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Leprosy Review

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

LEPRA

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

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

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Editor's Choice

This issue of *Leprosy Review* demonstrates the breadth of interest in leprosy with articles ranging from health education programmes in Tanzania (p. 57) to detailed studies of retroviral infection and leprosy on rhesus monkeys (p. 6). We also continue the debate on the use of Rifampicin/Ofloxacin/Minocycline (ROM) treatment for single-lesion leprosy. Dr Katoch has contributed an editorial highlighting some of the microbiological problems of treating mycobacterial disease with single-dose therapy. Killing all the organisms with a single dose of antibiotics may be impossible when some mycobacteria are in a resting or dormant phase. In the Letters section Dr Ramu (p. 78) offers further comments on both the ROM trial and the management of single-lesion cases.

Various studies of leprosy vaccines, most recently the Malawi trial, have shown that BCG vaccination protects against leprosy but we still do not understand how this protection is conferred and why it cannot be enhanced by adding *Mycobacterium leprae* to the vaccine. Gormus *et al.* (p. 6) report on the genetic component of this effect by looking at the protection afforded by BCG and *M. leprae* vaccination in two monkey species with differing susceptibilities to leprosy. Rhesus monkeys are susceptible to paucibacillary disease and were protected by BCG vaccination and this protection was slightly enhanced by addition of *M. leprae* but in Sooty Mangabey Monkeys BCG vaccination only slowed the development of multibacillary disease. These results suggest an important genetic component for the protection afforded by BCG vaccination and emphasize the need to have BCG protection studies done in different regions where the populations may have different disease susceptibilities.

A clinical series from Vellore reports on patients with renal transplantation and leprosy. Even in this small series these immunosuppressed patients responded well to conventional multidrug therapy.

The latest report from Zimbabwe suggests that although only small numbers of patients are being diagnosed there transmission is continuing. A worrying feature of this report is that 33% of patients had visible deformities at the time of diagnosis.

Thank you to all those people who responded to the questionnaire about the poster series. We felt very encouraged by your replies and will be continuing the poster series but in alternate issues of the Journal. Please keep us posted with your suggestions and comments.

DIANA N. J. LOCKWOOD

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Editorial

IS THERE A MICROBIOLOGICAL RATIONALE FOR SINGLE-DOSE TREATMENT OF LEPROSY?

Therapy of any infectious disease is based on some general principles: (i) administration of appropriate drug(s) to which the organism is susceptible; (ii) drug(s) should be able to reach the site of action and stay in the system long enough; (iii) therapy may need to be repeated to reduce the viable load below detectable limits, i.e. culture negativity. In various bacterial diseases, treatment is continued beyond the point of achieving sterility so that relapses are reduced to acceptably low limits. These principles have been followed for the management of tuberculosis when treatment is given for 3–4 times the duration required for achieving culture negativity. The principle is to eliminate both metabolically active and dormant persisters to a level where host immunity disposes of residual organisms. These aspects have been considered when planning various multidrug therapy (MDT) regimens for leprosy during the last 15 years.[1,2] However, as *Mycobacterium leprae* is not cultivable *in-vitro* theoretical considerations have been based on the results of multiplication and killing/inhibition in the mouse footpad model. The treatment of leprosy has progressed through many phases. Drugs like rifampicin, dapsone, and clofazimine were initially selected on the basis of mouse footpad experiments. Based on the calculations of the proportion of *M. leprae* killed after one or more doses of rifampicin, regimens were designed to kill an estimated viable load and to prevent the emergence of drug resistance. These regimens (popularly known as WHO regimens) have been used all over the world and have led to a major decline in the prevalence of the disease.[3,4] But after reduction of well-established (tuberculoid and lepromatous) cases, the spectrum of the disease has shifted to fresh evolving cases and single-lesion cases. The encouraging experience with MDT and availability of newer potent compounds has given confidence to try ever shorter regimens.[3,5] This thinking has culminated in the development of a single-dose regimen comprising of rifampicin, ofloxacin and minocycline (ROM) for the treatment of single-lesion cases. This regimen has now been recommended for implementation in treatment programmes, so that such cases can be declared 'cured' before the deadline of 2000 AD. This regimen is really 'revolutionary' and moves from a era of life-long therapy to one-day treatment. This has also stirred up much needed debate which the earlier WHO regimens had escaped. Debate on the rational of the new ROM regimen needs to consider the experience and lessons from the earlier WHO regimen(s) as the justification for ultrashort regimens is based on the overall 'success' of the older regimens.[5]

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Experience with current/old WHO regimens

Published results show that WHO regimens were generally more effective than dapsone monotherapy in terms of faster clinical response, faster reduction of viability and lower rates of late complications like relapses.[3,4] The initial recommendations of treatment for a minimum of 6 months for paucibacillary (PB) cases and 2 years for multibacillary (MB) leprosy worked in the majority of cases. However, several difficulties and limitations in both the management of PB and MB leprosy with these regimens have also become apparent.[6] There are problems of residual persisting activity and late reactions/relapses in paucibacillary cases treated with 6-months fixed-duration regimen.[7] The problem of persisting viable bacilli 'persisters' in a significant proportion of initially highly-bacillated MB cases was also observed by several investigators.[8–11] These results may be interpreted in various ways. While rapid decrease in viable populations as seen in the mouse footpad and other viability parameters was a heartening development, it was apparent that killing efficiency is not always predicted by the mouse footpad. If the calculations of 99·9% killing with a single dose of rifampicin were also reproducible in man, then there would have been no problem. It was observed that there was a rapid decrease in viable populations initially but little effect on dormant or nonmultiplying bacillary populations. Viable bacteria could be detected or grown in about >10% of these cases after 3–24 months of treatment.[8–11] As the potent bactericidal drug rifampicin only stays in the system for a couple of hours, this can only eliminate bacteria multiplying on that day. These limitations occur inspite of one (dapsone) or two drugs (dapsone and clofazimine) being administered continuously. The presence of these persisters and the possible consequences have not been addressed. It has been assumed that the host response would eliminate residual viable bacteria. It was also postulated that after the initial doses there were no additional benefits of MDT as a continuous decline in bacteriological indices is seen.[12] It is unlikely that the effect of 3 months, 12 months or 24 months treatment is the same. Inability to discriminate between the outcome of different treatment times is probably due to inadequate follow-up and the limitation of testing methods. The situation in paucibacillary leprosy is not severe, the premature termination of treatment leads to persistence of activity, late complications like late reactions/relapses in a section of cases which could have been reduced by appropriate modifications.[7] But in multibacillary cases, the consequences have been worse. In trials with excellent follow-up (e.g. Marchoux trial) relapses have occurred almost in the same proportion as the persisters were seen in various studies and most of these relapses occurred 6–9 years later.[13] This experience shows that bacteriological aspects have to be considered and it is wrong to draw overoptimistic conclusions especially in cases with demonstrable proof of viable bacilli. Leaving behind live organisms may be a risky idea in leprosy and should be kept in mind while planning regimes in present or future.

Management of single-lesion cases with single-dose treatment

Rifampicin, ofloxacin and minocycline are well-established drugs which have shown reasonably high bactericidal activity against *M. leprae*. Even though there are no indepth investigations, it has been generally assumed that single-lesion cases are paucibacillary cases with a good immunity and low bacterial load.[14,15] As discussed above, experience with current MDT shows that these calculations and assumptions do apply regardless. Despite the

presence or one or a few skin lesions, *M. leprae* may be multiplying in internal organs and the actual load may be much higher.

Assuming that a particular case has 10–100 million organisms and if 0·1–1·0% are left unkilled, this leaves a million live bacilli. The drugs only act on metabolically-active organisms and the half lives of these drugs vary from 3 to 5 hours for rifampicin, to 7 to 8 hours for ofloxacin, and 12–18 hours for minocycline. Therefore, these drugs will only eliminate organisms which are metabolically active during that period when these drugs are in the body. These compounds may act synergistically to achieve better killing kinetics. They will also prevent the development of drug-resistant organisms to these compounds. However the bacterial populations which are not in the growth phase or are dormant will not be affected by this drug combination. The result will be possibly the same even if 2–3 more compounds are added up.

The results of the multicentre trial show that this regimen is well tolerated and with few immediate problems. However, in a short follow-up of 18 months, the clinical response has been slower than with the current WHO regimen and more than 50% of cases were still active.[15] If one compares experience with the previous studies, the response of single-lesion cases has been much better to WHO regimen or slightly modified regimens.[16–18] Nearly 95–100% inactivity was achieved in those trials by one year.[16–18] In the present case even the response to current WHO regimen has not been that good. One interpretation could be that we are dealing with a different situation. In the earlier era, most of the single-lesion cases were established tuberculoid cases with some immunity to limit disease. However, the new single-lesion cases may be evolving early cases—and they may progress into lepromatous or tuberculoid types. The relatively slower response to the WHO regimen itself may support this hypothesis. Some of the single-lesion cases may self-heal, ROM may accelerate healing in some by killing some metabolically active *M. leprae* but in others there may be no antibacterial effect. Leprosy lesions are not a synchronous culture of bacteria which can be instantaneously killed. It may be inappropriate to consider all these cases as low-bacillated 'paucibacillary' with their *M. leprae* actively multiplying and easily killed when drugs are administered. Synchronous cultures of cultivable mycobacteria are extremely difficult to generate and sustain even in the artificial test tube conditions. The experience with MDT regimens in MB as well as PB cases shows clearly that we are not dealing with synchronous actively multiplying organisms. Whether *M. leprae* multiplies after 10–12 days or 1–2 days (as per calculations of Dr Hastings) may be debatable but it is certain that all *M. leprae* do not multiply on the same day. The number of required pulses cannot be predicted with certainty and can only be decided by well-conducted trials. It is rather strange to base therapy on the killing observed in the mouse footpad but conveniently choose to ignore the presence of viable *M. leprae* demonstrated by the same technique. The ROM regimen has a poor microbiological rational which cannot be theoretically defended. This has been further substantiated by a relatively slower response as seen in the trial.

In the changing era of leprosy elimination when a major chunk of cases has already been eliminated, at least from the registers, it is difficult to understand the logic of designing and rushing with a regimen with poor theoretical chance of achieving reasonable antibacterial effect. As the initial response has been below the expected levels, large scale introduction of this regimen in the field may have serious consequences. Long term follow-up (up to 10 years as some of them could be potential MB types) and indepth debate about the likely consequences should be carried out. While in doubt, the benefit should rest with the patient and not with theoretical optimism.

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Protective Immunization of monkeys with BCG or BCG plus heat-killed *Mycobacterium leprae*: clinical results

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Summary Rhesus and sooty mangabey monkeys (RM and SMM) were vaccinated and boosted with BCG or BCG + low dose (LD) or high dose (HD) heat-killed *Mycobacterium leprae* (HKML). One group was not vaccinated. Except for a group of controls, all monkeys were challenged with live *M. leprae*. All animals were studied longitudinally to determine antileprosy protective efficacy. BCG reduced the numbers of RM with histopathologically-diagnosed leprosy by 70% and slowed and ameliorated the appearance of symptoms. BCG + LDHKML reduced the number of RM with leprosy by 89% and BCG + HDHKML by 78%. BCG did not protect SMM from developing leprosy, but disease progress was slowed; disease in SMM was exacerbated by the addition of HKML to the vaccine. RM, as a species, are prone to paucibacillary (PB) forms of leprosy, whereas SMM are prone to multibacillary (MB) forms. Thus, BCG vaccination offers significant protection from clinical disease and slows/ameliorates the rate of progression/degree of disease at the PB end and appears to at least ameliorate symptoms at the MB end of the leprosy spectrum. BCG + HKML protects at the PB end and exacerbates disease progress at the MB end of the leprosy spectrum.

Introduction

There have been numerous field trials in various human populations to determine the antileprosy immunoprophylactic efficacy of *Mycobacterium bovis*, strain bacillus Calmette-Guerin (BCG) alone or in combination with killed *M. leprae*. Five controlled[1–5] and two case-control or cohort studies[6,7] have been reported using BCG alone, with striking

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variations in results. Protective rates using BCG alone ranged from near 20 to 80%. The Venezuelan study included subjects immunized with heat-killed *M. leprae* (HKML) plus BCG.[2] This latter study concluded that there was no difference between BCG alone *vs* BCG in combination with HKML in protective efficacy. The study was difficult to clearly interpret, however, because no placebo group was included and the results were of marginal statistical significance.[2] Thus, many questions remain unanswered concerning the ability of either BCG alone or BCG + killed *M. leprae* to impart protection against clinical leprosy. Reasons for the wide differences in the effectiveness of BCG alone in leprosy protection from one study to another also remain to be understood.

Several explanations have been proposed as possible reasons for the variations in results observed in the efficacy of BCG to protect against leprosy.[6] One suggestion is that prior exposure to differing types of mycobacteria in the environment may differentially alter the susceptibility of individuals in different parts of the world to infections with *M. leprae* and/or alter the responses to mycobacteria-containing vaccines.[8,9] Another possibility is that BCG preparations from different sources and/or batches or lots were used in many of the reported studies, which might produce variations in immunizing potency.[10,11] Differences in natural history of infection and disease, such as variations in the ratios of tuberculoid (TT) to lepromatous (LL) forms observed in populations in different parts of the world or differences in population genetics have also been suggested as explanations.[6]

In the present studies, many, if not all, of these weaknesses were controlled or eliminated. All of the monkeys were born, reared and maintained in the southern United States, were similar to one another in age and were randomized among our groups according to sex. The same BCG (Glaxo) lots and concentrations were used in all cases; the *M. leprae* used for immunization was all from a single purified and heat-killed batch; and the live *M. leprae* used to challenge the animals was all from a single source. Another important aspect of these studies is that rhesus monkeys (RM), as a species, tend (>80%) to develop TT forms, (Gormus, BJ *et al*, p. 24) whereas sooty mangabey monkeys (SMM) tend (>80%) to develop LL forms of leprosy.[12–15] Thus, the relationship between natural history of disease and immunizability can be examined directly by comparative vaccine studies between RM *vs* SMM.

Methods

ANIMALS

Forty-five Chinese rhesus monkeys (RM) (*Macaca mulatta*), 2–3 years old, born and maintained in our breeding colony at the Tulane Regional Primate Research Centre (TRPRC), all with presumed similar natural exposures to environmental agents, were divided into 4 experimental groups (3 vaccine groups and 1 unvaccinated control group—all *M. leprae* challenged) of 10 (3 females and 7 males/group). There was also one group of 5 unvaccinated, non-*M. leprae* challenged normal controls (Table 1).

Thirty-five sooty mangabey monkeys (SMM) (*Cercocebus torquatus atys*), aged 3–10 years, were purchased from the Yerkes Regional Primate Research Center's breeding colony, Atlanta, GA, USA (where they were born and reared). The SMM were divided into 4 *M. leprae*-challenged experimental groups and one normal, unchallenged control group of 7 animals per group (2 females and 5 males/group) (Table 1).

Table 1. Monkey immunizations

Group	#RM	#SMM	Total # Monkeys	BCG*	HKML Dose*	*M. leprae* Inoc
1	10	7	17	No	0	Yes
2	10	7	17	Yes	0	Yes
3	10	7	17	Yes	$1{\cdot}6 \times 10^9$	Yes
4	10	7	17	Yes	16×10^9	Yes
5	5	5	10	No	0	No

Abbreviations: RM, rhesus monkeys; SMM, sooty mangabey monkeys; BCG, Bacillus Calmette-Guerin, Glaxo (present manufacturer, Evans Medical, UK); Inoc, inoculation with live *M. leprae*.

*Monkeys were boosted with the same doses of BCG or BCG + HKML as those used for vaccination; RM were boosted 5 weeks and SMM 7 weeks post-vaccination.

SELECTION OF BCG

Freeze-dried BCG was purchased from three sources: 1, Glaxo strain (ST1077) from Evans Medical Limited, Liverpool, England; 2, strain #1331 (batch 590) from the Staatens Seruminstitute, Copenhagen, Denmark; and 3, Merieux strain from Connaught, Inc., Willowdale, Ontario, Canada.

We obtained a single lot of each of the Copenhagen and the Merieux BCG's, whereas we had on hand a quantity of ampoules of BCG from the Glaxo Company, Middlesex, England and obtained a new shipment of the Glaxo strain from Evans Medical, Liverpool, which presently owns the Glaxo Company. The Evans shipment included multiple lot #'s. Thus, we used mixtures of several lot #'s of the Glaxo strain for preliminary testing and the same mixtures for all immunizations and boosting. BCG's were stored at 2°–8°C wrapped in foil to protect from light. BCG's were checked for viability prior to use (see below). The following Glaxo lot #'s were utilized: G4386DA, D428, W1533A (Evans), E2528A (Evans).

BCG from each of the 3 sources was tested by intracutaneous (IC) injection of 0·1 ml (10^6–10^7 viable units) into 2 RM. The resulting reactions at 2–3 weeks postvaccination (PV) were in excess of 1-cm diameter induration with ulceration at both Glaxo sites, 5 mm and negative at the two Copenhagen sites, respectively, and negative at both Merieux sites. Forty-eight-hour TB test results of the six RM at 3 weeks PV gave positive results in the same 3 RM (2 Glaxo and 1 Copenhagen BCG recipient) and negative results in the other three RM. Boosting with the respective three BCG's at 4 weeks PV gave approximately 1-cm erythematous indurations in the four Glaxo and Copenhagen RM's and 1- and 1·5-cm ulcerated indurations in the two Merieux recipients at 48-hr postboosting. Based on these observations, we chose the Glaxo BCG for use in the present vaccine studies.

PREPARATION OF HEAT-KILLED *M. LEPRAE* (HKML) FOR VACCINATION

In 1988, two armadillos were inoculated at the Armed Forces Institute of Pathology (AFIP) with SMM-origin *M. leprae* isolated from lepromatous nodules from a SMM (G930); a third armadillo was inoculated with *M. leprae* from a second SMM (D172). Both G930 and D172 had been experimentally inoculated with *M. leprae* taken originally from a SMM (A015) with naturally-acquired leprosy.[12,16] Livers and spleens were taken from the three armadillos when

leprosy became sufficiently advanced and were stored frozen (−70°C) until shipment to the laboratory of Dr Patrick J. Brennan (Department of Microbiology, School of Veterinary Medicine, Colorado State University, Fort Collins, CO, USA) for isolation and purification of *M. leprae* by the Draper method.[17] A total of 735 g of liver and 257 g of spleen all at approximately 10^9 *M. leprae*/g of tissue was shipped to Dr Brennan. A portion of one liver (47·89 g) yielded 228 mg of G930 *M. leprae* (approximately $6{\cdot}6 \times 10^{11}$ organisms) and 47·85 g of a second liver yielded 190 mg of D172 *M. leprae* (approximately $5{\cdot}5 \times 10^{11}$ organisms). The *M. leprae* preparations were heat-killed (autoclaved), lyophilized and shipped to the TRPRC for monkey immunizations. These procedures were performed by Dr Brennan's laboratory under contract #AI-52582 from the National Institute of Allergy and Infectious Diseases.

IMMUNIZATIONS WITH BCG OR BCG PLUS HKML

Monkeys were vaccinated with BCG alone or BCG + high-dose (HD) HKML or BCG + low-dose (LD) HKML by IC injection of 0·1 ml of the appropriate suspension. HKML was weighed so that LD tubes contained 0·275 mg of *M. leprae* from each of two armadillos, i.e. one inoculated with *M. leprae* from SMM D172 and another inoculated from SMM G930, for a total HKML dose of 0·55 mg ($1{\cdot}6 \times 10^9$ HKML). The HD tubes contained twice as much of each of the two *M. leprae* preparations for a total of 1·1 mg or $3{\cdot}2 \times 10^9$ HKML. Immediately prior to use, Glaxo BCG was reconstituted to $10–26 \times 10^6$ viable units/ml with sterile distilled water (or, in the case of the Evans Medical-origin Glaxo strain, with sterile saline, as recommended by the manufacturer) and was placed in ice in the dark after reconstitution; 0·1 ml was used as such for BCG-only recipients or was mixed with a LD or HD HKML tube using a 0·5-ml insulin syringe, the suspension was reaspirated into the syringe and the suspension injected into a single site in the dorsal scapula area of each monkey. All 3 vaccine groups received the same dose of BCG. Table 1 shows the monkey groupings for immunizations and boosting and the amounts of BCG or BCG + HKML used for immunization and for boosting. Primary vaccinations were carried out on day 0; boosting at 5 (RM) or 7 (SMM) weeks; and challenge with live *M. leprae* was at 10 (RM) or 15 (SMM) weeks.

BCG viability and growth was confirmed by Dr Thomas M. Schinnick, Division of Bacterial and Mycotic Diseases, Centers for Disease Control, Atlanta, GA, USA. At least 30% viability was confirmed in ampoules from all lot numbers, but exact viable counts could not be determined due to clumping.

PREPARATION OF LIVE ML FOR CHALLENGE

In September, 1991, armadillos were inoculated at the AFIP with *M. leprae* taken from lepromatous (LL) dermal nodules of SMM D173, which had been subinoculated from a case of natural leprosy in SMM A015[18] and had been subpassaged through SMM A022 prior to inoculation into D173.[13] For *M. leprae* inoculations (monkey challenge), one of these armadillos was sacrificed (on 26/5/91 for RM challenge and another on 8/9/92 for SMM challenge); LL nodules, spleen and liver were harvested and shipped overnight on ice to the TRPRC where each tissue was processed separately for *M. leprae* isolation by methods previously published.[13] Briefly, tissues were cut into small pieces, fat removed and pieces minced and homogenized in cold phosphate-buffered saline using a Dounce homogenizer

with a 40 MI mortar and Teflon pestle (Wheaton Scientific, Millville, NJ, USA), passed through gauze and centrifuged at 200 × **G** for 5 min. at 4°C. The acid-fast bacilli (AFB) in the supernatant were counted and morphologic indices (MI) determined by the method of Shepard & McCrae.[19]

MONKEY INOCULATIONS

Monkeys were inoculated with *M. leprae* suspensions by combined IC and intravenous (IV) routes using 2 IC sites per ear, the tip of the nose, outer forearms and outer calves. IV inoculations were made via the saphenous vein. Details have been previously published.[13] *M. leprae* suspensions for RM challenge had an MI of 8% and for SMM MI = 10%.

CLINICAL OBSERVATIONS

Animals were observed daily and examined in detail 3–4 times per year or more, depending on the status of the animal, and the clinical aspects of the disease were recorded. The Ridley–Jopling system was used to classify leprosy immunohistopathologically,[20] with the exception that classification at the paucibacillary (PB) end of the spectrum differs slightly in RM from humans. The classification Ind/TT (Indeterminate/tuberculoid) describes a lesion with rare to few AFB, containing epithelioid and/or multinucleated giant cells, but with fewer lymphocytes than usually seen in human TT leprosy (Gormus, BJ, *et al.* p. 24). Nasal smear samples were taken on microscope slides at each time of observation for staining with Ziehl-Neelsen for the presence of AFB in nasal secretions.

HISTOPATHOLOGIC DETERMINATIONS

Biopsies were taken at intervals from dermal inoculation sites and/or from sites of dissemination for analysis of the lesions and for documentation of clinical leprosy after staining with H&E and Fite-Faraco, as previously reported.[21,22] A diagnosis of leprosy was made on the basis the presence of acid-fast bacilli (AFB): 1, in nasal secretions (since we have previously determined that the presence of AFB in such secretions is the first indication of dissemination of leprosy beyond areas of dermal inoculation; and/or 2, within areas of inflammatory infiltration at inoculation sites at a time when clearance of AFB had occurred in a significant number of animals; or 3, in disseminated dermal sites (that had not been inoculated with *M. leprae*). Leprosy was classified histopathologically according to the Ridley–Jopling system,[20] with the exception that at the PB end of the spectrum differ slightly in RM from humans, as previously noted (Gormus BJ *et al*, p. 24). For purposes of this report, however, results are given as PB or MB. MB will include borderline to lepromatous forms on the Ridley–Jopling spectrum;[20] PB includes indeterminate, tuberculoid and borderline tuberculoid forms.

DETECTION OF SERUM PGL-I ANTIGEN LEVELS

Serum PGL-I levels were detected in serum samples by a dot-ELISA method; results were expressed as 0; +/− (0·5) and 1+ to 4+, as previously described.[12,23]

STATISTICAL ANALYSES

All statistical calculations were performed using statistical programs for the Macintosh Computer. Longitudinal comparisons between groups were performed by Mancova analysis except for the cumulative numbers of animals with disease *vs* time data. The latter statistical comparisons were performed by Fisher's exact method at each time point.

Results

REACTIONS TO IMMUNIZATIONS WITH BCG OR BCG+HKML

In RM, reactions at the sites of vaccination peaked within 1–2 weeks and averaged about 17 mm in diameter for BCG + HKML and 8 mm for BCG alone (Figure 1(a)); reactions to

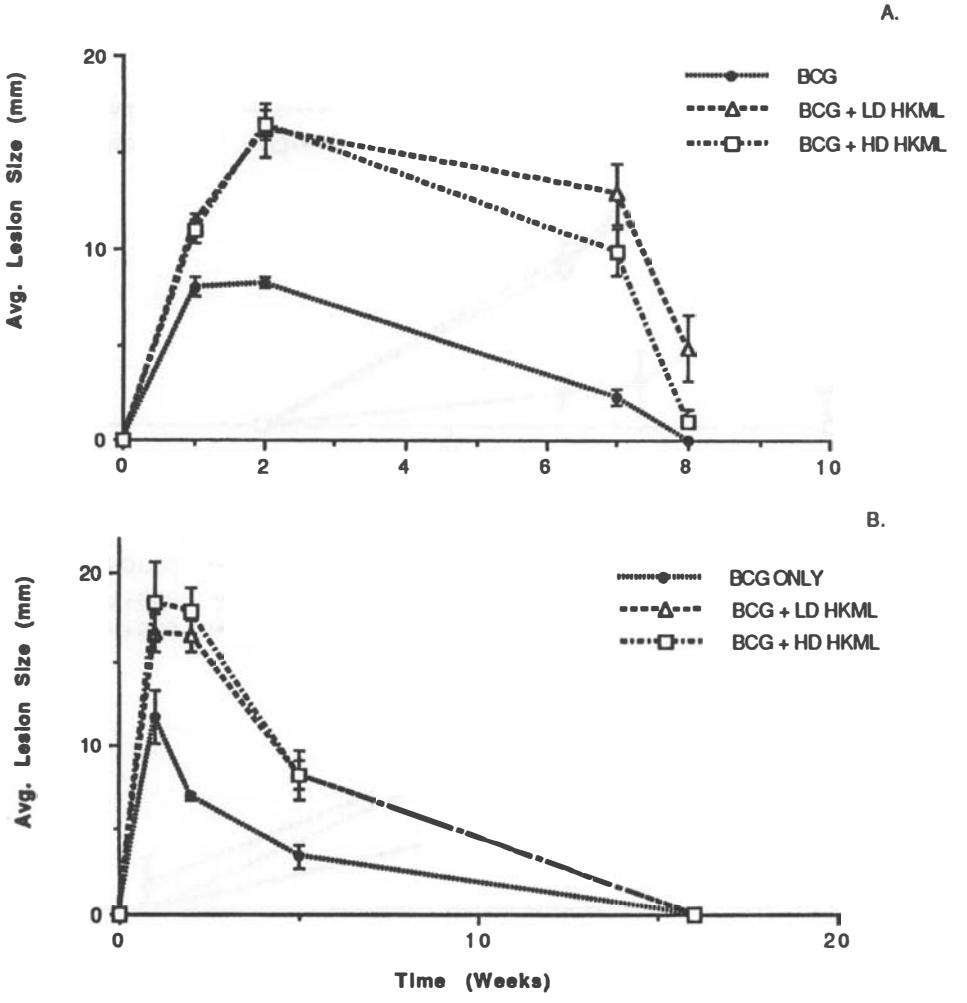

Figure 1. Average reaction sizes over time (+/− 1 standard error of the mean, SEM) at dermal sites of primary immunization (a) or boosting (b) in RM (10/group).

boosting peaked within 1 week near 17·5 mm for BCG + HKML and 12 mm for BCG alone (Figure 1(b)). In SMM, reactions to vaccination also peaked within 1–2 weeks and averaged between 10 and 15 mm for BCG + HKML and 5·5 mm for BCG alone (Figure 2(a)); reaction sizes similar to those resulting from vaccination were observed within 2 weeks postboosting (Figure 2(b)).

CLINICAL OBSERVATIONS IN RM AFTER CHALLENGE WITH LIVE *M. LEPRAE*

The clinical results for RM are shown in Table 2 and graphically in Figure 3 and are described in detail below. RM as a species are more resistant than SMM to leprosy; on the average, more than 80% of RM develop PB forms of experimental leprosy, depending on the

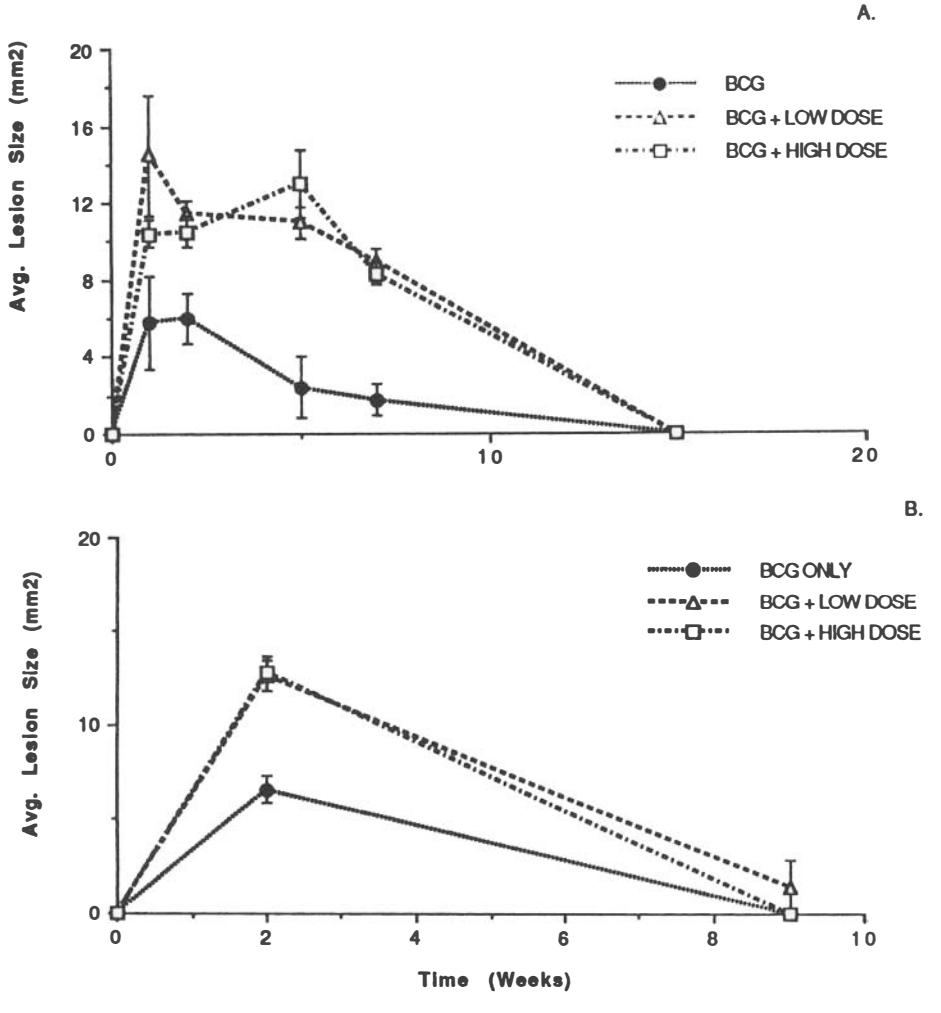

Figure 2. Average reaction sizes over time (+/− 1 SEM) at dermal sites of primary immunization (a) or boosting (b) in SMM (7/group).

experiment (Gormus, BJ *et al*, p. 24). In the experiments to be described herein, larger than usual numbers of unvaccinated, control RM developed leprosy, presumably due to high MI's, the quality of the inoculum and the numbers of ML inoculated (Table 2; Figure 3). By 1198 days PI, 9 of 10 unvaccinated RM had developed biopsy-positive leprosy compared to 3 BCG only, 1 in BCG + LDHKML and 2 in the BCG + HDHKML vaccinated groups (Figure 3). These numbers did not increase over the subsequent period of observation (more than 1500 days).

In RM, within the first 2–3 months postinoculation (PI), reactions and clinical appearances of leprosy at dermal sites of inoculation might be misleading due to the local injection of relatively large numbers of *M. leprae*.[14,15] By 3 months PI, most leprosy-resistant RM have cleared the AFB from dermal inoculation sites (Table 2 and Gormus, BJ *et al*, p. 24). Thus, we have focused below on results beginning at 91 days PI and thereafter in RM.

UNVACCINATED GROUP

We will publish separately a detailed accounting of the histopathologic results of these studies (Baskin, GB *et al*, manuscript in preparation). For the present purposes, histopathologic results will be given only as PB *vs* MB. During the 91–330 day period PI, the unvaccinated group of RM showed the following (Table 2): one RM (K576) had AFB in nasal secretions, K656 had PB leprosy at dermal inoculation sites, L124 had PB at inoculation sites and K971 had disseminated (Dssm) MB leprosy at dermal sites. During that period, two of the remaining 6 RM did not show histopathologically-documentable leprosy and 4 did not have lesions warranting biopsy. Nine of the 10 unvaccinated RM (positive controls) developed clinical signs of leprosy with solidly-staining AFB documentable in biopsies and nasal secretions during the period of observation reported upon herein (1542 days). It was necessary to treat seven of the 10 unvaccinated RM.

