb is already available at the Sanger Centre, Cambridge.

#### Tuberculosis vaccine research

A major programme of *M. bovis* vaccine development is currently under way. The objectives are to produce a vaccine that protects against infection and a diagnostic test that differentiates between vaccinated and infected animals. The VLA is a member of the animal models task force for the World Health Organisation global programme for TB vaccination, whose aim is to improve co-ordination with human TB vaccine research.

Potential live vaccine candidates are now being screened using an aerosol challenge model. In collaborative work with the Centre for Applied Microbiology and Research (CAMR), two auxotrophic mutant candidates of BCG were shown to confer similar protection against *M. bovis* as BCG without compromising the ability of current tests to diagnose true infection. These are promising results and further work in this area is in progress.

Work on subunit vaccine development centred on DNA vaccination using immuno-dominant M. bovis genes is on-going. Also collaborative work with the National Institute of Medical Research (NIMR) demonstrated the possibility of a therapeutic vaccine against a pre-existing M. bovis infection. In cattle, the immunizing effects of DNA vaccination were improved when the vaccine was administered intramuscularly rather than intradermally. Several DNA vaccination schedules have now been developed, none of which compromises the diagnostic tuberculin skin test.

In collaboration with AgResearch of New Zealand, an intratracheal M. bovis challenge model for cattle has been validated. This will be used in immunological diagnostic test development and in vaccine evaluation.

#### Molecular typing of M. bovis

Spoligotyping of M. bovis isolates is now a routine test activity for MAFF. Additional discrimination between types is desirable and a second PCR-based technique known as variable numbers of tandem repeats (VNTR) under development at the VLA promises to provide this.

#### Diagnostic assays for bovine tuberculosis

VLA has developed an *M. bovine* antigen-specific lymphocyte proliferation assay for wildlife. This is now being used in collaborative work in the Republic of Ireland where a study of immune responses in wildlife inoculated with BCG is in progress.

Steps are also being taken to produce a wildlife gamma interferon assay. This will be an ELISAbased test similar to that available for cattle. In cattle, studies have concentrated on developing tests to differentiate vaccinated and infected animals. Experiments using mixtures of various M. *bovis* components have indicated the potential for specially designed peptide cocktails to allow the required discrimination.

<sup>\*</sup> Ministry of Agriculture, Fisheries & Food, UK.

#### Epidemiological research

The Epidemiology Department, in collaboration with several universities, is currently performing two inter-related MAFF-funded studies, both utilising geographic information systems. The first is examining the locations of past tuberculosis incidents and assessing the possible role of environmental risk factors, such as climate, trace elements and wildlife. The second is a molecular epidemiological analysis examining the spatial distribution of *M. bovis* sub-types.

Two case-control studies, funded by the Milk Development Council and MAFF respectively, are also in progress examining a range of possible variables, particularly husbandry factors, which might contribute to the risk of a herd developing tuberculosis.

#### Surveillance activities

VLA provides a range of surveillance services to MAFF, including the supply of tuberculin. Over 5 million doses of tuberculin have been supplied to Animal Health Offices throughout the country. VLA also provides a post mortem examination service and in the process of isolating *M. bovis*, has cultured and typed over 5000 cattle samples.

#### PubMed Central: creating an Aladdin's cave of ideas

#### From the British Medical Journal, 322, 6 January 2001:

Starting this week, research articles from the *BMJ* will be freely available from PubMed Central, the new web based repository that will archive, organise, and distribute peer reviewed reports from biomedical journals (http://pubmedcentral.nih.gov). This will be in addition to their continuing free availability on bmj.com. The *BMJ* articles join those from 15 other journals. More are expected to follow suit.

PubMed Central's distinguishing characteristic is that it offers the full text of articles, free to users. Think of it as the logical extension of Medicine, which offers the bibliographic details of articles and their abstracts. It depends on publishers and societies transferring peer reviewed articles to PubMed Central, which, like Medline, is funded by the US National Institutes of Health.

