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Leprosy Review

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

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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

PRIMUM NON NOCERE,[1] THE ETHICS OF TRIALS OF LEPROSY CHEMOTHERAPY

It has always been my view that the demand that the physician does no harm applies to the chemotherapy of leprosy as to every other area. This communication has been stimulated by two recent events. In response to a paper[2] describing a trial of combined chemotherapy, in which one of the regimens included pyrazinamide, a drug previously shown[3] to be without effect against *Mycobacterium leprae*-infection of mice, I discussed,[4] 'the *injunction* [emphasis added] against the use in patients of drugs not already shown effective in mice . . .'. My discussion elicited a response,[5] in which the writer, who had not been involved in the original paper, objected strongly to my use of the word 'injunction'. After permitting me to defend my choice of words,[6] the editor declared the issue closed.

The second event that moved me to produce this communication was my participation in a recent international meeting, at which mention was made of two ongoing clinical trials: one in which an inhibitor of dihydrofolate reductase, which had previously been shown to be ineffective in *M. leprae*-infected mice, was administered both alone and in combination with dapsone or dapsone + rifampicin; and the second involving rifampicin and isoniazid, a drug previously shown[3] to be ineffective in mice, together with a commercially available combination of a long-acting sulphonamide with a dihydrofolate reductase inhibitor. The ethics of these trials were not discussed.

According to my understanding, developed when serving on several committees concerned with the ethical aspects of clinical research, the ethics of experimental chemotherapy in man revolve about two primary considerations: the freely given and informed consent of the subjects; and a judgement with respect to the relative weights of potential risks to the subjects participating in the study, and potential benefits to the individual and to society. Although the requirement to obtain the subject's informed consent has been dealt wtih extensively elsewhere,[7] much remains to be said with respect to the issue of risk *vs* benefit.

Administration of any drug imposes risks of toxicity and other side-effects, known or unexpected. Of this, everyone is aware, and all acceptable clinical trial protocols contain provisions for periodic interviews, clinical examinations, and laboratory procedures that are intended to obtain evidence of any undesirable effects of the drug before these have become clinically apparent. Perhaps a less obvious risk is that inherent in withholding established treatment. Once the efficacy of dapsone in the chemotherapy of leprosy, or of isoniazid in the chemotherapy of tuberculosis, had become established, it was no longer ethical to include in clinical trials groups of subjects to whom only placebos were administered. Similarly, because of the striking efficacy of rifampicin, the THELEP

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Scientific Working Group recognized that it would be unethical, in the trials of combined chemotherapy then being planned,[8] to include a control regimen of dapsone monotherapy.

Obviously, risks are relative, and must be carefully weighed against the benefits expected. The patient with leprosy may certainly expect to benefit from participating in a clinical trial, and, therefore, may ethically be exposed to the risks inherent in the trial of any new drug, including that resulting from the withholding of drugs of proven efficacy, should this be required. At the same time, it is incumbent upon those responsible for the trial both to minimize these risks and to maximize expected benefits. These requirements require elaboration.

The risks of exposure to a new drug and the withholding of established treatment may be reduced by minimizing the numbers of patients involved in the trial, the duration of the exposure to the new drug, and the period during which the proven drugs are to be withheld. To measure the efficacy of a new bactericidal drug, it may be deemed necessary to administer it as monotherapy to patients with previously untreated multibacillary leprosy. In such a case, the risks to patients may be minimized by recruiting the minimal number of patients—approximately 10—required to yield a reasonably precise measure of the rate at which *M. leprae* are initially killed, and by minimizing the duration of the monotherapy. If, for example, the drug is expected to exhibit bactericidal activity similar to that of rifampicin, it need be administered for no longer than 1 month, measuring the proportion of viable organisms within several days of the first dose, and at weekly intervals thereafter.

To place patients at risk in a clinical trial so inappropriately designed that no possible benefit can result is clearly unethical; unavoidable risks must be balanced by certain benefit. Yet, it is debatable how often the capability of a given trial-design to yield meaningful results is considered as a component of the benefit to be expected. Take, as an example, a field trial of a new regimen, in which the endpoint is to be relapse or failure to relapse. In designing the THELEP field trials at Karigiri and Polambakkam, the numbers of patients to be recruited were determined only after decisions had been taken with respect to the rate of relapse expected and the degree of precision desired. It became clear that a minimum of 400 patients was required per regimen, if we wished to be able to distinguish between relapse rates of 1% and 2% per year, with an *alpha* error of 0·05 and a *beta* error of 0·20. Clearly, to have allocated fewer patients per regimen, in order to test more regimens among a limited number of patients, might have resulted in an inconclusive trial, i.e, the patients would have been placed at risk without the possibility of benefit.

A similar case was that of the disposition of the patients who had been recruited into the THELEP controlled clinical trials at Bamako and Chingleput, once the 2 years of treatment had been completed.[8] At that time, there was considerable interest in observing these patients during an additional period without treatment. Regretfully, however, the Steering Committee decided that, on ethical grounds, it could not support such an additional study. Although it felt that it might be acceptable to follow, without additional treatment, those patients who had been treated by 1 of the 2 'maximal' regimens—rifampicin + dapsone + clofazimine or prothionamide administered daily for 2 years, the same could not be held to be true for those patients who had been treated by the 'minimal' regimen—a single large initial dose of rifampicin followed by daily dapsone for 2 years. Even more important, however, was the recognition that, because the endpoint was to be relapse, the numbers of patients involved (215 patients distributed among 6 regimens)

were so small that the follow-up study was unlikely to yield information of any value. Thus, no benefit could be expected that would justify the expected risk, particularly to those patients who had not been treated by a maximal regimen.

The injunction against the use in man of drugs not already shown to be effective against *M. leprae* in mice should be understood in this context. More than once in the recent past, considerable effort has been invested to justify clinical trial of a drug that was shown not to be effective against *M. leprae* in mice. The arguments advanced in favour of trying the drug, despite the lack of activity in *M. leprae*-infected mice, have included the compelling need for new drugs, and the logic of employing a drug with a given mechanism of action.

Whenever a new antimicrobial is to be tried, especially if it is to be administered alone, not only must the toxic potential of the drug be considered, but also the possibility that the drug will prove not to be effective, at the same time that established therapy is withheld. That a drug will prove not to be effective in the chemotherapy of leprosy appears particularly likely in those cases in which the drug has been demonstrated to be without effect against *M. leprae* in the mouse.

That the drug was shown to be inactive in mice has been attributed to shortcomings of the *M. leprae*-infected mouse as a test system. That the mouse footpad system possesses shortcomings is without question. However, these may not simply be assumed, but must be demonstrated in the case of a drug which ought logically to be active against *M. leprae*, but is found inactive. In any event, for the reasons noted above, and in the absence of a widely accepted substitute for the *M. leprae*-infected mouse, proceeding to clinical trial in the absence of evidence that a drug is active in the mouse cannot be considered ethical. The interested investigator could better, and more ethically, employ his skills in the search for an explanation of the unexpected failure of a drug to be active. In fact, such a search may itself yield important information.

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References

[1] Veatch RM. *Case studies in medical ethics*. Harvard University Press, Cambridge, Mass., 1977, 8.
[2] Katoch K, Sreevatsa, Ramanathan U, Ramu G. Pyrazinamide as a part of combination therapy for BL and LL patients—a preliminary report. *Int J Lepr*, 1988; **56:** 1–9.
[3] Shepard CC, Chang YT. Activity of antituberculosis drugs against *Mycobacterium leprae*. *Int J Lepr*, 1964; **32:** 260–71.
[4] Levy L. Letter to the Editor. *Int J Lepr*, 1988; **56:** 621–2.
[5] Chatterjee BR. Letter to the Editor. *Ind J Lepr*, 1989; **61:** 518.
[6] Levy L. Letter to the Editor. *Ind J Lepr*, 1990; **62:** 404–5.
[7] Beecher HK. *Research and the individual*. Boston: Little Brown, 1970.
[8] Subcommittee on clinical trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. THELEP controlled clinical trials in lepromatous leprosy. *Lepr Rev*, 1983; **54:** 167–76.

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Editorial

MANAGEMENT OF PLANTAR ULCERS—THEORY OR PRACTICE?

Introduction

Nerve damage and its complications are the major causes of stigma in leprosy, caused by reaction against *Mycobacterium leprae* in the nerves.[1–3] Solid staining bacilli can be found in trunk nerves long after completed leprosy treatment.[4] Reactions cause reversible or irreversible, partial or total nerve damage.[3,5]

Damage in trunk nerves of the extremities causes impairment of sensory, motor and sudomotor function of the hands and feet. Loss of sensation deprives the extremities of protection against injuries, causing ulcers and septic conditions that lead to deterioration of the limbs, and result in severe physical and social disability.[1,3]

Neuritis and its consequences are preventable but, in spite of this, leprosy patients are still suffering from ulcers. There are programmes where 50% or more of all new patients are reporting with a WHO disability grade of 1 or more.[6–8]

Ulcers and ulcer care constitute a large problem in the management of leprosy. In leprosy hospitals the majority of beds in surgical units are occupied by ulcer cases. Beds utilized for preventive surgery are comparatively few.

During the courses in ulcer management at ALERT (All Africa Leprosy and Rehabilitation Training Centre), we teach that if we know why, how and when ulcers are formed, how ulcers heal and what prevents some ulcers from healing, we can know how to prevent and treat them.

The prevalence of ulcers in leprosy programmes evokes some questions:

Do the workers in leprosy management have enough knowledge about the pathomechanisms of ulcer formation to prevent and treat ulcers?
2 Has recent research contributed essential knowledge to our understanding of prevention and treatment?
3 Are present treatment programmes adequate?

Why are ulcers formed?

It is well understood that loss of sensation of a sole of the foot allows various types of trauma to attack the foot unnoticed.[1]

Sensory testing helps leprosy workers to identify cases at risk of suffering ulcers.[9–11]

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Such tests have to be performed in the field, where the patients are. Consequently they have to be simple and repeatable.

Threshold values for light touch are measured with nylon filaments calibrated to bend at specific weights.[12] Patients not responding to a 10-g filament are more likely to get ulcers.[13,14] Some normal feet are not able to feel the 10-g filament, especially in the heel area.[15]

The qualities of sensations that are needed to protect a foot from injuries are not fully understood. Vibration perception threshold studies, using fixed frequency and varying amplitudes, have shown that patients with disintegration of the tarsal bones have more severe impairment of vibration sense in affected feet than in the contralateral unaffected feet.[14,16] In some ongoing studies of the restoration of plantar sensation, patients are reporting returning sensation as an awareness of the ground they are stepping on, qualities of sensation for which it seems to be difficult to design a simple and repeatable assessment.[17,18]

How are ulcers formed?

Mechanical factors cause ulcers on hands and feet. In the absence of a protective sensation patients injure themselves. A range of mechanical forces from approximately 50 g/cm^2, closing the capillaries and causing ischaemic ulcers, to above 80 kg/cm^2, causing penetration of the skin, is in action.[1]

The most common force is the repetitive moderate stress caused by normal walking, which ranges from 2 to 5 kg/cm^2. Occasionally, the mechanical stress may reach peak pressures above 5 kg/cm^2, especially when feet are unprotected and deformed. During normal walking a foot experiences about 725 impacts per km.[19] A person who has sensation will immediately react with discomfort and pain on overload and alter his/her pattern of walking or take a rest. If that person or people around him are unaware of and do not look for physical signs of overload, damage may happen unnoticed. Consequently, awareness and physical examination *must* compensate for loss of sensation. It seems difficult to create this understanding and make a patient practice what he should have learnt.[8,20]

Penetrating objects and burns are examples of direct trauma.[1] Classical examples are stones in a shoe or penetrating thorns. Exposure to low heat over a long time can cause severe burns. Walking barefoot on hot stones or riding in a lorry, with the feet on top of the gear box, are typical causes. Blisters, the size of the whole sole, may be the result.

Ischemic ulcers are mainly caused by tight shoes, shoestraps or bandages.[1] All that is needed to cause damage is very low pressure over a long time. New footwear and wrongly applied bandages and splints are typical causes.

Leprosy patients may not feel pain when they step on infected ulcers.[1] Infection is spread to deeper tissues causing the involvement of bones, joints and tendon sheaths, loss of tissue and mobility.

Where are ulcers formed?

The distribution of ulcers depends on mechanical factors.[1,21] A leprosy worker

understanding this will be able to identify risk factors and give proper advice to patients at risk.

Fortunately three out of four ulcers occur on the forefoot. Ulcers on the lateral part of the sole and under the fifth metatarsal base and on the heel have a high risk of severe complications.

Several methods are available that evaluate the pressure points under the sole, but only the Harris mat is usable under field conditions.[22] The rubber mat, with ridges of different heights, gives a footprint on a piece of paper, where higher pressure is registered as a deeper colour. The Harris mat can be applied on top of differing walking surfaces and be cut to fit the inside of shoes. The equipment, consisting of the mat, a rubber roller, stamp, ink and some paper for printing, is easy to carry in the field.

Dynamic and static foot pressure has been studied in insensitive, neuropathic feet, using pressure transducers, barographic images, and image-processing systems which are sometimes microprocessor-controlled.[23–30] Some authors[27] claim that the measurement of vibration perception threshold alone (considered a bedside method) may be useful in identifying patients who are at risk of suffering from ulcers. Foot pressure studies are used to determine the specific areas that are at risk of developing ulcers. Unfortunately these methods are not usable in the field.

Modern computerized methods that produce graphic displays of position and magnitude of pressure under the sole as well as the position in and proportion of the stance phase are now available. They increase our understanding of dynamic forces during walking. Some authors claim that such investigations provide information about structural changes, e.g. in the metatarsal heads or tarsal bones, and can be helpful in guiding orthopaedic surgeons to suitable early corrective action.[23,24] Peak pressure studies give valuable information in the design of protective footwear.[24,25,28]

Studies that give us a deeper understanding of the dynamic forces causing tarsal disintegration and allow us to identify risk factors or very early signs of deterioration are welcome.[16,30] Our present experience is that once the process of deterioration has started it is difficult to stop. Tarsal disintegration condemns a leprosy patient to wear special footwear for life. Such patients often have to have amputations.[62]

How do ulcers heal?

Tissue damage heals by scar formation. Primary healing leaves a minimum of scar. Secondary healing leaves a bulky and hard fibrotic lump of a scar. Tissue from the sole of the foot, the palm of the hand, the pulp of the fingers and toes is unique and difficult to replace. Loss of tissue in the heel is serious. The forefoot has some wider margin for tissue loss. Tissue loss must be kept to a minimum.[1,21,31–33]

Factors preventing healing are infection, sequestra, insufficient immobilization, poor circulation, tension in tissues due to atrophy and scars, and foreign bodies. Such factors also influence the quality of scar. To our knowledge, the healing ability in leprosy patients is not impaired.[33] Can healing be accelerated? Electrostimulation has been tried for many years. Studies indicate that high voltage stimulation and low intensity direct current stimulation of decubitus ulcers does accelerate healing.[34,35]

Many 'healing agents' have been suggested, but it causes confusion among leprosy workers to claim superiority of a specific agent and deflects them from the essentials in

ulcer care—i.e. keeping ulcers clean and immobilizing the ulcerated feet. One author[33] emphasizes that special topical agents add nothing essential to ulcer care. Ulcers usually fail to heal for lack of attention, not for lack of a specific topical agent.

Antibiotics are overused. Many of the strains found in ulcers are resistant to our common antibiotics.[36–39] Widespread and indiscriminate use of antibiotics only adds to the number of resistant strains and very little to the treatment. Very few cases really need antibiotics. Antibiotics are necessary only in cases who show general signs of a septic condition. Antibiotics should never be a substitute for surgery or general basic care.

The majority of patients with plantar ulcers are not hospitalized but in their own homes. Consequently the time and money currently being spent on developing more or less fancy remedies should be spent on developing and teaching home care.[8–10]

How can ulcers be prevented?

Prevention of ulcers begins with early case detection, a team work that involves everyone from the leprosy control manager to the health worker, the physiotherapist and the surgeon.

A formula that emphasizes that the prevention of disability is a concern and responsibility of every health worker could look like this:

$$LM = LC + POD + PRS$$

(LM = Leprosy Management, LC = Leprosy Control, POD = Prevention Of Disability, PRS = Preventive and Rehabilitative Surgery).

1 Leprosy management is incomplete without disability prevention.[40]
2 Prevention of disability must not only be a concern of the physiotherapy, occupational therapy, orthopaedic workshop and health education staff in their own clinics. It must also be an integral part of leprosy management.[8,9]
3 It must be emphasized that surgery should be used not only to salvage definite disasters but also to prevent disability.[3]
4 To achieve this, leprosy control staff, POD staff and surgeons must all work together.

What a surgeon finally discovers in his operating theatre depends on the efficiency of disability prevention, treatment and case selection in the field. The surgeon should:

1 participate in training,
2 pay visits to the field to establish and develop routines for patient selection,
3 develop surgical treatment in the field, and
4 integrate basic surgical activities into peripheral hospitals and clinics.

The leprosy surgeon is an underutilized resource in leprosy management. This may be the fault of the surgeon. The demands in the operating theatre may deflect the surgeon into problem-solving too late. Problems start in the field where the patients are, but surgeons tend to be involved only when problems are large and irreversible, i.e. patients who have major septic conditons or major disabilities in need of extensive surgical intervention.

Early nerve lesions are reversible, but it must be admitted that we still have not

mastered the treatment of neuritis in spite of years of research.[62] Patients deteriorate during and after neuritis treatment. Many leprosy surgeons believe that nerve decompression, mainly of the ulnar and posterior tibial nerves, combined with corticosteroid treatment, helps in minimizing nerve damage.[42–45] The timing of surgery is important, and the surgeon is often brought in too late. Great responsibility rests on field staff in identifying and selecting cases early enough. Well-trained field staff and well-developed policies for the treatment of neuritis are essential for success. Neuritis is best treated by a team.

There has been no miracle remedy discovered that keeps dry skin moist or removes excess dry skin other than soaking in water, oiling and rubbing with a stone (pumice, ceramics or any stone cut to obtain a flat surface).[46] Most dry and cracked feet will become soft and smooth after 1 week of daily treatment.

Insensitive feet must be protected with footwear with a soft insole that evenly distributes pressure and a hard undersole that protects against any penetration of sharp objects. Different types of rocking devices are also essential to further neutralize pressure points. Moulds are a necessary but controversial aid, because ill-fitting moulds do more harm than good.[1,47]

Patient acceptability of protective footwear is a problem in many programmes, because most leprosy shoes look different from ordinary footwear. Since this creates a new stigma they are often not accepted, but few acceptable alternatives are available.[47–49]

One publication does describe a plastic sandal which can be mass produced at a low cost,[48] which seems to be well accepted by the population. It has a controlled rigidity and a certain rocking effect, a hard-wearing plastic sole and a soft insole which can be changed when worn out. The shoe is durable and can easily be repaired either by a local shoemaker in the street or by the patient.

Trials are under way with commercially made shoes that are high enough to allow a protecting soft sole to be inserted. More sophisticated methods of analysing the dynamics of different footwear can facilitate the design of protective shoes acceptable to the patients.[23–25,58] Local shoe factories can modify commercial models. Simple studies measuring the effect of such arrangements would be welcomed.

How can ulcers be cured and prevented from recurring?

Much of the recent literature on ulcer care is concerned with advanced ulcer treatment and high technology assessment methods. More studies at field level would be welcomed. Has the enthusiasm for MDT and the large reduction of patients in our programmes lessened our interest in the numbers of leprosy patients who are at risk of developing disabilities? There are publications indicating that the incidence rate of disability may be higher after treatment than during treatment.[7] Are the at-risk patients caught early enough? Is the identification of at-risk patients being delegated? To the community? To the patients themselves? It may very well be that in the future the responsibility for prevention of disability and caring for the disabled should be that of the general health care services or the community,[40] but until this responsibility has been so delegated it remains with the leprosy control programme.

Ulcer prevention and treatment is basically a management problem. It is a matter of applying simple basic principles:[1,46,47]

—Soak and oil the dry skin.
—Inspect the soles of feet.
—Use protective footwear. Change the walking pattern. Rest whenever there are signs of tissue trauma.
—Clean, trim, immobilize and cover ulcers.
—For deep ulcers, apply appropriate surgical measures.
—After ulcers have healed, re-evaluate the foot for further preventive measures. Is preventive or corrective surgery needed? Is there a need for prescribing another type of footwear?

It is amazing how much time and effort is spent in looking for *fata morgana*, 'the healing shoe', 'the healing ointment' that should be spent in the training of staff and the development of proper routines for the prevention and treatment of ulcers.

Treatment starts with the field workers identifying and diagnosing the cases.[50] Today ulcer cases in many programmes are either sent to a central hospital for treatment, or not treated at all. In some field programmes the ulcer care offered ends with a symbolic soaking, superficial trimming and bandaging once every 4 weeks; patients believe in the ritual as performed in the field clinic but do not understand it and make no effort to copy or repeat it at home.

While studying the treatment of ulcers in many programmes and the patients' behaviour, 'classical' health education does not seem to have been very effective.[20] Self-examination and self-care must be taught, and practised where the patients normally live. Teaching situations where patients share experience with other patients are recommended.[10]

In many institutions the average stay for ulcer patients is as high as 3 months. Patients tend to get dependent on their hospital beds. They show confidence in the nicely-smelling solutions and beautifully coloured dressings, and do not believe that anything essential that is done could be repeated in their homes. Leprosy field workers complain that patients who are discharged from hospitals and treated in the field feel deprived of the special medicines and material used in hospitals and show a lack of confidence in the treatment in the field clinics.