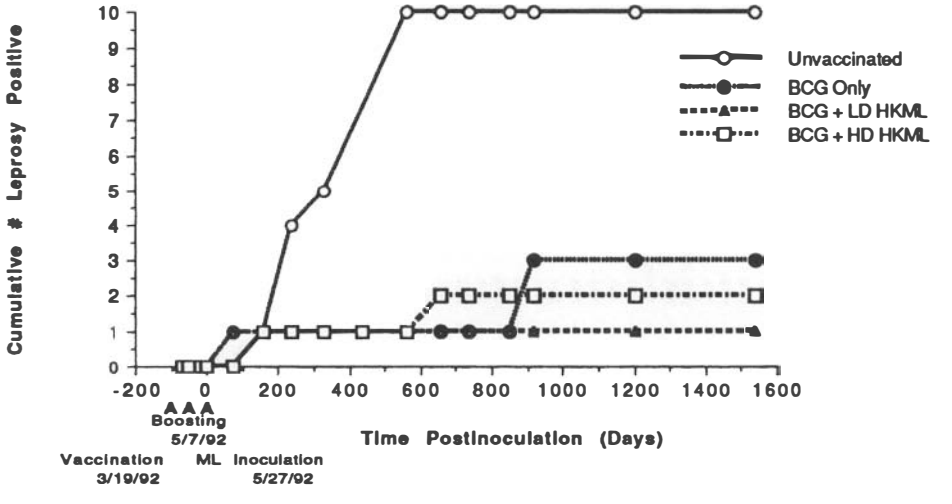

Figure 3. Cumulative number of leprosy-positive RM, based on biopsy results Ridley–Jopling classifications of infiltrations of AFB-positive dermal lesions, in the unvaccinated or vaccinated groups over the course of observation after live *M. leprae* challenge.

Table 2. Clinical results—RM

Days PI		91-330					331-560					561-850					851-1197					1198-1542				
		N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes
Group I	K131	–	–	ND	–	reg	–	–	ND	–	reg	1+	–	ND	–	prog	–	–	ND	–	reg	4+	–	ND	–	slow prog.
	K262	–	–	–	–	NVL	–	–	PB	–	prog	1+	–	ND	–	prog	–	+	PB	–	prog	4+	+	ND	+	prog
	K574	–	–	ND	–	NVL	–	–	ND	–	NVL	–	+	PB	–	prog	4+	+	PB	–	prog	–	+	PB	+	nc, prog
	K576	4+	–	ND	–	prog	4+	+	MB	–	ENL, prog	4+	+	MB	–	prog	2+	+	MB	+	prog	–	+	ND	+	nc, healing
	K656	–	–	PB	–	prog	–	–	ND	–	resis	–	–	–	–	resis	–	–	ND	–	resis	–	–	ND	–	resis
	K941	–	–	ND	–	prog	–	–	ND	–	static	4+	–	ND	–	st, prog	–	–	PB	–	resis	–	–	ND	–	st, resis
	K966	–	–	–	–	NVL	–	–	ND	–	static	3+	–	ND	–	st, prog	4+	–	ND	–	st, prog	–	–	PB	+	resis
	K971	–	+	MB	–	prog. suscep	4+	+	MB	–	prog	–	+	ND	–	static	4+	+	MB	+	prog, suscep	–	+	MB	+	st, healing on Rx
	K975	–	–	PB	–	NVL	1+	–	PB	–	static	4+	–	ND	–	st, prog	–	+	neuritic PB	+	st, nc	ND	ND	ND	+	sac
	L124	–	–	PB	–	st, prog	–	+	PB	–	prog	–	+	ND	–	st, static	–	+	ND	–	st, static	–	+	neuritic PB	+	nc, st, prog
Group II	K452	–	–	ND	–	NVL	1+	–	ND	–	prog	4+	–	ND	–	prog	2+	–	ND	–	NVL	–	–	ND	–	reg
	K477	–	–	ND	–	NVL	–	–	ND	–	NVL	4+	–	ND	–	prog	–	–	ND	–	st, reg	–	–	ND	–	st, reg. sac
	K700	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL, resis	–	–	ND	–	NVL	–	–	ND	–	NVL
	K833	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	+	debil, wt loss	–	–	ND	+	On Rx	–	–	ND	+	healing on Rx
	K948	–	+	ND	–	prog	4+	+	ND	–	prog	–	–	ND	–	static	–	–	PB	–	st, reg	–	–	ND	–	static
	K968	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	L060	–	–	MB	–	static	–	–	–	–	reg	4+	–	–	–	prog	–	–	ND	–	reg	–	–	neuritic MB	+	nc, sac
	L123	–	–	ND	–	NVL	–	–	ND	–	NVL	3+	–	ND	–	prog	–	–	ND	–	st, reg	–	–	prob.neuritic PB	–	nc, sac, reg
	L129	–	–	ND	–	NVL	–	–	–	–	NVL	–	–	–	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	L132	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	neuritic PB	–	nc	–	–	–	–	neuritic dis
Group III	K201	2+	–	ND	–	NVL	2+	–	ND	–	prog	–	–	ND	–	static	4+	+	MB	–	nc, prog, sac	dead	N/A	ND	dead	dead
	K325	–	–	ND	–	NVL	–	–	–	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K545	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K690	–	–	ND	–	NVL	–	–	–	–	NVL	–	–	ND	–	NVL	–	–	–	–	NVL	–	–	ND	–	NVL
	K699	–	–	ND	–	NVL	–	–	–	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K808	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	st
	K895	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	st	–	–	ND	–	NVL
	K913	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K915	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K967	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
Group IV	J616	–	–	ND	–	st, NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K282	–	–	ND	–	st	–	–	ND	–	NVL	4+	–	ND	–	–	–	–	–	–	st	–	–	ND	–	st
	K537	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	st, NVL	–	–	ND	–	NVL	–	–	ND	+	arthritis
	K568	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K569	–	–	ND	–	NVL	–	–	–	–	digit absorb	–	–	ND	–	st	–	–	ND	–	st	–	–	ND	–	NVL
	K629	–	–	ND	–	prog	–	–	ND	–	prog, st	4+	–	ND	–	–	4+	–	PB	–	prog	4+	+	neuritic MB	+	nc, healing/Rx
	K705	–	–	ND	–	died	–	–	died	–	died	N/A	N/A	N/A	N/A	dead	N/A	N/A	N/A	N/A	dead	N/A	N/A	N/A	N/A	dead
	K964	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL
	K974	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	–	–	NVL
	L273	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	ND	–	NVL

*abbreviations: absorpt, absorption; AFB, acid-fast bacilli; Asp, aspiration; Bx, biopsy; debil, debilitated; Dssm, disseminated; ENL, erythema nodosum leprosum; MB, multibacillary; N/A, not applicable; N-AFB, nasal-acid-fast bacilli; nc, neuritic complications; ND, not done; NVL, no visible leprosy; PB, paucibacillary; prob, probable; prog, progressive disease; reg, regressive disease; resis, leprosy resistant; RM, rhesus monkey; Rx, chemotherapy; sac, sacrificed; st, self-trauma; Suscep, susceptible; wt, weight.

BCG ONLY GROUP

During the interval of 91–330 days PI, in the group vaccinated and boosted with BCG alone, K948 showed Dssm progressive leprosy at dermal sites; inadvertently, no biopsies were taken, however, and histopathologic documentation of leprosy was not possible in that RM during that period (Table 2). L060 had MB leprosy at inoculation sites. There was no other visible clinical leprosy among the remaining 8 RM in the BCG-only group at this time. Thereafter, over a period of 331–1542 days PI, a total of 3 RM demonstrated histopathologically-documentable leprosy: 1 (L132) with transient neuritic PB during the 851–1197 day PI period, 1 (L060) with initial MB that regressed into neuritic MB and 1 (K948) with transient PB disease during the 851–1197 day interval. A fourth (L123) had histopathology consistent with neuritic leprosy near the TT end of the spectrum, but no AFB could be seen; it was designated as a probable neuritic PB leprosy-positive, but will not be considered as positive histopathologically for calculations. Only one of the 3 (M948) had disease at Dssm dermal (scrotal) sites. L060 and L132 had AFB prominently present within dermal nerves. M948 spontaneously healed, leaving a total of 2 of 10 with persisting histopathologically documentable leprosy and a third RM which failed to show AFB in biopsies in the BCG-only group. Five of the BCG-only-vaccinated group of RM transiently developed AFB-positive nasal secretions over the 331–1197 days PI period, including the 3 dermal biopsy-positive RM. By 1197 days PI, all 10 BCG-only RM were nasal secretion-negative for AFB. There were three self-trauma (st) cases: one of the 3 involved a RM (K477) with no visible signs of leprosy other than a transient nasal AFB-positivity between 561–850 days PI. It was necessary to treat only 2 of the 10 BCG-only-vaccinated RM. There were fewer biopsies taken for study in the vaccinated groups of RM because there were far fewer lesions to biopsy.

These observations show that, as of the present time PI, vaccination/boosting with BCG alone protects RM by 70% based on AFB-positive histopathology and by at least 50% based on AFB-positive or -negative histopathology and nasal secretion AFB-positivity. These degrees of protection are significant by the Fisher's exact method ($p < 0{\cdot}01$, 70%; and $p < 0{\cdot}05$, 50%) compared to 9 of 10 with persisting leprosy in the unvaccinated (positive control) group.

BCG + LD HKML AND BCG + HD HKML GROUPS

Among both of the RM groups vaccinated with BCG + LD and HD HKML, only 3 RM (K201, K282 and K629) became nasal AFB-positive during the 91–850 day period (Table 2). One of the 3 (K282) reverted to nasal-negativity by 851 days PI but continued to self-traumatize. The other 2 AFB-positive RM in these groups developed MB (K201) or neuritic MB (K629) leprosy at dermal inoculation sites. There were no cases of Dssm dermal leprosy among the 20 BCG + LD and HD HKML vaccine groups of RM. There were 6 RM in these groups with persistent st (Table 2). It was necessary to treat only 2 of the 20 RM in the BCG + HKML groups. One additional RM (K201) in these 2 groups was sacrificed due to leprosy complications and another (K705) died of acute gastric dilatation, unrelated to leprosy, to our knowledge.

Altogether, in both groups of BCG + HKML vaccinees, three of 20 RM developed persisting, documentable leprosy. Compared to 9 of 10 unvaccinated RM with persisting leprosy, there was 89% protection in the BCG + LDHKML group and 78% protection in the BCG + HDHKML group (statistically significant, $p < 0{\cdot}001$, Fisher's exact method).

Table 3. Clinical results—SMM

Days PI		210–330					331–510					511–840					841–1170				
		N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes	N-AFB	Dssm	Bx	Rx	Notes
Group I	M920	–	–	MB	–	nc, ENL, reg	–	–	PB	–	nc, reg	–	–	ND	–	spon cure	–	–	ND	–	spon cure
	M924	2+	+	MB	–	nc, prog	–	+	MB	–	reg	3+	+	PB	+	reg	1+	+	neuritic PB	+	nc, healing
	M927	4+	–	MB	–	nc, digit abs, resis	4+	+	MB	–	nc, prog	4+	+	MB	–	nc, reg	2+	+	ND	+	deform
	M930	2+	+	MB	–	nc, prog	3+	+	MB	+	nc, prog	–	+	MB	+	healing on Rx	–	+	ND	+	healing on Rx
	M931	4+	+	MB	–	nc, st, prog	4+	+	MB	+	died on d.430	N/A	N/A	N/A	+	dead	N/A	N/A	N/A	N/A	dead
	M942	–	–	MB	–	st, resis	–	–	ND	–	reg	–	–	PB	–	nc, static	–	–	PB	+	died-neoplasm
	M949	4+	+	MB	–	nc, prog	4+	+	MB	+	neuritic, prog	–	+	MB	+	healing on Rx	–	+	ND	+	healing on Rx
Group II	M919	4+	–	MB	–	reg	4+	–	ND	–	reg	3+	–	MB	–	reg	–	–	ND	+	st, NVL
	M928	4+	+	MB	–	prog, severe	4+	+	MB	+	died on d.518	N/A	N/A	N/A	+	dead, gastric Asp	N/A	N/A	N/A	+	dead
	M929	–	–	ND	–	NVL	–	–	ND	–	NVL	–	–	MB	–	prog	3+	+	MB	+	st, prog
	M933	4+	+	MB	–	nc	4+	+	MB	+	nc, prog	4+	+	MB	+	healing on Rx	–	+	ND	+	healing on Rx
	M934	2+	–	MB	–	prog	–	+	MB	–	reg	–	+	MB	+	nc, static/reg	–	+	ND	+	healing on Rx
	M935	–	–	ND	–	NVL	–	–	ND	–	st, NVL	–	–	ND	–	NVL	–	–	PB	–	st, prog
	M936	–	–	ND	–	uveitis, NVL	–	–	ND	–	NVL	–	–	ND	+	nc, uveitis	–	–	ND	+	sacrificed
Group III	M922	–	–	PB	–	nc	–	–	ND	–	nc	–	–	ND	+	NVL	–	–	ND	–	NVL
	M937	4+	+	MB	–	prog	4+	+	MB	+	prog	4+	+	MB	+	deform.	–	+	ND	+	healing on Rx
	M940	4+	+	MB	–	nc, prog	4+	+	MB	+	ENL	–	+	ND	+	healing on Rx	–	+	ND	+	healing on Rx
	M943	4+	+	MB	–	prog	4+	+	MB	+	ENL	–	+	ND	+	healing on Rx	–	+	ND	+	healing on Rx
	M946	4+	+	MB	–	prog	4+	+	MB	+	ENL	–	+	ND	+	healing on Rx	–	+	ND	+	healing on Rx
	M947	2+	+	MB	–	prog	4+	+	MB	+	prog	4+	+	MB	+	prog	–	+	ND	+	deform, healing
	M951	4+	+	MB	–	prog	4+	+	MB	–	ENL	4+	+	MB	+	prog	–	+	ND	+	healing on Rx
Group IV	M923	2+	+	MB	–	prog	–	+	ND	–	spon.healing	1+	+	PB	–	neuritic BT-TT	4+	+	ND	+	deform.
	M932	4+	+	MB	–	nc, prog	4+	+	MB	+	ENL, died	N/A	N/A	N/A	N/A	dead	N/A	N/A	N/A	N/A	dead
	M938	4+	+	MB	–	nc, prog	4+	+	MB	–	prog	2+	+	MB	+	static/prog	2+	+	ND	+	healing on Rx
	M939	3+	–	MB	–	nc, prog	4+	–	MB	–	prog	4+	+	N	+	nc, static/prog	–	+	ND	+	healing on Rx
	M948	3+	+	MB	–	prog	4+	+	MB	+	ENL	N/A	N/A	N/A	N/A	dead	N/A	N/A	N/A	N/A	dead
	M950	4+	–	MB	–	prog	4+	+	MB	–	prog	4+	+	MB	+	deform., prog	–	+	ND	+	healing on Rx
	M952	3+	+	PB	–	prog	4+	+	MB	–	static/prog	3+	+	MB	+	prog	–	+	ND	+	healing on Rx

abbreviations: absorpt, absorption; AFB acid-fast bacili; Asp, aspiration; Bx, biopsy; debil, debilitated; deform, deformities; Dssm, disseminated; ENL, erythema nodosum leprosum; MB, multibacillary; N/A, not applicable; N-AFB, nasal-acid-fast bacilli; nc, neuritic complications; ND, not done; NVL, no visible leprosy; PB, paucibacillary; prog, progressive disease; reg, regressive disease; resis, leprosy resistant; Rx, chemotherapy; sac, sacrificed; st, self-trauma; spon, spontaneous; Suscep, susceptible; SMM, sooty mangabey monkey; wt, weight.

CLINICAL OBSERVATIONS IN SMM AFTER CHALLENGE WITH LIVE ML

The clinical results for unvaccinated and the three groups of vaccinated SMM (Table 3, Figure 4) were strikingly different from those observed in RM. At dermal sites of *M. leprae* challenge, there were indurated lesions two months PI in all 21 unvaccinated (control), BCG alone and BCG + LD HKML groups of SMM; six of the seven BCG + HD HKML group had similar lesions at 2 months. Based on prior studies of experimental leprosy in SMM, it was not surprising that essentially all dermal lesions had BL–LL (MB) histopathology at this time.[13–15] These lesions are not considered to be entirely indicative of the clinical susceptibility status of the animals, but rather, due in part to the dermal inoculation of relatively high numbers of *M. leprae* locally into a species that is inherently more susceptible to MB forms of leprosy than RM.[14,15] Beginning at 4 months PI, some of the lesions began to spontaneously disappear or diminish in some animals, progress in others and disseminate to uninoculated sites (including the nasal mucosa) in many SMM (Table 3).

By 7 months (210 days) PI, lesions had cleared in 3 of the 7 BCG animals (M929, M935 and M936). Thus, we report in detail data beginning at 210 days PI, a point at which resistant SMM had begun to distinguish themselves clinically from susceptible animals. We consider the relative status of groups 210 days PI and thereafter as being relevant to and reflective of possible anti-*M. leprae* immunization/vaccination. By 210 days PI, all SMM in the unvaccinated and the BCG + HKML groups were histopathologically leprosy-positive, compared to 4 in the BCG-only vaccinated group (Figure 4). By 800 days PI, 2 additional BCG-only SMM became leprosy-positive (Figure 4), for a total of 6 leprosy-positive SMM in this group over the course of study. The details of disease progression in the SMM groups beginning at 210 days PI are as follows (Table 3).

UNVACCINATED GROUP

During the 210–330 days PI period, all 7 unvaccinated SMM had MB lesions at sites of

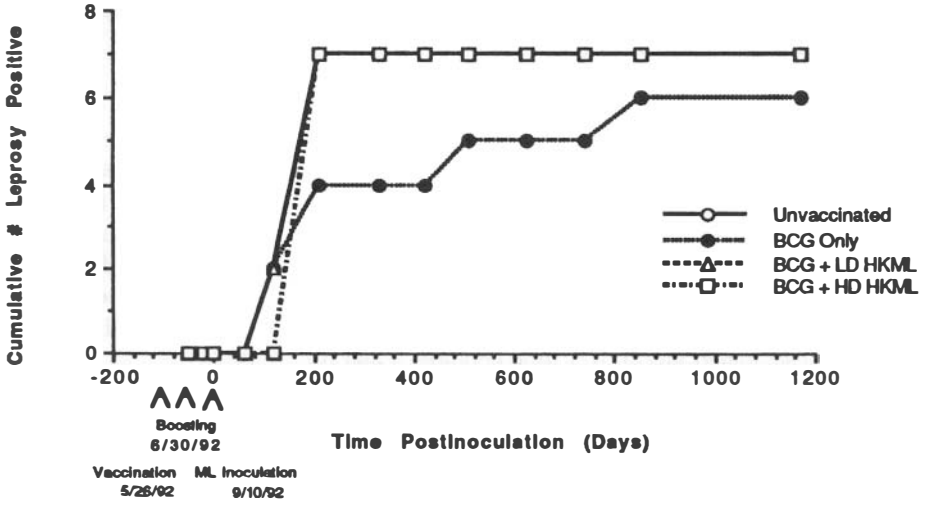

Figure 4. Cumulative number of leprosy-positive SMM, based on biopsy results using Ridley–Jopling classifications of infiltrations of AFB-positive dermal lesions, in the unvaccinated or vaccinated groups over the course of observation after live *M. leprae* challenge.

dermal inoculation, 4 had lesions at Dssm dermal sites and 5 had AFB-positive nasal secretions. Between 420 and 510 days PI, 3 of the 7 SMM in this group were placed on multidrug therapy (MDT, rifampicin, clofazimine, dapsone) due to the progression of clinical disease (Table 3; Figure 4). Eventually, over the course of observation, spanning 1170 days, 6 of the unvaccinated group were treated due to Dssm or localized (M942) leprosy and one spontaneously cured (M920). M931 died on day 430 PI, one day after MDT initiation, presumably due to the severity of the disease. M942 developed a liver neoplasm at near 1170 days PI and was humanely sacrificed.

Altogether, six unvaccinated SMM developed neuritic complications (nc) such as nerve edema or physical deformities, along with other persisting symptoms of leprosy; 5 developed *M. leprae* disease and one developed PB leprosy (M942) (the 7th SMM, M920, developed the only case of ENL in this group, during the 210–330 days PI period and subsequently spontaneously healed of all leprosy signs).

BCG ONLY GROUP

The disease progression in the BCG group was slower in that, during the 210–330 days PI period, lesions were smaller, less numerous and 4 BCG-vaccinated SMM had MB leprosy (2 with Dssm dermal leprosy together with AFB-positive nasal smears) (Table 3; Figure 4). This approached significance (Fisher's exact method, $p = 0{\cdot}09$) compared to 7 cases of *M. leprae* leprosy (4 Dssm and AFB-positive nasal secretions) in the unvaccinated group during the 210–330 days PI period (Table 3). During the 331–510 days PI period, 2 BCG-only vaccinated SMM (M928 & M933) were placed on chemotherapy (Table 3). M928 died soon thereafter due to leprosy. During the 841–1170 days PI period, M935 newly-developed PB leprosy at sites of ML inoculation resulting in the loss of statistical significance relative to the control group. By 1170 days PI, there were 5 MB cases, one PB case and one SMM (M936) with little or no visible leprosy (NVL) except uveitis, requiring chemotherapy. M928 died of causes unrelated to leprosy approximately six months after the initiation of treatment.

There were 3 SMM with nc and no SMM with ENL in the BCG-only vaccinated group of SMM (M933, M934 & M936) (Table 3).

BCG + LD HKML GROUP

During the period of 210–330 days PI, 6 SMM in this group were positive for Dssm MB leprosy and one for PB leprosy at dermal inoculation sites (M922). All but the PB case were nasal secretion-positive for AFB (Table 3). The PB case went on to spontaneously heal. The other 6 were successfully placed on chemotherapy by 840 days due to the rapid progression, continued Dssm and exacerbation of the clinical symptoms. The number and severity of the lesions became significantly greater ($p < 0{\cdot}05$, Mancova) in the BCG + LD HKML group than in the unvaccinated group over time (Figures 5 and 6).

Two cases of nc were observed in this group of SMM over the course of this study; four cases of ENL (M940, M943, M946 and M951) were observed by 510 days PI.

BCG + HD HKML GROUP

All seven SMM in the BCG + HD HKML group were nasal-positive for AFB between 210 and 330 days PI and all were histopathologically positive for dermal leprosy (6 MB and 1

PB). All but one SMM (M939) showed Dssm by 510 days PI. By the 841–1170 days PI interval, all 7 SMM in the BCG + HD HKLM group had developed Dssm lesions; 4 of the 7 HD HKML group had developed physical signs of nc. Before 840 days PI, all 7 BCG + HD HKML SMM were either on chemotherapy or (two) had died secondary to ENL episodes (Table 3).

Similar to the BCG + LD HKML group, leprosy progressed much more rapidly and, with time, became visibly more severe in the BCG + HD HKML group than in the unvaccinated group (Figures 5 and 6). The average number of lesions per monkey was greatest in the unvaccinated, control SMM group over a period of 100–450 days PI (Figure 5). Thereafter, the average number of lesions spontaneously decreased in the unvaccinated group while the number of lesions continued to increase significantly in the BCG + HKML groups of SMM over the ensuing 300 days of observation (Figure 5). Over the first 200 days PI, the average lesion size was similar in all 4 groups of SMM; by 310 days PI, the average lesion size was greatest in the control group, but continued to increase in the BCG + HKML groups; and by 720 days PI, the average lesion size was significantly greatest ($p < 0{\cdot}05$, Mancova) in the BCG + HKML groups and had diminished in the unvaccinated and the BCG only groups (Figure 6). The BCG-only group maintained essentially the lowest average number of lesions and the lowest average lesion size over the course of our observations, but there was no statistical significance (Figures 5 and 6).

PHENOLIC GLYCOLIPID-I ANTIGEN LEVELS IN SERA OF VACCINATED AND UNVACCINATED RM AND SMM

There was no detectable PGL-I antigen found in sera from any of the RM in this study (data not shown). Readily detectable levels of PGL-I antigen were found in sera of the four groups of SMM (Figure 7). Compared to the unvaccinated group, PGL-I antigen levels reached

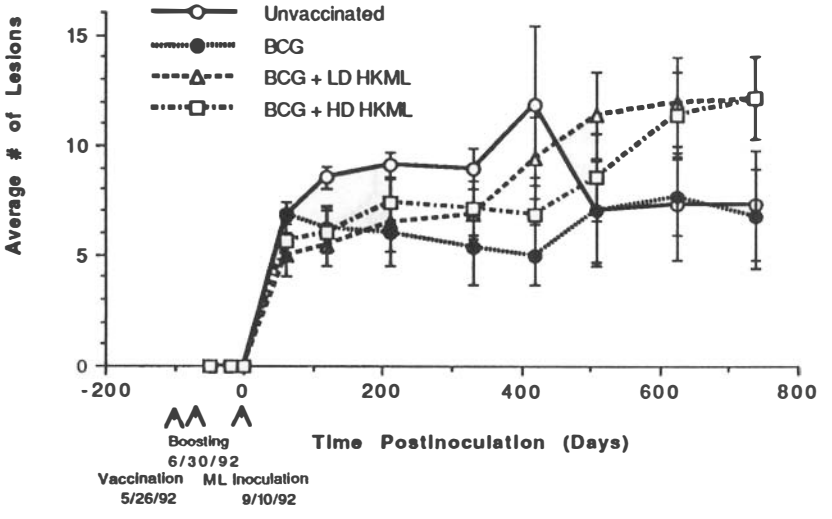

Figure 5. Average number of lesions (+/− 1 SEM) observed longitudinally after challenge of SMM groups with live *M. leprae*.

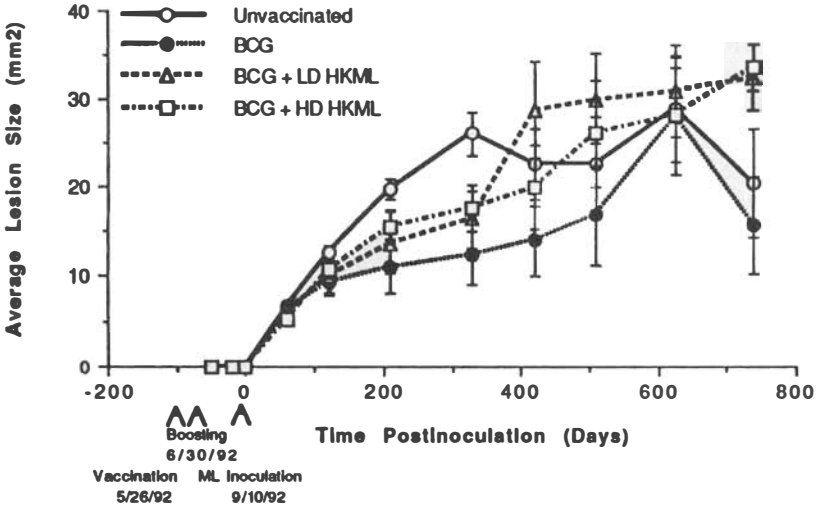

Figure 6. Average lesion size (+/− 1 SEM) observed longitudinally after challenge of SMM groups with live *M. leprae*.

statistically significant higher maximal levels ($p < 0{\cdot}0025$, Mancova) in the SMM BCG + LD HKML group, but not in the BCG + HD HKML group; the PGL-I levels rose more slowly and attained lower maximal levels in the BCG only group, but was not significantly different from controls.

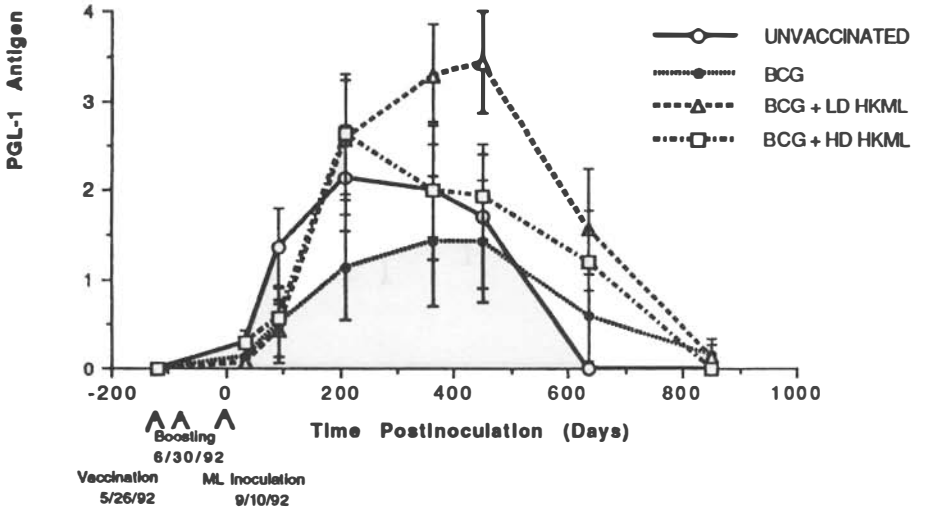

Figure 7. Average PGL-I antigen levels (+/− 1 SEM) in serum samples obtained longitudinally prior to vaccination, after vaccination, after boosting and at intervals after challenge with live *M. leprae* in SMM groups.

Discussion

The vaccination results in RM, which, as a species, generally develop PB forms of leprosy in approximately 80% of cases, show that BCG alone offers 70% protection of RM against clinical leprosy, based on lesion bioposy histopathologic results spanning 3·5 years after challenge with live *M. leprae*. A total of 3 of the 10 BCG-only-vaccinated RM had biopsy-documentable leprosy and another had mononuclear cell infiltration, but no AFB were present. Five of the 10 BCG-only-vaccinated RM, including the 3 biopsy-positives, had transient episodes of AFB-positivity in nasal secretions. In the SMM species, which generally develop MB forms of leprosy in over 80% of cases,[12–15,18,22,24] however, the results show that there is no statistically significant decrease in the total numbers of SMM with sustained histopathologically-documentable leprosy in the long term (approximately 3·5 years) with BCG alone. SMM vaccinated with BCG alone developed disease more slowly with fewer and smaller lesions. There was a lowered PGL-I antigen level in the serum of SMM in the BCG-vaccinated group over most of the time of observation, consistent with a presumably lowered bacterial burden, but this was not statistically significant compared to unvaccinated controls.

We used the same mixtures of batches of BCG, all of the Glaxo strain, to vaccinate both the RM and SMM; similar numbers of live ML with similar MI's were used to challenge both the RM and SMM; the inocula were from the same original source and each ML batch had been subpassaged from the same SMM through an armadillo for monkey inoculations. The major obvious difference between the RM and SMM study was the monkey species. In view of the close phylogenetic and immunologic similarities between RM, SMM and humans, the results strongly suggest that the ability of BCG to protect populations against clinical leprosy depends on the susceptibility of a given population to MB *vs* PB leprosy, which is known to vary among humans geographically. Thus, the data offer at least one explanation for variations in previous studies of antileprosy protective effects of BCG vaccination.[1,3–5,25] The prior studies in Uganda, Burma, New Guinea, south India and Malaŵi showed a variation from 20 to 80% protection by BCG alone. The majority of leprosy cases in those regions are non-lepromatous forms, but the exact make-up of clinical populations and the natural histories of disease and ratios of types of disease vary from one region to the other.[6] A human study in southern Viet Nam, where there is a variable range of 30–70% lepromatous cases, depending on the region, concluded that BCG offered protection against non-lepromatous leprosy but had no protective effect against lepromatous leprosy.[7] Our results are consistent with those conclusions, but suggest that the speed of progression of symptoms and the severity or degree of disease symptoms may be lessened in MB-prone patients by vaccination with BCG alone. At any rate, the data herein suggest that BCG alone is statistically effective in protection of many individuals from leprosy and is safe to use as a vaccine; at worst BCG may provide little or no protection against leprosy in some individual recipients. BCG has been convincingly shown to protect human populations in Malaŵi[6,25] and elsewhere.[1–5,7]

The protective efficacy of BCG alone as a vaccine was enhanced in RM by the addition of HKML together with BCG. A recent follow-up report from Malaŵi showed a reduced risk of leprosy in humans under the age of 15 vaccinated with BCG + killed *M. leprae* compared to BCG alone, but overall, in all age groups, there was no improved benefit by the addition of killed *M. leprae* to the effective BCG vaccine.

Contrary to the RM results, vaccination of MB leprosy-prone SMM with BCG + HKML caused the disease to become more severe clinically and increased the rate and degree of

progress to the point of threatening the lives of the animals if not quickly placed on chemotherapy at the outset of observed dissemination and progressive clinical symptoms. Serum PGL-I levels are presumably proportional to the bacterial load;[12,23] significantly higher PGL-I levels in the SMM BCG + LD HKML group and lower levels (not statistically significant) in the BCG only group compared to controls are, therefore, consistent with the clinical observations indicating that BCG + LD HKML renders SMM more susceptible to the progression of the disease and BCG alone may at least slow the progression and/or degree of MB disease in SMM. Compared to the unvaccinated group, PGL-I levels in the BCG + HD HKML-vaccinated SMM failed to significantly correlate with the clinically observed increased susceptibility to LL leprosy in that group, contrary to expectations. These observations suggest that the immune mechanisms of leprosy susceptibility are complex, that immune responses to vaccination are dose-dependent and do not necessarily directly correlate proportionately with effects on clinical leprosy susceptibility. The absence of detectable levels of PGL-I antigen in the sera of RM from unvaccinated or vaccinated groups is consistent with our clinical observations that RM, as a species, are more resistant than SMM to MB forms of leprosy.

The results suggest that caution should be exercised in the use of HKML in BCG vaccine preparations for use in human populations since it is not possible to determine *a priori* which humans will be susceptible to MB *vs* PB forms of leprosy. In consideration of our observations and of the demonstrated failure of killed *M. leprae* to add significantly to BCG's protective efficacy in humans,[2] it appears prudent to avoid the use of killed *M. leprae* altogether in BCG vaccines.

We do not yet know an exact explanation for the opposing results in RM *vs* SMM in protective ability of HKML together with BCG other than the species difference in susceptibility towards PB *vs* MB forms of leprosy. Comparative longitudinal immunologic studies on these RM and SMM have provided some clues, however, as to some aspects of the immune mechanisms involved in the differences we have observed and will be reported elsewhere (Gormus, BJ *et al*, p. 24).