#### A phenomenal advance

The *BMJ* has joined PubMed Central because we agree with Nick Cozzarelli, editor of the *Proceedings* of the National Academy of Sciences of the United States of America (also on PubMed Central), that 'free access to the scientific literature would be a phenomenal advance in scientific publishing—the greatest in our lifetime.'<sup>1</sup> We want to align ourselves with an initiative which if successful, will benefit science and so clinical medicine and patient care. From the *BMJ*'s point of view, we think that better papers might be submitted to us if we offer authors a route to publication both on paper and on PubMed Central. And we think that many people might see our original articles on PubMed Central and then jump to bmj.com to download PDF versions and for accompanying editorials, commentaries, and rapid responses—thereby increasing traffic to our site.

Whether the initiative will succeed is unclear; certainly most scientific publishers are hoping it will fail. But PubMed Central is the first initiative really to take account of how fundamentally the world wide web has changed the landscape of scientific publishing. On the face of it traditional scientific publishers have moved with the times, migrating their paper journals on to the web in their thousands. But most of these are no more than electronic facsimiles of the paper product. Some journals, such as the *BMJ*, have begun to exploit the properties of the web.<sup>2</sup> But access controls and the high costs of electronic subscriptions have reproduced the same fragmentation of information that was the despair of the paper world.

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What the architects of PubMed Central realised was that the quality control and distribution functions of journals could be uncoupled on the web in a way unthinkable in paper. They recognised that the costs of peer review were relatively low—as most peer reviewers do it for nothing—and that the costs of electronic distribution were trivial compared with those of paper, printing, binding, and postage of the paper journal. If, say, US taxpayers would pick up the distribution costs (as they have done the costs of Medline) then publishers could dispense with this function entirely. Free information would mean that libraries could stop subscribing, thereby releasing money back to researchers.

Some of that money had previously ended up in publishers' profits, so unsurprisingly, publishers were loudest in their condemnation of PubMed Central. But when economic forces and the interests of the scientific community converge, publisher opposition may not succeed.

#### Sugar coatings; glycoproteins in immunity and protein folding

The *Wellcome Trust Review 2000* of research projects and major initiatives, volume 9, describes a wide range of exciting activities, supported by the Trust, in pursuance of its mission to '.. foster and promote research' with the aim of improving human and animal health.' From an impressive list, one example has the above heading and a summary which reads:

'Many proteins have sugar molecules, essential to their form and function, attached to parts of their polypeptide chains. Such glycoproteins are particularly common on the surfaces of pathogens, so our immune system has sugar-binding proteins that initiate the destruction of invaders—a defence arm being investigated by Professor Kurt Drickamer and colleagues at the University of Oxford. Meanwhile, a collaboration between researchers in Bucharest, led by Dr Stefana Petrescu, and Oxford, led by Professor Raymond Dwek, is exploring the role of sugars in the folding of the enzyme tyrosinase, key to the production of the pigment melanin in human cells.'

The first paragraph continues:

"The recognition of sugars on the surfaces of microorganisms is one way in which the body distinguishes potential pathogens from its own cells. The sugar-binding proteins (animal lectins) that mediate this recognition are part of the first line of defence against infection, preceding the antibodymediated (adaptive) immune response. If the lectin system fails at a critical time, such as during early childhood or in AIDS patients, the body's susceptibility to infections increases. At the Glycobiology Institute, University of Oxford, the animal lectins group—Professor Kurt Drickamer, Dr Maureen Taylor and Dr Russell Wallis—are working to understand how lectins neutralize pathogens, and how naturally occurring human mutations in the lectin genes affect the body's defences."

Further information: The Wellcome Trust, 183 Euston Road, London NW1 2BE email: marketing@wellcome.ac.uk

#### **Dora M. Scarlett MBE**

Dora Scarlett, founder of Seva Nilayam, died on Wednesday March 28th after a short illness.

She attended hospital in Madurai 2 weeks before, after which she decided to return home to Seva Nilayam. She was 95.

Everything that Village Service Trust does as an organization originated with Dora. As many of you will know, Dora went to India in 1959 and founded Seva Nilayam in 1962, barely leaving India for the rest of her life. At first it was extremely simple: some everyday medicines handed out at the door of a mud hut. But over the years it developed; volunteer nurses came, funding was secured from agencies and individuals around the world, sister organisations Arogya Agam and Vasandham were launched, and the work grew from the original clinic to embrace tuberculosis and community health campaigns

and women's development and Aids. Work which has been replicated throughout Theni District, south India and beyond. None of this would have happened without Dora's forceful personality, tenacity and inspiration. All of us who worked with, met or corresponded with Dora will have special memories of her, and the way she touched our lives.