Treatment of simple ulcers

To effectively reach all patients in need it is necessary that:

1 Ulcer care should be decentralized to the lowest possible level, and given as close to the patient's home as is possible by:
   (a) Developing and teaching home care. Since most patients are at home and many institutions are sited far away, relatives or village health workers should treat ulcers. The advantage of this would be quicker treatment, the patients remaining in their homes and developing a better understanding and commitment to the process of care.
   (b) Encouraging minor procedures to be performed in peripheral leprosy or general clinics either by leprosy control staff or by trained general health staff.
   (c) Engaging and training staff in peripheral general hospitals to help with the basic surgical management of ulcers and septic conditions.

2 Leprosy workers should be taught to differentiate between ulcers suitable for treatment in the field and those which need to be referred to a hospital for possible surgery.

Physical examination has to be taught and practised. Probing is an excellent way of differentiating between superficial and deep ulcers.[38,51] A simple probe can be made from an unfolded paperclip, sterilized by the flame of the spiritlamp that is used for skin-smear taking, which is normally carried on field trips.

3 Methods of immobilization should be developed and implemented that allow the patients a certain level of mobility but still immobilize the ulcers.

Encouragingly enough there are a number of publications describing different casting techniques, carrying out clinical trials on ulcer healing[51–53] and studies on pressure reduction.[54–57]

The moulded double-rocker plaster shoe is a cheap and simple device which patients accept. It is reasonably effective compared to the classical below knee close contact plaster cast.[58–61] Both methods are useful in the ambulatory treatment of ulcers.

Several different new materials that have been tested are more durable than conventional plaster (POP), but POP is easier to apply. Self-setting materials like PU-resin-impregnated bandages have better mechanical and physical properties but are significantly more expensive and potentially more hazardous than POP.[54]

Treatment of complicated ulcers

First, the patient must be prevented from walking on the ulcer, and second it must be decided where the patient should be treated.

Most of the cases will need surgical intervention, and depending on the resources and levels of staff training, many patients can be treated in peripheral clinics. We are dealing with simple surgical procedures all aiming at eliminating infection, by drainage and removal of infected tissue, and restoring the plantar surface.

Cases suffering from serious septic conditions or from tarsal disintegration or high risk ulcers need to be treated by a worker who has had training in leprosy surgery.[63,64]

Grossly deformed feet may need extensive surgical correction and special footwear to prevent further ulcers. This treatment is very time-consuming, and means that the surgeon is occupied a long time treating a small number of patients.[38,65]

Procedures involving the bone require a lengthy healing time, but this may be necessary in order to prevent the ulcers recurring. Replacement of lost plantar skin is difficult and controversial since the skin outside the plantar surface is inferior to plantar skin.[67–69]

The damaged heal is the most difficult disability to treat, since it is almost impossible to make a shoe for a foot with a destroyed heel. There are a few publications that recommend a flexor digitorum brevis myocutaneous flap or a fasciocutaneous island flap from the instep of the sole for covering the heel. The reported results are good, but the procedures are time consuming and require training and experience. It is rewarding for the workers involved to observe how well the skin from the instep integrates with the heel skin.[71,72]

A number of flap techniques that have been reported take skin not only from the surroundings but also from further away on the body.[73–75] Free flaps have been used with success. Since, generally speaking, flap techniques are difficult and time consuming

because microvascular procedures are involved, very few centres will have the skills and resources to perform them. It should also be noted that flaps are insensitive and have a lower threshold for bearing weight than the original skin of the foot, and therefore can easily ulcerate.

After surgery, when healing has started, immobilization in a plaster cast, e.g. a window cast,[58] and/or with a pair of crutches, may be sufficient. This allows the patient to remain mobile during the period of aftercare.

After the healing of major septic surgery it is important to protect the foot. The patient should not be allowed to put any weight on his/her foot before proper footwear is available. At this stage pressure registration to help design the shoe can be of value.[38,66]

Malignant degeneration occasionally occurs in plantar ulcers. It has been pointed out that a high proportion of the malignant looking ulcers have been grades of pseudo-epitheliomatous hyperplasia (or epithelioma cuniculatum), which can be treated by local excision. Malignancies are usually of a fairly low grade and can be treated by conservative resections and amputations.[76–78]

Some feet do not allow any weight bearing. Different devices for taking the weight off the foot have been designed, such as cuff bearing and patella tendon bearing (PTB) devices. They are all difficult to make, and difficult for the patients to wear. Often the only remaining solution is an amputation. Many patients are definitely much more mobile and do better after amputation and limb-fitting.[79]

Programmes for artificial limbs require good material and worker skills. The period between an amputation and the application of the prosthesis can be long and frustrating for the patient. In the ALERT programme there has been a positive reaction to a temporary prosthesis given shortly after amputation. At first the acceptance of the temporary prosthesis was poor but this has gradually improved. The construction of this temporary prosthesis is simple, cheap, and easy to produce. It consists of a plastazote-lined PTB-shell with a wooden peg, with rubber on its end. It is intended to be worn for 6 months, when it can be easily adjusted as required. When the time comes to have the permanent prosthesis fitted, the patient's stump is conditioned and his/her walking training easier.

Ideally the best preventive measure would be to restore sensation to the sole of the foot. Previous attempts to restore sensation in the foot have not been very successful,[80] because, for a start, proper material for nerve grafting has not been available. With the introduction of the freeze-thawed muscle graft, grafting has now become possible. Ongoing clinical trials have shown some interesting and promising results. Sensory qualities are returning after resection and grafting of part of the posterior tibial and median nerves.[17,18]

Conclusion

In theory it is known why, how, and where ulcers form, and there is experience in basic ulcer management, methods which are simple to understand, cheap and easy to perform and which have been tested and practised for many years. It is recognized that the implementation of such knowledge for the benefit of the patient in need of ulcer prevention and ulcer care is a management problem, and also that many leprosy control units do not have fully-developed programmes for ulcer management. It is a matter of

teamwork, in which leprosy control, POD and PRS staff must participate in a well-planned and integrated manner.

The necessary infrastructure is basically present in most leprosy control programmes. The implementation, or upgrading, of such an integrated programme is a matter of training of and co-operation with existing staff. In future leprosy institutions should function as training centres for POD and PRS. Integration with general health care services should be promoted. Leprosy surgeons should participate in these developments as trainers.[81]

Recent research seems to have concentrated on refining and deepening our understanding of the pathomechanisms for ulcer formation. Unfortunately, treatment research has concentrated mainly on models suitable for the more-developed countries, where the majority of leprosy patients do not live. In a period where the prevention of disability and ulcer management seem to be living in the shadow of multidrug therapy, research projects studying the problems of disability prevention and ulcer management should be promoted. Research aiming at preserving sensation should also be given priority.

It is unlikely that any new leprosy hospitals of the traditional model will be built in the future. New programmes will have to solve their need for hospital beds in other ways. Decentralized ulcer management requires only a modest amount of not very expensive equipment. Existing resources in general health care could be mobilized. In a decentralized model more patients, now without access to ulcer care, can be helped at an earlier stage, thereby preventing complete destruction.

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References

[1] Brand PW, Fritschi EP. Rehabilitation in leprosy. *Leprosy. Medicine in the Tropics.*
[2] Jopling WH. Leprosy stigma. *Lepr Rev*, 1991; **62:** 1–12.
[3] Srinivasan H. Nerve damage, surgery and rehabilitation in leprosy. *Trop Med Parasitol*, 1990; **41:** 347–9.
[4] Pereira JH, Palande DD, Gschmeissner SE. Mycobacteria in nerve trunks of long-term treated leprosy patients. *Lepr Rev*, 1991; **62:** 134–42.
[5] Ross P, Waters MFR. Reversal reactions in leprosy and their management. *Lepr Rev*, 1991; **62:** 113–21.
[6] de Rijk A. ALERT. Personal communication.
[7] Ponnighaus IM, Boerrigter G, Fine PEM, Ponnighaus LM, Russel J. Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malawi. *Lepr Rev*, 1990; **61:** 366–74.
[8] Watson JM. Disability control in a leprosy control programme. *Lepr Rev*, 1989; **60:** 169–77.
[9] Becx-Bleumink M, Berhe D, Mannetje W't. The management of nerve damage in the leprosy control services. *Lepr Rev*, 1990; **61:** 1–11.
[10] Watson JM. Preventing disability in leprosy patients. The Leprosy Mission.
[11] Bell-Krotoski J. Hand screen for early detection and monitoring of peripheral neuropathy. Part II. *The Star*, 1992; Vol. **5,** No. 3, 3–7.
[12] Bell-Krotoski J, Tomancik E. The repeatability of testing with Semms–Weinstein monofilaments. *J Hand Surg*, 1987; **12A:** 155–61.
[13] Birke JA, Sims DS. Plantar sensory threshold in the ulcerative foot. *Lepr Rev*, 1986; **57:** 261–7.
[14] Hammond CJ, Klenerman P. Protective sensation in the foot in leprosy. *Lepr Rev*, 1988; **59:** 147–354.
[15] Currie HC. ALERT: Personal communication.

[16] Klenerman P, Hammond C, Kulkarni VN, Mehta JM. Vibration sense and tarsal disintegration. *Ind J Lepr*, 1990; **62:** 422–8.
[17] Pereira JH, Palande DD, Subramanian A, Narayanakumar TS, Curtis J, Turk JL. Denatured autologous muscle graft in leprosy. *Lancet*, 1991; **338:** 1239–40.
[18] Kazen RO. Unpublished material. ALERT.
[19] Sankaran B. *Biomechanics of normal foot, gaitanalysis and clinical applications.* Proceedings of the National Workshop on Footcare in Leprosy. April 1990, Bombay.
[20] Wele DS. Health education for the successful implementation of MDT. *Ind J Lepr*, 1990; **62:** 3.
[21] Price EW. The care of the foot. *Leprosy in Theory and Practice.* Bristol: John Wright & Sons Ltd. 1964.
[22] Harris RI, Beath T. (1947) 'Canadian Foot Survey', Nat. Res. Council Canada. Appendix B.
[23] Patil KM, Srinath MS. New image-processing system for analysis, display and measurement of static and dynamic foot pressures. *Med & Biol Eng & Comput*, 1990; **28:** 416–22.
[24] Arcan M, Brull MA. A fundamental characteristic of the human body and foot, the foot-ground pressure pattern. *J Biomechanics*, 1976; Vol. **9:** 453–7.
[25] Bransby-Zachary MAP, Stother IG, Wilkinson RW. Peak pressures in the forefoot. *J Bone Joint Surg [Br]*, 1990; **72-B:** 718–21.
[26] Sabato S, Yosipovitch Z, Simkin A, Sheskin J. Plantar trophic ulcers in patients with leprosy. *Int Orthopaedics*, 1982; **26:** 203–8.
[27] Boulton AJM, Hardisty CA, Betts RP, Frank CI, Worth RC, Ward JD, Duckworth T. Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy. *Diabetes Care*, 1983; **6:** 26–33.
[28] Pollard JP, Le Quesne LP, Tappin JW. Forces under the foot. *J Biomed Eng*, 1983; **5:** 37–40.
[29] Hughes J, Clark P, Klenerman L. The importance of the toes in walking. *J Bone Joint Surg [Br]*, 1990; **72-B:** 245–51.
[30] Sims DS Jr, Cavanagh PR, Ulbrecht JS. Risk factors in the diabetic foot. *Phys Ther*, 1988; **12:** 1887–1901.
[31] Srinivasan H. Plantar ulcers and corrective surgery. Determining factors in localization of foot-ulcers in leprosy patients. *Lepr India*, Supplement No. 3A, 1965.
[32] Srinivasan H. Heel ulcers in leprosy patients. *Lepr India*, 1976; **48:** 355–61.
[33] Srinivasan H. Do we need trials of agents alleged to improve healing of plantar ulcers? *Lepr Rev*, 1989; **60:** 278–82.
[34] Carley PJ, Wainapel SF. Electrotherapy for acceleration of wound healing: Low intensity direct current. *Arch Phys Med Rehabil*, 1985; **66:** 442–6.
[35] Kloth LC, Feedar JA. Acceleration of wound healing with high voltage monophasic, pulsed current. *Phys Ther*, 1988; **68:** 503–8.
[36] Palande DD, de Severy C, Rajagopalan MS. Plantar ulcers with osteomyelitis underneath. A bacteriological study. *Lepr India*, 1977; **49:** 322–9.
[37] George M, Bhatia VN, Kar HK, Roy RG. Anaerobic flora in trophic ulcers in leprosy patients. *Ind J Lepr*, 1985; **57:** 334–40.
[38] Duffy JC, Patout CA, Jr. Management of the insensitive foot in diabetes: Lessons learned from Hansen's disease. *Military Medicine*, 1990; **155:** 575–9.
[39] Ganlöv G. Unpublished material. ALERT.
[40] Noorden SK. A look at world leprosy. *Lepr Rev*, 1991; **62:** 72–86.
[41] Srinivasan H. *Background notes on foot-care in leprosy patients.* The National Workshop on foot care in leprosy. Bombay 1990.
[42] Rao KS. *Neuritis and foot deformities in leprosy.* The National Workshop on foot care in leprosy. Bombay 1990.
[43] Palande D. Some clinical and laboratory signs indicating external compression of a nerve trunk in leprosy: details and rationale. *Lepr Rev*, 1976; **47:** 35–9.
[44] Palande D, Muthuraj M. Surgical decompression of posterior tibial neurovascular complex in treatment of certain chronic plantar ulcers and posterior tibial neuritis in leprosy. *Int J Lepr*, 1975; **43:** 36–40.
[45] Carayon A, Giraudeau P, Disy P. La composante neuro-vasculaire dans les ulceres plantaires de la lepre. *Medecine Tropicale*, 1978; **38:** 453–78.
[46] Premkumar R, Pannikar VK, Fritschi E. Foot soaks for callosities and fissures. *Ind J Lepr*, 1990; **62:** 478–82.
[47] Brand PW. *Insensitive feet. A practical handbook on foot problems in leprosy.* The Leprosy Mission, 1986.
[48] Antia NH. Plastic footwear for leprosy. *Lepr Rev*, 1990; **61:** 73–8.
[49] Kulkarni VN, Antia NH, Mehta JM. Newer design in foot-wear for leprosy patients. *Ind J Lepr*, 1990; **62:** 483–7.
[50] Srinivasan H. Newer tasks for leprosy workers. *Ind J Lepr*, 1990; **62:** 409–15.
[51] Birke JA, Novick A, Graham SL, Coleman WC, Brasseaux DM. Methods of treating plantar ulcers. *Physical Therapy*, 1991; **71:** 116–22.
[52] Coleman WC, Brand PW, Birke JA. The total contact cast. *J.A.P.A.*, 1984; **74:** 548–552.

[53] Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP III, Drury DA, Rose SJ. The total contact casting in treatment of diabetic plantar ulcers. *Diabetes Care*, 1989; **12:** 384–8.
[54] Wytch R, Ashcroft GP, Ledingham WM, Wardlaw D, Ritchie IK. Modern splinting bandage. *J Bone Joint Surg [Br]*, 1991; **73-B:** 88–91.
[55] Kaplan M, Gelber RH. Care of plantar ulcerations: comparing applications, materials and non-casting. *Lepr Rev*, 1988; **59:** 59–66.
[56] Birke JA, Sims DS Jr, Buford WL. Walking casts: effect on plantar foot pressures. *J of Rehabilitation Research and Development*, **22:** 18–22.
[57] Novick A, Birke JA, Graham SL, Koziatek E. Effect of a walking splint and total contact cast on plantar forces. *J Prosthet and Orthot*, **3:** 168–78.
[58] Borssén B, Lithner F. Plastar casts in the management of advanced ischaemic and neuropathic diabetic foot lesions. *Diabetic Medicine*, 1989; **6:** 720–3.
[59] Pring DJ, Casiebanca N. Simple plantar ulcers treated by below-knee plaster and moulded double-rocker plaster shoe—a comparative study. *Lepr Rev*, 1982; **53:** 261–4.
[60] Joseph B, Joshua S, Fritschi EP. The moulded double-rocker plaster shoe in the field treatment of plantar ulcer. *Lepr Rev*, 1983; **54:** 39–44.
[61] Diamond JE, Sinacore DS, Mueller MJ. Moulded double-rocker plaster shoe for healing a diabetic ulcer. *Physical Therapy*, 1987; **67:** 1550–2.
[62] Job CK. Nerve damage in leprosy. XII leprosy congress, state-of-the-art lecture. *Int J Lepr*, 1989; **57:** 532–9.
[63] Mehta JM, Sane SB. *Rehabilitation of foot handicaps.* The National Workshop on foot care in leprosy. Bombay 1990.
[64] Carayon A, Chevallard A. Evolution des lésions osseuses du pied lépreux vers la dislocation du tarse et du métatarse. *Revue de chirugie Orthopédique*, 1990; **76:** 579–82.
[65] Lang-Stevenson AI, Sharrard WJW, Betts RP, Duckworth T. Neuropathic ulcers of the foot. *J. Bone Joint Surg [Br]*, 1985; **67-B:** 438–42.
[66] Stein H, Simkin A, Joseph K. The foot-ground pressure distribution following triple arthrodesis. *Arch Orthop Traumat Surg*, 1981; **98:** 263–9.
[67] Palande DD, Rajoo DP, Rajagopalan MS. Skin grafting for plantar ulcers in leprosy. *Lepr India*, 1976; **48:** 739–43 (Suppl.).
[68] Shaw WW, Hidalgo DA. Anatomic basis of plantar flap design: Clinical application, with discussion by G. Reading. *Plast Reconstr Surg*, 1986; **78:** 637–51.
[69] Curtin JW. Functional surgery for intractable conditions of the sole of the foot. *Plast Reconstr Surg*, 1977; **59:** 806–11.
[70] Morrison WA, McK Crabb D, McC O'Brien B, Jenkins A. The instep of the foot as a fasciocutaneous island and as a free flap for heel defects, with discussion by D. H. Harrison. *Plast Reconstr Surg*, 1983; **72:** 56–65.
[71] Shah A, Pandit S. Reconstruction of the heel with chronic ulceration with flexor digitorum brevis myocutaneous flap. *Lepr Rev*, 1985; **56:** 4–48.
[72] Gravem PE. Heel ulcer in leprosy treated with fasciocutaneous island flap from the instep of the sole. *Scand J Plast Reconstr Hand Surg*, 1991; **25:** 155–60.
[73] Amarante J, Costa H, Reis J, Soares R. A new distally based fasciocutaneous flap of the leg. *Br J Plast Surg*, 1986; **39:** 338–40.
[74] Sakai S, Terayama I. Modification of the island subcutaneous pedicle flap for the reconstruction of defects of the sole of the foot. *Br J Plast Surg*, 1991; **44:** 179–82.
[75] Hong G, Steffens K, Wang FB. Reconstruction of the lower leg and foot with the reverse pedicle posterior tibial fasciocutaneous flap. *Br J Plast Surg*, 1989; **42:** 512–16.
[76] Srinivasan H, Desikan KV. Cauliflower growths in neuropathic plantar ulcers in leprosy patients. *J Bone Joint Surg*, 1971; **53-A:** 123–32.
[77] Ochsner PE, Hausman R, Olsthoorn PGM. Epithelioma cuniculatum developing in a neuropathic ulcer of leprous etiology. *Arch Orthop Traumat Surg*, 1979; **94:** 227–31.
[78] Girdhhar M, Mohan L, Arora SK, Gupta M, Basu PK, Mishra SD, Mukhija RD. Squamous cell carcinoma developing in trophic ulcers of leprosy—report of 2 cases. *Ind J Lepr*, 1990; **62:** 126–8.
[79] Fleshmann K, Hill P, Fritschi EP. Rehabilitation by amputation. *Lepr Rev*, 1976; **47:** 41–9.
[80] Mcleod JG, Hargrave JC, Gye RS, Pollard JD, Walsh JC, Little JM, Booth GC. Nerve grafting in leprosy. *Brain*, 1975; **98:** 203–12.
[81] Virmond M, Duerksen F, Goncalves A. Report and evaluation of Brazilian experience in the rehabilitation of patients with leprosy. *Lepr Rev*, 1989; **60:** 214–20.

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Evaluation of the autoimmune response in leprosy

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Summary Immunological responses to a panel of antigens were evaluated in 27 patients with lepromatous and 20 patients with tuberculoid leprosy and compared with 24 pulmonary tuberculosis patients, 25 systemic lupus erythematosus patients and 41 healthy blood donors. Some autoantibody specificities were extensively studied for the first time in mycobacterial infections. Striking immunoserological abnormalities were found in patients with lepromatous leprosy, particularly in those presenting with relapse.

Inhibition assays were performed, providing a tool for further analysis of the binding range of specific anti-N.D.O. BSA antibodies and strengthening the suggestion of molecular mimicry reactions between cytoskeletal proteins, host stress proteins and *Mycobacterium leprae* antigens or stress proteins. A significant serological overlap between lepromatous leprosy and autoimmune diseases is indicated.

Introduction

The presence of antibodies (Abs) against nucleic acids and nucleoproteins is considered to be the hallmark of systemic lupus erythematosus (SLE). Antibodies which react against several determinants have been reported, however, in a broad spectrum of autoimmune disorders and infectious diseases.[1–3] In the present study, we investigated immunoserological responses to other than specific *M. leprae* antigens in patients with leprosy and re-

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analysed autoantibody specificities, in an attempt to clarify the mechanisms involved in the autoantibody production and the clinical significance of these Abs.

Special interest was given in the comparison of the autoantibody profile of leprosy with that of tuberculosis (TBC), since causative infectious agents are considered similar in structure and morphology and similar host defence mechanisms are involved, although their clinical course differs. Patients with SLE served as a control group, since SLE, a model for the study of autoimmune responses, offers the opportunity to study similar immune aberrations in chronic mycobacterial infections and autoimmune diseases.