Acknowledgments

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Impaired responses to *Mycobacterium Leprae* antigens in rhesus monkeys experimentally inoculated with simian immunodeficiency virus and *M. leprae*

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Summary Seven of eight rhesus monkeys (RM) coinfected with simian immunodeficiency virus (SIV) and *Mycobacterium leprae* harboured acid-fast bacilli (AFB) at sites of dermal inoculation and/or at disseminated sites at times of humane sacrifice (up to 270 days post-*M. leprae* inoculation) due to SIV-induced debilitation or, in one long term survivor's case, to date over 3 years post-*M. leprae* inoculation. Detectable AFB were cleared in biopsies of inoculation sites of RM inoculated with *M. leprae* alone after 63 days postinoculation; these sites have, so far, remained AFB-negative, thereafter.

Compared to animals infected with *M. leprae* alone, RM coinfected with SIV plus *M. leprae* showed: 1, completely suppressed serum antibody responses to *M. leprae*-specific PGL-I antigen, but strong anti-SIV Gp120 antibody responses; 2, impaired sensitization of blood mononuclear cells (MNC) to *in vitro* recognition of *M. leprae*-specific antigens in blastogenic stimulation assays; 3, impaired *in vitro* responses of blood MNC to nonspecific (ConA) blastogenic stimuli; and 4, early post-*M. leprae* inoculation, there was a significant incremental diminution of percentages of blood CD4+CD29+ T-cells in addition to the existing SIV-induced diminished percentages of CD4+CD29+ T-cells.

The results indicate that humoral and cellular immune responses to *M. leprae* antigens are compromised in *M. leprae*-inoculated RM previously infected with SIV. These results provide an immunologic basis for the demonstration of enhanced *M. leprae* persistence or leprosy susceptibility in SIV-*M. leprae* coinfected RM.

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Introduction

It is well established that human immunodeficiency virus (HIV)-positive patients are rendered more susceptible than virus-negative persons to secondary infections with *Mycobacterium tuberculosis*[1–3] and other opportunistic infectious agents. SIV is very similar to HIV-2 and causes AIDS in RM with fatal symptoms and sequelae essentially identical to AIDS in humans, e.g. lymphadenopathy, diarrhoea, destruction of CD4+ T-cells, a decreased blood MNC CD4:CD8 ratio, and increased susceptibility to lymphomas and opportunistic infections.[4–8]

We reported that RM infected with both SIV and *M. leprae* are more susceptible to clinical leprosy than RM infected with *M. leprae* alone.[4,5] This observation led us to predict an increase in the incidence of leprosy worldwide, secondary to the AIDS pandemic.[4] This prediction has not been consistently confirmed to date, however, for unknown reasons.[9–14] Data from one field study was consistent with our observation of an increased risk of leprosy in HIV-positive individuals, finding a 4·6-odds ratio in increased multibacillary (MB) leprosy risk (and 8·3 for tuberculosis risk) among HIV-positive patients in Tanzania.[9] Other reports failed to find a significant association in the aggregate populations studied,[10–14] but two of these studies found a significantly increased leprosy relapse rate among HIV-positive African leprosy patients after completion of antileprosy chemotherapy.[10,14] Another study showed diminished blastogenic and skin test responses to *M. leprae* antigens among HIV-positive tuberculoid leprosy patients, consistent with the possibility of increased leprosy risk.[12]

The controversial nature of the reported studies suggests that subtle, undetected factors could be disguising the true relationship between AIDS and leprosy in the reported epidemiological studies. Our observations are based on direct disease signs and immunologic determinations in a controlled experimental model system,[4,5] whereas observations in humans are correlative, based on the presence or absence of antibody to HIV in identifiable leprosy patients.[9–14] In the present study, we have utilized this model to further study the possibility of clinical and immunologic interactions between SIV and *M. leprae*. The results are consistent with increased *M. leprae* persistence and probable enhanced leprosy susceptibility due to impaired immune responses to *M. leprae* in SIV-coinfected RM compared to those infected with *M. leprae* alone.

Methods

ANIMALS

Rhesus monkeys (*Macaca mulatta*), 3–4 years old, were born and reared at the Tulane Regional Primate Research Center. Eight RM which had been inoculated with SIV 8–10 months previously and four normal control RM were inoculated with *M. leprae*. At the time of *M. leprae* inoculation, 3 of the 8 SIV-inoculated RM were showing acute AIDS symptoms (L156, J314, and I510, Table 1); the remaining 5 RM were negative for AIDS symptoms. All RM were clinically and immunologically followed longitudinally after *M. leprae* inoculation.

INOCULATIONS

An armadillo previously inoculated with *M. leprae* taken from a sooty mangabey money (SMM) developed progressive, disseminated lepromatous leprosy and was humanely killed.

Table 1. Clinical results of SIV/*M. leprae* coinfected RM

Coinfected RM*	Histopath DX†	Days PI‡	SAIDS Status§
L156	PB	16	+
M368	MB	49	+
J717	PB	19	+
J314	MB¶	270	+
I510	MB¶	160	−**
I877	−	118	+
J703	PB	119	+
J798	MB¶	146	+

* Coinfected RM received SIV 8–10 months prior to *M. leprae*.

† Histopath DX = histopathological diagnosis (PB, paucibacillary; MB, multibacillary) at necropsy (except for J798, which remains alive).

‡ Days PI, number of days after *M. leprae*-inoculation that the animal was euthanized (except for J798—which first was observed to have AFB-positive nasal secretions and inoculation site biopsies on day 146 and continues nasal-positive on day 1137).

§ AIDS status at time of necropsy (except J798 which developed AIDS symptoms approximately 3 years post-*M. leprae* inoculation and is alive).

¶ RM J314, I510 and J798 had nasal secretions strongly positive for acid-fast bacilli (AFB), indicating systemic dissemination of leprosy.

** I510 was euthanized on day 160 PI due to complications secondary to an unrelated condition; I510 had AFB at dermal sites of inoculation with MB histopathology and had AFB-positive nasal secretions, but was had no evidence of AIDS at necropsy.

M. leprae was harvested from its spleen. All armadillo procedures, including inoculation, husbandry and organ harvests were performed by Dr Richard B Truman at the Research Branch, National Hansen's Disease Center, Baton Rouge, LA, USA. Contaminating SIV from SMM does not cause detectable AIDS symptoms in and does not survive passage through armadillos (Gormus, BJ, Murphey-Corb, M., unpublished observations). The spleen was obtained aseptically, minced and homogenized in cold phosphate buffered saline using a Dounce homogenizer with a 40 Ml mortar and Teflon pestle (Wheaton Scientific, Millville, NJ, USA), passed through gauze and centrifuged at $200 \times G$ for 5 min at 4°C. The AFB in the supernatant were counted and morphologic indices (MI) determined by the method of Shepard & McCrae.[15] RM were inoculated with *M. leprae* suspensions by combined intradermal (ID) and intravenous (IV) routes using 2 ID sites per ear, the tip of the nose, lateral forearms and lateral calves. IV inoculations were made via the saphenous vein. The inoculum contained $2{\cdot}24 \times 10^8$ AFB/Ml with an MI of 7%. A total of 1·5 Ml ($3{\cdot}4 \times 10^8$ AFB) was inoculated by the ID route and 2·0 Ml ($4{\cdot}5 \times 10^8$ AFB) by the IV route, for a total of $7{\cdot}8 \times 10^8$ ($5{\cdot}5 \times 10^7$ solidly staining) AFB/RM.

SIV_{Delta} B670 at the standard (5×10^{-3}) dilution was thawed and inoculated IV via the saphenous vein, as previously reported.[4,16]

CLINICAL OBSERVATIONS

Animals were observed twice daily and examined in detail monthly or more frequently, depending on the status of the animal. Clinical aspects of AIDS and leprosy were recorded at each time of observation. The Ridley–Jopling system was used to classify leprosy histopathologically,[17] with the exception that classification at the paucibacillary (PB) end of the spectrum differs slightly in RM from humans, as previously noted (Gormus BJ, *et al*, submitted for publication). For purposes of this report, however, leprosy will be described as multibacillary (MB) or PB. MB will include borderline to lepromatous forms on the Ridley–Jopling spectrum;[17] PB includes tuberculoid to borderline tuberculoid forms. AIDS was diagnosed as previously described.[5–8]

ELISA

The assays were performed as previously reported.[4,16,18] Baseline sera were obtained prior to *M. leprae* or SIV inoculations and at intervals after inoculations and were stored frozen for later ELISA evaluations of *M. leprae*-specific anti-PGL-I IgG and IgM[4,18] and for SIV anti-Gp120 antibodies.[4,16] Natural ML PGL-I was used as antigen (Ag). PGL-I was provided by Dr Patrick J. Brennan, Colorado State University School of Veterinary Medicine, Fort Collins, CO, USA under NIH contract #1-AI-52582. Anti-PGL-I results are presented for individual monkeys as OD_{490} *vs* time. Anti-Gp120 was assessed by examining serial 2-fold dilutions from 1:50 to 1:25,600, together with known standard positive and negative sera, as previously reported.[4,16] Individual RM results from the first four dilutions (1:50–1:400) of anti-Gp120 antibody ELISA's are presented as OD_{590} *vs* time. Gp120 antigen for ELISA was a recombinant product provided by Dr Ronald Montelero, Department of Microbiology, University of Pittsburgh School of Medicine, USA.

BLASTOGENESIS

Heparinized blood was used to prepare buffy coats which were centrifuged on Ficoll/Hypaque, washed and suspended in RPMI-1640 containing 20% heat-inactivated human AB serum (HuABS), glutamine and penicillin/streptomycin. The mononuclear cell (MNC) fraction was used at 2×10^6/Ml for *in vitro* blastogenesis studies with or without 100 μg/Ml of ML sonicate antigen (MLS) or 1 or 10 μg/Ml of Concanavalin A (ConA). U-bottom 96-well microtiter plates were used. Two $\times 10^5$ MNC per well were incubated at 37°C in 5% CO_2 in triplicate for 5 days with stimulant or media prior to pulsing for 18 hr with 1 μci of ^{3}H-thymidine/well. Thereafter, cells were washed and harvested on a cell-harvester and quantified by scintillation counting. Results are presented as means +/− one standard deviation (SD) of replicate absolute cpm.

PERIPHERAL BLOOD LYMPHOCYTE (PBL) SUBSETS

Whole EDTA blood was obtained longitudinally, stained with mouse anti-human monoclonal antibodies and examined by flow cytometry, as previously reported.[19,20] Monoclonal antibodies with the following specificities were used: CD4, CD8, CD2, CD20 and CD29. CD2 and CD20 subsets were chosen to quantify the total T- and B-cells, respectively; CD4 and CD8 were examined to determine the T-helper and T-suppressor percentages, respectively, since these cells are known to be involved in responses to *M. leprae* antigens;

and the CD4+CD29+ subset was monitored because this group contains the T-helper inducer and T-memory cells and is known to be progressively diminished in RM with advancing AIDS.[19] Results are presented as the group mean % of total PBL at different time points + or −1 standard error of the mean (SEM) *vs* time.

SIV ANTIGENEMIA ASSAY

SIV antigenemia was detected using a commercially available enzyme-linked immunoassay kit specific for the p26 antigen of SIV (Coulter Immunology, Hialeah, FL), as previously reported.[20] The cut-off point for antigenemia was an OD value <0·03. Data from individual RM are plotted as Ng/Ml of blood calculated from a standard curve.

STATISTICAL ANALYSES

A statistical package for Macintosh computer was utilized for data analysis. Mancova was used where possible to compare longitudinally-determined lymphocyte subset percentage changes with time after *M. leprae* inoculation in RM groups infected with *M. leprae* alone or together with SIV. Mancova was made difficult for longitudinal comparisons over an extended period, however, due to the deaths of some RM at various time points, resulting in the complete elimination by the statistic of all prior time points for that animal (i.e. total loss of one value of N at all time points) for each death that occurred prior to the end of the study. Therefore, the unpaired Student's *t*-test was additionally used for PBL subset data analysis to statistically compared group averages. The *t*-test was also used for analysis of blastogenic data.

Results

CLINICAL

Seven of the 8 SIV/ML coinfected group were euthanized due to AIDS or, in the case of animal I510 due to unrelated causes, within 270 days postinoculation (PI) with ML (Table 1). Six of the 7 euthanized AIDS-positive RM (L156, M368, J717, J314, I510 and J703) had AFB-positive lesions at necropsy, consistent with leprosy or *M. leprae* persistence at dermal inoculation sites. The 7th euthanized, AIDS-positive RM (I877) had MNC infiltration and nerve involvement at inoculation sites but no readily identifiable AFB were seen. The 8th RM in the coinfected group (J798) developed persistent AFB-positive nasal secretions by 146 days post-*M. leprae* inoculation, indicative of leprosy dissemination. J798 remains alive with strongly AFB-positive nasal secretions and chronic AIDS more than 3 years PI (Table 1). At necropsy, two of the euthanized coinfected RM (J314 and I510) had AFB-positive inoculation sites as well as AFB-positive nasal secretions, indicative of disseminated leprosy (Table 1). Thus, 7 of the 8 coinfected RM had signs of possible leprosy or AFB persistence at inoculation sites, 3 of the 8 having disseminated leprosy, within 270 days PI. Among the 4 control RM which received only *M. leprae*, 2 (J446 and M361) had identifiable AFB (PB histopathology) at dermal inoculation sites at 27 and 63 days PI; the other 2 RM (J675 and J265) had PB histopathology at day 27 PI. The lesions regressed after day 27 in J675 and J265 and after 63 days in J446 and M361; there has been no further evidence of *M. leprae* persistence in any of the 4 control RM to date 1137 days PI.

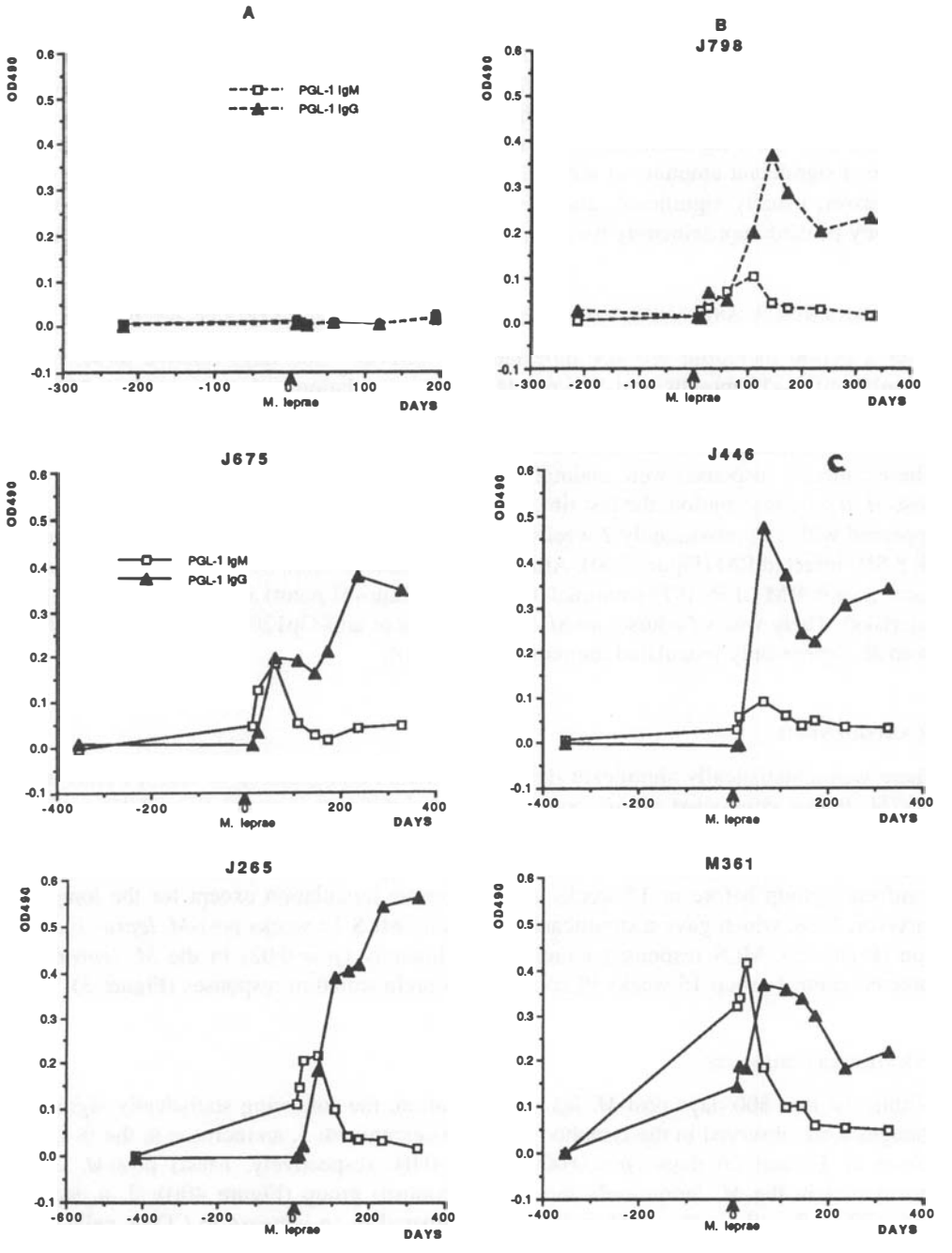


Figure 1. Longitudinal serum IgG and IgM anti-PGL-1 responses in 8 SIV-*M. leprae* coinfected RM ((a) & (b)) and 4 *M. leprae*-infected control RM (c). The mean +/− one standard error of the mean (SEM) of seven of the coinfected RM are shown in (a); the data for coinfected, long-term survivor RM, J798, is plotted separately (b) from the remaining 7 coinfected RM to emphasize its similarity to the 4 *M. leprae*-only infected controls (c). The *X*-axis is in reference to the time of *M. leprae* inoculation. The earliest time point is post-SIV inoculation. Time 0 represents the day of *M. leprae* inoculation.

ANTIBODY RESPONSES TO *M. LEPRAE*-SPECIFIC PGL-I ANTIGEN

With the exception of J798, over a period of observation spanning approximately 1 year post-*M. leprae* inoculation, none of the 8 SIV/*M. leprae* coinfected group produced any significant serum IgG or IgM antibody response to the ML-specific PGL-I cell-wall antigen (Figures 1(a) and (b)). J798, a long term survivor, and all 4 *M· leprae*-only inoculated (control) RM produced significant amounts of anti-PGL-I antibody, the IgG isotype predominating along with lesser, usually significant, quantities of the IgM isotype (Figure 1(b) and (c)). IgG antibody peaked approximately between 100 and 150 days post-*M. leprae* inoculation.

SIV ANTIGENEMIA AND ANTIBODY RESPONSES TO SIV GP120 ENVELOPE ANTIGEN

Over a period including pre-SIV inoculation (−232 to −300 days relative to *M. leprae* inoculation), 8–10 months post-SIV/pre-*M. leprae* inoculation and up to death or 235 days post-*M. leprae* inoculation, anti-Gp120 responses were significant in all SIV-inoculated RM after the appearance of SIV antigenemia (Figure 2(a)). Only the 1:50 dilution-data are shown. These antibody responses were maintained until death or, in J314 and J798, up to 235 days post-*M. leprae* inoculation, the last time point studied. The first detectable antigenemia peak appeared within approximately 2 weeks post-SIV inoculation, but disappeared thereafter, in all 8 SIV infected RM (Figure 2(a)). After *M. leprae* inoculatiion, SIV antigenemia was again detectable in RM L156, I877 (minimal, but above the cut-off point) and J703 (Figure 2(a), see asterisks). There was, of course, no SIV antigenemia or anti-Gp120 response in control sera from *M. leprae*-only inoculated animals (Figure 2(b)).

BLASTOGENESIS

There was a statistically significant decrease in ConA responses ($p = \cdot 0015$, *t*-test) in the SIV/*M· leprae* coinfected group, compared to a significant increase ($p = 0{\cdot}01$) in ConA responses in the *M. leprae*-only inoculated group pre- *vs* 15 weeks post-*M. leprae* inoculation (Figure 3). There were no statistically significant responses to MLS in the ISV/*M. leprae* coinfected group before or 15 weeks after *M. leprae* inoculation except for the long-term survivor, J798, which gave a significant response to MLS 15 weeks post-*M. leprae* inoculation (Figure 3). MLS responses increased significantly ($p = 0{\cdot}02$) in the *M. leprae*-only infected control group 15 weeks PI compared to preinoculation responses (Figure 3).

LYMPHOCYTE SUBSETS

Within the first 300 days post-*M. leprae* inoculation, the following statistically significant changes were observed in the lymphocyte subsets examined: 1, an increase in the % CD2+ subset at 13 and 26 days ($p = 0{\cdot}009$ & $p = 0{\cdot}04$, respectively, *t*-test) post-*M. leprae* inoculation in the *M. leprae*-only inoculated (control) group (Figure 4(a)); 2, a decrease in % CD4+ T-cells in the coinfected group compared to an increase in CD4+ cells in the *M. leprae*-only inoculated group during the first 109 days post-*M. leprae* inoculation time period ($p = 0{\cdot}007$, Mancova) (Figure 4(b)); and 3, there was a significant incremental decrease in the already depleted CD29+ subset of CD4+ T cells during the 62 days post-*M. leprae* inoculation period in the SIV/*M. leprae* coinfected group, compared to the *M. leprae*-only inoculated group over the same time period ($p = 0{\cdot}0496$, Mancova) (Figure

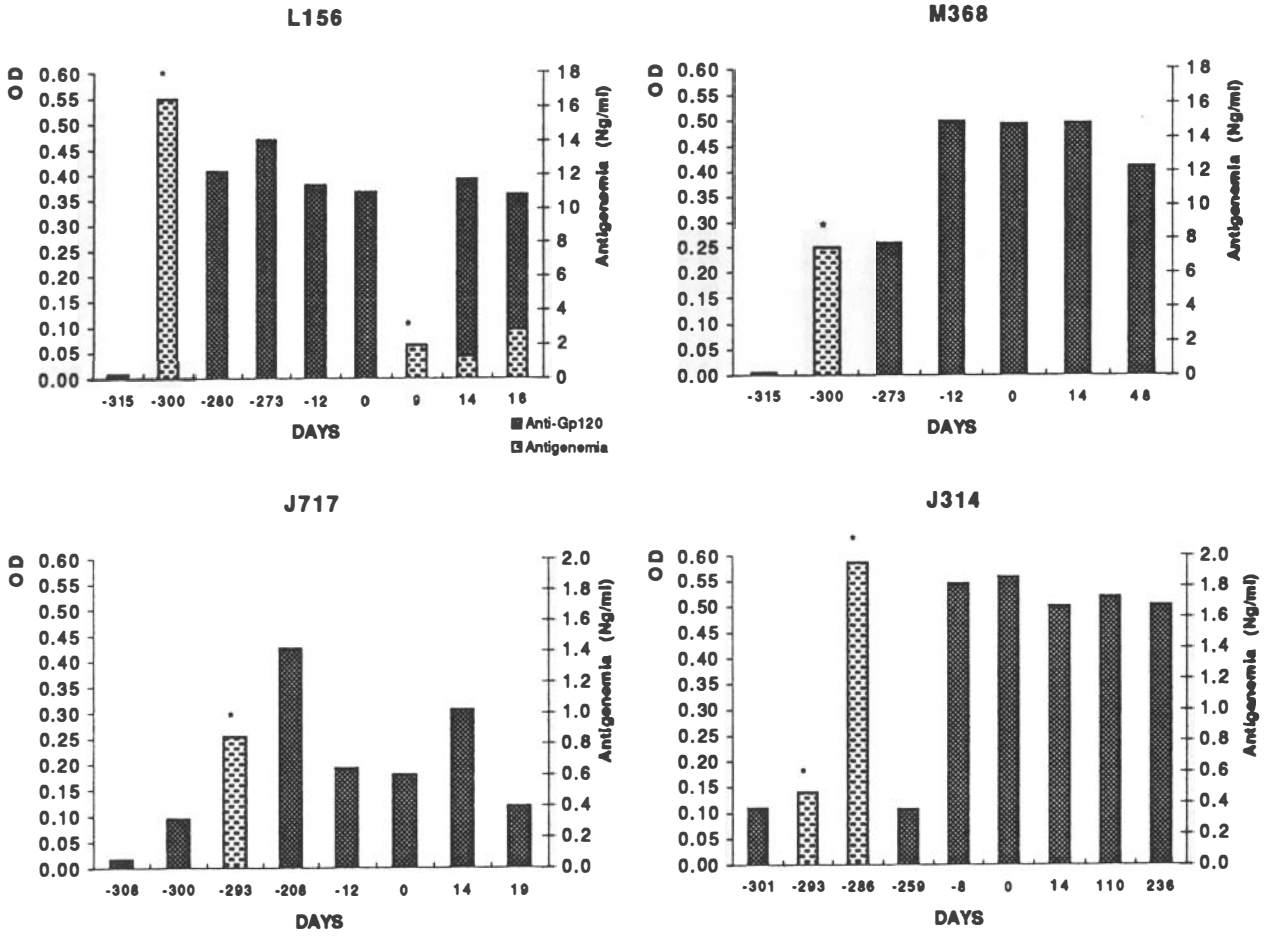


Figure 2. Longitudinal serum antibody responses (1:50 dilution) to SIV envelope antigen Gp120 and SIV antigenemia in 8 SIV-*M. leprae* coinfected RM (a) and 4 *M. leprae*-infected control RM (b). The earliest time points (−230 to −316 days) are pre-SIV inoculation in coinfected RM. Time 0 represents *M. leprae* inoculation. Asterisks show SIV antigenemia results at time points where no anti-Gp120 ELISA's were done.

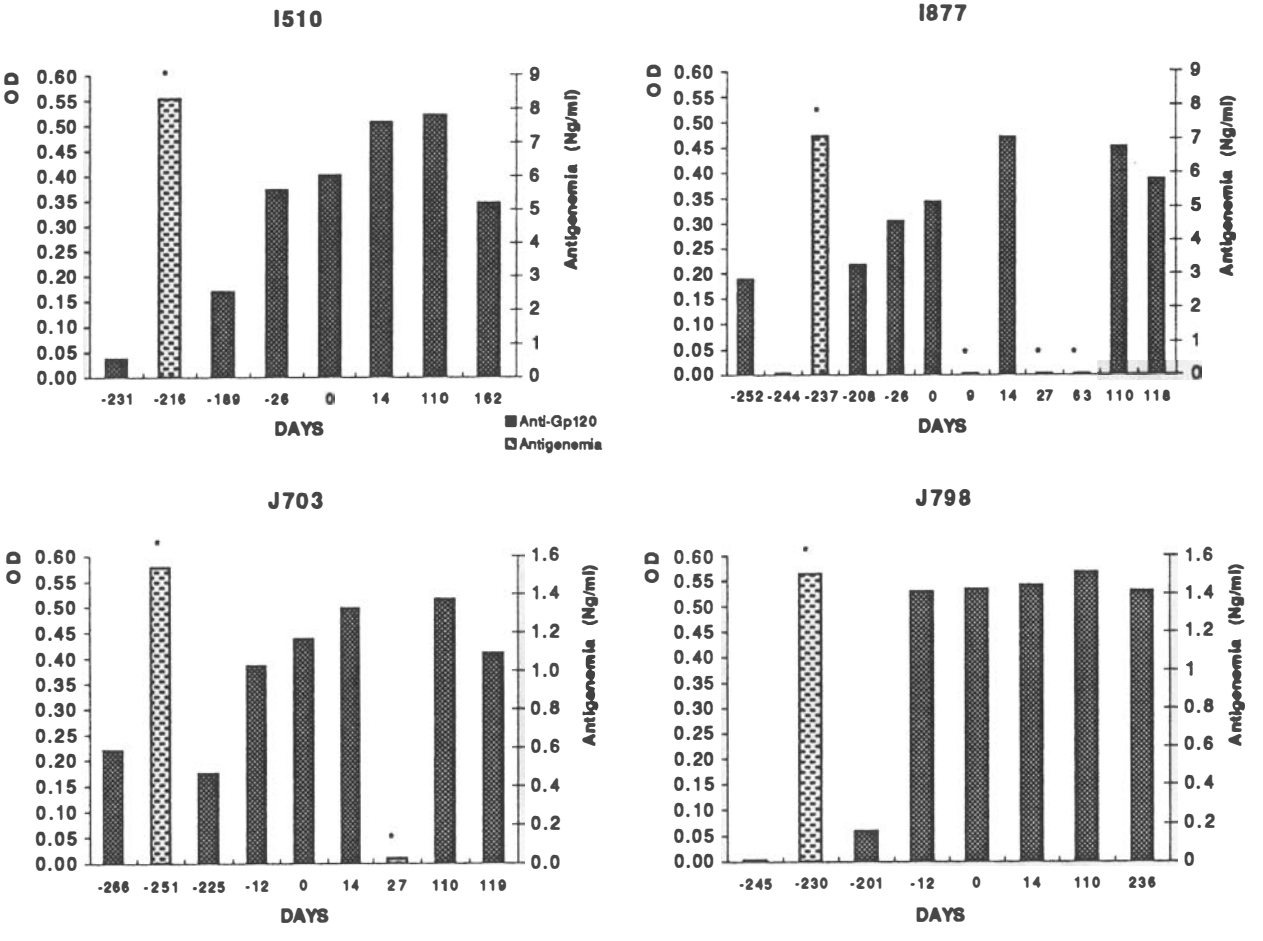
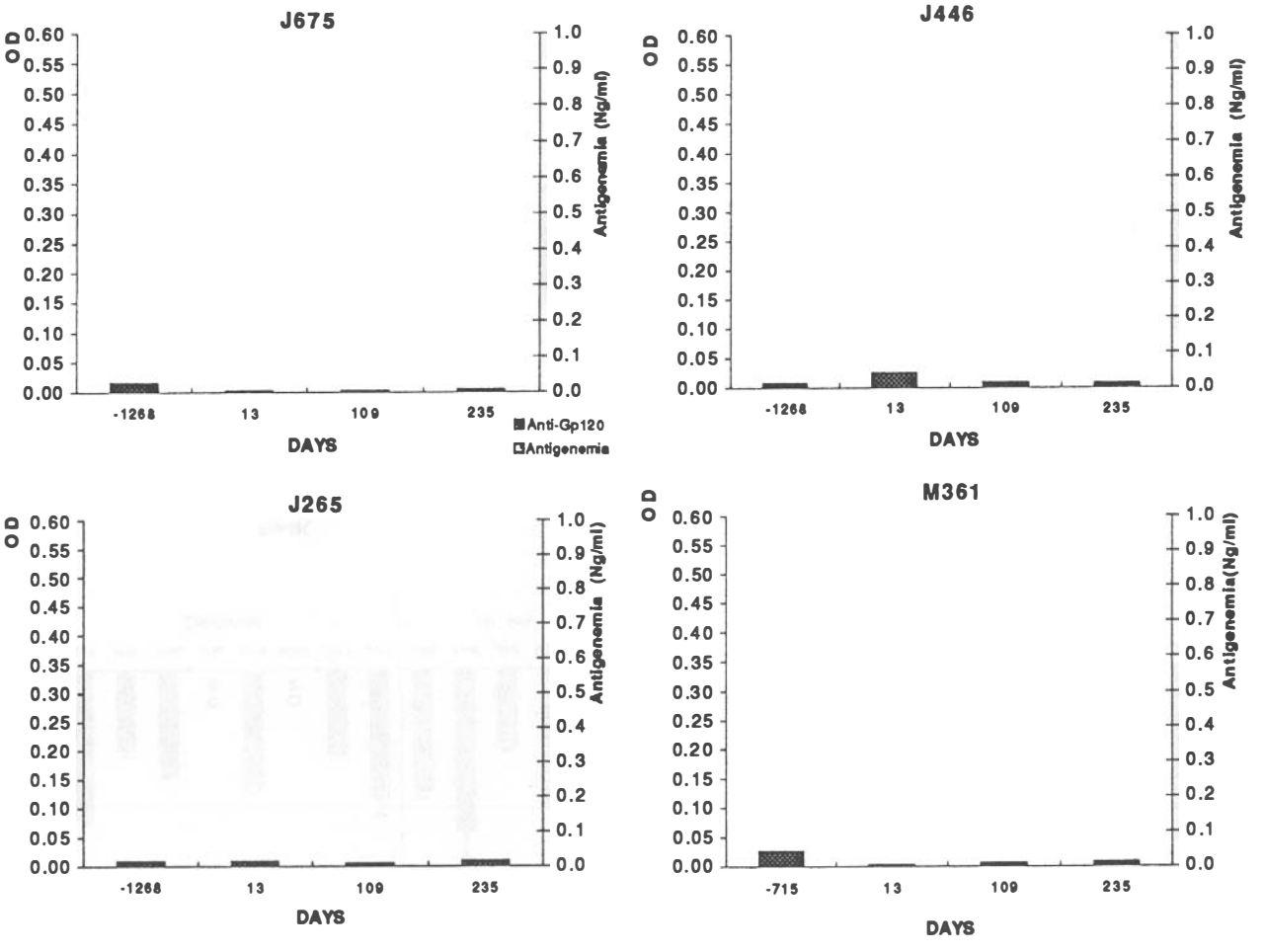


Figure 2a continued


J675
OD
Antigenemia (Ng/ml)
-1268
13
109
235
DAYS
Anti-Gp120
Antigenemia
J446
OD
Antigenemia (Ng/ml)
-1268
13
109
235
DAYS
J265
OD
Antigenemia (Ng/ml)
-1268
13
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235
DAYS
M361
OD
Antigenemia(Ng/ml)
-715
13
109
235
DAYS

Figure 2b

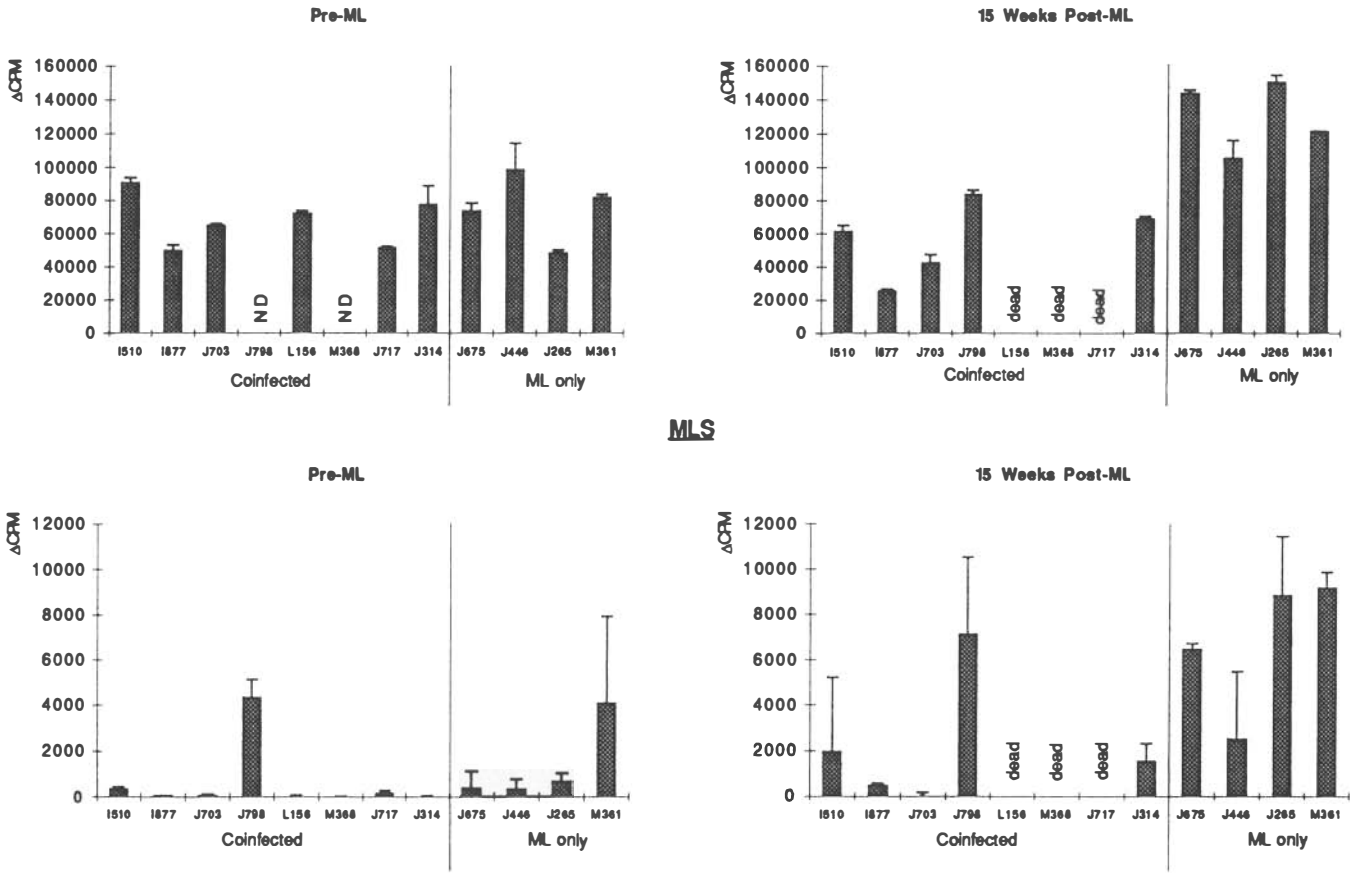

Figure 3. *In vitro* blastogenic responses to ConA (upper) and to MLS antigens (lower) in 8 SIV-*M. leprae* coinfected RM (left panels) and 4 *M. leprae*-infected control RM (right panels). The mean cpm +/− 1 standard deviation of the mean are shown for triplicate wells containing antigen or mitogen after subtraction of media-only controls.