Dora was buried on Friday at Seva Nilayam. Hundreds of people attended her funeral that took place in the beautiful garden she had created and loved so much.

#### WHO: two new publications on the elimination of leprosy as a public health problem

#### 1. Guide to eliminate leprosy as a public health problem. First edition 2000.

This a booklet of 39 pages, A5 format, with emphasis on the 'final push' to eliminate leprosy as a public health problem. The sub-heading to the title page reads: 'Multidrug therapy cures leprosy, stops transmission and prevents disabilities. Available free of charge at all health centres.' From the Contents list, the main headings are—the final push to eliminate leprosy; what is leprosy?; how to diagnose leprosy; treating leprosy; management and complications and how you can eliminate leprosy from your community. There are numerous, high quality illustrations of the most important aspects of the control strategy and excellent illustrations on pages 20 and 21 of the four blister calendar packs for multidrug therapy—PB adult treatment (green), MB adult treatment (red), PB child treatment (blue) and MB child treatment (yellow). The booklet has been developed in collaboration with the Global Alliance for the Elimination of Leprosy: Member States of the World Health Organisation, Danish International Assistance (DANIDA), International Federation of Anti-Leprosy Associations (ILEP), Nippon Foundation, Novartis Foundation for Sustainable Development and the World Health Organisation. WHO/CDS/CPE.CEE/2000.14

#### 2. Eliminate leprosy from the world

This is a document of 32 page, A3 format, dealing with 'Communication, concepts and support material' in the form of a 'communication tool box', aiming to change the image of leprosy, with emphasis on elimination through case detection and the treatment of all cases with multidrug therapy. The opening page refers to the elimination of leprosy from Africa and some of the pictures are clearly African, with overall art direction from Madagascar, but the illustrations, concepts and support material have potentially valuable application almost worldwide. The subject matter covers posters, displays, patient information, booklets for community health workers and decision makers. Production: World Health Organisation and Novartis Foundation for Sustainable Development.

#### Biopsy of Skin Lesions in Leprosy by Kiyoshi Harada, Tokyo, Japan, 2001

This booklet of 74 pages is the second edition of the author's contribution on the above subject, with emphasis on stains, pathogenesis and classification. Apart from tables and diagrams, it includes 32 colour plates of high quality illustrating the histopathology of leprosy lesions, stained with conventional haematoxylin and eosin and the Fite-Faraco technique for bacilli, together with the author's own periodic acid-carbol pararosanilin or -silver stain. The most important parts of the Summary (page 71) read as follows:

For pathological studies of leprosy, Haematoxylin & Eosin and Carbol fuchsin 'acid fast' stain are commonly used.

However, mycobacteria are divided into acid-fast and chromophobic by their staining affinities.

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The chromophobic bacilli are characterized by a complete loss of their carbon fuchs stain and their carbol fuchs in 'acid-fastnesss' can be stored by prior periodic acid oxidation.

Harada has introduced the modification of Nyka's periodic acid-carbol fuchsin or Lillie's PAS allochrome stain, and of Gomori-Grocott's chromic acid-methenamine silver—periodic acid pararosanilin allochrome and periodic acid-methenamine silver—for demonstrating two types of mycobacteria.

The principle of the methods is that the first step is the oxidation of mycobacterial glycolipid to aldehydes  $-CHOH-CHNH_2 \rightarrow -CHO$  and the second step is the demonstration of aldehydes with carbon pararosanilin or methenamine silver R-CHO+2ArNH<sub>2</sub> $\rightarrow$ R-CH(NHAr)<sub>2</sub> or R-CHO+2[Ag(NH<sub>3</sub>)<sub>2</sub>]+H<sub>2</sub>O $\rightarrow$ -COOH+2Ag+4NH<sub>3</sub>+2H.

In this paper, periodic acid-carbon pararosanilin or -silver is used for demonstrating both types of bacilli and their host-parasite relationships.

Mycobacteriosis are characterized by tubercle formation or Yersin type of disease.

In most people, the leprosy bacilli fail to established themselves in the tissue; the disease, therefore, rends to be self-healing and self-limiting. Few people develops the disease 'leprosy'.

Leprosy is the atypical Yersin (lepromatous) type of mycobacteriosis. Histoid may be a true Yersin type of disease. It is confused by the presence of epithelioid cell granuloma in the nerves in the tuberculoid and borderline leprosy.