Materials and methods

PATIENTS

Sera from 47 hansenians (23 men/24 women) were examined. The disease classification was: 20 with lepromatous, 14 with tuberculoid, 7 with borderline-lepromatous and 6 with borderline-tuberculoid form. For the presentation of our results, however, lepromatous and borderline-lepromatous groups are given with the term 'LL', whereas all other subgroups with 'TT'. The mean age was 60 years and the average disease and treatment duration 27 and 18 years, respectively. The Bacteriological (0–6^+) and Morphological Index (0–100%) were calculated.[4] A division in active or inactive disease followed, in accordance with clinical, histological and bacteriological data.

Control sera were obtained from (i) 24 patients with active, cavitary pulmonary TBC (mean age—54 years), whose diagnosis was based on clinical, radiological and bacteriological data; (ii) 25 SLE patients who met the revised criteria of the American Rheumatism Association;[5] and (iii) 41 healthy blood donors (C).

ANTIGEN–ANTIBODIES

Native double-stranded DNA (dsDNA) from calf thymus, cardiolipin (cl) from bovine heart, human IgG, Sm/RNP, bovine actin (act) and myosin (mys), s1-nuclease, goat peroxidase-conjugated antibody specific to human μ- and γ-chain were purchased from Sigma Co. Bovine serum albumin was purchased from Serva Co. Single-stranded DNA (ssDNA) was prepared after boiling dsDNA for 10 min at 100°C and chilling in ice for 5 min. N.D.O. BSA solution was kindly provided by Dr P. Brennan and D. Chatterjee, Department of Microbiology, University of Colorado (USA).

ENZYME-LINKED IMMUNOSORBENT ASSAYS

Previous methods with minor modifications were followed. Polystyrene flat bottomed plates were coated with the following antigens: (a) dsDNA, 50 μg/ml in tris-buffered saline (TBS), pH = 7·4; (b) ssDNA, 5 μg/ml in TBS; (c) Sm/RNP, 20 μg/ml in borrate buffer, pH = 8·6; (d) cl, 50 μg/ml in absolute ethanol; (e) act, mys, 10 μg/ml in carbonate-bicarbonate buffer (CBC), pH = 9·6; (f) human IgG, 50 μg/ml in phosphate-buffered saline (PBS); (g) N.D.O. BSA, 1:1000 in CBC.

For anti-dsDNA especially, a step with s1-nuclease (50 IU/ml in PBS) followed. Afterwards, the patient's serum which had been diluted was added (1:600 for N.D.O. BSA, 1:200 for Sm/RNP, 1:100 for cl, act, mys, human IgG and 1:50 for ssDNA,

dsDNA). Finally, plates were incubated for 1·5 hr at 37°C with peroxidase labelled goat anti-human IgG or IgM antibody (1:2000 for Sm/RNP, ssDNA, act, mys, human IgG, 1:1000 for cl, dsDNA, N.D.O. BSA). Pooled serum was used as the normal reference serum. Optical density (OD) readings of control wells were subtracted from test values. The value of human pool plus 3 standard deviations was estimated as the normal cut-off point.

COMPETITIVE IMMUNOENZYME ASSAYS

Inhibition fluid phase assays were performed to study the binding range of specific anti-N.D.O. BSA Abs. A dilution giving 50% of maximal binding for anti-N.D.O. BSA Abs was chosen for these assays and the test antibody was mixed with various dilutions of the inhibitor heterologous antigen (3–300 μg/ml) for 1 hr at 37°C. Single- and double-stranded DNA, Sm/RNP, actin, myosin, and cardiolipin served as inhibitors (Figures 2–4). The mixture was allowed to react with the immobilized antigens on the plates for 1 hr at 37°C. Finally, monospecific anti-μ or anti-γ peroxidase labelled antibody was added at 1 μg/ml. Results were expressed as percent inhibition of anti-N.D.O. BSA activity:

$$\% \text{ Inhibition} = \left(1 - \frac{\text{OD with Inhibitor} - \text{Background}}{\text{OD without Inhibitor} - \text{Background}}\right) \times 100$$

Results

Frequencies of Abs against single-stranded DNA, cardiolipin, human IgG, actin, and myosin in the groups studied are shown in Table 1. High levels of anti-ssDNA (IgG) Abs were found in LL (37·03%) and TBC (33·30%), but were significantly lower, however, than in SLE (80%, Figure 1). Anti-cl (IgM) Abs in LL (29·60%) showed a trend to difference with TBC. SLE sera, however, contained high levels of anti-cl Abs of both isotypes (IgG 60·10%, IgM 36%). Antibodies against human IgG (IgM isotype) were elevated in LL (25·92%) and detected in the sera of all hansenians with relapse at the time of the study.

Antibodies against cytoskeletal proteins were detected in remarkably higher levels in LL than other groups. Anti-act (IgG) Abs in LL (57·10%) showed difference with other

Table 1. Autoantibody frequencies (%) in the groups studied

	Groups				
Antibodies	LL	TT	TBC	SLE	C
Anti-ssDNA (IgG)	37·03	20·00	33·33	80·00	7·31
Anti-ssDNA (IgM)	7·40	10·00	8·33	44·00	4·87
Anti-cl (IgG)	14·81	0	8·33	60·00	4·87
Anti-cl (IgM)	29·62	10·00	8·33	36·00	2·43
Anti-IgG (IgM)	25·92	10·00	8·33	20·00	2·43
Anti-ACT (IgG)	57·14	10·00	8·33	36·00	7·31
Anti-ACT (IgM)	38·09	10·00	16·66	24·00	2·43
Anti-mys (IgG)	47·61	0	8·33	24·00	4·87
Anti-mys (IgM)	71·42	10·00	16·66	4·00	2·43

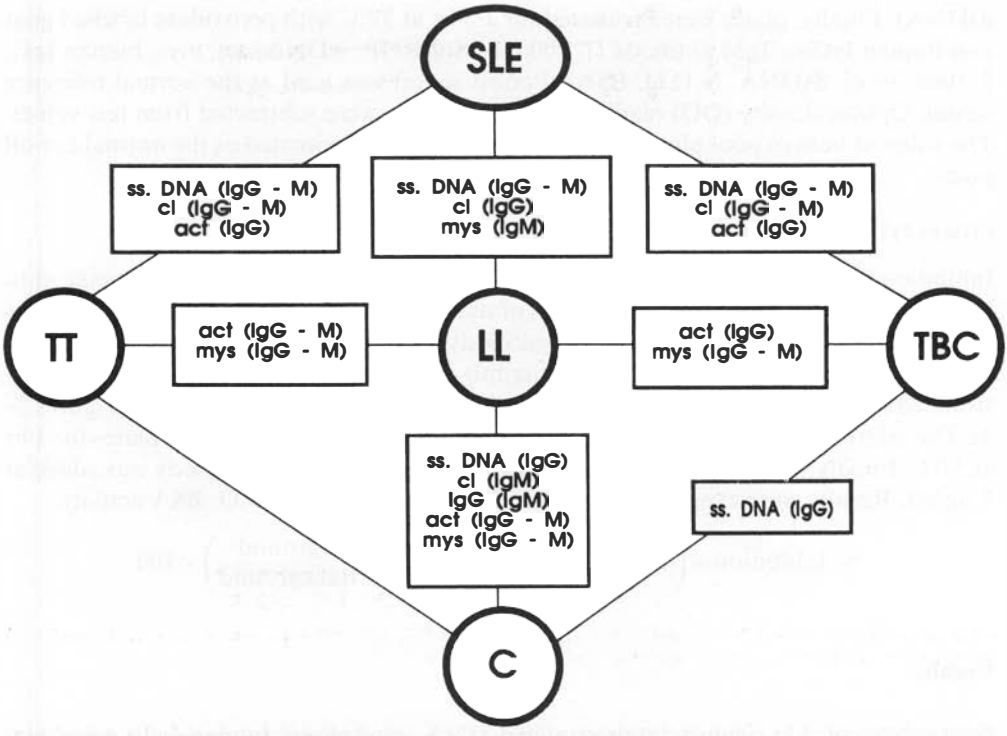

Figure 1. Significant differences ($p < 0{\cdot}05$) among groups (Fisher's exact test).

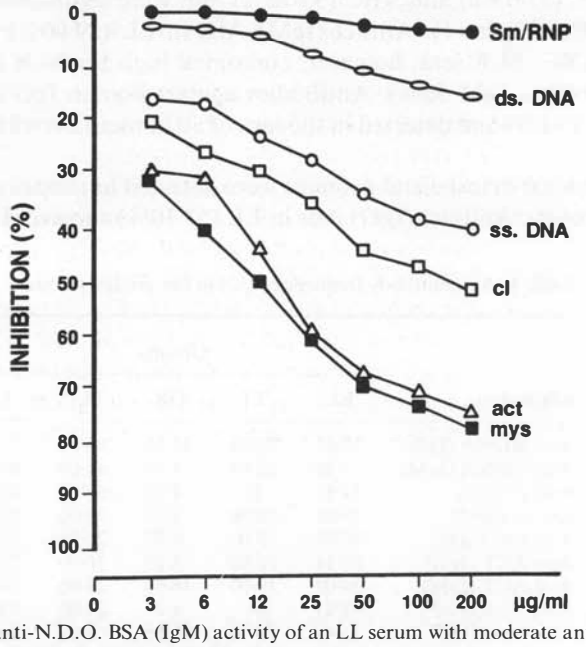

Figure 2. Inhibition of anti-N.D.O. BSA (IgM) activity of an LL serum with moderate anti-N.D.O. BSA (IgM) and high levels of anti-act (IgM), anti-mys (IgM) and anti-cl (IgM).

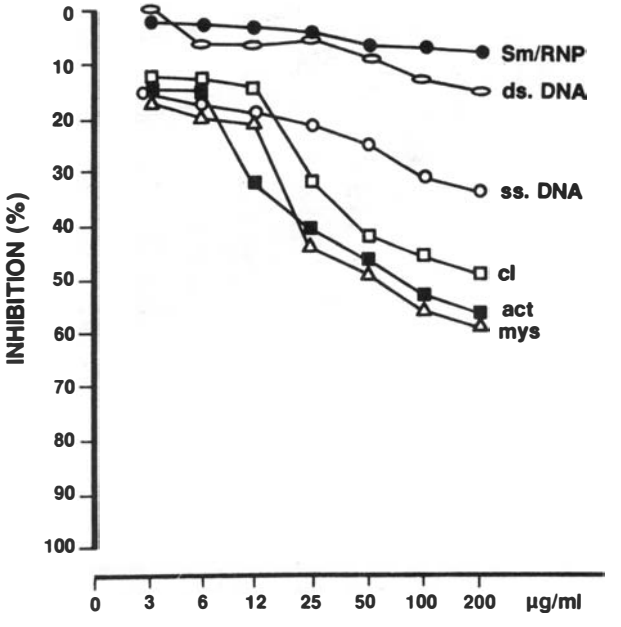

Figure 3. Inhibition of anti-N.D.O. BSA (IgM) activity of an LL serum with high anti-N.D.O. BSA (IgM) and moderate levels of anti-act (IgM) and anti-mys (IgM).

groups besides SLE (Figure 1) whereas anti-act (IgM) Abs in LL (38·09%) presented a difference only with TT. Anti-mys (IgG) Abs in LL (47·60%) showed a difference with TT, TBC, and C, whereas anti-mys (IgM) Abs in LL were detected in notably high frequency, higher than all other groups. Anti-act (IgM) and anti-mys (IgM) were strongly correlated with anti-N.D.O. BSA (IgM) Abs ($p = 0{\cdot}039$ and 0·0017, respectively, Fisher's exact test).

Anti-N.D.O. BSA (IgM) Abs proved to be specific for LL (62·90%) in accordance with previous reports,[6] whereas anti-N.D.O. BSA (IgG) were detected in both LL (85%) and TT (66%). Anti-dsDNA Abs (IgG and IgM) were specific for SLE (64% and 28%) as well as anti-Sm/RNP (44% and 24%). Differences between LL and C resulted for all Abs, besides anti-ssDNA (IgM) and anti-cl (IgG) (Figure 1). The lepromatous leprosy group and TBC differed in the prevalence of anti-act (IgG) and anti-mys (IgG and IgM) Abs. No differences were verified between TT and TBC as well as between TT and C (not included in Figure 1). Differences between multibacillary and paucibacillary leprosy resulted only for Abs against cytoskeletal proteins ($p = 0{\cdot}040$). In all, 2 lepromatous leprosy sera and 1 borderline-lepromatous leprosy serum were selected for inhibition assays. Inhibition by single-stranded DNA, cardiolipin, actin, and myosin was only partial, but higher by actin and myosin. No inhibition resulted by characteristic lupus autoantigens (dsDNA, Sm/RNP) (Figures 2–4).

Discussion

Infection with *M. leprae* induces considerable changes in the humoral immune system, which involve aberrant responses, often associated with autoimmune syndromes.[7]

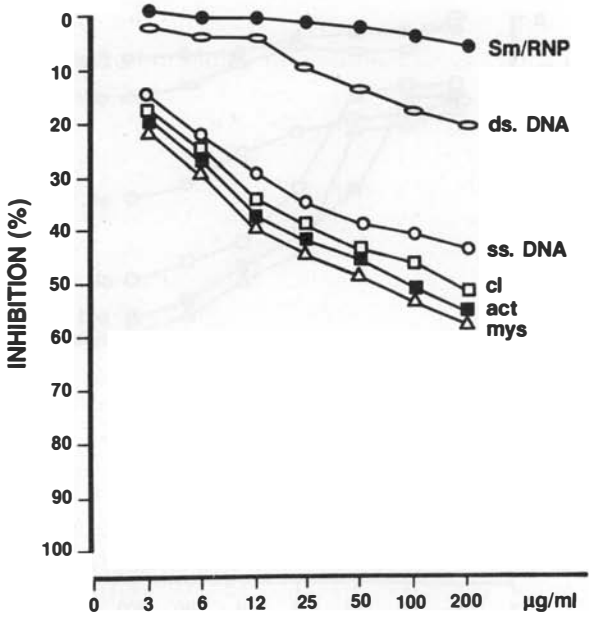

Figure 4. Inhibition of anti-N.D.O. BSA (IgG) activity of BL serum with moderate anti-N.D.O. BSA (IgG) and high levels of anti-ssDNA (IgG), anti-act (IgG), anti-mys (IgG) and anti-c1 (IgG).

Autoantibodies in mycobacterial infections have been previously reported,[7–9] but their origin and clinical significance have not been clarified. This stimulated us to examine a broad profile of Abs, in an attempt to further clarify the mechanisms involved in their production and their clinical associations.

Idiotypic similarities between leprosy and SLE have been hypothesized, since Mackworth-Young *et al.*[10] have produced monoclonal Abs with highly conserved idiotypes for SLE and leprosy. Several mechanisms may account for the broad autoantibody profile in lepromatous leprosy, such as polyclonal B-cell activation, suppressor T-cell deficiency and molecular mimicry reactions between microbial and host agents, which may lead to cross-reactions, resulting in autoimmune phenomena.[11]

In this study, we compared the autoantibody profile of LL and TT with that of TBC and SLE. Our findings first indicate the detection of anti-ssDNA (IgG) Abs besides SLE in LL and TBC, as previously reported.[2,3,10] Some authors have suggested cross-reactions with mycobacterial DNA[2,3,8] and others[10] that anti-ssDNA might arise by expansion of a pool of precursors in the normal antibody repertoire, in state of polyclonal B-cell activation. The inability to detect SLE characteristic Abs probably indicates that autoimmunity is expressed in a structured fashion that cannot be attributed to a random escape from absolute control and the inducing stimuli or cellular defects in SLE are probably disease specific.[2] High levels of Abs against cytoskeletal proteins were found in LL patients. There is a striking lack of information, however, concerning Abs against cytoskeletal proteins in mycobacterial infections. The prevalence of anti-act (IgG) Abs was higher in LL (57·10%) than all other groups—besides SLE—whereas for anti-act (IgM) Abs, difference was shown only in comparison with TT and C (Table 1, Figure 1).

Anti-act (IgM) were positively correlated with anti-N.D.O. BSA (IgM) Abs ($p = 0{\cdot}0039$), a correlation which was further strengthened by inhibition of anti-N.D.O. BSA (IgM) activity by actin (60–70%) (Figures 2–4). Anti-mys Abs were detected in significantly higher prevalence in LL (47% IgG, 71·40% IgM) than in other groups (Figure 1). Anti-mys (IgM) were also correlated with anti-N.D.O. BSA (IgM) Abs and a partial inhibition of anti-N.D.O. BSA (IgM) Abs by myosin was recorded.

The investigation of antigens involved in the immune response against tuberculosis and leprosy bacilli led to the observation that a variety of heat shock or stress proteins (HSP 60, HSP 70) which are expressed in host cells under stress conditions, present great sequence homology with mycobacterial stress proteins[13] which are considered among the immunodominant targets of both antibody and T-cell responses.[14,15] Moreover, some stress proteins are known to modulate the action of cytoskeletal proteins and other protein complexes[16] and this functional association may result in parallel recognition, as stress proteins are strong immunogens and are expressed in active disease. This is strengthened also by the results of the present study, as Abs against cytoskeletal proteins were mainly detected in active disease.

Differences beween multibacillary and paucibacillary disease were found only for Abs against cytoskeletal proteins, further increasing the probability that cytoskeletal proteins, this group of highly conserved proteins, are involved in molecular mimicry reactions with *M. leprae* antigens or stress proteins, another group of conserved proteins. A network of parallel recognitions or even successive cross-reactions between host stress proteins, cytoskeletal proteins and *M. leprae* antigens or stress proteins could therefore be suggested.

This hypothesis becomes more intriguing in the light of recent findings, that stress proteins may be expressed on cellular membranes, near MHC II antigens, during the antigen recognition process.[16,17] Similarities between host stress proteins and *M. leprae* antigens or stress proteins, could aid the survival of *M. leprae* in avoiding the host immune response. We are a long way, however, from ascertaining this suggestion as well as the hypothesis of some authors,[18] that recognition of sequences unique in mycobacterial stress proteins could lead to immunity, whereas recognition of common sequences in human and mycobacterial stress proteins could trigger autoimmunity.

From the comparison of the autoantibody profile in the groups studied, we found that LL differs significantly from TT and TBC, mainly as regards Abs against cytoskeletal proteins, while it possesses an intermediate position between TT, TBC and SLE, as regards other autoantibodies. Previous suggestions[8], that generalized humoral immuno-serological abnormalities in LL are only remote sequellae of the disease, due to its chronic nature, are in dispute, since (a) striking differences in the autoantibody profile between LL and TT, TBC were shown, although minor divergences in mean disease duration and patient age were recorded; (b) autoantibody levels were correlated neither with disease and treatment duration nor with patient age; and (c) some responses were associated with active LL, assuming in this way clinical significance. Further studies will have to be done to verify the role of heat shock proteins in mycobacterial infections.

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References

[1] Shoenfeld Y, Schwartz RS. Immunologic and genetic factors in autoimmune diseases. *N Engl J Med*, 1984; **311:** 1019–29.

[2] Bonfa E, Llovert R, Scheinberg M, De Souza JM, Elkon KB. Comparison between autoantibodies in malaria and leprosy with lupus. *Clin exp Imm*, 1987; **70:** 529–37.

[3] Sela O, El-Roeing A, Isenberg DA, Kenedy RC, Colaco CB, Pinkhas J, Shoenfeld Y. A common anti-DNA idiotype in sera of patients with active pulmonary tuberculosis. *Arthritis Rheum*, 1987; **30:** 50–6.

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

[5] Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*, 1982; **25:** 1271–7.

[6] Young DB, Dissanayake S, Miller RA, Khanolkar SR, Buchanan TM. Humans respond predominantly with IgM immunoglobulin to the species specific glycolipid of *Mycobacterium leprae*. *J Infect Dis*, 1984; **149:** 870–3.

[7] Rawlinson WD, Basten A, Hargrave JC. Clinical significance of changes in serum proteins, immunoglobulins and autoantibodies in leprosy. *Int J Lepr*, 1987; **55:** 277–85.

[8] Rea TH, Quismorio FP, Harding B. Immunologic responses in patients with lepromatous leprosy. *Arch Dermatol*, 1976; **112:** 791–800.

[9] Turk JL, Bryceson ADM. Immunological phnomena in leprosy and related diseases. *Adv Immunol*, 1971; **13:** 209–66.

[10] Mackworth-Young C, Sabbaga G, Schwartz RS. Idiotypic markers of polyclonal B-cell activation. *J Clin Invest*, 1987; **79:** 572–81.

[11] Oldstone MBA. Molecular mimicry and autoimmune disease. *Cell*, 1989; **50:** 819–20.

[12] Furukawa F, Kashihara M, Imamura S, Ohshio G, Hamashima Y. Evaluation of anti-cardiolipin antibody and its cross-reactivity in sera of patients with lepromatous leprosy. *Arch Dermatol*, 1986; **278:** 317–19.

[13] Young RA, Elliot TJ. Stress proteins, infection and immune surveillance. *Cell*, 1989; **59:** 5–8.

[14] Watson JD. Leprosy: understanding protective immunity. *Immunol Today*, 1989; **10:** 218–21.

[15] Lewin R. Stress proteins: are links in disease. *Science*, 1988, **240:** 1732–3.

[16] Kaufmann SHE. Heat shock proteins and the immune response. *Immunol Today*, 1990; **11:** 129–35.

[17] Born W, Happ MP, Dallas A, Reardon C, Kubo R, Shinnick T, Brennan P, O'Brien R. Recognition of heat shock proteins and $\gamma\delta$ cell function. *Immunol Today*, 1990; **11:** 40–3.

[18] Cohen IR. An eclectic summary of the symposium on autoimmunity. *Immunol Today*, 1989; **10:** 394–5.