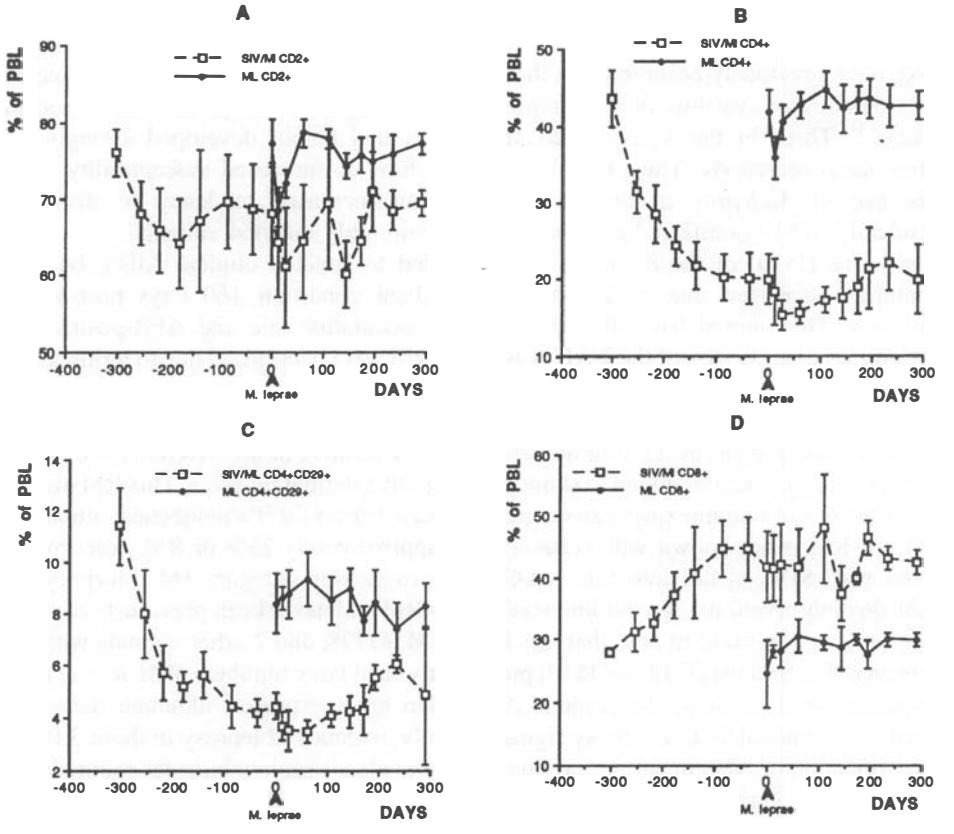

Figure 4. Longitudinal PBL subset analysis (mean +/− 1 SEM) by flow cytometry of CD2+ (a), CD4+ (b), CD4+ CD29+ (c) and CD8+ (d) T-cell subsets in 8 SIV-*M. leprae* coinfected RM and in 4 *M. leprae*-infected control RM. The *X*-axis is in reference to the time of *M. leprae* inoculation; the *Y*-axis represents the % of total PBL; the earliest time point (approximately −300 days) is pre-SIV; and time 0 represents the day of *M. leprae* inoculation.

4(c)). There was no change in the % CD8+ subset in the SIV/*M. leprae* coinfected *vs* an increase in this subset in the *M. leprae*-only inoculated group during the 62 days post-*M. leprae* inoculation period (Figure 4(d)); this difference was not significant. There was a transient increase in CD20+ B-cells in the SIV/*M. leprae* coinfected group and a decrease of longer duration in CD20+ B-cells in the *M. leprae*-only inoculated group early after *M. leprae* inoculation, but this difference was also not statistically significant.

Discussion

The clinical results are consistent with our previous suggestions derived from experimental studies in RM that SIV/ML coinfection enhances the susceptibility of RM to leprosy.[4] Seven of 8 SIV/*M. leprae* coinfected RM developed signs of leprosy or *M. leprae* persistence that were sustained until necropsy or, in one surviving case, to date 37 months post-*M. leprae* inoculation. Control RM, inoculated with *M. leprae* only cleared AFB from dermal *M. leprae*

inoculation sites by 27 or 63 days PI and have remained AFB-negative to date, 1137 days after *M. leprae* inoculation.

We have previously observed that the appearance of *M. leprae* in nasal secretions is an early indication of systemic dissemination of clinical leprosy in experimentally inoculated monkeys.[18] Three of the 8 coinfected animals studied herein developed strongly AFB-positive nasal secretions. Thus, the clinical data show an increased susceptibility towards persistence of *M. leprae* at dermal sites and an increased tendency to disseminate systemically in SIV coinfected compared to *M. leprae*-only infected animals.

Only one (I510) of the 8 coinfected RM failed to develop clinical AIDS, but it was prematurely sacrificed due to an unrelated medical condition 160 days post-*M.leprae* inoculation. This animal had MB leprosy at an inoculation site and AFB-positive nasal secretions at necropsy. Six of the 7 AIDS-positive RM were necropsied due to terminal AIDS within 270 days post-*M.leprae* inoculation.

The 7th AIDS-positive animal, the long-term survivor, remains alive with disseminated MB leprosy. The long term survivor has strongly AFB-positive nasal secretions first observed by 160 days PI, but has continued to show AFB-negative dermal biopsies. This RM displayed essentially normal immune responsiveness. The exact reason for it's uniqueness among the 8 coinfected RM is not known with certainty, but approximately 25% or RM experimentally infected with SIV_{B670} fall into this AIDS-slow progression category (M. Murphey-Corb, unpublished observations). To our knowledge, this RM had never been previously exposed to *M. leprae*. It is important to note that this latter RM, #J798, and 2 other animals with AFB-positive nasal secretions (J314 and I510) presumably shed large numbers of *M. leprae* into the environment as a result of the copious AFB-laden nasal exudates, although these 3 RM showed only minimal visible leprosy signs. The only evidence of leprosy in these 3 RM was the identification of AFB in nasal secretions and/or evidence seen in biopsies routinely taken from *M. leprae* inoculated monkeys. J798 has had an AFB-positive nasal status for approximately 3 years, but began to show symptoms of chronic AIDS 1137 days post-*M. leprae* inoculation and approximately 1350 days post-SIV infection. It is doubtful that humans with clinical characteristics similar to J314, I510 or J798 would have been recognized as leprosy patients. An ambulatory human patient similar to J798 might have exposed hundreds of contacts with *M. leprae* during such a time period while having few, if any, gross clinical symptoms of AIDS or leprosy. The possible implications of this observation for the future of leprosy among human populations remain to be seen.

The immunologic data provide a basis for the clinical observations. The impaired nonspecific (ConA) and *M. leprae*-specific blastogenic responses in *M. leprae*-SIV coinfected RM are in agreement with one study in humans showing abrogated *in vitro* blastogenic responses and skin test responses to *M. leprae* antigens in HIV-positive tuberculoid leprosy patients.[12] We previously reported the progressive loss of *M. leprae* skin test responses with time after SIV inoculation of an *M. leprae* infected RM.[4] Thus, systemic T-cell responses to *M. leprae* antigens appear to become compromised in blood and skin in leprosy-AIDS coinfected cases even though leprosy lesion histopathology may resemble that present in HIV-negative leprosy cases.[12]

The totally suppressed antibody responses to *M. leprae*-specific PGL-I cell wall antigen in 7 of 8 SIV/ML coinfected RM compared to significant responses in *M. leprae*-only infected RM indicates that SIV abrogates primary antibody responses to this *M. leprae* antigen in all of the coinfected RM except the long term survivor (J798). The impaired antibody responses appear to effect the primary, and not the secondary or memory compartment, as suggested by

the long-term presence of undiminished levels of anti-Gp120 antibodies beyond the known half-life of immunoglobulins. Unfortunately, in the design of this study we did not anticipate the need for testing for responsiveness to unrelated antigens. This will be included in a future protocol.

Since the CD4+CD29+ subset contains helper-inducer and memory cells, it is conceivable that the *M. leprae*-specific immunologic impairments may be associated with a pre-existing SIV-induced diminution of CD4+ and CD4+CD29+ T-cell subsets that is observed in most SIV-positive RM.[4,19,20] The longitudinal PBL subset data indicate that, in SIV-positive RM, an early additional small, but statistically significant loss occurs in the CD4+CD29+ T-cell subset after *M. leprae* inoculation. The CD4+CD29+ subset deficit is known to correlate with rapid AIDS progression in RM (19), but further investigations will be required to determine whether this specific defect contributes to the enhanced susceptibility to *M. leprae* persistence and dissemination in coinfected RM.

Previously, we reported that RM inadvertently coinoculated with SIV simultaneously with *M. leprae* (prior to our knowledge that captive sooty mangabey monkeys, the source of the *M. leprae* inoculum, carry SIV asymptomatically) developed AIDS and leprosy and produced anti-PGL-I IgG antibody responses.[4] This is in contrast to the observations herein which revealed a complete inhibition of anti-PGL-I responses in 7 of 8 coinfected RM. A probable explanation for this discrepancy is twofold: 1, RM in the former study most likely received extremely low doses of SIV, inadvertently present as a contaminate in the *M. leprae* inoculum, compared to known lethal doses of cryopreserved SIV experimentally given in the present study; and 2, RM in the former study[4] were simultaneously infected with ML and SIV, whereas in the present study, RM were inoculated with SIV 8–10 months prior to *M. leprae*. Surprisingly, the clinical results of an additional study now in progress suggest that lethality is greater when SIV is given to RM simultaneously with *M. leprae* compared to SIV being given prior to *M. leprae* (Gormus, BJ *et al*, unpublished observations). Thus, it appears that the effect of coinfection with the two agents depends, among other things, on the doses given and the relative timing of the two infections. Experiments are planned to examine in greater detail the effects of relative timing of the 2 infections, including *M. leprae* infection soon after SIV inoculation. Studies are now in progress to examine the effects of SIV infection on leprosy reactivation in leprosy-quiescent *M. leprae* infected animals.

The present data do not permit us to explain with certainty why studies from the field fail to consistently detect an interaction between HIV and leprosy among human populations. The results suggest that susceptibility to clinical leprosy is enhanced in leprosy cases coinfected with the AIDS virus. It is difficult to absolutely prove this point due to the generally observed rapid lethality of the combined infections observed in RM.

The rapid lethality observed in most SIV/*M. leprae* coinfected RM is a possible partial explanation for the failure of field studies to consistently detect an interaction between HIV and *M. leprae*. If a significant percentage of HIV-coinfected leprosy patients with a secondary HIV infection were to succumb early, prior to leprosy recognition (and/or, perhaps, prior to recognition of AIDS), it could conceal the true effect of coinfection.

If it is hypothesized that visible leprosy clinical symptoms are largely the result of the immune response to *M. leprae*, another possible explanation, suggested by the present immunologic results, is that clinical symptoms fail to appear in coinfected cases due to the AIDS virus-induced suppression of the immune response to *M. leprae* antigens. If so, coinfected patients would tend to be systematically excluded from study populations. Taken together, our clinical and immunologic data present a strong argument that some

systematic factor is being overlooked in field studies that have failed to find an association between AIDS and increased leprosy susceptibility.[10–14]

The specific effect of SIV on the course of *M. leprae* infection is dependent on several variables and is deserving of continued study. The possible implications of our observations for future resurgence of increased numbers of leprosy cases worldwide would seem to demand a very through investigation of and resolution to questions we have raised. Our studies are direct, not depending on epidemiological correlations, using a nonhuman primate model that is phylogenetically very similar to humans to reach our conclusions. The results imply that it may not be readily possible to determine the true epidemiologic relationship between HIV and *M. leprae* infections by studying human populations. Our conclusions are disturbing because they continue to portend a possible drastic increase in future leprosy cases in AIDS/leprosy-endemic areas without detection before it is too late to take effective preventative measures.

Acknowledgments

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Leprosy and renal transplantation

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Summary Nine cases of leprosy in patients treated at a large renal transplant centre in South Asia are described. Three had leprosy diagnosed before transplantation and had either completed or were continuing chemotherapy at the time of transplantation. One showed exacerbation of undisclosed leprosy after transplantation. Five patients developed the disease for the first time 22 months to 12 years after transplantation. Immunosuppression did not adversely affect the treatment of leprosy in any of the patients though concurrent liver disease required cessation of rifampicin in one patient.

Introduction

Renal transplantation is now available for treatment of chronic renal failure in many hospitals in tropical areas where leprosy is endemic. Also, renal disease is an important cause of morbidity and mortality in patients with leprosy,[1,2] therefore, leprosy is a disease to be considered in tropical renal transplant programmes.

Presented below is the experience with leprosy at the largest renal transplant centre in South Asia where 1667 patients have received transplants so far. Patients from all parts of India, Bangladesh, Nepal and Sri Lanka are treated. Approximately 90% are followed up for 1 year after transplantation and then referred to the care of local physicians. Many do not return for regular follow-up and treatment of complications. At times, patients who had received their transplants elsewhere are referred here for treatment. The cases described below include the first leprosy patient reported to be accepted as a renal transplant recipient.[3]

Leprosy diagnosed before transplantation

PATIENT NO. 1

A female patient was diagnosed to be having systemic lupus erythematosus at the age of 19

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 0305-7518/98/069040+06 $1.00

years. She was on treatment with prednisolone and azathioprine for 4 years when she developed an anaesthetic patch on the elbow with ulnar nerve thickening. A biopsy showed borderline–tuberculoid leprosy for which she took dapsone for 5 years. During this period steroids were continued but azathioprine was discontinued. When next seen in the hospital the patient was 40 years old and showed no evidence of leprosy; but had chronic renal failure. She received an allograft from her mother which was rejected. A transplant from an unrelated donor was then performed, at another hospital. Antirejection therapy was with high doses of steroids and azathioprine, to which cyclosporin A (CsA) was added after the second transplant. There was no recurrence of leprosy at the time of death a year later.

PATIENT NO. 2

A male with chronic renal failure due to IgA nephropathy received a renal transplant from his brother when he was 28 years old. Thirteen months prior to the transplant the patient developed an anaesthetic patch on the back diagnosed to be tuberculoid leprosy and received dapsone for one year. His father had leprosy but was not living with the family for 15 years. This story was forthcoming only when an exacerbation of the disease was noted two years post-transplant, and he was restarted on dapsone. When he was last seen at follow up 2 years after the transplant he was well.

PATIENT NO. 3

A 42-year-old male, reported in detail earlier,[3] had end stage diabetic nephropathy for which he received a renal transplant from his sister. Five months earlier the patient noticed an anaesthetic patch on the back, which was diagnosed as tuberculoid leprosy and treated with dapsone. Dapsone was continued after the transplantation. Post-transplant immunosuppression was with prednisolone and azathioprine. The leprous lesion showed no sign of activity in spite of enhanced immunosuppression for an episode of acute rejection and appeared completely healed with the continuing dapsone therapy at his death from chronic rejection one year after transplantation.

Leprosy untreated before transplantation

PATIENT NO. 4

A female with chronic renal failure of unknown aetiology was 40 years old when she received a renal allograft from an unrelated donor. Post-transplant immunosuppression was by prednisolone and azathioprine. Six and a half years later she developed anaesthetic erythematous skin patches on the left forearm diagnosed as borderline-lepromatous leprosy and erythema nodosum leprosum. The patient admitted having noticed hypoanesthetic, hypopigmented patches at the same site 6 months prior to transplantation, for which she had not taken treatment. She was put on multidrug chemotherapy with dapsone, rifampicin and clofazamine and advised to continue the treatment for 5 years. Rifampicin was withdrawn due to chronic liver disease. This patient died of liver cell failure hepatitis B virus (HBV) related 4 years after the diagnosis of leprosy.

Leprosy first manifesting after transplantation

PATIENT NO. 5

A male with chronic renal failure of unknown aetiology received a renal transplant at the age of 37 years, from his father. After having been on immunosuppression with prednisolone and azathioprine for 22 months he developed nodules, widely distributed over the body. A biopsy of one of these showed histoid leprosy. There was no history of leprosy in the past or contact with leprosy. He was discharged from hospital after having been started on dapsone, clofazamine and rifampicin and advised to continue chemotherapy at a hospital near his home. Follow-up information is not available.

PATIENT NO. 6

A male received a renal transplant from his brother, for chronic renal failure due to end stage renal failure of unknown aetiology, when he was 39 years old. Immunosuppression was with prednisolone and azathioprine. Six years after transplantation he developed diffuse erythematous papules diagnosed as lepromatous leprosy and was treated with dapsone, clofazamine and rifampicin. This patient also did not have leprosy earlier, nor contact with leprosy. He returned home to continue treatment. Follow up information is not available.

PATIENT NO. 7

A male received a renal allograft for end stage membranoproliferative glomerulonephritis type 1, when he was 48 years old, from his brother. The patient received prednisolone and azathioprine immunosuppression. Seven years later he developed a large hypoanaesthetic patch on the leg which was diagnosed as borderline–tuberculoid leprosy. His father had leprosy 25 years earlier. Treatment with dapsone, clofazamine and rifampicin was started and the patient was discharged to return home with the advice to continue chemotherapy under the care of a local physician. Follow-up information is not available.

PATIENT NO. 8

A female with end stage renal disease of unknown aetiology received a renal allograft from her brother, when she was 26 years old. One year after transplantation she developed abnormal liver function with HBV and active cytomegalovirus infection. Six years later while on maintenance immunosuppression with prednisolone and azathioprine she presented with multiple skin lesions diagnosed as borderline–lepromatous leprosy with erythema nodosum leprosum. There was no past history of leprosy or known contact with the disease. Treatment was started with dapsone, rifampicin and clofazamine. Chemotherapy was discontinued because of worsening liver function and replaced with dapsone and clofazamine alone when liver function tests improved. The patient died of chronic liver disease ten and a half years after transplantation. At the time of death there was no clinical evidence of leprosy for which she was still being treated.

PATIENT NO. 9

A male received a renal allograft from his daughter, in another hospital when he was 48 years

old. The disease causing chronic renal failure was not known. He was on immunosuppression with prednisolone, azathioprine and cyclosporin A. Twelve years later the patient was referred to this hospital with good renal function but with infiltrated lesions of the face and ears; without nerve thickening. Skin smears from the ears, cheek, arms and back showed large numbers of lepra bacilli. A diagnosis of lepromatous leprosy was made. This patient also did not give a past history of leprosy or contact with the disease. The patient was started on dapsone, rifampicin and clofazamine. He continued treatment with periodic checkups. CsA level was done 10 days after rifampicin was within the normal range. Patient did not have acute rejection episode after starting MDT. The bacterial indices and skin lesions had improved at last follow up after 30 months.

Discussion

Leprosy in relation to renal transplantation features in reports from Western centres as a diagnostic conundrum occurring unexpectedly in emigrant patients.[6] It also features as a response to news of patients with leprosy being used as renal donors and expressing a rightful indignation against their exploitation by the donor kidney trade.[8] Less understandable is the unexpressed exaggerated fear of this disease,[8] especially when keeping in mind that leprous granulomas are extremely rare in the kidney,[2] that the disease is amenable to treatment, and less communicable, and less likely to be resistant to chemotherapy than tuberculosis.

The different associations shown by the cases presented above, have been described earlier. A number of patients with known active or inactive leprosy have undergone renal transplantation. Patients with lepromatous disease[4] on antileprosy chemotherapy at the time of transplantation showed continued healing of leprosy, despite immunosuppression. The same is true for patients in the tuberculoid end of the leprosy spectrum as in cases 1 and 3.[3] Patients who have completed chemotherapy at the time of transplantation may not have a recurrence as in case 1, and even if the disease was of the lepromatous type.[4,5] Recurrence has however been reported.[6] Untreated or incompletely treated disease may exhibit an unexpected exacerbation[7] as in cases 4 and 2 respectively. Continuation of antileprous chemotherapy is required if there is incomplete or inadequate treatment before transplantation. We do not practice or recommend secondary chemoprophylaxis.

Leprosy may be diagnosed for the first time after transplantation,[10] as in cases 5 to 9 presented here. Such patients may or may not have been in contact with leprosy,[4] as in four of the five cases presented above. Though infection after transplantation cannot be excluded, the natural history of leprosy makes it possible that some of these patients had unrecognised latent leprosy which manifested as a result of immunosuppression.

Cases 4 and 8 demonstrate the problem of antileprosy chemotherapy in the presence of liver disease which is an important cause of morbidity and mortality in renal transplant patients. The decision to discontinue rifampicin is difficult, but as seen in our patient, may not seriously affect the course of the disease. In such a situation there are no guidelines regarding the duration of antileprosy chemotherapy. When unhindered multidrug therapy is possible the current recommendations regarding duration should suffice.

In our limited experience of MDT with a CsA treated patient there was no adverse effect on graft function due to rifampicin–CsA interaction; dapsone and clofazamine have no such reported interaction. However prednisolone dose was doubled in those receiving rifampicin as part of the MDT.

Table 1. Clinical details of patients with leprosy and kidney transplant

Pt No.	Age at diagnosis	Renal disease	Immunosupprn.	Leprous skin	Leprous N. lesion	Skin biopsy	BI	Treatment	Follow-up after treatment
Leprosy diagnosed before transplantation									
1	23	SLE	PCA	Single anaesthetic	R. ulnar N. thick	BT	Neg.	DDS 100 mg 5 years	No recurrence 1 year. Died of CRF
2	26	IgA	PA	Single anaesthetic	Normal	Chronic inflamm.	Neg.	DDS 100 mg 2 years	Well 2 years LFU
3	42	DN	PA	Single hypoesthetic	Normal	Indeterm. leprosy	NA	DDS 100 mg 1 year	Well 1 year Died of CRF
Leprosy untreated before transplantation									
4	47	ESRD	PA	Ill defined anaesthetic patches	L. ulnar N. thick	BL, ENL	1.25	R 6 months C,DDS 2 years	Improved 4 years Died of LCF
Leprosy first manifesting after transplantation									
5	37	ESRD	PA	Multiple nodules	Normal	Histoid L	3	MDT	Improved 10 mo. LFU
6	45	ESRD	PA	Multiple erythematous papules	Normal	LL	5.5	MDT	LFU
7	55	MCGN-I	PA	Anaesthetic patches leg	Normal	BL	NA	MDT	Improved 7 mo. LFU
8	32	ESRD	PA	Multiple hypopigm. patches	Normal	LL	4.65	C,DDS	Improved 4 years Died of LCF
9	60	ESRD	PCA	Multiple hypopigm. patches. ENL	Normal	LL	4.5	MDT	Improved at 30 months

BI—Bacterial Index; SLE—systemic lupus erythematosus, DN—diabetic nephropathy; ESRD—end stage renal disease; MCGN—mesangiocapillary glomerulonephritis; P—prednisolone; A—azathioprine; C—cyclosporin A; LFU—lost to follow up; CRF—chronic renal failure; LCF—liver cell Failure; NA—not available; C—clofazamine.

Leprosy occurs later in the post-transplant period than tuberculosis.[9] Patients on CsA immunosuppression manifest tuberculosis earlier than those not receiving it.[10] There is insufficient data to comment on the effect of CsA on leprosy. Acquired immune deficiency syndrome with profound T-cell suppression is not associated with a higher incidence of leprosy,[11] indicating CsA immunosuppression and its attendant T-cell depression is unlikely to exacerbate the disease.

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The National Leprosy Control Programme of Zimbabwe a data analysis, 1983–1992

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Summary Prevalence and detection rates of leprosy in Zimbabwe as well as patient characteristics were reported by the National Leprosy Control Programme over the 10-year period 1983–1992. The control programme made a new start in 1983 when multidrug therapy was introduced. Prevalence per 10,000 population declined steeply from 3·78 in 1983 to 0·52 in 1987. Prevalence continued to decline to 0·22 in 1992 and was highest in the north-eastern provinces. After an initial increase, the detection rate per 10,000 had declined from 0·19 in 1985 to 0·08 in 1992. The proportion of refugees among new cases had gradually increased since 1988 and amounted to one third in 1991 and 1992.

An analysis of records of 802 cases who were newly detected from 1983 to 1992 showed that 51% were of the multibacillary (MB) type, 33% had visible disabilities at detection, 5% were under 15 years of age while the average delay time was 2·6 years. Patients with disabilities reported a longer delay time, were more often men and had more often the MB type of leprosy.

The data suggest that transmission of leprosy is low but that cases are not diagnosed early enough to prevent transmission altogether.

Introduction

Between 1955 and 1964, several thousands of leprosy patients were contained in two large leprosaria in Zimbabwe, and given dapsone monotherapy. The leprosaria were closed in 1964 and the first ambulatory treatment programme was set up. Over 6000 patients were registered between 1964 and 1975. The programme almost fully collapsed during the years of struggle for independence between 1975 and 1980.

A new National Leprosy Programme was implemented in Zimbabwe at the end of 1983[1,2] with assistance of the Associazione Italiana Amici di Raoul Follereau. The

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purpose of the programme was to detect patients in an early stage of the disease and treat them with multidrug therapy (MDT) in order to provide cure, interrupt transmission and prevent leprosy-related disabilities.

In May 1991, the World Health Assembly adopted a resolution (WHA44.9)[3] to eliminate leprosy as a public health problem by the year 2000, defining elimination as the reduction of prevalence below 1 case per 10,000 population. This goal has been achieved in Zimbabwe since 1987, when the nationally registered prevalence rate dropped to 0·5 cases per 10,000 inhabitants. Since then, the transition from a vertical to a horizontal programme has begun.[1]

Patient data from the national leprosy control programme were analysed in the second half of 1993 in order to provide an overview of achievements in the 10 years since 1983 and to use this information as a basis for the planning of activities in the years to come. The present report of this analysis describes the leprosy situation in Zimbabwe as it developed during the 10 years from 1983 to 1992.

Methods

The leprosy control service was re-established in 1983. The programme was based on a nation-wide implementation of the WHO-recommended (MDT)[4] regimens and on the integration of leprosy control into the general health services at the national, provincial, district and clinic level. Four specialized staff formed the national leprosy unit. Eight general health workers were given training in leprosy, both locally and at the All Africa Leprosy & Rehabilitation Training Center (ALERT), and subsequently appointed as provincial leprosy officers (PLOs). They were charged with the implementation of MDT in the provinces, and with the in-service training of general health staff.[1,2] Additionally, a total of 26 leprosy 'scouts' who had at least secondary school education and had worked in the health sector before, often as (environmental) health assistants, were trained within the leprosy programme to detect new cases and follow up on defaulters. Typically, a scout works in one district and accompanies other health workers who go to the field to run under five and/or vaccination clinics, provide supervision, inspect drinking water systems or the hygienic condition of markets, schools, restaurants etc. Wherever he goes, the scout will inquire into the occurrence of symptoms suggestive of leprosy, visit possible cases and patients currently under treatment. Scouts are employed in areas of high endemicity in the North and North-East; although they formally report to the district medical officer, it is the provinical leprosy officer who coordinates and supervises the work of the leprosy scouts within his province. Community health workers in Zimbabwe were trained to distinguish the most frequently occurring skin diseases including leprosy and will refer any suspected cases; he or she will also refer any known leprosy patients who show signs of complications.

When a new case of leprosy was detected, the patient and those around him or her were given extensive explanation about the nature of the disease, risk of transmission, treatment etc. and all those living near the patient were inspected for signs of leprosy. Depending on the circumstances, this could lead to the performance of a survey in a school or on a farm, particularly if multiple cases were detected or if the patient was found to be infectious (smear-positive).

Registration of patients started in September 1983. Though most of the patients who

first enrolled had previously been treated with dapsone monotherapy, they were, regardless of their clinical status, all registered for a final course of MDT, to avoid any impression of discrimination. After 1986, previously treated patients were only accepted for an additional course of MDT if they showed clinical or bacterial signs of active leprosy. Skin smears were taken when a patient entered the programme and at the last review before he was released from treatment (RFT). All skin-smears from leprosy patients in Zimbabwe were taken to the Parirenyatwa University Teaching Hospital in Harare and stained and read by one senior laboratory technician at the public health laboratory, who was provided with adequate equipment and specifically trained for this work at ALERT; refresher courses were provided at regular intervals. Repeated skin smears were prepared if there was any doubt at all about the correct classification of a patient. A multibacillary patient (MB) was defined as any patient having a positive skin-smear result. Tuberculoid patients (TT and BT) were classified as paucibacillary (PB) while lepromatous patients (BB, BL and LL) were classified as MB; these definitions did not change over the period of observation. MDT consisted for paucibacillary patients of 100 mg dapsone each day for 6 months accompanied by 600 mg (8 mg/kg) rifampicin monthly.[5] For multibacillary patients, MDT consisted of 100 mg dapsone and 50 mg clofazimine per day and 600 mg (8 mg/kg) rifampicin plus 300 mg clofazimine per month for a total duration of 24 months.

Assessment of patients, which was done every 3 months, included examination of the skin, palpation of the nerves, sensory tests, voluntary muscle tests and disability grading according to WHO-criteria.[6] A patient was considered to be disabled when he had at least one disability grade II or III.

Data on prevalent and newly-detected cases of leprosy were given in the Annual Leprosy Reports, which were based on the quarterly Leprosy Reports from each of the provinces. More detailed information on leprosy patients was derived from a computerized database which was created from the original patient records, the ZIMLEP forms, a variation of the internationally known OMSLEP forms. A new ZIMLEP form was designed in 1988 because of some shortcomings in the old one. Data recorded in the years 1983 to 1987 were rearranged to be compatible with the new format. For every patient the first record, filled out when he entered the programme, was included in the database. In addition, the corresponding last record, filled out when the patient was released from treatment (RFT-record) was found for 58% of those who entered the programme. Not all patients who ever entered into the programme appeared in the computer register, due to computer problems since the start of the programme. Using the patients ZIMLEP forms the register was made as complete as possible, but so many years later a lot of ZIMLEP forms were missing. The final database contained 3605 records, of which 802 were from newly detected patients. Comparing the total of new cases of the period 1984–1992 between the database and the Annual Leprosy Reports, 77% of the new cases of the annual reports could be found in the database.

National Censuses were carried out in Zimbabwe in 1982 and 1992 and all rates are based on denominator information derived from the census reports by interpolation. Refugees are included both in the censuses and the registration of leprosy patients.

