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Leprosy Review

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

British Leprosy Relief Association
LEPRA

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

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

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Editorial

THE MANAGEMENT OF NERVE DAMAGE IN THE LEPROSY CONTROL SERVICES

Leprosy is an infectious disease which causes disability and deformity due to the damage of peripheral nerves. In the control of leprosy, as an infectious disease, the provision of effective and adequate chemotherapy to as many patients as possible is the most important single measure for interrupting the chain of transmission of the infection and for curing the patients. Today multidrug therapy treatment (MDT) is the most effective of leprosy.

The provision of MDT should be given top priority in the control of leprosy.

Early effective chemotherapy will also prevent the development of disabilities in many new patients. This is an indirect effect of anti-leprotic treatment.

At present there are several million people in the world who are disabled due to leprosy. To the patients, their families, as well as to the general public, deformities have often much more significant implications than the infection itself. Deformities may lead to stigmatization and ostracism. If resources are available, chemotherapy and care for established deformities may be given concurrently. For the individual patients these two aspects are often inseparable. In our opinion there is no room for rehabilitation services without effective treatment, i.e. MDT.

One may argue whether there is a justification for the treatment of established deformity, including the care of ulcers and reconstructive surgery, in the absence of such care for patients with deformities due to other diseases. We think that the rehabilitation services for leprosy patients should be an integral part of the general rehabilitation services in which all patients with deformities are included.

The *prevention* of disability and deformity is, however, certainly an integral part of the leprosy control services. One aspect in the prevention of disability is the early detection and appropriate treatment of reactions which involve the nerves. Another means of control of disability is health education which is aimed at the promotion of self-care by patients.

This Editorial will concentrate on how the following two aspects can be handled by the leprosy control services:

The early detection and appropriate treatment of nerve damage and reaction; and
The prevention of increase of disability in patients with irreversible nerve function loss before secondary complications have occurred.

We have chosen to concentrate on these two aspects for the following reasons:

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The early detection of reactions is a responsibility of the leprosy control staff. A common idea is that a reaction occurs in the presence of nerve tenderness and pain. However, many reactions occur without these signs. If a reaction is treated promptly and adequately, irreversible nerve damage will be prevented or limited. Although it is common practice that patients who need treatment with corticosteroids are managed in hospital I think that, in particular for operational reasons, it is preferable that many of them are treated by paramedical staff in the field. Measures to prevent increase of disability in patients with irreversible nerve damage and before complication have occurred should be applied in the field. A common problem is the absence of a plan of action to apply disability prevention measures.

The early detection and treatment of leprosy reactions

EARLY DETECTION OF RECENT NERVE DAMAGE

Recent nerve damage is damage to the nerves which has existed for a short period of time. This may have led to nerve function loss. The nerve damage can be reversed if appropriate treatment is given. Recovery of nerve function loss is likely when the loss has existed for less than 6 months. The sooner the damage is detected and treated, the better are the chances for recovery. In some instances, in particular in case of foot drop, recovery may still occur after 6 months.

Loss of nerve function loss may occur in an obvious way, or silently.

Obvious nerve function loss usually occurs quickly and is noticed and reported by the patients. It is accompanied by nerve pain and tenderness on palpation. There may be dramatic changes in appearances, such as foot drop.

Silent nerve function loss, however, can easily be missed, because it occurs without nerve pain, and often without the patient noticing nerve discomfort. There may be no obvious appearances due to muscle weakness. Changes in sensation are not visible and can only be detected by sensation testing. Sensation and/or muscle strength changes occur gradually over a period of weeks to months. Many patients fail to report these changes, unless they are specifically asked. They may think that these changes are an inevitable consequence of the disease or due to the anti-leprotic treatment. Loss of sole and palm sensation often occur silently. If not detected and treated in time these sensation changes may lead to lifelong problems of recurrence of wounds and wound complications.

Leprosy reactions and nerve damage may develop prior to the start of anti-leprotic treatment. The symptoms may be the reason for a patient to attend the medical services. Nerve damage may occur during the treatment; then it often occurs during the first few years after the start of chemotherapy. Nerve damage may also develop after the patient has completed a course of chemotherapy. BT patient especially, who have been treated with a 6-month course of MDT, may then develop a reactional episode after release from MDT.

SENSATION AND MUSCLE STRENGTH TESTING

In several manuals and textbooks the techniques of sensation and muscle strength testing are discussed in detail. We recommend the two books which are written by Jean M

Watson: *Preventing disability in leprosy patients* and *Essential action to minimise disability in leprosy patients.*

Sensation testing (ST)

Sensation testing is done for the eyes, hands and feet. Sensation testing of the cornea is only needed when there are blink problems. If blink is normal, corneal sensation is normal.

On the soles and the palms a defined number of standard points should be tested. The number of points may vary from programme to programme. What is important is that the same points are tested everytime. In the ALERT Leprosy Control Programme 10 standard points on palms and soles are tested.

Sensation testing is usually done with the tip of a ballpoint pen. The touch should be light, just enough to dimple the skin. The pressure stimulus thus put on the skin can vary from 5 to 30 g depending, e.g., upon the thickness and stiffness of the skin and the way the pen is handled. A problem with the use of the ballpoint pen is that it is not possible to standardize the pressure stimulus put on the skin. To get a standardized stimulus on the skin some experts advise the use of monofilaments which apply different forces. At ALERT the 10-g filament was found adequate to detect loss of sensation in the sole.

Under routine field conditions the use of the ballpoint pen, although not a standardized method, is often preferable. A ballpoint is always available and there is no excuse for not doing sensation testing.

Voluntary muscle testing (VMT)

For use in the field the muscle strength is usually graded as strong, weak or paralysed.

Strong—full range movement in the joint and normal resistance.

Weak—full or partial movement in the joint and reduced resistance.

Paralysed—no movement in the joint and no resistance. When the eyelid is paralysed, the lid gap should be estimated.

It requires practice to learn the normal strength in the hands of, e.g., a young man, an old woman or a child. The strength of one side should always be compared with that of the other side.

Practical exercises in VMT and ST examinations should be included in the training and refresher courses of the staff. In addition, the performance of the staff should be assessed regularly by experienced supervisors and a physiotherapist, if available.

Recording of findings

Results of VMT and ST examinations should be recorded on standard forms. Examples of such forms are given in the books written by Jean Watson and in the ALERT manual for field treatment of leprosy reactions.

Results of sensation and muscle strength testing at the time of diagnosis of leprosy should always be recorded, also if sensation and strength are normal. These so called baseline records should serve as the basis for a plan of action and for comparison with results of later examinations.

In order to limit the amount of paperwork, only those findings which are different

from previous examinations may be recorded. However, any changes in sensation and/or muscle strength, whether improvement or deterioration, should be recorded.

The frequency of nerve function testing

Because recent nerve function loss can be reversed, ST and VMT examinations should be done at certain times and intervals. The interval can be different for different categories of patients.

Of course all patients should be examined at any time they present with complaints which can be caused by nerve function loss. It is our experience that with experienced staff and patients who have been exposed to the examinations, nerve function testing will not take more than 4 minutes per patient. We should like to stress that the examinations should be done routinely, whether or not a patient has any complaints. We experienced that over 65% of the patients who were found with recent nerve function loss did not present complaints spontaneously. When asked, some of the patients said that they had noticed loss of sensation and/or muscle strength; others had not noticed anything.

Another advantage of routine testing is that we do not have to rely on the observations of the patients. If proper records are kept the results of subsequent tests can easily be compared with those of previous examinations. Whether or not noticed by the patient, deterioration of nerve functions can be detected and appropriate action can be taken. ST and VMT examinations should be done: 1, at the time of diagnosis of leprosy; 2, during the course of chemotherapy; and 3, after release from chemotherapy.

1 *At the time of diagnosis of leprosy*

Nerve function loss which is found at the time the patient is diagnosed with leprosy should not be accepted as an irreversible condition. Especially in patients without deformities, loss of sensation and/or muscle strength may be reversible.

It is often not easy to obtain accurate and reliable information from the patient about the period the nerve function loss exists. We should take our time for questioning the patient. Sometimes it may be advisable to ask the patient to come back after 1–2 weeks and question him/her again.

If, from history, it appears that the nerve function loss exists for less than 6 months, the patient should be given a course of treatment that includes corticosteroid.

2 *During the course of chemotherapy*

Ideally sensation and muscle strength examinations should be done every month. If this is not possible, a frequency of testing of once every 3 months should be the minimum. During the initial phases of implementation of MDT, when the number of patients under chemotherapy is high, it may not always be possible to do the examinations with all patients at the defined intervals.

However, certain categories of patients should be examined at regular intervals:

New BT patients during the whole course of MDT,
New BL patients, during the first 2–3 years of MDT,
Women during pregnancy and during the first few months after delivery.

With these patients VMT and ST should be done at monthly intervals. Other categories of patients could be examined less frequently.

3 *After release from chemotherapy*

New nerve damage which develops after release from chemotherapy may be a sign of a late reversal reaction or a relapse. It is often very difficult, if not impossible, to distinguish between a reversal reaction and a relapse. Since the clinical symptoms in both conditions are due to similar immune responses to mycobacterial antigens, the available techniques cannot give a conclusive answer. In the routine leprosy control services the appropriate treatment of new nerve damage should be given the highest priority. The diagnosis and treatment of a possible relapse is less of an emergency and should be considered after insufficient response to the treatment with a corticosteroid. I think that it is unjustified to wait for the results of several examinations which are aimed at reaching the most likely diagnosis, while not treating the patient for the new nerve function loss.

How often can we expect new nerve function loss after patients have been released from MDT? In the ALERT Leprosy Control Programme about half of the reversal reactions which were diagnosed in BT patients developed after release from MDT. However, it is very likely that more patients than we found develop new nerve damage after their release from MDT. This is based on our experience that in several patients, who did not have nerve function loss at the time of their release from MDT, irreversible nerve function loss was found 1 year or more after discontinuation of MDT. This observation has urged us to consider means of continuing the regular contact with BT patients after the 6 months of MDT. Because it has been experienced that after 6 months of MDT very few relapses occur, the treatment and the period of treatment can be considered sufficient to cure the vast majority of the BT patients. Therefore, continuation of chemotherapy after the 6 months of MDT is not needed or advisable.

In order to diagnose reactions at an early stage, patients should be seen at regular intervals for follow-up examinations. The usual recommendation for surveillance of PB patients is once a year for a period of 2 years. This frequency is certainly adequate for detection of relapses, but insufficient for the early diagnosis of new nerve function loss. I should like to recommend that BT patient be encouraged to attend for checkups at 3-monthly intervals during the first 1–2 years after release from MDT.

The frequency of occurrence of reactions which involve the nerves

The frequency of occurrence of reactions is related to the type of MDT regimen. It is a general observation that ENL reactions occur less frequently in patients who are treated with the WHO-recommended MDT regimen, compared with other MDT regimens. It is likely that the anti-inflammatory action of clofazimine prevents ENL reactions.

In the ALERT Leprosy Control Programme we observed an increase in the number of patients who were diagnosed with a reversal reaction which affects the nerves, since the implementation of the WHO-recommended MDT. Such an observation should be interpreted with caution, because: available data about reactions during the days of dapsone monotherapy are incomplete; and the observed increase in reactions may well be related to better observations in the more closely supervised services.

Among 682 new patients we analysed the number of patients who developed a reaction which required treatment with a conticosteroid. The reactions were either diagnosed prior to the start of anti-leprotic treatment or occurred within the first year after the start of treatment with MDT.

The following results were obtained:

		Type of reaction			
		Reversal reaction		ENL reaction	
Class.	No. of new patients	No. of patients	%	No. of patients	%
TT	40	—	—	—	—
BT	304	60	19·7	—	—
BL	249	105	42·2	12	4·8
BL	99	10	10·1	11	11·1
Total	692	175		23	

We can make the following conclusions.

Of the 198 reactions, 175 (88·4%) are reversal reactions and 23 (11·6%) are ENL reactions.

Of the 304 BT patients, 60 (19·7%) were diagnosed with a reversal reaction. Because several patients who developed new damage after release from MDT did not attend the services promptly, the actual number of BT patients who developed a reaction will be higher. The highest percentage of reversal reactions is found among BL patients; out of 249 patients 105 (42·2%) developed a reversal reaction. Ten out of 99 LL patients (10·1%) developed a reversal reaction.

Because the observation period was limited to 1 year after the start of MDT we can expect that with the extension of that period more patient will be detected with a reaction.

THE MANAGEMENT OF PATIENTS WHO NEED A CORTICOSTEROID

It is common practice that patients who need treatment with a corticosteroid are managed by a medical officer. This often implies referral of patients to a hospital. There is no doubt that corticosteroids can be dangerous if not properly used. Patients should be checked for contra-indications before a course of corticosteroids is started and for side-effects during the treatment. However, when the management of patients on corticosteroids is the responsibility of medical officers only, we will deprive many patients from adequate treatment of their reaction, because:

In many leprosy endemic areas doctors are scarce, and those available usually work at great distances from the homes of the patients;

Many patients are unable to be admitted for several months or to attend an outpatient department of a hospital. Common reasons are the family situation, work obligations, economic problems and lack of transport;

Hospital in- and outpatient facilities are often insufficient to provide services to all patient who need them.

We estimated that in the ALERT Leprosy Control Programme in the days when all patients who needed a course of prednisolone had to be referred to hospital, at least 60% of the patients did not receive the treatment. This was because either they were referred but did not go to hospital, they were not referred or they could not be admitted. We found that this situation had a negative effect on the motivation of the field staff to do regular ST and VMT examinations. Our observations urged us to develop a plan of action for the treatment of leprosy reactions in the field. A detailed manual for field treatment of leprosy reactions was written. Major responsibilities for the selection, treatment and follow-up of the patients were given to the leprosy control supervisors. After the staff had been trained, the treatment of reactions was introduced in three out of the twelve districts of the control area in early 1987. During the year thereafter the several technical and operational aspects of the management of the patients with a reaction in the field were supervised and monitored. As a result of this some procedures and technical aspects were amended. During 1988 the field treatment of reactions was extended in five districts. It is the intention that by 1990 the treatment will have been introduced in the whole control area.

CRITERIA FOR TREATMENT WITH CORTICOSTEROIDS IN THE FIELD

In the ALERT Leprosy Control Programme patients with one or more of the following signs are considered for treatment with prednisolone in the field:

1 Pain or tenderness on palpation in one or more nerves, with or without loss of nerve function.
2 Change in VMT of less than 6 months duration. The change can be from strong to weak, from weak to paralysed, or from strong to paralysed.
3 Change in ST of less than 6 months duration. A change is considered significant when one finds:
In a hand: undoubted loss of ST in two or more points, occurring in the area of the same nerve trunk, i.e. either in ulnar or median area;
In a foot: undoubted loss of ST in two points or more.

PATIENTS WHO SHOULD BE REFERRED TO HOSPITAL

We defined ten categories of patients who should not be treated with prednisolone in the field, but be referred to hospital. These are patients who, beside recent nerve damage, have one or more of the following conditions:

Severe ENL.
Deep ulcer(s).
Nerve abscess.
Corneal ulcer, keratitis, iritis or iridocyclitis.
Suspicion of tuberculosis or any other systemic disease.
Positive urine test for glucose and or protein.
Recent nerve damage 1 year or more after release from MDT.
Pregnancy.
Age of less than 12 years.
Deterioration of nerve function while under 40 mg of prednisolone, the highest dose of the drug which is given in the field.

In case it appears impossible for a patient to go to hospital, or in case a patient needs some time to make necessary arrangements before going to hospital, some of the above categories of patients may be considered for treatment in the field or for initial start of corticosteroids in the field. This applies to patients with severe ENL, pregnant patients, children between the age of 6 and 12 years, and patients who develop nerve damage 1 year or more after release from MDT.

In order to rule out the conditions given above, a history is taken and the patients were examined prior to the decision about treatment with prednisolone in the field. Patients suspected of dysentery, found with conjunctivitis, trachoma or scabies are treated for these conditions in the field. Because many patients suffer from worm infestation, which may exacerbate under the treatment with prednisolone, all patients are routinely given a broad spectrum antihelminthic. History taking, examination of the patients, recording of findings, and the decision about the place of treatment are all responsibilities of the leprosy control supervisors.

CORTICOSTEROID REGIMEN

The most commonly used corticosteroid for the treatment of reactions is prednisolone. For the treatment of severe ENL usually a course of a few weeks duration is given. The recommended course for the treatment of reversal reactions varies widely in terms of the initial dosage and the duration of the treatment. At ALERT a course of 6 months duration, with an initial dosage of 40 mg prednisolone daily, was common practice. For operational reasons a 6 months course was considered too long for field conditions. We decided to give a standard course of prednisolone of 12 weeks duration, as follows:

40 mg daily for 2 weeks,
30 mg daily for 2 weeks,
20 mg daily for 2 weeks,
15 mg daily for 2 weeks,
10 mg daily for 2 weeks,
5 mg daily for 2 weeks.

After we observed that about one third of the BL patients who were treated with this course of prednisolone developed a repeat reaction, the period of treatment of BL patients was extended to 20 weeks. The course of the treatment for these patients was changed as follows:

40 mg daily for 2 weeks,
30 mg daily for 4 weeks,
20 mg daily for 4 weeks,
15 mg daily for 4 weeks,
10 mg daily for 4 weeks,
5 mg daily for 2 weeks.

RESULTS OF FIELD TREATMENT OF REACTIONS

From the experience we gained during the first 2 years of reaction treatment in the field, which was implemented by the leprosy control supervisors, we came to a number of observations and conclusions:

The majority of the patients can be managed in the field. Of the 198 patients who were diagnosed with a reaction, 144 patients (72·7%) were treated in the field, 42 patients (21·2%) were treated in hospital, 2 patients (1·0%) refused treatment and for 10 patients (5·1%) the data were incomplete. Most of the patients who were treated in the hospital were referred for an associate condition, some patients presented themselves at the hospital without referral.

In the 144 patients who were treated in the field no side-effects or complications due to the prednisolone were observed.

Of the first 55 BL patients who were treated with the 12 weeks course of prednisolone, 20 patients (36·0%) developed a repeat reaction. The repeat reaction either occurred during the low tail dose of the drug, at the end of the course or some time after finishing the treatment. In BT patients a similar problem was not observed. This confirms the finding by e.g. Naafs *et al.* (1979) that the antireaction treatment should be longer for BL than for BT patients.

The very fact that field staff can take action in case of reactions and often observe dramatic improvement within a short period of time, has had a positive effect on their motivation for doing regular ST and VMT examinations.

The attitude of the patients is very positive.

Field treatment of reactions has a positive effect on the esteem and credibility of the leprosy control services.

The results are satisfactory and encouraging. We classified the results as good, moderate and poor. Results are considered good if the patient got complete recovery of the nerve function loss which was found before treatment with prednisolone was started. Results are considered moderate if recovery of some of the nerve function loss was achieved. Results are poor if there is no recovery of the nerve function deficit. The results of the treatment were assessed immediately after the patient had finished the course of prednisolone. Of the 144 patients who were treated in the field, 12 patients had not yet completed their course of prednisolone at the time of assessment. Of the 132 patients who had completed the treatment, 105 patients (79·5%) achieved good results, 12 patients (9·1%) achieved moderate results and 15 patients (11·4%) poor results. It is possible that in the latter patients the reaction treatment was begun too late. In some we had to rely on the history for the duration of nerve function loss. Further recovery of the nerve function deficit may still occur after the course of prednisolone had been finished. This was not assessed.

An additional benefit of the management of patients with reactions in the field is that it is substantially less expensive than the management of patients with reactions in hospitals. This applies to the cost of the services, but also to the cost to the patients.

The prevention of increase of disability in patients with irreversible nerve damage

IRREVERSIBLE NERVE DAMAGE

Irreversible nerve damage is damage to the nerves which cannot be reversed because it has existed for a long period of time. This is usually 6 months or more.

If recovery of nerve functions is not possible any more, measures have to be taken to prevent any further disability. If patients are detected at an early stage of the disease they are not yet disabled. Unfortunately, some of the patients have already established disability at the time of diagnosis of the disease.

In some leprosy control programmes, and in particular in those which apply active case-detection methods, less than 10% of the new patients are reported with a disability at the time of diagnosis of leprosy. However, in many programmes this figure is over 10%, even over 20%. Data about disabilities in new patients usually refer to those with a disability grade of 2 (WHO disability grading of 1988). Patients with a disability grade of 1 are often included in those without disability. This gives an incorrect picture about the magnitude of the disability problem. Patients with a grade 1 disability constitute a substantial proportion of those with disabilities. These patients are at risk of developing complications due to the nerve function loss.

In the ALERT Leprosy Control Programme we found that out of 856 new patients who were diagnosed during 1987, 532 patients (62·1%) did not have any disability, 166 patients (19·4%) had a disability grade of 1 (the highest disability of eyes, hands and feet) and 158 patients (18·5%) had a disability grade of 2.

THE PREVENTION OF INCREASE IN DISABILITY BEFORE COMPLICATIONS HAVE OCCURRED

Health education which is aimed at the promotion of self-care by patients and the support of patients by their families is an important measure in the control of disabilities. This should be within the possibilities of the service which are responsible for the control of leprosy. During their contact with the patients the staff should take the opportunity to discuss with the patients how to protect their eyes, hands and feet and prevent them from injuries and wounds. If patients and their problems are taken seriously, this will increase their motivation to apply self-care measures. Patients should, as much as possible, be encouraged to buy their own Vaseline and oil. They should not be dependent on the distribution of these items by the medical services. This also applies to the provision of appliances for the protection of insensitive eyes, hands and feet. If footwear, which is suitable for insensitive soles, is available at the local market, patients should be encouraged to buy them. However, appropriate footwear is not always available, or is too expensive to be affordable. In several countries footwear programmes exist. Unfortunately, they often concentrate their attention on hospitalized patients, who already have foot deformities. The provision of footwear, which is designed to prevent the occurrence of wounds to outpatients, is often neglected. Or footwear is offered which is not acceptable because it identifies the patients as suffering from leprosy. Local shoemakers could be involved in making suitable and acceptable footwear. Since the majority of the patients with insensitive soles have normal shaped feet, standard size sandals will be appropriate for many patients. Where it is a rule that medical treatment should be provided free of charge, usually no funds are available for footwear. Or the funds are grossly inadequate. Also because people tend to take better care of appliances for which they have paid, a contribution by the patient would be an added advantage.

The provision of protective footwear by the medical services is a major undertaking. The selection of footwear which is suitable under the prevailing circumstances is one aspect. The availability of materials and financial resources are others. However, the planning and organization of a service which provides footwear without interruption and for life is the biggest and most difficult part of the undertaking. Footwear, although appropriate to protect insensitive soles, will hardly be effective if supplies are interrupted. If a continuous supply cannot be guaranteed, it is, we feel, better that footwear is not

offered by the services. Instead, the patients should be encouraged to buy the most suitable shoes at the local markets. So we come back to the promotion of self-care, through health education, as the most important and often the only available means of prevention of increase of disability.

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Preliminary observations on experimental leprosy in tupaias (*Tupaia belangeri yunalis*)

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Summary The *Tupaia belangeri yunalis* (tree shrew) is one of the primitive primates. They were inoculated subcutaneously in the footpad or intravenously with *Mycobacterium leprae* from a patient with multibacillary leprosy. As controls, the footpads of CFW mice were inoculated with the same suspension of *M. leprae*. The results showed growth of acid-fast bacilli (AFB) in the footpads of locally inoculated CFW mice and in the footpads of both locally and intravenously inoculated tupaias. Whereas the numbers of AFB declined in the footpads of CFW mice after 12 months, they increased in the tupaia footpads, up to $2{\cdot}44 \times 19^9$ AFB/g of tissue. The footpads of one tupaia were swollen, which on section revealed a granulomatous infiltration, including foamy and heavily infected macrophages. *M. leprae* were also seen in the branches of cutaneous nerves. Also AFB occurred in some viscera. Preliminary studies indicate that the AFB multiplying in tupaias are *M. leprae*.

Introduction

In 1960 Shepard[1] showed that *Mycobacterium leprae* could be transmitted to animals by showing that *M. leprae* multiplied locally when inoculated into the footpads of mice, and thus, the era of experimental leprosy was ushered in. However, bacterial multiplication in the footpads was limited and the local lesions did not resemble lepromatous type leprosy. Since then many pathologists and bacteriologists have established some new experimental models, for example, T/900R mice (whose immune mechanism were suppressed by thymectomy and whole body irradiation), armadillo and nude mice models. Recently scientists have studied the nonhuman primate model of leprosy, such as the chimpanzee,[2] mangabey monkey[3,4] and rhesus monkey,[5] and found that these animals developed generalized lepromatous-like leprosy. The aim of this paper is to study the susceptibility of tupaia (*Tupaia belangeri yunalis*) to *M. leprae*, with the hope of establishing it as an experimental leprosy model.

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Materials and methods

THE SOURCE, BODY-WEIGHT AND TEMPERATURE OF TUPAIAS

Thirteen tupaias (Figure 1) from Kunming, Yunnan Province were used. The animals had been observed under laboratory conditions for 1 month before the experiment.

At the beginning of the experiment the body-weight of tupaias ranged from 112 to 152 g (mean 134 g). The daytime body temperature (rectal) ranged from 38·6 to 40·6°C (mean 39·7°C). The surface temperature of footpads of all animals was < 32°C.

Figure 1. Tupaia (*Tupaia belangeri yanalis*).

SOURCE OF *M. LEPRAE* AND ROUTES OF INOCULATION

A biopsy of skin was obtained from an untreated patient with multibacillary leprosy and suspensions of *M. leprae* in normal saline prepared and counted for AFB by the method previously described.[6]

Two routes were used: the suspension of *M. leprae* which contained $2{\cdot}0 \times 10^7$ bacilli/ml was inoculated intravenously in 9 tupaias. Each tupaia was inoculated with 0·5 ml; and 4 tupaias were inoculated in both hind footpads subcutaneously. Each footpad was inoculated with $5{\cdot}0 \times 10^4$ bacilli. Simultaneously, 20 CFW mice were inoculated with $1{\cdot}0 \times 10^4$ bacilli/0·03 ml into the right-hind footpad, as control.

EXAMINATION OF ACID-FAST BACILLI (AFB) IN THE TUPAIAS BEFORE EXPERIMENT

Examination of faeces

After the perianal region of each experimental animal had been cleansed with 70% alcohol cotton wool swabs, a sterilized swab was inserted into the rectum approximately 2 cm in depth to obtain a specimen of faeces. The specimens were homogenized in glass tubes and left to settle for 30 min after which the supernatants were removed and

centrifuged at 3000 rpm for 30 min. The supernatants were discarded and the sediments were used for preparing two smears for each specimen. The smears were stained by the Ziehl–Neelsen method.[1]

Examination of tissues

Prior to inoculation with *M. leprae*, homogenates of tissues from 3 tupaias were examined, including the ear, footpads, sciatic nerve, tongue, lymph nodes and the internal organs. The direct smears as well as the tissue sections were made for detecting AFB and calculation using improved Hanks' techniques.[6,7] No AFB were detected in any tissues from uninoculated tupaias.

BACTERIOLOGICAL AND HISTOPATHOLOGICAL EXAMINATION OF INFECTED TUPAIAS

After inoculation, one or two animals were killed for bacteriological and histopathological examination at intervals of 1–3 months. The tissues from these tupaias were weighed and the bacteriological examinations were carried out using the same methods mentioned above.

A part of the above-mentioned tissues were fixed in Bouins' solution and embedded in paraffin for routine histopathological examination. The sections were cut at 5 μm and stained by haematoxylin and eosin stain (H and E) and by Wade–Fites' stain for AFB.