Évaluation de la réponse auto-immune dans la lèpre

G. Kroumpouzous, A. Vareltzidis, M. Konstadoulakis, G. Avgerinou, G. Anastasiadis, H. Kroubouzou, A. Panteleos et A. Tosca

Résumé Les réponses immunologiques à une série d'antigènes ont été évaluées dans 27 cas de lèpre lépromateuse et 20 de lèpre tuberculoïde et comparées à 24 cas de tuberculose pulmonaire, 25 cas de lupus érythémateux systémique et aux réponses de 41 donneurs de sang sains. Certaines de ces spécificités auto-anticorps étaient étudiées extensivement pour la première fois dans les infections mycobactériennes. Nous avons observé des anomalies immuno-sérologiques frappantes chez des patients atteints de lèpre lépromateuse, en particulier chez ceux qui ont rechuté.

Des tests d'inhibition ont été effectués, qui faciliteront l'analyse plus poussée du spectre de réactivité des anticorps spécifiques anti-N.D.O. ASB et aideront à prouver la suggestion de l'éxistence de réactions de mimétisme moléculaire entre les proteines cyto-squelettiques, les proteines de stress de l'hôte et les antigènes de *Mycobacterium leprae* ou les proteines de stress. On a observé un chevauchement sérologique significatif entre la lèpre lépromateuse et les maladies auto-immunes.

Evaluación de la respuesta autoinmuna en la lepra

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Resumen En 27 pacientes con lepra lepromatosa y 20 con lepra tuberculoide, se evaluaron las respuestas inmunológicas a una selección de antigenos, y se compararon con 24 pacientes con tuberculosis pulmonar, 25 con lupus eritematoso sistémico y 41 donantes de sangre sanos. Se estudiaron extensamente algunas de las especificidades de autoanticuerpo por primera vez en las infecciones micobacterianas. Se descubrieron anormalidades inmunoserológicas impresionantes en los pacientes con lepra lepromatosa, especialmente en los casos de recaída.

Se realizaron ensayos de inhibición, resultando en una herramienta para un análisis adicional de los anticuerpos específicos anti-N.D.O. BSA, reforzando la posibilidad de reacciones miméticas moleculares entre las proteínas citoesqueletales, las proteínas producidas por estrés en el huésped, y antigenos de *Mycobacterium leprae* o proteínas del estrés. Los resultados indican una coincidencia serológica significativa entre la lepra lepromatosa y las enfermedades autoinmunas.

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Modulation of peripheral blood derived monocytes/macrophages from leprosy patients using 'tuftsin' for production of reactive oxygen intermediates

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Summary Phagocytic cells respond to a variety of membrane stimulants by producing reactive oxygen intermediates (ROI), i.e. O_2^-, H_2O_2 and OH· metabolites. Plasma membrane activation is associated with superoxide generating NADPH oxidase, thereby causing the production of these toxic species. Stimulation of phagocytic cells also results in activation of purine catabolism, which directs the metabolic flux through xanthine oxidase to produce the superoxide anion. We previously observed that BL/LL macrophages (Mϕ exhibited a premature inability to undergo tuftsin stimulated phagocytosis and microbicidal activity. The present study was undertaken to measure ROI levels in the absence and presence of 'tuftsin' pulsing as a function of *in vitro* culture age and also correlated these levels with adenosine deaminase (ADA) activity. The latter is known to be a contributor of O_2^- generation and is also involved in the maturation of the monocyte/macrophage system. The behaviour of normal and tuberculoid monocytes/macrophages were more or less the same, either in the presence or absence of tuftsin, i.e. they showed a progressive increase in ROI production until day 3, then tapered off in older cultures by day 7. In contrast, after day 1, the lepromatous macrophages were unable to undergo tuftsin mediated stimulation for the production of ROI and ADA activity. These findings indicate a defective Mϕ function in lepromatous patients towards tuftsin pulsing, thereby supporting our earlier observations. Thus BL/LL Mϕ behaved as if they were aged after 1 day of *invitro* culture, which may account for an inability to handle *Mycobacterium leprae* for efficient killing.

Introduction

Mononuclear phagocytes are indispensable to both natural and acquired host immunity. *M. leprae* is an obligate intracellular pathogen that is ingested by and proliferates within

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the cells of the monocytes/macrophages. The inability of macrophages in lepromatous leprosy (LL) patients to efficiently kill *M. leprae* is a predominant feature of this form of leprosy and consequently the macrophages in these patients are found to be loaded with *M. leprae*.

Phagocytic cells respond to a variety of membrane stimulants by the production and extracellular release of reactive oxygen intermediates (ROI), i.e. O_2^-, H_2O_2 and OH· metabolites. The production of these potentially active metabolites has been correlated with the intracellular killing of invading pathogens.[1,2] Recent studies have shown that intracellular pathogen may escape killing mechanisms either by inhibiting the production of ROI or by neutralizing these intermediates.[3] Phagocytosis or activation of plasma membrane enzymes by stimuli is initiated by the rapid consumption of molecular O_2 to form oxygen radicals by the NADPH oxidase system. Furthermore, the purine salvage pathway, xanthine oxidase, has also been implicated as an important contributor of O_2^- release by the phagocytic cells.[4,5] In this pathway adenosine deaminase (ADA) controls the amount of substrate (xanthine) available to xanthine oxidase, which is also required for normal immune function.[6]

In our previous study, the biphasic variation was observed during phagocytosis and the microbicidal response profile of monocytes/macrophages to 'tuftsin' stimulation against *Staphylococcus aureus*, *M. tuberculosis* and *M. leprae* as a function of culture age, corresponding to that seen with normal, BT/TT and BL/LL Mϕ led us to postulate aberrant maturation drives in BL/LL cultures (oxidative burst heterogeneity) of monocytes/macrophages.[7,8] This is further supported by low levels of endogenous serum tuftsin in lepromatous patients.[9]

In view of the aberrant phagocytic and microbicidal functions noticed in BL/LL culture, the present study was undertaken to measure the ROI production as a function of culture age after tuftsin pulsing and to correlate the results, with ADA activity, known to be involved in the maturation profile of monocytes/macrophages.

Materials and methods

PATIENTS

A total of 27 normal, 27 BT/TT and 22 BL/LL individuals, classified according to their clinical and histopathological findings, were assayed for ROI production and ADA activity. The patients were registered at the leprosy clinic, Department of Dermatovenereology, AIIMS, New Delhi. Patients received anti-Hansen's chemotherapy for less than 6 months in few cases, while most were fresh, untreated cases.

HUMAN MONONUCLEAR CELL VIABILITY AND PURITY

In brief, peripheral blood mononuclear cells (PBMC) were isolated by density gradient separation on Ficoll-paque. The interphase cells were collected, washed with cold Hank's balanced salt solution (HBSS) and suspended in RPMI-1640 (Gibco-Biocult) medium containing 10% human AB serum (heat-inactivated) containing the appropriate antibiotics, at a concentration of $1–2 \times 10^6$ cells/ml. This was then distributed equally into 24-well plates (Linbro, Flow Labs) and incubated for 3 h at 37°C in a moist atmosphere containing 5% CO_2. The non-adherent cells were removed by washing with pre-warmed

HBSS (37°C) and the monocyte enriched monolayers were then cultured in RPMI 1640-10% AB serum.[7] The adherent cells were removed at varying time intervals (1–7 days) by cold treatment and scraping with a rubber policeman. Before each assay, the adherent cells from the same individual were pooled, counted and tested for viability by tryphan blue exclusion. Routinely the yield of adherent cells was 10–15% of PBMC with a viability ranging from 95 to 97% and non-specific esterase positivity ranging from 90 to 95%. The number of adherent monocytes/macrophage were maintained at $0{\cdot}4 \times 10^5$ cells/100 μl/well in 96 well flat bottom plates for all subsequent experiments. All experiments were done twice and each sample was taken in duplicate wells.

SUPEROXIDE ANION ASSAY

Production of the superoxide anion was based on superoxide dismutase inhibitable reduction of ferric cytochrome C.[10] On the appropriate day of the assay, monocytes/macrophages were transferred to 96 well plates and were allowed to adhere for 2 h at 37°C in 5% CO_2 95% air. The media was removed and cells were washed with 0·1 ml of pre-warmed phenol red free HBSS to ensure uniform monocyte/macrophage monolayers on the bottom of the wells. The monolayers were covered with 80 μl of cytochrome C (4 mg cytochrome C/ml of phenol red free HBSS) and pulsed with tuftsin (0·22 μM and 0·88 μM). PMA (32 nM) was used as a positive stimulant. A replicate assay was performed in the presence of 20 μl of SOD (0·03 mg SOD/ml of HBSS) to verify the contribution of O_2^- to the reduction of cytochrome C. The reading was taken in an ELISA reader at 550 nm. Since the cells and cytochrome C solution in the plates were in no way disturbed by the measuring procedure, the plates were allowed to incubate for additional time intervals (30, 60 and 90 min) and reread. The amount of O_2^- produced was calculated from the extinction coefficient for the absorption of reduced cytochrome C, minus oxidized cytochrome C as read at 550 nm by the formula $21 \times 10^3\ M^{-1}\ cm^{-1}$. In the experimental conditions described above, the amounts of O_2^- produced per well, was expressed as follows:

$$\text{nanomoles } O_2^- \text{ per well} = \frac{\text{absorbance at 550 nm}}{6{\cdot}3} \times 100.$$

HYDROGEN PEROXIDE ASSAY

The assay of H_2O_2 production was based on HRPO-dependent oxidation of phenol red by H_2O_2 into a compound with increased absorbance at 600 nm.[10]

We added 100 μl/well of phenol red solution (PRS) to the cell monolayers. The PRS contained 140 mM NaCl, 10 mM potassium phosphate buffer, pH 7·0, 5·5 mM dextrose, 0·56 mM (0·2 g/L) phenol red and 19 U/ml of HRPO. Varying concentration of stimulant (tuftsin 0·22 μM and 0·88 μM) was added. PMA (32 nM) was used as positive control. Another set was kept without any stimulant. The blank was set up by putting an assay (without any cells) containing phenol red solution. The plates were incubated for the desired time period in humidified 5% CO_2–95% air chamber. Reaction was stopped with 10 μl of 1 N NaOH. The reading was taken in an ELISA reader at 600 nm. A standard curve for H_2O_2 was established for each plate using H_2O_2 ranging from 1 to 40 μM concentration with 100 μl of PRS and incubating for the desired time period at 37°C. The

amounts of H_2O_2 liberated by monocyte cultures was calculated through the standard curve.

ADENOSINE DEAMINASE ACTIVITY

Adenosine deaminase activity was measured essentially by the method of Tritsch *et al.*,[11] i.e. based on the rate of decrease in absorbance of adenosine at 265 nm.

The monocytes/macrophages monolayer was stimulated with tuftsin (0·22 μM and 0·88 μM). Another set of cells was treated with PMA (32 nM) as positive controls. One set of cells was kept without any stimulant. Cells were incubated for 1 hour. After the incubation, cells were lysed by adding 200 μl of chilled 0·5% triton X-100. The cells were scraped gently. The cell lysate was added to another tube containing 40 μl 1 mM adenosine, 60 μl tris buffer, 1·063 M, pH 7·3, and 100 μl of H_2O, and the decrease in absorbance at 265 nm was recorded. A change in 1·0 absorbance is considered to be equivalent to 0·13 μmol of adenosine deaminated.[12] Results are expressed as nmole ADA activity/hr/10^6 cells.

STATISTICAL ANALYSIS

All the experiments were done in duplicate and the results were expressed as the mean $\pm$ SD of the total number of patients in each group. Statistical analysis was done by Student's *t*-test.

Results

O_2^- PRODUCTION

The basal levels of O_2^- production on day 1 by monocytes of unstimulated cultures of normal and BL/LL subjects were within the same range (normal 0·57 $\pm$ 0·45 nmol/hr/10^6 cells, BL/LL 0·55 $\pm$ 0·41 nmol/hr/10^6 cells) while the basal level was higher in BT/TT Mϕ, i.e. 1·19 $\pm$ 0·35 nmol/hr/10^6 cells. When these cultures were stimulated with PMA (32 nM) and tuftsin (0·22 μM) they showed increased O_2^- production in normal and BT/TT Mϕ as compared to unstimulated monocytes ($p < 0·01$), whereas the BL/LL monocytes failed to show the response. However, PMA is able to stimulate O_2^- production in BL/LL monocytes (1·48 $\pm$ 0·25 nmol/hr/10^6 cells). At higher concentration of tuftsin (0·88 μM), normal and BT/TT Mϕ failed to show O_2^- release and the levels are the same as unstimulated cultures.

The 3-day-old cultures showed a progressive increase in O_2^- production in normal as well as in BT/TT macrophages upon stimulation, while BL/LL Mϕ almost showed the basal levels. In normal individuals, the 3-day-old Mϕ cultures showed a 3-fold increase in O_2^- production, by any of the stimulants (PMA 32 nM or tuftsin 0·22 μM) (Table 1); 3-day-old BT/TT Mϕ also showed approximately a 2-fold increase in O_2^- production by the same stimulants as compared to the unstimulated Mϕ of the same culture age. The basal level of O_2^- production was higher in BT/TT Mϕ as compared to normals (normal 0·49 $\pm$ 0·22 nmol/hr/10^6 cells, BT/TT 1·28 $\pm$ 0·45 nmol/hr/10^6 cells).

The 7-day-old Mϕ cultures of all groups under identical conditions behaved very

Table 1. Day and dose response profile for superoxide anion production by normal and leprosy monocytes/macrophages

Unstimulated	PMA (32 nM)	Tuftsin (0·22 μM)	Tuftsin (0·88 μM)
1-day-old culture			
N 0·57 ± 0·45	1·26 ± 0·72	0·86 ± 0·87 (A)	0·47 ± 0·35
T 1·19 ± 0·35	1·98 ± 0·92	1·47 ± 0·47 (B)	1·14 ± 0·84
L 0·55 ± 0·41	1·48 ± 0·25	0·55 ± 0·18 (C)	0·45 ± 0·20
3-day-old culture			
N 0·49 ± 0·22	1·17 ± 0·89	1·33 ± 0·85 (D)	1·09 ± 0·50
T 1·28 ± 0·45	2·30 ± 0·60	1·9 ± 0·80 (E)	1·50 ± 0·59
L 0·79 ± 0·35	0·93 ± 0·78	0·35 ± 0·13 (F)	0·31 ± 0·16
7-day-old culture			
N 0·40 ± 0·27	0·62 ± 0·48	1·07 ± 0·59 (G)	0·73 ± 0·26
T 0·94 ± 0·30	2·13 ± 0·60	1·2 ± 0·48 (H)	0·90 ± 0·59
L 0·30 ± 0·047	0·39 ± 0·09	0·20 ± 0·10 (I)	0·19 ± 0·05

Results expressed (nmol/hr/10^6 cells).

N = normal ($n = 13$); T = tuberculoid ($n = 13$); L-lepromatous ($n = 8$) values expressed as mean ± SD [n as in ( )].

A–B = $p < 0{\cdot}01$; A–C = p = NS*, B–C = $p < 0{\cdot}001$, E–F = $p < 0{\cdot}001$, E–H = $p < 0{\cdot}05$; H–I = $p < 0{\cdot}001$.

* NS = not significant.

differently. The O_2^- production tapered off in all groups as the culture aged at any of the concentration of tuftsin.

H_2O_2 RELEASE

The H_2O_2 production was also measured in these cultures as a function of culture age (1–7 day). 1-day-old normal monocytes produced a basal level of 17·75 ± 2·3 nmol/hr/10^6 cells. When these cells were stimulated with PMA (32 nM), the levels of H_2O_2 rose to 476·75 ± 36·7 nmol/hr/10^6 cells. Tuftsin (0·22 μM) stimulation caused a 3-fold increase in H_2O_2 production when compared to basal level of 1-day-old cultures. The basal levels of BT/TT and BL/LL Mϕ cultures on day 1 were almost the same (8·39 ± 4·9 nmol/hr/10^6 cells and 7·3 ± 1·5 nmol/hr/10^6 cells, respectively). PMA stimulation showed higher H_2O_2 release in both the cases, and tuftsin stimulation (0·22 μM) showed approximately a 5–6-fold increase in H_2O_2 production. At a higher concentration of tuftsin (0·88 μM), normal and BT/TT Mϕ of 1-day-old cultures showed an inhibitory effect, whereas the levels of H_2O_2 produced by BL/LL Mϕ were comparatively less than 0·22 μM tuftsin stimulation. On the whole, a 3-fold increase in H_2O_2 production was observed when compared to the basal levels.

The 3-day-old cultures of normal and BT/TT behaved in a similar manner in the production of H_2O_2 under optimal conditions, whereas BL/LL Mϕ behaved differently. The basal production of H_2O_2 in normal and BT/TT Mϕ was almost the same (24·25 ± 2·8 nmol/hr/10^6 cells and 25·3 ± 12·0 nmol/hr/10^6 cells, respectively) although there is a slight

increment when compared to 1-day-old cultures. The BL/LL Mϕ showed lower levels of H_2O_2 production in unstimulated cultures ($5{\cdot}34 \pm 0{\cdot}65$ nmol/hr/10^6 cells). PMA stimulation showed a 20-fold increase in H_2O_2 production in all the groups. Tuftsin (0·22 μM) showed a 3–4-fold increase in H_2O_2 production in normal and BT/TT while there was approximately a 6-fold increase in BL/LL Mϕ cultures. At higher concentration of tuftsin (0·88 μM), the normal and BT/TT Mϕ showed basal levels similar to unstimulated cultures, while BL/LL Mϕ showed a 4-fold increase compared to the unstimulated cultures.

The 7-day-old cultures showed a decline in H_2O_2 production in all 3 groups when compared to 3-day-old cultures of unstimulated Mϕ, and although there is a decrease in H_2O_2 production in the 7-day-cultures, the fold increase within the same group in 3-day- and 7-day-old cultures are comparable.

ADA ACTIVITY

In 1 day Mϕ of normal and BT/TT, after pulsing with tuftsin (0·22 μM), the ADA activity was almost the same (normal $22{\cdot}75 \pm 7{\cdot}02$ nmol/hr/10^6 cells; BT/TT $28{\cdot}39 \pm 7{\cdot}2$ nmol/hr/10^6 cells). The unstimulated cultures of normal and lepromatous types were unable to show detectable ADA activity, while the tuberculoid Mϕ did show this activity ($24{\cdot}37 \pm 1{\cdot}6$ nmol/hr/10^6 cells). Surprisingly, the lepromatous cultures showed higher ADA activity ($126{\cdot}12 \pm 33{\cdot}47$ nmol/hr/10^6 cells) on stimulation. At a higher concentration of tuftsin, the BT/TT and BL/LL Mϕ showed almost the same ADA activity. In 3-day-old normal cultures, tuftsin pulsing showed a 3-fold increase in ADA activity, while tuberculoid Mϕ failed to show a similar response. The BL/LL Mϕ also failed to show any detectable ADA activity in stimulated or unstimulated cultures. Higher tuftsin concentration (0·88 μM) showed less ADA activity than the unstimulated cultures.

In 7-day-old normal cultures there is a decrease in ADA activity in stimulated cells when compared to 3-day-old cultures. The unstimulated cultures failed to show any detectable ADA activity.

Discussion

Tuftsin is an endogenous immunomodulator for macrophage phagocytic and microbicidal functions.[13] One of the most important mechanisms of intracellular killing of ingested micro-organisms or pathogens by mononuclear cells is the generation of toxic oxygen products[1,14] through NADPH oxidase or xanthine oxidase pathways. The NADPH oxidase is dormant in non-activated phagocytes. It is activated when phagocytes are exposed to the appropriate stimuli and thereby contributes to the microbicidal activity of these cells. Infection leads to increased xanthine oxidase activity, thus also contributing to the release of toxic oxygen radicals. In this study we have compared the release of O_2^-, H_2O_2, and ADA activity in response to tuftsin pulsing on monocytes/macrophages derived from leprosy patients as a function of *in vitro* culture age. Our results show that 0·22 μM tuftsin is the optimal dose for *in vitro* stimulation, while higher doses of tuftsin (0·88 μM) show an inhibitory effect. This is in accordance with observations by others.[5,15]

The monocytes/macrophages were pulsed with tuftsin and the time kinetics were

studied at 30, 60 and 90 min to determine the optimal time for the maximal release of these metabolites. Maximal release was obtained at 60 min (data not shown). The present study clearly demonstrates that tuftsin augments the release of ROI even in the absence of a phagocytic event.[11,16,17,18] Moreover, the release of ROI was related to the age of monocyte derived macrophages as well as the clinical spectrum of the disease.

The basal values of O_2^- released by unstimulated macrophages of tuberculoid individuals was higher than that of lepromatous and healthy subjects. Though in general the 3-day-old macrophage cultures showed maximal levels, the age of the macrophages did not alter the pattern of release. Similarly, tuftsin also showed maximal effects by day 3 on tuberculoid macrophages. In contrast, lepromatous macrophages were not stimulated by tuftsin. Hydrogen peroxide release was also maximal on day 3 for tuberculoid and normal as compared with lepromatous Mϕ. At all time points, the latter showed the lowest levels of H_2O_2. It was interesting to discover that tuftsin significantly improved H_2O_2 release of the hitherto poor lepromatous Mϕ. Tuberculoid and normal Mϕ needed a 3-day period to reach maximal levels, while lepromatous Mϕ released maximal levels on day 1. Lepromatous macrophages produced 50% as much H_2O_2 as that of normal macrophages upon stimulation with PMA or tuftsin, supporting the observations of Nathan *et al.*[19] Thus this immunomodulator had a differential effect on ROI production as it was ineffective in improving O_2^- release from the lepromatous Mϕ. Interestingly, tuftsin in lower concentrations was a more effective stimulator than at higher concentrations.