Moreover, leprosy is essentially a disease of peripheral nerves. In very early infection, Schwann cells of cutaneous nerves is a first identifiable target organ of mycobacterium leprae.

Also, leprosy is an immuno-defect disease for mycobacterium leprae. Even in tuberculoid leprosy there is an immunodeficiency.

As a result, in all types of leprosy, even in tuberculoid, lymphocytes could not be cooperated with infected macrophages. Macrophages, therefore, could not be activated, not capable to kill the organism and not ability to alteration into epithelioid cells. However, in the tuberculoid and borderline, lymphocytes could be cooperated only with infected Schwann cells of a nerve. Schwann cells could be activated, capable to kill the organism and transform to epithelioid cells and perhaps Langhans cells in tuberculoid and in less extent in borderline. Therefore, cell mediated immunity is of special importance in dealing with the infection and evolution of leprosy caused by mycobacterium leprae.

Hence, the pathological features of leprosy reflect the infection and response of the disease.

Interpretation of the evidence concerning pathological sign is as follows:

1. Schwann cells of a cutaneous nerve is a first demonstrable target organ of mycobacterium leprae.

- 2. In the evolution of disease
  - A. Without response, there is an evident of two ways of bacillary spread; a. infected to neighbouring Schwann cells in a nerve, terminally and centripetally and b. infected to accumulated macrophages around a nerve in subpapillary layer. c. alteration of bacillated Schwann cells and macrophages into Lepra cells. d. No focalization of lymphocytes around a nerve.
  - A'. In regressive stage of lepromatous, if immunity is more low, alteration of histiocytes into Yersin type of cells.
  - B. With response, a. accumulation of lymphocytes around an infected nerve b. alteration of Schwann cells into epithelioid cells and perhaps Langhans cells.

*Further information*: Kiyoshi Harada MD, Research Laboratory, National Sanatorium Tamazenseiyen, Higashimurayama, Tokyo, Japan.

#### Leprosy project promotes disabled meet

At a significant get-together function to mark the Silver Jubilee Year of Bombay Leprosy Project (BLP), patients affected by leprosy and other physically disabling diseases assembled to relate the job satisfaction they derived in working together without experiencing a feeling of isolation.

Dr R. Ganapati, Director, BLP observed that there are several ways of fighting stigma associated with leprosy and to a lesser extent with the visibly disabled patients in general. BLP has found that offering employment opportunities to such patients in an integrated manner without isolating them in institutions is the best way of avoiding social ostracism.

Dr T. Sreedhar, Deputy Director, All India Institute of Physical Medicine and Rehabilitation, Mumbai, The chief guest in his address informed even school and college principals were not aware of the Disability Act-1995 which recommends equal rights to the disabled persons. He recounted the story of a student who underwent post-polio surgery as a result of which she missed college attendance for more than three months, with the Principal refusing admission to her though the Disability Act 1995 prevailed upon all Institutions of learning to show the maximum possible concession to disabled persons. However, armed with a letter from Dr. Sreedhar, reminding the Principal of this Act, the child again sought admission and was permitted to join.

To Mr P. P. Hirani, the celebrated photo-journalist, who has visited several rehabilitation institution elsewhere, community based rehabilitation practiced by BLP was a novel experience. He referred to the disabled as 'Children of a Greater God' and confessed that these persons will spread the positive message.

The meeting concluded with a vote of thanks from Dr C. R. Revankar, Deputy Director, BLP.

#### UN says up to half the teenagers in Africa will die of AIDS

From the British Medical Journal, volume 321, page 67, 8 July 2000:

AIDS will cause early death in as many as half of the teenagers living in the hardest hit countries of southern Africa, causing population imbalances nearly without precedent, according to a report released last week by UNAIDS, the Joint United Nations Programme on HIV/AIDS.

Demographers predict that two thirds of the 15 year olds in Botswana will die of AIDS before reaching age 50. Although that is clearly the world's worst scenario, researchers predict that in any country where 15% of adults are now infected, at least 35% of those who are currently teenagers will eventually die of AIDS.

The AIDS epidemic is already measurably eroding economic development, educational attainment, and child survival—all key measures of a nation's health—in much of sub-Saharan Africa, according to the report.