Results

Within one year of inoculation AFB were not found in the smears from the footpad homogenates of tupaias which had been inoculated with *M. leprae* by either route. However, from 12 months after inoculation there was evidence of enhanced growth of AFB in footpads of tupaias (Table 1), while the number of AFB in the CFW mouse footpads showed a decline. The average level of AFB was $8{\cdot}01 \times 10^5$, $2{\cdot}04 \times 10^6$ and $5{\cdot}34 \times 10^5$/footpad (fp) at 6, 10 and 12 months respectively after inoculation.

HISTOPATHOLOGICAL OBSERVATION AND DISSEMINATION OF AFB IN THE TUPAIAS

Six months after inoculation only a few AFB were seen in the tissue sections of the nose, ear, testes, heart, kidney, liver, spleen, lung, lymph nodes and sciatic nerve. No countable

Table 1. Multiplication of AFB in the footpads of tupaias

	No. of AFB/g tissue at different times after inoculation		
Groups	12 months	13 months	18–19 months
Intravenous inoculation	$1{\cdot}93 \times 10^6$	$2{\cdot}92 \times 10^8$	$1{\cdot}74 \times 10^7$
Subcutaneous inoculation	$2{\cdot}81 \times 10^6$	not done	$2{\cdot}44 \times 10^9$

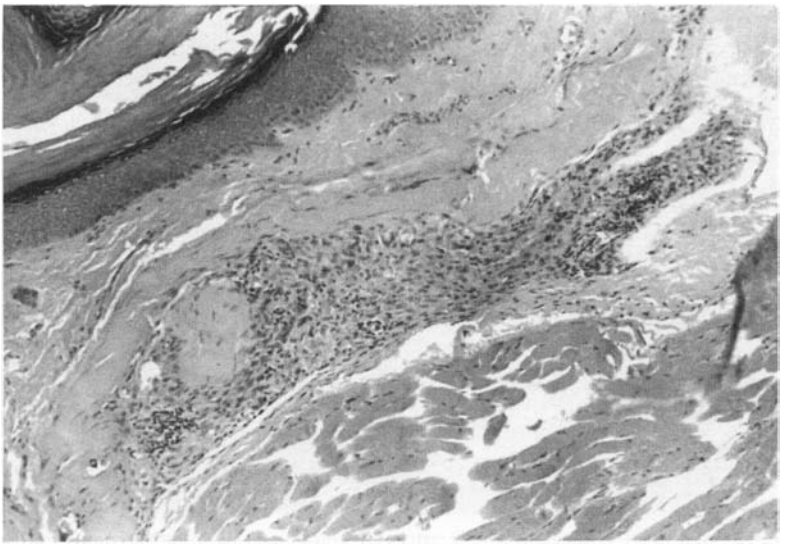

Figure 2. Twelve months after inoculation, a patchy infiltration, mainly histiocyte and macrophages, were shown under the fascia of tupaia footpads (haematoxylin and eosin stain × 40).

AFB were found in the tissue homogenates, nor any significant pathological change in the tissue sections, at this time. However, a countable number of AFB ($6{\cdot}79 \times 10^5 \sim 1{\cdot}34 \times 10^7$/g tissue) were found in the above-mentioned tissue homogenates at 12 months after inoculation. The microscopic examination of tissue sections revealed small foci of macrophages with AFB. Focal or patchy cellular infiltrates were found in the mid-dermis, subcutis, fascia, striated muscle and the intermuscular connective tissue. Macrophages predominated in these infiltrates (Figure 2).

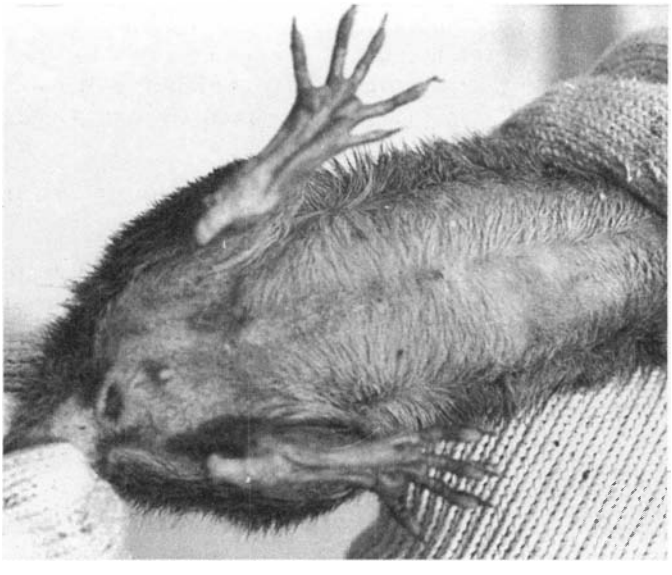

Figure 3. The footpad of a tupaia showing slight swelling.

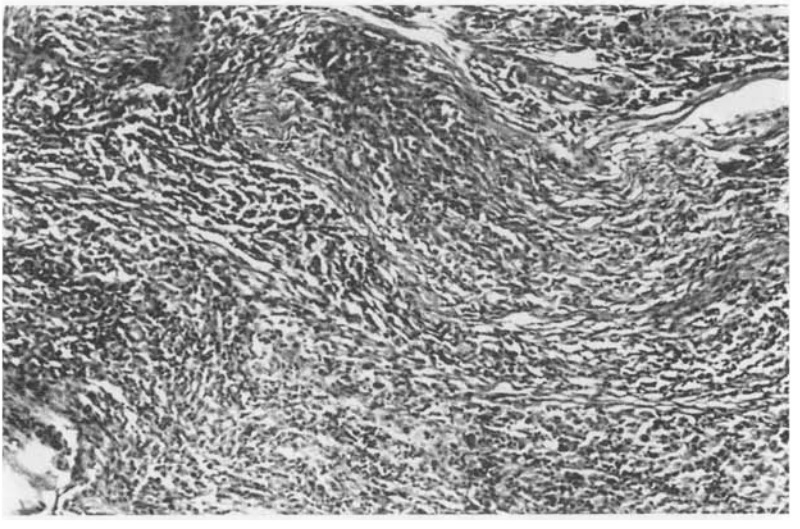

Figure 4. Eighteen months after inoculation large patches of granulomatous infiltrate containing a great number of bacilli. Some macrophages had foamy cytoplasm (haematoxylin and eosin stain × 40).

At 18 months after inoculation, the footpads swelled remarkably in one locally inoculated tupaia, in which there were $2{\cdot}44 \times 10^9$AFB/g tissue (Figure 3). Histopathological examination revealed a subepidermal Unna's zone and large patches of granulomatous infiltrate, in which the macrophage predominated in the mid and deep layer of the dermis, subcutis, striated muscles and intermuscular connective tissues. The cytoplasm of some macrophages were of a foamy appearance. Perineurium and nerve fibres of the small branches of cutaneous nerve were destroyed in various degrees (Figures 4 and 5). A large number of intact AFB and globi were seen in the acid-fast stained sections.

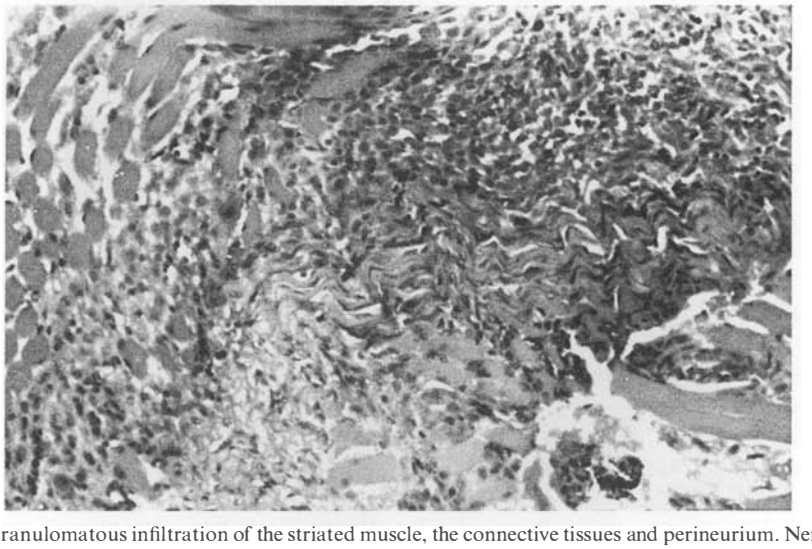

Figure 5. Granulomatous infiltration of the striated muscle, the connective tissues and perineurium. Nerve fibres of the small branches of cutaneous nerve were destroyed in varying degrees (haematoxylin & eosin stain × 80).

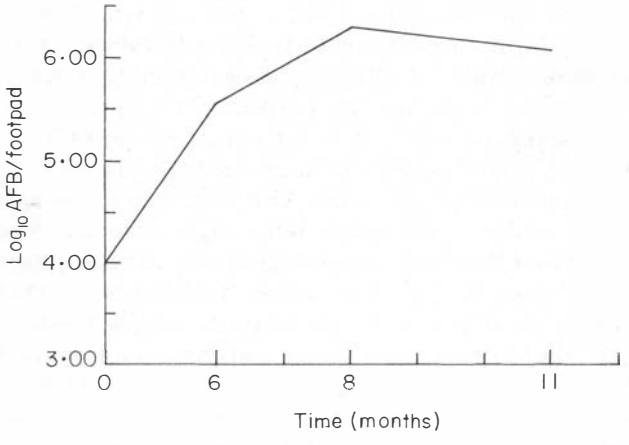

Figure 6. Growth curve of tupaia derived AFB in the footpads of CFW mice.

IDENTIFICATION OF AFB IN THE TUPAIAS

In order to ascertain whether the AFB growing in the tupaia footpads were identical to *M. leprae*, the following experiments were performed.

Growth in vitro

Eighteen months after infection with *M. leprae* the AFB from tupaia footpads were inoculated onto 7H-10 Middlebrook and Lowenstein–Jensen media. No growth of acid-fast organisms was obtained on these media incubated at 32°C or 37°C for 4 weeks.

Growth pattern and drug sensitivity in CFW mouse footpads

AFB harvested from a tupaia with a progressive infection were inoculated at a dose of $1{\cdot}0 \times 10^4$ AFB into both hind footpads of groups of CFW mice. Their rate and pattern of growth of CFW mice was identical with that of *M. leprae* (Figure 6). The other groups of similarly infected CFW mice were used to determine their sensitivity to dapsone and to rifampicin using the continuous method of assessment. The results showed that they were susceptible to 0·01% dapsone and 0·003% rifampicin in the mouse diet.

Discussion

More recently some investigators were interested in using primates for the study of experimental infections with *M. leprae*. They found that animals such as the chimpanzee, mangabey monkey and rhesus monkey could develop a generalized leprosy infection similar to that in patients with lepromatous-type leprosy. Owing to the high cost and expertise required for the successful long-term maintenance of those larger primates, some scientists are attempting to use smaller and more primitive primates. For example, in China the readily available tupaia has recently been used to study viral infection,

including human rotavirus,[8] hepatitis A[9] and hepatitis B virus.[10] In our laboratory the tupaias were inoculated with a suspension of *M. leprae* by intravenous and subcutaneous routes. Our main purpose was to investigate the susceptibility of the tupaia to *M. leprae* and eventually to establish a new model of experimental leprosy. The results indicated that 6 months after the tupaias were inoculated with *M. leprae* AFB were not found to be growing and no significant histopathological change in the tissues of inoculated animals was noted. However, 6 months later, a few AFB were seen in the tissue sections of the nose, ear, testis, heart, kidney, liver, spleen, lung, sciatic nerve and footpad. In the same period the AFB in the CFW mouse footpads gradually increased from $8{\cdot}05 \times 10^5$ up to $2{\cdot}04 \times 10^6$ bacilli/footpads after which the number of AFB declined. On the other hand by 18 months the number of AFB in the tupaia footpads increased up to $2{\cdot}44 \times 10^9$ bacilli/g of tissue. Moreover, the footpads were swollen and one section revealed a predominately macrophage infiltrate, many of the macrophages contained AFB and some a foamy cytoplasm; a picture resembling that seen in patients with lepromatous-type leprosy.

It is of interest that maximum growth of AFB in the tupaia occurred in the footpad, the site with a lower body temperature ($< 32°C$), which is in line with the preference of *M. leprae* for cooler sites in man and in other species of animals used as models for experimental leprosy. The preference of the AFB for cooler sites in the tupaia, their inability to multiply *in vitro* and their sensitivity to antileprosy drugs, particularly dapsone as well as rifampicin, are all consistent with these AFB being *M. leprae* and preliminarily establishing the tupaia as a new and valuable model of experimental leprosy.

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Lepr Rev (1990) **61,** 19–24

Antibodies to the phenolic glycolipid-1 antigen for epidemiologic investigations of enzootic leprosy in armadillos (*Dasypus novemcinctus*)

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Summary Other than man, nine-banded armadillos (*Dasypus novemcinctus*) are the only known natural hosts of leprosy with high rates of disease. The origin, range and risk of their infection is not yet clear and a better description of the rate of leprosy over the armadillo's range is needed. Both histopathological examination of armadillo ear tissues and serologic screening for IgM antibodies to the phenolic glycolipid-1 (PGL-1) antigen of *Mycobacterium leprae* are good relative indices of enzootic prevalence. A survey of 216 armadillos from Louisiana and Florida detected infection only among Louisiana animals. Average antibody prevalence (12·5%) was five times higher than the fully disseminated disease rate described histopathologically (2·7%). The differences in antibody and histopathological prevalence are due to the sensitivity of the methods for detecting early infection. Histopathological examinations describe an advanced disease. The higher antibody prevalence of wild armadillos is not likely to be the result of false positive serologies from self-healing infections or other casual encounters with *M. leprae* as might be mimicked by lepromin injection. The environmental reservoir of *M. leprae* represented by infected armadillos is greater than could be previously estimated.

Introduction

A leprosy-like disease was first reported among wild armadillos (*Dasypus novemcinctus*) in 1975.[1] The aetiologic agent was confirmed to be *Mycobacterium leprae* in 1983,[2] and today leprosy is recognized as a naturally acquired enzootic infection of nine-banded armadillos.[3] The origins, range and risks of armadillo leprosy are not yet known. But exposure to armadillos could be an important risk factor in some human infections.[4,5]

Armadillos may represent a large reservoir of potentially infectious contacts. Though they occupy a much greater range, enzootic leprosy is reported only among armadillos in Louisiana, Mississippi, Texas, Argentina and Mexico.[2,6–11] Besides man, they are the only highly endemic natural hosts of leprosy. Their natural infection may be exploitable for modelling purposes and a better description of the rate of infection over their range is needed.

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Earlier studies described enzootic prevalence by histopathologically detecting acid-fast bacilli (AFB) in dermal nerves of armadillo ear tissues. Ear biopsies successfully identify fully disseminated armadillo leprosy 92–100% of the time.[2,7,12] But, this manifestation occurs only in the late stages of armadillo leprosy.[12,13] We recently developed an enzyme-linked immunosorbent assay (ELISA) that detects armadillo IgM antibodies[3] to the chemically defined and apparently species specific phenolic glycolipid-1 (PGL-1) antigen of *M. leprae*.[14] In laboratory infected animals, the ELISA becomes positive *in a third of the time required for AFB to become detectable* in ear tissues and has good predictive value for developing fully disseminated leprosy.[13] To determine the enzootic prevalence rates describable by these two methods in field applications, we surveyed armadillos in Louisiana and Florida, and examined the likelihood of false positive serology in armadillos exposed to killed *M. leprae* in lepromin.

Materials and methods

ARMADILLOS, SERA, AND TISSUE SAMPLES

A total of 186 wild armadillos were captured at night along open levees in 2 parishes in south central Louisiana: 131 Iberville, 55 Point Coupee. An additional 58 armadillos were similarly obtained from various field locations in Louisiana and returned to the laboratory for further study. Serum samples from 30 Florida armadillos were collected by Dr E E Storrs (Florida Institute of Technology, Melbourne, USA) and provided through the National Institutes of Allergy and Infectious Disease (Dr Darrell Gwinn, NIAID leprosy project officer). Serologic samples from Louisiana armadillos were taken by subclavian puncture or in capillary tubes following close excision of a toenail. A 1×2 cm snip of ear was also taken from Louisiana animals and preserved in buffered formalin for later histopathological examination. The 30 florida armadillos had been previously necropsied with no evidence of leprosy infection found.

ELISA

Using the method previously described, serum samples were tested in an ELISA for IgM antibodies to the phenolic glycolipid-1 (PGL-1) antigen of *M. leprae*.[3] The PGL-1 antigen was prepared by Dr P Brennan (Colorado State University, Ft Collins, USA) and provided through contract with NIAID. Resulting ELISA absorbencies were judged for positive and negative reaction using definitions previously determined. Specificity was confirmed by absorbing presumed positive sera with whole *M. leprae* and other mycobacterial species. Absorbencies of true positive sera were significantly reduced following absorption with *M. leprae* but not altered by absorption with other mycobacterial species.[3]

HISTOPATHOLOGY

Ear tissues and lepromin biopsies were prepared according to methods previously described and examined for granulomatous inflammation and acid fast bacteria within macrophages and dermal nerves.[12,15]

LEPROMIN

Lepromin, prepared from armadillo tissues, was given intradermally to the abdominal skin as 0·1 ml containing 1·6 * 10^7 *M. leprae*. After 21 days the test site was examined and biopsied.[15] The 58 laboratory housed armadillos received varied lepromin regimen. Group 1 was 7 armadillos which eventually developed fully disseminated leprosy as a result of experimental inoculation with from $1*10^6$ to $1*10^7$ *M. leprae*. Lepromin was given mid-way in the experimental infection. Animals were serologically sampled prior to injection and twice again in 3-week intervals. Group 2 was 43 un-inoculated recently captured armadillos. Each received a single lepromin and was serologically sampled before injection and twice again in 3-week intervals. Group 3 consisted of 2 additional uninfected armadillos which received 8 repeated lepromin injections once every 3 months for 24 months. They were serologically sampled every 3 months at the end of each 21-day lepromin interval. Group 4 had 2 armadillos which were experimentally inoculated with *M. leprae* but resisted disseminated infection for at least 50 months prior to lepromin injection. They received 8 lepromin injections once every 3 months for 24 months and were serologically sampled at the end of each lepromin interval. Similarly, Group 5 was 4 armadillos which also had resisted an experimental infection for at least 50 months. They were given a single lepromin injection and serologically sampled before and twice again in 3-week intervals.

STATISTICAL ANALYSIS

Statistical comparisons were made using the SAS 6.03 program package (Statistical Analysis Systems, Cary, North Carolina USA).

Results

ENZOOTIC PREVALENCE

A total of 23 (12·5%) Louisiana armadillos had detectable antibodies to the PGL-1 antigen. None (0/30) of the Florida armadillos had detectable IgM antibodies to PGL-1 (Table 1). Absorption with *M. leprae* significantly reduced the resulting ELISA absorbencies of positive sera (paired-*t*; $p < 0{\cdot}05$); but absorption with other mycobacterial species failed to have significant effect (data not shown). Antibody prevalence rates between Louisiana and Florida differed significantly (Fisher's exact test; $p < 0{\cdot}05$); but rates between groups of Louisiana armadillos were not significantly different. Prevalence determined by histopathological examinations of armadillo ear tissues was significantly lower than antibody prevalence. Armadillos in both Louisiana parishes had detectable AFB in ear tissues (2/55 Point Coupee; 3/131 Iberville) resulting in an average histopathologic prevalence of 2·7%. All armadillos with detectable AFB in ear biopsies had detectable IgM antibodies to PGL-1. IgM antibodies to PGL-1 were also detected in the absence of AFB in ear tissues. The 30 Florida armadillos had been previously necropsied and found to be free of infection. Differences in histopathologic prevalence rates failed to show statistical significance.

Table 1. Leprosy prevalence in wild armadillos

Location	Detection method			
	Serologic		Histopathological	
	Positives per total sampled	% positive	Positives per total sampled	% positive
Louisiana	23/186	12·5[a]	5/186	2·7
Iberville parish	14/131	10·6	3/131	2·3
Point Coupee parish	9/55	16·3[b]	2/55	3·6
Florida	0/30	0	0/30	0

[a] = Significantly higher than Florida (Fisher's exact $p = 0{\cdot}026$).
[b] = Not significantly different from rate in Iberville parish (Fisher's exact $p = 0{\cdot}183$).

Table 2. Effect of lepromin on ELISA-IgM for PGL-1 in armadillos

Group ID and size	Status	Lepromins given	Sampling		Mean ELISA	
			Number	Interval	Initial	Change
1 n = 7	Experimentally infected and succumbed	2	3	3 weeks	0·925 ± 0·428	0·056 ± 0·093
2 n = 43	Not infected naive	1	3	3 weeks	0·300 ± 0·158	0·046 ± 0·166
3 n = 2	Not infected naive	8	9	3 months	0·134 ± 0·100	0·006 ± 0·155
4 n = 2	Experimentally infected but resistant	8	9	3 months	0·326 ± 0·154	0·022 ± 0·112
5 n = 4	Experimentally infected but resistant	1	3	3 weeks	0·390 ± 0·064	0·040 ± 0·053

ELISA absorbencies $< 0{\cdot}580$ indicate no detectable antibody; 0·580 to 0·710 are equivocal; and $> 0{\cdot}710$ indicate positive detectable antibody.

LEPROMIN AND ANTIBODY RESPONSE

Exposure to *M. leprae* through lepromin had no significant influence on humoral IgM to PGL-1 in any of the groups tested (Table 2).

Discussion

M. leprae infection in wild armadillos prompts consideration of zoonotic transmission. Some strong associations relating exposure to armadillos and human leprosy have

already been drawn.[4–6] The relative risks for enzootic leprosy would seem dependent on a variety of host factors and the likelihood of susceptible individuals having some significant interface with infected armadillos. Estimates of simple prevalence are useful for the latter.

Earlier reports on enzootic leprosy estimated prevalence by detecting acid-fast bacteria within dermal nerves of armadillo ear tissues. In Louisiana, some 90% of the armadillos are susceptible to experimental *M. leprae* infection and eventually succumb to fully disseminated leprosy with doses as low as 10^3 organisms.[12] However, reported histopathological prevalence rates vary widely by locale from 0 to 30%. Statewide averages for Louisiana and Texas range only between 2 and 4·9%.[2,6–9] The 2·7% histologic prevalence rate seen here among Louisiana armadillos is in keeping with those previous estimates.

Louisiana PGL-1 antibody prevalence was nearly 5 times higher than the rates described histopathologically. Antibody surveys in human populations find relatively high prevalence but appear to have low predictive values.[16–18] Better correlation is seen with armadillos. PGL-1 IgM has good predictive value for developing fully disseminated leprosy in experimental infections. The antibodies evolve slowly and first appear only about 6 months after inoculation. There is probably marked dissemination of *M. leprae* before this time.[13] PGL-1 IgM also is not affected by casual encounters with *M. leprae* mimicked here by lepromin injections. Though in man lepromin may elicit humoral responses to other *M. leprae* antigens;[19] human volunteers receiving heat killed *M. leprae* vaccine also do not develop detectable PGL-1 IgM.[20] Armadillos are highly susceptible to leprosy and it *seems* unlikely *that* any significant proportion of their infections self-heal.[12] Histopathologic examinations describe an advanced disease in armadillos and the differences in armadillo antibody and histologic prevalence seem related to the stage of infection detected. The high antibody prevalence of wild armadillos indicates they are a much greater reservoir of *M. leprae* than was previously believed. How they came to be infected with *M. leprae*, and the distribution or impact of their infections is not yet known.

Leprosy is either indigenous to armadillos or they have acquired the disease; perhaps by contact with infected humans.[6,7] Armadillos are not native to the USA; but began expanding their range north from Mexico in about 1880. Another group was accidentally introduced in the state of Florida around 1925. Today armadillos range from Argentina to as far north in the USA as Oklahoma and the Carolinas.[21] The distribution of enzootic leprosy over their range is unclear. Most early investigators thought the disease was concentrated in Texas and Louisiana. Enzootic leprosy is found only in animals from the southern migration. Neither these or other studies have found leprosy in Florida armadillos;[6] but Amezcua[11] and Martinez[10] also report enzootic infection in armadillos outside the USA. To date no prevailing trends have been identified. Some of the seeming disparities may be related to the sensitivity of histopathological screening methods used in earlier studies. The low expected rate of fully disseminated disease in armadillos requires large sample sizes for reliable interpretation. Histopathological methods seem better suited for confirming the etiology of suspected cases, or for surveys that necropsy large numbers of armadillos. Serologic surveys probably have better promise for describing the actual geographic distribution of enzootic leprosy. The antibodies are detected more frequently and can describe an earlier stage of disease. Additional surveys over the range of armadillos will bring important insight into the origins and risks of armadillo leprosy.

Acknowledgments

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Mycobacterium leprae reactive T cell clones from lepromatous leprosy patients after prolonged dapsone chemotherapy

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Summary The proliferative responses of peripheral blood mononuclear cells (PBMC) to *Mycobacterium leprae* and BCG were studied in two groups of leprosy patients: a group of 8 lepromatous patients who had been on treatment for more than 20 years (TLL) and a group of 8 untreated lepromatous leprosy patients (ULL). The mean response to *M. leprae* of the TLL group was 6195 cpm with 5 of the 8 patients responding positively. The mean response to *M. leprae* of the ULL group was 617 cpm, with only 1 patient showing a positive response. The corresponding proliferative responses to BCG were 19,908 cpm in the TLL group and 7908 in the ULL group.

Thirteen *M. leprae* reactive clones were established from 2 TLL patients and 5 *M. leprae* reactive clones were established from 2 tuberculoid leprosy patients. Seven of these clones, 4 from the TLL patients and 3 from the tuberculoid (TT) patients could be studied further. Three of the TLL clones responded specifically to *M. leprae*, while one of the clones exhibited a broad cross-reactivity to other mycobacteria. All of these clones were of the CD4+CD8− phenotype.

Our findings suggest that responsiveness to *M. leprae* can be detected *in vitro* in a proportion of LL patients who have undergone prolonged chemotherapy, and that this response involves *M. leprae* reactive CD8+CD8− T cells, of which some appear to be specific to *M. leprae*.

Introduction

It is well documented that lepromatous leprosy patients do not respond to *M. leprae*

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antigens in lymphoproliferative assays.[1-3] This nonresponsiveness has been reported to persist in lepromatous patients who have been on chemotherapy for more than 10 years.[4] Furthermore, the degradation of *M. leprae* in host tissue appears to take place very slowly.[5] Thus an investigation of this nonresponsiveness, particularly in relation to its duration and its possible reversal, would require the study of patients who had undergone even longer periods of chemotherapy. A unique opportunity for such a study exists in Sungai Buloh where one of the most comprehensive of the earlier trials of dapsone has been conducted.

In this study, a small number of LL patients, who had undergone more than 20 years of chemotherapy, were screened for responsiveness to *M. leprae* in proliferation assays. Some of these long-treated patients were found to respond to *M. leprae*. In addition, T-cell clones which recognize *M. leprae* could be raised from some of these patients using standard techniques.

Materials and methods

PATIENTS

Untreated and long-treated (20 years) LL patients, classified according to the criteria of Ridley & Jopling,[6] were the main subjects of this study. Tissue slides of the long-treated patients (TLL) were re-examined (by DSR) independently of the immunological results and only those classified as having lepromatous leprosy were included in this study. Most of the long-treated patients were residents of Sungai Buloh, while the untreated patients were new cases in the hospital awaiting classification and treatment. Two TT patients were also included in the study. Patients whose T cells were considered suitable for cloning were informed about the procedure and told that they would be bled twice a month for the initial period of the study. The most acceptable arrangement was to take 20–30 ml of blood from the subject once a fortnight with allowances for rest periods when the need for PBMC was not so critical.