Our results show a high level of H_2O_2 release by BL/LL cultures as compared to O_2^-; molecular O_2 is reduced to O_2^- within the monocytes/macrophages at a site accessible to SOD, so that H_2O_2 is more likely to be secreted than O_2^- throughout the spectrum. Similar observations or failure to get sufficient O_2^- release has been noticed by other workers using lepromatous macrophages.[20,21,22] Mature macrophages are known to be associated with high SOD activity. The high H_2O_2 levels with BL/LL Mϕ observed in our study further support the view that they appear to be fully differentiated or matured. The level of differentiation and age of *in vitro* culture can be correlated with the production of reactive oxygen intermediates and biochemical enzymes associated with monocytes/macrophages. Tuprin *et al.*[23] have shown that small monocytes produce increasing amounts of H_2O_2 with increasing culture age *in vitro*. In addition, these cells were stimulatory towards LPS and γ-IFN. However, large monocytes showed decreased H_2O_2 production with increasing age of culture, an observation similar to our findings. It was also observed that peripheral blood PMNs of lepromatous patients were able to reduce Nitroblue tetrazolium[24,25] with an enhanced endogenous SOD activity.[26] Further, since *M. leprae* contained SOD activity, it is probably able to protect itself from the effect of the superoxide radical by converting O_2^- to the less toxic H_2O_2.[27] Therefore, when lepromatous leprosy or its like occurs, the multiplication/killing of *M. leprae* within the Mϕ is inhibited by the interaction between H_2O_2 and O_2^- and this is important for the subsequent release of other toxic radicals like OH$\cdot$ and O_2^1.[3] All these results led us to speculate that despite H_2O_2 generation in BL/LL patients another important metabolite like O_2^- is also essential to effectively kill *M. leprae*. The unresponsiveness of Mϕ to modulation, and its failure to become sufficiently activated by tuftsin, as seen in present study, especially in BL/LL Mϕ, could result in growth or multiplication of *M. leprae* inside the macrophages which is one of the characteristic features of lepromatous leprosy.[28] It also seems that the T cell activation and specific lymphokine secretion as well

Table 2. Day and 1-dose response profile of monocytes/macrophages cultured *in vitro* (1 day–7 day) of normal and leprosy patients for production of hydrogen peroxide

Unstimulated	PMA (32 nM)	Tuftsin (0·22 μM)	Tuftsin (0·88 μM)
1-day-old culture			
N 17·75±2·3	476·75±36·7	43·08±13·2 (A)	3·19±0·14
T 8·39±4·9	297±166	42·28±11·3 (B)	2·2±0·3
L 7·3±1·5	228±51·5	44·68±9·7 (C)	25·68±8·6
3-day-old culture			
N 24·25±2·8	692·25±32	79·96±8·9 (D)	30·3±4·2
T 25·3±12	507±34·2	95±32·7 (E)	32·12±13·5
L 5·34±0·65	231±42·8	31·5±1·62 (F)	21·12±6·8
7-day-old culture			
N 7·32±2	307·75±37	30±8·5 (G)	12·79±5·7
T 8·3±1·6	249±50	35·4±5·4 (H)	20·5±5·0
L 2·8±1·7	155±11·7	19·9±5·59 (I)	22·6±2·3

Results expressed (nmol/hr/10^6 cells).
N = normal ($n=8$); T = tuberculoid ($n=8$); L-lepromatous ($n=8$) values expressed as mean ± SD [n as in ( )].
A–D = $p<0{\cdot}001$; B–E = $p-<0{\cdot}001$; C–F = $p<0{\cdot}001$; D–G = $p<0{\cdot}001$; E–H = $0<0{\cdot}001$; F–I = $p<0{\cdot}05$.

as the unresponsiveness of macrophages for activation could also be linked to aberrant Mϕ function in LL patients.

Fischer *et al.*[6] have shown the importance of ADA for normal macrophage function and for the maturation of monocytes to macrophages. A hereditary deficiency of ADA has been shown to be associated with defective cellular and humoral immunity.[29]

In our study, except in 1-day BL/LL macrophage, measurable ADA activity was not detected in 3-day- and 7-day-old cultures. Since no measurable ADA activity was seen after 60 min of tuftsin pulsing, a parallel 15-min experiment was conducted with tuftsin pulsing to discover if ADA activity was detectable any earlier, but measurable ADA activity was not detected in these cultures. Interestingly, we found a direct relationship between ADA activity and O_2^- generation in normal and BT/TT groups.

Our findings show that fresh monocytes (1 day old) from either end of the spectrum of leprosy have basal production of metabolites, and after pulsing with an optimal dose of tuftsin the levels of these metabolites increase progressively. This increase was statistically significant ($p<0{\cdot}01$) (Tables 1–3). The basal level of ROI production is consistent with our earlier findings that the rate of microbicidal activity by Mϕ from all 3 groups did not appear to be impaired.[8] The 3-day-old cultures of normal and BT/TT Mϕ behaved similarly in the absence of any stimulant, but on stimulation showed a progressive rise in ROI production, a finding similar to that seen with human monocytes when they differentiate to macrophages *in vitro*.[27] The macrophages of BL/LL patients behaved as if they had prematurely aged and differentiated. In all 3 groups, the 7-day-old cultures failed to generate ROI production.

Table 3. Day and dose response of monocytes/macrophages derived from peripheral blood of normal and leprosy patients for adenosine deaminase activity

Unstimulated	PMA (32 nM)	Tuftsin (0·22 μM)	Tuftsin (0·88 μM)
1-day-old culture			
N ND	44·12 ± 5·32	22·75 ± 7·02 (A)	14·0 ± 11·9
T 24·37 ± 1·6	19·65 ± 10·88	28·39 ± 7·2	38·17 ± 4·07
L ND	ND	126·12 ± 33·47	37·91 ± 22·5
3-day-old culture			
N 31·17 ± 1·05	54·00 ± 26·2	93·16 ± 31·9 (B)	22·7 ± 6·4
T 30·9 ± 6·7	37·3 ± 7·9	25·4 ± 9·2	15·5 ± 6·5
L ND	ND	ND	ND
7-day-old culture			
N ND	43·36 ± 22·0	49·40 ± 5·5 (C)	15·75 ± 6·2
T ND	ND	ND	ND
L ND	ND	ND	ND

Results expressed (nmol/hr/10^6 cells).
N = normal ($n = 6$); T = tuberculoid ($n = 6$); L-lepromatous ($n = 6$).
ND = not detectable.
Values expressed as mean ± SD [n as in ( )].
A–B = $p < 0{\cdot}001$; B–C = $p < 0{\cdot}01$.

The possible cause of decreased ROI production seen with older cultures could be due to several possibilities. These are (a) an increased activity of H_2O_2 scavengers after day 3 of culture,[27] (b) specific enzyme/enzymes defects associated with ROI production; and (c) the functional heterogeneity of monocytes/macrophages as suggested by Norris *et al.*[30] Therefore, the differentiation of monocytes to macrophages *in vitro* involves a gradual transition of morphologic, physiologic, and biochemical changes, and the survival of a given pathogen inside it may depend on the level of differentiation of the monocyte that it infects.

This is the first reported study measuring ROI intermediates and ADA activity from the monocytes/macrophages of leprosy patients after tuftsin pulsing as a function of the age of culture. It is tempting to speculate that in addition to the protective mechanisms of the pathogen, biochemical factors are also involved in the defective macrophage function of lepromatous patients. We are currently measuring the levels of different second messengers like $[Ca^{++}]_i$, cyclic nucleotides and tuftsin receptor sites/affinities on the monocytes/macrophages derived from the leprosy individuals in the presence and absence of tuftsin stimulation.

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References

[1] Babior BM. Oxygen-dependent microbial killing by phagocytes. *N Engl J Med*, 1978; **298:** 659–68.

[2] Nathan CF, Nogueria N, Juangbhrich C, Ellis J, Cohn ZA. Activation of macrophages *in vivo* and *in vitro*. Correlation between hydrogen peroxide release and killing of *Trypanosoma cruzi*. *J exp Med*, 1979; **149:** 1056–68.

[3] Murray HW, Cohn ZA. Macrophage oxygen-dependent antimicrobial activity. I. Susceptibility of *Toxoplasma gondii* to oxygen intermediates. *J exp Med*, 1979; **150:** 938–9.

[4] Chan TS. Purine excretion by mouse peritoneal macrophages lacking adenosine deaminase activity. *Proc Natl Acad Sci USA*, 1979; **76:** 925–9.

[5] Tritsch GL, Niswander PW. Purine salvage pathway enzyme activity in Tuftsin stimulated macrophages. *Ann NY Acad Sci*, 1983; **419:** 87–92.

[6] Fischer D, Weyden MBV, Snyderman R, Kelley WN. A role for adenosine deaminase in human monocytes maturation. *J Clin Invest*, 1976; **58:** 399–407.

[7] Iyer RR, Prasad HK, Bhutani LK, Rao DN. Modulation of human lepromatous monocytes-macrophages functions *in vitro* by tuftsin. *Int J Immunopharmac*, 1990; **12:** 847–58.

[8] Iyer RR, Prasad HK, Bhutani LK, Rao DN. Effect of tuftsin stimulation on the microbicidal activity exerted by blood monocytes-macrophages of leprosy patients. *Int J Immunopharmac*, 1990; **12:** 859–69.

[9] Kaur J, Khare S, Bhutani LK, Rao DN. Enzyme immunoassay of phagocytosis stimulating tetrapeptide 'Tuftsin' in normal and leprosy sera. *Int J Lepr*, 1991; **59:** 576–81.

[10] Pick E, Mizel D. Rapid microassays for the measurement of superoxide and hydrogen peroxide production by macrophages in cultures using an automatic enzyme immunoassay reader. *J Immunol Methods*, 1981; **46:** 211–26.

[11] Tritsch GL, Niswander PW. Adenosine deaminase activity and superoxide formation during phagocytosis and membrane perturbation of macrophages. *Immunol Commun*, 1981; **10:** 1–8.

[12] Tritsch GL. Adenosine aminohydrolase inhibition in cosolvent buffer mixtures. *Arch Biochem Biophys*, 1974; **161:** 698–74.

[13] Najjar VA. Tuftsin, a natural activator of phagocytic cells: an overview. *Ann NY Acad Sci*, 1983; **419:** 1–11.

[14] Johnston RB, Godzik Jr. GA, Cohn ZA. Increased superoxide anion production by immunologically activated and chemically elicited macrophages. *J Exp Med*, 1978; **148:** 115–27.

[15] Tzehoval E, Segal S, Stabinsky Y, Fridkin M, Spirer Z, Feldmna M. Tuftsin (an Ig. associated tetrapeptide) triggers the immunogenic function of macrophages: general implications to activation of programmed cell. *Proc Natl Acad Sci USA*, 1978; **75:** 3400–4.

[16] Hartung HP, Toyka KV. Tuftsin stimulates the release of oxygen radicals and thromboxane from macrophages. *Immunol Lett*, 1983; **6:** 1–6.

[17] Hartung HP, Toyka KV. Augmentation of oxidative and arachidonate metabolism in macrophages by tuftsin (Thr-Lys-Pro-Arg). *Agents Actions*, 1984; **15:** 38.

[18] Kain Z, Alkan M, Ghaimovitz G, Segal S, Fridkin M, Levy R. Human peritoneal macrophage activity is increased by tuftsin. *Immunol Lett*, 1989; **21:** 257–61.

[19] Nathan CF, Kaplan G, Levis WR, Nusrat A, Witmer MD, Sherwin SA, Job CK, Horowitz CR, Steinman RM, Cohn ZA. Local and systemic effects of intradermal recombinant interferon-Y in patients with lepromatous leprosy. *N Engl J Med*, 1986; **315:** 6–15.

[20] Holzer TJ, Nelson KE, Schauf E, Crispen RG, Andersen BR. *Mycobacterium leprae* fails to stimulate phagocytic cell superoxide anion generation. *Infect Immun*, 1986; **51:** 514–26.

[21] Marolia J, Mahadevan PR. Superoxide production from macrophages of leprosy patients after stimulation with *Mycobacterium leprae*. *J Biosci*, 1987; **12:** 273–9.

[22] Marolia J, Mahadevan PR. *Mycobacterium leprae* mediated stimulation of macrophages from leprosy patients and hydrogen peroxide production. *J Biosci*, 1988; **13:** 295–303.

[23] Tuprin J, Hersch HE, Lopez-Berestein. Characterization of small and large human peripheral blood monocytes: effects of *in vitro* maturation of hydrogen peroxide release and on the response of macrophage activation. *J Immunol*, 1986; **136: (II)** 4194–8.

[24] Goihman-Yahr MG, Rodriguez-Ochoa, Aranzaz UN, Inardi ME, Gomez de Ocanto A, Convit J. *In vitro* activation of neutrophils by suspensions of *Mycobacterium leprae*. *Int J Lepr*, 1970; **47:** 570–4.

[25] Lim SD, Kim WS, Kim GS, Good RA, Park BH. NBT responses of neutrophils and monocytes in leprosy. *Int J Lepr*, 1974; **42:** 150–3.

[26] Niwa Y, Sakane T, Miyachi Y, Ozaki M. Oxygen metabolism in phagocytes of leprotic patients: enhanced endogeneous superoxide dismutase activity and hydroxyl radical generation by clofazamine. *J Clin Microbiol*, 1984; **20:** 837–42.

[27] Nakagawara A, Nathan CF, Cohn ZA. Hydrogen peroxide metabolism in human monocytes during differentiation *in vitro*. *J Clin Invest*, 1981; **68:** 1243–52.

[28] Samuel DR, Godal T, Myrvang B, Song YK. Behaviour of *Mycobacterium leprae* in human macrophages *in vitro*. *Infect Immun*, 1973; **8:** 446–9.

[29] Giblett ER, Anderson JE, Cohen F, Pollera B, Meuwissen HJ. Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. *Lancet*, 1972; **2:** 1067–9.
[30] Norris DA, Morris RM, Sanderson RJ, Kohler RF. Isolation of functional subsets of human peripheral blood monocytes. *J Immunol*, 1979; **123:** 166–72.

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Modulation des monocytes/macrophages dérivés du sang périphérique de malades lépreux en utilisant 'Tuftsin' pour produire des intermédiaires de l'oxygène activé

S. Khare, L. K. Bhutani et D. N. Rao

Résumé Les cellules de phagocytes répondent à divers stimulants de la membrane en produisant des intermédiaires de l'oxygène activé (ROI), c'est-à-dire les métabolites O_2^-, H_2O_2 et OH·. L'activation de la membrane plasmatique est associée à l'opxydase NADPH génératrice de superoxyde, ce qui provoque la production de ces substances toxiques. La stimulation des phagocytes aboutit également à l'activation du catabolisme de la purine, qui dirige le métabolisme, par la voie xanthine-oxydase, vers la production de l'anion superoxyde. Nous avions observé auparavant que les macrophages BL/LL (Mø) perdaient prématurément leur faculté de subir la phagocytose et l'activité microbicide stimulées par la tuftsine. L'objet de cette étude était de mesurer les taux de ROI avec ou sans flux de 'tuftsine' en fonction de l'âge de la culture *in vitro* et aussi de rapporter ces taux à l'activité adénosine-déaminase (ADA). On sait que cette dernière contribue à la production de O_2^- etr joue un rôle dans la maturation du système monocyte/macrophage. Le comportement des monocytes/macrophages mormaux et tuberculoïdes était similaire en présence ou en l'absence de tuftsine, c'est-à-dire qu'il présentait un accroissement progressif de la producton de ROI jusqu'au jour 3 de culture, puis un ralentissement sur les cultures plus vieilles, au jour 7. Par contre, après le jour 1, les macrophages lépromateux n'étaient pas capables d'être induits par la tuftsine à produire ROI et à activer ADA. Ces résultats mettent en évidence une déficience de la fonction Mø chez les patients lépromateux envers le flux tuftsine, ce qui confirme nos observations précédentes. Ainsi les macrophages BL/LL se comportent comme s'ils étaient déja vieillis après un jour de culture *in vitro*, ce qui expliquerait leur impuissance à éradiquer efficacemnt *Mycobacterium leprae*.

Modulación de los monocitos/macrófagos de la sangre periférica de pacientes leprosos, usando 'Tuftsin' para la producción de productos intermedios de oxígeno reactivo

S. Khare, L. K. Bhutani y D. N. Rao

Resumen Les céculas fagocítas responden a muchos diferentes estimulantes de membrana mediante la producción de productos intermedios de oxígeno reactivo (ROI), por ejemplo, los metabolitos O_2^-, H_2O_2 y OH·. La activación de la membrana plásmica está asociada con oxidasa NADPH que genera superóxido, causando de este modo la producción de estas especies tóxicas. La estimulación de células fagocíticas también resulta en la activación del catabolismo purínico que dirige el flujo metabólico a través de la oxidasa xantínica para producir el anión de superóxido. Hemos observado con anterioridad que los micrófagos BL/LL exhiben una inhabilidad prematura de fagocitosis estimulado por el 'Tuftsin', y de actividad microbicida. El estudio actual fue realizado para medir los niveles de ROI en la ausencia y presencia de pulsación de 'Tuftsin', en función de la edad del cultivo en vitro, y también correlacionar estos niveles con la actividad de deaminasa adenosínica (ADA). Se sabe que éste es un contribuidor a la generación de O_2^-, y también está implicada en la maduración del sistema monocito/macrófago. El comportamiento de monocitos/macrófagos normales y tuberculoides es más o menos idéntico, sea en la presencia o ausencia de 'Tuftsin', es decir, hubo un aumento progresivo de la producción de ROI hasta el día número 3, luego hubo una disminución gradual en los cultivos más viejos. Vuelta en cambio, después del día 1, no se podían estimular los macrófagos lepromatosos mediante 'Tuftsin' para que tengan actividad ROI y ADA. Estos resultados indican una función Mϕ defectuosa a la pulsación de 'Tuftsin' por parte de los pacientes lepromatosos, confirmando nuestras observaciones anteriores. Así, el Mϕ BL/LL se comportó como si se hubiera envejecido después de un día en un cultivo en vitro, lo cual puede explicar su letalidad ineficaz frente a *Mycobacterium leprae*.

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Reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate for an antileprosy vaccine, *Mycobacterium w*

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Summary Immunotherapy with a candidate for an antileprosy vaccine, *Mycobacterium w*, was given in addition to standard multidrug therapy (MDT) to 53 multibacillary lepromin negative patients belonging to BB, BL and LL types of leprosy (vaccine group). An equal control group received MDT and injections of micronized starch as placebo. Both the vaccine and placebo were administered intradermally every 3 months. The patients were evaluated at determined intervals by clinical, bacteriological and histopathological parameters and lepromin testing. Reactional episodes were analysed with reference to incidence, onset, frequency and severity during and after release from treatment (RFT). Incidence of reversal reaction (RR) was marginally higher in the vaccine group (22·6% vaccine group *vs* 15% control group). All cases with a history of downgrading type 1 reaction developed RR during therapy. Most episodes occurred within the 1st year of the commencement of therapy—50% developing within 3 months. Late reversal reaction (after RFT) were observed in 3·8% of cases in both groups, and 50% of the reactors in the control group and 33% in the vaccine group had repeated reactional episodes. Incidence of neuritis associated with RR as well as isolated neuritis was similar in both groups.

Introduction

This study forms part of a large-scale immunotherapeutic clinical trial of a candidate for an antileprosy vaccine, *Mycobacterium w* (*M.w*), which is currently in progress at the Dr. RML and the Safdarjang Hospitals of New Delhi in association with the National

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Institute of Immunology and the Institute of Pathology (Indian Council of Medical Research), New Delhi. Multibacillary leprosy patients receiving immunotherapy with *M.w* along with MDT have shown a distinctly better clinical improvement and a more rapid bacterial clearance than those who received MDT alone.[1,2] There was lepromin conversion in all BB, 85% BL and more than 80% LL patients after 8 doses of vaccine, but in only 40% BB and 0% BL and LL patients under MDT alone.[2] In the vaccine group, the percentage of BL and LL cases becoming clinically and bacteriologically inactive after 24 pulses was 100% and 66·6%, respectively, whereas in the control group it was only 50% and 15%, respectively.[2] Histopathologically, 75% LL cases and 85% BL cases receiving MDT and vaccine either showed upgrading along the spectrum or a clearance of granuloma from the dermis, in comparison with 50% BL and 33·3% LL cases in the control group.[3]

In this paper we have analysed the data of 106 cases who have completed 2 years of therapy with special reference to the incidence, onset, frequency and severity of reversal reaction (RR) observed during therapy and after RFT.

Materials and methods

SUBJECTS AND DESIGN

Phase II/III immunotherapeutic trials with *M.w* were started in January 1987. Patients reporting to the Urban Leprosy Centres of 2 hospitals in Delhi were screened by clinical, immunological, bacteriological and histopathological criteria. Patients with no previous history of antileprosy treatment (a) falling in the BB, BL and LL spectrum of the disease (according to the Ridley–Jopling Scale); (b) showing the presence of bacilli in slit skin smears; (c) having lepromin A (armadillo derived) negativity initially and (d) having features of BB, BL and LL type of disease histopathologically were inducted into the study. Standard MDT as recommended by NLEP of India[4] was given to all those enrolled. In addition, half of the patients received *M.w* vaccine and the other half received an injection of micronized starch as placebo. The allotment of the patients was done in a randomized manner according to a code supplied to the attending physician. Random testing of urine for the presence of dapsone was carried out in all patients before their induction to this study in order to confirm that they had not recently received treatment with dapsone.[5]

The trials were single blind, in which the Head of the Department of Dermatology, Venereology and Leprology knew the group to which each patient belonged, whereas the patients and the attending physicians, as well as the investigators carrying out the histopathology, BI and clinical scores, did not know whether the patient was receiving the vaccine or placebo. In all, 106 patients participated in this study and are either taking or have had regular treatment for at least 24 months.