The disease's ultimate toll on the region, however, is likely to be far more severe than what is evident today, the report found. 'The demographic effects will only be getting worse in the coming years, even if by some miracle HIV infection suddenly stopped,' said Peter Piot, director of UNAIDS. 'I believe we are only at the beginning of the actual impact on societies of AIDS.'

According to the report, there are now 34.3 million people infected with HIV worldwide, of whom 1.3 million are children under the age of 15. About 5.4 million people were infected last year.

Last year 2.8 million people died of AIDS; a total of 19 million have died since the epidemic was first recognized 20 years ago. About 13.2 million children, the vast majority in Africa, have lost at least one parent to the disease.

There are a few success stories in an otherwise grim picture. The infection rate in Uganda has fallen to around 8% of the adult population from a peak of 14% in the early 1990s, thanks to strong prevention campaigns and the increased use of condoms.

Despite earlier fears of an epidemic in Asia, the rate of infection remains generally low. In Thailand the heterosexual epidemic has been curbed, although the virus is spreading fast through shared needles and unprotected sex between men.

Strong campaigns in some of these countries have shown that it is possible to slow the epidemic. But the report also said that there must be a massive increase in political will.  $\Box$ 

*Report on the Global HIV/AIDS Epidemic 2000* is available from UNAIDS, 20 Avenue Appia, 1211 Geneva 27, Switzerland, or at www.unaids.org.

Full story in News Extra at bmj.com

#### Interleukin 2 increases CD4 T cell counts in people with HIV

The following account appeared in the British Medical Journal volume 321, page 196, 22 July 2000. bmj.com:

Adding interleukin 2 to anti-retroviral drugs substantially increases the CD4 T cell count and decreases the viral load of HIV, according to a multicentre trial sponsored by the National Institutes for Health (*JAMA* 2000;284:183–9).

The combination treatment may further extend the immune competency and therefore the life span of people infected with HIV. The two year study, led by Drs Richard Davey Jr and H. Clifford Lane of the National Institute for Allergy and Infectious Diseases, enrolled 82 patients and randomized them into two groups. Nearly all the patients were male.

Forty three patients received antiretroviral drugs alone, and 39 patients received antiretroviral drugs plus intermittent therapy with subcutaneous interleukin 2 at a starting dose of 7.5 mIU twice a day for five days every 8 weeks.

The choice of antiretroviral was left to the patients and their physicians, but both groups had similar proportions of patients who were taking protease inhibitors (89% of those in the interleukin group; 80% of those taking only an antiretroviral). Patients with serious AIDS defining illnesses were excluded from the study.

Enrolment criteria included either a baseline CD4 count of  $200-500 \times 10^6$  or 14% of all T cells, a viral load of less than 10 000 copies of HIV-1 RNA, and no previous treatment with interleukin 2.

Additionally, patients had to be free of treatment with systemic steroids, chemotherapy, and cytotoxic agents for at least 4 weeks before the trial.

Of the initial 82 patients enrolled, 78 completed the study. After 1 year, patients who had been receiving both interleukin 2 and antiretroviral drugs sustained a greater increase in CD4 counts than those given antiretrovirals alone, with an average increase of 112% compared with 18%. Moreover, there was a dose related increase in CD4 count with increasing dose of interleukin 2.

Full story in News Extra at bmj.com

#### **Changes in the STOP TB Campaign**

From *Connect*, the Newsletter of the International Federation of Anti-Leprosy Associations (ILEP)-No. 2, Winter 2000/01:

Changes to the STOP TB Campaign and the organization of TB activities in WHO have just been announced by the Director General, Dr Gro Harlem Brundtland. Dr J. W. Lee, formerly special Representative of the Director-General, is appointed as Director of SPOT TB, with intermediate effect. STOP TB will have two components—one of which will be the Secretariat of the STOP TB initiative, headed by an Executive Secretary, Dr Jacob Kumaresan. The second component will continue to fulfill WHO's normative and technical responsibilities in TB and will be coordinated by Dr Mario Raviglione. For further information, please contact the STOP TB Secretariat at stoptb@who.int

#### Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment

This is the title of an important and interesting article published in *The New England Journal of Medicine*, 1999;341:1174–9, by Annelies van Rie *et al.* from the University of Stellenbosch in South Africa, The Catholic University of Leuven in Belgium and the International Union against Tuberculosis and Lung Disease in Paris, France. The *Abstract* reads as follows:
*Background* For decades it has been assumed that postprimary tuberculosis is usually caused by reactivation of endogenous infection rather than by a new, exogenous infection.