LYMPHOCYTE TRANSFORMATION TEST

Mononuclear cells were separated from the patient's peripheral blood by density centrifugation on a Ficoll/Hypaque gradient (Pharmacia, Sweden). The peripheral blood mononuclear cells (PBMC) were cultured at a concentration of 10^5 cells/well, in 96 well U-bottom trays in the presence of antigens. The trays were incubated for 6 days at 37°C in a humidified atmosphere of 5% CO_2 in air. On the 6th day, the cultures were pulsed with 0·045 MBq. ^{3}H-thymidine (specific activity $= 185 \times 10^3$ mol^{-1}) for 4 hours, after which they were harvested with a Skatron harvester (Norway). The radioactivity incorporated was determined by liquid scintillation spectroscopy. The results were expressed as the mean value of counts per minute (cpm) of triplicate cultures. A subject was considered a responder to a given antigen when cpm Δ cpm = (cpm of PBMC + Ag) − (cpm of PBMC) > 2000 and T/C = (cpm of PBMC + Ag)/(cpm of PBMC) > 2.

M. LEPRAE INDUCED T CELL CLONES

The procedure for raising *M. leprae* reactive T cell clones has been described elsewhere.[7]

Briefly, 20×10^6 peripheral blood mononuclear cells were cultured in complete medium (RPMI 1640 + 10% AB serum + 50 μg/ml gentamycin) with 10 μg/ml soluble *M. leprae* antigen (Batch CD 52) in 25 cm^3 flasks (Costar). The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 in air for 6 days. On the 6th day the cells were washed and recultured with fresh autologous irradiated (2200 rad) feeder cells and antigen. Three days later the cells were washed and cloned in 60-well Microtest plates (Nunc) by limiting dilution. After 10–12 days cells from positive wells were transferred to 96-well flat-bottomed trays (Nunc) with fresh irradiated autologous feeders + antigen + recombinant interleukin-2 (IL-2, Cetus). Then, 3–5 days later, growing cultures were transferred to 24-well plates (Nunc) with 1×10^6/ml autologous irradiated feeder cells + 10 μg/ml of soluble *M. leprae* antigen + 100 U recombinant IL-2. Recombinant IL-2 and fresh medium were added on day 3. This cycle was repeated every 7th day until there were enough cells for study.

ANTIGEN INDUCED PROLIFERATION OF T CELL CLONES

To test the antigen reactivity of the clones in a proliferative assay, adherent cells from 10^5 irradiated PBMC were added to each well of a 96-well flat-bottomed tray as antigen-presenting cells. 10^4 cloned T cells and antigens at optimal concentration were also added. Antigens were added in triplicate. The plates were incubated at 37°C in a humidified atmosphere of 5% CO_2 in air. On the 3rd day the cultures were pulsed with 0·045 MBq ^{3}H-thymidine for 4 hours, after which they were harvested with a Skatron harvester (Norway). The results were expressed as the mean value of cpm of each triplicate. A clone was considered a responder to a given antigen when Δ cpm = (cpm of cultures with T-cell clone + antigen + APC) − (cpm of cultures with T-cell clone + APC) > 1000 and T/C = (cpm of cultures with T-cell clone + antigen + APC)/(cpm of cultures with T-cell clone + APC) > 2.

ANTIGENS

The *M. leprae* antigens, soluble (CD 60 and CD 52) and whole (CD 46), were provided by Dr R J W Rees (Mill Hill, London), from the IMMLEP (WHO) *M. leprae* Bank. BCG and PPD were obtained from the Statens Serum Institute, Copenhagen, Denmark. The following soluble antigens, Scrofulin, Kansasin, Aviumin, Flavescin, Xenopin, Duvalin, Nonchromogencin, Smegmatin, Vaccin, Gordonin, Phlein, Tuberculin and Mw, made by the ultrasonication of a panel of fast- and slow-growing mycobacteria, were kindly provided by Dr J L Stanford and Dr G Rook, Middlesex Hospital Medical School, London, U.K.

Results

Peripheral blood mononuclear cells (PBMC) from 8 clinically, bacteriologically and histopathologically classified lepromatous leprosy patients, who have not yet been treated (ULL) and from 8 long-treated (> 20 years), clinically improved and bacteriologically negative lepromatous leprosy patients (TLL) were tested for *in vitro* proliferation to *M. leprae* and BCG antigens (Figure 1). The mean response to *M. leprae* in the TLL group was 6195 cpm with 5 of the 8 patients responding positively. The mean response to *M.*

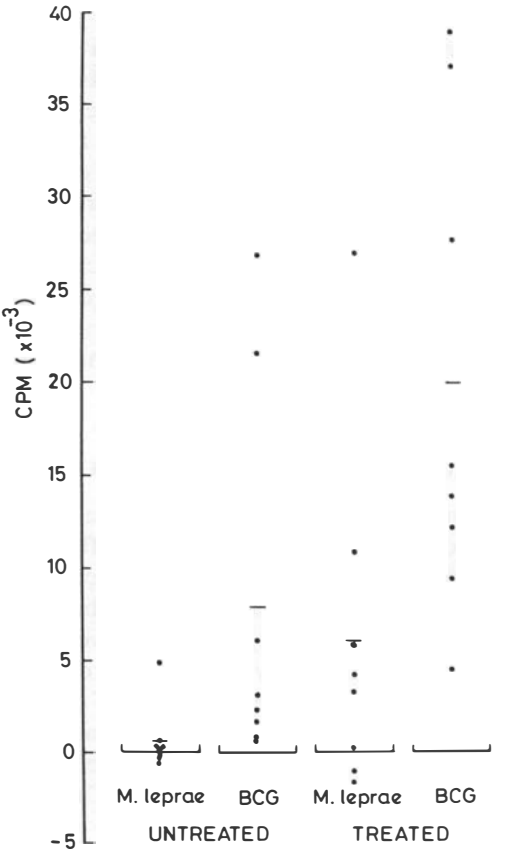

Figure 1. Proliferative responses to BCG and *M. leprae* in ULL and TLL patients. Each dot represents the proliferative response of one patient which is expressed in mean cpm of triplicate cultures. Horizontal bars represent the mean response of the group.

Table 1. Preliminary screening of antigen reactivity of T cell clones from TLL patients

Patient	LSH				LLH					
Clone	2/4D	5/4C	7/5E	8/7D	2/1C	3/3B	2/9D	2/7C	4/1D	6/6A
Antigen										
Control	1254	738	755	461	421	731	370	180	288	314
CD 52	6821	5919	2961	3691	40746	23487	24596	26971	14918	5215
CD 46	201	229	681	390	713	666	255	389	425	154
BCG	504	713	1265	6202	699	2725	5508	661	687	673
PPD	326	419	637	9624	1419	647	2061	1779	546	308

CD 52 is a soluble *M. leprae* antigen.
CD 46 is a whole *M. leprae* antigen.
The results are expressed in mean cpm of triplicate cultures.
Positive responses are underlined.

Table 2. Antigen reactivity and surface phenotype of T cell clones from TLL and TT patients

	TT			LL			
Patient	EL/1	SB/1	SB/2	LSH 5/4C	LSH 2/4D	LLH 6/6A	LLH 2/9D
Control	312	983	375	921	606	895	191
CD 52	5358	7138	13680	5502	12437	6090	18007
CD 46	1193	405	638	621	893	605	205
BCG	493	436	307	491	1089	444	1459
PPD	331	277	657	366	1493	586	1967
Scrofulin	328	348	695	487	524	790	2170
Kansasin	587	285	548	190	282	639	98
Aviumin	325	268	268	285	443	1421	1553
Flavescin	646	361	392	171	450	421	2055
Xenopin	336	372	412	446	396	1620	1382
Duvalin	421	530	327	448	482	321	233
Nonchromogencin	310	209	165	198	216	459	217
Smegmatin	457	278	272	157	291	427	144
Vaccin	283	150	343	369	253	709	4716
Gordonin	380	191	391	238	175	537	4413
Phlein	40	245	259	677	401	1272	208
Tuberculin	808	247	327	474	437	585	5219
Mw	744	372	284	380	663	1476	5179
Phenotype CD4	+	+	+	+	+	+	+
CD8	−	−	−	−	−	−	−

Results are expressed in mean cpm of triplicate cultures.
Positive responses are underlined.

leprae of the ULL group was 617 cpm, with only 1 patient showing a positive response. The difference in response to *M. leprae* between the two groups was not statistically significant ($p > 0{\cdot}3184$, Wilcoxon Rank Sum Test). The corresponding proliferative responses to BCG were 19,908 cpm in the TLL group and 7908 in the ULL group.

To determine the characteristics of the responding cells from the TLL patients, 13 T cell clones, against *M. leprae*, were successfully raised from the PBMC of 2 of these 8 patients. For comparison five *M. leprae* induced T cell clones were also raised from 2 tuberculoid leprosy patients. In the preliminary screening of the TLL clones, 6 clones were found to be specific, 4 clones were cross-reactive and 3 clones were non-reactive (Table 1). All of the 5 clones raised from the TT patients were found to be specific for *M. leprae* in the preliminary screening.

Seven of these clones, 4 from the TLL patients and 3 from the TT patients, could be studied further by assessing their proliferative responses to soluble antigens from a panel of 13 cultivable mycobacteria (Table 2). Three TLL clones responded specifically to *M. leprae*, while one clone exhibited broad cross-reactivity, with responses to various other mycobacteria. All 7 of the T cell clones were of the CD4+CD8− phenotype (Table 2).

Discussion

There is a good correlation between the *in vitro* proliferative response and the *in vivo* cell mediated immunity throughout the clinical spectrum of leprosy.[2] The *in vitro* response to

M. leprae has been found to be negative in untreated LL patients. Furthermore, earlier studies have suggested that the cell mediated immune response to *M. leprae* remains negative even after prolonged treatment.[4] However, such studies have been time limited as the first effective chemotherapeutic agent, dapsone, was only introduced in the late 1940s. Sungai Buloh is one of the few places which made an early start in assessing the efficacy of dapsone for the treatment of leprosy. Patients from these trials have been on prolonged treatment and were carefully monitored throughout and after the period of treatment. They thus represent a unique source of study especially for the effects of prolonged treatment.

In this study we were able to examine the responses of 8 such long-treated patients and to compare them with those of untreated LL patients. Five of the long-treated patients showed a positive response to *M. leprae* so that the mean response to *M. leprae* of the TLL group was 6195 cpm. The mean response to *M. leprae* in the ULL group was 617 cpm, with only 1 patient showing a positive response. It is possible that some of these long-treated patients had at some stage passed through a responder phase such as a borderline tuberculoid phase. This idea is supported by the fact that several of these patients were classified as LLs. The others could not be classified further than LL, either for technical reasons or because the lesions were resolving. There were no definite cases of the primary LLp group, a rarity in Malaysia. In an earlier study, LL patients (bacteriologically negative for 8–20 years) who were immunized with *M. leprae* or *M. leprae* and BCG failed to develop a delayed type hypersensitivity to *M. leprae*.[8] This was attributed to antigen persistence. It is thus interesting that immunological responsiveness should now be demonstrated in a similar group of patients who have undergone an even longer duration of treatment. There is also evidence that patients similar to ours, in some cases, do regain their lepromin positivity (Dr M F R Waters, personal communication).

The establishment and study of T cell clones from these long-treated LL patients revealed that their ability to respond to *M. leprae* is due to cells of the CD4+ phenotype. The establishment of CD4+ clones from tuberculoid patients have been reported previously.[9,10] More recently there have been reports of CD8+ *M. leprae* reactive T cell clones raised from a borderline lepromatous leprosy patient[11] and from the lesions of a lepromatous leprosy patient.[12] To the best of our knowledge, this is the first report of *M. leprae* reactive CD4+ T cell clones isolated from the PBMC of lepromatous leprosy patients. These clones display response patterns similar to the other *M. leprae* reactive CD4+ T cell clones that have been isolated from leprosy patients in that they range from a pattern of strict specificity to patterns of broad cross-reactivity.

Our study shows that at least some lepromatous leprosy patients have the potential for generating T cell responses to *M. leprae* specific as well as *M. leprae* cross-reactive epitopes.

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Leprosy in Portugal 1946–80: epidemiologic patterns observed during declining incidence rates

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Summary Compulsory notification of leprosy in Portugal formed the basis for the establishment of a national patient registry used in an epidemiological study. Highest incidence rates were observed in the coastal counties in the middle of Portugal and particularly in the municipalities with a high annual rainfall. Peak incidence rate in males was observed at the age of 25–29 years against 50–59 in females. A continuous and increasing decline in incidence rates was observed throughout the observation period, 1946–80. Towards the end of the period the slopes of the incidence curves seemed to be identical with those observed in other countries where leprosy has previously been eradicated. This is consistent with the notion that towards the end of an endemic situation no new transmission of the disease occurs, and the incidence curve takes the shape of the right part of the distribution of incubation periods which apparently is uniform in leprosy, irrespective of time and place. The pattern observed in other areas during declining incidence rates, of an increase in age at onset by year of onset together with a lack of increase in age at onset by year of birth was confirmed by the Portuguese data, also consistent with a break in the transmission of the disease a long time before the final termination of the endemic situation.

Introduction

Data necessary to assess secular trends in leprosy have been scarce. Apart from the National Leprosy Registry of Norway,[1] national schemes for the provision of data necessary for community based planning, administration, and evaluation of leprosy control programmes on the one hand and for epidemiological studies of leprosy on the other have been rare. However, during the last decades, the importance of careful registration of leprosy patients has been realized and stressed in an increasing number of

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countries. Thus, sources of data (e.g. Refs 2–9) have eventually evolved that are useful in epidemiological studies.

In Portugal, the necessity of acquiring data for planning, administration and evaluation of leprosy control programmes was realized rather early.[2] Thus, in 1947, the notification of all leprosy cases to a central agency was legally authorized and over the years a considerable amount of data has been filed.

Today, there is a need in many countries to evaluate leprosy control programmes and to assess secular trends. In Portugal, opportunity is offered to meet this need.

Based on some of the information at hand, a computerized register has been established, comprising all cases of leprosy in the country notified after 1945. This register provided the source material for the present analyses which attempt to elucidate the epidemiology of leprosy and to obtain knowledge relevant to control programmes in areas where leprosy is still prevalent.

Materials and methods

NOTIFICATION AND REGISTRATION OF LEPROSY CASES

Compulsory notification of leprosy cases was introduced by a decree of 2 August 1947. The central registry was established at the National Centre for Leprosy, Hospital Rovisco Pais (the Centre), in the middle of the country. Concomitantly, mandatory hospitalization was introduced for infectious patients, unless satisfactory domiciliary care could be provided. Activities under this decree were supervised by Instituto de Assistencia aos Leprosos (the Institute) affiliated with the General Directorate of Health in Lisbon. Diagnostic criteria were established by the Centre for the definition of leprosy and for the various types of the disease. The Madrid classification was adopted in 1953 and replaced by the Ridley–Jopling classification in 1968–69. Close contacts were established with the faculties training the medical profession.

Every physician in the country was required to notify all the leprosy cases he diagnosed. In the case finding and reporting the physicians were assisted by a number of mobile teams established by the Centre in 1958. Each team consisted of a physician, a nurse and a social worker, who were responsible for patients under domiciliary care. The mobile teams played an important role in the standardization of the reporting with respect to diagnostic criteria and regimens for treatment and follow-up. After 1973, their functions were gradually transferred to the general health centres, or to specialized out-patients' departments in the larger cities.

An individual notification form (Table 1) was filled out for each patient, by the physician, and sent to the Centre. After 1976 a copy of the form was sent to the Institute as well. When changes were observed in the condition of the patient the central agencies were notified.

By a decree of 1976 the Institute was made responsible for the organization and administration of all leprosy control activities. Accordingly a central file consisting of all notified cases was established for epidemiological and administrative purposes. At the same time, mandatory hospitalization of infectious cases was abolished. Gradually the activities became more decentralized, and in 1984 a third decree actually closed the Institute. Its objectives, however, were maintained and integrated together with all

Table 1. Items of personal data used in the notification of leprosy cases in Portugal

Notifying unit	*Clinical data:*
Name	History including reactions
Central serial number	Symptoms and signs
Date of registration	Lepromine reaction
Year of onset	Tuberculin reaction
Date of birth	Microbiological findings
Birthplace	Histological findings
Place of residence at onset	Type of leprosy
Place of residence at registration	Other diseases
Occupation	
Education	*Relatives:*
Sex	Names and relationships with lepromin reaction and central serial
Marital status	number (if affected with leprosy)
	Follow up information:
	Subsequent microbiological findings
	Year when cured
	Year of death

organizational structures into the division of Primary Health Care under The Ministry of Health.

ADDITIONAL SOURCES OF DATA

Data on the total population were derived from general population censuses conducted in 1940, 1950, 1960, 1970 and 1981, published by the National Institute of Statistics. Information on emigrants and their eventual return to Portugal was obtained from official statistics, and meteorological observations obtained during 1931–60 on precipitation, air humidity and temperature were provided by the National Meteorological Services.[3]

METHODS

From 1980 onwards data were transferred to a computerized register. As the basis for computer registration, a photocopy was used of the notification form, after the necessary codes were added. Items of personal data are shown in Table 2. Identification of the forms was secured during the computer registration by the consecutive generation of identification numbers. Furthermore, each patient, when first registered, had been allotted a central serial number generated by the Institute identifying all patient notifications.

Registration errors were to a large extent controlled by registering all forms twice for computerized comparison. Inequalities were detected and corrected. To avoid the registration of unacceptable values or invalid codes, valid ranges and codes were specified for each item of personal data. Inevitably, some patients, for various reasons, had more than one notification form. To avoid duplicate records the forms were marked with the central serial number of the patients.

Case ascertainment could not be directly assessed because no independent source of information was available. Yet the local system of case finding, enforced since 1947 with

Table 2. Items of personal data transferred to the computer file

Identification no. (generated)	Type of leprosy
Central serial no.	Lepromin reaction
Date of registration	Year of cure
Year of onset	Year of death
Date of birth	
Birthplace	*Relatives:*
Place of residence at onset	for each:
Place of residence at registration	Central serial no. (if ill)
Occupation	Relationship
Sex	Lepromin reaction
Marital status	Ill—not ill.

compulsory notification entrusted to all physicians, assisted by the mobile teams supervising and guiding health personnel at the local level, should provide sufficient ascertainment. In addition, case ascertainment was indirectly evaluated on the basis of register delay, i.e. the period between onset and registration (Table 3). A long delay might cause under-registration. Obviously, this delay decreased during the first years after 1947. Measured as median difference between years of registration and onset, the delay remained below 1·3 years after 1950.

Likewise, over-registration, i.e. cases being falsely diagnosed as leprosy, could not be directly assessed due to lack of sources of information. Forms representing such cases were immediately removed from the files by the central agencies. However, the careful follow-up examinations, organized and conducted by the mobile teams, ensures that the number of such cases not removed from the files has remained low.

Completeness of reporting in terms of stated year and place of birth, year of onset, place of residence, and type of leprosy increased from 1947 onwards (Table 4).

The study period was defined to cover 1946–80. In spite of an increasing case

Table 3. New cases of leprosy in Portugal with median of the delay period between onset and registration, by year of onset

Year of onset	Number of patients	Delay (median years)
1947–50	615	1·8
1951–55	647	1·3
1956–60	512	0·8
1961–65	344	1·1
1966–70	239	0·8
1971–75	168	1·2
1976–80	104	1·0
1947–80	2629	1·2
–1947	1194	
1981–83	32	
Unknown	646	
Total	4501	

Table 4. Incompleteness in reporting of data on leprosy patients in Portugal, 1947–80, by year of registration

Year of registration	Lack in registration of			
	Year of birth (%)	Birth place (%)	Year of onset (%)	Type of leprosy (%)
1947–50	14·5	0·3	13·0	5·4
1951–55	12·9	0·3	6·9	2·5
1956–60	11·2	0	7·0	0·4
1961–65	8·2	0·4	6·6	0·6
1966–70	3·1	0	3·7	0·3
1971–75	2·8	0	12·7	1·4
1976–80	3·6	1·5	11·9	1·5
Average	8·04	0·3	8·8	1·7

ascertainment during the first years after 1947, these years were included. To confine the epidemiological analyses only to the later decades, e.g. after 1950–55, would imply the loss of a considerable amount of important information. Furthermore, most analyses are based on year of onset rather than year of registration which to some extent adjust for the increased activities in case finding after 1947. Still, some patients taken ill in 1946 might have died before the scheme of notification was introduced in 1947. However, even the 5-year case fatality rate in untreated leprosy in Norway in the last century was no more than 5%[1] which probably is an overestimate in the present situation. Accordingly, the inclusion of the year 1946 was considered justified.

The analyses were restricted to continental Portugal with a population in 1960 of approximately 8,890,000 inhabitants, increasing from 7,920,000 in 1940 to 9,290,000 in 1981. The municipality (concelho) was the smallest geographical unit for reporting the residence of the patients, aggregating into 18 districts (distrito).

When not otherwise specified, incidence rate in the present study refers to year of onset rather than year of registration. In each case the year was recorded when the first symptom was observed by the patient. Insidious onset and social stigma are factors which might influence the patient's recall, tending to postpone the time of onset. Still, year of onset is preferred as the basis for the present analyses relating more to epidemiologic aspects than the purely administrative implications of year of registration. Incidence rate is defined as annual number of new patients, according to year of onset, per 100,000 population.

Average incidence rate is an attack rate referring to the complete observation period and is defined as total number of patients whose year of onset was within the observation period, multiplied by 100,000 and divided by the number of inhabitants in the middle of the observation period, i.e. in 1960 and by the length of the observation period, i.e. 35 years.

Sex ratio was calculated as the ratio between male and female incidence rates multiplied by 100.

Type index was calculated as the lepromatous (LL and LB) fraction of all patients. Clinical form was recorded as lepromatous, borderline, tuberculoid, indeterminate (or

previous clinically equivalent diagnostic groups) or unknown and refers to the form reported at registration.

Possible statistical associations between incidence rates and a set of independent, environmental variables were tested in simple and stepwise linear regression analyses.[12]

Results

Of 4501 patients registered, 1659 were considered to have had their onset prior to 1946 and 34 after 1980. Furthermore, place of residence at onset was unknown in 6 cases. Thus 2802 cases occurring during the observation period remained for analysis.

GEOGRAPHICAL DISTRIBUTION

The overall average incidence rate amounted to 0·86 per 100,000 per year, varying, however, considerably from district to district (Figure 1, Table 5). Apart from Faro (2·06)

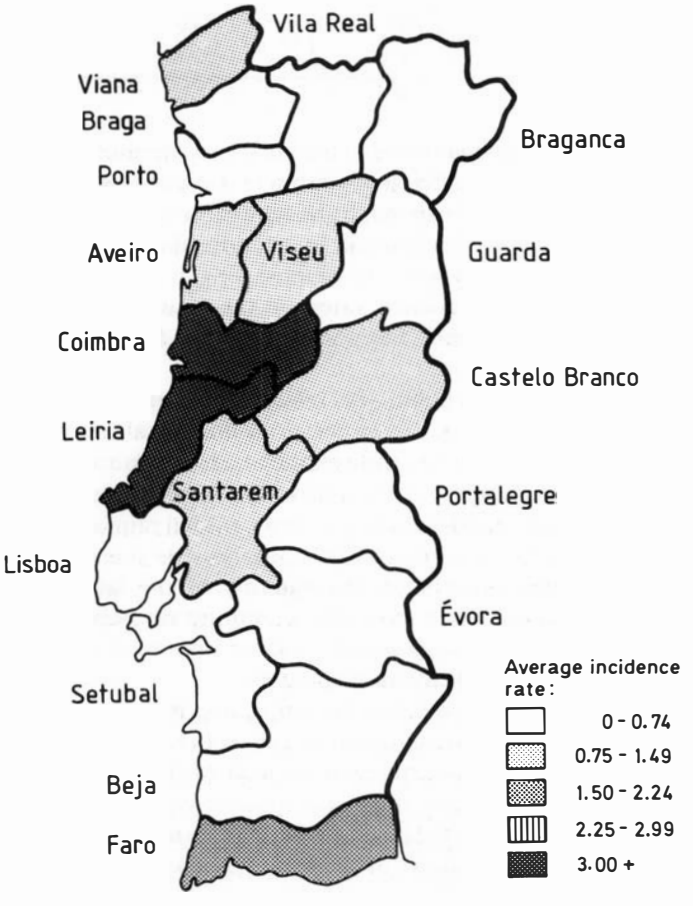

Figure 1. Average incidence rates of leprosy in Portugal, 1946–80 by district.

Table 5. Incidence rates of leprosy in continental Portugal by year of onset and district of residence at onset

District of residence	Year of onset							
	1941–45	1946–50	1951–55	1956–60	1961–65	1966–70	1971–75	1976–80
Aveiro	1·62	2·98	1·66	1·40	1·06	0·59	0·46	0·20
Beja	0·07	0·14	0·28	—	0·54	0·45	0·70	—
Braga	0·84	1·54	0·93	0·86	0·37	0·49	0·22	0·15
Braganca	0·09	0·09	0·26	0·17	0·55	0·10	—	—
Castelo-Branco	1·29	2·32	2·11	1·45	0·73	0·44	0·24	0·17
Coimbra	3·18	6·71	6·19	4·01	2·77	2·54	1·56	0·61
Evora	0·19	—	0·18	—	0·10	—	—	—
Faro	2·18	3·99	3·21	2·33	2·11	1·14	0·85	0·84
Guarda	0·27	0·52	0·27	0·07	0·07	0·35	0·19	0·19
Leiria	4·80	7·05	6·44	5·32	2·61	0·99	0·67	0·29
Lisboa	0·23	0·46	0·38	0·34	0·32	0·12	0·16	0·15
Portalegre	0·42	0·20	0·61	0·21	0·34	0·38	0·28	0·28
Porto	0·53	0·88	0·61	0·55	0·33	0·36	0·19	0·11
Santarem	1·48	2·22	1·65	1·21	0·79	0·50	0·37	0·23
Setubal	0·89	1·99	1·24	0·66	0·50	0·40	0·16	0·07
Viana do Castelo	1·74	2·11	2·52	2·45	1·33	0·93	0·40	0·16
Vila Real	1·01	0·64	0·93	1·18	1·03	0·57	0·38	0·30
Viseu	1·31	1·93	1·87	1·77	1·12	0·79	0·44	0·24

in the South, the disease was concentrated in the middle of the country and particularly in the two districts along the Atlantic Coast, Coimbra (3·45) and Leiria (3·24), rendering the impression that *proximity to the ocean* might be related to high incidence rates; however this association seemed to be relatively weak. In the municipalities bordering the Atlantic Ocean, the average incidence rate was 1·06 against 0·84 in the inland ones. In a simple linear regression of average incidence rates in the municipalities on whether the municipality was coastal or inland, the association was found to be not significant ($p > 0{\cdot}05$).

The geographical distribution might also relate to climatic variables. No association was found with mean air temperature.[3] However in municipalities with a mean annual rainfall[3] of 800 mm or more (Figure 2), the average incidence rate was 1·26 against 0·50 in the other municipalities implying a relative risk of 2·5. In a simple regression analysis of average incidence rates in the municipalities on mean annual rainfall, a strong association was found ($p = 0{\cdot}001$). In a stepwise regression analysis of average incidence rates on mean annual rainfall and coast/inland, the entering of the latter variable increased multiple R significantly ($p = 0{\cdot}0003$), implying an interaction between the two independent variables, i.e. among municipalities with the same amount of annual rainfall, highest incidence rates were found in coastal municipalities.

The organization of the municipalities encompassing in most cases urban as well as rural areas, precluded direct differentiation into urban and rural specific incidence rates. However, considering the main municipality in each district as more urban than the rest of the municipalities, average incidence rates of respectively 0·50 and 1·07 were observed, implying higher rates in rural dwellings. Even more pure urban areas were obtained by studying the rate in main municipalities of 100,000 inhabitants or more as recorded in the 1960 census. In these larger municipalities which all represent cities, an average incidence rate of 0·29 was observed.