Vaccine—dosage, administration and regimen

The vaccine was injected intradermally in the deltoid region. A total of 8 vaccine doses were given at 3 monthly intervals. The first dose was 1×10^9 autoclaved bacilli in 0·1 ml physiological saline (0·85% NaCl). Subsequent doses contained 5×10^8 killed bacilli.

Placebo

This consisted of 1 g micronized starch (Sarabhai Chemicals, Baroda, India), dissolved in 100 ml of distilled water and autoclaved. Dosage, administration and regimen was similar to that of the vaccine.

Lepromin

Armadillo lepromin containing 4×10^7 killed bacilli per ml, supplied by WHO, was used for the study.

Multidrug therapy (MDT)

This consisted of 2 weeks of intensive therapy with 600 mg rifampicin, 100 mg clofazimine and 100 mg of dapsone daily. Subsequently, the patients received for 2 years the WHO recommended regimen of 600 mg of rifampicin and 300 mg clofazimine once a month supervised plus 100 mg dapsone and 50 mg clofazimine daily, self-administered. Drug regularity was checked by randomly conducting a spot test for DDS in the urine[5] and by counting the tablets.

EVALUATION

General

Patients were evaluated clinically by Ramu's clinical score[6,7] at 6 monthly intervals. Bacterial indices (BIs) were calculated at 3 monthly intervals according to Ridley's logarithmic scale.[8] A 0·1 ml dose of lepromin A (armadillo derived) was injected every 3 months. An induration of more than 3 mm diameter was taken as positive. Histopathological examination of a typical skin lesion was done every 6 months.

For Reaction

A proforma sheet for leprosy reaction was filled in at the time of the patient's induction and subsequently during each reactional episode. The present and past history of reaction, detailed clinical findings (with special reference to exaggeration of existing skin lesions), appearance of fresh lesions and their density and distribution were noted. The presence or absence of constitutional symptoms like a rise in temperature, malaise, insomnia, anorexia, pain/tenderness of peripheral nerves, recent development of sensory and motor deformities, joint and muscle pain, eye changes, testicular tenderness and swelling, lymph nodes, spleen and liver enlargement were carefully recorded. The grading of the RR and the treatment administered was also documented. RR was graded as mild or severe.[9] Mild reactions were managed with rest, physiotherapy and non-steroidal anti-inflammatory drugs (NSAID) for a period of 6 weeks. Severe cases were managed with initial hospitalization, physiotherapy, oral steroids (for 12–20 weeks) along with NSAID whenever necessary.

The diagnosis of reaction was made clinically. In doubtful cases skin biopsy was carried out to confirm the clinical diagnosis. Lepromin testing was done during each episode of RR.

Table 1. Number of cases enrolled in study

Type of leprosy	MDT + vaccine (vaccine group)	MDT + control (control group)	Total
BB	14	14	28
BL	14	14	28
LL	25	25	50
Total	53	53	106

Table 2. Incidence of type 1 reactions previous to therapy

Group	DG* type 1 reaction	Isolated neuritis
Vaccine	3/53 (2-BL, 1-BB)	2/53 (1-BB, 1-LLs)
Control	3/53 (2-BL, 1-BB)	2/53 (2-BL)

Figures in parentheses indicate break up according to type of leprosy.
* DG = downgrading.

Table 3. Incidence of reversal reaction (RR) during therapy

Group	Number of cases					
	Reversal reaction			Isolated neuritis		
Vaccine	BB	BL	LL	BB	BL	LL
	4/14	5/14	3/25	1	0	1
	Total 12/53 (22·6%)					
Control	BB	BL	LL	BB	BL	LL
	4/14	3/14	1/25	0	1	0
	Total 8/53 (15·1%)					

Results

Table 1 gives the number of patients belonging to different types of leprosy who were inducted into the study, i.e. 106, with the vaccine and control group each containing 50%.

Table 2 describes the incidence of type 1 reactions and isolated neuritis observed before or at the time of the patients' enrolment in this study—3 cases had downgrading type 1 reaction and 2 cases had a history of isolated neuritis in each group.

Table 3 depicts the incidence of RR and isolated neuritis observed during the 2 years of therapy in both vaccine and control groups according to the spectrum of leprosy.

Table 4. Time of onset of reversal reactions after initiating therapy

Group	No. of patients with RR	Time of onset of RR (months)				
		0–3	3–6	6–12	12–24 or >24	After RFT (late reversal reaction)
Vaccine	12	5	2	4	—	1+(1*)
Control	8	4	1	2	—	1+(1*)

A patient from the vaccine group and 1 from the control group had had previous episode of RR while under MDT.

Table 5. Frequency of reversal reactions

Group	No. of patients	No. of patients showing		
		1 episode	2 episodes	>2 episodes
Vaccine	12	8 (66·6)*	4 (33·3)	—
Control	8	4 (50)	2 (25)	2 (25)

* Numbers in parentheses are percentages.

Table 6. Severity of reversal reactions

Group	No. of episodes	Mild	Severe
Vaccine	16	9 (56·3)*	7 (43·7)
Control	15	10 (66·6)	5 (33·3)

* Numbers in parentheses are percentages.

In the vaccine group 22·6% of cases developed RR in comparison to 15·1% in the control group during the 2-year follow-up period. This difference is not statistically significant (proportion test, $z = 0{\cdot}993$). In the BB group incidence of RR was the same (28·6%) in both groups whereas among both BL and LL patients, this was 20·5% in the vaccine group and 10·2% in the control group. This difference is not statistically significant (proportion test, $z = 1{\cdot}255$). All cases with a history of downgrading reaction in both groups developed RR after therapy.

We observed 2 cases of isolated neuritis in the vaccine group (1 BB case with left ulnar nerve and 1 LL case with right ulnar nerve involvement). These 2 cases had a previous history of ulnar neuritis. In the control group, out of the 2 BL cases with a previous history of neuritis, only 1 developed ulnar neuritis.

As is evident in Table 4, the onset of all reversal reactions were seen within 1 year of the initiation of therapy in both groups, 50% developing reactional episodes within 3 months

irrespective of the type of leprosy—4 patients (3 within 6 months and 1 after 22 months of RFT) had late reversal reactions. All 4 patients at the time of late RR had negative BI, higher positivity of lepromin reaction and histopathologically non-specific infiltration, i.e. a mild to moderate degree of lymphocytic infiltration in the dermis.

In the control group, 50% of the cases with RR had 2 or more reactional episodes, whereas only 33% of cases with RR in the vaccine group had multiple episodes of reaction (Table 5).

A marginally higher percentage of severe type of reactional episodes were observed in the vaccine group compared to the control group (43·7% *vs.* 33·3%) (Table 6). However, this difference was not statistically significant ($z = 0{\cdot}595$).

In both groups (except 1 BB and 1 BL case in the control group) patients with RR had lepromin conversion either before or at the time of reaction. In the control group, lepromin conversion was transiently observed at the time of RR and subsequently there was a reversion to negativity.

Discussion

Reversal reactions commonly occur in borderline leprosy patients and are associated with an abrupt rise in cell mediated immune responses to mycobacterial antigens.[10] They are most frequently seen during the initial phases of the introduction of chemotherapy.[10] But this reaction is rarely observed among LL patients, possibly due to their inability to mount CMI responses to this pathogen.

Following immunostimulation, a rise in the incidence of RR even in the LL group is easy to predict. It has been reported in 3 out of 4 LL patients given multiple injections of Transfer Factor by Hastings & Job.[11] Convit *et al.*[12] observed a reversal reaction associated with lepromin conversion in indeterminate leprosy cases who had been administered multiple injections of a vaccine containing heat killed *M. leprae* and BCG. The reaction was not seen if either *M. leprae* and BCG were given alone. In another study from Bombay, India, where killed ICRC bacilli was administered in addition to chemotherapy with DDS, 5 out of 96 LL cases developed reversal reaction.[13]

In our study an equal percentage of BB patients in the vaccine and control groups developed reversal reaction but among BL and LL patients a higher incidence of RR was observed in the vaccine as against the control group (20·4% *vs.* 10·2%). An interesting observation among the LL vaccinated patients was that 3 of them had RR episodes. These 3 cases were highly bacilliferous (BI 6+, 5+ and 4+). After the 1st dose of vaccine two of them developed mild RR during the 3rd month of therapy) with minimal BI fall. The 3rd patient presented with a reactional episode at the 9th month with a BI fall from 5·8+ to 3·5+. All of them demonstrated lepromin conversion. Therefore, in full agreement with Bhatki *et al.*,[13] there appears to be little relationship between bacillary load and occurrence of RR. This is also supported by the observation that more than half of the cases developing RR had the onset of reaction within the first 3 months of treatment initiation, despite minimal BI fall during this period.

Higher incidence of RR in the vaccine group could be due to a rapid stimulation of cell-mediated immunity. This would explain the slightly higher incidence of a severe form of RR in the vaccine group. But once the reaction is controlled with steroids, the relapse of reaction is less frequent among vaccinated patients. This may probably be due to a steady

and gradual build up of cell-mediated immunity with subsequent vaccination. Immunochemotherapy with *M.w* along with chemotherapy possibly results in a rapid clearance of mycobacterial antigens and establishes a delicate balance between antigens available for immune reactions and host responses.

The major problem associated with RR is that of neurological complications leading to deformities. In our series, 4 out of 16 episodes of RR in the vaccine group and 3 out of 15 episodes in the control group had neuritis (right lateral popliteal nerve leading to foot drop (1), left facial nerve with resultant facial paralysis (1), unilateral ulnar neuritis (3), bilateral ulnar neuritis with claw hand (1) and unilateral ulnar neuritis with claw hand (1). All patients with neuritis were managed with oral steroids, physiotherapy and the affected part of the anatomy was rested. This resulted in complete motor recovery in all but 1 case (in the vaccine group). This patient underwent reconstructive surgery for claw hand after RFT. Isolated neuritis was observed in 2 cases in the vaccine group and 1 case in the control group.

Thus, the vaccine did not precipitate any additional neurological complication—an important observation in the context of introducing an immunomodulator. This clinical finding was corroborated by the histological observation that after vaccination, no damage or increased intra- or perineurial lymphocytic infiltration was seen in dermal nerve twigs.[3]

In conclusion, it appears that *M.w*, the candidate for an antileprosy vaccine can be safely used as an adjunct to existing MDT, a finding based on its ability to cause rapid clinical and bacteriological improvement and histological upgrading.

References

[1] Talwar GP, Zaheer SA, Mukherjee R, Walia R, Misra RS, Sharma AK, Kar HK, Mukherjee A, Parida SK, Suresh NR, Nair SK, Pandey RM. Immunotherapeutic effects of a vaccine based on a saprophytic cultivable mycobacterium, *Mycobacterium w*, in multibacillary leprosy patients. *Vaccine*, 1990; **8:** 121–9.

[2] Talwar GP, Zaheer SA, Suresh NR, Parida SK, Mukherjee R, Singh IG, Sharma AK, Kar HK, Misra RS, Mukherjee A. Immunotherapeutic trials with a candidate anti-leprosy vaccine based on *Mycobacterium w*. *Trop Med Parasitol*, 1990; **41:** 369–70.

[3] Mukherjee A, Zaheer SA, Sharma AK, Misra RS, Kar HK, Mukherjee R, Talwar GP. Histopathological monitoring of immunotherapeutic trials. *Int J Lepr*, 1992; **60:** in press.

[4] Indian Association of Leprologists (IAL). Consensus on treatment regimens in leprosy and the problems of drug delivery. *Ind J Lepr*, 1984; **56:** 158–9.

[5] Naik SS, Sahasrabudhe RV. Comparative study of different drug compliance tests available in leprosy. *Ind J Lepr*, 1988; **60:** 270–6.

[6] Ramu G, Desikan KV. A follow up study of borderline tuberculoid leprosy under sulphone monotherapy. *Ind J Lepr*, 1988; **60:** 26–33.

[7] Iyer CGS, Balakrishnan S, Ramu G. A comparison of low and conventional dosages of dapsone in the treatment of lepromatous leprosy in India. *Lepr Ind*, 1977; **49:** 372–88.

[8] Ridley DS, Hilson GRF. A logarithmic index of bacilli. *Int J Lepr*, 1967; **35:** 184–6.

[9] Waters MFR. Treatment of reaction in leprosy. *Lepr Rev*, 1974; **46:** 337.

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

[11] Hastings RC, Job CK. Reversal reaction in lepromatous leprosy following transfer factor therapy. *Am J Trop Med Hyg*, 1978; **27:** 1004.

[12] Convit J, Ulrich M, Aranzazu N. Vaccination in leprosy—observations and interpretations. *Int J Lepr*, 1980; **48:** 62–5.

[13] Bhatki WS, Chulawala RG, Bapat CV, Deo MG. Reversal reaction in lepromatous patients induced by a vaccine containing killed ICRC bacilli—A report of five cases. *Int J Lepr*, 1983; **51:** 466–72.

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Poussées réactionnelles chez les lépruex multibacillaires a MDT avec ou sans immunothérapie par *Mycobacterium w*, un eventuel vaccin contre la lèpre

H. K. Kar, A. K. Sharma, R. S. Misra, K. R. Beena, S. A. Zaheer, R. Mukherjee, A. Mukherjee, S. K. Parida, R. Walia, N. S. K. Nair et G. P. Tamwar

Résumé En plus de la thérapeutique multidrogue standard (MDT), 53 lépreux multibacillaires, négatifs à la lépromine et appartenant aux types de lèpre BB, BL et LL (groupes de vaccination) ont reçu une immunothérapie avec un bacille qui pourrait éventuellement devenir un vaccin contre la lèpre, *Mycobacterium w*. Un groupe de témoins en nombre égal a reçu MDT et des injections d'amidon micronisé comme placebo. Le vaccin, comme le placebo, était administré en injection intradermique tous les 3 mois. Les paramètres cliniques, bactériologiques et histopathologiques et le test à la lépromine étaient évalués à intervalles déterminés chez les malades. On a noté, pour chaque épisode de réaction l'incidence, le début, la fréquence et la sévérité pendant et après la cessation du traitement (RTF). L'incidence des réactions lépreuses (RR) a été légèrement plus élevée dans le groupe vacciné (22,6% dans le groupe vacciné contre 15% dans le groupe témoin). Tous les cas présentant une histoire de réaction de déclin type 1 ont présenté une poussée réactionnelle pendant le traitement. Le plus grand nombre des épisodes s'est produit au cours de la première année de traitement, dont 50% dans les premiers 3 mois. Des réactions lépreuses tardives (après RTF) ont été observées dans 3,8% des cas dans les deux groupes, et 50% des malades réagissant dans le groupe témoin et 33% dans le groupe vacciné ont eu des épisodes réactionnels répétés. L'incidence des névrites associées à RR, comme celle des névrites isolées, a été similaire dans les deux groupes.

Reacción invertida en los pacientes leprosos multibacilares después de tratamiento multidroga con y sin inmunoterapia y una posible vacuna antileprosa, *Mycobacterium w*

H. K. Kar, A. K. Sharma, R. S. Misra, K. R. Beena, S. A. Zaheer, R. Mukherjee, A. Mukherjee, S. K. Parida, R. Walia, N. S. K. Nair y G. P. Talwar

Resumen Se administró una posible vacuna antileprosa, *Mycobacterium w*, en conjunto con una terapia multidroga (MDT) normal, a 53 pacientes multibacilares lepromin-negativos, de los tipos BB, BL y LL de lepra (el grupo vacunado). Un grupo de control de igual magnitud recibió MDT e inyecciones de almidón micronizado como placebo. Se administró la vacuna y el placebo por vía intradérmica cada 3 meses. Se controlaron los pacientes a intervalos regulares mediante parámetros clínicos, bacteriológicos e histopatológicos, y pruebas de lepromin. Se analizaron casos de reacción con referencia a incidencia, comienzo, frecuencia y severidad, durante y después de darles de alta del tratamiento (RFT). La incidencia de reacción invertida (RR) era levemente superior en el grupo vacunado (22,6% para el grupo vacunado comparado con 15% del grupo de control). Todos los casos con antecedentes de una reacción Tipo 1 de degradación desarrollaron RR durante la terapia. La mayoría de casos ocurrieron en menos de 1 año del comienzo de la terapia, 50% de ellos en menos de 3 meses. Se observó reacción invertida retardada (después de RFT) en un 3,8% de casos en ambos grupos, y un 50% de los reactores en el grupo de control y 33% del grupo vacunado tuvieron incidentes de reacción repetidos. La incidencia de neuritis asociada con RR, además de neuritis aislada, era similar en ambos grupos.

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Does the introduction of WHO-MDT influence trends in the incidence of leprosy?—the Malaŵian experience

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Summary There has been an average annual decline in detection rates of all types of leprosy in Malaŵi of around 11·6% between 1977 and 1991. There was no obvious acceleration or slowing down of this decline following the introduction of WHO/MDT in 1983–84. Disability ratios stayed at the same level of about 11% during the 15 years covered by this paper suggesting that patients did not self-report earlier after 1983–84 which might have masked an underlying accelerated decline in detection rates. Thus it is concluded that the influence of WHO/MDT on the pattern of leprosy over a period of time, in a country like Malaŵi, is so far not noticeably different from any influence dapsone monotherapy might have had.

Introduction

It is now well known that shortening anti-leprosy treatment—e.g. by implementing the WHO recommended multi-drug-therapy (WHO/MDT)[1] markedly decreases the number of patients on treatment (prevalence rates).[2,3,4] Expectations that multi-drug-treatment would break chains of transmission faster than dapsone monotherapy and thus lead to a noticeable decline (or an acceleration in the decline) of incidence rates have so far not been fulfilled.[5,6,7] On the other hand, there are detection rate data which have been interpreted to show such an effect.[8]

Leprosy control activities in Malaŵi have been intensified since 1966 with the assistance of the British Leprosy Relief Association (LEPRA). Given the continuity of main operational methods (e.g. passive case finding and mobile treatment) at least since 1973,[9] we feel that a description of detection rates in Malaŵi covering the period before and after the introduction of WHO/MDT in 1983/84 is a useful contribution to the ongoing discussion on the influence of multi-drug-treatment on the patterns of leprosy over time.[10] Because detection activities in Malaŵi were constant over time, trends in detection rates can be assumed to reflect trends in incidence rates.

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Methods

Methods of leprosy control work in Malawi up to 1983 have been described in detail in a previous publication.[9] WHO/MDT was introduced in the whole country between April 1983 and December 1984. The procedure adopted was to review patients on treatment at that time and to release those from treatment who (i) had paucibacillary leprosy (PB), had been treated for at least 4 years and whose lesions were inactive at the time of review *or* (ii) had multibacillary leprosy (MB), had been treated for at least 5 years and whose slit skin smears had been negative for at least 5 years. All other patients were given WHO/MDT: 6 monthly doses for PB leprosy and until smear negativity for MB leprosy (but for not less than 2 years during which period the patient had to take at least eighteen monthly doses). This review procedure led to a great reduction in the prevalence rate of leprosy. The cadre of staff called clinic attendants was therefore made redundant. As a consequence anti-leprosy treatment was from then on given on a monthly basis by leprosy control assistants (LCAs) rather than on a weekly basis by clinic attendants. All LCAs were equipped with motorcycles and great efforts were made to keep them mobile at all times. In general, as before, there was one LCA in each administrative district in Malawi but larger districts continued to have two LCAs. They continued to be supervised by assistant field officers, field officers and medical officers.

Until 1982 the taking of slit skin smears had been prompted by a clinical suspicion of MB leprosy but with the introduction of WHO/MDT slit skin smears were taken from *all* newly registered patients. Further new operational developments which added to the workload of LCAs were (i) the introduction of active surveillance after completion of treatment of PB leprosy patients and (ii) the intensification of care for all patients who were left with disabilities after completion of treatment.

In parallel with the introduction of WHO/MDT a computerized National Register

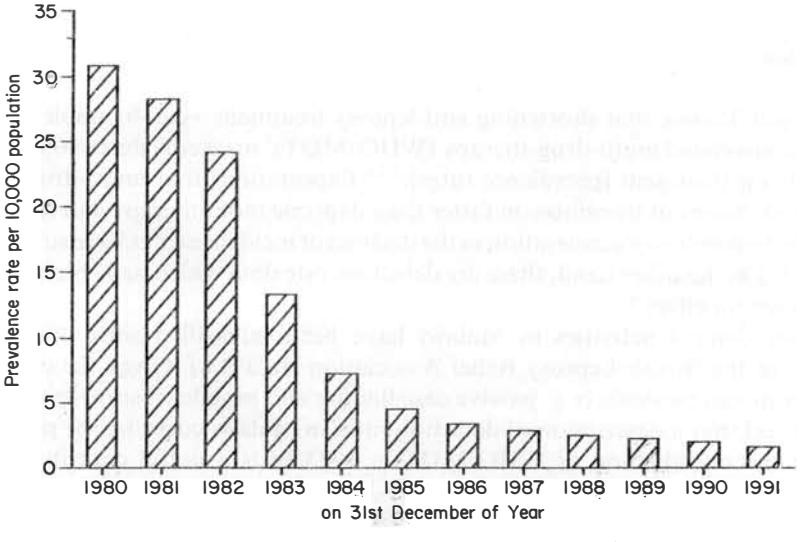

Figure 1. Prevalence rates of leprosy patients on treatment in Malawi per 10 thousand population, 1980–91.