*Methods* We performed DNA fingerprinting with restriction-fragment-length polymorphism analysis on pairs of isolates of *Mycobacterium tuberculosis* from 16 compliant patients who had a relapse of pulmonary tuberculosis after curative treatment of post-primary tuberculosis. The patients lived in areas of South Africa where tuberculosis is endemic. Medical records were reviewed for clinical data.

*Results* For 12 of the 16 patients, the restriction-fragment-length polymorphism banding patterns for the isolates obtained after the relapse were different from those for the isolates from the initial tuberculous disease. This finding indicates that reinfection was the cause of the recurrence of tuberculosis after curative treatment. Two patients had reinfections with a multidrug-resistant strain. All 15 patients who were tested for the human immunodeficiency virus were seronegative.

*Conclusions* Exogenous reinfection appears to be a major cause of postprimary tuberculosis after a previous cure in an area with a high incidence of this disease. This finding emphasizes the importance of achieving cures and of preventing anyone with infectious tuberculosis from exposing others to the disease.

Particularly if confirmed in other parts of the world, these findings in South Africa have important implications for our current efforts to control this disease. An extract from the *Introduction* reads:

<sup>6</sup>Before the introduction of antituberculous medication, there was little recognition of the distinction between endogenous reactivation and exogenous reinfection in patients who had multiple episodes of tuberculosis, since untreated established tuberculous lesions may be alternately active and dormant. Effective treatment regimens made possible the sterilization of pulmonary lesions, but it was accepted that subsequent episodes of tuberculosis were almost invariably caused by endogenous reactivation. The complete sterilization of a lesion became possible with improved treatment regimens, especially with the introduction of rifampin, a drug with a potent sterilizing effect. With short-course combination therapy consisting of isoniazid, rifampin, and pyrazinamide, the relapse rate dropped from 21 percent to 1 to 2 percent. In this era of effective treatment regimens, the notion that multiple episodes of tuberculosis in one patient are almost always caused by endogenous reactivation may be questioned. It is now possible to characterize the genotype of *Mycobacterium tuberculosis* by DNA fingerprinting, which can show whether a new episode of the disease is caused by infection with the same strain that caused a previous episode or by a different strain.

In this study we used DNA fingerprinting to determine the relative frequency of endogenous reactivation and exogenous reinfection in patients with multiple episodes of postprimary tuberculosis. We aimed to determine the importance of this distinction in terms of the definition of cure, the efficacy of current treatment regimens, and the control of tuberculosis.'

### And the closing paragraph of the Discussion-

'The controversy with regard to endogenous as opposed to exogenous pathogenesis of tuberculosis is of importance in the planning of clinical trials and national tuberculosis-control programs. If, in areas with a high incidence of the disease, postprimary episodes of pulmonary tuberculosis after previous cure result predominantly from exogenous reinfection, as indicated by our results, the effectiveness of a drug regimen cannot be evaluated on the basis of the relapse rate without the additional information provided by RFLP analysis of bacterial isolates. In the evaluation of national tuberculosis-control programs for areas in which the disease is endemic, restriction fragment-length polymorphism (RFLP) analysis can prove the effectiveness of the currently used treatment regimens. "Cure" in a patient who later has another episode of tuberculosis is not necessarily an incorrect concept. The more likely possibility is that he or she has a new infection after the cure. The emphasis should thus be placed on achieving cure in patients and on prompt case detection to prevent reexposure to sources of active tuberculosis.'

## 244 News and Notes

## Erratum

In the March issue of *Leprosy Review*, the figures in the paper by Kumar *et al.* (Involvement of male genitalia in leprosy, pp. 70–77) were accidentally transposed. We apologize for this error, and for any inconvenience that it may have caused.



Figure 5. Infiltrated plaque lesion on the scrotum in LL leprosy.

Figure 6. Multiple necrotic ENL lesions on glans penis in LL leprosy.

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Article submission. Articles submitted for publication in Leprosy Review should be sent to the Editor at the following address: Diana Lockwood, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be indicated clearly below the title of the article. Degrees and diplomas are not to be included.

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