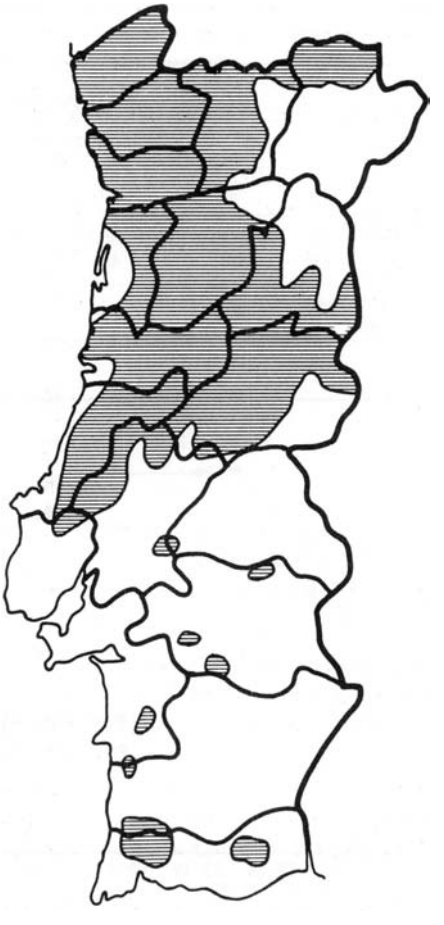

Figure 2. Areas in Portugal with a mean annual rainfall of 800 mm or more.

During the observation period population growth varied considerably from area to area. However, in a simple linear regression analysis of average incidence rate on relative population growth (increase 1930–60/population 1930), no association was found ($p > 0{\cdot}05$).

DISTRIBUTION BY SEX, AGE AND TYPE

Leprosy occurred more frequently in males than in females, the male proportion of all patients was 54·6% (Table 6). Median age at onset was 34·4 years in males and 35·1 years in females. However, the distribution of cases by age at onset differed considerably; highest age specific incidence rate in males was observed at the age of 25–29 years while the highest rates in females was observed at the age of 50–59 years (Figure 3). Lepromatous leprosy represented the most common type of the disease with a type index of 61·2%; 63·1% in males and 58·9% in females (Table 7). The age distribution varied

Table 6. Leprosy cases in continental Portugal with year of onset, 1946–80, by sex and average incidence rate in the district of residence at onset

			Average incidence rate in district					
			−0·74		0·75–3·0		3·1+	
Sex	Total no.	%	No.	%	No.	%	No.	%
Male	1529	54·6	467	59·3	568	54·9	494	50·4
Female	1273	45·4	320	40·7	466	45·1	487	49·6
Total	2802	100·0	787	100·0	1034	100·0	981	100·0

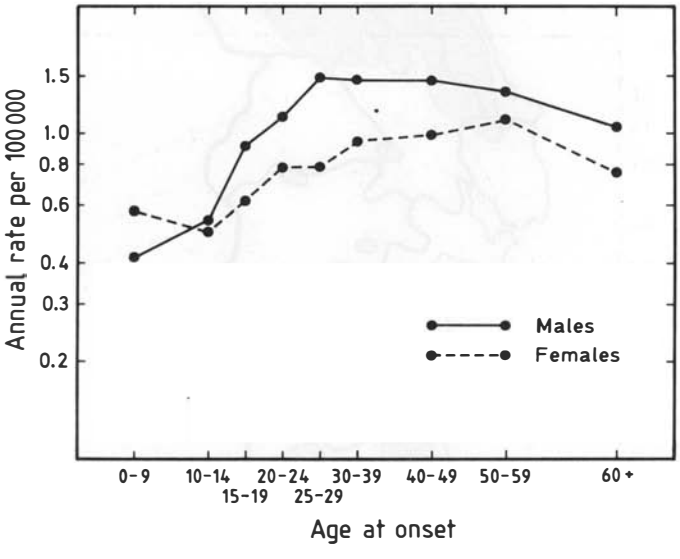

Figure 3. Age and sex-specific incidence rates of leprosy in continental Portugal, 1946–80.

according to the type of disease, with a high age at onset in tuberculoid cases, and particularly among females (Figure 4).

In these patterns geographical differences were observed. A relatively low proportion of male cases was particularly found in the high incidence districts (Leiria and Coimbra) (Table 6). In these districts a high proportion of patients was observed with onset before the age of 20 (19·6%) compared with the low incidence districts (14·3%) (Table 8). Identical trends were found in males and females.

No association was found between the type index and average incidence rate of the district of residence, either in males or females (Table 7).

SECULAR TRENDS

In all parts of the country incidence rates declined continuously and with an increasing relative fall throughout the observation period (Figure 5(a)). The steepest fall was

Table 7. Proportion of all leprosy cases with lepromatous leprosy by sex and average incidence rate in the district of residence of onset. Based on all cases in continental Portugal with year of onset 1946–80

		Average incidence rate in district		
Sex	Total (%)	−0·74 (%)	0·75–3·0 (%)	3·1+ (%)
Male	63·1	62·5	64·1	62·6
Female	58·9	57·5	62·7	56·3
Average	60·0	60·0	63·4	59·4

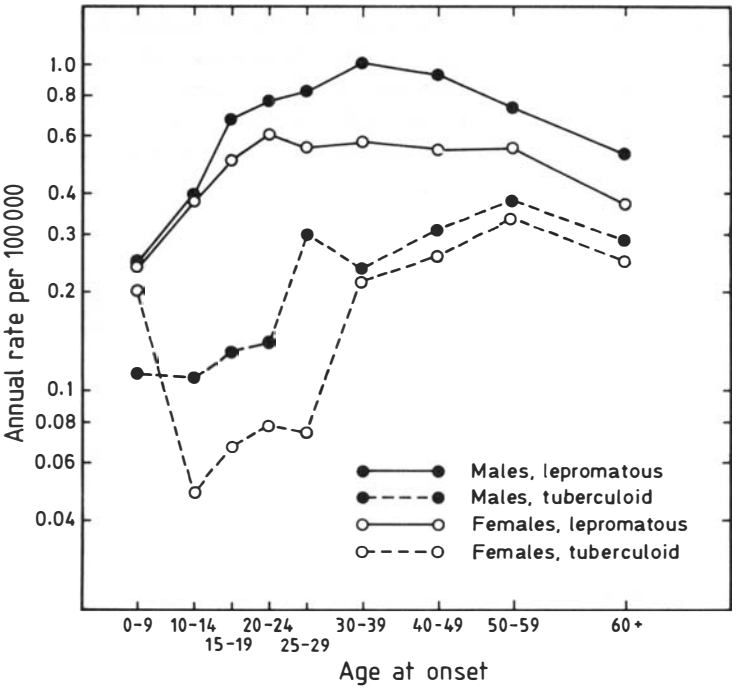

Figure 4. Average age, sex and type specific incidence rates of leprosy in continental Portugal, 1946–80.

observed in the districts with the highest rates, namely Coimbra and Leiria (Figure 1, Table 5). In these two districts the decline from 1946–50 to 1951–55 was relatively small suggesting a more stable level of approximately 8–10 per 100,000 per year prior to 1945.

The pattern in the distribution of new cases by age at onset changed considerably during the observation period implying an increasing age at onset (Figure 6). Thus the median age at onset changed from 30·0 years in 1946–50 to 43·5 in 1976–80, and the risk ratio based on age-specific incidence rates of 60+ to 0–9 years of age increased continuously from 1·0 in 1946–50 to 39·0 in 1976–80.

Table 8. Proportion of all leprosy cases with age at onset less than 20 years by sex and average incidence rate in the district of residence of onset. Based on all cases in continental Portugal with year of onset 1946–80

		Average incidence rate in district		
Sex	Average (%)	−0·74 (%)	0·75–3·0 (%)	3·1+ (%)
Male	17·8	14·3	18·9	19·7
Female	18·1	14·4	19·2	19·6
Average	18·95	14·3	19·0	19·6

On the other hand in the analysis of birth cohorts this pattern was not found. If any trend at all, the results seemed to suggest rather the contrary: onset in consecutive birth cohorts tended to shift over to younger age groups (Figure 7).

Concomittantly, sex ratio increased from 1·2 in 1946–50 to 1·7 in 1976–80 (Figure 8). In lepromatous leprosy the sex ratio increased from 1·2 to 1·8 and in tuberculoid from 1·1 to 1·4.

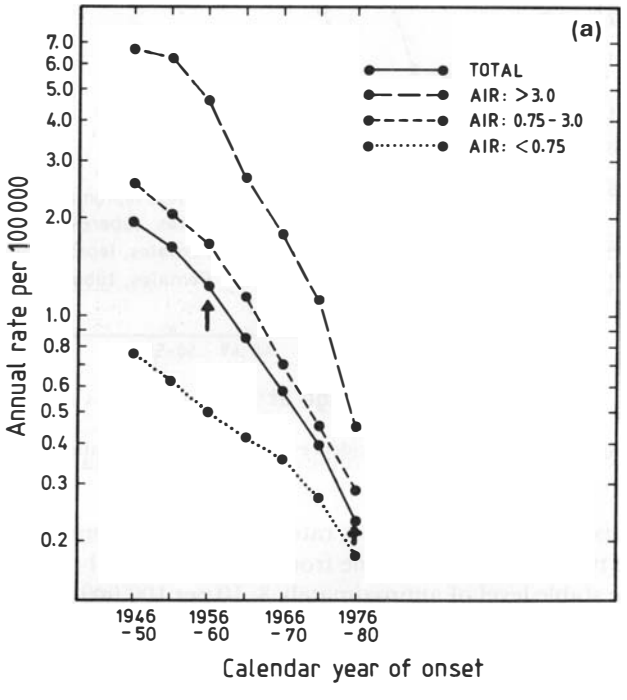

Figure 5. (a) Incidence rates of leprosy in continental Portugal, 1946–80, in districts grouped according to average incidence rates. Crude rates by year of onset.

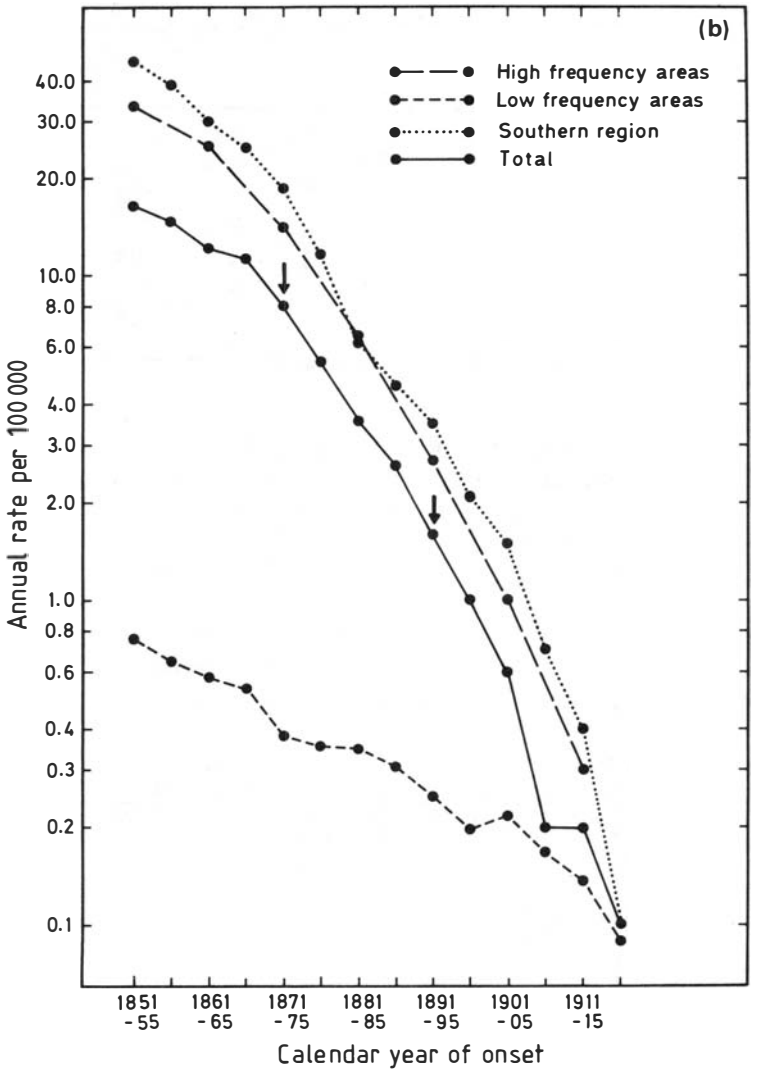

Figure 5. (b) Incidence rates of leprosy in Norway, 1851–1920 in various areas. Crude rates by year of onset[1].

Type index decreased from 68·0% in males and 64·6% in females in 1946–50 to 43·1% and 34·7% respectively in 1976–80 (Figure 9).

Discussion

Problems of case ascertainment will relate to any collection of data used as a basis for epidemiological analyses, and particularly to data on a disease so closely associated with social stigma as leprosy. On the other hand, in a chronic disease for which a complete cure is obtainable, necessitating long periods of individual follow-up, medical records are essential. These conditions have formed the basis for epidemiological research in some countries.[1,4–11] In Portugal a special administration was established devoted to leprosy

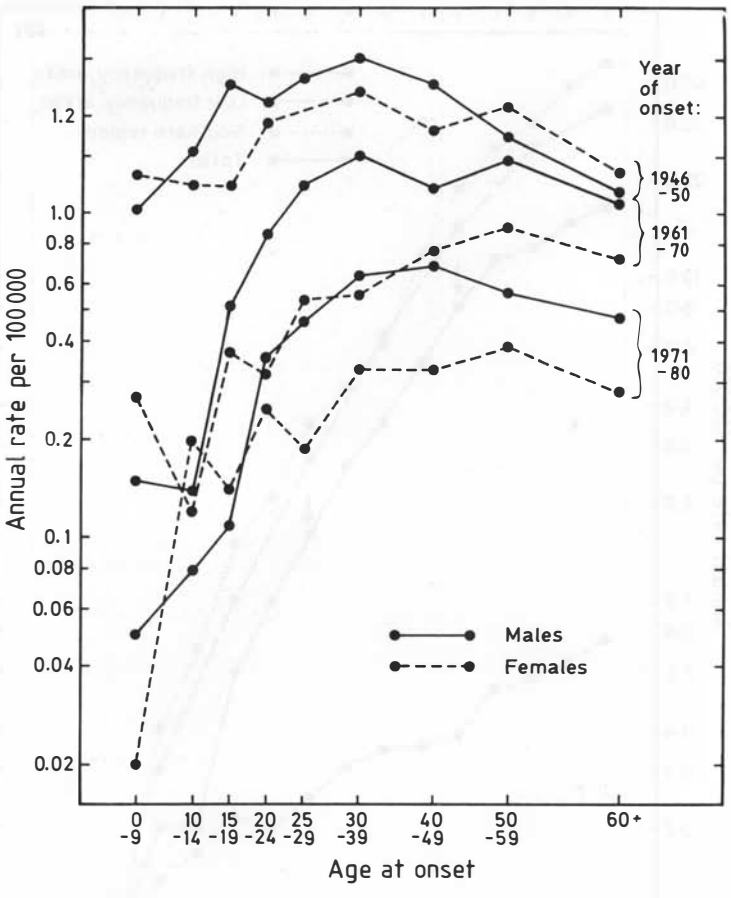

Figure 6. Incidence rates of leprosy in continental Portugal, 1946–80. Age- and sex-specific rates by year of onset.

control,[2] and solely due to its organization there is no reason to believe that the data at hand are less reliable than those obtained in the other schemes. Furthermore, compared with the Norwegian Leprosy Registry,[1] the delay in registration between onset and notification was somewhat shorter in Portugal (0·8–1·8 years against 1·2–2·0 years in Norway (Table 3), while the data were slightly less complete (Table 4).

As in most other areas under epidemiological surveillance, the occurrence of the disease in Portugal varied considerably from district to district. First of all, leprosy was far more common in rural than urban areas, which apparently represents a general phenomenon in leprosy[1,14–18] and supports the recommendation to search for and identify possible specific environmental factors.[16] No negative association was found with urban development in terms of rapid population growth, so this aspect of urban dwelling apparently plays no role in the protection against leprosy.

Next, the association with rainfall observed in Norway[1] was also found in Portugal, interacting with proximity to the sea, and implying a high incidence in coastal municipalities with a high annual rainfall. Since leprosy elsewhere is found also in a very

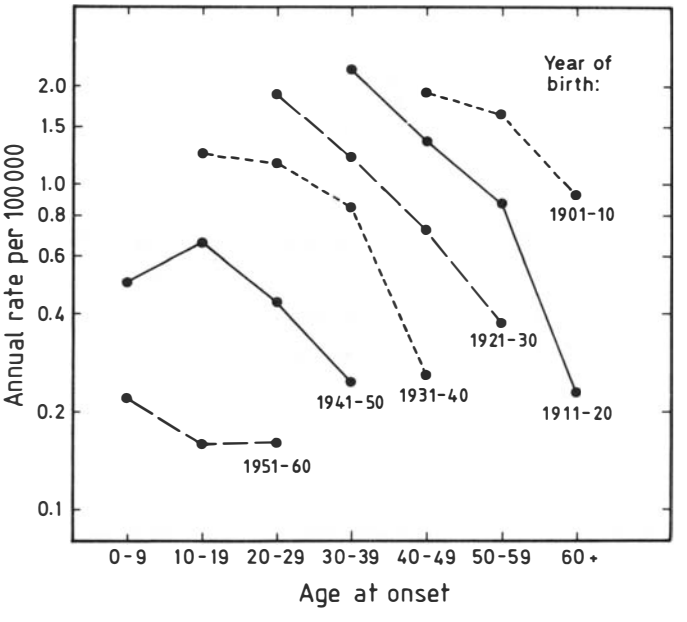

Figure 7. Incidence rates of leprosy in continental Portugal, 1946–80. Age-specific rates by year of birth.

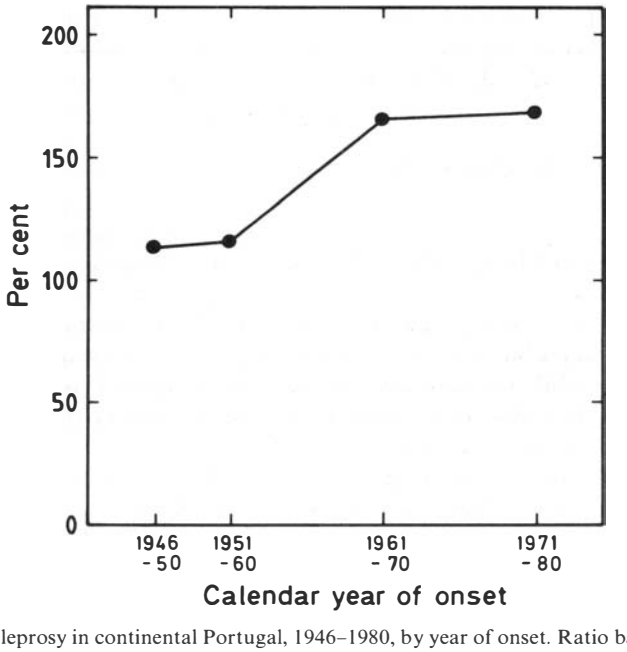

Figure 8. Sex ratio of leprosy in continental Portugal, 1946–1980, by year of onset. Ratio based on sex-specific incidence rates.

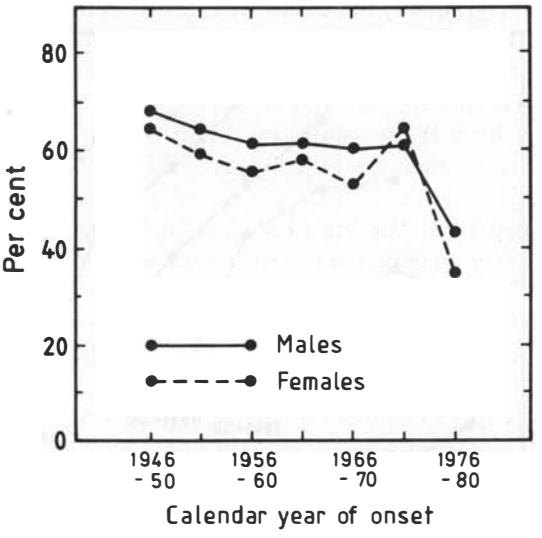

Figure 9. Type index of leprosy in continental Portugal, 1946–80, by sex and year of onset.

dry environment, high air humidity does certainly not represent a necessary aetiological factor. However possible sources of environmental *Mycobacterium leprae*[17,19,20] may be influenced by climatic variables, of which air humidity seems relevant also from an ecological point of view. The issue will not be further discussed here but needs clarification in future studies.

As in most other areas under epidemiological surveillance, leprosy was more frequent in males than in females. Peak incidence rates in males were observed at 25–29 years of age against 50–59 years in females (Figure 3). If females are mainly infected within the household, i.e. early in life, the opposite would have been anticipated which has also been observed in other studies.[13] Whether the finding in Portugal is caused by a longer period of diagnostic delay in females will not be further pursued. Moreover, age at onset was higher in tuberculoid than in lepromatous leprosy, particularly in women (Figure 4). A longer incubation period in lepromatous leprosy would suggest the opposite finding. However, a delay in casefinding in less conspicuous (i.e. tuberculoid) females might explain this result as well.

As in Norway the Portuguese data covered a period of continuous decline. No sources are available to assess whether the decline started from a plateau in the 1930–40s or whether the rates were far higher at the beginning of the century. Still, the decline observed was considerable, representing a ratio of risks from 1946 to 1980 of 8·2. The annual relative decline,[13] calculated as

$$\sqrt[n]{i_o/i_n}$$

where n denotes number of years (here, 35) and i_o and i_n the incidence rates of the first and the last 5-year periods (here, 1·96 and 0·24 per 100,000 per year respectively), was 1·06 which is close to the declines observed in Norway and recently in Venezuela.[13] Also, for this reason, the data seem comparable with those of studies already published on declining incidence rates.[1,4–11]

In many ways the decline bore a striking resemblance to the development observed in

Norway. Not only did a gradually increasing decline occur, but the slope of the incidence curve in Norway, 1871–95 (Figure 5(b)) was identical with the one in Portugal, observed in 1956–80 (Figure 5(a)). Admittedly some factors (which might or might not be identical), have caused the decline both in Norway and Portugal, but certainly the question arises—why have these factors produced the same slope of decline in two countries so far from each other, not only in space and time, but also in terms of leprosy control strategy?

Most likely the slope is not determined by these factors. Rather the pattern of decline probably represents a general phenomenon in leprosy which occurs after the spread of the infection has ceased. Thus the incidence curve may, to a large extent, be interpreted as reflecting the right part of the distribution curve of the incubation period in leprosy. The slope of the incidence curve reflects the diminishing number of cases observed towards the right tail of the distribution curve, and is apparently not determined by the factors causing the interruption of the spread of the infection. Furthermore, the form of the incidence curve on a logarithmic scale is consistent with the principle suggested by Sartwell that the frequency curve of incubation time takes the form of a logarithmic normal curve.[21]

This interpretation sheds light on a phenomenon observed in Norway.[1] During a period of high incidence (i.e. still spread of the infection), isolation of infectious cases was strongly associated with the subsequent decline of the incidence rate, while towards the end of the epidemic (i.e. the part of the incidence curve determined by the incubation period), this association gradually vanished; leprosy disappeared regardless of the degree of isolation.

Towards the end of the epidemic in Portugal the age specific incidence rates showed, to an increasing extent, that new cases represented patients of higher age (Figure 6). This trend might be caused by two mechanisms.[22] Either a postponement of infection to a higher age has led to a higher age at onset. Alternatively it might be caused by the possibility already mentioned that the late patients had longer incubation periods. Infected when incidence rates were higher they would tend to be more frequent than the younger patients with the same period of onset, the latter infected when incidence rates were lower and thus less frequent. A cohort analysis (Figure 7) did not show an increasing age at onset in consecutive birth cohorts, and thus ruled out the possibility of a postponement of infection to higher age groups. This finding also supports the notion that the slopes of the incidence curves are influenced by cases with increasingly long incubation periods. Similar trends are observed in some countries in which data for such analyses are available.[1,4,9,13,22]

However, this does not rule out a mechanism of a postponement of infection in other situations. The mechanism is most likely the cause of the relatively low proportion of young patients notified in low incidence areas (Table 7), where infection in the community at large is supposed to play a relatively more important role (vide infra).

Sex ratio was always above 100 and increased during the observation period, and more so in lepromatous than in tuberculoid leprosy. Similar trends have been observed also in other countries.[21] Apart from a registration bias, women leading more secluded or protected lives within the household (i.e. 'protected' against notification), the higher rates in males may reflect that males, in addition to the risk of household infection, which is equal in the two genders, also bear a risk of being infected in the community at large. Risk of infection in the community is higher in the gender that has the most extensive extra household contacts, i.e. usually males.

The secular trend of an increasing sex ratio is consistent with the fact that during declining incidence rates, the risk of getting infected in the household declines due to a declining number of leprosy infected households. The risk of infection in the community, on the other hand, remains as long as infectious patients exist within the area. Thus the relative importance of infection in the community increases, which is consistent with the increasing sex ratio observed. Alternatively a shorter incubation period in females could effect the same pattern. However, a high sex ratio observed in low incidence areas (Table 6) supports the former interpretation.

The interpretation of the data on type index may involve far more uncertainty. Thus it may be speculated that a more pronounced secular increase of sex ratio in lepromatous than in tuberculoid leprosy may be related to the assumption that only persons with a high susceptibility are infected (and subsequently taken ill) in the community at large (namely, males), and these persons develop lepromatous leprosy due to their low resistance. This may also explain why type index in general is higher in males than in females. On the other hand the secular decline of type index observed in both genders in Portugal (Figure 9) is not consistent with an increasing proportion of cases with long incubation periods, provided lepromatous cases have the longest incubation periods, nor with an increasing relative importance of infection in the community at large. In China,[4] Japan[6,7] and Venezuela[10] an increasing type index has been observed towards the end of the epidemic, while in India[5] the opposite trend has been observed (i.e. the same as in Portugal). These conflicting observations may be due to two different lines of event: on one hand, an increasing resistance in the population against leprosy produces both a fall in incidence and a lower proportion of lepromatous cases, while, on the other hand, longer incubation periods and greater importance of infection in the community at large (compared to infection in the household) tend to give a higher proportion of lepromatous cases. Thus, in Norway, an increasing type index was observed in males against a decreasing type index in females.[1]

Also other difficulties arise in the interpretation of the data. Thus, the age distribution of new cases indicates a higher age at onset in females than in males (Figure 3), which is inconsistent with the hypothesis of females leading more secluded lives and thus not being infected in the community at large; however, this pattern changed by time (Figure 6). Later, a shift towards higher age groups was particularly observed in males consistent with an increasing importance of infection in the community at large.

On the other hand the age distribution of cases suggests a higher age at onset in tuberculoid than in lepromatous leprosy (Figure 4), inconsistent with a longer incubation period in lepromatous leprosy. In the several epidemiological schemes now under way the clarification of such issues represents important aims necessary to obtain a more comprehensive understanding of the epidemiology of leprosy.

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The sociocultural dimension in leprosy vaccine trials

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Summary This paper briefly describes organizational, operational, and sociocultural aspects of the phase-III clinical trials of the ICRC anti-leprosy vaccine in Maharashtra, India. Our experience is that vaccine trials can be launched quickly and more cost effectively by using the services of health personnel from the existing public health infrastructure. That is why the trials could be launched in just 4 months after receiving the financial grant from the Indian Council of Medical Research, New Delhi (India). At the community level, a person-to-person approach in Health Education scores over audio-visual aids and the mass media. The compliance in target groups is increased when preventive programmes are backed-up by curative services and when their privacy and daily routine are not disturbed.