Age was calculated as the difference between year of birth and year of detection; delay time as the difference between (self-reported) age at onset of symptoms and age at detection in years. Proportions were compared by means of the χ-squared test,

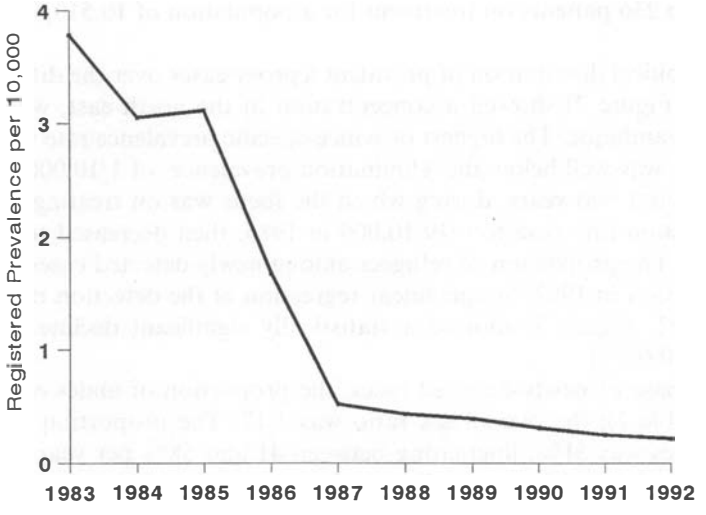


Figure 1. Annual registered prevalence of leprosy in Zimbabwe 1983–1992 per 10,000 population.

computed from a 2 × 2 table with the actual counts, while averages were compared with the Wilcoxon rank sum test.

Results

Prevalence of leprosy in Zimbabwe declined steeply during the years 1983 till 1987 (Figure 1 and Table 1). From 1987 onwards the prevalence rate dropped below 1 case per 10,000 population and continued to decline. At the end of 1992 the prevalence rate had

Table 1. Prevalence and incidence of leprosy in Zimbabwe, 1983–1992. Source: Annual reports, national leprosy control programme

Year	Prevalent cases*	Registered prevalence†	Incident cases	Detection rate‡
1983	3000	3·78	110	0·14
1984	2500	3·05	78	0·10
1985	2625	3·11	162	0·19
1986	1451	1·67	146	0·17
1987	463	0·52	135	0·15
1988	403	0·43	106	0·12
1989	370	0·39	140	0·15
1990	311	0·31	102	0·10
1991	250	0·25	81	0·08
1992	236	0·22	86	0·08

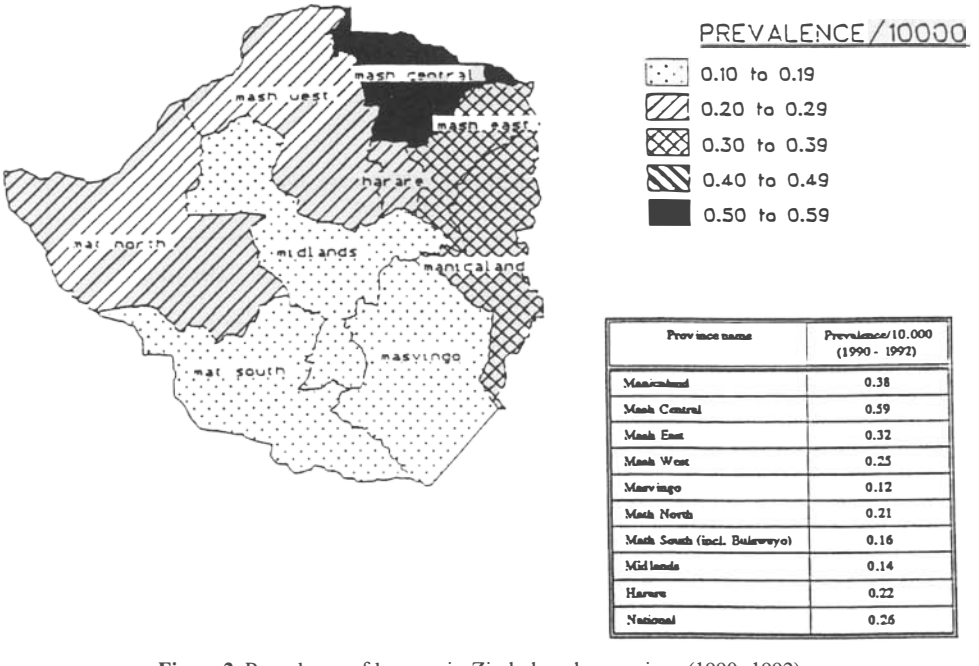
* patients under treatment on 31 december.
† per 10,000 end-of-year population.
‡ per 10,000 mid-year population.

been reduced to 236 patients on treatment for a population of 10,510,516 people (0·22/10,000).

The geographical distribution of prevalent leprosy cases over the different provinces in 1990–1992 (Figure 2) showed a concentration in the north east, where Zimbabwe borders on Mozambique. The highest province-specific prevalence rate was 0·59/10,000, however, which was well below the 'elimination prevalence' of 1/10,000.

After the initial two years, during which the focus was on treating already known cases, the detection rate rose to 0·19/10,000 in 1985, then decreased to 0·08/10,000 in 1992 (Table 1). The proportion of refugees among newly detected cases had risen from 6% in 1988 to 35% in 1992. Simple linear regression of the detection rates by calendar year (1985–1992, Figure 3) showed a statistically significant decline of 0·016 cases/10,000/yr ($P < 0·0001$).

In the database of newly-detected cases, the proportion of males exceeded 50% in most years (Table 2); the overall sex ratio was 1:17. The proportion of MB patients among new cases was 51%, fluctuating between 41 and 58% per year. Patients of the MB-type occurred somewhat more frequently among men (55%) than among women (46%, $P < 0·05$). The average age of newly-detected leprosy patients was generally between 40 and 45, with an overall average of 42·7 years. Five percent of newly detected cases was under 15 years of age. The overall mean age was not statistically different between male and female or between PB and MB patients. The average delay time in new cases was 2·6 years; 11% of cases had experienced their first symptoms more than 5 years before the detection date while one third of these had not been detected within 10 years



Province name	Prevalence/10.000 (1990 - 1992)
Manicaland	0.38
Mash Central	0.59
Mash East	0.32
Mash West	0.25
Masvingo	0.12
Mash North	0.21
Mash South (incl. Bulawayo)	0.16
Midlands	0.14
Harare	0.22
National	0.26

Figure 2. Prevalence of leprosy in Zimbabwe by province (1990–1992).

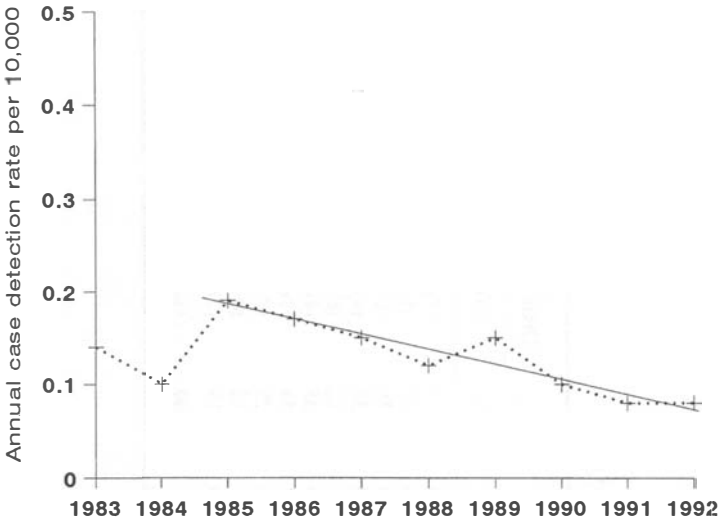


Figure 3. Annual detection of leprosy cases in Zimbabwe 1983–1992 and the simple linear regression line through the points for 1985–1992.

of onset of symptoms. Delay times exceeded 5 years in 16% of men versus 8% in women ($P < 0{\cdot}002$).

The proportion of new patients with at least one grade II or III *disability*, calculated over the period 1983–1992, was 33%, i.e. one out of three. A comparison of patients with and without disabilities is presented in Table 3. Patients with disabilities reported a longer delay time, were more often men, were older and had more often multibacillary leprosy. Stratification by delay time showed that a higher disability rate among men was particularly clear among patients with a delay time of 1 to 5 years (data not shown).

Information on treatment assigned at entry into the programme was missing for 19% of newly-detected cases in the years 1983–1987 and for 8% in the years 1988–1992. Only 14 out of 691 cases (2%) were recorded as receiving another treatment than MDT and this proportion hardly varied from year to year. Fifteen out of 353 patients who were registered as being of the MB-type received (at least on paper) the treatment regimen for PB patients. Twenty-seven PB-patients received the regimen for MB-patients, 21 of whom had been classified as borderline-tuberculoid.

Information on duration of treatment was available for 366 out of 802 cases (46%). Of the 197 patients on the PB-regimen, 38 were released from treatment within 180 days and another 111 within 360 days. Of the 161 patients on an MB-regimen, 23 completed their treatment within 540 days, another 22 within 720 days, while 45 continued beyond 900 days.

Assessments of disabilities both at the beginning and completion of treatment were available for 265 out of 802 newly-detected cases (33%). Twenty-four patients out of 180 (PB: 13/103, MB: 11/77) had developed grade II or III disabilities while under treatment; 15 out of 81 patients who had disabilities at entry had regressed.

Table 2. Characteristics of new leprosy patients in Zimbabwe 1983–1992. Source: patient records as described in text.

Year	Number of new cases	Average age		% Men			Multibacillary			Disabled			Delay time	
		(m)	(yrs)	#	(m)	%	#	(m)	%	#	(m)	%	(m)	(yrs)
1983	8	(0)	40·4	8	(0)	100	4	(0)	50	1	(1)	14	(0)	3·6
1984	88	(0)	42·3	42	(0)	48	38	(1)	44	22	(8)	28	(1)	2·4
1985	116	(1)	43·7	57	(2)	50	66	(3)	58	35	(6)	32	(2)	2·5
1986	94	(2)	45·0	52	(3)	57	45	(2)	49	33	(4)	37	(7)	3·8
1987	96	(3)	43·1	50	(1)	53	49	(0)	51	12	(6)	13	(3)	2·7
1988	87	(2)	40·0	48	(2)	56	41	(3)	49	35	(4)	42	(17)	2·4
1989	118	(0)	45·0	66	(0)	56	65	(3)	57	55	(7)	50	(24)	2·1
1990	77	(1)	45·3	44	(0)	57	34	(1)	45	25	(7)	36	(12)	3·2
1991	64	(3)	34·1	37	(0)	58	26	(1)	41	12	(0)	19	(4)	1·9
1992	54	(5)	41·4	22	(2)	42	31	(1)	59	19	(2)	37	(12)	2·0
Total	802	(17)	42·7	426	(10)	54	399	(15)	51	249	(44)	33	(82)	2·6

(m): number of patients for which information is missing.

Table 3. Comparison of patients with and without grade II or III disabilities at the time of detection

	Disabilities				
	yes		no		
	#	(%)	#	(%)	
Type of leprosy					
MB	138	(56)	239	(48)	
PB	107	(44)	261	(52)	$P < 0.05$
Sex					
Females	92	(37)	258	(52)	
Males	155	(63)	241	(48)	$P < 0.001$
Delay time*					
0	29	(13)	119	(26)	
1-5	149	(66)	301	(65)	
6-10	32	(14)	28	(6)	
> 10	15	(7)	15	(3)	$P < 0.001$
mean ± s.e.	3.5 ± 0.27		2.3 ± 0.21		$P < 0.001$
Age*					
< 15	6	(2)	24	(5)	
15–24	17	(7)	69	(14)	
25–34	26	(11)	85	(17)	
35–44	48	(20)	95	(19)	
45–54	71	(29)	109	(22)	
55–64	41	(17)	72	(14)	
≥65	35	(14)	43	(9)	$P < 0.001$
mean ± s.e.	47.1 ± 1.00		40.8 ± 0.75		$P < 0.001$

* Age and delay time in years.

Discussion

PREVALENCE AND INCIDENCE

The dramatic drop in prevalence of leprosy during the first 5 years of activities is not surprising, as MDT was now abundantly available and intake criteria were generous.[7] The observation that prevalence has continued to decline after 1987 is more encouraging. The low current prevalence levels (257 prevalent cases in 1994, a rate of 0.24/10,000[8]) suggest that transmission of leprosy is low in Zimbabwe. This is confirmed by the observation that incidence has decreased from 1985 to 1992 with 1989 as the only exception. This exception is probably due to the influx of refugees from neighbouring Mozambique around that time. Between 10,000 and 20,000 refugees from Mozambique had been placed in camps in Zimbabwe by the end of 1984; this number suddenly rose to 130,000 in 1989. The prevalence of leprosy in Mozambique was 8.86 per 10,000 in 1994[8] while the prevalence in Zambia was 2·26. In southern-adjacent South Africa, the prevalence was 0·09 per 10,000 population, while Botswana did not report any cases at all in 1994.[8]

BCG coverage among 1 year olds in Zimbabwe rose from 64% in 1981 to 86% in 1987 and has stabilized at the level of 80% since[9]. This may have contributed to the present low transmission of leprosy in Zimbabwe,[10] although it should be remembered

that an effect of BCG vaccination on adult leprosy incidence takes at least 15 years to become observable. The observed low detection rate among children is more likely to be influenced by the favourable BCG-coverage.

The observed decreasing incidence of leprosy is only valid if the case-finding activities were maintained at the same level. We were not able to compare registered cases to the total number of cases of leprosy in the country.[11] Unfortunately, the cost of detecting a case of leprosy increases as incidence decreases. In addition, fewer resources are available for this work as leprosy becomes less and less of a public health problem.[12] A proportion of 37% of new cases with disabilities grade II or III in 1992 (Table 2) is high compared to other countries in Africa[13] and suggests that cases are not diagnosed as early as would be desirable if transmission were to be blocked completely.[2,11] The presence of disabilities was clearly related to a long delay time (Table 3). However, there does not seem to be a systematic rise or fall of the disability rate over time. The association of the disability rate with age, sex and MB-type is well known.[14]

DATA QUALITY

Although 110 incident cases were detected in 1983 (Table 1), the records of only eight of these cases were available for analysis (Table 2); for 1984, the records of 88 cases were available while 78 were counted in the annual report. Clearly, the registration of new cases was incomplete in that initial period during which all efforts were focused on getting large numbers of known patients started on MDT.

Errors in recording of information and in data processing may have occurred and this could partly explain why some patients seem to have received the wrong treatment regimen. Information on duration of treatment and progression or regression of disabilities during treatment may have been affected by errors in linking information recorded at entry into the programme and at discharge. All information in Tables 2 and 3, however, was derived from the entry record of each patient and has not been affected by problems of record-linkage.

SIGNS OF LATTER DAYS FOR LEPROSY

The question whether special epidemiological characteristics can be described in situations where leprosy is dying out has been raised by Irgens.[15] He suggested that new cases will be older at detection in such situations and more often of the lepromatous type. The present data do not show a gradual increase of age at detection or of the type-index over time (Table 2). However, the proportion of MB-patients in Zimbabwe is high compared to other African countries such as Burkina Faso (4%), Tanzania (18%)[16] or Malawi (20%),[12] data from northern Malawi[17,18] yield an MB-proportion of only 6%. A possible explanation for this high percentage could be that the few cases that occur in areas where leprosy is dying out generally have a weaker resistance resulting in a predominance of multibacillary leprosy (Dr J. A. Warndorff, personal communication, *cf.*[17]). A study in the Shoa administrative region in Ethiopia in the years 1984–1988 showed an MB-proportion of 43% not accompanied by a shift to older age-groups.[19]

INTEGRATION WITH OTHER HEALTH SERVICES

The national leprosy unit was reduced in 1991 from 4 staff to 2 part-time staff who were at the same time involved in tuberculosis control. This adjustment was a consequence of the reduction of the leprosy prevalence coinciding with a rising incidence of tuberculosis. Since donors made less money available for leprosy control in low-prevalence countries, the continuation of leprosy control in Zimbabwe was dependent on a further integration of tuberculosis and leprosy control activities. From 1992 onwards, staff from both programmes were integrated on the provincial and district levels as well. A similar attempt at integration was reported from India.[20]

A further step towards integration was made in the area of rehabilitation of leprosy patients with disabilities. The existing leprosy rehabilitation schemes were independent of the nationwide community-based rehabilitation programme which dealt with non-leprosy-related disabilities. A project was therefore started in 1991 with assistance of the Leprosy Mission International to train rehabilitation staff at different levels of the health system on the treatment and rehabilitation of leprosy patients.[2] By reviewing together with local leprosy staff the leprosy cases actually under treatment at the time, discussions on referral of leprosy patients to the community-based rehabilitation programme can take place. Full integration of leprosy patients in the community-based rehabilitation programme is expected in approximately 3 years.

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Evaluation of a sustained 7-year health education campaign on leprosy in Rufiji District, Tanzania

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Summary To assess the impact of a 7-year intensive health education campaign about leprosy delivered by workers of the Kindwitwi Leprosy Trust to schoolchildren and general public in Rufiji District. Knowledge, attitude and beliefs towards leprosy were measured in Rufiji and compared to neighbouring Kisarawe District as control. Lessons learned from this analysis may be useful for the planning and evaluating of health education campaigns.

Interview of schoolchildren, general public, community leaders, traditional healers and medical staff in both districts.

A stratified randomized sampling scheme was used, with stratification for urban and rural settings. A representative sample of schoolchildren, general public, community leaders, traditional healers and medical staff in Rufiji District and in the control area of Kisarawe District was interviewed. The interviews were partly structured and partly open. The results of the interviews were analysed in the context of epidemiological leprosy data from 1985 till 1995, and demographic data of both districts. Data entry and statistical analysis was done using FileMaker Pro, Stata and Excel computer packages.

We did not observe positive effects of the health education campaign on the indicators regarding early diagnosis of leprosy with less disability. Leprosy case detection was declining in both districts.

We found that the campaign had a favourable impact on the knowledge and the

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attitude of schoolchildren in Rufiji District. We could demonstrate a relationship between increased knowledge of leprosy and a positive, less stigmatizing attitude. Knowledge of leprosy was better in Rufiji as compared to Kisarawe, but only among schoolchildren. We found indications that low level of education, rural residence, older age, female gender and Moslem religion were associated with stigmatizing attitudes and beliefs towards leprosy. Knowledge about leprosy reactions among medical staff interviewed was not optimal.

The exact outcome of the sustained campaign in Rufiji District was difficult to assess because no comparison could be made with the situation prior to the campaign. However, the health education campaign was associated with increased knowledge and diminished tendency to stigmatize leprosy among schoolchildren. Health education campaigns have to be sustained and have to cover a broad sector of the society in order to induce behavioural changes in the community. The focus of health education should be rural communities and schools, and pay special attention to women, religious leaders and traditional healers. Awareness of diagnosis and treatment of leprosy reactions among medical staff should be improved.

Introduction

Health education campaigns aim to effect change of the behaviour of the receiver of the message in such a way that his or her health status improves and that as a result the disease ceases to be a public health problem. It is believed that good quality health education can influence behaviour and lifestyles and will have improve health.[1,2] Comprehensive health education about leprosy aims at reducing the stigma of leprosy to that patients with incident leprosy or a leprosy reaction report early to medical services, remain compliant with therapy and have a good chance of successful rehabilitation in the community. The awareness and knowledge of leprosy together with a positive attitude towards leprosy victims among individual patients, among the general public, religious and community leaders, and medical staff are necessary to fight the stigma of leprosy. However, increased knowledge does not necessarily leads to changed attitudes towards leprosy, neither among leprosy patients themselves,[3] nor medical staff,[4] nor in the community.[5,6]

The most effective health education activities can be considered to be those which address the above mentioned categories of people and which are continuous. Of the methods used, group education sessions in schools are considered to be more effective than mass education by media (radio/TV/newspapers) or individual education.[7] One of the most effective ways of transmitting knowledge is said to be educating primary schoolchildren, who take the received message home to discuss it with their parents. However, others[8] did not show that this mechanism played a role in the transmission of knowledge. In addition, it is shown that the education of leprosy can also adversely affect attitudes of children.[8]

Special attention for the health education of women, often bearing the responsibility for the health status of the family and influential in the opinion of the community, could be crucial for the success or impact of health education.[9] In addition, the role of traditional healers and religious leaders is important.[4]

Concerning the evaluation of health education, three levels can be distinguished: first the health education process, second the immediate impact on knowledge and behaviour, and third the outcome of health education in terms of better health and epidemiological

indicators.[10] In leprosy, where many factors determine its secular epidemiological trend, like genetic predisposition, socioeconomic status, level and spread of the infection, and where epidemiological changes tend to take a long period of time, it is difficult to measure the possible outcome of health education on incidence and prevalence of leprosy, or, by approximation, the case detection and registered prevalence rates. The proportion of disabled among new cases would be a sensitive indicator for early diagnosis. Other factors which can be evaluated are the possible impact on general knowledge of leprosy and on attitudes and beliefs towards the disease among the population.

In Tanzania, health education to patients and general public attending health units is a routine task of the general medical staff, assisted by specialized tuberculosis and leprosy control coordinators at regional and district level. The various categories of medical staff are taught about leprosy during their curriculum by teachers knowledgeable about leprosy. This knowledge is refreshed by discussions on the job with the leprosy coordinators as well as during post graduate seminars. It is the task of the regional and district tuberculosis and leprosy coordinators to teach at health training institutions within their jurisdiction. They ensure that the latest policies of the government regarding tuberculosis and leprosy control are known to staff diagnosing and treating these cases. In some areas in Tanzania additional community health education activities are carried out, mostly from an existing hospital or institution specialized in leprosy care.

Attention towards leprosy in Rufiji, including health education, started in 1964, when the late Rev. Fr. R.G.P. Lamburn, an Anglican missionary who died in 1993, began rehabilitation of the old Kinwitwi leprosy village in Rufiji District in Tanzania, by improving feeding, clothing, housing and medical treatment. He was able to reshape the derelict village into a well-organized one with a large communal field to promote agricultural self-sufficiency. He got the help of devoted people from Tanzania and from overseas.

In 1982, the Rufiji Leprosy Trust was founded, which offered logistic support to the District Tuberculosis and Leprosy Coordinator (DTLC) and which began the intensive public information campaigns and education about the true nature of leprosy. Since 1988 this programme was extended to the islands in the river delta.

The aim was to aid the early identification of new cases by making people aware of the signs and symptoms of leprosy, and by telling them that there is effective drug therapy available. It was hoped that by increasing the knowledge, the fear and stigma of leprosy would be reduced and patients would come forward for treatment and remain active members of their own communities.

Rufiji Leprosy Trust employed a full-time Leprosy Education Officer who worked under the supervision of the DTLC and whose responsibility was to give talks in schools, adult education centres, etc., illustrated with films and slide shows. Films about leprosy and other health topics in Kiswahili language were shown in every village in the district, attracting large numbers of people. Posters, T-shirts and stickers were distributed with messages in Kiswahili and Arabic (for those only literate in Arabic of the Koran). Seminars were held for leaders of the ruling party, the Chama Cha Mapinduzi (CCM). Other seminars were conducted specifically aimed at health workers and at traditional healers. In addition a person from Kindwitwi Leprosy Village, the 'Leprosy Scout', visited villages ahead of the education team and gave the account of his life story, in order to make cultural and language barriers as small as possible.[11] He had a charismatic personality and ability to convince people to seek treatment for their disease.

Once yearly during World Leprosy Day, district wide singing and drama competitions

were organised amongst schools and youth groups, contributing to the message that 'Leprosy can be cured'.

This paper reports on the results of an evaluation of the impact of this health education campaign in Rufiji District in comparison to a control district (Kisarawe). The findings are related to demographic data and leprosy patient statistics of Rufiji and Kisarawe Districts from the National Tuberculosis and Leprosy Programme (NTLP) of Tanzania, covering the period 1985 to 1995.

Materials and methods

The routine quarterly reports of the National Tuberculosis and Leprosy Programme from 1985 to 1995 were used to analyse the leprosy case notification and its trend in both districts.

Demographic data, including population size and socioeconomic status, were obtained from the 1988 census[12–14] data of Tanzania.

We chose to look at urban and rural communities in Rufiji and match them with similar areas in Kisarawe in a quasi-experimental case-control approach. This method of evaluation is considered suitable in such situations.[15] Existing differences in demographic characteristics were dealt with in the multivariate analysis, controlling for the variables concerned. The district capitals were chosen because these were the urban areas in both districts. The rural villages were chosen from a list from the population census of 1988 showing different wards and their populations. The selection was random.

Once the areas had been chosen we decided to look at all health facilities, all primary schools, all offices of the ruling party and a representative sample of the general public, i.e. individuals over 15 years of age, and traditional healers, within the boundary of the area chosen.

In July 1994, during a 2-week period a team of 10 individuals conducted the interviews in the Rufiji and Kisarawe Districts. The team consisted of health education specialists, social scientist, social workers and regional and district tuberculosis and leprosy supervisors. They were involved in pre-testing of the questionnaires in order to familiarize themselves with the topic and standardize the approach.

Pupils were randomly chosen from the school register. The aim was to have at least 100 pupils per school. In each health facility all staff involved in providing medical/nursing care including untrained staff, were interviewed. The general public was chosen at market places, hospital outpatient departments, ferry crossings, secondary schools, and even a memorial service, with the aim of getting as many people as possible over 15 years old. As many community leaders as were available in the offices were interviewed. Traditional healers were chosen in Rufiji District from the Rufiji Department of Culture and Education register of traditional healers. Unfortunately Kisarawe had no such register and few people would admit to being or using a traditional healer. We did not include registered leprosy patients in our interviews.

Knowledge, attitudes and beliefs were evaluated by interviewing schoolchildren, general public, medical staff, community leaders and traditional healers in both districts. The questionnaires were anonymous. The answers were open, but for each question a checklist in the margin assisted the interviewer to check the completeness of the answer. This later facilitated coding according to the best fit of the answers. The questionnaires were first field tested in Dar es Salaam in order to find out the duration of the interview, the completeness of

the questions, the appropriateness of the checklists and other practical aspects, and were adapted accordingly.

The questionnaire included questions about personal characteristics of the respondent like age, sex, education, profession, religion and name of the village or school.

There were questions to find out if the person remembered attending a health education seminar on leprosy and who were the organizers. Then followed questions on knowledge of leprosy and attitude and beliefs towards leprosy patients. Other questions were included for specific categories of persons interviewed.

The questions pertaining to knowledge used in the questionnaires included:

1 How does one contract leprosy?
2 What category of patients are able to spread the infection?
3 Can you mention the signs and symptoms of leprosy?
4 Is leprosy curable? If yes, how? Where would you go for treatment?
5 Does everyone who contracts leprosy end-up being handicapped? If not, how does one end-up being handicapped?
6 Do you know a relative or acquaintance who has ever suffered from leprosy?

The questions pertaining to attitude and belief in relation to stigma in the questionnaires were:

1 What sort of people usually get leprosy?
2 Would you play or share food with an exleprosy patient? Would you play or share food from the same plate with an exleprosy patient? If not, why?
3 Would you shake hands with an exleprosy patient? If not, why?
4 Would you rent a room in a house where you know someone has leprosy? If not, why?
5 Would you marry into a family which is known to have had a leprosy patient? If not, why?

Additional questions asked of medical staff:

1 Do you know the signs and symptoms of leprosy reactions?
2 Do you know the treatment of leprosy reactions?
3 Who is responsible for the diagnosis, treatment and care of a leprosy patient in your clinic?
4 Who is responsible for defaulter tracing of a leprosy patient in your clinic?

Questions to traditional healers and community leaders were not similar to the above but instead aiming to analyse their exposure to leprosy seminars and role in leprosy control, which for traditional healers included:

1 Do you treat leprosy?
2 How many patients consult you last year?
3 Have you noticed an increase or decrease of leprosy patients, and what could be the reason?
4 There is a general belief that if one breaks a traditional taboo, like eating forbidden food, one can contract leprosy. As a traditional healer what is your opinion?
5 Have you ever attended a seminar, workshop or meeting on modern treatment for leprosy?
6 What did you learn and how have you benefited from this knowledge?

Specific questions for community leaders included:

1 How many leprosy patients do you know in your area?
2 How do those suffering from leprosy treat themselves?
3 What would you do if someone close to you contracted leprosy?
4 Are you aware of any community health education programme on leprosy?
5 What has been your role as a leader?
6 How has the community benefited from this programme?
7 Would you say leprosy patients are now better prepared to visit modern health units than prior to the educational visits and if yes, can you explain?
8 Would you say the average person is now less likely to discriminate or isolate leprosy patients as a result of the educational visits?

The team interviewed a total of 1,711 people in the two districts: 1,120 schoolchildren, 534 members of the public, 96 medical staff, 47 community leaders and 17 traditional healers. The numbers of individuals interviewed and their characteristics were as shown in Table 1 and Table 2.

The answers on the questionnaires were recorded in previously defined categories. The results were entered in the computer using FileMaker Pro database programme and analysed in Excel and Stata software packages.

Table 1. Characteristics of schoolchildren, general public and medical staff interviewed in Rufiji and Kisarawe Districts

Group	Characteristics	Rufiji	%	Kisarawe	%
Schoolchildren	interviewed	507	(100)	613	(100)
	average age	14 years		14 years	
	% female	239	47	324	53
Religion	moslem	470	93	451	74
	christian	32	6	158	26
	other	5	1	4	1
Residence	urban	154	30	311	51
General public	interviewed	345	(100)	99	(100)
	average age	31 years		37 years	
	% female	173	50	55	56
Education	primary	141	41	52	53
	secondary	119	34	29	29
	none/other	82	23	18	18
Religion	moslem	307	89	50	51
	christian	33	10	48	48
	other	5	1	1	1
Residence	urban	140	41	28	28
Occupation	farmer	166	48	34	34
Medical staff	interviewed	44	100	42	(100)
	average age	34 years		32 years	
	% female	30	68	29	69
Religion	moslem	31	70	19	45
	christian	13	30	23	55
Residence	urban	28	64	25	60
Profession	clinical officer	6	14	8	19
	nurse	27	61	17	40
	other	11	25	17	40

Table 2. Characteristics of community leaders and traditional healers interviewed in Rufiji District

Group	Characteristics	Rufiji	%
Community leaders	interviewed	47	(100)
	average age	45 years	
	% female	6	13
Education	primary	27	57
	secondary	4	9
	none/other	16	34
Religion	moslem	32	68
	christian	12	26
	other	3	6
Residence	urban	19	40
Occupation	farmer	19	40
Traditional healers	interviewed	17	(100)
	average age	52 years	
	% female	3	18
Education	primary	5	29
	secondary	0	
	none/other	12	71
Religion	moslem	17	100
Residence	urban	9	53

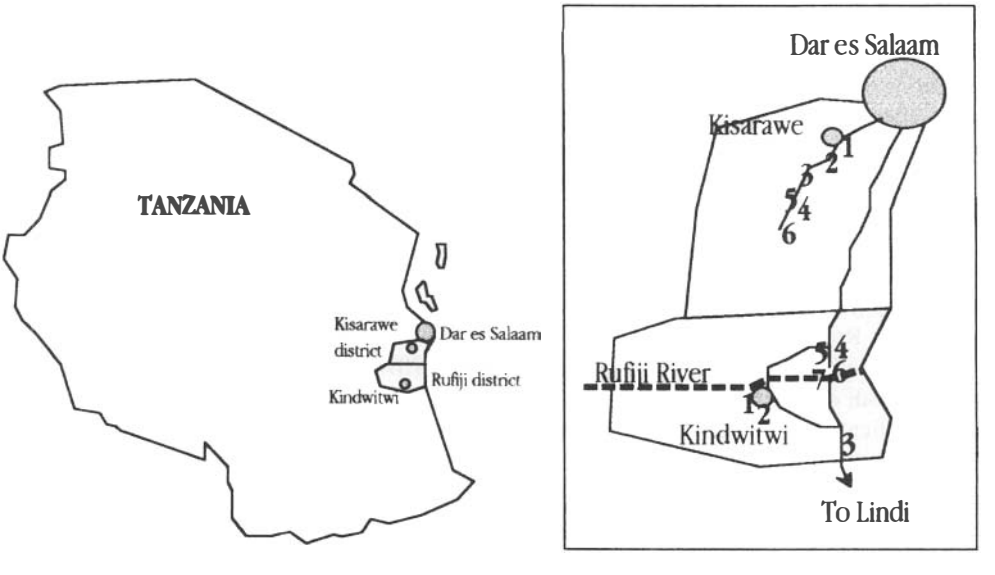

Figure 1. Map of Tanzania and detailed map of Rufiji and Kisarawe Districts with indication of the places where the interviews were held.

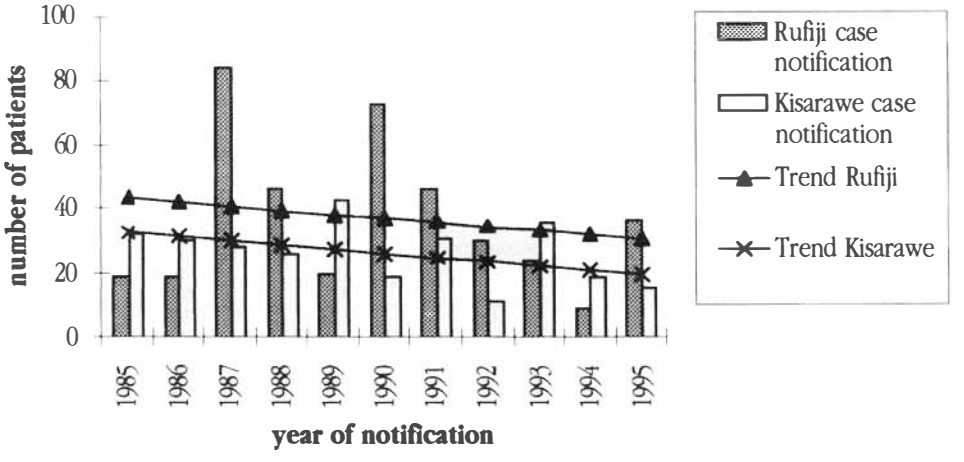

Figure 2. Case notification in absolute numbers and trend in case notification from 1985 to 1995 in Rufiji and Kisarawe Districts.