Table 1. Prevalence rates of leprosy patients on treatment in Malawi 1980 to 1991

	Year											
	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Patients on treatment 31st December	18862	17925	15867	9042	5116	3240	2529	2207	2024	1895	1773	1438
Population (× 1,000)	6,117	6,340	6,571	6,811	7,060	7,319	7,589	7,869	8,160	8,463	8,777	9,105
Prevalence rates per 10 thousand	30·8	28·3	24·1	13·3	7·2	4·4	3·3	2·8	2·5	2·2	2·0	1·6

was set up and LCAs notified the National Register of all new patients, their year of birth, sex, classification, slit skin smear results, disabilities and their residence at registration. Statistics for the period prior to 1983 are based on manually compiled data.

National Censuses were carried out in Malawi in 1977 and 1987 and all rates are based on figures derived and projected from the census reports.[11,12]

All new patients registered for anti-leprosy treatment and thought to be Malawian citizens are included in the data presented. Care was taken to exclude foreigners (e.g. Mozambican refugees) from the calculations.

For the purpose of this paper a patient is considered to have a disability if according to the 1960 WHO disability grading system[13] there was at least one score of 2 or higher at registration.

A multibacillary patient was, until 1982, defined as anyone registered as a new BB, BL or LL case with a positive slit skin smear result (BI > 0) or else as a new LL case with no slit skin smear result but clinical findings typical for lepromatous leprosy. From 1983

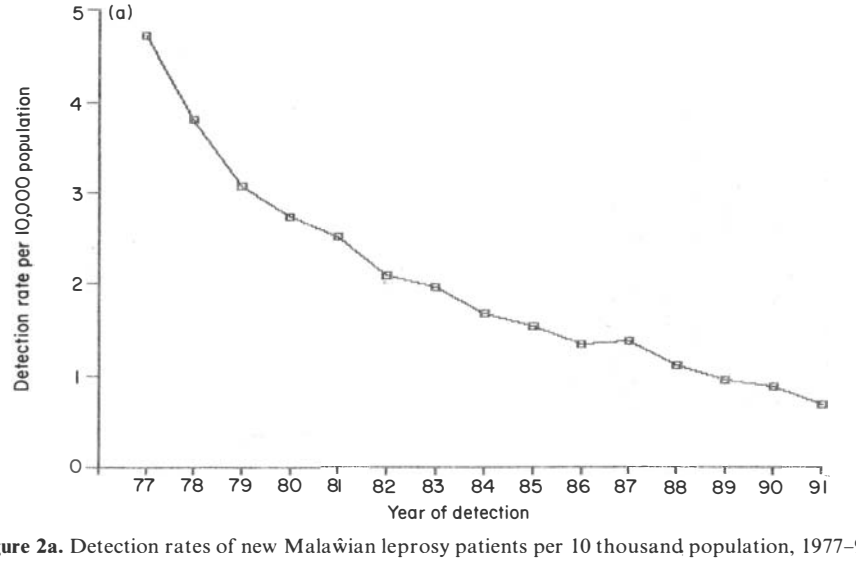

Figure 2a. Detection rates of new Malawian leprosy patients per 10 thousand population, 1977–91.

Table 2. Detection rates of new Malawian leprosy patients, 1977 to 1991

	Year														
	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Patients detected during year	2598	2179	1818	1672	1601	1372	1348	1197	1135	1029	1093	907	810	781	638
Population (× 1,000)	5,499	5,697	5,903	6,117	6,340	6,571	6,811	7,060	7,319	7,589	7,869	8,160	8,463	8,777	9,105
Detection rate per 10 thousand	4·7	3·8	3·1	2·7	2·5	2·1	2·0	1·7	1·6	1·4	1·4	1·1	1·0	0·9	0·7
Annual reduction/increase of the detection rate (in percent)		−19·0	−19·5	−11·2	−7·6	−17·3	−5·2	−14·3	−8·5	−12·6	2·4	−20·0	−13·9	−7·0	−21·2

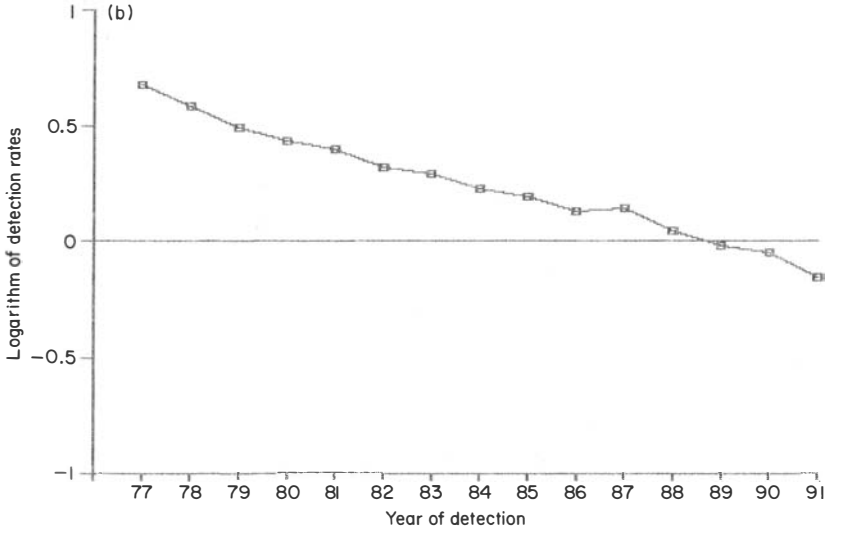

Figure 2b. Logarithmic detection rates of new Malawian leprosy patients per 10 thousand population, 1977–91.

onwards a MB patient is defined as any patient with a slit skin smear result of a BI of 2 or higher. In our experience these two definitions of MB leprosy are virtually the same.

Results

Figure 1 and Table 1 show prevalence rates of leprosy in Malawi from 1980 until 1991. Prevalence rates declined most steeply during the years 1983 and 1984 when WHO/MDT was introduced. At the end of 1991 the prevalence rate had been reduced to 1438 patients on treatment per 9,104,600 people (1·58 per 10,000).

Detection rates per 10,000 population from 1977 until 1991 are shown in Figure 2a and Table 2. The rate fell from 4·7 per 10,000 in 1977 to 0·7 per 10,000 in 1991. This represents an average annual reduction (geometric mean of the decline) of 11·6%. Table 2 also shows (in percentage) the variation in the detection rates per year. The annual 'reduction' varies from an increase of 2·4% from 1986 to 1987 to a reduction of 21·2% from 1990 to 1991. Figure 2b shows detection rates after logarithmic transformation and, as expected from Figure 2a, demonstrates a log-linear relationship between years of detection and detection rates. There is no change in the trend (decline) of detection rates at any time after introduction of WHO/MDT.

Figure 3 and Table 3 show multibacillary ratios from 1977 to 1991. From 1977 to 1982 these ratios are based on the patients in those parts of the country which were used in an analysis of the epidemiology of leprosy in Malawi in a previous paper.[14] From 1983 onwards ratios are based on all newly registered patients in Malawi. A doubling of the multibacillary ratio from about 10% to 20% can be observed between 1977 and 1985. From then onwards the multibacillary ratio appears to have remained constant.

Disability ratios among newly registered patients are presented in Table 4. This ratio of patients with any disability score greater than one varies between 9% and 13% per year without any apparent underlying trend.

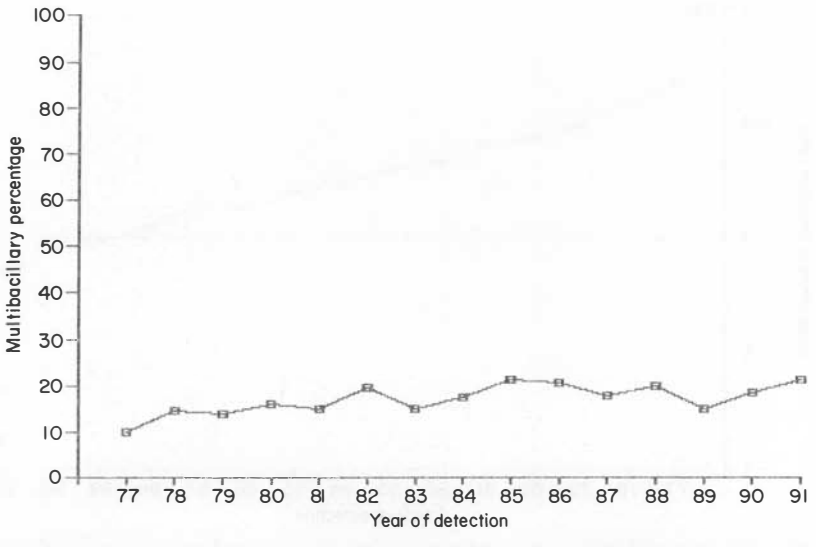

Figure 3. Proportion (%) of new Malawian leprosy patients with multibacillary leprosy, 1977–91.

Discussion

We have shown in this paper that the average annual decline in detection rates of all types of leprosy in Malawi has been around 12·5% since 1977 (Figures 2a, 2b and Table 2) and that there was no obvious acceleration or slowing down of this decline in the wake of introducing WHO/MDT in 1983–84. These data argue against WHO/MDT exerting any influence on the patterns of leprosy over time, in a country like Malawi, other than the influence dapsone monotherapy might have had.

This argument is only valid in so far as operational methods and characteristics of patients remained the same after the introduction of WHO/MDT. Concerning operational methods we mentioned that the number of staff (and thus opportunities for new leprosy patients to self-report) were reduced following the dramatic decline of prevalence rates by 1985. However, this operational change, if it mattered, could only have resulted in an accelerated decline of detection rates—which is not seen. The operational change could not have masked an underlying genuine acceleration in decline and the reduction in staff therefore appears to be irrelevant for the point in question.

Concerning characteristics of patients we have shown that disability ratios remained constant between 1977 and 1991 and that there was no noticeable change at any time after 1983–84 (Table 4). This supports the suggestion that the introduction of WHO/MDT did not result in earlier self-reporting which again could have masked an underlying genuine acceleration in the decline of detection rates. (Nor did the introduction of WHO/MDT result in higher disability ratios because of later self-reporting which could have been the effect of the reduction of staff.)

As a further characteristic of patients we describe the multibacillary ratios among newly registered patients (Figure 3, Table 3). It appears that the rise in multibacillary ratios came to an end after the introduction of WHO/MDT and has remained constant

Table 3. Proportion of new Malawian leprosy patients with multibacillary leprosy

	Year														
	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Patients detected during year	2598	2179	1818	1672	1601	1372	1348	1197	1135	1029	1093	907	810	781	638
Patients on whom the MB ratio is based	1602	941	831	831	794	641	1348	1197	1135	1029	1093	907	810	781	638
Percentage of patients with MB leprosy	9·8	14·5	14·0	16·1	15·0	19·7	14·8	17·4	21·1	20·7	17·7	19·7	14·8	18·3	21·2

Table 4. Proportion of new Malawian leprosy patients with a disability > 1

	Year														
	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Patients detected during year	2598	2179	1818	1672	1601	1372	1348	1197	1135	1029	1093	907	810	781	638
Patients on whom the disability ratio is based	1602	941	831	831	794	641	1348	1197	1135	1029	1093	907	810	781	638
Percentage of patients with a disability > 1	10·1	11·6	12·8	13·4	9·9	11·8	9·0	12·9	12·5	11·1	9·8	11·7	7·9	11·3	11·9

since 1985. However, this variable is more difficult to interpret than the disability ratios because there were both a slight change in the definition in 1983 and a change of practice which we have mentioned. In addition, it could be argued that control services including slit skin smear services improved during the Seventies and early Eighties and that the rise in the multibacillary ratio resulted from this general improvement of quality. Thus there are three alternative explanations for the pattern of multibacillary ratios shown: (i) the rise in the multibacillary ratio until 1985 was merely due to operational circumstances *or* (ii) the rise was an indicator of the end phase of an epidemic[15] which declined no further in the late Eighties *or* (iii) the introduction of WHO/MDT led to earlier case finding which caused a break in the rise of the multibacillary ratio. The third possible explanation is not supported by the patterns of detection rates and disability ratios. It therefore seems likely that operational circumstances and a declining epidemic shaped the pattern of multibacillary ratios shown rather than the introduction of WHO/MDT.

On the whole we therefore conclude on the basis of the experience in Malaŵi that a variety of factors (e.g. BCG vaccination,[16,17] socioeconomic changes, leprosy control efforts) led to a steady reduction in detection rates of leprosy (and a parallel trend in incidence rates) in the late Seventies and throughout the Eighties and that this decline has not been accelerated by WHO/MDT so far.

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References

[1] WHO Study Group. *Chemotherapy of leprosy for control programmes.* Technical Report Series No. 675. WHO: Geneva, 1982.

[2] Becx-Bleumink M. *Multidrug therapy in the control of leprosy; a field study*. Academisch Proefschrift, Universiteit van Amsterdam. 1992; page 168.

[3] Steenbergen GJ. Leprosy control in Zambia. *World Health Stat. Q.* 1991; **44:** 30–5.

[4] Day R, Lever P, Asri M. Leprosy control in 7 districts of South Sulawesi, Indonesia, 1986–91. *Lepr Rev*, 1992; **63:** 247–54.

[5] *Consensus development statement on the chemotherapy of leprosy.* Greenville, SC. 1992; page 4.

[6] Pirayavaraporn C, Peerapakorn S. The measurement of the epidemiological impact of multidrug therapy. *Lepr Rev*, 1992; **63:** (Supplement) 84s–92s.

[7] Lienhardt C, Fine PEM. Controlling leprosy—Multidrug treatment is not enough alone (Editorial) *BMJ*, 1992; **305:** 206–7.

[8] Cartel JL, Spiegel A, Nguyen Ngoc, Moulia-Pelat JP, Martin PMV, Grosset JH. Leprosy in French Polynesia. The possible impact of multidrug therapy on epidemiological trends. *Lepr Rev*, 1992; **63:** 223–30.

[9] Boerrigter G, Pönnighaus JM. Ten years' leprosy control in Malawi (Central Africa)—I; Methods and outcome after treatment. *Lepr Rev*, 1986; **57:** 199–219.
[10] Fine PEM. Reflections on the elimination of leprosy (Editorial) *Int J Lepr*, 1992; **60:** 71–80.
[11] Malawi Population Census 1977, Final Report. National Statistical Office, Zomba, Malawi. 1980.
[12] Malawi Population and Housing Census 1987, Preliminary Report. National Statistical Office, Zomba, Malawi. 1987.
[13] WHO Expert Committee on Leprosy. Technical Report Series No. 189. WHO. Geneva, 1960.
[14] Pönnighaus JM, Boerrigter G. Ten years' leprosy control in Malawi (Central Africa)—II; Patterns of endemicity since 1973. *Lepr Rev*, 1986; **57:** 221–36.
[15] Irgens LM. Leprosy in Norway. *Lepr Rev*, 1980; **51** (Suppl 1): 1–130.
[16] Pönnighaus JM, Fine PEM, Sterne JAC, Wilson RJ, Msosa E, Gruer PJK, Jenkins PA, Lucas SB, Liomba NG, Bliss L. Efficacy of BCG vaccine against leprosy and tuberculosis in northern Malawi. *Lancet*, 1992; **339:** 636–9.
[17] Baker DM, Nguyen-Van-Tam JS. BCG vaccine and leprosy (Letter to the Editor). *Lancet*, 1992; **339:** 1236.

Lepr Rev (1993) **64,** 227–235

L'introduction de l'OMS-MDT a-t-elle eu une influence sur l'incidence de la lèpre?—l'expérience malawienne

GJALT BOERRIGTER ET JORG M. PONNIGHAUS

Résumé On a noté une baisse moyenne annuelle d'environ 11,6% des taux de détection de tous les types de lèpre à Malawi entre 1977 et 1991. Il n'a pas été observé d'accélération ou de ralentissement évident de cette baisse suite à l'introduction de l'OMS-MDT en 1983–84. Les taux d'infirmité sont restés les mêmes, à savoir d'environ 11%, durant les 15 années couvertes par cet article, ce qui tend à suggérer que les patients ne sont pas revenus se présenter en consultation plus tôt après 1983–84 et pourrait masquer une diminution accélérée sous-jacente des taux de détection. On a ainsi conclu que l'influence de l'OMS-MDT dans le schéma de la lèpre dans un pays tel que le Malawi durant cette période de temps n'est jusqu'ici pas sensiblement différent de l'influence que le dapsone pourrait avoir en monothérapie.

¿Influencia la introducción de WHO-MDT las tendencias en torno a la frecuencia de la lepra?—La experiencia adquirida en Malawi

GJALT BOERRIGTER Y JORG M. PONNIGHAUS

Resumen Se ha registrado una declinación media anual en los porcentajes de detección de todos los tipos de lepra en Malawi de aproximadamente un 11,6% entre 1977 y 1991. No hubo una aceleración o reducción manifiesta en esta declinación a partir de la introducción de WHO/MDT en 1983–84. Las relaciones de invalidez permanecieron al mismo nivel de aproximadamente un 11% durante los 15 años que abarca este estudio, sugiriendo que los pacientes no informaron su condición por sí propios con mayor anterioridad, después de 1983–84, lo cual podría haber disimulado una declinación acelerada subyacente en los porcentajes de detección. Así pues, se concluye que la influencia de WHO/MDT ejercida sobre el patrón de la lepra durante cierto período de tiempo, en un país como Malawi, no es hasta la fecha marcadamente diferente de cualquier influencia que pudiera haber ejercido una monoterapéutica a base de dapsona.

Lepr Rev (1993) **64,** 236–249

The effects of World Health Organization chemotherapy on imported leprosy in Auckland, New Zealand, 1983–90

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Summary Between January 1983 and December 1990 in Auckland, New Zealand, 87 patients (28 paucibacillary disease (PBD) and 59 multibacillary disease (MBD)) commenced WHO multidrug therapy (MDT).

All were immigrants from the Pacific Islands (65) or Asia (22). A total of 57 patients had already received non-WHO regimens, some continuously, but often intermittently, for many years; 30 patients received WHO MDT only. By December 1990, 50 had completed treatment, with 1 relapse and 1 late reaction, both in patients with PBD treated with WHO MDT only. There have been no relapses in those treated with WHO MDT after prior leprosy treatment.

In those with MBD, type II leprosy reactions were less common (16%) in those treated only with WHO MDT than in those treated continuously before 1983 with older regimens (64%). Type I leprosy reactions occurred in about 20% of both these groups. The bacterial index fell faster in those who had had a prolonged prior treatment beginning WHO MDT than in those starting WHO MDT as their initial leprosy chemotherapy.

Overall we found WHO MDT was well accepted and the compliance good, but 13 patients (15%) left Auckland before treatment was completed and 6 (7%) during follow up.

Introduction

Auckland, New Zealand, has the largest Polynesian population in the world. For many years large numbers of immigrants have entered New Zealand from the South Pacific islands of Western Samoa, the Cook Islands, the Tokelau Islands, Tonga and Fiji. Recently refugees have arrived from South-East Asia. Many of the inhabitants of these countries suffer from endemic leprosy, therefore people infected with *Mycobacterium leprae* have entered New Zealand. Leprosy does not occur in people who have not lived outside New Zealand.

We report here our experience of leprosy using the World Health Organization multi-

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drug therapy regimen (WHO MDT) at the Auckland Hospital infectious disease unit from the introduction of this treatment in January 1983 to December 1990.

In 1982 WHO officially recommended that leprosy should be treated with MDT.[1] This decision was made because of the growing incidence of both primary and secondary dapsone resistant leprosy and the recognition that paucibacillary (PB) disease (PBD) needed shorter treatment than was then generally being used. Paucibacillary disease includes indeterminate polar tuberculoid and borderline tuberculoid leprosy in the Ridley–Jopling classification[2] and in 1982 included cases with a bacteriological index (BI) of 1+ according to the Ridley scale. This was modified in 1988 to include only those with negative bacteriology. Multibacillary disease (MBD) is all mid-borderline to lepromatous leprosy and from 1988 also included any with a positive BI with particular care in the classification of borderline tuberculoid disease.[3]

World Health Organization MDT for PBD is 6 months of daily dapsone with monthly rifampicin; for MBD it is daily clofazamine and dapsone with monthly rifampicin and clofazamine given under supervision. It is recommended that MBD treatment continue until skin smears are negative or for a minimum of 2 years.

Methods

Demographic, investigational, treatment and outcome data (i.e. age, sex, ethnicity, duration of previous treatment, disability, treatment, drug side effects, reactions, compliance, BI and outcome) were taken from the case notes of all patients treated for leprosy at the Auckland Hospital infectious disease unit from 1983. All patients are managed as outpatients unless particular complications (e.g. severe reaction, osteomyelitis) necessitate admission, which was uncommon.

A disability index was assessed from records of clinical examination and the maximum disability at any stage was recorded. Disability was graded as minor, moderate or severe.[4]

Treatment was described as: WHO MDT, where it was absolutely as recommended, modified WHO MDT (i.e. WHO MDT plus extra drug or extended duration of treatment) or other (i.e. that not providing minimum MDT).[5]

Reactions were classified as Type I or II. We defined long-term reaction treatment as courses of prednisone or thalidomide (for Type II reactions) given for longer than 3 months.

Compliance was evaluated by checking the dates on which each monthly pulse dose was given. We classified a patient as compliant if he/she took the dose within 14 days of the due monthly date. All monthly doses were given under supervision, either to patients returning to the infectious disease unit or by public health nurse visits at home or work.

The BI was measured yearly using the Ridley–Jopling Classification from split skin smears examined by G.C. On initial examination bilateral smears from the nose, ear lobes, elbows, fingers and skin lesions were tested and subsequently 4 to 6 sites were tested. Testing of finger dorsa was added in the mid-1980s but, because patients found this uncomfortable, they were tested again only towards the expected end of treatment. For the same reason, we rarely re-evaluated nasal smears after the usual intial rapid clearing from that site.