Introduction

More than 100 years after the discovery of the causative organisms, *Mycobacterium leprae*, leprosy continues to be a major public health problem in many developing countries. Although a number of effective drugs are now available, non-compliance in drug therapy and the emergence of drug resistant *M. leprae* are two major stumbling blocks on the road to control of the disease. Global attempts are being made to evolve a strategy for immunoprophylaxis of leprosy through the development of a vaccine.

In 1979, a 'candidate' anti-leprosy vaccine was prepared at the Cancer Research Institute, Bombay (India), using gamma-radiation killed ICRC bacilli.[1] The organism, a slow growing mycobacterium, probably belonging to *M. avium intracellulare* complex, exhibits antigenic cross reactivity with *M. leprae*. This is the scientific basis for their use in the vaccine preparation.

The vaccine induces lepromin conversion in about 55% of multibacillary (MB) leprosy patients, and in 95% of the lepromin negative individuals. The conversion in some patients is associated with tissue bacillary clearance and even reversal reaction.[1,2] The immune conversion is stable for about 5 years.[3] The data indicate that the vaccine could be used both for immunotherapy, as an adjunct to drugs, and immunoprophylaxis. The

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vaccine was cleared for large scale phase-III trials by the Drug Controller of India in 1984. Till then it had been tried only on multibacillary (MB) leprosy patients and on healthy lepromin negative individuals in urban settings where medical facilities were readily available. In this trial the vaccine would be administered to healthy volunteers, irrespective of their lepromin status, in far flung villages where health facilities are not fully developed. This could be a major operational constraint. Therefore, a pilot study (extended phase-II incorporating feasibility of this large scale phase-III trials) was carried out in Palghar and Satpati near Bombay (Figure 1) under field conditions.[4] It was obvious that if the volunteers were asked to report to the village clinic, the compliance would be low. The pilot study revealed the pattern of life in the rural areas and the best time for vaccination. As it is given as a single dose, its acceptability is high.

Hypersensitivity to *M. leprae* antigen, to which residents of an endemic area are continuously exposed, has been implied in the pathogenesis of neural lesions in leprosy.[5,6] It was feared that vaccination may lead to nerve damage in lepromin positive individuals. Another purpose of the Satpati studies was therefore to investigate adverse effects, if any, of the vaccine, especially in lepromin positive contacts. But no untoward effects have been observed in any group during the last 5 years.[4] Further, it was observed that the ICRC vaccine does not stimulate formation of *M. leprae* specific antibodies,[4] which have been implicated in hypersensitivity reactions and in formation of immune complexes that might suppress cell mediated immunity,[5,6] the dominant host defence against *M. leprae*.

This paper describes the available options, study design, operational and sociocultural aspects of this trial and how various problems were overcome.

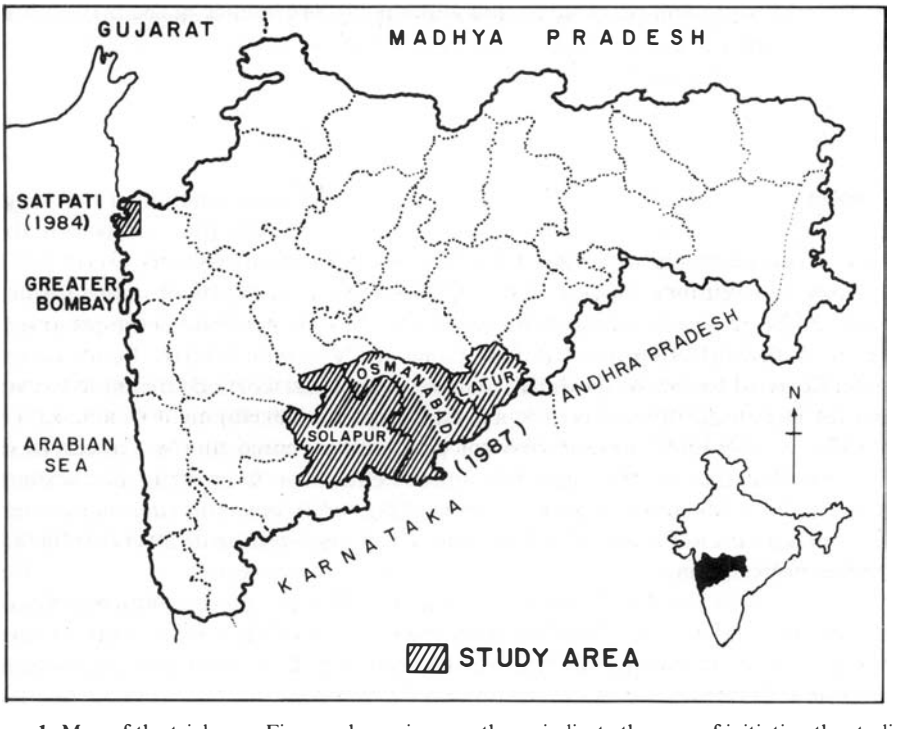

Figure 1. Map of the trial area. Figures shown in parentheses indicate the year of initiating the studies.

Table 1. Profile of the trial area

Features	Solapur	Osmanabad	Latur
1. *Estimated mid-year (1987) population (1×10^6)	2·19 million	1·18 million	1·38 million
2. Area (km^2)	15,017	7369·5	7264·9
3. Population density (per km^2) (1981)	174	136	177
4. Proportion of rural population (1981)	70·79%	84·61%	54·61%
5. Literacy (1981)	40·68%	35·36%	34·62%
6. **Prevalence of leprosy per 1000 population (1987)	5·8*	9·3	10·9
7. **Total number of registered leprosy patients (1987)	12,795	10,968	15,164
Date of launching the vaccination programme	3 Feb. 1987	8 June 1987	12 Oct. 1987

Source: *District Census Handbook* (1981 census) Series-12 compiled by Maharashtra Census Directorate, Bombay (India). Published in 1986.

* Only certain *talukas* of Solapur were taken up for the trials. Prevalence in these areas was 8·5/1000.

** Based on figures provided by Leprosy Eradication Bureau, National Leprosy Eradication Programme (NLEP), Government of Maharashtra.

The trial area

The trials were launched in February 1987 in the Southeastern part of Maharashtra, India. The project area includes 3 districts—Solapur, Osmanabad and Latur—on the south-eastern fringe of Maharashtra state (Figure 1), where the prevalence of leprosy is between 8 and 10 per 1000. The total population in the project area is about 5 million. The geographic and sociodemographic profile and leprosy prevalence in the project area are delineated in Table 1.

Organizational aspects

The Indian Council of Medical Research, New Delhi (India) sanctioned the project in October 1986. A major challenge was that the trials had to be initiated within about 4 months. The Government of Maharashtra gives a high priority to leprosy control. It is a vertical programme that is looked after, at the head office of the Health Directorate, by a very senior officer with the rank of Joint Director. In the rural areas the programme is implemented through Leprosy Control Units (LCUs) which have, besides qualified medical officers, a number of specially trained paramedical workers designated as leprosy technicians (LTs). Each unit covers a population of 200,000 to 400,000. LCUs are responsible for the entire leprosy control programme, consisting of treatment of the patients, identification of new cases, and leprosy education to increase the awareness of the disease. They also generate epidemiological data on leprosy through regular periodic house-to-house surveys. Each LT is responsible for a population of 20,000 to 25,000. He regularly conducts village leprosy clinics, and even makes frequent home visits. He is in constant touch with the community, with whom, over the years, he has established an excellent rapport. Two options were available to us namely (a) to create a separate independent infrastructure exclusively for the trial, and (b) to work in close cooperation with the State Government's leprosy control programme.

The creation of a separate infrastructure for the vaccine trials had the advantage of

having the entire staff under one command, but this was outweighed by the numerous disadvantages: (i) a preparatory phase of a few years would be required for training the staff and for carrying out a fresh survey to gather baseline information; (ii) it would take many years to establish a proper rapport with the community, without which no programme would have any chance of success; and (iii) the study would have been expensive.

We therefore preferred the second option and worked in collaboration with the existing health infrastructure of the State Government in the trial area. Though this approach posed an apparent problem of dual administrative control, it was due to this very approach that the large scale trial could be launched within a few months of receiving the financial grant. The collaboration also provided access to readily available epidemiological data on leprosy.

Study design

OBJECTIVES

The objective of the trial is to find the relative efficacy of ICRC vaccine over BCG, in terms of lowering the incidence of leprosy in healthy household contacts (HHC) of leprosy patients. The trial is double blind, randomized and controlled. Leprosy is diagnosed and classified as per Indian Consensus classification[7] with a modification that borderline leprosy has been further divided into borderline tuberculoid and borderline lepromatous. Accordingly, in this trial, leprosy is classified into 6 types namely indeterminate, tuberculoid, borderline tuberculoid, borderline lepromatous, lepromatous and pure neuritic.

The choice was between (i) a study of absolute efficacy of the ICRC vaccine in which the vaccine or a placebo would be administered to eligible volunteers; and (ii) a study to determine the comparative efficacy of ICRC vaccine versus an existing mycobacterial vaccine (BCG) in reducing the incidence of leprosy.

The first option would be, scientifically, the best approach and fewer numbers of volunteers would have to be vaccinated, since the placebo offers zero protection. However, ethically speaking, no eligible volunteer should be deprived of the beneficial effects, if any, of a vaccine. Moreover, the trial would not be strictly double blind unless the 'control' causes an identical local response.

The second option would not provide information on the absolute efficacy of the vaccine but had the advantage that the trial would be strictly double blind because the local response induced by both vaccines would be identical. BCG vaccination is a national programme. BCG itself has given varying protection against leprosy in different trials.[8,9] A candidate leprosy vaccine should give substantially higher protection than BCG if it has to be adopted as a national modality for leprosy immunoprophylaxis, that is why we chose the second option and used BCG as the control arm of the trial.

The capacity of a vaccine to lower the incidence of a disease is the acid test of its efficacy. Therefore in the trial this was the only parameter used. No attempt was made to measure the immunological parameter(s). The idea of subjecting the HHC to laboratory immunological procedures, even in a subset of vaccinees, was rejected, since it would have created an impression of preferential treatment to certain groups in the population. Also in general, any invasive investigation would result in non-compliance.

THE TARGET POPULATION

As mentioned below, under field conditions there is often overdiagnosis. Therefore, to be certain only HHC of patients exhibiting active lesions at the time of intake in the trial were vaccinated. A household is defined as a group of persons who live together and have their main meals prepared in the same kitchen. The HHC constitute a high risk group.[10] They are aware about the disease and are already motivated to accept possible prophylactic measures against leprosy. Since the HHC include both lepromin positive and negative individuals, this group will be a sub-set of the general population. Therefore the results of this trial could be generalized to the entire population. But this approach has the disadvantage that a large population would have to be covered over a vast geographical area to get the required number of eligible HHC.

Multidrug therapy (MDT) was introduced in late 1987 in 7 hyperendemic districts of Maharashtra State including the 3 districts selected for the vaccine trial. In this WHO-sponsored study, MDT is given only to leprosy patients diagnosed as 'active' by specially trained doctors. The initiation of MDT in the trial area introduced another variable because MDT, for even a short period, is known to 'cure' leprosy or clear up early lesions of leprosy. Therefore, after July 1988, vaccine has been given to eligible HHC of all those leprosy patients who are on WHO-sponsored MDT. However, a separate record is kept of those patients on MDT who are clinically active and inactive, at the time of vaccination.

Among the HHC, one of the possible approaches would be to vaccinate only the HHC of MB leprosy patients, since it is recognized that they run the highest risk of contracting the disease. The relative risk being 7 times that observed in a non-contact.[10] This approach has been rejected because: (a) the number of MB patients is declining fast because of early detection and treatment, and (b) lepromatous rate in dark skinned populations is low. Consequently, an enormously large population would have to be covered over a wide area to get the requisite number of HHC. This would pose problems of logistics and communication. Moreover, it is accepted that non-lepromatous patients can not only transmit leprosy, but the relative risk is higher than the non-contacts.

STATISTICAL ASPECTS

According to the State Health Authorities for Leprosy Control, the average annual incidence of all forms of leprosy in the HHC is 4–5 per 1000 per year. Through a quick sample survey, it is observed that there is often over-diagnosis to the extent of 20–30%. Therefore, the overall incidence is assumed to be 3·5 per 1000 per year for estimating the size of the trial population. BCG coverage in the trial area, as judged by the presence of a BCG scar, is about 30%. As mentioned earlier, BCG has given varying protection against leprosy in various trials. A protection of 25–30% was observed in the BCG trial at Madras (India).[9] This is also considered to be the likely protection offered by BCG in the trial area. Presuming a vaccine efficacy of 33·3% over that of BCG for a 5% level of significance (one-tailed test), power of significance 90% and 30% losses during follow-up, the sample size for the two-arm trial with a 5-year follow-up would be about 31,000 (Table 2). A vaccine with an efficacy of lower than 33·3% would only be of academic interest. This means that with an average of 4 contacts per household (the national average), the household contacts of 8000 to 10,000 leprosy patients would have to be vaccinated. The

Table 2. Sample size for the trial (with 30% BCG coverage)

[a] 1-tail = 0·05.
1-β = 0·90.

Follow-up period	Mean incidence	Assumed vaccine efficacy of 33·3% over BCG	Assumed vaccine efficacy of 50% over BCG
2 years	8·75	66,262	25,636
5 years	17·5	30,908	12,736

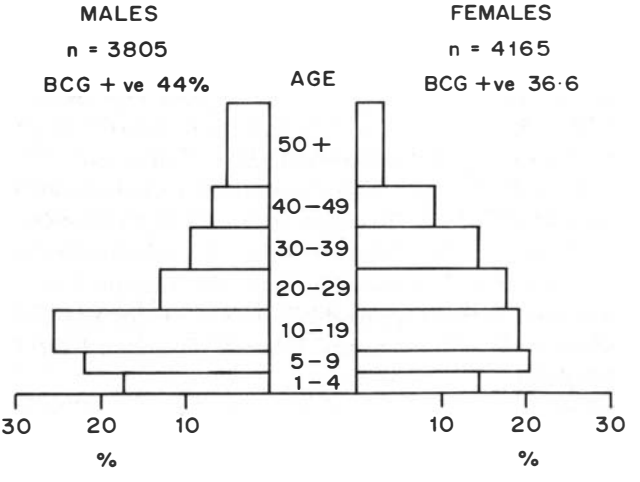

Figure 2. Age distribution of healthy household contacts.

age distribution of the target population based on the analysis of 7960 vaccinees is shown in Figure 2.

RANDOMIZATION

All human trials would have limitations for operational and ethical reasons, and are thus unlikely to be perfect. Design of the trial always takes into account variables and constraints likely to influence the outcome of the trials. However, some unforeseen variables may crop up during the course of the trial. It is essential that all the variables, known and unforeseen, should equally affect both study and control groups. This can be assured only by proper randomization which was achieved using the following procedure.

The vials containing ICRC and BCG vaccines are randomly assigned and so are their positions (left or right) in the satchel. In the field the eligible volunteers among the HHC are registered as they come (randomly). During vaccination, the first eligible HHC in the household receives the vaccine from the left side of the satchel. The second HHC receives vaccine from the right side of the satchel. Other contacts receive the vaccine alternatively from the left or right side of the satchel. When the vaccine in one of the 2 vials is finished,

the pair is discarded even if the other vial contained vaccine. A new pair is used and vaccination starts with the vial in the left side of the satchel.

The 'blindness' of the trial is ensured as follows: (i) identical coded vials are used for the ICRC and BCG vaccines; (ii) both the vaccines are randomly paired; (iii) a separate double blind preliminary study was done to ensure that both vaccines induce identical local response; and (iv) information on the type of vaccine used (codes) will not be available to the field units. The codes are kept at the central headquarters of the project at Bombay.

Biological products

Vaccines used in the trial are: (i) ICRC vaccine ($0{\cdot}5 \times 10^9$ gamma-radiation killed organisms per dose); (ii) BCG vaccine obtained from BCG Laboratories, Madras (India). Standard dose consists of 0·1 mg moist weight of BCG = $2\text{–}4 \times 10^5$ colony forming units of Danish strain 1331. An entire batch (No. 838) has been kept aside for the trial. Both vaccines are administered intradermally in the right deltoid region and produce a comparable local reaction consisting of delayed inflammation and ulceration that heals in 4–6 weeks. It is not advisable to inject the full dose of BCG in the already sensitized Indian population, since it could produce untoward reactions. BCG therefore is given as 1/5 of the standard dose. This dose was selected on the basis of preliminary studies. At this level the local reaction is similar to that induced by the ICRC vaccine. The vaccines are carried to the villages in vaccine carriers (approved by UNICEF for Expanded Programme of Immunization) and are used within 6 hours. Unused vaccines are returned to the Project Office for further disposal.

Operational aspects

A field unit has been established at Solapur city, with office and laboratory space. This city is 428 km from Bombay and is well connected by railways and road. A sub-station was subsequently established at Latur city, about 150 km away from Solapur. Both offices have facilities for maintaining the cold chain for the vaccines. The vaccine is brought from the Cancer Research Institute, Bombay in dry ice and is immediately transferred to a deep freezer in the project office at Solapur. It is stored in similar condition in the sub-station at Latur. BCG vaccine is reconstituted on the day of use.

Before starting the vaccination in a new administrative unit ('taluka'—equivalent to a county) all aspects of the vaccine project, including the design of the trial, are discussed with local health authorities at various levels. Special meetings are held with LCU staff. A small public function in which local leaders, media-men and members of the community, including students, participate, is held to create awareness in the population. Similar meetings are held at the village level. At the meetings all aspects of the trials are discussed including possible side-effects of the vaccine. Households are told that their participation is entirely voluntary; no incentives are offered and no coaxing is done. They are assured that any problem would be promptly attended to.

Each vaccine team consists of a doctor, trained male and female paramedical personnel from the project staff and one LT and a medico-social worker. On the day of

vaccination, the vaccine team reaches the village before 7.00 am by which time most village folk are awake. The sunrise in the trial area is approximately 5.45 am and 6.30 am in summer and winter respectively. The doctor meets the village leaders, who send their representative with the vaccine team. On the basis of the list of patients provided by the LCU, the patients are visited on a house-to-house basis. The head of the household is told by the doctor about the vaccines. The simultaneous survey, clinical examination and vaccination are completed before 10 am, by which time the villagers leave for work. On average, about 4–6 families are examined and 20–30 HHC vaccinated by one team every day. There are four teams and they vaccinate about 20 days in a month.

The vaccinees are given a pamphlet which explains clearly, in the local language, the sequence of events following vaccination which is similar to that of the BCG vaccine. Being an ongoing national programme the villagers are well aware of the sequence of events following BCG vaccination. This makes acceptance of the ICRC vaccine easy.

The HHC are thoroughly clinically examined by the doctor for evidence of leprosy. The presence of BCG scar is also recorded. Female HHC are examined with the help of the trained female paramedical worker in the team. HHC with suspicious signs of leprosy are excluded from the trial. Simultaneous to the clinical examination, the vaccines are randomly given in the right deltoid region. Regular BCG vaccination in childhood is given on the left deltoid region in India. The scar due to the vaccines used in this trial would remain a permanent evidence of vaccination on the right deltoid region. Since no other vaccine is given in this part of the body, there would be no problem of identifying volunteers during the follow-up phase.

Only HHC of both sexes, between 1 and 65 years of age participate in the study. Pregnant women and persons with chronic debilitating diseases, severe malnutrition, history of allergic reactions, epilepsy and tuberculosis are excluded from the trial.

Immediate follow-up

The team visits the vaccinees periodically to remove any apprehension in case of minor side-effects. A follow-up protocol has been so designed that it covers all the major sequence of events in the take-up of the vaccine and the protocol can be completed by any trained paramedical worker. The immediate follow-up visits helped us quickly establish rapport with the vaccinees. In addition to the follow-up visits, a system of feedback through postal intimation has been devised for the benefit of vaccinees who may be absent during the visits. The vaccinees are given the address of the Project Office to which they may write or are advised to contact the Medical Officer of the nearest Primary Health Centre. The address of the Project Office is printed on the above mentioned pamphlet and illiterate vaccinees are requested to seek the help of a literate person to write to the Project Office. A system of feedback from the local health workers was also devised. The health workers are advised to inform postally or in person (whichever was more convenient). The feedback system is so effective that even minor problems (usually secondary infection at the vaccination site) are promptly attended to. If the family is poor, a blank postcard is given so that the vaccinee may again inform about his condition. If the vaccinee prefers to visit the office in person, he/she is immediately given the return bus fare on producing the bus ticket. This system of re-imbursement prevented any financial loss to the vaccinee.

Sociocultural aspects

Successful implementation of field trials requires the compliance of the eligible volunteers, which in turn depends on the tolerance of the community towards the disease. Based on the experience from the pilot study at Palghar and Satpati,[4] it was anticipated that the following factors may result in non-cooperation and non-compliance: (a) fear or stigma about leprosy; (b) ignorance about the disease; (c) lack of motivation; (d) disturbance in daily routine; and (e) fear of injectables and invasive techniques.

But the above-mentioned problems did not crop up since we took sociocultural aspects into consideration in the study design and operational strategy. We recognized that the village leaders are highly respected and that their support is essential for the success of any programme. We make it a policy to explain to them the facts about the vaccine. Assistance from the village leaders also ensures community cooperation. India has a male dominated society and it is usually the father who decides all matters including acceptance of prophylactic measures. For these reasons working through a senior male member of the family is highly effective.

Even in a relatively urbanized district like Solapur, the overall literacy rate is barely 40·68% (Table 1). Therefore we had decided to educate the target groups in the community. Each member of the vaccine team is trained in health education and the doctors accompanying the team are postgraduates in community medicine.

Linguistically, Akkalkot taluka of Solapur district has a large number of Kannada speaking people while Osmanabad and Latur districts are predominantly Marathi speaking. The team members know Marathi (the official state language) and make a special effort to learn a few terms used in daily parlance in colloquial Kannada.

Since it is a common practice to use audio-visual aids for health education, we made a film on the vaccine which was found useful for discussions with healthy personnel. Subsequently, we learnt that at the level of the community a personal approach in communication scored over 'hi-tech' audio-visual aids, so we stopped screening the film at community level. Our experience is that mass media and audio-visual aids are only a supplement, and not a substitute, to a person-to-person approach.

The services of the doctor in the primary health centre are usually clinic-based and principally curative. Doctors seldom visit each house for delivery of preventive services like immunization which is mostly done by paramedical workers. The presence of doctors in our vaccination teams increased the confidence of target groups and improved compliance. Our approach also involved treatment of minor ailments which came to our notice while vaccinating. It has been our experience that, to be more effective, all preventive services should be backed by curative services (at least for minor ailments) by the same team.

Repeated follow-up of vaccinees and feedback from vaccinees by postal intimation and prompt treatment of any problem removed apprehensions and instilled confidence in the target groups. The target groups soon realized that the vaccine is rather innocuous, does not interfere with daily routine and that any problems are promptly attended to. These factors are responsible for the very high compliance of 95%. There are minor variations in compliance in various sociocultural and linguistic groups which are not statistically significant to be mentioned here. Since our teams reached the village early in the morning, about 90% of the permanently resident (enumerated) HHC were covered. The vaccine is well received in neighbouring villages probably because such news spreads by word of mouth.

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The role of intrahousehold contact in the transmission of leprosy

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Summary This study examines the role of intrahousehold contact in the transmission of leprosy using the case control methodology. The study was done in the leprosy control area of the Community Health and Development (CHAD) Programme of the Christian Medical College. Three age, sex and village matched controls were selected for each case. This study shows that persons with intrahousehold contact with leprosy have a higher risk of acquiring leprosy compared with those who did not (RR 2·509; 95% confidence limits 1·23–5·109).

Introduction

Leprosy control programmes world-wide have aimed at interrupting the transmission of leprosy by reducing the reservoir of the infection by treating the leprosy patient. The question that must be answered is the degree of risk involved in close contact with leprosy patients. All previous studies done on this aspect of leprosy have used the cohort model and were of long duration and consequently expensive. This study which has used the case control model is one of the first of its kind in India.

Materials and methods

The study was conducted in a Survey, Education and Treatment (SET) Unit of the National Leprosy Eradication Programme (NLEP) situated at Asanambut, North Arcot District. This Unit is attached to the Department of Community Health, Christian Medical College, Vellore. Asanambut lies 40 kilometres south-east of Vellore Town, ringed by the hills of the Jawadhi Range. The area is rural and its predominant crops are Paddy, Ragi and flowers. The health care is provided by the Primary Health Centre in Madanur. Leprosy has been carried out in this area since 1971 and the prevalence of leprosy is 38·66/1000 population.

Health care is offered to the leprosy patients by a mobile team consisting of a medical

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officer, a non-medical supervisor, the leprosy paramedical worker of the concerned unit, pharmacist, physiotherapist, a smear technician, village leprosy worker, occupational therapist and a shoemaker. The mainstay of the leprosy team is the leprosy paramedical worker (PMW).

Case control methodology was used. Patients detected between July 1983 and December 1984 in the Asanambut SET Unit were chosen as cases for the study. From this list those who had died or permanently left the area by the time the study was done (5 cases) were deleted from the list.

Three controls were chosen for each case from the Survey register of the Asanambut Control Unit. The cases were matched with controls with regard to age, sex and geographical location. After the list of controls were chosen for each case from the Survey register by matching for age, sex and village three controls were chosen by random from the list of controls. The controls were ± 2 years of the year of birth of the case, of the same sex and from the same village.

From each subject the following information was obtained: basic demographic profile, educational status and occupational status. The duration of disease and date of diagnosis was obtained from patient records. A clinical examination was done on all the subjects for the presence, and if positive, the type of leprosy. The entire household in which the subject was residing was examined clinically for leprosy. Since a 100% coverage was essential, multiple visits up to five times was necessary.

Results

Table 1 shows the age and sex distribution of cases. This table shows a male: female ratio of 1:12:1. The two groups were examined to assess the comparability of cases and control. There was no major difference in the educational status of cases and control except in the proportion of these who attended middle school. This difference, however, was statistically significant (Table 2). There was no major difference in the occupational status of cases and controls (Table 3).

Table 4 indicates the frequency of BCG vaccination in cases and controls. The controls had a slightly higher incidence of BCG vaccination which might indicate a protective influence of BCG on the occurrence of leprosy. However, the difference was not statistically significant (Table 4).

The frequency of household contact among cases was significantly higher than in

Table 1. Age and sex distribution of cases

Age group	Male	Female	Total	Percentage
0–10	10	6	16	22·22
11–20	6	7	13	18·05
21–30	5	5	10	13·88
31–40	5	6	11	15·27
41–50	5	5	10	13·88
51–60	3	2	5	6·94
More than 60	4	3	7	9·72
Total	38	34	72	

Table 2. Educational status in cases and controls

Educational status	Cases	Controls	Critical ratio
Illiterate	32 (44·4%)	83 (38·4%)	0·588
Primary School	29 (40·3%)	56 (35·18%)	0·487
Middle School	5 (6·9%)	39 (18·05%)	2·29
High School	4 (5·6%)	18 (8·33%)	0·184
Higher School	2 (2·8%)	0 (0%)	—

Table 3. Occupational status in cases and controls

Occupation	Cases	Controls	Critical ratio
Unemployed	1 (1·4%)	8 (3·7%)	0·119
Student	20 (27·8%)	59 (27·3%)	0·03
Landless labourer	30 (47·7%)	76 (35·2%)	0·628
Housewife	8 (11·1%)	26 (12·03%)	0·071
Skilled labour	3 (4·2%)	6 (2·8%)	0·114
Private enterprise	2 (2·8%)	3 (1·4%)	0·112
Land owner	8 (11·1%)	28 (12·9%)	0·14
Govt. service	—	6 (2·8%)	—
Others	—	4 (1·8%)	—

Table 4. BCG status in cases and controls

BCG status	Cases	Controls	Total
Positive	3 (4·2%)	14 (6·4%)	17
Negative	69 (95·8%)	202 (93·6%)	271
Total	72 (100·0%)	216 (100·0%)	88

Odds ratio:	0·627
95% confidence limits:	0·076 to 2·427
Chi-square:	0·1875
p:	0·05

Table 5. Frequency of intrahousehold contact in cases and controls

Intrahousehold contact	Cases	Controls	Total
Positive	19 (26·4%)	27 (12·5%)	46
Negative	53 (73·6%)	189 (87·5%)	242
Total	72	216	288

Odds ratio:	2·509
95% confidence limits:	1·23 to 5·109
Chi-square:	6·761
p:	less than 0·01

the controls. There is a 2·5 times greater chance of a household contact acquiring leprosy compared with a person without contact. This difference is statistically significant (Table 5).