Results

DEMOGRAPHIC DATA AND PATIENT STATISTICS

Rufiji District is the southernmost district of the Coastal region of Tanzania. In 1994 Rufiji District had an estimated population of 174,000[12] and had an area of 13·3 square kilometre.[13] It has some 100 villages which are served by 47 dispensaries, 4 health centres and a number of health posts as well as a district hospital. It is bisected by the Rufiji river from east to west making travel in the rainy seasons from the south to the north very difficult (Figure 1). In 1994 Kisarawe District, which borders the capital of Tanzania, Dar es Salaam, had an estimated population of 219,000 and it had a surface of 6·9 square kilometre. The analysis of the most important indicators of development according to the 1988 census[14] showed that adult literacy was 40% and 36% in Rufiji and Kisarawe respectively. In Rufiji 6% of the rural population had access to piped water, 0·2% had electricity and 73% had a toilet, as compared to 2%, 0·3% and 85% respectively in Kisarawe. The average number of people per room in a household was 2·6 in Rufiji and 2·5 in Kisarawe.

The leprosy case notification data[16] of Rufiji and Kisarawe Districts from 1985 to 1995 are as shown in Figure 2. In Rufiji more new cases were detected than in Kisarawe, even more so when related to the population size. The average case detection rate per 10,000 population was 2·4 in Rufiji and 1·3 in Kisarawe. The fluctuation in the annual case notification was highest in Rufiji District and showed a high peak in 1987 when the health education campaign started. Both districts show a downward trend of similar magnitude (4% to 6% average) in case notification. The cumulative leprosy case notification data of Rufiji and Kisarawe Districts from 1985 to 1995 showed that in Rufiji district 409 new cases were diagnosed out of whom 10% were children below the age of 15 and out of whom 33% had a disability grade 1 or 2. In comparison, during the same period in Kisarawe District 291 new cases were diagnosed out of whom 7% were children below the age of 15 and out of whom 35% had a disability grade 1 or 2. In Rufiji there were slightly more children (not significant) and more disabled patients among the newly detected ($p < 0{\cdot}001$). There were no significant changes in

the proportions of disabled and children below 15 years among the new cases detected over the years and notably no decrease in the proportion of disabled. The treatment results of multibacillary and paucibacillary patients were very favourable, with cure and treatment completed rates of over 90% in both districts, which had remained approximately constant over the years since 1985.

RESULTS OF INTERVIEWS

Schoolchildren

In total 1,120 pupils were interviewed from 13 different schools, 7 schools from Rufiji and 6 from Kisarawe District. The average number of pupils interviewed per school was 86, which was 16% of the registered enrolment of 7,015 pupils, ranging from 7% to 88% between different schools. The mean age of the interviewed pupils was 14–15 years for all schools, ranging from 5 to 23 years. The male:female ratio among the interviewed children was the same in all schools. The two groups of schoolchildren were different in religion and residence, with more christians and pupils of urban setting in the Kisarawe sample. The most significant findings were that the 74% of pupils from schools in Rufiji reported to have had visitors in school talking about leprosy, compared to 3% in Kisarawe. Among the Rufiji pupils, 17% (88/507) reported to have been absent during such talks. Inclusion or exclusion of these absentees in the analysis did not significantly influence the outcome between Rufiji and Kisarawe Districts.

Questions pertaining to knowledge of schoolchildren (Table 3) Knowledge of one or more signs and symptoms of leprosy was present among 90% of the Rufiji and 74% of the Kisarawe pupils. In Rufiji, 57% of the pupils were aware that leprosy can lead to skin lesions and disabilities, while in Kisarawe only 35% thought of this combination. The knowledge of this combination was regarded as more complete. The remainder mentioned either skin lesions or disabilities as signs and symptoms of leprosy. Both in Rufiji and Kisarawe 59% of the pupils knew how one contracts leprosy.

In Rufiji 75% of the pupils thought that leprosy is a curable disease versus 52% in

Table 3. Knowledge of schoolchildren on aspects of leprosy in Rufiji as compared to Kisarawe District

Knowledge of schoolchildren	Rufiji ($N = 480$)		Kisarawe ($N = 584$)		p
	N	%	*N*	%	
Knows one or more signs and symptoms of leprosy.	431	90	435	74	0·000
Knows proper mechanism of transmission by infection and close contact.	275	57	346	59	0·000
Mentions stigmatizing way of contracting leprosy (taboo, curse, sins, etc.).	16	3	42	7	
Knows leprosy is curable with chemotherapy.	362	75	302	52	0·000
Thinks leprosy cannot be cured.	103	21	266	46	
Every leprosy patient ends up being handicapped.	274	57	343	59	0·368
Only unrecognized patients not going for treatment will become disabled.	164	34	157	27	0·017

Table 4. Attitudes and beliefs of schoolchildren in Rufiji compared to Kisarawe

Attitudes and beliefs of schoolchildren	Rufiji *N*	(*N* = 480) %	Kisarawe *N*	(*N* = 584) %	*p*
Willing to play or share food with a schoolmate who is a leprosy victim.	181	38	145	25	0·000
Advise a schoolmate with signs and symptoms suspect for leprosy to go to a modern health facility.	393	82	491	84	0·345
Does not mention a stigmatizing way of which person is likely to get leprosy (taboo, curse, sins, family, etc.).	316	66	360	62	0·212

Kisarawe, and answers regarding treatment were similar in both districts: either by modern medicine (96%) or by traditional medicine (4%).

In Rufiji 57% and in Kisarawe 59% of the pupils thought that leprosy inevitably leads to disabilities and in Rufiji 34% of the pupils thought that this was due to unrecognised disease and late or no treatment, versus 27% of the pupils in Kisarawe.

Questions pertaining to attitude and beliefs of schoolchildren (Table 4) In Rufiji the children were more willing to play or share food with a schoolmate having leprosy than in Kisarawe, although this willingness was generally low: 38% and 21% in Rufiji and Kisarawe, respectively.

The majority of children (over 80%) in both districts would refer a leprosy suspect to modern health services.

Approximately the same proportion of children in Rufiji and Kisarawe districts thought that anybody could contract leprosy, 66% and 62% respectively, only 9% and 11% respectively thought that leprosy was related to sinful behaviour, eating forbidden food or witchcraft. The remaining 27% and 28% did not know how one contracts leprosy.

Attitude and beliefs associated with knowledge of schoolchildren Multivariate analysis,

Table 5. Knowledge of general public on aspects of leprosy in Rufiji as compared to Kisarawe District

Knowledge of general public	Rufiji *N*	(*N* = 345) %	Kisarawe *N*	(*N* = 99) %	*p*
Knows one or more signs and symptoms of leprosy.	273	79	81	82	0·773
Knows proper mechanism of transmission by infection and close contact.	72	21	23	23	0·004
Mentions stigmatizing way of contracting leprosy (taboo, curse, sins, etc.).	135	39	54	55	
Knows leprosy is spread by untreated leprosy patients.	124	36	59	60	0·000
Mentions stigmatizing way of spreading leprosy.	46	13	14	14	
Knows leprosy is curable with chemotherapy.	299	87	90	91	0·07
Thinks leprosy cannot be cured.	20	6	8	8	

adjusting for age, sex showed that children willing to play or share food with a schoolmate with leprosy were less likely to come from Kisarawe (OR = 0·6, 95% confidence intervals 0·5–0·8), were belonging to the older age groups (OR = 1·6, 95% confidence intervals 1·1–2·2) and knew that leprosy is curable (OR = 1·6, 95% confidence inteervals 1·1–2·2), but were less likely to know how leprosy is contracted (OR = 0·7, 95% confidence intervals (0·5–0·9).

Mentioning stigmatising predisposition to get leprosy was associated with moslem religion (OR = 1·3, 95% confidence intervals 1·1–1·6), with lack of knowledge of signs and symptoms (OR = 0·7, 95% confidence intervals 0·5–0·99), how leprosy is contracted (OR = 2·5, 95% confidence intervals 1·1–5·7), and with lack of knowledge that leprosy is curable (OR = 0·3, 95% confidence intervals 0·2–0·5). There was however no difference between the two districts.

General public

The characteristics of the people interviewed in the two districts were similar except regarding religion, residence and profession.

In Rufiji 29% (97/340) of those interviewed remembered having attended a seminar or meeting on leprosy and in Kisarawe District this proportion was 4% (4/97) and all of them could indicate that Rufiji Leprosy Trust were the organizers of such seminars. Both in Rufiji and in Kisarawe the respondents indicated that 18% of them had a relative or acquaintance with leprosy, and this was higher among the rural population (21%) than among people from urban settings (12%).

Questions pertaining to knowledge of the general public (Table 5) Interviewees of the two districts did not show any significant differences between responses to the questions about signs and symptoms, way of contracting the disease, which category of patient is infectious and whether leprosy is curable. Approximately 80% of the people in both districts could mention one or more signs and symptoms. The fact that leprosy can be spread in the community by infection and through close contact with a leprosy patient was known by 21% in Rufiji and 23% in Kisarawe. Breaking a taboo, sinful behaviour, curse from God, hereditary, etc. was given by 39% in Rufiji and 55% in Kisarawe as reason of spread of leprosy, the difference being statistically significant. The proportion knowing that untreated leprosy patients can spread the disease was significantly different between Rufiji (36%) and Kisarawe (60%). The knowledge on curability of leprosy with chemotherapy was generally high, and was not significantly higher in Kisarawe (91%) than in Rufiji (87%).

Table 6. Attitudes and beliefs of general public in Rufiji compared to Kisarawe

Attitudes and beliefs in general public	Rufiji ($N = 345$)		Kisarawe ($N = 99$)		p
	N	%	N	%	
Willing to shake hands with exleprosy patient.	157	46	45	45	0·992
Willing to share food from the same plate with and exleprosy patient.	137	40	44	44	0·178
Does not mention a stigmatizing way of which person is likely to get leprosy (taboo, curse, sins, family, etc.).	252	73	65	66	0·025

Analysis of knowledge of signs and symptoms of leprosy, adjusting for attendance of a leprosy seminar, having a relative or acquaintance with leprosy, age, sex, urban or rural residence, religion and level of education, showed that only knowledge on leprosy transmission was higher in Kisarawe district (OR = 2·4, 95% confidence interval 1·4–4·3). No other differences were found between the districts. The determinants for good knowledge about leprosy were older age and higher educational level. Having a relative or acquaintance with leprosy was not associated with better knowledge of leprosy, nor was attendance at a seminar or meeting on leprosy.

Questions related to attitude and beliefs among general public (Table 6) Questions about stigmatizing attitude and behaviour, like sharing food from the same plate or shaking hands with a patient and which type of people are likely to get leprosy, were not answered in a significantly different way between Rufiji and Kisarawe Districts. In both districts on average 40% to 45% of the people were willing to shake hands and to share food from the same plate. A difference existed between answers to the question which person can get leprosy: 73% in Rufiji and 65% in Kisarawe thought that anyone could contract leprosy, and in Rufiji 18% and in Kisarawe 30% associated stigmatizing beliefs with contracting leprosy.

Attitude and beliefs associated with knowledge of general public Multivariate analysis with attitude as the dependent variable and having attended a seminar, having a relative or acquaintance with leprosy, knowledge of leprosy, age, sex, residence, religion and level of education as the independent variables, showed that willingness to shake hands was significantly associated with knowledge that leprosy is an infectious disease (OR = 1·7, 95% confidence interval 1·1–2·8), with urban residence (OR = 2·4, 95% confidence interval 1·4–4·0), with younger age (OR = 0·97, 95% confidence interval 0·96–0·99) and with not following the moslem religion (OR = 0·5, 95% confidence interval 0·3–0·9). There was no difference between the districts.

The willingness to share food from the same plate was significantly associated with better knowledge of signs and symptoms of leprosy (OR = 2·5, 95% confidence interval 1·3–5·0) and of the infectiousness of leprosy (OR = 2·1, 95% confidence interval 1·2–3·5), with younger age (OR = 0·97, 95% confidence interval 0·96–0·99) and with not following the moslem religion (OR = 0·4, 95% confidence interval 0·2–0·9). There was no relationship with residence in either district.

Stigmatizing belief about contracting leprosy was significantly associated with knowledge of the infectiousness (OR = 2·0, 95% confidence interval 1·1–3·6), female gender (OR = 0·8, 95% confidence interval 0·6–0·9) and lack of primary education (OR = 0·4, 95% confidence interval 0·2–0·9). There was no difference between districts.

In neither district could positive or negative attitudes and beliefs be shown to be

Table 7. Knowledge of medical staff of leprosy in Rufiji compared to Kisarawe

Knowledge of medical staff	Rufiji ($N = 44$)		Kisarawe ($N = 42$)		p
	N	%	*N*	%	
Knowing the treatment of leprosy with MDT	22	50	6	14	0·001
Knowing the signs and symptoms of a leprosy reaction	22	50	9	21	0·011
Knowing the treatment of a leprosy reaction with prednisolone.	11	25	13	31	0·708

associated with attendance at leprosy seminar, having a relative or acquaintance with leprosy and knowing that leprosy can be cured.

Medical staff

Clinical Officers (Medical Assistants and Rural Medical Aides), Nurses and subordinate staff were interviewed at 2 hospitals and 4 different peripheral health units in Rufiji and Kisarawe Districts. Their characteristics were comparable and differed only in religion, reflecting the overall situation in both districts.

Questions pertaining to knowledge of medical staff (Table 7) Among the medical staff in Rufiji 32% (14/44) said to have an acquaintance or relative with leprosy compared to 57% (24/42) in Kisarawe.

The proportion of medical staff with knowledge of signs and symptoms of leprosy and the mode of transmission was high among staff in both districts, being 98% and 100% respectively. The transmission of leprosy by infection was properly known by 80% (30/44) of the staff in Rufiji and 69% (29/42) in Kisarawe, the difference not being statistically significant.

The proportion of the staff who knew that leprosy can be treated with multi drug treatment (MDT) in Rufiji was 50% (22/44) and in Kisarawe 14% (6/42). The difference was most pronounced among clinical officers and the subordinate staff, and was highly statistically significant.

Only 50% (22/44) of the Rufiji and 21% (9/42) of the Kisarawe medical staff knew the signs and symptoms of severe leprosy reactions. The difference was mostly attributable to better knowledge among the subordinate staff interviewed in Rufiji district.

The proportion of staff who knew that a severe reversal reaction should be treated with prednisolone was 25% in Rufiji and 31% in Kisarawe district, the difference not being statistically significant, except among the nurses, in favour of Kisarawe district.

Questions pertaining to attitude and beliefs of medical staff (Table 8) The proportion of staff giving an affirmative answer to the questions whether they would marry in a family with leprosy, share food from the same plate and shake hands with an ex leprosy patient, were not statistically different between Rufiji and Kisarawe, except for shaking hands with leprosy patients, in favour of Kisarawe.

Attitude and beliefs associated with knowledge of medical staff Multivariate analysis of an association between positive attitude and beliefs and the knowledge of leprosy and leprosy

Table 8. Attitude and beliefs of medical staff in Rufiji compared to Kisarawe

Attitudes and beliefs of medical staff	Rufiji ($N = 44$)		Kisarawe ($N = 41$)*		p
	N	%	N	%	
Willing to shake hands with exleprosy patient	35	80	37	90	0·038
Willing to share food from the same plate with an exleprosy patient	26	59	31	76	0·063
Willing to marry from a family with a leprosy patient	22	50	28	68	0·06

*one individual not evaluated.

reactions, controlling for sex, age, profession, residence, religion and having a relative or acquaintance with leprosy in, showed no statistically significant difference between the districts to exist, except just significantly in the willingness to share food with a leprosy patient, in favour of Kisarawe district (OR = 5·5, 95% confidence intervals 1·0–29·7).

Nurses and subordinate staff were less likely to shake hands (OR = 0·0, 95% confidence intervals 0·00–0·1). The willingness to marry in a family with leprosy was associated with lack of knowledge of the signs and symptoms (OR = 0·1, 95% confidence intervals 0·02–0·6), but was associated with knowledge of the treatment of reversal reactions of leprosy (OR = 4·4, 95% confidence intervals 1·2–2·9).

Perception of responsibilities of medical staff in leprosy control In Rufiji 68% (30/44) of the staff felt that the diagnosis and treatment of and care for leprosy patients is the sole responsibility of the DTLC, compared to 31% (13/42) in Kisarawe. But this difference did not exist between the person in-charge of the units (Clinical Officers). 75% of the staff in Rufiji and 66% in Kisrawe felt that the DTLC was the only person to do the defaulter tracing of leprosy patients, the difference not being statistically significant.

Community leaders

Out of a total of 47, only 4 community leaders could be interviewed in Kisarawe District, making comparison between the two districts unfeasible. From the leaders interviewed in Rufiji 64% knew one or more leprosy patients within their jurisdiction. Seven-four per cent of them were aware of the health education campaigns from Kindwitwi and mostly so because they had been contacted first. Many of them played an active role in the campaign by conveying the message, making home-visits and referring patients in need. The majority (93%) believed that the campaign has increased the knowledge of leprosy and the availability of effective modern treatment. Out of them, the majority of the leaders (83%) thought that the main effect on community members of the campaign has been to increase knowledge about leprosy and modern treatment, and 17% thought that only reduction of fear and stigma was most important. However, 46% of them believed that reduction of fear is the most important mechanism to reduce discrimination or isolation of leprosy patients. They were not asked any specific questions concerning their knowledge, attitudes and beliefs about leprosy.

Traditional healers

Out of the 17 traditional healers interviewed only one could be interviewed in Kisarawe District due to the lack of a centralized registration of traditional healers in Kisarawe. Therefore comparison between the two districts is not feasible. Less than half (41%) of the interviewed healers stated that they treat leprosy. They were consulted by 81 leprosy patients during the past year and claimed to have cured 60 of them (74%). This claim could not be verified. They believed that leprosy is decreasing and gave the availability of effective modern treatment as the reason (80%). A minority (20%) felt that also traditional treatment (in combination with modern medicines) contributed to the decrease. On the other hand, 94% of them agreed that breaking a traditional taboo can cause leprosy. Out of the traditional healers interviewed, only 47% had attended a seminar or meeting on leprosy where they learned about good results of modern treatment and the necessity for referral of patients. No other more specific questions concerning their knowledge, attitudes and beliefs about leprosy were asked.

Discussion

The socioeconomic status of the people of the two districts is very similar, according the national census data. Nevertheless, Kisarawe district is in easy reach of Dar es Salaam, while Rufiji is much farther away and partly separated by the Rufiji river, which is difficult to cross in the rainy seasons. In Rufiji district leprosy is a bigger problem than in Kisarawe district. The higher case notification and higher proportion of disabled among new cases denote that in Rufiji cases are detected in a more advanced stage of the disease than in Kisarawe. A possible explanation could be that the appeal of the activities of the Rufiji Leprosy Trust and the presence of a charismatic person like the late Rev. Fr. Lamburn, attracted (disabled) leprosy patients from neighbouring districts, including Kisarawe. The high fluctuation in the case detection in Rufiji was probably a result of availability of clothing and supplementary food at Rufiji as well as health education activities. Nevertheless, both Rufiji and Kisarawe Districts showed largely similar downward trends in annual case detection of leprosy, as well as a very favourable compliance of leprosy patients to treatment. It is worrying that no downward trend could be observed in the proportion of disabled and children below 15 years among new cases diagnosed.

The results of the interviews show that people in Rufiji District have had more exposure to health education seminars and meetings than in Kisarawe, and that they remembered well that these were organized by Kindwitwi Leprosy Trust.

We are aware of the difficulties concerning getting a real true picture of one's attitudes and beliefs using interviews. In-depth interviews with a more extensive questionnaire and with more than one control question would be more appropriate for this purpose. Observation would be even more valid. Nevertheless, for the purpose of comparison we have categorized the many different answers given into a few prevailing attitudes and beliefs.

Among schoolchildren, the overall knowledge of leprosy and the place to go for treatment was high and was higher in Rufiji than in Kisarawe. However, knowledge about mechanisms of becoming disabled was low in both districts. The attitude and beliefs of the schoolchildren were low in both districts, especially the willingness to play or share food with a leprosy victim, but were better in Rufiji than the Kisarawe. These differences can be attributable to exposure to health education.

The effect of health education was less clear among the general public. Knowledge of leprosy was high in both districts. It appeared that attending seminars on leprosy in Rufiji District has not directly increased the knowledge on mode of transmission of leprosy as compared to Kisarawe. In addition, increased knowledge of parents attributable to having their children exposed to health education at school, as is shown to exist in some studies,[5] apparently did not have much influence, reflecting similar findings in other studies.[8] The peculiar finding that Kisarawe general public scored so much higher in knowledge of spreading of leprosy by untreated leprosy patients is difficult to explain, but fits the general impression that knowledge of leprosy was slightly higher in Kisarawe. This question also served as a control for the stigmatizing answer of how one contracts leprosy. However, we were not informed of the levels of knowledge before the campaign in Rufiji and could therefore not measure a change over time. Neither were we aware of any differential exposure of the population of Kisarawe to any other health education about leprosy by multimedia (radio, TV or newspaper), or the influence of living close to Dar es Salaam. Stigmatizing attitude and beliefs were prevalent in both districts and were associated with lack of knowledge of leprosy, lower education level, female gender, rural residence, older age group and Moslem religion.

Table 9. Comparison of level of knowledge and attitude towards leprosy of Rufiji, Kisarawe and two studies in India

Knowledge/attitude	District	School children	General public	Study[6] %	Study[5] %
Knowing signs and symptoms of leprosy	Rufiji	90%	79%	64	50–64
	Kisarawe	74%	82%		
Knowing mode of transmission	Rufiji	57%	21%	48	
	Kisarawe	59%	23%		
Knowing leprosy is curable	Rufiji	75%	87%	48	
	Kisarawe	29%	91%		
Willing to share food with a leprosy victim	Rufiji	38%	40%	2–6	1–23
	Kisarawe	25%	44%		

Good knowledge and positive attitudes among the public could not be shown to be associated with having attended a leprosy seminar or having a relative or acquaintance with leprosy.

Compared with data from studies in India[5,17] and in Tanzania[7,18] the level of knowledge and attitude found in both Rufiji and Kisarawe can be considered similar or better. In Table 9 an overview of the findings about knowledge and attitude in this study is presented, compared to the findings in two other studies in India.[5]

Among medical staff knowledge of signs and symptoms and mode of transmission of leprosy was high, which reflects results found in staff in another African country.[4] Knowledge about MDT and the diagnosis of leprosy reactions was higher among staff of Rufiji compared to Kisarawe District. The knowledge of treatment of reactions with prednisolone was generally low and not different between the two districts. Attitudes and beliefs among health workers were generally positive, and higher than among schoolchildren and general public. Although no uniform relationship of attitude and beliefs with (lack of) knowledge of leprosy was found, some respondents' lack of knowledge on how to treat a leprosy reaction was associated with a stigmatizing attitude. In both districts, better knowledge among medical staff about the details of leprosy (treatment and reactions) seemed to be associated with stigmatizing attitude. This is a peculiar finding for which we have no explanation other than mentioned in literature, that increased knowledge not necessarily leads to better attitude.[5,6] A majority of the medical staff in both districts thought that working with leprosy patients is the responsibility of the DTLC only. In Rufiji district less responsibility for leprosy control was perceived to be given to the general staff, while at the same time they were more knowledgeable in diagnosing reactions and treating leprosy patients with MDT, and were less stigmatizing towards the patients.

Most community leaders stated that the health education campaign had increased the knowledge of leprosy in the community, but few mentioned that it had achieved much to reduce the fear and the stigma of leprosy. They were therefore well aware of the actual situation, as found by this evaluation.

The traditional healers perceived the leprosy problem to be decreasing, resulting from decreasing consultations by leprosy patients or suspects. They were therefore sensitive to the trend of leprosy casefinding in their districts. They had a very high level of stigmatizing beliefs themselves, but nevertheless were aware of the potential of modern treatment. Their claim of treating a substantial number of leprosy patients was not further verified. It would be worthwhile to get more details on their approach to and treatment of leprosy, in order to have more

specific messages for them and better utilize their influence. Traditional healers and community leaders were not asked the same questions as the general public. This omission made further comparison with the general public, and more detailed (multivariate) analysis, impossible.

We did not interview registered leprosy patients to find out whether health education activities contributed to their early recognition of signs and symptoms of the disease and a decision to go early for modern treatment. This knowledge would have contributed much to the analysis of effectiveness of health education.

Conclusion

We could not compare our findings with levels of knowledge and attitudes prior to the health education campaign, which would have been preferable. However, comparing the two districts with and without a sustained leprosy health education campaign, we found that the campaign has had a favourable impact on the knowledge and the attitude of school-children in Rufiji District. Among them we could demonstrate a relationship between increased knowledge of leprosy and a positive, less stigmatizing attitude.

We found indications that low level of education, rural residence, older age, female gender and Moslem religion were all associated with stigmatizing attitudes and beliefs towards leprosy.

Medical staff knew how to diagnose and treat leprosy, but few were confident in the diagnosis and treatment of leprosy reactions. Among them, lack of knowledge of diagnosis of leprosy and treatment of leprosy reactions was associated with stigmatizing attitudes. Also the epidemiological indicators show a high level of and little downward trend in the proportion disabled among newly-diagnosed cases. We could not establish a causal relationship between health education and increasing numbers of new leprosy cases diagnosed in early stages of disease. Fluctuating levels of case detection were probably also associated with availability of food and clothing supplements at Rufiji, in combination with health education outreach work by the Rufiji Leprosy Trust team.

We recommend that future health education activities focus on rural communities and schools and that women should be fully represented in the audience. It is advisable to continue to involve community and religious leaders and pay special attention to the traditional healers and further explore their current wisdom and expertise. Medical staff should be fully aware of leprosy treatment and leprosy reactions. Evaluation of outcome of health education campaigns can only complete when also leprosy patients themselves are included.

Acknowledgments

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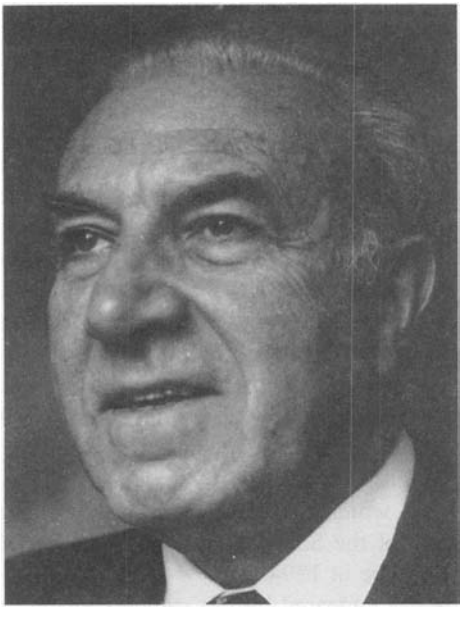
Obituary



WILLIAM H. JOPLING, 1911–1997

Dr William Jopling, well known to nearly all leprologists of his generation through his writings, research and friendship, died on 21 August 1997 at the age of 86. He was a specialist in leprosy, a humane physician and a family man who enjoyed life.

Born of British parents in Italy, he went to school in England and then studied medicine at St Bartholomew's Hospital, London. Later he gained the FRCP at both the London and Edinburgh Colleges. After undertaking a variety of junior hospital posts, he travelled as ship's surgeon on a six months voyage to the Far East. This was followed by appointment as Government Medical Officer in the Southern Rhodesia (now Zimbabwe) Medical Service, where at one time he was the only doctor for some 70,000 patients scattered over a huge area, about the size of Yorkshire. This proved to be an impossible assignment, and he was obliged to spend the war in Africa. He decided to learn more about leprosy after learning that a leprosy patient of his could only travel by rail if ankle deep in lime! He also took the patient to hospital by car. Subsequently, he paid visits to a leprosarium and spent one of his leaves there. After the war he returned to London, and took a post at the Hospital for Tropical

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Diseases where he was later appointed Consultant Leprologist. He also became Consultant in Tropical Dermatology at St John's Hospital for Diseases of the Skin, and he retained both these posts until his retirement. Other appointments included membership of the Editorial Board of *Leprosy Review* over a number of years. His contributions were always valuable.

William Jopling's eminence was as a clinician. He was an astute observer, with shrewd judgement with an understanding of his patients that owed much to the time he devoted to them; there was nothing he would not do for a patient in need, and many became devoted to him.

He seldom initiated research, but the dependability of his clinical judgement made him an invaluable and much sought after research partner, and for many years he was a central figure in the Hospital for Tropical Disease's leprosy research programme. When in 1950 the Jordan Hospital was established to cater for 24 leprosy inpatients at Earlswood in Surrey, the Jopling family were put in residence. (A situation that initially caused embarrassment among the local community.) Although there were only a small number of patients the proximity to London offered an outstanding opportunity for clinical research. These patients, perhaps the most intensively investigated leprosy patients anywhere at any time, became a model for what could be achieved in pilot trials. This hospital closed in 1967 when it became possible to treat the patients on an outpatient basis in London, but the programme continued. Jopling's first researches were therapeutic evaluations, old drugs versus new. This was a field that he never gave up, and later he conducted an early trial of multidrug therapy in Malta. He had a matter-of-fact turn of mind, and a preference when permissible to simplify. These qualities were much needed at a time when orthodox leprology was weighed down with niceties as the distinction between reactional tuberculoid and tuberculoid in reaction, borderline and dimorphous, and this was true particularly in relation to the classification with which his name is linked. His work in this field, which did so much to clarify the understanding of leprosy, was recognized by the award of the Sir Rickard Christophers medal of the Royal Society of Tropical Medicine and Hygiene in 1994.

His good humour and commonsense endeared him to students; teaching was one of his more important contributions to leprosy, and beyond that to tropical dermatology and medical practice in the tropics. In addition to lectures and articles Jopling was the author of a range of books that were all well received. His main work, *Handbook of Leprosy*, has just reached its fifth edition. Other titles were *Treatment of Tropical Diseases*, *Differential Diagnosis for Practitioners in the Tropics*, and *Travellers Guide to Health Protection Abroad.*

William Jopling was a generous friend, and long after retirement he remained in touch with old colleagues from around the tropics. In his younger days he was an athlete and rugby player, and he enjoyed fishing. Among his other interests he composed music, setting poems to song. He was a man of political conviction, and in a tolerant sort of way a supporter of left-wing causes. During the last three years he suffered progressive illness and failing eyesight, remaining always outwardly cheerful and grateful for his good fortune. He was twice married, and is survived by his first wife, their three sons, a daughter and eleven grand children.

D. S. RIDLEY

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Letters to the Editor

EDITORIALS, SEPTEMBER 1997 BY W. C. S. SMITH AND P. FINE & D. K. WARNDORFF

Editor,

These two timely editorials[1,2] are thought provoking. The overtones of criticism and sarcasm on leprosy elimination strategies make interesting reading.

While I can understand that remarks by the authors are prompted by their desire to effect refinement in scientific tools (basic as well as operational) and to improve assessment methods of routine control programme, I have to offer some comments, which is best done by considering both the articles together.

A constant and sincere attempt to effect reduction in prevalence rates (PR) seems to be going on throughout the world. Allowance has to be given for some unavoidable operational fallacies in coordinating the process and data collection of such gigantic magnitude and measuring the rates accurately. What is of tremendous practical importance is that we are trying to reduce the problem load of a strange disease known for its chronicity not fitting into a conventional epidemiological pattern through improved case detection from sources where patients are hitherto hidden for a long time. Rates based on incident cases reported at any point of time do not reflect such hidden elements nor also they indicate how long they were hidden. At the global level this perhaps is the best what one can do. This exercise has to be done, by harnessing the only tool available viz. manpower of diverse competence resting with governments and NGOs, motivated, half-motivated or not motivated. The MDT network is also widened to the best possible extent in highly diverse and difficult terrain's of the world.

The crude PR as reported by member nations of WHO is understandably coming down. Analysis of data generated by WHO tells us that something is happening—the coverage is increasing and with it new areas/populations are getting access to diagnosis and treatment, this is mainly due to integration of MDT services within the general health care system. This is an encouraging sign. In the absence of precise methods satisfying 'rigorous epidemiological standards' to measure the incidence of a chronic communicable disease with a built-in non communicable component of nerve damage and its sequale, PR with all its fallacies pointed out by the authors is the only index which gives a reasonably fair idea of the progress of leprosy elimination process. I believe that even without knowing incidence trends we can eliminate the disease, though it is desirable to know such trends for academic purposes.

As regards the target of 'zero disability rate', it seems an utopian dream at the present moment. Still in many parts of the world highly disabled patients are detected for the first time. In some sparsely populated inaccessible pockets, close to 40% of newly detected cases have grade II disabilities, indicating the magnitude of backlog cases precluding the possibility of accurate assessment of incidence rates, let alone disability rates. Moreover, nerve damage including 'quiet nerve paralysis' is occurring to a significant extent, according to some to an alarming degree even among patients already detected and brought under treatment. There is no accepted information collection system in relation to such events happening after detection. Any concept of zero incidence or zero disability rate at the global level is unthinkable, given the current systems of data gathering. WHO being globally responsible seems to be doing its best to collect data from member countries. Each one of these countries has its own reporting system, the disability component of which is very primitive and unreliable.

Was it not Dr Paul Fine who lamented 'will we understand leprosy before it disappears'? He was

presumably in a pessimistic mood about understanding leprosy, while he has distinctly expressed his optimism about the disappearance of the disease. Indeed since he said this in 1994, the situation has improved (and not deteriorated) with special strategies spearheaded by WHO to unearth new cases and implement short course chemotherapy. If we had any qualms we might never have got started.

As regards the interesting concept of making a disease disappear by not looking at it is perhaps applicable to highly inaccessible pockets. Inspite of heavy odds people have started looking at them after all. Even if one looks at all of them all the time, I am afraid leprosy will not reveal its true incidence rates! This is the reason why the problem of raising funds, as rightly pointed out by Dr Fine assumes tremendous significance as it poses a threat for future research in leprosy and may lead to less people looking at this disease. This will indeed be a tragedy.

Even laymen in India have felt the tangible reduction in the disease burden in both rural and urban communities, though by the application of strict standards of incidence criteria, leprosy elimination still poses considerable challenges. I believe that eliminating most or even some of the problems should be most welcome under the current constraints. While understanding of basic aspects of transmission (as proposed by Dr Cairns Smith) as well as further refinement of operational and reporting strategies (as Dr Fine would have it) will not only lead to elimination and perhaps even to a 'world without leprosy', but also to total understanding of the disease by all of us concerned.