Discussion

The data have shown that both cases and controls are comparable with respect to educational status, occupational status and BCG vaccination. The study has shown a significantly higher risk in those exposed to leprosy within the household. The risk was 2·5 times greater in the exposed group compared to those in the unexposed group. This is similar to other studies done in the same district[1] where a similar risk of 2·4 was obtained.

This study has been done using the case control methodology and has obtained results which are comparable to other studies in the area.[1–5] The other studies have used the cohort design and hence have been costly and long-drawn. The case control model offers a quick, cheap and comparable alternative.

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SPECIAL ARTICLE

A re-appraisal of clinical and bacteriological criteria in the implementation of multiple drug therapy for leprosy control programmes and proposals for their better use

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Introduction

The recommendations made by the World Health Organization (WHO) in 1982 for the treatment of all leprosy patients in control programmes with multiple drug regimens of relatively short duration[1] have been implemented, to a varying extent, in most leprosy-endemic countries. By the time of the XIIIth International Leprosy Congress in the Hague in 1988,[2] it was reported that over 2 million of the approximately 5 million registered cases of leprosy worldwide had been put on multiple drug therapy (MDT) and of those, over a quarter had completed their treatment and were no longer considered to have active disease.[3] The proper implementation of MDT brings about a remarkable reduction in prevalence in a period of 5–10 years, accompanied by improvement in child and disability rates, and in the longer term, a reduction in incidence.[4] Given such an effective tool for the control of leprosy, it is quite possible that its more determined use would reduce the worldwide problem of this disease by more than 75% by the year 2000. Nevertheless, it is now clear that the rate and extent of implementation of MDT in some parts of the world, notably in the continent of Africa, is disconcertingly slow. It is therefore important to review the situation and try to identify factors which are impeding the implementation of a form of treatment which is not only available and affordable but highly effective. In previous publications,[5,6] we expressed concern about the quality and standards of slit-skin smear bacteriological investigation in peripheral units of leprosy control programmes and called for a radical revision of the present approach. Our more recent experience from site visits to control programmes in Africa and South-east Asia, support the conclusion that the examination of slit-skin smears remains '. . . the weakest link in most leprosy control programmes.'[7,8]
inherent in providing reliable laboratory services for slit-skin smear bacteriological examination in the field may, at least in some leprosy control programmes, be a deterrent to the expansion of MDT implementation. In a recent issue of *Leprosy Review*, Vettom & Pritze described some of the problems which may be encountered in the important matter

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of quality control of smears from leprosy projects in different parts of the world.[9] Nash *et al.*, writing from Papua New Guinea in the same issue, comment that '. . . we cannot afford to rely totally on laboratory services, which are often inaccessible or unreliable in developing countries', and they propose the use of a clinical 'leprosy score chart', as opposed to bacteriological criteria, for grouping patients for MDT in leprosy control programmes.[10] There is little doubt that many national control programmes face serious difficulties in the establishment and maintenance of laboratory facilities for the proper examination of slit-skin smears in the field and it would be deplorable if this has to be rated as an unsolvable impediment to the implementation of MDT, especially if drugs, clinical expertise and other components of a potentially effective programme could be made available. Is there a possibility that this has indeed delayed the introduction of MDT in some parts of the world, thus depriving patients of a highly effective form of treatment? If this is the case, would it be reasonable to modify the present approach by proposing the use of well defined clinical, rather than strictly bacteriological criteria, in control programmes? In this communication we explore this question with particular attention to (a) the allocation of leprosy patients to paucibacillary (PB) or multibacillary (MB) groups, and (b) the determination of the end point (24 months or longer?) for chemotherapy in MB patients. Proposals are then made for operational changes which have the main objective of increasing the number of patients on MDT without unnecessary delay, whilst at the same time preserving reasonable standards of care and management.

Allocation of patients to PB or MB regimens

In 1982, the WHO publication *Chemotherapy of leprosy for control programmes*[1] advised the allocation of all leprosy patients in need of specific treatment into either paucibacillary or multibacillary groups for the purpose of MDT. Paucibacillary leprosy included Indeterminate (I) and tuberculoid (T) leprosy in the Madrid classification, and I, TT and BT in the Ridley–Jopling classification with bacterial index (BI) < 2 according to the Ridley scale *at any site*. Multibacillary leprosy included both lepromatous (L) and borderline (B) in the Madrid classification and polar lepromatous (LL), borderline lepromatous (BL) and mid-borderline (BB) leprosy in the Ridley–Jopling classification with BI of 2 or greater according to the Ridley scale *at any site*.[1,11] The crucial importance of BI being less than 2 in PB cases was based on the understanding that these patients have a total bacillary load of less than 10^6, with negligible risk of developing drug resistant mutants. This use of the BI, for the grouping of patients for PB or MB regimens, has been followed by many control programmes implementing MDT since 1982 and probably widely interpreted as indicating that facilities for slit-skin smear examination are a pre-requisite for its introduction.

National leprosy control programmes were required, at least ideally, to provide widely available and efficient laboratory services and assure uniform and reliable slit skin smear investigation in the field, including a system of quality control and continuous supervision.[1] Yet a recent independent evaluation of one of the most developed and ambitious specialized leprosy control programmes[7] has shown that 40% of the posts for laboratory technicians were vacant (in some places up to 83%), 10% of those in position were not trained and only 40% of the registered patients had skin smear investigation. This situation is by no means exceptional.

Despite the fact that the techniques for the taking, staining and reading of smears are not particularly demanding, there is continuing evidence that it is difficult to set up and maintain the necessary standards and uniformity. The reliability and validity of slit-skin smear BI examination in the field depends on experience in taking and fixing the smears as well as on strict adherence to the prescribed laboratory techniques—procedures often performed by different individuals (paramedical workers and laboratory technicians). The result is interpreted by a third person (medical officer or senior paramedical worker) who does not supervise the investigation but relies heavily on it in making his decisions. A lapse of quality at any stage of the procedure will render the results unreliable, including the possibility of false negative results.[6] Vettom & Pritze writing recently in this journal[9] described a multicentre study on the reliability of slit-skin smears from control projects in different parts of the world. Correlation was judged to be satisfactory but the taking of smears was unsatisfactory in 26%; staining unsatisfactory in 22% and reading unsatisfactory in 36% (Table 2 of the publication). Furthermore, in the 29 participating laboratories, 10 different staining methods for AFB were used (Table 3 of the publication) with wide variation in techniques. Even in well established laboratories there seems to be room for improvement in standardization and quality.

Before further reviewing the situation it should however be underlined that the BI examination is scientifically sound and valuable, provided the uniformity and reliability of the investigations can be assured. Leprosy institutions and projects which have reliable laboratory services should be encouraged to use it and further improve their services. However, the majority of leprosy control programmes do not have such facilities and standards. The question then arises: 'Is it feasible, with the existing infrastructure and resources, and within a reasonable period of time, to make reliable bacteriological investigation available to every patient needing MDT? And if this is not possible, what should be the course of action?' Perhaps the time has come to reconsider the present methodology of MDT implementation in control programmes and suggest an alternative operational strategy including the reorganization of laboratory services. The WHO Expert Committee on Leprosy (1988) defines 'a case of leprosy' as a 'person showing clinical signs of leprosy *with or without bacteriological confirmation of the diagnosis* . . .'.[8] In the same Report it was concluded that there are clinical and operational reasons 'for including all smear-positive cases in the multibacillary group'. Therefore, a BI of 2 is no longer considered as the dividing point and the categorization of patients for MDT regimens is made simply on positive or negative bacteriological investigation of the slit-skin smear. However, these developments do not solve the problems in control programmes where laboratory services remain inadequate and standards of bacterial examination low, and it is of interest that the Third Coordinating Meeting on Implementation on Multidrug Therapy concluded that there is a need for modification of current instructions in the method of MDT delivery with particular reference to 'non-insistence on slit-skin smear taken under certain situations'.[12] In practice there is significant diversity in leprosy control programmes in the methods used to group patients for MDT. Some programmes group all clinically BB, BL and LL cases, whether skin smear positive or negative, as well as BT cases with 10 or more lesions (skin and nerve), as multibacillary.[13] Others have opted to group patients on clinical grounds alone.[14] It has been suggested that patients with disseminated multiple lesions with negative BI, when in doubt, should be treated as MB cases.[15] In Papua New Guinea a 'score chart' to assist the clinical categorization of the patient is already in use.[10]

In order to avoid further confusion, it seems reasonable to consider alternatives to the bacteriological examination criteria for the grouping of the patients and the main purpose of this paper is to propose that the allocation of patients to PB and MB treatment regimens and a decision on the termination of the treatment in MB cases should be based, with very few exceptions, entirely on clinical criteria. This would clearly need the development of standardized and detailed guidelines for the instruction of staff in individual leprosy control programmes. Correlation between the clinical findings, immunological response and bacterial index has been well documented[16] and the possibility that the number of lesions at the onset may be of practical value for the grouping of the patients for PB and MB regimens deserves further study. In this context it is of interest to note that a recent report by Deguerry *et al.*[17] indicated that the number of macules (defined as all kinds of patches, either flat or partly or wholly elevated), may be a more important indicator of the probability of relapse, than regularity of treatment. A clinical system for grouping patients for MDT requires further attention, including the relation between the number of skin (or skin and nerve) lesions, classification and bacteriological positivity. It is intended to present data on this in a separate publication.[18]

In view of the proven value of lepromin testing, including the use of lepromin A, as an aid to classification (but not diagnosis) its value in grouping patients, together with any other specific skin or serological test which may be developed, clearly needs consideration. On balance however, and in the control programme situation under consideration here, any additional benefit may be outweighed by the 3-week period before reading, the need to assure regular supplies of lepromin, syringes and needles, the training requirements for proper use and interpretation, and the possible risk of spreading hepatitis B and HIV infections. Even more importantly, the performance of a test which is incomprehensible to the average patient, together with the inherent 3-week delay, militates against the policy of 'presentation, diagnosis, allocation of regimen and treatment with MDT as soon as possible', which we would like to see established in all programmes which have appropriately trained staff.

By contrast, clinical examination, if completely and sympathetically carried out (using female staff where needed), is understandable to the average patient. By and large it is appreciated, and may improve contact and communication between health worker and patient whilst at the same time offering greater opportunities for the prevention, detection and treatment of disability due to nerve damage. The 'shift' of emphasis from a 'laboratory-dependant' approach to one which is clinically orientated may in fact be expected to strengthen the status of the patient as a participant, rather than a passive recipient, whilst also facilitating the wider and more rapid expansion of MDT to those who need it, provided the necessary orientation and training of staff can be achieved.

The use of the slit-skin smear technique, especially under field conditions, is a matter of considerable concern in relation to the possible spread of hepatitis B or human immunodeficiency (HIV) virus infection in either patients or health workers. The WHO has provided guidelines for the prevention of transmission during the performance of this procedure[19,20] but those who have first hand experience of health services in developing countries may agree that they are far more likely to be put into practice in a supervised, central laboratory than in a peripheral laboratory or field unit.

Multibacillary leprosy: 24 months treatment or longer?

The WHO recommendations of 1982[1] are for triple drug therapy (rifampicin, clofazimine,

dapsone) in multibacillary cases for a minimum of 2 years, but whenever possible, up to smear negativity. Since some MB cases have a BI of 6 at the onset and since it drops (regardless of the type of treatment used) by 0·6–1 log per year,[21] it is quite possible that MDT would have to continue for several years after the completion of 24 doses of treatment, if smear negativity is chosen as the end point. Apart from the fact that this could almost triple the total cost of treatment in many patients, its adoption as a general policy would be operationally difficult to maintain and would undermine one of the most important attractions of MDT as being defined and of relatively short duration. A recent workshop organized by the Armauer Hansen Institute in Germany and attended by leading scientists in the leprosy field, reviewed in detail the duration of MDT and the criteria for the termination of treatment in MB cases.[22] It was evident that neither skin smear BI evaluation, histopathology, immunological tests nor an assessment of clinical progress can alone indicate the point at which to stop treatment in the individual patient. Clinical improvement during treatment, especially in active and previously untreated cases in fact occurs much earlier than any move in the BI scale, often earlier with MDT than with dapsone monotherapy. Studies in Malta have shown that 20·7% of treated MB patients remain bacteriologically positive for 5 to 12 years without relapsing.[23] Furthermore, neither the regimen used, nor its duration appear to have any effect on microbial persistence.[24]

From an operational point of view the precise time taken to 'cure' a patient, especially if the 'end-point' is based on bacteriological findings, is far less important than the average duration of treatment needed to prevent disability (other than that which was established at the onset) and produce an acceptably low relapse rate after treatment. In practice many control programmes have elected to routinely stop MDT in MB cases at 24 months (or 24 doses in 36 months) irrespective of bacteriological positivity, and the results, in the periods of observation so far, are extremely encouraging with regard to the low rate of relapse. Reports of rifampicin resistance, recently published,[25] underline the importance of regular monthly attendance for supervised medication, whilst at the same time doing all possible to ensure adherence to the prescribed daily domiciliary intake of dapsone and clofazimine by the patient. But experience to date from many control programmes seems to indicate that a 24-month period of regular triple therapy for MB patients is satisfactory. Is there any good reason for the performance of *routine* slit-skin smear at this point or subsequently?

Proposals

As a basis for discussion, but with emphasis on changes which can be made with the minimum of delay, we propose the following:

1 'Routine' smears

The 'routine' (often meaningless) use of slit-skin smears in control programmes should be stopped. Their use should be reserved for selected cases, with specific indications decided by control programmes and outlined in their guidelines.

2 Peripheral 'one-man' laboratories

Peripheral, unsupervised, 'one-man' units should be scaled down and in most cases phased out altogether.

3 A central or reference laboratory

Either as part of a general laboratory, or as a sub-unit, one central or reference laboratory of high quality should be available at district, provincial or central level, depending on the health services and the leprosy control programme structure, for the examination of smears under the best conditions.

4 Smear taking and selection of sites

In view of the crucial importance of the selection of sites and the taking of smears, short, intensive re-training courses, supported by written and illustrated instructions (in appropriate languages) should be arranged for all those who will be entrusted with this procedure. This must include precise instructions on fixation, labelling of slides, record-keeping and despatch of slides to the central or reference laboratory for staining and interpretation. A similar short module for the taking of smears (not the selection of sites) should be arranged for senior staff in reference laboratories. This will necessitate an efficient system for the despatch of reports back to the control units with the minimum of delay. These measures should help to achieve acceptable and comparable standards within and between programmes.

5 Hepatitis B and AIDS virus

The possible risks should be taken seriously. All staff involved in handling the slit-skin smears should be aware of the possible risks of viral infection from hepatitis B or AIDS and be familiar with the guidelines for protection issued by WHO.[15,16]

6 Allocation of patients to pauci- or multi-bacillary regimens

In principle this should be made on the basis of clinical criteria only, except in selected, doubtful cases. Guidelines on how to do this, training modules for all grades of field staff and appropriate written and illustrated material (in local languages) all require expert input and production. This process also calls for a built-in system to enable senior staff to check the accuracy of allocation in control programmes, together with careful monitoring of clinical outcome (see 8 below).

7 The duration of MDT for multi-bacillary cases

Rather than continuing to smear negativity (at all sites), a period of 24 months triple drug therapy should be accepted as adequate. Unless in exceptional doubtful cases, smears should *not be routinely taken* at this point or subsequently. The decision to stop treatment at 24 months will thus be based on (a) the record of regular attendance for 24 supervised months doses, (b) any available evidence that compliance to unsupervised daily medication has been satisfactory, and (c) the clinical findings.

8 Diagnosis of relapses

Relapse rate is perhaps the most reliable criterium for the assessment of the effectiveness

of treatment and control measures. However, the diagnosis of relapse is not always easy, particularly in paucibacillary cases. It is strongly recommended that suspected relapse cases should be thoroughly investigated in referral centres before a diagnosis of relapse is accepted.

9 Technical support

At regional/district level, particularly in integrated programmes, it is essential to provide and maintain clinical expertise for complications and difficult cases alongside laboratory services, for the guidance and support of paramedical workers.

10 Operational research

The above changes call for careful prospective planning and the monitoring (and rapid solving) of problems which may arise during their implementation. The proposals in paragraph 6 above, call for expert advice and it would be helpful if this and the other operational changes described in this paper could be addressed by an expert committee or group, with attention to a plan of action, funding, training modules, supervision, monitoring and research. The latter should include retrospective studies from well-run programmes on the relationship between (a) the number of skin lesions and (b) the number of skin and nerve lesions on the one hand, and the classification (TT, BT, I etc) as used in the current MDT grouping on the other. These results should in turn be analysed in relation to eventual clinical outcome and relapse rates. Comparative studies, in terms of cure and prevention of disability in patients allocated to regimens on clinical grounds alone, as opposed to those allocated on combined clinical and bacteriological grounds, could also be carried out. However, neither these, nor any of the studies mentioned above, should be regarded as a reason to delay the implementation of the operational changes proposed in this paper.

Summary and conclusions

Behind the appraisal of criteria above and our proposals, is the question 'To what extent and for what purpose should slit-skin smears be used in programmes implementing MDT?' The answer may lie somewhere between the extreme of abolishing them altogether and the present situation, in which many people seem to think that a comprehensive service has to be provided at many levels, including the periphery, almost regardless of quality and with minimal supervision.

Our plea is twofold: (1) the much wider use of standardized clinical, as opposed to bacteriological, criteria for the grouping of the patients, the termination of treatment in multibacillary cases and follow up, and (2) the abolition of the *routine* use of slit-skin smear examination in the field, coupled with the phasing out of unsupervised peripheral units of doubtful quality and the identification of one laboratory at central or provincial level which is able to provide a reliable, high quality service for smears in selected cases. Clearly these proposals will not solve all the operational and methodological problems. There is an urgent need for research on the best ways to implement MDT on a large scale. But the truth of the matter is that 7 years after the WHO recommendations[1] and for

reasons which have so far been poorly defined, less than half the world's registered cases have so far received MDT. Most of the registered cases continue to take a form of treatment, dapsone monotherapy, which was condemned over 10 years ago as being hazardous on account of the dangers of resistance. From the estimated world total of 10–12 million cases, WHO has suggested that as many as 8 million cases may still be in need of MDT.[3] If we are trying to move towards a goal of 'MDT for all by the year 2000', there may still be a long way to go. Operational problems are experienced in every control programme and there is an urgent need to find the right solutions through well coordinated operational research. Would it be an exaggeration to say that *the* current priority in leprosy control is the establishment of a permanent international committee to identify, as rapidly as possible, the main factors which are impeding the implementation of MDT, so that realistic solutions may be found?

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SPECIAL ARTICLE

Plastic footwear for leprosy

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Summary The anaesthetic foot in leprosy poses the most major problem in the rehabilitation of its patients. Various attempts have been made to produce protective footwear such as the microcellular rubber-car-tyre sandals. Unfortunately these attempts have had little success on a large scale because of the inability to produce them in large numbers and the stigma attached to such unusual footwear. While such footwear may be superior to the 'tennis' shoe in protecting the foot from injury by the penetration of sharp objects, it fails to distribute the weight-bearing forces which is the major cause of plantar damage and ulceration in the anaesthetic foot. This can be achieved by providing rigidity to the sole, as demonstrated by the healing of ulcers in plaster of paris casts or the rigid wooden clog.

A new type of moulded plastic footwear has been evolved in conjunction with the plastic footwear industry which provides footwear that can be mass produced at a low price and which overcomes the stigma of leprosy. Controlled rigidity is provided by the incorporation of a spring steel shank between the sponge insole and the hard wearing plastic sole. Trials have demonstrated both the acceptability of the footwear and its protective effects as well as its hard wearing properties.

Introduction

Plantar ulceration poses the single greatest problem in the rehabilitation of leprosy patients. While a patient with facial or hand deformities can continue to work even in a limited manner, ulceration of the foot poses a far more difficult problem. Once damaged, the foot continues to ulcerate even with the trauma of limited locomotion. The unsightly swollen foot under smelly bandages not only carries a stigma and social repulsion, but also prevents the patient from reaching his work place and carrying out even relatively sedentary activities. Unlike facial and some hand deformities, till now surgery has had little to offer in the correction of plantar ulceration except sequestrectomy, debridgement and occasional skin graft or flap cover which also break down from subsequent trauma to the anaesthetic foot.

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Materials and methods

Care of anaesthetic feet and provision of footwear have been taught and extensively practised by patients, but with poor results outside the precincts of the leprosarium. The most effective means of healing plantar ulcers is not by antibiotics and dressing but bed rest, immobilization in a plaster of paris cast, or the use of a solid wooden clog. Unfortunately all of these have only proved to be temporary expedients. The car tyre-microcellular hand-sewn sandal is extensively employed within the leprosarium, and although an improvement on the ordinary 'chappal' or 'tennis' shoe, it still has several disadvantages. It cannot be produced in bulk and depends on the microcellular insole for softness, for providing protection from thorns and for providing a durable though flexible sole. As explained later, this non-rigid footwear does not provide the basic requirement for the distribution of pressures which is the chief cause of plantar damage. Another major handicap of this sandal is that it stands out from all normal footwear; being exclusively used by leprosy patients, it carries its own stigma which prevents most patients from wearing it in public outside leprosaria. The patient therefore prefers to wear the common tennis shoe to hide the deformity and to avoid being conspicuous as a sufferer of leprosy.

The normal foot, even in barefoot walking, is protected from injury by sensation provided to the sole by the median and lateral plantar branches of the posterior tibial nerve. This protection is not only against sharp objects, like thorns and nails, as is commonly believed, but more important, pain prevents the build-up of excessive pressures generated under bony pressure points in the foot which is the major cause of damage in feet that do not have normal protective sensation. Ernest Price as early as 1959, in a WHO workshop on Deformities in Leprosy held at Karigiri, demonstrated this by charting the frequency of the sites of plantar ulceration in the leprous foot; this followed a regular pattern along the weight-bearing areas of the foot, the most common site being under the ball of the great toe where pressure reaches its height during the take-off thrust when walking and running. With his customary simplicity and elegance he also demonstrated the difference in pressures in the normal foot as compared to that in the feet of leprosy patients at various stages of sensory loss or damage using an inked paper for footprint impressions. This has been published in detail in his Chapter on 'Care of the Feet' in the second edition of *Leprosy in Theory and Practise*.[1] In this he also describes the preulcerative stage where 'the degree of anaesthesia may be minimal'; this is caused by aseptic traumatic fat necrosis due to unconscious build-up of excessive pressure; this ultimately results in scarring of the deeper tissues, which in turn makes the area susceptible to even lesser trauma, and leads ultimately to frank ulceration and infection which may eventually result in osteomyelitis and necrosis of the underlying bone.

Another factor which further predisposes the anaesthetic foot to ulceration is the intrinsic muscle paralysis associated with nerve damage. This results in the claw deformity of the toes and shift of the protective sesamoid bones from under the head of the first metatarsal.[2] Drop foot also results in maldistribution of pressures to the anterior part of the foot.

The reason that plantar ulcers heal with rest and elevation in a plaster of paris cast or the wearing of wooden clogs demonstrates the importance of distribution of pressures on a larger surface of the foot, preventing the building of excessive pressures under bony points in a supple foot which does not have normal protective sensation. While the plaster

cast and rigid rocker may be ideal for the distribution of pressures, they are impractical for everyday use because of their total rigidity which makes walking difficult and because of their unacceptable appearance. It is therefore important to devise a method which permits controlled rigidity with a certain degree of rocker action as well as some degree of flexibility.

An ideal footwear should have the following requirements:

(a) Above all it should protect the feet from the major known causes of ulceration, i.e. by distribution of pressure and preventing injury by sharp objects.

Besides this, it should also have the following qualities:

(b) It should be aesthetically acceptable and not carry the stigma of leprosy.
(c) It should be mass produced at reasonable cost and be readily bought off the shelf in various sizes like any other footwear; preferably it, or a similar model, should be used by the general population.
(d) Can be modified in its external shape and colour at intervals to prevent the development of stigma.
(e) Should be hard wearing and usable on different terrain.
(f) Easy to repair, preferably by the patient himself/herself.
(g) Quick wearing components should be replaceable and purchased readily.
(h) Should be water resistant and impervious to secretions from ulcers.
(i) Easy to clean.
(j) Should be comfortable to wear.

Bombay is one of the largest centres for the production of plastic footwear, and the author decided to explore the possibility of utilizing the locally available expertise and facilities to devise a suitable footwear for leprosy patients which would incorporate some or all of the abovementioned criteria. Through a prolonged process of trial and error and utilizing the contacts with various sections of this industry, the following footwear has been evolved which meets many if not all of the requirements.

Description of footwear

This shoe consists of three components (Figures 1, 2(a), (b) and 3).

1 Single unit extruded hard wearing plastic sole together with the uppers. This extruded shoe has the shape of some of the normal sandals sold in the market but has the following modifications.

(a) Thicker sole for longer wearing.
(b) Permits concealing of moderate deformities of the foot and toes.
(c) Has enough ventilation to prevent maceration of the skin.
(d) A heel counter to prevent lateral mobility.
(e) Increased depth to accommodate an 8 mm thick sponge insole.
(f) A depression to accommodate the steel shank.

2 Steel shank. A spring steel shank 240×40 mm and 1 mm thick with a curve commensurate with the curve of the sole is fitted in the depression on the superior surface of the plastic sole underneath the sponge insole. After a process of trial and error the

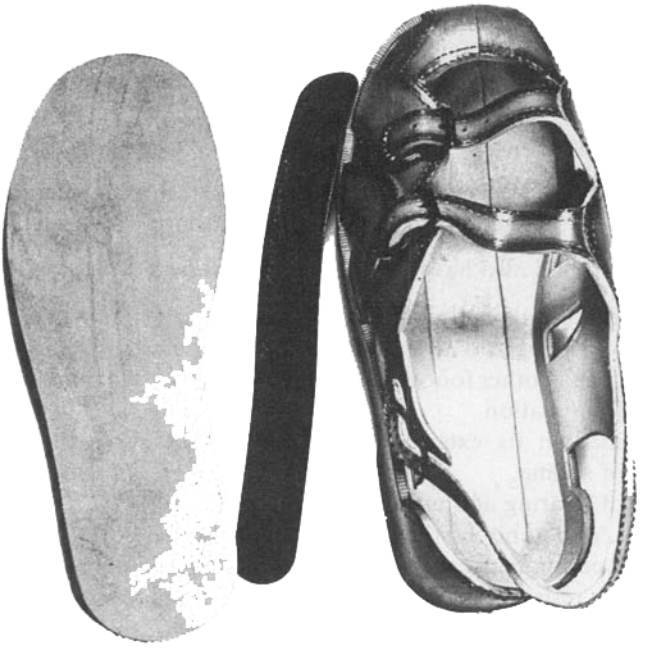

Figure 1. Components of footwear. From left to right: EVA insole, steel shank and view of the footwears plastic uppers showing the depression for the steel shank on the superior surface of the plastic sole.

present shank has been found to provide adequate rigidity to the sole for distribution of pressures and yet permits a degree of flexibility for comfortable locomotion. It is virtually indestructible and also prevents injury by thorns and nails.