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SINGLE-DOSE RIFAMPICIN, OFLAXICIN AND MINOCYCLINE (ROM) THERAPY FOR SINGLE LEPROSY LESIONS

Editor,

A single dose of drugs for the large number of single-lesion cases detected annually in endemic countries would help in keeping the elimination of leprosy on schedule. A multicentre trial involving 1381 patients followed-up for 18 months after the dose was published in the *Indian Journal of Leprosy*[1] and presented at the recently concluding XXth Biennial Conference of the Indian Association of Leprologists. Some of the participating centres presented the findings in their patients included in the trial. Comments on the trial and possible indications for single-dose therapy are given below.

The study did not consider: 1, site; 2, size; and 3, classification of the lesions as important factors when including the patients. The significance of these is considered with illustrations where available.

Site. In the clinical transparencies presented by one centre, there were at least two showing macular lesions on the face. It is well known that it is difficult to elicit sensory loss on face lesions on account of the rich nerve supply. Therefore diagnosis of macular lesions on the face poses a problem.

Certain sites, e.g. face, hands and feet are considered as strategic since regional nerve trunks, ulnar and lateral popliteal and when palmar and plantar lesions are present (not uncommon in some parts of South India) median and posterior tibial nerves are involved. Even though they may not be enlarged at the time of examination often *Mycobacterium leprae* lurk in these nerves. During therapy

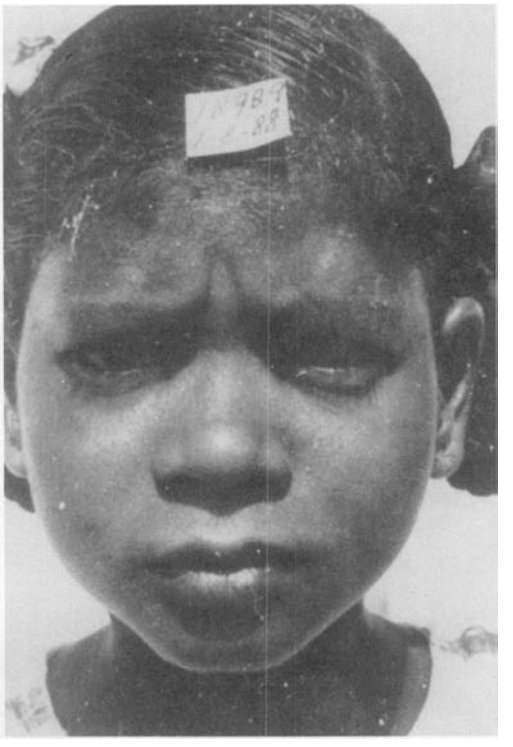

Figure 1.

or after as a part of reversal reaction acute painful neuritis may be encountered in these nerves. In the rifampicin, oflaxacin and minocycline (ROM) trial neuritis was observed in 3 cases. It would be interesting to have the incidence of neuritis according to site of lesions. The significance would be great when ROM is administered as routine and the patients are not seen afterwards resulting in disabilities.

Size. The larger the size, the greater the number of nerves involved in the dermis. Consequently the number of bacilli would also be more. Such lesions are also prone to reversal reaction; they would provide instances of treatment failure due to inadequate treatment.

This is illustrated in Figure 1, where a large BT lesion covers most of the race; the raised edge can be seen on both sides of the forehead. Powdery scales are the embers of a reversal reaction during paucibacillary multidrug therapy (PB–MDT). Steroid therapy stemmed the damage in the facial and trigeminal nerves, which could have resulted in lagophalmos and corneal anaesthesia followed by the dire consequence of exposure keratitis. Such a case is not suitable for single-dose ROM without followup.

Classification. In all the centres participating in the trial enough expertise was available for bacteriological examination. Only negative cases were included. Even so the clinical transparencies presented by two centres differed in clinical characteristics. One of the centres presented raised lesions with prominently thickened nerves, whereas another presented macular lesions. One of the lesions from the former, presented a lesion with rounded edges which could have been classified as midborderline leprosy.

Figure 2 shows a rounded lesion on the cheek with abrupt inner and sloping outer edges with a normal centre. The erythema denotes activity. A skin smear from the outer edge was positive for acid-fast bacilli (AFB) with a BI of 2. This was the only lesion observed.

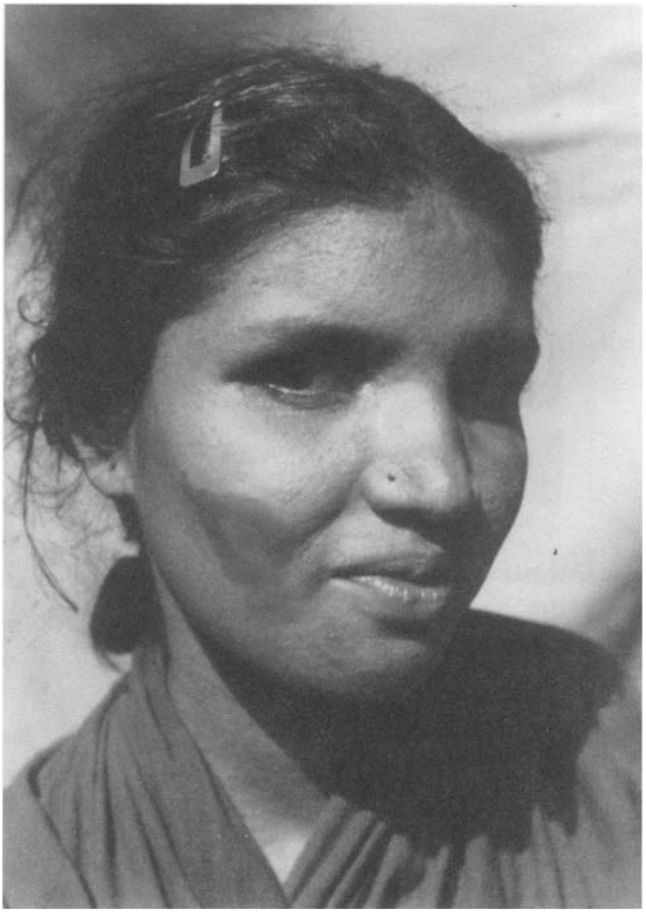

Figure 2.

Figure 3 is of a single lesion in one year after PB–MDT. An extension of the lesion can be identified where the previous edge can be seen, and beyond it another edge which seems to be in the process of advancing. The edge here and proximally is sloping. The surface is rugged. Sensations were impaired. A femoral cutaneous nerve can be seen coursing under the hypopigmend area of the lesion—BI 2 + Classification BL (histological) following treatment failure.

Figure 4 depicts a large hypopigmented lesion, flat, with ill-defined margins. Sensations were diminished—BI 1 + Classification (macular) BL.

These cases are presented to emphasize that all single lesions should not be considered as paucibacillary. It is also useful to remember that relapsed lesions of lepromatous or BL leprosy, particularly those flowing dapsone monotherapy, may present as single papules or macules or plaques. Skin smears would be strongly positive.

While the outcome in the trial as regards complications has been similar to that of PB–MDT, it should be noted that in PB–MDT the patient is under medical care for 6 months and under surveillance for 2 years. Patients after a single dose of ROM would be unobserved.

Indications for ROM single-dose therapy: Firm instructions on the use of ROM should be issued, perhaps on the lines given below:

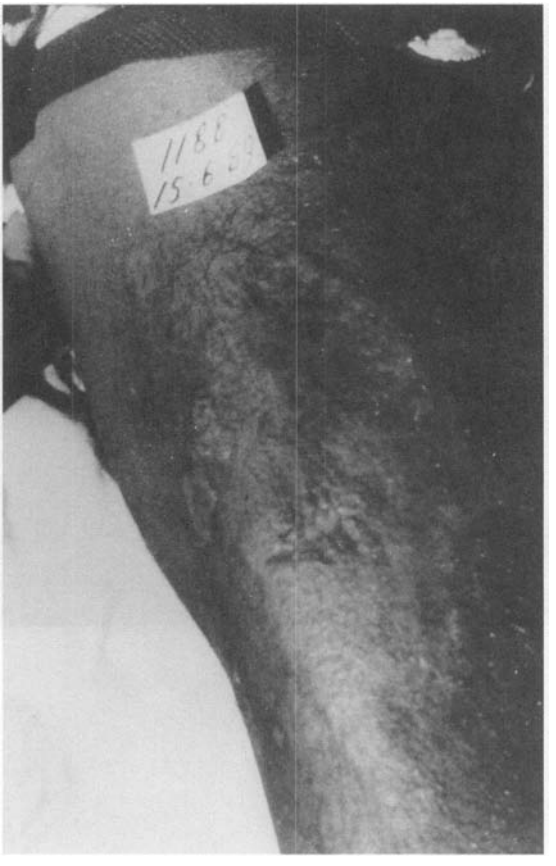

Figure 3.

1 A single dose may not be harmful in single nonleprosy lesions diagnosed as leprosy in the field.
2 Lesions with equivocal sensory loss. The usual advice is to keep the patients under surveillance till either signs of leprosy develop or the lesion disappears. ROM single-dose therapy might abort the lesion.
3 Early single macular lesions (Indeterminate) which are observed to heal in 11% of cases (Lara & Nolasco)[2] would benefit from the treatment.
4 Tuberculoid major lesions which were found to heal, scar or never downgrade in a study of the natural evolution or leprosy (Ramanujam)[3] are likely to respond early to treatment.

The above listed types of single lesions would cover nearly 95% of single lesions in the field. Five per cent of cases would call for care in classification and management to minimise disabilities and treatment failure.

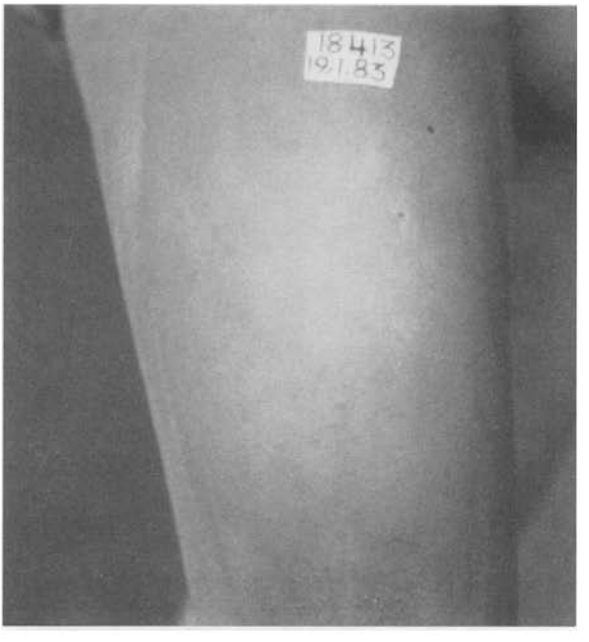

Figure 4.

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UVEITIS IN LEPROSY PATIENTS WHO GOT INACTIVE CONDITION IN PRE-WHO/MDT ERA

Sir,

Among the various ocular diseases caused by leprosy, complications of the uveal tissue are considered to be the leading courses of blindness.[1] Apart from uveitis relating to active leprosy, the occurrence of uveal inflammation long after the disease becomes inactive as defined by standard criteria is also well known.[2] In Japan leprosy has almost been eradicated, but doctors frequently see the inflammatory conditions in anterior chambers of leprosy patients even though their disease has long been quiescent.[3] Our study examined the cases of on-going uveitis in patients whose leprosy had been quiescent for more than 10 years.

Patients and methods

In April 1995, 598 cases (mean age: 70·8 years) were registered in our hospital (Tama-Zenshoen, Tokyo, Japan). They were Japanese and Koreans therefore having the same ethnic origin. They were composed of 341 cases of lepromatous leprosy (LL), 217 cases of borderline leprosy (B) and 36 cases of tuberculoid leprosy (TT). Of 598, we excluded all 36 cases of TT, 4 cases of under 40 years and 1 active pulmonary tuberculosis. In the residual 557 cases, 416 cases (244 of LL, 172 of B) could attend at both the dermatological and ophthalmological clinics during the years from January 1993 to April 1995. Based on the annual medical examination, any other diseases which can cause uveitis, such as sarcoidosis, Behçet disease, toxoplasmosis, Harada's disease and adult T cell leukemia/lymphoma have not been found in these registered cases.

Of the 416, 69 cases had positive skin smears for AFB or any active skin lesions during the past 10 years. As for all remaining 347 cases (mean age: 71.0 years), the leprosy condition was inactive for more than 10 years bacteriologically and dermatologically. All these 347 were treated before current regimens as WHO/MDT were adopted in Japan, and most of them received dapsone (DDS) monotherapy.

Among the 347, 69 cases (mean age: 68.0 years) were found to have uveitis based on the inflammatory findings such as flare, cells or keratic precipitates in their anterior chamber. Some of them had irregular pupils and posterior synechiae also. Binocular phthisis was found in 24 cases (mean age: 78.8 years). Some of these were suspected to have been caused by acute or insidious uveitis from their medical records. However, we could not clarify the reliable histories of each phthisic eye (blindness, loss of light perception) for all 24 patients. Fifty cases (mean age: 76.7 years) had corneal disorders which were composed of corneal opacity and/or corneal ulcer. For these 50, there was no evidence of uveitis so far as the views of their anterior chambers were available using slit-lamp, but on the other cases the examinations of their anterior chambers were difficult because of their severe corneal opacity. The remaining 204 cases (mean age: 70·2 years) had neither uveitis nor corneal disorders. Anesthetic cornea and other ocular diseases of conjunctiva, sclera, lens and posterior part of eyeball were not examined in this study. The leprosy classification in each group of 347 cases is summarized in Table 1.

Table 1. Results of ophthalmological examination of 347 cases

Type of leprosy	No. of cases	Binocular phthisis	Corneal* disorder	Uveitis (group 1)	Disease free† (group 2)
LL	188	20	30	45	93
BL	68	2	17	19	30
BB	43	2	3	4	34
BT	48	0	0	1	47
Total	347	24	50	69	204
Mean age	71·0	78·8	76·7	68·0	70·2

*No uveitis was found so far as the views of their anterior chambers were available using slit-lamp. In the other cases the examination of anterior chamber was difficult because of their severe corneal opacity.

†Neither uveitis nor corneal disorder was found.

In the 69 with uveitis (group 1) and the 204 with neither uveitis nor corneal problems (group 2), we conducted the following studies: (1) the types of leprosy were compared; (2) 52 cases of group 1 and 56 cases of group 2 consented to undergo the gonioscopic examination of the limbic area for the search of iris pearls; and (3) serum samples of all cases of group 1 and group 2 were taken at the time of each ophthalmological examination, and IgG and IgM fractions of the Mycobacterium leprae (ML)-specific

anti-phenolic glycolipid-I (PGL-I) antibody were measured by ELISA. The procedure was basically the same as that described elsewhere using NT-P-BSA.[4] The titer was considered positive at ≧0.08 OD for PGL-I-IgG and ≧0.380 OD for PGL-I-IgM. The seropositivity of the PGL-I-IgG and/or PGL-I-IgM were deemed positive for the anti-PGL-I antibody.

The significance of differences was calculated from 2×2 contingency tables using Yete's test.

Results

1 The comparison of the prevalence of uveitis between the two groups by type of leprosy is shown in Table 2. Uveitis was found significantly more often in LL (32·6%) and BL (38·8%) cases than in BB (10·5%) or BT (2·1%) cases.

2 Iris pearls were found in 19 of the 52 (36·5%) cases of group 1 and in none of the 56 of group 2

Table 2. Prevalence of uveitis by type of leprosy, comparison between the two groups

	No. of cases (%)	group 1 case (%)	group 2 case (%)
LL	138 (100)	45 (32·6)	93 (67·4)
BL	49 (100)	19 (38·8)	30 (61·2)
BB	38 (100)	4 (10·5)	34 (89·5)
BT	48 (100)	1 (2·1)	47 (97·9)

Significant difference was found between;
LL and BB; $p < 0{\cdot}05$
LL and BT; $p < 0{\cdot}0001$
BL and BB; $p < 0{\cdot}05$
BL and BT; $p < 0{\cdot}0001$

Table 3. Detection of iris pearls in group 1 and group 2

	group 1 cases with iris pearls /all examined (%)	group 2 cases with iris pearls /all examined (%)
LL	14/33 (42·4)	0/38 (0)
BL	5/17 (29·4)	0/10 (0)
BB	0/2 (0)	0/8 (0)
Total	19/52 (36·5)	0/56 (0)

(Table 3). They were recognized as small round white particles usually on the surface of iris near the limbus.

3 The seropositivity results of the anti-PGL-I antibody assay are shown in Table 4. The rates of seropositivity in group 1 were higher than those of group 2 for all types of leprosy, and a significant difference was found for BL cases. For BB and BT, the number of cases were too small to be statistically evaluated.

Discussion

Among 347 cases without TT, aged more than 40 years old and keeping inactive condition of leprosy for more than 10 years, we found 69 cases (19·9%) of on-going uveitis.

It is generally accepted that intraocular involvement occurs often in LL, less often in BL, and never in tuberculoid leprosy. However, some recent reports show that BB and BT cases can also develop uveitis.[1,6] In our study, although the rates of uveitis in LL and BL were significantly higher than those in BB and BT, some BB and BT cases were also found to have uveitis. Noteworthy is the high rate of uveitis in our BL cases (38·8%), even higher than in LL cases (32·6%), though significant difference was not seen.

Chronic iritis is believed to be neuroparalytic to the small nerve of the iris from its early stage, particularly affecting autonomic supply.[7] In recent reports discussing postural changes in intraocular pressure, patients with immunologically unstable leprosy showed significant postural changes compared to patients with immunologically stable leprosy.[8] Other reports discussing 'pupil cycle time' also show that all LL, BL and BT leprosy cases involve conditions affecting the autonomic nerves.[9] If the

Table 4. Results of anti-PGL-I antibody assay*

	group 1 seropositive cases/total (%)	group 2 seropositive cases/total (%)
LL	28/45 (62·2)	47/93 (50·5)
BL	19/19 (100)†	5/30 (16·7)†
BB	2/4 (50·0)	9/34 (26·5)
BT	1/1 (100)	4/46 (8·7)
Total	50/69 (72·5)	65/204 (31·9)

*At least one of the two antibodies, PGL-I-IgG and PGL-I-IgM, was positive by ELISA.

†$p < 0·0001$.

autonomic dysfunction and the bacterial load during the active phase of leprosy can be assumed to account for the development of uveitis, they may explain the high rates of uveitis in the BL cases of our study.

We found iris pearls in 19 cases (36·5%) of 52 of group 1 but none in 56 of group 2 with close examination using gonioscopy. Since the iris pearls often change their locations,[10] repeated examinations of anterior chamber might increase the prevalence of iris pearls. Although iris pearls are miliary lepromas staying for years in iris stroma,[11] some small iris pearls, however, are calcified and do not respond to systemic therapy.[10,11] Further study of the relationship between the iris pearls and another factors like duration of active leprosy or the chemotherapy which had been administered during their active phase is currently undertaken seeking the etiology and character of these iris pearls.

The serological responses to ML-specific PGL-I antigen have been used to complement the clinical evaluation of leprosy patients.[12,13] From our results, comparing the seropositive rates between the two groups, the rates of positive cases in group 1 were higher than those in group 2 for all types of leprosy, and a significant difference was found for BL. B-group leprosy is immunologically unstable, and BL patients can develop both types of leprosy reaction.[14] Before modern treatment, the feasibility of reactions in B-group patients may have led to lower levels of chemotherapy and therefore inadequate bacterial clearance resulting in high levels of ML-specific antibodies. Our results may indicate the past history of insufficient chemotherapy especially in BL cases with uveitis. Further study on the more cases of BB and BT is needed to better understand the uveitis in B-group leprosy. The seropositivity of all our

cases, independent of uveitis, may also indicate the manner of formation of ML-specific antibodies of the cases who were treated in pre-MDT era.

The follow-up observation of all our cases hereafter might throw light on a part of uveitis-related tragedy which can occur on the patients who have already anesthetic limbs. We are also expecting to share our findings on the B-group leprosy with more other cases of the same or different ethnic groups. Long-term follow-up studies of the ocular diseases in the cases treated by WHO/MDT are also of great interest for the study on the relationship between the uveitis and the chemotherapy.

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COMMENT: ULNAR ABSCESS—4 MONTHS AFTER RELEASE FROM CONTROL WITH PAUCIBACILLARY-MULTIDRUG THERAPY

Editor,

We have read the case report: 'Ulnar abscess: 4 months after release from control with paucibacillary-multidrug therapy' published in *Leprosy Review* Vol. 68.2. 1997. The conclusion: 'Thus the use of steroids is a useful means to treat nerve abscesses and should be tried before surgical intervention' is too hasty. In the last 7 years we have examined more than 5000 nerves and operated more than 600, therefore we feel justified in making the following comments:

1 The authors say that 'the swelling reduced to the size of a 3-mm nodule' but fail to say what was the size of the swelling prior to the treatment.

2 The size of a swelling is no clinical evidence of abscess. Large oedema of the ulnar nerve up to 20 mm (as against the normal 3 mm) have been photo-documented by us.

3 There is no mention of sensory and motor deficit but no quantification is given. Therefore the assertion that following steroid 'motor power improved' has no meaning, moreover there is no record of sensory improvement, although sensory improvement may occur faster and more consistently than motor.

4 The authors use indiscriminately the words 'abscess' and 'segmental necrotizing granulomatous neuritis' (SNGN). On page 173 they write about abscess and on page 174 say '... the clinical presentation ... is more in favour of a localised nerve pathology probably a segmental necrotizing granulomatous neuritis'. These two entities are not the same. As defined by surgical textbooks an abscess is a collection of pus;[1] which implies a cavity and a collection. While in SNGN, as described by the original authors,[2] there is no cavity and no pus collection.

5 It is possible that the authors have confused a large oedema with abscess. We apologize for quoting our book. 'We have had two cases where we made a clinical diagnosis of abscess beyond doubt; yet on the operation table we were faced with oedema. Unless surgical exploration is done, the clinical diagnosis can always be questioned. The assumption that an abscess disappears by itself (*or even with drugs*) is against all principles of surgery. This wrong clinical impression is due to the fact that whenever there is an abscess there is a certain amount of oedema too. With large dosages of steroids, the oedema is brought under control and therefore it *appears* that the abscess too has reduced in size, when actually only the oedema-component of the swelling has diminished, but the physician will believe that the abscess has disappeared.[3]

6 SNGN can reduce with steroids and this could be a valid explanation. But abscesses do not disappear with steroids, and even in the unlikely hypothesis that in this case steroids reduced an abscess, a single case is not sufficient reason for changing surgical principles.

We have reported on 145 *true* nerve abscesses operated by us.[4] All those patients had been on steroids for a minimum of 6 months to 3 years; in none of these cases did the abscesses disappear and this was the reason why they were referred to us.

7 Among the conditions which masquerade as nerve abscess we have to include, in the case of ulnar nerve, abscesses of the supratroclear lymph node (see photo N.33 in our book, and page 96).

In conclusion, the authors can say that a SNGN can decrease with steroids but cannot maintain that: 'The usefulness of steroid therapy in the treatment of leprosy nerve abscess is demonstrated in this case report' because they do not have a case. Such a statement is dangerous as it may send the wrong signals down the line. For years we have been saying that cases of neuritis should be referred to surgery before it is too late. A paper which claims that steroids can cure nerve abscess is the last thing we really need. An abscess, if not excised surgically, will sooner or later break into a sinus. We have seen too many discharging sinuses, and not only from the ulnar nerve.

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Lepr Rev (1998) , 89–94

Teaching Materials and Services

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If you need more information apply: Dr P. S. S. Sundar Rao, Schieffelin Leprosy Research and Training Centre, Karigiri 632 106, North Arcott District, Tamilnadu, South India. Fax 91-416-74274.

Diploma in community-based rehabilitation management, new course, India

This course of one-year duration, aims at training practical managers at grass roots levels using multidisciplinary approaches to community-based rehabilitation, relevant to both National and International programmes.

Graduates preferably with experience are eligible. Tuition fee will be Rs. 6,000/-; Board and Lodging, about Rs. 750/- per month.

Karigiti is easily approachable from Madras (Chennai) or Vellore.

For further details Contact The Director/Registrar, SLR & TC, Karigiri, Tamil Nadu-632 106, India.

Managing Health Programmes in Developing Countries, Harvard, USA

The above course is run annually by Harvard School of Public Health. This year's course will run from 15 June–7 August 1998. The following is taken from the brochure:

Purpose

Managers of health care organizations in developing countries face enormous challenges. While public demand for services has steadily grown, financial and human resources have become increasingly unstable and insufficient. Managers are coping daily with inadequate facilities and supplies, poorly-trained and/or poorly-motivated staff, insufficient information for decision-making, rapidly changing technology and fluctuating political support. There is tremendous pressure to initiate positive change within such demanding circumstances. Health sector reform has only increased the need for competent managers.

This Harvard School of Public Health program, sponsored by the Harvard Health Management Group and the Center for Continuing Professional Education, has been developed to enhance the skills of mid-career health care managers in developing countries. It allows the mid-career manager who does not have the option of enrolling in a lengthy degree program to gain advanced skills for organizational success.

The faculty for the program are experts in the field of health care management, and familiar with the particular challenges facing health care managers in developing countries. Participants will also learn from dynamic exchanges with fellow members of the program. In addition, a number of special seminars on topics from HIV/AIDS to Operations Research are held.

Who should attend

This program has been especially designed for managers and health professionals from developing countries who work in both government and private sector health organizations, including curative (hospital) and preventive health programs, at the national, provincial and district levels. It will also be of interest to health care managers from industrialized nations who work in developing countries. The course is limited to individuals with professional health care experience, but prior formal training in management is not required or expected.

Space in this program is limited and each year more qualified candidates apply than can be admitted. It is therefore important for interested individuals to apply early.

For further details—course content, fees, financial assistance—write to: Vivien Goldman, Course Director, Harvard School of Public Health, 677 Hungtingdon Avenue, SPHI-1210, Boston, Mass 02115, USA. Fax: 1 617 432 1323. email: vgoldman@sph.harvard.edu. Internet site: http://www.hsph.harvard.edu/mhpcd.html.

Training for the handicapped in photography, VRC, India

The Vocational Rehabilitation Centre (VRC), an institution run by the Ministry of Labour, Govt. of India, in Mumbai is conducting a training programme in photography for handicapped persons including leprosy-cured patients in collaboration with the Bombay Leprosy project (BLP), an NGO working with the aim of integrating leprosy patients with other handicapped people.

A review of this six-month training course was held on 20 October 1997 at the VRC. On this occasion, Mr R. Narasimham, Sr. Superintendent of VRC said that he has always been concerned about the plight of leprosy patients since his studenthood and assured to provide the best services through VRC. The experience of VRC shows that leprosy patients receiving training in a non leprosy institution contribute to abolish stigma.

Dr R. Ganapati, Director, BLP while applauding the efforts made by the VRC to bring the leprosy-cured persons into the mainstream of their vocational training for handicapped, expressed the need for offering such training particularly in sophisticated fields such as photography, computers and electronics, etc. These professions are assuming importance in the modern age of advancing technology. The trainees who undergo practical training on the technical aspects of medical and commercial photography will promote BLP's novel concept of harnessing the skills of the handicapped even in areas of research. These patients will assist the 'documentation cell' of the project and thereby augment research in leprosy.

Mr V. Y. More, Instructor, VRC, Mr T. P. Mirajkar, Rehabilitation Officer, BLP and Mr P. Narayanasamy, Manager, BLP participated in the review.

'Sustaining Leprosy Related Activities—Guidelines for Responding to Change', ILEP

The introduction of multidrug treatment (MDT) for the treatment of leprosy has radically changed the

extend and nature of the leprosy problem. Millions of leprosy patients have now been successfully treated. However, leprosy is a continuing problem, since leprosy cases occur each year. It is therefore essential to sustain leprosy services. Yet the structure and size of these services must change. In many countries, this is already happening, combining with other disease control programmes and integrating into primary health care services. Also, financial responsibilities are bound to shift towards governments and local non-governmental organizations (NGOs). It is vital to carefully assess the need and plan for these changes. These Guidelines are the outcome of a workshop organized by International Federation of Anti-Leprosy Associations (ILEP) and Netherlands Leprosy Relief Associations (NSL) held in Amsterdam, The Netherlands in September 1996. During the workshop, leprosy experts and health planners discussed various issues and aspects related to the improvement of the sustainability of leprosy services. The resulting guidelines are intended to facilitate this process. They are directed to programme managers and policy makers and follow a stepwise and participatory planning approach.

The booklet is divided into three parts. The first part deals with the necessary situational analysis of existing services. Part two describes the possible planning steps in the process of organisational change. The last section describes useful strategies and mechanisms in the implementation of the desired change.

The booklet is available, free of charge to personnel active in this field, from: International Federation of Anti-Leprosy Associations (ILEP), 234 Blythe Road, London, W14 0HJ, UK. Fax: +44 171 371 1621; E-mail: ilep@ilep.org.uk.

Diagnosis and treatment of skin infections, 1997, Blackwell Science Ltd, UK

Blackwell Science Ltd., Oxford have recently published a book on the above subject, edited by Professor Marwali Harahap, Professor of Dermatology, School of Medicine, University of North Sumatra, Medan, Indonesia. It is a hardback of 448 pages, plus a detailed index. The main chapter headings are—principles of anti-infective therapy, staphylococcal and streptococcal skin infections, parasitic infections, skin infections with AIDS and HIV-immunocompromised patients, fungal infections, leprosy and infections in dermatological surgery. The text is illustrated with colour plates of high quality. With the exception of the Editor. two contributors from the UK and one from Germany, all the authors are from the USA, many of them with long experience of treating a wide range of patients, including immigrants and those of Hispanic origin. Price £89.50. Available from Blackwell Science Ltd., Osney Mead, Oxford, Oxford OX2 0EL, United Kingdom, or through recognized medical bookshops.

Essentials of Leprosy, sixth edition. L. J. Yoder and J. M. H. Pearson

The 6th edition, 1996 of this extremely well-known booklet has recently appeared, including a chapter on Leprosy in the Eye by E Zijp and a complete set of new colour plates from A. Colin McDougall, Oxford, UK. As in previous years this booklet comes from Talmilep, Teaching and Learning Materials in Leprosy, a joint project of the International Federation of Anti-Leprosy Associations (ILEP) and is obtainable, essentially free of charge, through The Leprosy Mission International, 80 Windmill Road, Brentford, Middlesex TW8 0QH, United Kingdom. There are 16 chapters, covering all main aspects of leprosy, plus two appendices, one dealing with the taking and interpretation of skin smears and the other with biopsies. This is an outstandingly good source of information and one which has already had a highly successful track record of distribution worldwide for many years. The format and appearance of the Sixth Edition have been markedly improved and it is to be hoped that it will achieve distribution and acceptance without delay, in all countries with a continuing leprosy problem.

A distance-learning resource for tropical medicine

From the Wellcome Trust in London comes the news of the *Tropical Medicine Resource (TMR)* now operating from the Wellcome Centre, which enables anyone with IBM-compatible hardware and commercially available Windows-based software to access its archives. The TMR Bulletin, *Focus*, August 1996, reports that in its first appraisal of the service over 160 centres in 44 countries participated. The results are now being analysed.

TMR appreciates that there are still many countries where the technology does not allow participation. Where a beginning is possible, an effort is being made to target universities and other centres of learning, while remembering the needs of 'students who may be new to computers, with English as their professional, but (at best) their second language, and perhaps working under difficult conditions (e.g. in Sri Lanka by generator, after a hurricane!) ... TMR stands alone but is best used to complement other sources of reliable information, not least, experienced teachers and practitioners with sound local as well as academic knowledge'.

Consultations between Robyn Young of TMR and AIM are proceeding, and it is hoped that avenues of collaboration which can benefit AIM members will be found.

Information can be obtained from: The Wellcome Trust, Tropical Medicine Resource, 210 Euston Road, London NW1 2BE, UK, Tel: (44) (0)171-611 8460, Fax: (44) (0)171-611 8472.

ECHO: Selecting medical supplies for basic health care

Selecting Medical Supplies for Basic Health Care, R. Skinner, J. Townsend, V. Wells, ECHO, 1995, 30 p.

In view of the great financial pressures experienced by health services, there is a critical need to ensure that the best and most efficient use is made of all supplies. For many years WHO's Model List of Essential Drugs has been helping countries meet their highest priority treatment needs with a well-chosen list of basic low-cost products. As yet no one had developed a satisfactory model list of essential medical supplies to complement the drugs list. With its new publication, Equipment for Charity Hospitals Overseas (ECHO) has provided a list which facilitates choice of the most appropriate supplies for basic medical care. The authors identify the essential stocks that should always be available; and give advice on priority setting for procurement and good supply management in medical stores, hospitals and clinics.

The authors stress that a model list has to be transformed into a standardised local list. They encourage the setting up of standard practice protocols, which can guide health workers into more cost effective clinical practice by specifying the appropriate medical supply items to use in diagnosis and care.

The publication will be useful for health ministries, supply organizations, health care institutions and development agencies.

Available from: Echo International Health Services. Ullswater Crescent, Coulsdon, Surrey CR5 2HR, UK. Price £3.

Pharmacy Library Pack, TALC, UK

The high cost of drugs and supplies is one cause of the financial difficulties hospitals and health centres are experiencing. The *Pharmacy Library Pack* has therefore been produced to help managers of pharmaceutical systems to use their drugs budget cost effectively. The Pack was compiled by an expert group from four UK organizations: ECHO International Health Services, The Essential Drugs Project, The Robert Gordon University School of Pharmacy, and Teaching Aids at Low Cost (TALC).

Eleven items cover the main functions of the drug supply system: acquisition, holding, dispensing and rational and economic use. They have been chosen with the needs of hospital directors and managers, pharmacists and storekeepers in mind. The Pack contains: WHO Model List of Essential Drugs; WHO Financing Essential Drugs: Report of a WHO Workshop 1988 and Ten Questions to Ask About Revolving Drug Funds (Tropical Doctor); MSH International Drug Price Indicator Guide; CMC Guidelines for Donors and Recipients of Pharmaceutical Donations, and of Medical Equipment Donations; AHRTAG How to Manage a Health Centre Store; MSF Essential Drugs—Practical Guidelines; WHO Guidelines and Sterilisation and Disinfection Methods Effective Against HIV; British National Formulary; MSF Clinical Guidelines, Diagnostic and Treatment Manual; WHO/CDR Leaflets: Management of the Patient with Diarrhoea and Acute Respiratory Infections; and WHO/DAP Indicators: How to Investigate Drug Use in Health Facilities.

Available (as a complete pack form only) from: TALC, P.O. Box 49, St Albans, Herts AL1 5TX, UK. Tel: +44 1727 853869, fax: +44 1727 846852. Price: £47 surface mail, £62 airmail.

Leprosy in childhood, revised and updated 1997—slide set

This set of slides was originally produced and widely distributed in the early 1970's, based on the experience of Dr Colin McDougall in the national leprosy control programme in Zambia. Many of the clinical pictures are thus African, but the main clinical messages are applicable to patients in other parts of the world and the definitions and criteria for diagnosis, classification of leprosy and the treatment of all patients with regimens of multiple drug therapy (MDT) are based on current WHO recommendations. Whilst most of the transparencies are of children, this set of slides and the text are also suitable for teaching and learning about the main features of leprosy in adults. Dr Felicity Savage contributed to a revision in 1989, which included a rewriting of the test for those whose first language is not English. The set has recently (1997) been further revised, to include reference to changes in the chemotherapy of leprosy, as advised by WHO.

Colour transparency teaching set (24 slides) with explanatory text (20 pages). Cost: Self-mounting sets with text, £5.50.

Available from TAC: Teaching Aids at Low Cost, PO Box 49, St Albans, Herts AL1 4AX, United Kingdom. Tel: (0)1727 53869; Fax: (0)1727 46852.

Order forms, with details of postal costs and description of sets mounted, in file/folder, or on slide/tape, are available from TALC above.

INASP-Health

INASP-Health is a demand-led initiative based on the recommendations of the 1994 London conference 'Getting health information to developing countries', hosted by the *British Medical Journal*. It is supported by the Overseas Development Administration (UK) and the British Medical Association.

Over the next 3 years we are introducing a unique programme to help you achieve your goals. The programme offers:

- A point of reference for the health information provider (HIP) community: HIP organizations, health librarians, funding agencies, and others committed to the provision of **reliable information for health workers in developing countries**.
- An evolving picture of information needs and provision in the developing world, helping to prioritize future strategies.

- An advocatory structure to promote cost-effective initiatives and to lobby for increased political and financial commitment to HIP activities.

Contact: Dr Neil Pakenham—Walsh Programme Manager, INASP-Health (Oxford Office) 27 Park End Street, Oxford OX1 1HU, United Kingdom.

14th Board Meeting of the Novartis (previously Ciba-Geigy) Leprosy Fund, Basel, Switzerland, June 1997

Chaired by Professor K. M. Leisinger, this Fund met recently in Basel to consider current programmes in various parts of the world and new applications for support. Originally directed almost exclusively to case finding and the implementation of multiple drug therapy (or improving programme conditions so that this would be possible), the Fund has now extended its support to some aspects of disability prevention and management, preferably linked, however, to case finding and MDT. The invited experts are Dr N. M. Chitimba (WHO, Africa), Professor S. R. Pattyn (Tropical Medicine Institute, Antwerp, Belgium), Dr H. Sansarricq (previously Leprosy Unit, WHO, Geneva) and Dr A. C. McDougall (Department of Dermatology, Oxford, UK). Progress in projects already receiving support was reviewed from Indonesia, Mexico, Turkey, Nepal, Ethiopia, China and Madagascar. Dr N. M. Chitimba reported on the main discussions and recommendations of the recent *7th Expert Committee on Leprosy*, held in Geneva. The Leprosy Fund operates within the *Novartis Foundation for Sustainable Development* and is prepared to consider applications from agencies working in the field of leprosy whose main objective is the elimination of leprosy as defined by WHO.

Revista de Leptologia, Fontilles, Spain

We are grateful to the Medical Director of Fontilles Leprosarium, Alicante Province, Spain, Dr Terencio de las Aguas, for continuing to send copies of the *Revista.* The January–April issue, 1997, carries an extremely detailed review of immunology in leprosy (72 pages), accompanied by 313 references. This must surely represent the most comprehensive review of the state of immunological knowledge in leprosy so far published in Spanish and it is to be hoped that it will achieve wide circulation in Spanish-speaking endemic countries. As usual the reviews of recently published articles, with summaries in Spanish, are also a valuable source of information on all aspects of the disease. *Further enquiries*: Sanatorio San Francisco de Borja, 03791, Fontilles, Alicante, Spain.

Lepr Rev (1998) **69,** 95–104

News and Notes

Leprosy beyond the year 2000

The following editorial is reprinted from *The Lancet*, Volume 350, No. 9093:

The World Health Organization has as one of its goals the 'Elimination of leprosy as a public health problem by the year 2000'. The 'problem' in this context is defined by WHO as a prevalence of 1 case per 10,000 population. We are not talking about the total eradication of *Mycobacterium leprae*. The wisdom of a timed objective for a disease that has an 8–10 year incubation period may be questioned but there is no harm in having targets of this sort, provided success is not claimed misleadingly. Over the past year, in *Leprosy Review* and elsewhere, there have been rumblings of doubt about the wisdom of focusing on prevalence, especially when the calculation counts those on anti-leprosy therapy to the neglect statistically of then long-term disability. Multidrug therapy with dapsone, rifampicin, and clofazimine achieves good microbiological 'cure' but the immunological and neurological toll of leprosy still affects some 4 million people.

Leprosy remains an endemic disease in 28 countries but it still strays across borders—a Los Angeles clinic has 500 cases on its books and sees 30 new ones a year. There is no specific vaccine and surprisingly little is known about how *M. leprae* is transmitted. The control strategy has, in the era of dapsone resistance, focused on case finding and multidrug therapy. This approach has been very successful. Argument over whether prevalence rather than incidence is the right measure of success must not be allowed to detract from the fact that the toll of leprosy has fallen impressively over the past decade. Back in 1985 the WHO estimate of period prevalence was 10–12 million cases worldwide. In 1996 it was 1·4 million, but that includes 560,000 new cases.

On Dec 14–16, at WHO in Geneva, there are meetings of SAPEL, the Special Programme to Eliminate Leprosy, which is aimed at treating previously unreached leprosy patients. SAPEL may not be the right forum for the admission that this particular WHO target is likely to be missed but it is the opportunity to discuss once more the fact that while the prevalence has been falling, incidence has not. Childhood cases, a reflection of transmission now, may even be increasing, and evidence is emerging for nasal carriage rates of *M. leprae* DNA that points to there being new cases well into the 21st century.

The incidence-versus-prevalence argument is not a mere academic one. A presumption that the year 2000 target will be achieved is already flavouring the whole leprosy scene. Scientific research has almost been squeezed off the agenda for the international leprosy conference in Beijing next September. The Japanese Sasakawa Foundation has been giving $10 million a year for leprosy control; that source will surely dry up once 'elimination' has been declared. In India, the main focus of leprosy, there is enormous political pressure to push for elimination and that it is taking precedence over the long-term needs of patients. In one Indian state the vertical leprosy programme has already been cancelled, patients being referred on to local health services that seem ill-prepared to handle them; and non-governmental organisations have been told to stop their rural leprosy programmes.

One public-health doctor was recently sent to some Indian islands with a mission to declare them leprosy-free in the year of India's 50th anniversary. That district must have been thought a promising candidate. sadly, the prevalence there in 1997 was 7 per 10,000 not 1. And, sadly, leprosy will be a 'public health problem' beyond the year 2000.

Gender issues in the elimination of leprosy in India

The following is reprinted from *TDR News*, No. 52, 1997:

A meeting of leprosy control personnel and social science researchers was held at the Agharkar Research Institute, Pune, India, 26–28 November, 1996 to discuss gender issues in the elimination of leprosy in India. Participants, including members of the Gender and Tropical Diseases Task Force, heard and discussed the results of a study of gender differences in the impact of leprosy. The study was conducted between 1993 and 1996 by Dr Shobha Rao and colleagues from the Agharkar Research Institute in four districts of Maharashtra State, in which four urban and four rural or tribal sectors were selected. Research questions included whether gender issues affected timing and mode of detection, treatment-seeking behaviour and compliance, the impact of the disease on social, family and personal life, and the role of the family in mediating this impact. Only registered cases were included in the study.

Several interesting differences were observed between the sexes:

- a sharp decline in the female age group during the adolescent period (ages 11–19), a period coinciding with the arrangement of marriage in India
- a sharp increase in female cases between age 20 and 25, compared to males
- significantly fewer females were detected through voluntary reporting, compared to active case dêtection in the community
- in urban areas, sex differences in registered cases were minimal, but in rural and tribal areas, significantly more males were registered than females
- many women reported that pregnancy and child-bearing exacerbated the disease but they were not informed about these risks when going for treatment
- nonleprosy health personnel were poorly trained to recognize early symptoms of the disease
- family support was of key importance in determining the course of disease, coping and treatment
- much superstition existed concerning leprosy in the larger community, and it was often associated with sins in a past existence.

A draft manual entitled, Gender Approach in the Elimination of Leprosy, was presented and discussed at the meeting. The suggestions of participants concerning its content and design are now being incorporated for final publication.

Gender differentials in tuberculosis: the role of socioeconomic and cultural factors. P. Hudelson

The following summary of the above review article is reprinted from *Tubercle and Lung Disease*, **77**, 391–400:

Summary This paper reviews current knowledge about the role that socio-economic and cultural factors play in determining gender differentials in tuberculosis (TB) and tuberculosis control. The studies reviewed suggest that socio-economic and cultural factors may be important in two ways: first, they may play a role in determining overall gender differences in rates of infection and progression to disease, and second, they may lead to gender differentials in barriers to detection and successful treatment of TB. Both have implications for successful TB control programmes. The literature reviewed in this paper suggests the following:

- Gender differentials in social and economic roles and activities may lead to differential exposure to tuberculosis bacilli:
- The general health/nutritional status of TB-infected persons affects their rate of progression to disease. In areas where women's health is worse than men's (especially in terms of nutrition and human immunodeficiency virus state), women's risk of disease may be increased;

- A number of studies suggest that responses to illness differ in women and men, and that barriers to early detection and treatment of TB vary (and are probably greater) for women than for men. Gender differences also exist in rates of compliance with treatment;
- The fear and stigma associated with TB seems to have a greater impact on women than on men, often placing them in an economically or socially precarious position. Because the health and welfare of children is closely linked to that of their mothers, TB in women can have serious repercussions for families and households.

The review points to the many gaps that exist in our knowledge and understanding of gender differentials in TB and TB control, and argues for increased efforts to identify and address gender differentials in the control of TB.

Illustrated History of Tropical Diseases

The Wellcome Trust, London has published a 454-page book on the above subject and their descriptive brochure reads as follows:

The discovery and investigation of tropical diseases has long fascinated scientists and non-scientists alike. This meticulously researched and richly illustrated book traces the history of humankind's understanding of these diseases from the earlier written records to the most sophisticated findings of today.

Tropical disease was first recognized as a separate branch of medicine at the turn of the century and this book emphasizes the spirit and personality of those individuals who devoted their lives to understanding these diseases and working out how to treat them.

The *Illustrated History of Tropical Diseases* has been published to mark the sixtieth anniversary of the founding of the Wellcome Trust, one of the world's major supporters of research into tropical disease and in the history of medicine.

Each of the book's 41 chapters is written by a scientific expert in the field, presenting a unique historical perspective and a real understanding of the conditions described. Written for a general scientific audience, each chapter includes a brief introduction into the aetiology of the disease and includes information on its current status and treatment. This unique work will appeal to everyone with an interest in tropical diseases and their treatment.

The *Illustrated History of Tropical Diseases* (hbk; 454pp; 488 colour and b/w images). ISBN: 1869835 86 7 Price: £35.00 plus post and packaging of £5.00 (UK); £11.50 (EU); £15.00 (elsewhere).

Changing the course of infection: the LACK antigen in leishmaniasis

The following appeared in *TDR News*, **No 52**, March 1997:

New evidence from the world of mice and leishmanias indicates that a lone antigen might be responsible for orchestrating the entire response of a host to a parasite. Making mice tolerant to a single leishmanial antigen can completely change the course of infection—from one of susceptibility to one of resistance.

SUB-SETS AND SECRETIONS

Each year, more subsets of T cells seem to be described. Th1 (T helper 1) and Th2 cells are subsets of T cells which were first described nearly ten years ago. Each of these subsets secretes a different repertoire of cytokines; for instance, Th1 cells produce interferon-γ (IFN-γ), amongst others, while Th2 cells produce interleukin-4 (IL-1). The outcome of an infection can be determined by the balance between these different cells and their cytokine secretions.

After infection, a boost in Th1 cells and IFN-γ occurs in mice that are resistant to *Leishmania major*, whereas a boost in Th2 cells and IL-4 occurs in mice that are susceptible to *L. major*. If the activity of IFN-γ is suppressed in a resistant mouse, the mouse is no longer able to resist the progression of the disease. Conversely, if the activity of IL-4 in a susceptible mouse is suppressed in the first week of infection, the Th2 response is prevented and a healing Th1 response emerges.

IL-4 appears to be the main inducer of the Th2 response and, at the same time, the main inhibitor of the Th1 response. An early burst of IL-4 production occurs in the lymph nodes of infected susceptible mice, and a study by Valérie Julia, Minoo Rassoulzadegan and Nicolas Glaichenhaus (Resistance to *Leishmania major* induced by tolerance to a single antigen. *Science*, 1996, 274:421–423) was directed at identifying which parasite antigens trigger this early burst of IL-4 and at how to lessen the Th2/IL-4 response.

THE LACK ANTIGEN

The authors found evidence that a single leishmania antigen, known as LACK (leishmania homolog of receptors for activated C kinase), triggers the early burst of IL-4 and plays a pivotal role in determining whether or not a mouse is susceptible to infection with *Leishmania major*. When susceptible mice were made tolerant to LACK prior to infection (by transgenic expression of LACK in the thymus), they responded to *L. major* with Th1 cells rather than Th2 cells and were resistant to infection.

Thus there was a reversal of the normal process after mice became tolerant to the single antigen. The authors hypothesize that susceptibility to murine leishmaniasis is determined by the ability of the infected host to mount a strong Th2 response against one or a few antigens (as well as by the loss of ability to generate a Th1 response—an early hypothesis).

IMPLICATIONS FOR VACCINE DEVELOPMENT

The study indicates the importance of choosing which immunogen(s) to include in a vaccine. Whole leishmania parasites will induce a Th2 response if given alone subcutaneously. However, if given with IL-12 (which enhances the Th1 response and IFN-γ), a protective response will emerge. Hence both the immunogen and the secondary stimulus are important.

Source: TDR Communications, WHO, 1211 Geneva 27, Switzerland (UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases).

Action in International Medicine (AIM, London)

The following is extracted from the 'Mission Statement' of AIM:

AIM is an international consortium of health and health-related professional organisations. Its membership now exceeds one hundred institutions and spans thirty-five countries. It is nonpolitical and, through its members, represents the voice of the health care professional worldwide.

Drawing upon its extensive international membership and related organisations, and working through its International Advisory Panel, AIM is able to assemble at short notice multidisciplinary teams of doctors, nurses, other health care professionals, economists, management consultants, development consultants, engineers and educators.

Operating in impoverished regions of the world, these teams are able to identify rapidly those components of health care delivery which are excellent and those which fall short of accepted norms in terms of that region's ability to provide an adequate health service to the indigenous population.

Armed with this information, AIM, working with and through local bodies, is then able to enlist the support of appropriate organisations active and experienced in health development and thereby to

mobilize appropriate project teams necessary to redress the imbalance in a sustainable manner in the region under consideration.

Within the context of its over-riding goal, AIM has set out to champion the cause of the first referral hospital and primary health care, i.e. District Health Systems, throughout the developing countries and the impoverished regions of the north. To this end, it actively supports and encourages its member organisations to involve themselves in:

Lobbying: the active lobbying of governments and other related institutions to accept the concept of basic health care as a human right for all and to recognize the importance of district health systems in making this a reality.

Research and Education: the direct support of health care professionals operating at the front line of health care delivery in impoverished regions, by way of research, information dissemination, education and training.

District Health Project Implementation: the pioneering and support of innovative district health projects through direct involvement and by catalysing others with appropriate experience.

Further information: Action in International Medicine, 125 High Holborn, London WC1V 6QA, UK. Tel: 44 (0) 171 405 3090. Fax 44 (0) 171 405 3093.

Why India will not be able to erradicate Hansen's Disease (leprosy) by 2000 AD. Kunal Saha, India

The following is the summary of a remarkable publication in the *Star* Carville, Louisiana, USA, April–June 1997:

Summary The National Leprosy Eradication Program (NLEP) of the Government of India has undertaken the gigantic task of eliminating Hansen's disease (leprosy), as a public health problem from India within 2000 AD. To fulfil this pledge they have established an extensive field network consisting of a vast army of paramedical and medical workers for early detection and treatment of patients, with MDT, an operationally convenient mode of mass treatment. However, in the present conditions existing in India, this method has its own limitations. Wrong statistics, rural eco-system, poverty, unhygienic over-crowded living conditions, poor sanitation, undernutrition, illiteracy and above all, stigma are the obstacles for the implementation of the NLEP. Unless this socioeconomic backwardness is corrected, MDT alone will not be able to eliminate leprosy from India in the near future. More attention is to be focussed on epidemiological surveillance, timely finding of cases (including new patients and relapsed cases), improving the quality of MDT implementation and drug delivery, overcoming fear, shame and discrimination associated with the disease in the Indian society. More importance has to be paid to preventing disabilities by teaching the patients self eye-and-foot-care. Rehabilitation programs to expatient with or without deformities, is to be geared up. Reconstructive surgery, which is an ancillary for rehabilitation, is in its infancy. Proper training of the paramedical workers who are the backbone of NLEP is far from expectations. They will need more expertise, compassion, trust and dedication. The apathetic attitude of the medical community, governmental indifference and corruption in the administrative apparatus have undermined the proper execution of the NLEP.

The author believes that unless the present socioeconomic disparity, existing in India, is removed which needs strong political will, MDT alone will not be able to eradicate leprosy from the subcontinent in the 21st century. Perhaps MDT plus an effective vaccine is the answer for the Indian semifeudal and semiindustrial heterogeneous and unequal society.

The author is Professor Kunal Saha, previously Professor of Immunology in Delhi University and his views on the current leprosy control situation in India are of considerable importance and interest. Few Indian nationals have felt able to record their views in print in such forthright terms, but his opinions will strike a familiar note with those who have taken part in successive Independent Evaluations of the

National Leprosy Eradication Programme, which invariably revealed defects, many of which remained uncorrected from one evaluation to another. This 5-page article should be studied in the original by those who have responsibility for the control/elimination/eradication of leprosy in India and serious attention given to points of weakness identified so clearly by Professor Kunal Saha.

Part II of his paper appeared in the July–September 1997 issue of the *Star*, page 12.

Myanmar (Burma): Third Independent Evaluation of the Leprosy Elimination Programme, 4–18 November, 1997

The Third Joint WHO and Union of Myanmar *Independent Evaluation of the Leprosy Elimination Programme in Myanmar* took place between 4th and 18th November, 1997 in order to assess progress and to identify measures to accelerate the elimination of leprosy as a public health problem. The terms of reference were—1) assess progress in the leprosy programme since 1990, with special focus on the year 1993, and to identify critical components in need of strengthening, 2) validate reported data, including patient diagnosis, classification and multiple drug therapy (MDT) services, 3) assess the level of awareness in the community and in leprosy patients, 3) ascertain the level of competence, contribution and commitment of health staff involved in planning, management and delivery of leprosy elimination services at different levels and 5) to identify priority areas/activities needed to accelerate the attainment of the goal of elimination of leprosy at national and sub-national levels by the year 2000.

Six out of 7 divisions and 2 out of 7 states were selected for field visits, to include 25 districts and 46 townships, to be examined by 5 teams each composed of two national experts and one external expert. The latter were—S. Barua (Japan), R. Day (Indonesia), A. C. McDougall (United Kingdom), J. O. Simon and L. R. Talukder (Bangladesh), all invited by the South East Asia Regional Organisation (SEARO) of WHO in New Delhi as temporary advisers.

Teams were despatched to cover both moderate and (previously) high endemic areas in various parts of the country in order to obtain information at state/division, township and rural health centre levels. This was recorded in detail on prepared questionnaires from which data were pooled and analysed on return to the Department of Health in Yangon (Rangoon). The areas under examination included well-established programmes in which MDT had been started in 1989, together with those of lower prevalence in which it has been introduced as recently as 1995/6.

All participants reported good progress in leprosy control generally, with strong political commitment and high levels of motivation in both vertical and basic health care staff. The decision to fully integrate leprosy services into the primary health care programme in mid-1991 has proved successful, including considerable input from midwives in the delivery of MDT to patients in or near their homes. In order to ensure maximum coverage to cases so far undetected, in the time available before the year 2000, participants agreed that there is a need to—1) expand information, education and communication (IEC) activities, including the development of posters in adequate numbers and other material in Myanmar (Burmese) for the general population (which has a literacy level of 83%) and 2) develop innovative approaches for ethnic and border populations, who, in contrast, are illiterate in both Myanmar and their own languages. leprosy Elimination Campaigns (LEC), already established in 16 areas of the country, may be extended to cover the whole of Myanmar in 1998.

Myanmar is one of the countries which contribute to 91% of the world problem of leprosy. At the beginning of 1997, WHO reported 18,758 cases registered, with 100% MDT coverage; a cumulative total of 148,982 cases cured by MDT; 6,935 cases detected in 1996. The estimated number (1996) of individuals presenting disabilities due to past or present leprosy is 41,000 emphasising the continuing need to strengthen activities in disability prevention and management on a considerable scale, including self-care and community-based rehabilitation (CBR).

In the early years of the history of leprosy in Myanmar, the country was confronted with an

enormous problem, one of the worst in South-East Asia. In 1973, no fewer than 245,000 cases were registered and when the main project started prevalences of 40 per thousand, or even higher were not exceptional in school surveys in Central Myanmar. Today, the registered figure is below 20,000 for the first time since records began and school surveys yield extremely few cases. The elimination of leprosy will be achieved at national and many sub-national levels in the near future, but there is a need to maintain the existing contribution of the basic health services, together with a vertical element down to township level, at least until the year 2000, and possibly longer.

A. Colin McDougall

WHO Action Programme on Essential Drugs: Worldwide-Web Service on Internet

The Action Programme on Essential Drugs' homepage on the World-Wide-Web service on the internet offers the user a range of information on the functions and activities of the Programme. This information, which is frequently updated, introduces users to the essential drugs concept, national drug policies, and the work of WHO and the Action Programme in developing countries.

The titles of selected WHO, DAP and other pharmaceutical publications are available on the homepage, to increase awareness of available resources.

The actual content of carefully selected publications can be viewed. For example, feature articles from the English version of the *Monitor* are available from issue 19 onwards and users can also obtain and print out the Guidelines for Drugs Donations (see p. 6).

You can find DAP's homepage on the WWW:http://www.who.ch/programmes/dap/DAP_Homepage.html

Further information: Essential Drugs Monitor, WHO, CH-1211 Geneva 27, Switzerland.

'DOTS' treatment for tuberculosis hailed as milestone advance

Kraig Klaudt Public Affairs and Advocacy Officer, Global TB Programme has recently written as follows:

Thank you for your interest in World TB Day. The 1997 campaign was a monumental success, as the DOTS strategy was acclaimed around the world as being *the biggest health breakthrough of this decade*, in terms of the number of lives to will be able to save. Increasingly, governments, health officials and NGOs are picking up the challenging to use DOTS more widely.

To sustain this momentum, the World Health Organization is already preparing for World TB Day 1998. On 24 March of next year, we are planning to highlight '*DOTS Success Stories*' and '*TB Disaster Stories*' throughout the world.

I would like to invite you to contribute to our preparation of these stories. You are encouraged to send us examples of successes and innovations you have discovered in your country using the DOTS strategy to control TB. For example:

Creative ways to assure that TB treatment is always observed;
Effective strategies to extend DOTS to reach neglected groups;
Useful ways to increase the morale of DOTS health workers;
Innovative methods to overcome resistance to DOTS by health authorities; and
Successful strategies to increase political and financial commitment for DOTS

Also, send us examples of TB control disasters or lost opportunities which you may be aware of in your country or community. For example;

Local outbreaks of multidrug-resistant TB;

Careless treatment practices which may be encouraging MDR TB;
Descriptions of TB control or TB research projects which are wasting resources; and
Blatant examples where TB has been neglected by politicians or health authorities.

We will present some of the most compelling descriptions of DOTS successes and TB disasters in our *1998 Report on the TB Epidemic* and in our World TB Day publicity efforts next year. For the information to be most useful, please try to send it to my attention before October 1997.

I am convinced that our collaborative advocacy efforts can help make it possible to provide DOTS coverage to at least 70 per cent of tuberculosis cases within the next decade.

This circular letter is accompanied by a package of press notices describing the impact of DOTS (directly observed, short course) treatment worldwide. *Further information*: Global TB Programme, WHO, 1211 Geneva 27, Switzerland.

Malabsorption of rifampicin and other antituberculosis drugs

Under the heading of 'Persistent fever in pulmonary tuberculosis', the *British Medical Journal* of 14 December 1996, pages 1543–45, describes the case of a 47-year-old male patient, admitted to hospital in the United Kingdom with active pulmonary tuberculosis and treated with a standard regimen of rifampicin, isoniazid and pyrazinamide. After an initial satisfactory response, the patient failed to improve and sputum was found to be positive two months after starting treatment. Other aspects of the case, including detailed investigations in a London teaching hospital, are described and the discussion centres on the possibility that persistent fever and lack of response were related to malabsorption of antituberculosis drugs. At one point a very low serum rifampicin level was recorded and the Comment section includes the following:

Drug malabsorption as a cause of persistent fever applies to this case. Rifampicin, a derivative of rifamycin (from *Streptomyces mediterranei*) is 60% protein bound, 60% excreted in bile, and 10–15% excreted in urine (hence the orange urine). Its half life is four hours but can be up to 14 hours in biliary obstruction.

In a small study from Hyderabad, India, there was a 50% fall in the plasma concentration time curve of rifampicin in undernourished patients. This was attributed to both malabsorption and increased renal clearance. This effect was in part offset by reduced plasma protein binding. As there is increased renal clearance, the urine is still orange despite low plasma concentrations.

It was initially recommended that rifampicin should be taken when fasting, but having breakfast was shown to have no significant effect on absorption. Later, however, when the dietary constituents of breakfast were analysed separately, 50 g of fat reduced rifampicin levels by 20–50%, whereas 100 g of glucose and two egg whites had no effect.

Several cases of rifampicin malabsorption have been reported. In 1978, a 28 year old diabetic patient with pulmonary *M. tuberculosis* resistant to isoniazid and malabsorption of rifampicin was successfully treated with intravenous rifampicin. In France a diabetic child with coeliac disease had selective malabsorption of rifampicin and not isoniazid.

More recently, there has been evidence of drug malabsorption in HIV positive patients, even in the absence of malabsorptive symptoms. In one of the reports two patients with HIV infection and tuberculosis became resistant to rifampicin, of whom one became resistant also to isoniazid after initially being sensitive. Serum concentrations of all antituberculous drugs except pyrazinamides were low in both patients. Therapeutic drug monitoring is therefore essential in such patients as persistently low drug concentrations select for multiple drug resistance.

In the case that we have presented, the persistent fever seemed to be related to malabsorption of antituberculous drugs. Such malabsorption may be due to cytokine destruction of villi, undiagnosed gastrointestinal tuberculosis, chronic pancreatitis (due to high alcohol intake), bacterial overgrowth, pre-existing coeliac disease, or small bowel lymphoma. The malabsorption is mild (normal serum B_{12}

and serum and red cell folate concentrations and a plasma albumin concentration that corrected with nasogastric feeding) and may be selective for rifampicin.

PATH: Programme for Appropriate Technology in Health, USA

This Organization in the USA previously produced a series of publications dealing with the most important tropical diseases and technologies needed for their better control. Amongst these was an issue on leprosy, produced nearly 10 years ago, which achieved the widest circulation of any in the series and had to be reprinted to cover a nationwide distribution in the Philippines. Limited funding has led to the withdrawal of '*Directions*', but PATH is still active in the field of tropical diseases, notably in the area of diagnostic test development. A general description of the current aims and activities reads as follows:

Path (Programme for Appropriate Technology in Health), a nonprofit, nongovernmental, international organization, has emerged a leader in state-of-the-art health programming since its beginning in 1977. With headquarters in Seattle, Washington, and programme and project sites in Seattle; Washington, D.C.; Jakarta and Lombok, Indonesia; Nairobi, Kenya; Manila, Philippines; Bangkok, Thailand; and Kiev, Ukraine; PATH is well suited to develop and deliver culturally-sensitive programmes to people throughout the world.

PATH's mission is to improve health, especially the health of women and children. An emphasis is placed on improving the quality of reproductive health services and on preventing and reducing the impact of widespread communicable diseases. PATH identifies, develops, and applies appropriate and innovative solutions to public health problems. This is accomplished by exchanging knowledge, skills, and technologies with governmental and nongovernmental partners in developing countries and with groups in need elsewhere.

In all activities, PATH works in partnership with organizations and companies closely tied to the end users of health services. Staff work cooperatively with health clinics, community-based groups, ministries of health, nongovernmental organizations (NGOs), private-sector companies, and funding agencies—bridging gaps that prevent efficient and effective delivery of health services and fostering partnerships that lead to improved health in the developing world.

Since 1977, PATH has managed more than 800 health and family planning projects in 85 developing countries. International and national health and family planning agencies, governments, foundations, corporations, and individuals support PATH's efforts.

In recognition of its expertise in specific areas, PATH has been designated by the World Health Organization (WHO) as a Collaborating Center in three technical areas: Research in Human Reproduction; Acquired Immune Deficiency Syndrome (AIDS); and Hepatitis B Vaccination. As a Collaborating Center, PATH provides technical assistance to WHO and to ministries of health.

Policies and broad programme strategies are formulated by the Board of Directors. Members of the Board represent several developing countries and the United States as well as a variety of disciplines.

Further information: PATH, 4 Nickerson Street, Seattle, WA 98109-1699, USA.

Gillis W. Long Hansen's Disease Center, USA stays open

Readers of the latest issue of *The Star* from the Gillis W. Long Hansen's Disease Center, 5445 Point Clair Road, Carville, LA 70721-9607, USA, may have been surprised to see a reference in the letter by Susan Cookson to a newspaper report, suggesting that Carville may be closing. Carville may be changing, but it is not closing—Robert R. Jacobson, Director, Division of National Hansen's Disease Programs/Gillis W. Long Hansen's Disease Center, has kindly written to clarify the situation, as follows:

A Bill passed Congress last Fall authorizing transfer of our facility to the State of Louisiana for use as a Center for Training 'At Risk Youth' (mainly high school dropouts) in various occupations after

helping them to obtain a high school diploma. The Bill authorized moving all of our activities to a new site in nearby Baton Rouge, Louisiana, over a period of several years. If all went according to plan we would move short-term care to Baton Rouge within the next year and would have the same bed capacity and sufficient staff to continue as we do now. This would allow us to admit patients for Hansen's disease related complications and rehabilitation, just as we do now. The permanent patient residents of Carville would be offered an assisted living allowance to live where they wished and would be able to return for Hansen's disease related care to whatever extent necessary. Those who did not wish to leave would continue to be cared for here at Carville for the foreseeable future, though eventually they would probably be moved to a single facility in Baton Rouge where we would continue to oversee their care. Their numbers are, of course, gradually declining since their average age is well over 70 and no new cases have been allowed to remain for long-term care for over a decade now.

Our research facility is, of course, already in Baton Rouge at Louisiana State University under a 20 year lease and will continue there. Our facility at Carville is a beautiful site, but we at present utilize only about one-third of the space to varying degrees and it is very costly to maintain. The changes, if all goes according to plan, will allow us to do everything we're now doing, but at a much lower cost.

Robert R. Jacobson MD, Ph.D

TALMILEP—new videos required for catalogue

We are currently updating our existing video catalogue on Leprosy & Related Subjects to be published next year. TALMILEP is an action group working within ILEP (International Federation of Anti-Leprosy Association). The function of TALMILEP is to make teaching and learning materials in leprosy available to those who need them.

Apart from leprosy, we are particularly interested in videos on joint leprosy/tuberculosis programmes and rehabilitation.

If you have produced a video for the purpose of staff training or public education and you would like others to know about it, please send a sample copy to:

ILEP Co-ordinating Bureau, 234 Blythe Road, London W14 0HJ, UK. Att: Marilyn Holderness.

It can then be assessed and information about your video advertised in this forthcoming catalogue, together with an assessment and a rating made by TALMILEP, stating the address where it may be bought or hired and the cost.

Errata

Leprosy and the Internet, J. S. Gilbody,. Volume 68, page 367: The email address should read as follows: alltra@globalnet.co.uk. Postal address: One Rookswood Close, Hook, Hampshire RG27 9EU, UK.

Teaching Materials and Services, Volume 86, page 396: Leprosy Control in Myanmar, 1948–1973. The address to obtain this booklet should read as follows: Dr B. Zuiderhoek, Fideliolaan 102, 1183 PP Amstelveen, Netherlands.

Leprosy Review poster: Eye examination

The A3 poster enclosed with this issue of *Leprosy Review* is the fourth in a series of four covering important areas of management and research in leprosy and is distributed free to subscribers to the Journal. Additional copies are available from Lepra, Colchester, UK. Further posters are also being planned. 'A questionnaire on the posters is to be published in the September issue so that the choice of topic and other aspects can be guided by you the reader. So please do let us know what you think.'

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Dr 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 clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

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

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

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