3 Closed cell 18 shore plastic insole. This 8 mm thick EVA insole available in the market is impervious to water and secretions, provides adequate cushioning and is more durable than softer sponges used in normal footwear or the traditional microcellular sponge. The semirigid shank further distributes pressures on this insole and reduces its wear under pressure points. The insole is the least durable part of the shoe and can be purchased as an accessory which can be slipped in and, if necessary, glued into the shoe by the patient himself.

The report of the earlier model of the shoe tested at the Kondhwa Leprosy Hospital (to be published shortly) revealed acceptability to both male and female patients but had to be modified to provide a heel counter and thicker and better designed straps to prevent their breakage. The thicker straps avoiding sharp angles in the later models have not only overcome this flaw but can be readily repaired by the patient himself or the street cobbler by simple heat-jointing with a heated metal strip. The six month trial of the shoe at Kondhwa demonstrated not only the protection of healed ulcers but also the healing of moderate ulcers when the shoes were worn without any dressing.

This long lasting shoe at the modest price of US $10 per pair meets most of the requirements for leprosy footwear and we hope will prove to be a major advance in the rehabilitation of leprosy patients. We feel it could be worn with advantage by all leprosy patients, for every leprosy patient has the risk of potential damage due to nerve

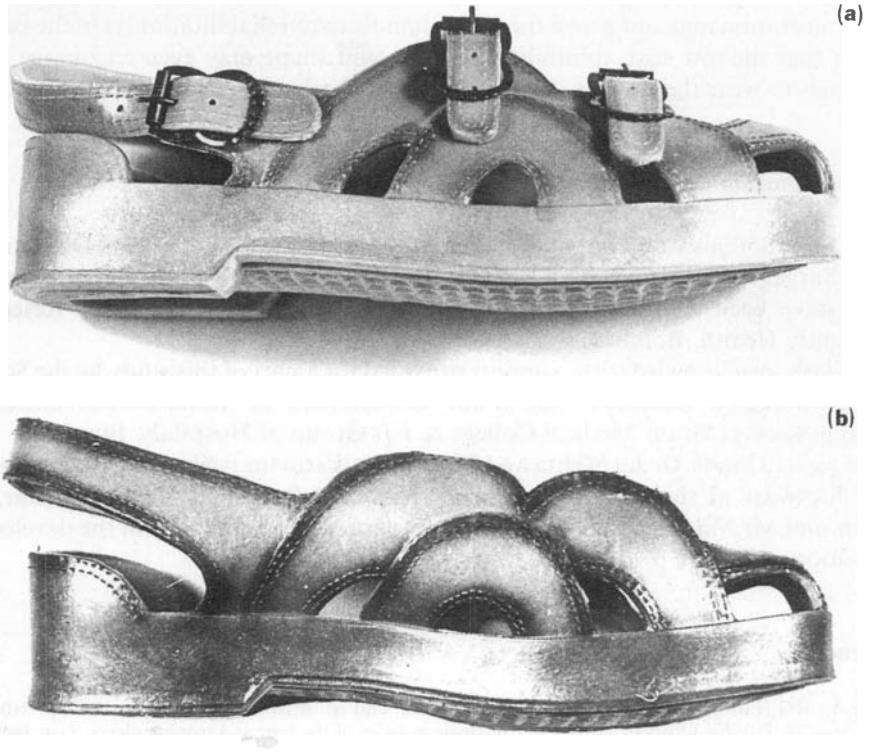

Figure 2(a) and (b). Lateral views of the footwear showing the deformity-concealing yet ventilating pattern of the uppers.

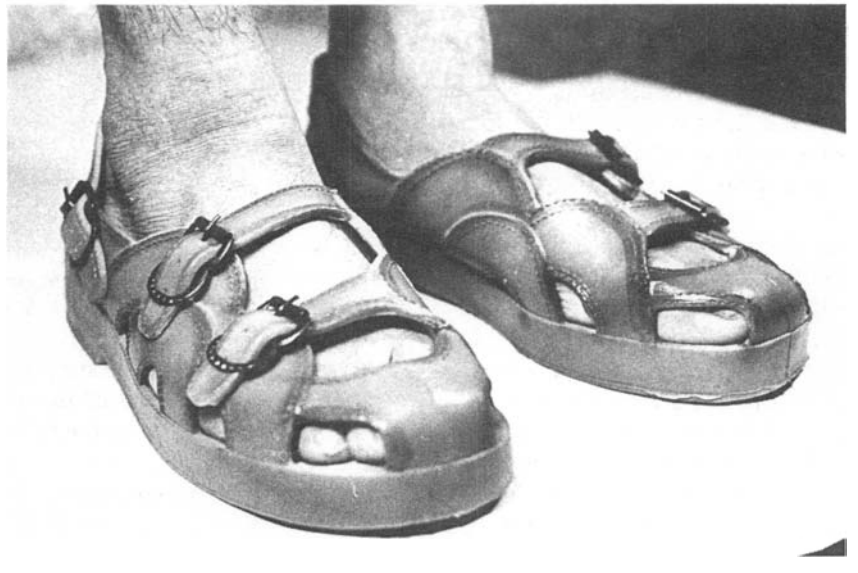

Figure 3. View of footwear when worn.

involvement. It is also hoped that in association with the newer forms of nerve release, plantar ulceration may not prove the major handicap to rehabilitation as in the past. It is also felt that the low cost, durability, comfort and shape may even encourage normal individuals to wear these shoes if sold in the open market, thus improving acceptability.

Acknowledgments

The early part of this study was undertaken by the author while at the Tata Department of Plastic Surgery, J.J. Group of Hospitals, Bombay. After the author's retirement, the studies have been conducted in co-operation with the Foundation For Research in Community Health, Bombay.

We wish to acknowledge the support provided for a part of this study by the Scientific and Technological Research Cell of the Government of Maharashtra, through the Research Society, Grant Medical College & J.J. Group of Hospitals, Bombay.

We wish to thank Dr Jal Mehta and Mr V N Kulkarni for trials of the different models of the footwear at the Kondhwa Leprosy Hospital, Pune and Dr M Uplekar, Dr S Arolkar and Mr Madhusudan Rokle for their participation and help in the development of this footwear.

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Lepr Rev (1990) **61,** 79–81

Letters to the Editor

HOW TO DETECT LEPROSY IN SOME PATIENTS WITH ONLY LOCALIZED SENSORY LOSS

Sir,

Now and then, particularly in endemic areas, we are confronted with a situation where in the presence of only symptoms, a definitive diagnosis or exclusion of active infection with leprosy remains unfulfilled. Three such cases presented here highlight this point.

Case No. 1

A 16-year-old boy from the state of West Bengal came with sensory loss over the left foot of 6 months' duration. On examination there was loss of fine touch, thermal and pin-prick sensations on the dorsum of the left foot extending to the posterior and lateral parts of the lower third of the leg including the heel. Regional and sensory nerves coursing the area were not thickened or tender. No other lesions were seen on the entire skin surface and there was no history of leprosy in the family. Biopsy of the skin from the dorsum of the foot and the left sural nerve were reported normal after examining multiple sections for acid-fast bacilli (AFB).

Case Nos 2 and 3

Two men from the state of Bihar aged 21 years and 42 years sought advice for numbness over the lateral part of the dorsum of the right hand of 6 months' and 9 months' duration respectively. Previous consultation with the neurologist had disclosed no abnormality. As in the first case, the sensory deficit was on the dorsal aspect of the thumb, index finger and extended downwards along the lateral one-third of the right hand to the wrist. The rest of the skin appeared normal. A biopsy of the cutaneous branch of the radial nerve which courses over the lateral border of the wrist was done. Histopathology showed no evidence of leprosy.

Comment

The cardinal signs that justify a diagnosis of leprosy are: (1) clinical features of nerve involvement like loss or impairment of sensation on a skin patch or an extremity, and thickened or tender nerve(s); and (2) demonstration of *Mycobacterium leprae* in the skin by slit-skin skin smears which will reveal acid-fast bacilli. The clinical and routine laboratory criteria for the classification of leprosy across the spectrum from tuberculoid to lepromatous, along with the inclusion of the indeterminate variety has definitely helped workers to comprehend the severity of the disease and satisfactorily monitor drug therapy. The 3 patients seen here from highly endemic areas of the country had only localized sensory loss. The histopathology of the nerves showed no evidence of leprosy. This makes it difficult to decide whether to give the benefit of therapy or withhold it. Eminent workers with lifelong experience in leprosy have faced such problems[1,2] and have suggested that a thorough histological study for the presence of perineural infiltrate and/or AFB in the biopsy

specimen should be undertaken, in the absence of which the patients had to be followed up because it was felt that no one should be unnecessarily branded as having leprosy.

These patients may represent the early stage of the disease,[1] or it is also possible for the infection to have been arrested by the body's immune mechanisms. Since the former requires therapy it is vital to develop tests to distinguish these two conditions and this is not possible with the investigations currently in vogue. The limited use of serological studies in endemic areas using both *Mycobacterium leprae*-specific monoclonal antibody[3] and *M. leprae*-specific antigen[4] has been evaluated and found useful in identifying the multibacillary cases, but in the rest there was slender or no correlation between the presence of disease and seropositivity. The relevant differential diagnoses in our patients include pressure neuropathies like carpal tunnel syndrome, peripheral neuritis caused by the ingestion of drugs containing heavy metals, traumatic neuropathy, and metabolic causes like diabetes mellitus and amyloidosis. There was no evidence to suspect any of these conditions.

Leprosy is primarily a neural disease and future research must aim at developing a test that can detect the lurking AFB or its antigenic components in the biopsy from the peripheral nerve(s) in the early stages of infection. Till this is achieved our advice to medical and paramedical field workers must be to send such patients to the nearest centre for appropriate investigations and, in the absence of any confirmatory evidence, they must be followed up in their respective places to note whether they develop other signs of the disease.

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New Delhi 110022, India

V RAMESH, UMA SAXENA
& R S MISRA

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REPLY: THE USE OF XYLENE (XYLOL) IN MEDICAL LABORATORIES

Sir,

I was interested in Dr A C McDougall's comments and questions concerning the deterioration of acid-fast colouration of mycobacteria during the examination of smears (*Lepr Rev*, 1989, **60:** 67).

In my experience *Mycobacterium leprae* in smears is irregular in its retention of acid-fast stain. On occasion the colouration may withstand immersion oil, xylene or mountant, but at other times it unaccountably fades. This unpredictability applies to all forms of bacilli, solid, fragmented and granular, and to bacilli from different sites in the same patient. For this reason I would recommend that a leprosy smear be examined as soon as it is stained; it can be left fixed and unstained until a suitable time.

Once the colouration is lost the only sure way to restore it is to restain the smear as for a tissue section, but using a slightly modified technique as follows. Immerse the smear in xylene for 15 min, rehydrate, stain in cold carbol fuchsin for 15 min, dry in air, apply a drop of turpentine (pinene) to one side of the smear and tilt the slide so that the turpentine flows over the smear, differentiate immediately without drying in 25% acetic acid, wash in water, dry, counterstain and examine. The staining and bacterial morphology are restored.

The foregoing remarks apply to smears from patients. In tissue homogenates, and in smears from some animals, *M. leprae* for some reason holds the acid-fast dye much more strongly. Similarly smears of *M. tuberculosis* and BCG hold acid-fast dye tenaciously, which is not due only to the higher temperatures at which these organisms are usually stained since *M. leprae* stained in the same way may not retain its colouration so well. The explanation presumably lies in the active principle of the component involved in the staining reaction, which is not yet clearly identified. The fatty products surrounding the bacilli in a smear may also play a role.

The Hospital for Tropical Diseases MARIAN J RIDLEY
St Pancras Way, London NW1 0PE

COMMENT ON 'LEPROSY IN CHILDREN'

Sir,

In their study 'Leprosy in Children' (*Lepr Rev* 1989; **60,** 202–5) Sehgal & Joginder claim; 1, a poor correlation between clinical and pathological findings in their young patients; and 2, that children have poorly developed immunity relative to adults.

Regarding deficient immunity, since 24 of their 25 patients had no acid-fast bacilli evident by slit-smears or histopathology, the converse appears to operate if control of pathogens is taken as one marker of immunity.

More important, on the data presented by the authors, I question whether all the 'paucibacillary' children actually had leprosy, and whether their types of leprosy are as stated. The 'BB' cases cannot be so on the Ridley–Jopling classification since a positive bacterial index is necessary for that label. The 'BT' and 'BB' cases with 'non-specific' histology are obviously not histologically proven leprosy. The 9 children with clinically and histologically 'BT' disease could, on the information presented, have had leprosy; but given the doubt about the other cases, were their skin biopsies histopathologically pathognomonic? (There are many causes of granulomatous dermatitis, and in the absence of bacilli in characteristic sites, only those cases with undisputed endoneurial granulomatous disruption of dermal nerves should be admitted as definite cases of leprosy.)

One possible explanation for the doubts about these cases may lie in inadequate examination for bacilli in slit-skin smears and histological sections. The authors could also indicate how certain they were of the diagnoses on clinical grounds, and whether the lesions improved on chemotherapy.

In studies such as this, where various parameters are being correlated, the greatest precision possible should be utilized to define the patient study group, and to ensure that the patients actually have the disease in question. The final statement—that clinical criteria should be the mainstay of diagnosis of leprosy in children—is questionable. Given the well-known problems in establishing a diagnosis in many suspect cases[1–3] it is important to separate operational criteria for diagnosis from those used for leprosy research. In the latter, stricter criteria must be used.

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Lepr Rev (1990) **61,** 82–87

Teaching Materials and Services

AIDS and tuberculosis

In a number of developing countries, particularly in sub-Sahara Africa, infection with both, *Mycobacterium tuberculosis* and HIV, is highly prevalent. Persons with both infections have an increased risk of developing clinical TB (in a study in Florida, the prevalence of clinical TB among AIDS patients of different ethnic groups corresponded to the prevalence of TB infection) and of further transmitting TB infection. Therefore, some of these countries are facing, or will have to face, a rapid upsurge of the TB problem. Salient points of the association between TB and HIV are:

TB infection in individuals also infected with HIV is highly likely to progress to clinical TB.
2 It is possible that TB also accelerates the evolution from HIV infection to overt disease (AIDS).
3 HIV may be transmitted among TB patients through unsterile injections used in TB treatment (e.g. streptomycin).
4 TB often occurs as an early, or even the first, clinical manifestation of AIDS.
5 If, because of underlying HIV infection, there is an increase in the incidence of clinical TB, this will lead to higher transmission rates in the general population (especially family contacts, health personnel).
6 In HIV-infected patients the clinical TB picture is often different from that usually seen in adult-type tuberculosis, and includes unusual extra-pulmonary manifestations—e.g. lymphatic involvement and intracranial tuberculomas. Case finding and diagnosis are therefore more difficult.
7 Optimal treatment duration and adverse reaction rate in HIV infected TB patients is still unknown. (Reactions have especially been observed with thiacetazone).

All this points to a need to strengthen TB control. WHO recommend the following steps:

—Coordination by including an expert on TB on national AIDS Committees,
—Vigilance in hospitals and clinics to suspect TB in AIDS patients, and to treat TB promptly,
—Fully supervised anti-TB drug intake, at least in initial phase of therapy,
—Health education on HIV transmission for TB patients, voluntary serological tests and counselling,
—Where sterility of needles cannot be ensured, an entirely oral medication regime should be used.

BCG vaccination should be withheld from individuals with symptomatic HIV infection. (Summarized from *Weekly Epidemiological Record*, WHO, 28 April 1989.)

Leishmaniasis and HIV infection

The following is extracted from *TDR News*, Number 29, 1989:

'Increasing numbers of AIDS patients (or HIV-seropositive individuals) are being identified who also suffer from leishmaniasis, in some cases without previous history of this parasitic disease. There are theoretical and experimental reasons to believe that live parasites can and do persist following infection and recovery from leishmaniasis. When the immune response is depressed, leishmaniasis can manifest itself. It is therefore not surprising to see this association and it has been suggested that leishmaniasis should be considered as an opportunistic infection. Following the publication of the first few reports, we surmise that new cases of combined infections have probably not been published.

The TDR Leishmaniases Component and the Global Programme on AIDS and Parasitic Diseases Programme of WHO are interested in promoting research on the association of HIV and leishmaniases. We would like to hear from you if (a) you see cases of such combined infection, or (b) you are interested in and in a position to undertake research on this phenomenon.

Please write to: Dr Farrokh Modabber, Secretary, Steering Committee on Leishmaniases, TDR/World Health Organization, 1211 Geneva 27, Switzerland.'

Health Images, UK

Health Images has been set up in response to the increasing realization that pictures are desperately needed to help accelerate social change in poor countries. *HI* is the first and only organization in the UK to specialize in helping groups in poor countries to develop and mass produce their own locally relevant visual materials. *HI*'s aim is to promote the increased production and use of well-designed visual aids for learning about health and development, worldwide. Some of *HI*'s planned activities are outlined below.

Training Workshops
Training workshops in design, pre-testing and production will be held both in the UK and in underdeveloped countries. Workshops will last 2–3 weeks and aim to increase the number of people who can teach the skills required for making simple visual aids.

Printing Technology
Appropriate printing technology will be developed and disseminated. Initially, a portable silkscreen printing kit for use in refugee camps, schools, etc. has been designed and constructed.

Publications
A newsletter will be produced twice a year, carrying reports of work with visual materials from different countries. A practical manual 'Visual Aids: Designing, Pre-testing, Printing' was published in 1988.

Supply Scheme
HI will run a scheme to help small health projects, which cannot afford to produce their own materials locally, to develop effective visual aids.

Research/Consultancy
It is hoped that *HI* will be able to provide resource persons for consultancy or research work on visual materials.

Exhibitions
Exhibitions will be prepared on subjects relating to visuals. One exhibition, 'Visual Communication for Health and Development' will tour art colleges and galleries in the UK during the next 2–3 years. This exhibition is primarily intended to introduce art students and artists to the design of visual materials for use with non-literate audiences.

Initially, the address of the *HI* office will be Holly Tree Farm, Walpole, Halesworth, Suffolk, IP19 9AB, England (*Tel*: 098 684 402). Please contact us if you would like to know more about *HI*'s work.

WHO-assisted tuberculosis training courses

Dr A Kochi, Chief Medical Officer, Tuberculosis Unit, Division of Communicable Diseases, WHO, 1211 Geneva 27, Switzerland, has kindly provided the following list of WHO-assisted international tuberculosis training courses:

1 Annual training course on the epidemiology and control of tuberculosis, Paris, with field training in Algeria.
Address: Dr Annik Rouillon, Executive Director, International Union against Tuberculosis, 68 Boulevard St-Michel, 75006 Paris, France.

2 Annual WHO/Japan international tuberculosis course, at the Research Institute of Tuberculosis, Tokyo, with field training in the Republic of Korea.
Address: Dr N Umemura, Course Coordinator, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Keddaku Yobo Kai Kekkaku Kenkyujo, Kiyose-shi, Tokyo, Japan.

3 Advanced course for managers, Tokyo.
Address: Same as for No. 2.

4 Annual international training course on bacteriology of tuberculosis, at the National Reference Centre for Tuberculosis, Ottawa, Canada.
Address: Dr Adalbert Laszlo, Director of Course, Principal Scientist, National Reference Centre for Tuberculosis, Laboratory Centre for Disease Control, Health Protection Branch, L.C.D.C. Building, Tunney's Pasture, Ottawa, Ontario K1A OL2, Canada.

5 Annual international training course on tuberculosis at the National Tuberculosis Institute, Bangalore.
Address: Dr R V Kale, Chief Medical Officer, National Tuberculosis Institute, Directorate General of Health Services, No. 8, Bellary Road, Bangalore 560 003, India.

6 Annual All Africa leprosy and rehabilitation training course (with a chapter on tuberculosis), Addis Ababa, Ethiopia.
Address: Dr S J Nkinda, Director of Training, ALERT, PO Box 165, Addis Ababa, Ethiopia.

7 Training in the production and control of freeze-dried BCG vaccine, Statens Seruminstitut, Copenhagen, Denmark.
Address: Dr Jorgen Leerhoy, Quality Control Department, Statens Seruminstitut, Amager Boulevard 80, 2300 Copenhagen S, Denmark.

8 Training course on the epidemiology and control of tuberculosis and acute respiratory infections, Instituto Nacional de Epidemiologia 'Emilio Coni', Santa Fe, Argentina.
Address: Dr Eduardo Balestrino, Director, Instituto Nacional de Epidemiologia, Casilla de Correo 106, 3000 Santa Fe, Argentina.

9 Training courses on the epidemiology and control of tuberculosis in South America, Cuba and Mexico.
Addresses: Dr Padula, Director, Istituto Nacional de Epidemiologia, Ituzaingo 3520, Mar del Plata, Argentina.
Dr Germano Gerhardt, Director, Division Nacional de Pneumologia Sanitaria, Rua de Resende 128, 2° andar, 20 000 Rio de Janeiro, Brazil.
Dr Guido Chavez Montagno, Jefe Seccion Enfermedades Transmissibles, Ministerio de Salud, Calle 16 No. 7-39, Bogota, Colombia.
Dr Libertad Carreras, Jefa Grupo Tuberculosis, Ministerio de Salud, Le Habana, Cuba.
Dr Leonel Rojas, Coordinator, INERYCT, J.M. Infante 717, Casilla 9634, Santiago, Chile.
Dr Gonzalo Cano, Jefe, Programa de Tuberculosis, Mazarik 490, 8° Piso, Colonia Polanco, Mexico 5, D.F.
Dr Manuel Adrianza, Director Enfermedades Cronicas, Depto. de Tuberculosis, Ministerio de Sanidad Social, El Algodonal, Antimano, Caracas, Venezuela.

10 Regional training course on bacteriology at the Centro Panamericano de Zoonosis, Argentina.
Address: Dr Isabel N. de Kantor, Centro Panamericano de Zoonosis, CEPANZO (OPS/OMS), Calle Talcahuano 1660 esquina Cordoba, Martinez, Provincin de Buenos Aires, Argentina.

Disability in the developing world—short international courses. IDEA

International Disability Education & Awareness (IDEA) are offering the following course:

Multidisciplinary forums for sharing ideas and information and looking at the issues around

Development and Disability. July 16–21 (residential) at All Saints Pastoral Centre, Herts (accessible for disabled people).

For anyone concerned with disabled children and adults (including those with learning difficulties) in developing countries. Participants welcome from the fields of therapy, education, health, advocacy, disability politics, employment, social work etc. who are, or have been, working overseas or who are interested in the issues.

Details from: M. Greenhalgh, Administrator, IDEA, William House, 101 Eden Vale Road, Westbury, Wilts BA13 3QF, England.

FIELDLINCS Coordination and Technical Support Grants

Field Links for Intervention and Control Studies (FIELDLINCS) is a recently created programme designed to promote high quality field research on the TDR diseases—malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis and leprosy.

Field Links for Intervention and Control Studies (FIELDLINCS) is a recently created programme designed to promote high quality field research on the TDR diseases (malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy).

The three goals of FIELDLINCS are: (1) to provide training in epidemiology, entomology and social sciences for individuals conducting field research on intervention strategies, and implementing control programmes; (2) to promote field research networks as mechanisms for training in project design, methodologies and techniques of field research, and for project-to-project linkage to reduce the isolation of investigators; and (3) to work in close collaboration with TDR's disease-specific components to provide input into the selection and utilization of epidemiological, social science, and entomological methods appropriate for the study of tropical diseases.

For more information, please write to: Dr Jacqueline Cattani, FIELDLINCS Coordinator, TDR, World Health Organization, 1211 Geneva 27, Switzerland.

Takemi Program in International Health

The Takemi Program in International Health at the Harvard School of Public Health seeks applications for a limited number of fellowships for research and advanced training on critical issues of international health, especially those relating to developing countries. This interdisciplinary programme focuses primarily on mobilizing, allocating and managing scarce resources to improve health, and on creating sound strategies for disease control and health promotion. To address these issues, the Programme brings together at Harvard a small group of future leaders from around the world and from diverse disciplines. Through its fellowships for highly qualified individuals, the Takemi Program seeks to contribute to institutional development and to improvement of national health policy as well as to the advancement of knowledge.

The Takemi Program has four major objectives:

- to create better methods for mobilizing and using health resources in both rich and poor countries.
- to promote cooperative research and comparative analysis of health policies and programmes in different countries.
- to study transnational causes of ill health, such as population migration and disease transmission, and air and water pollution.
- to bring together leading health professionals and scholars from many nations for research and training.

The programme seeks to achieve these objectives through activities at Harvard and through the growing global network of Takemi Fellows.

For additional information contact: Michael R. Reich, Ph.D., Director, Takemi Program in International Health, Harvard School of Public Health, 665 Huntington Avenue, Building 1, Boston, MA 02115. *Tel*: 617-732-0686; *Telex*: 501003; *Fax*: 617-566-0365.

International Course Programme for 1990 ALERT

Course name	Participants	Dates in 1990	Requirements
(a) LEPROSY COURSES			
1. *Rural Area Supervisors Course* On Clinical Leprosy, Leprosy Control and Supervision	Senior and Junior Rural Area Supervisors	17 September–17 November (9 weeks)	Senior Rural Area Supervisors, should be in charge of Leprosy Control Activities for a large area, e.g. province. Junior Rural Area Supervisors should have not less than 5 years experience in leprosy.
2. *Doctors Course* Clinical Leprosy, Leprosy Control Programme Management	Medical Officers, involved or going to be involved, in clinical care of leprosy patients, management of Leprosy Control, or Training in Leprosy of Health Personnel	23 April–2 June (6 weeks)	Experience or familiarity with a Leprosy Control Programme desirable, but not essential. Additional in-service training in Leprosy Control for at least 2 weeks recommended.
3. *Short Doctors Course* Leprosy Control and Clinical Leprosy, including management of ulcers and simple septic surgery	Medical Officers with some experience (1 year or more) in leprosy, working mainly in hospitals	18 June–14 July (4 weeks)	Some experience in Leprosy is needed in this short course.
4. *Physiotherapy Course*	Physiotherapists, Occupational Therapists, other Paramedicals and Health Staff with experience in Leprosy Physiotherapy	(i) 23 April–2 June (6 weeks) (ii) 17 September–28 October (6 weeks)	
(b) TUBERCULOSIS COURSE	Medical Officers and Senior Health Staff involved in Tuberculosis Control	2–21 April (3 weeks)	Prior work or attachment with tuberculosis project is highly recommended.

Summary:

J	F	M	A	M	J	J	A	S	O	N	D
RAS			TB	DOC		DOC			RAS		
				PT					PT		

NB: (1) A good command of English is essential.

(2) An application form should reach ALERT at least 3 months before the start of the course.

International Course Programme for 1990 ALERT—(*continued*)

National Courses	Participants	Dates	Requirements
Medical Undergraduates	Final year Medical Students	3 weeks per group	Other Ethiopian and non-Ethiopian health personnel with limited responsibilities in leprosy work may be attached to these courses when places are available.
Student Nurses	Final year Student Nurses	2 weeks per group	
Health Assistants	H.A. on upgrading courses	2 weeks per group Dates still to be fixed.	

In-service Training

NB: The in-service training programmes are generally intended for further specialized training in specific fields.
Applicants for programmes listed under 1–5 are therefore required to possess prior experience in leprosy or to have participated in an appropriate formal course.

Programme	Qualifications required	Recommended duration
1. Clinical Leprosy	Medical Officers, Qualified Nurses, Medical Assistants	Minimum of 2 months
2. Clinical Leprosy and Leprosy Control	Medical Officers, Qualified Nurses, Medical Assistants	Minimum of 4 months
3. Septic Surgery and Amputation Surgery	Qualified General Surgeon, Surgical Residents, Medical Officers with good experience in surgery	3 months
4. Reconstructive Surgery	Qualified Plastic, Orthopaedic or General Surgeons, Surgical Residents, Medical Officers with good experience in Leprosy	Dependent on extent of training required and basic qualification 3 months
5. Physiotherapy	Physiotherapists, Occupational Therapists, Other Paramedical Health Personnel	4–6 months
6. Laboratory Techniques in Leprosy	Laboratory Technicians	1 month
	Laboratory Assistants	2 months
7. Dermato-histopathology techniques (in Armauer Hansen Research Institute)	Laboratory Technicians	3 months
8. Orthopaedic Workshop Techniques—making of protective footwear (Sandals, Plastazote)	—	6 months
9. Prosthetics	Orthopaedic Workshop Technicians	12 months

NB: A good command of English is essential in all courses.

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News and Notes

Retirement of Lepra's Fundraising and Publicity Director, Joy Maitland

Joy Maitland came to Lepra in 1973, the second person to be concerned with fundraising only. This post had been created in the late 1960s when prior to this fundraising had never been a major concern of charities in the post-war era, but the need was felt then by Lepra that such a person was needed.

Joy joined Lepra when a major expansion drive had been planned to coincide with its fiftieth anniversary in 1974. With these formidable events at the planning stage—The Royal Albert Hall had been booked for a fundraising event at which Lepra's Patron, HM The Queen, had consented to be present, but no one had been booked to lead the entertainment—Joy took over. Quite quickly the Albert Hall 'event' was changed to a Lord Mayor's dinner on the lines of the inaugural lunch which launched Lepra (then Belra) in 1924. However the 3-day week and its sequelae put paid to this and resulted in substantial donations to offset the disappointment for the Charity cancelling its celebrations.

Joy Maitland had good previous experience for the many faceted work she would become responsible for on joining Lepra. She had worked in hotels in Canada in her very early years, as a journalist, with films, and more recently with a large UK medical charity as part of the fundraising/publicity team and more recently still as the Gill-of-all-trades in a very small but important charity which regrettably demised shortly after Joy left it.

Within a year of joining Lepra, not only was Joy head hunted by a much bigger charity, but Lepra decided to move its headquarters out of London. Joy put up a strong case for the need of a growing charity of international fame to have a London address and this was accepted.

The expertise demonstrated by Joy, together with her enthusiasm for fundraising enabled her to take control of her inherited team of paid and voluntary staff stationed throughout the UK who had only recently been provided with a handbook to guide them. Previously it had been left to the individual to pursue whichever line of fundraising appealed to them most. Targets were set, training courses arranged, and a degree of professionalism gradually developed throughout the Lepra UK team.

Since this was the third medical charity that Joy had worked with she not only had a wide knowledge of the charity fundraising field, but also many friends in it. On the grounds that a person who give to one charity is likely to give to another, if given the opportunity, Joy soon arranged to swap mailing lists with other charities, thus enlarging the number of subscribers on whom Lepra relies. If people responded to one appeal a year, why not to two, or three or more. By careful pilot studies and monitoring results a successful mail appeal section was built up.

Although Joy enjoys fundraising, she will only do it if she has full confidence in the use to which the funds are to be put. Apart from attending meetings of the Medical Advisory Board Joy visited Lepra's work overseas and was introduced to the hardships of working in Sierra Leone before going to Malawi and India.

There are times when circumstances rightly influence an organization's structure. Lepra, in the 1970–80s, was a charity with its administrative headquarters in Colchester, its fundraising and publicity headquarters in London, with staff dotted around the country in 14 different offices, whilst its leprosy work was mainly in Malawi, India and Oxford. As a result, and since Joy had

demonstrated her ability, she was made a Director in 1974 and became responsible to the Executive Committee for the publicity and fundraising of Lepra. Although shared responsibility of this nature is usually frowned upon, the structure worked for Lepra with the two Directors working very closely together, but with clear divisions of responsibility.

This shared responsibility lead to, amongst other things Joy becoming closely involved with ILEP and its affairs. Most of those attending ILEP meetings were responsible for, and mainly interested in, the spending rather than the raising of money. Joy was able not only to introduce joint fundraising efforts, e.g. a fundraising film, and a universally accepted poster for World Leprosy Day 1989, but ensured that the status of fundraisers was improved by arranging meetings of the ILEP Publicity Committee, which she chaired for many years, to coincide with ILEP meetings. It was due to Joy that Lepra was invited to take on the Presidency of ILEP for 1984–86.

The status and ethics of fundraising have been of major interest to Joy during her career in the charity field. Not only has she encouraged training at all levels, but she has worked hard to gain acceptance of standards of advertizing and standardization of information distributed by charities in their literature—to achieve an agreed figure for the estimated number of leprosy patients in the world caused her much work.

In the UK Joy has been concerned with the ethics of fundraising on a wider basis. She was instrumental in setting up the ICFM, the Institute of Charity Fundraising Managers, a body which laid down standards and guidelines for charity fundraisers and which she chaired for many years.

For readers of *Leprosy Review* however Joy's achievements will be judged mainly on the amount of money she raised to be used in the fight against leprosy. The figures speak for themselves. In 1973 Lepra's income was £394,000. In 1989 it is estimated to be £2,607,000.

Well done Joy, and thank you. Happy retirement.

Francis Harris, *retired Director of Lepra*

Vaccine trials in India

The following is extracted from *Nature*, **340,** Number 6233, 1989:

After nearly four years of vacillation, the Indian government has agreed to launch a human trial of the anti-leprosy vaccine developed by the World Health Organization (WHO). India will be the third country, following Malaŵi and Venezuela, to test the vaccine.

The WHO vaccine, a combination of live BCG and heat-killed *Mycobacterium leprae* derived from armadillo, has been cleared by the drug controller and according to Dr A S Paintal, director general of the Indian Council of Medical Research (ICMR), the trial, to be funded by ICMR, will start in January 1990.

The decision, reached at an ICMR expert committee meeting early in July, brings to an end a long controversy that began at the time WHO proposed an Indian trial of the vaccine in 1985 (see *Nature*, 1985; **317:** 665). Although ICMR was keen, the proposal was voted down by a section of leprologists who claimed that a cheap, effective and safe indigenous vaccine was available and that there was no need to test the WHO vaccine (see *Nature*, 1987; **328:** 660).

Since then, two more candidate vaccines have emerged from Indian laboratories, prolonging the debate between those who favoured the WHO vaccine and those who favoured home-developed vaccines.

The plan is to use the BCG–*M. leprae* vaccine in phase-two trials on a few thousand healthy people to determine if there are any adverse effects. The trial will last 4 months. After that, the vaccine will be evaluated, along with two (or possibly three) Indian vaccines, in a single 'comparative' trial involving several thousand subjects at one location in south India. The vaccine that gives the best results, whether Indian or foreign, will be recommended for India's leprosy control programme.

Dr Paintal says the trial will be designed and conducted by a committee of experts chosen by ICMR. WHO will simply supply the vaccine and provide one scientist to sit on the monitoring committee. This arrangement constitutes a major change from earlier vaccine trials where WHO

assumed total control while Indian participation was limited to provision of infrastructural facilities and manpower.

The two Indian competitors in the race are the ICRC vaccine developed at the Cancer Research Institute (CRI) in Bombay and the vaccine developed at the National Institute of Immunology (NII) in New Delhi from a soil mycobacterium. A third Indian vaccine developed at the Central Drug Research Institute in Lucknow (from *Mycobacterium habana*) may also be included in the study.

Leprosy vaccines

The following is extracted from '*Tropical Diseases; Progress in International Research, 1987–1988*, UNDP/World Bank/WHO, Special Programme for Research and Training in Tropical Diseases (TDR), 1989:

M. leprae shows about 40% DNA sequence homology with *M. tuberculosis*, and the two organisms have much in common, including sensitivity to particular drugs and their ability to modulate the host immune response. The mycobacterial cell wall has been shown to act as a powerful adjuvant, potentiating immune responses to a variety of antigens. Both species can stimulate an intense delayed-type hypersensitivity in the host (a reaction that forms the basis for the tuberculin and soluble *M. leprae* antigen skin tests) and in the case of *M. leprae* infections, progression to severe disease is due largely to an inability of the host to mount this cell-mediated immune response.

There are thus two approaches to the use of leprosy vaccines: immunoprophylaxis, which seeks to prime the immune system to prevent the establishment of an infection; and immunotherapy, which seeks to boost suboptimal cell-mediated responses in order to prevent the development of severe forms of the disease. In addition, better understanding of the immune responses to *M. leprae* should help in identifying the patients who are most at risk of developing severe disease.

Vaccines for *immunoprophylaxis* currently undergoing field evaluation with TDR support are based on heat-killed *M. leprae* derived from armadillos. Two long-term trials are in progress. The one in Venezuela,[10] of which the intake phase has been completed, now includes more than 29,000 household and other contacts of known leprosy patients. In the other trial, in Malawi,[11] which will eventually involve 120,000 persons and cover an entire leprosy-endemic district, 95,000 persons have been enrolled to date. Both trials began in 1984–85, after preliminary sensitization studies on smaller numbers of individuals, using the killed *M. leprae* vaccine with or without BCG. No serious vaccination side-effects have been reported, although problems have been encountered with batch-to-batch variability of the soluble antigens used for skin-testing. Because of the long incubation period of leprosy, the trials are expected to last for 7–10 years, with periodic examination of subjects for the development of leprosy.

In India, two non-TDR-funded trials of leprosy vaccines, based on cultivable atypical mycobacteria have also been initiated.

Immunotherapy trials are continuing in China, France and the Philippines. These trials are comparing the heat-killed *M. leprae* vaccine and BCG, either alone or in combination, administered to lepromatous leprosy patients who show a negative skin-test (indicating impaired cell-mediated immunity). The aim is to determine the acceptability of repeated vaccination, and to determine how effectively the different vaccines enhance the immune response and lead to conversion to a positive skin test.

Research to develop synthetic vaccines based on specific antigens or antigenic subunits has been aided by the further characterization of proteins defined by genes isolated from material in the WHO *M. leprae* and *M. tuberculosis* recombinant DNA expression libraries (gene banks). The amino acid sequences of four proteins of different relative molecular mass (M_r)—18,000, 32,000,

65,000 and 70,000—have now been deduced from the DNA sequence, and this will help in elucidating all the T-cell-stimulating determinants (epitopes) present in them. Human *M. leprae*-specific T-cell clones have also been established that recognize unique recombinant proteins that are coded by genes in the *M. leprae* gene bank but not recognized by existing antibodies. At least three *M. leprae* proteins have been shown to have a striking DNA sequence homology with known stress or heat-shock proteins (HSP).[12] Research is proceeding into the significance of this finding. Heat-shock proteins are ubiquitous, being found in animals, bacteria, parasites and plants, and appear to play a complex role in the interactions between host and pathogens.

The recombinant mycobacterial analogue of the 64K (M_r 64,000) heat-shock protein from BCG is now in production in gram amounts for distribution by TDR to provide reference material for the identification of epitopes that might be included in candidate mycobacterial vaccines.

By using a shuttle plasmid, it has been possible to introduce foreign DNA into cultivable mycobacteria—in this case, the substitution into *M. smegmatis* of a marker gene coding for antibiotic resistance.[13] This represents the first step in the development of engineered cultivable mycobacteria, such as BCG, as vaccine vehicles to express protective antigens for *M. leprae*, *M. tuberculosis* and a variety of additional pathogens.

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Leprosy in children

The following is extracted from *Tropical Diseases; Progress in International Research, 1987–1988.* UNDP/World Bank/WHO. Special Programme for Research and Training in Tropical Diseases (TDR), 1989:

Children and tropical diseases; leprosy

- Because leprosy develops slowly and most of the advanced and easily recognized cases are seen among adults, leprosy in children tends to be an unrecognized problem. In leprosy endemic areas, however, the disease is by no means infrequent among children, with prevalence rates as high as among adults in some places. In one highly endemic area in South India, the prevalence rate among children under 15 was found to be as high as 32·5 per 1000.[21]
- Being rare among infants below 1 year of age, leprosy was long considered not to be transmitted congenitally, but recent indirect evidence indicates that congenital transmission resulting from placental crossing of *M. leprae* or its antigens can take place. In a study in an Ethiopian leprosy hospital, *M. leprae*-specific IgA and IgM antibodies were detected in the cord blood of 30–50% of babies born to lepromatous mothers,[22] and 2 infants with rising IgA and IgM antibodies developed clinical leprosy at 9 and 17 months of age.[23] The youngest age at which leprosy has been recorded is $2\frac{1}{2}$ months.[24]
- The occurrence of leprosy among children is a sensitive yardstick for gauging the status of the disease in a country or commmunity. For instance, a WHO Study Group identified the proportion of children 0–14 years old among all newly detected cases as an important operational and epidemiological indicator for leprosy control.[25] Application of this indicator in a recent study in 12 Latin American and Caribbean countries showed proportions varying from 8·9% in Brazil to 41·7% in Guyana.[26] The leprosy prevalence rate among children is also sometimes used for its predictive value to estimate total prevalence.[27]

- Fortunately, the preponderance of benign tuberculoid forms of leprosy in children usually permits fairly rapid treatment with relatively few sequelae. Children, moreover, are more readily accessible to leprosy control services than are adults, and school surveys provide good opportunities both for early case-detection and for health education.

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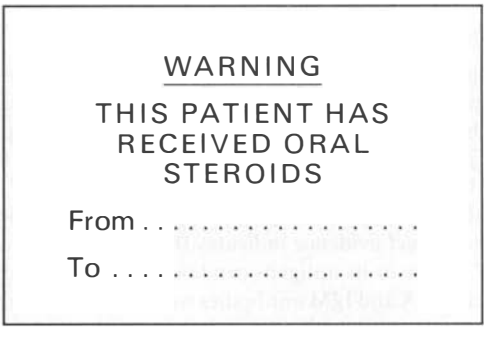
Oral steroids—card-carrying patients!

The Reverend L A Wiseman of the Leprosy Mission (Southern Africa), PO Box 890527, Lyndhurst JHB 2106, South Africa has supplied the following information on an idea developed by the Mission:

'One of the areas of concern to us is that of reaction in leprosy. Generally we find that the recommended doses of oral steroids are effective. Our concern is in the danger which patients face while they are on steroids should they meet with an accident or should they require surgery.

In order to obviate any problems The Leprosy Mission has prepared a label (see below) which states that the patient is receiving oral steroids. One label is placed on the card which the patient should carry on his/her person, one goes on his file at the local clinic, and also one on the patient's file at the nearest general hospital. In this way we hope to continue preventing other complications. Thus far we have found the system to be effective and believe that because of this red label, we have had no major problems.'



Polystyrene chips act as dummy patients for slit-skin smears

We are grateful to June Nash of The Leprosy Mission, PO Box 447, Madang, Papua New Guinea for the following suggestion for use of polystyrene chips such as are used as standard packing for drugs. They have found these chips very useful in the teaching of slit-skin smears. Each student is given a chip and asked to practise the squeezing, slitting and scraping technique on the polystyrene chips before they get to a patient. We have found that they are a very good representation of a human slit-skin smear, and that students, not to mention the patients, are much happier if they have practised before doing the actual thing!

Multi-centre field trial for ofloxacin use in leprosy—call for participants

The Scientific Working Group on the Chemotherapy of Leprosy (THELEP) is planning a multi-centre field trial to evaluate a multidrug regimen which would include ofloxacin, a fluoroquinolone with demonstrable activity against *Mycobacterium leprae*. Requirements for centre participation include:

(1) a well-organized out-patient treatment facility capable of receiving at least 100 new, untreated, or minimally treated (up to six months with dapsone therapy), multibacillary patients per year; (2) ability to follow up the patients regularly through a field organization; and (3) facilities to carry out routine biochemical and other tests to monitor for toxicity.

Qualified Centres interested in participating in this trial should send a letter of intent, providing information on their qualifications and facilities to: Dr S K Noordeen, Chief Medical Officer, Leprosy Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

Sasakawa Research Building, Bangkok, Thailand

On 2 October 1989 this building was formally handed over to the Ministry of Public Health in Thailand. Representatives from Japan included Professor Ishidate and Dr Yo Yuasa of the Sasakawa Memorial Health Foundation. It is adjacent to the present offices of the Leprosy Division in Bangkok and consists of a two-storey building with superb research facilities, including a large unit for the housing of mice under germ-free conditions. It is intended primarily for leprosy research but may develop work on other diseases in the future. Financial support will continue from the Sasakawa Memorial Health Foundation for the first 4 years of operation, thereafter reducing towards final support by the Ministry of Public Health after a further period of 4 years. Leprosy research activities, including a large nude mouse colony (see *Lepr Rev* (1983), **54,** 305–308 and (1988), **59,** 25–30) are in the process of transfer from the Raj Pracha Samasai Institute in Phra-Praedaeng to this Institute. Further enquiries: The Director, Sasakawa Research Building (Raj Pracha Samasai Institute), Dhivanond Road, Nonthaburi Province, Thailand.

Leprosy control in Thailand

In 1953 it was estimated by WHO that Thailand had 140,000 cases. In 1956, a new approach to leprosy control in Thailand was introduced at Khon Kaen Province of North-Eastern Region with assistance from WHO and UNICEF. The control programme was gradually expanded to cover all 72 provinces in 1976. Following the national policy, partial integration of leprosy control into provincial health services was undertaken in 66 provinces from 1971 to 1976. Two hundred and sixteen groups of 8634 health workers were trained for 3 days prior to integration.

By the end of 1982, it was reported that 93,086 cases had been detected and treated, of which 49,796 had been released from control. At that time 43,290 cases were on the registers. Multiple drug therapy was started in 1984 and at the time of writing (October 1989) all 73 provinces in Thailand are covered. Currently about 20,000 cases are on MDT. About 6000 cases are released from chemotherapy each year and about 2000 new cases detected. The annual incidence of new cases was in fact beginning to decline before the start of MDT in 1984 and it has continued to decline, steadily and significantly, since then. Disability and child rates have also declined. There has been a progressive transition from vertical (specialized) services for leprosy to a horizontal, integrated approach and at present only 6 provinces maintain a vertical system. Further enquiries: Dr Surusak Sampattavanich, Leprosy Division, Ministry of Public Health, Bangkok, Thailand.

McKean Rehabilitation Centre, Thailand

McKean Rehabilitation Centre, a service unit of the Church of Christ in Thailand, provides rehabilitation treatment for patients suffering from various diseases and accidental injuries.

Founded in 1908 by a medical missionary, Dr James McKean, the island was established as the first treatment centre for leprosy patients in Thailand. Beginning with bamboo shelters and basic care for their symptoms, the facilities and treatments developed until 1950 when a specific antileprosy drug became available. Dapsone then became standard treatment for leprosy until 1983, when the use of multidrug therapy was instituted by the medical staff of McKean.

By 1970 the number of people, including patients, staff and their families living on the island, was over 1000. Rehabilitation and integration into society then became the primary focus of the treatment for leprosy. Outpatient clinics were opened in surrounding villages and in the city of Chiang Mai so that patients with leprosy could come for treatment without leaving their families and communities. Admissions to the hospital facilities were limited to patients with complications requiring specialized short-term care or surgery. As cooperation with expanding public health services improved, the village clinics were closed and the Ministry of Health officially recognized McKean as the leprosy referral centre for northern Thailand. As spaces became available patients were admitted with problems other than leprosy, who could benefit from corrective surgery, physiotherapy or prosthesis.

In 1988, there were approximately 400 residents on the island including hospitalized patients, staff and their families, and the 100 elderly and handicapped residents of the social welfare village. The average number of patients in the wards was 70, down from about twice that amount only 10 years ago. Because of this trend towards outpatient treatment and fewer admissions of patients with complications, plans have been made to expand the services to include extended rehabilitation therapy for a greater number of people. The construction of a new patient facility is proposed to house all patients in an integrated therapy setting with the double purpose of erasing the stigma against leprosy and providing a more effective therapy setting for a greater variety of patients.

Further enquiries: Dr Trevor Smith, McKean Rehabilitation Centre, PO Box 53, Chiang Mai 50000, Thailand.

Indo–UK Workshop on Leprosy Research

We are grateful to Dr H Srinivasan for supplying details of the Indo–UK Workshop on Leprosy Research held at the Central JALMA Institute for Leprosy, Agra, India. Some 50 scientists participated in the proceedings of this 3-day Workshop held in February 1989.

The Workshop was inaugurated by Professor T Ramakrishnan, Emeritus Professor, Indian Institute of Science, Bangalore. Dr H Srinivasan, Director, CJIL, Agra welcomed the delegates and explained the purpose of the Workshop as: 1, To bring together scientists from the UK and India interested in leprosy research and related areas; and 2, To identify topics of mutual interest for possible collaborative research projects under the extended Indo–UK collaboration programme.

Three themes relevant to the National Leprosy Eradication Programme of India had been selected for consideration at this Workshop. They were: 1, recognizing leprosy early; 2, recognizing nerve involvement/damage early; 3, assessing efficacy of chemotherapy. The participants were drawn from a variety of disciplines such as dermatology, experimental medicine, leprology, immunology, microbiology, biochemistry, molecular biology, surgery, neurology and neurophysiology.

Invited speakers informed the delegates of the current status of the various disciplines involving leprosy. The participants were then divided into three groups to discuss one of the Workshop themes, identify topics of mutual interest for possible collaborative research projects and any other recommendations. The resulting recommendations and topics are given in detail in a report, which is available from Dr H Srinivasan at the above address.

Symposium of Leprosy Research, October 1990

The VI Santa Margherita Ligure Meeting is organized by the Amici di Raoul Follereau Organization and will be held on 3–7 October 1990 in Genoa, Italy. The topics covered are: genetics

of leprosy; biochemistry of *M. leprae*; drug development for leprosy; culture of *M. leprae*; experimental animal models; identification methods of *M. leprae*; immunology; leprosy reactions; multiple drug therapy of leprosy; implementation of MDT; vaccination and immunotherapy; and health services research.

The objective of the symposium is to exchange, in the interim between two International Leprosy Congresses, recent information and views and to promote further research. The symposium is open to those who are already engaged in leprosy research as well as others engaged in other research projects relevant to leprosy research. Each topic will be introduced by a position paper to be presented by an invited speaker. This will be followed by presentations of original research by other participants and discussion.

A limited number of grants, covering the journey and accommodation expenses, are available for participants who have important contributions to give but are unable to meet the expenses. The grants will be awarded, by request, on the ground of the abstract presented.

For further details write to: R. Manservisi, Associazione Italiana, Amici de Raoul Follereau, Via Borselli 4, 40135 Bologna, Italy.

Third Congress on Hansenology of Endemic Countries, Alicante, May 1990

The subjects included in this Congress to be held on 29–31 May 1990 are: bacteriology, immunology, experimental leprosy, pathology, subclinical infections, epidemiology and control, therapeutic prophylaxis, rehabilitation and social aspects.

If you are interested in attending please write for further details to: Dr Jose Terencio de las Aguas, Director Medico, 03791 Fontilles, Alicante, Spain.

Impairment of cutaneous sensibility in psoriasis, morphoea and necrobiosis lipoidica

A recent paper, 'Quantitative evaluation of cutaneous thermal sensation in psoriasis, morphoea and vitiligo', Sanjay Ghosh and B. Haldar, published in the *Ind J Derm Venereol Leprol*, 1989; **55:** 30–32, draws attention to the findings of impaired cutaneous sensibility in some (not all) cases of psoriasis and morphoea. Thermal sensation was studied using a commercially available instrument consisting of a test probe, a temperature sensor and control unit, with readings on a digital meter. Significant differences in sensory thermal thresholds were demonstrated between the lesions and the lesion-free contralateral site in 83% of psoriasis patients and 71% of morphoea patients. No differences were noted in vitiligo. The brief discussion is of considerable interest and the reference list valuable. This paper could well be read in conjunction with that of R J Mann and R R M Harman: 'Cutaneous anaesthesia in necrobiosis lipoidica' in the *Brit J Derm* 1984; **110:** 323–5. Both publications include a discussion of neuropathological findings in the skin which might account for the clinical changes. These reports should not be interpreted as detracting from the importance of sensory impairment as a classic finding in the skin lesions of leprosy (in many cases), but they are a reminder that such impairment may occasionally occur in other conditions.

Writing proposals for research grant applications

The following, written by Dr David Payne, of TDR and the Malaria Action Campaign, WHO, Geneva, is extracted from *TDR News*, Number 29, 1989 and gives those applying for research grants an idea of what information their application should contain.

1 *Why is the study necessary?*

The first step in approaching a new project idea is to ask oneself 'Why?'. Would the information gained from this study advance scientific knowledge and would this knowledge be important in the current research priorities on this subject.

It is often useful to turn the whole question around and ask oneself, 'If I were the person reviewing this proposal, what would I need to know about it to be reasonably sure it would produce worthwhile results?' Most reviewers would need to know the answers to the next four questions.

2 *What is to be measured?*
We need to be absolutely clear in our minds what has to be measured and how precisely; in a complex study many parameters may need to be determined.

For example, if we are measuring parasite rates, do we need prevalence or incidence, or both? To measure one without the other may not provide all the information we need. So whilst repeated 6-monthly point prevalence surveys of a random selection of the population could meet the needs of prevalence, incidence may require a monthly, longitudinal, house-to-house survey to cover all newborns and children up to 12 months of age. Obviously the resources required for the two options are vastly different.

3 *Can it be measured?*
It is one thing for something to be measured in theory, but quite another to ensure it can be meaningfully measured in fact.

For example, we can measure rainfall in a particular area very accurately with a whole range of rain gauges, but this will not tell us whether this is within the normal monthly range for this particular area. To do this we would need to have data for comparative periods in the past using the same, or an equivalent, collection technique. If these data were not available we would have to consider making our own longitudinal study and this could have serious implications in terms of project duration and cost.

4 *What sample size is required?*
One of the prime conditions to be met in any research study is to ensure that the experiments we conduct and the data we collate provide sufficient information to permit analysis with an acceptable degree of statistical confidence. The decision as to what is an adequate sample size varies depending on the aims of the study, but will require at least a reasonable guess as to what results are required and how precise these results should be. Of course we must also consider possible operational and demographical limitations which might complicate achieving the minimum sample size.

In addition to many technical publications dealing with the subject, the World Health Organization has available an up-to-date publication titled 'Sample Size Determination—A User's Manual'. The WHO publication reference number is WHO/HST/ESM/86/1.

5 *For how long should it be measured?*
The duration of the project should be sufficient to ensure that all the required data are collected, collated, and analysed. Remember, processing and writing up the data as the study progresses greatly facilitates the preparation of required periodic reports. Moreover this will help you to spot any deficiency in the protocol so that you can take appropriate remedial action. It is also important to allow time for the necessary preparatory work for the study itself and for analysis of results and writing up the study. Realistic work schedules should be calculated and established for each activity with allowances for unforeseen delays and operational difficulties.

Undoubtedly the path of the would-be researcher is not an easy one, with the spectre of rejection always hovering, but with careful thought, preparation and presentation, you *can* prepare a successful proposal.

Poona District Leprosy Committee, Annual report 1987–88

We are grateful to Dr Jal Mehta, Honorary President of Poona District Leprosy Committee, 35 Manisha, 2/A Moledina Road, Pune 411 001, Maharashtra, India, for supplying the Project's annual report.

It contains an outline of each department's work and unusually quotes from visitors on their impressions of the Project. Visitors were obviously inspired by what they saw and their comments must be an encouragement to the workers of Poona.

Copies are available from the above address.

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Professor J. L. Turk, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

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