Statistical analysis was done by the χ^2 test for univariate analysis and Student's t-test for group comparison. A logistic regression model was used with disability as the

Table 1. Yearly patient numbers treated in Auckland[5]

	Year MDT began in Auckland								
	1983	1984	1985	1986	1987	1988	1989	1990	Total
Cases in									
New cases	2	1	4	1	2	3	3	5	21
Additional	45	6	6	6	3	9	6	6	87
Cases out									
Early exit	1	2	1	2	0	3	2	3	14
Completed	9	6	21	1	2	2	7	2	50
Registered	35	33	17	20	21	25	22	23	

1. New cases: cases newly detected in the year indicated.
2. Additional: includes all cases whose treatment with MDT was started in Auckland in the year indicated.
3. Early exit: left the Auckland area prior to finishing treatment because of emigration (13) or death (1).
4. Completed: treatment with MDT completed in the year indicated.
5. Registered: those registered as leprosy cases and on treatment at year end. (It does not include those under surveillance.)

dependent variable and sex, type of leprosy, and ethnicity as the explanatory variables. BI were analysed as ordinal variables using the non-parametric Wilcoxon rank sum test.

Results

A total of 87 patients have been registered as having leprosy between January 1983 and December 1990 (Tables 1 and 2).

We divided patients into 2 treatment groups; i.e. those who had been treated before beginning WHO regimens (prior treatment group) and those who had not been treated before beginning WHO regimens (no prior treatment group) (Figure 1).

1. Prior treatment group (57 patients) (Table 3)

These patients had received treatment of various sorts before being transferred to WHO MDT regimens. They were divided into 2 further sub-groups.

(a) *Uninterrupted treatment group (23 patients).* These patients had usually been diagnosed in Auckland after the mid-1970s and had remained under our care for their entire management. They had usually been treated with 6 to 12 weeks of initial dapsone and rifampicin with or without additional clofazimine followed by dapsone monotherapy. Our own records provide reliable information about these patients—10 of these patients were from the Cook Islands, 6 from Samoa, 2 from Tonga, 3 from Cambodia and 2 from Vietnam.

(b) *Interrupted treatment group (34 patients).* These patients were treated with various regimens, usually prolonged dapsone monotherapy generally started in the Pacific Islands before the 1970s and subsequently continued in Auckland. In the majority

Table 2. Table of epidemiological data

	Total	Sex		Ratio	Race		Age at diagnosis (mean+S.D.) (years)	Duration of treatment prior to WHO MDT (mean ± S.D.) (years)
		M	F		Pacific	Asian		
Prior treatment								
1. Interrupted	34	19	15	1:0·75	31	3	20 (±10)	15 (±11)
(a) Paucibacillary	8	3	5		7	1	14 (±6)	5 (±3)
(b) Multibacillary	26	16	10		24	2	21 (±10)	18 (±11)
2. Uninterrupted	23	15	8	1:0·57	18	5	27 (±13)	6 (±11)
(a) Paucibacillary	9	5	4		5	4	27 (±15)	5 (±3)
(b) Multibacillary	14	10	4		13	1	27 (±12)	7 (±5)
No prior treatment	30	18	12	1:0·66	16	14	34 (±14)	Not applicable
(a) Paucibacillary	11	5	6		7	4	35 (±16)	
(b) Multibacillary	19	13	6		9	10	33 (±12)	**

1. M male, F female.
2. ** 9/19 had begun WHO MDT elsewhere: mean duration of their previous WHO MDT was 3 (± 1) years.

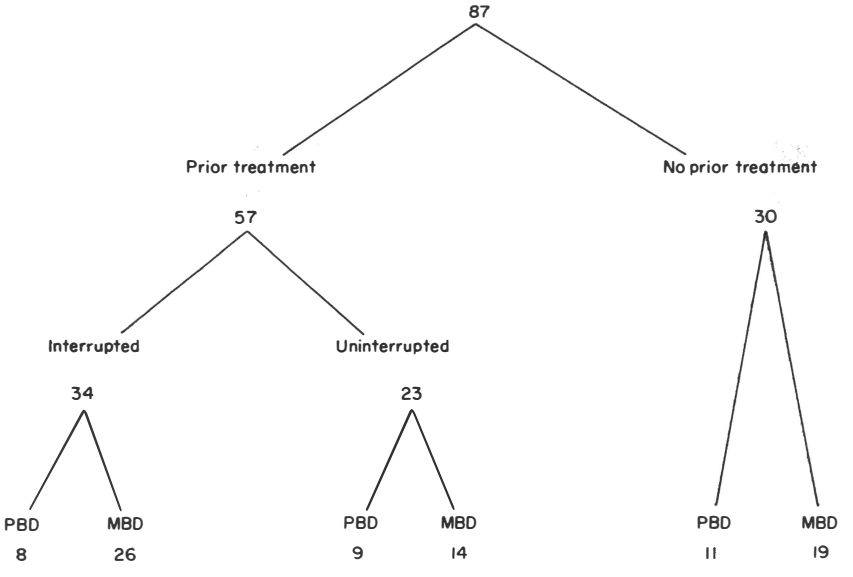

Figure 1. Patient summary.

treatment was further interrupted by return visits to the Pacific Islands and details of treatment there were difficult to define accurately. In all, 15 of these patients were from Samoa, 13 from the Cook Islands, 3 from Fiji (1 each from native Fijian, Fiji Indian and Fiji Malay stock), and 1 each from Tonga, the Tokelau Islands and Cambodia.

The mean 15 ($\pm$11) years of prior treatment in the interrupted group is significantly longer than the mean 6 ($\pm$4) years in the uninterrupted group ($t = 3{\cdot}89$, df (54); $p < 0{\cdot}001$).

2. No prior treatment (30 patients) (Table 4)

These patients had had no previous treatment before beginning WHO MDT—21 began their WHO Regimen in Auckland and 9 continued WHO MDT treatment begun elsewhere, mostly in refugee camps in South-East Asia; 11 were from Samoa, 5 from the Cook Islands, 7 from Cambodia, 3 from India and 1 each from Laos, Vietnam, the Pillippines and Pakistan.

EPIDEMIOLOGY

Details of sex, ethnicity, age at diagnosis and duration of previous treatment are summarized above and in Table 2. Patients were predominantly from Western Samoa (32) and the Cook Islands (28), but there was a higher proportion of South-East Asians (16), particularly Cambodians (11) among cases diagnosed since 1983. There was a non-significant trend for males to have MBD more than females ($\chi^2 = 3{\cdot}09$ $p < 0{\cdot}1$). The percentage distribution of PBD and MBD amongst the two main ethnic groups (Pacific Islanders and Asians) was similar. There has been an increase in mean age and a decreased duration of disease at diagnosis over the years.

Table 3. Data summary for patients in prior treatment group

	Prior treatment group (57)					
	Interrupted (34)			Uninterrupted (23)		
Classification:	PBD 8	26 MBD		PBD 9	14 MBD	
Skin smear:	−ve	−ve	+ve	−ve	−ve	+ve
	8	15	11	8	8	6
Regimen:						
WHO	5	9	8	7	6	6
Modified	3	0	0	2	0	0
Other	0	6	3	0	2	0
Side effects:	0	0	0	0	2	2
Reactions:						
Type I	0	1	0	0	0	1
Type II	0	0	6	0	1	6
Outcome:						
Early exit	1	0	4	0	1	2
Continue	0	1	2	0	0	4
Complete						
Lost to f/up	1	1	0	0	2	0
f/up	6	13	5	9	5	0
Median duration f/u (months) (range) (months)	23 (12–36)	32 (6–48)	9 (5–60)	36 (12–50)	58 (12–84)	nil

f/u: follow up regimen: see text for details.

DISABILITY

Disability (Table 5) was mild in 37 (42%), moderate in 24 (28%) and severe in 26 (30%). Paucibacillary disease was associated with less disability than MBD ($\chi^2 = 15$, $p < 0{\cdot}0001$). There was no significant difference in disability with respect to sex, ethnicity, treatment group or year of diagnosis.

TREATMENT REGIMENS

1. Prior treatment (57 patients) (Table 3)

(i) *Uninterrupted treatment group (23 patients)*

(a) PBD (9 patients)
In total, 7 patients received WHO MDT and 2 modified WHO MDT. These latter 2 had 2 years MB MDT: 1 because of extensive clinical BT disease and 1 because previous long-term low dose dapsone monotherapy (100 mg/week) raised concern about dapsone resistance, although it was not proved.

(b) MBD (14 patients)
In total, 12 patients received WHO MDT and 2 were given other treatment. Of the latter, dapsone was omitted in 1 because of previous haemolysis and the other,

Table 4. Data summary for patients in group with no prior treatment

	No prior treatment (30)	
Classification:	PBD 11	19 MBD
Regimen:		
WHO	8	19
Modified	3	0
Other	0	0
Side effects:	0	1
Reactions during treatment:		
Type I	2	3
Type II	0	3
Outcome:		
Early exit	1	5
Continue	3	13
Complete		
Lost to f/up	2	0
Relapse	1	0
Late reaction	1	0
F/up	4	1
Median duration f/up	18	10

Table 5. Disability according to ethnic group, disease classification, sex and age

	Disability						
	Minor		Moderate		Severe		
Disease Classification	M	F	M	F	M	F	Total
Pacific Islanders							
PBD	6	8	2	1	1	1	19
MBD	9	4	7	8	13	5	46
Asians							
PBD	2	4	2	1	0	0	9
MBD	2	2	3	0	5	1	13
Total	19	18	14	10	19	7	87

already smear negative with prolonged prior treatment, had only 12 months MB MDT because of noncompliance.

(ii) *Interrupted treatment group (34 patients)*

(a) PBD (8 patients)

In total, 5 patients received WHO MDT and 3 modified WHO MDT. Of the latter, all 3 had 2 years MB MDT, for the same reasons as in the PBD group with prior uninterrupted treatment discussed above.

(b) MBD (26 patients)

In all, 17 patients received WHO MDT and 9 were given other treatment. Of those latter 9, 1 who was already smear negative after prolonged treatment had only 6 months MB MDT because of noncompliance, 1 had had previous dapsone

haemolysis and 5 refused dapsone because of their concerns about its role in inducing reactions; 2 did not receive clofazimine, 1 because of concern about skin discolouration and another because of concern about other side effects.

2. *No prior treatment (30 patients)* (Table 4)

(a) PBD (11 patients)
In all, 8 received WHO MDT and 3 received modified WHO MDT. Of these latter 3, 1 received 30 months PB MDT because of a persistently active single skin lesion and 2 received 2 years of MB MDT because of extensive BT disease.
(b) MB (19 patients)
All received WHO MDT.

In all patients, where we omitted 1 drug of WHO MDT, the other components of the regimen were continued. We did not add alternative agents.

SIDE EFFECTS

1. Prior treatment (Table 3)

Side effects were suffered by 4 of 57 patients (7%) —1 man with MBD who had received rifampicin 10 years earlier developed rifampicin allergy after the 3rd monthly dose of WHO MDT. While on MB MDT 2 Pacific Islanders developed dapsone haemolysis, and 1 clofazamine enteritis.

2. No prior treatment (Table 4)

A Cambodian man (1 of 30 patients (3%)) developed a side effect, dapsone haemolysis.

Overall, dapsone haemolysis occurred in 5 of 87 patients (6%): 3 while receiving WHO MDT and 2 during prior treatment.

REACTIONS

1. Prior treatment (Table 3)

(a) PBD: none of 17 had reactions.
(b) MBD: in total 14 of 40 patients (35%) had reactions, of whom 12 had positive BI.
   i. *Uninterrupted treatment group*—7 of 14 patients (50%) had 8 reactions; 6 had type II reaction and 1 had both type I and type II reactions; and 6 needed long-term treatment, 5 changing to thalidomide from prednisone; 3 had first been treated for reactions before the introduction of WHO MDT.
   ii. *Interrupted treatment group*—7 of 26 patients (27%) had reactions; 6 had type II reactions and 1 a type I reaction; 2 of those with type II reactions remain on prednisone, 1 needed no treatment and the remaining 3 changed to thalidomide; 4 had been treated for reactions before the introduction of WHO MDT.

Table 6. Comparative reaction rates on earlier non-WHO regimens and WHO regimens alone

	Reactions			
	During prior, uninterrupted non-WHO treatment before 1983		During WHO treatment of group not previously treated, after 1983	
	Type I	Type II	Type I	Type II
PBD	1/9 (11)†	0/9	3/11 (27)	0/11
MBD	4/14 (29)	9/14 (64)*	3/19 (16)	3/19 (16)*
Total	5/23 (22)	9/23 (39)	6/30 (20)	3/30 (10)

* Comparison $\chi^2 = 8{\cdot}3$, $p < 0{\cdot}001$.
† Numbers in parentheses are percentages.
Notes:
1. Some patients had both Type I and II reactions: these figures refer to reactions, not patients.
2. The data in the group treated before 1983 refers to reaction rates during that time on non-WHO regimens, and not to reaction rates occurring in this group while on WHO regimens after 1983.

2. *No prior treatment* (Tables 4 and 6)

(a) PBD: 3 of 11 patients (27%) had type I reactions; 2 patients developed reactions on PB MDT, and needed long-term prednisone, and in 1 of them the reaction still continued after the completion of PB MDT, and because of clinical concern about a possible late relapse of disease due to steroid treatment, MB MDT was started 2 months after finishing PB MDT, and continued for 2 years. Prednisone was required for 20 months of this time. The 3rd patient had 6 months PB MDT in 1983, and at a routine review in 1989 was discovered to have developed bilateral ulnar nerve palsies and local inflammatory swelling. He was then given 12 months MB MDT because skin smears were reported to show BI 4+ at 1 site, but this was never confirmed on repeat smears. We therefore took the view that this was a reaction that had been both clinically and microbiologically misdiagnosed as relapse and MB MDT was stopped. He had developed no further abnormalities after 2 years follow up. Thus 1 of 11 (9%) had a late reaction.

(b) MBD: 5 of 19 patients (26%) had 6 reactions; 2 patients had type I reactions, 2 type II and 1 both; and 3 needed long-term steroid treatment.

Detailed records were available for the treatment given before the introduction of WHO MDT to the uninterrupted treatment group (Table 6). There was no difference in type I reaction rates between this group during earlier treatment and those treated only with WHO MDT: type I reactions occurred in about 20% of both. In contrast 64% (9 of 14) of our patients with MBD on uninterrupted treatment before 1983 had type II reactions compared with 16% (3 of 19) on WHO MDT ($\chi^2 = 8{\cdot}3$, $p < 0{\cdot}001$). Once MBD patients with prior treatment changed to WHO MDT, type II reactions were virtually limited to those with bacteria still present (i.e. B1 $\geqslant 1+$) on transfer; 71% (12 of 17) with B1 $\geqslant 1+$ had reactions subsequently compared with 4% (1 of 23) in those with B1 $= 0$ ($\chi^2 = 19{\cdot}6$, $p < 0{\cdot}001$).

COMPLIANCE

Compliance was good, with the majority of doses given on time, though for some this

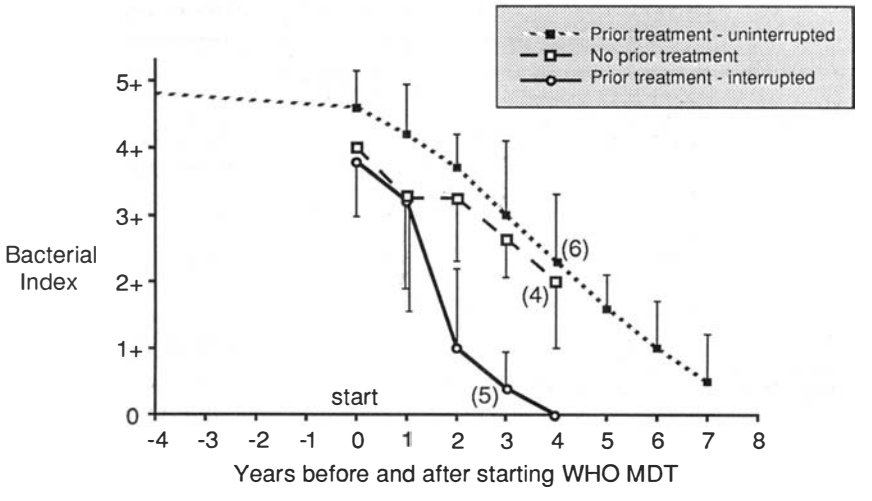

Figure 2.

required a great deal of work by medical and district health nursing staff. Compliance with PBD treatment was better than for MBD treatment, with a mean 91% (±16·9) of doses compliant for PBD and a mean 87% (±13·6) for MBD ($t = 4{\cdot}5$ df(84) $p < 0{\cdot}001$). There was no difference in compliance with age, ethnicity, sex or treatment group.

BACILLARY INDEX IN THOSE WITH MBD

Of 59 with MBD, 23 who had had prior treatment were smear negative at the time of transfer to MDT. Of the remaining 36, 28 had BI > 1, 6 BI = 1, and 2 BI = 0 (1 transferred from South-East Asia, already smear negative, and 1 with clinically MBD) at the start of the Auckland WHO MDT. In 15 of these patients with BI > 1 we have yearly BI available for 4 years while taking WHO MDT and this information is shown in Figure 2. While there was no difference in the initial BI between groups, there was a significant difference between counts in the interrupted and uninterrupted groups in years 3 and 4 ($p = 0{\cdot}01$ $n_1 n_2$ 5, 6 $t = 16$ in both years (Wilcoxon rank Sum test)). The mean 11·2 (±8·7) years of prior treatment in the interrupted group is longer than the mean 3·6 (±2·4) years in the uninterrupted group though not significantly so ($t = 1{\cdot}88$, df(9), $p < 0{\cdot}1$).

OUTCOME

By 31 December 1990 50 patients had completed their treatment (35 had completed WHO MDT, 5 modified WHO MDT and 10 other regimens); 14 patients did not finish MDT: 13 left Auckland, and 1 died on an unrelated cause. In all, 23 were registered (i.e. continuing treatment) on 31 December 1990.

We attempted a follow up of all patients for up to 5 years. Outcome according to treatment group is shown in Tables 3 and 4. Of those treated only with PB MDT, 1 patient has relapsed: a 20-year-old Samoan woman diagnosed with PBD in 1983 with BI = 0 but who had extensive clinical disease. She completed 10 months PB MDT with 100% compliance, but on review at 1 year had relapsed with extensive clinical disease and BI had

increased to 3+. MB MDT was started but she returned to Samoa after 2 months. Our incidence of relapse for PB disease in those with no prior treatment is thus 1 in 11 (9%). None of the 15 patients followed up who took PB MDT after prior treatment has relapsed.

So far only 1 patient with MBD and no prior treatment has finished WHO MDT so no relapse data is available for this group. None of the 23 patients followed up after receiving WHO MDT after prior treatment has relapsed.

Discussion

Despite the smaller numbers, our experience in Auckland with immigrant patients suffering from leprosy taking WHO MDT has many similarities to reports elsewhere.[3,6,7,8,9,10] An increase in cases of leprosy reported to the Centers for Disease Control in the U.S.A. was noted between 1978 and 1988, due mainly to refugees suffering from leprosy who came from Cambodia, Vietnam and Laos.[6] That experience is similar to ours.

Leprosy is said to have disappeared from the Cook Islands, with no active cases registered in 1989.[11] We still have Cook Islanders with active disease in our programme in 1993, making us uncertain about that statement. In 1990 there were 25 cases registered in Western Samoa.[11] The proportion of new patients with PBD (52%) and MBD (48%) is similar to both Western Samoa (44% PBD)[7] and Thailand (5% indeterminate, 42% tuberculoid, 36% borderline, and 17% lepromatous).[8] In our total patient group PBD (32%) is under-represented because immigrants previously treated for PBD did not present to us. The increase in mean age at diagnosis over the years has been noted elsewhere and remains unexplained.[3] Like others we found men more often affected[7,8] and more likely to have MBD,[4,7,8] though we did not find the difference in disability between sexes that has been reported elsewhere.[4]

In total, 30% of our patients were severely disabled, which is comparable to the 27% in Thailand,[8] but much more than the 5–17% found in Trinidad and Tobago[9] and in the total population surveys in Malaŵi where only 10% had any disability.[4] Our higher proportion could reflect ethnic difference in disease severity or in seeking medical care, or a more disabled selected immigrant population. Progression of disability while under our care was rare.

Dapsone haemolysis occurred in 5% of our patients. The incidence of significant haemolysis quoted by others varies from 'rare' to 16%.[12,13] Factors which are often associated with haemolysis, such as increased age, high dapsone dose, and glucose-6-phosphate dehydrogenase deficiency[12–14] did not occur in our patients. Clofazamine skin pigmentation was of concern to only 1 of our patients, and in Samoa[7] and elsewhere[3,9] there has generally been acceptance of this side effect. Rifampicin allergy[14] and clofazamine enteritis[14,15] are rare.

WHO have stated[3] that 'type I reactions have become relatively more prominent in leprosy control programmes since the introduction of MDT, probably because of better monitoring of patients'. We found no such increase, with about 20% having type I reactions before and after WHO MDT introduction. In contrast, 16% (3 of 19) of our patients treated only with WHO MDT for MBD had type II reactions, significantly less than the 64% (9 of 14) of our MBD patients who we had treated uninterruptedly before 1983. Type II reaction rates between 9% and 43% are reported for WHO MDT of MBD.[9,10] We found that for patients transferring to WHO MDT, type II reactions were

common in those with positive smears (71%) but rare in those who were smear negative.

Our difficulty in differentiating late reaction from relapse is similar to the experience of others.[9,10] Late reactions have been reported as occurring most frequently in the first 6 months after treatment but may still occur up to 4 years,[16] and in our case, ignoring the diagnostic uncertainty, 6 years after treatment stopped.

Compliance with treatment while in Auckland is good, but the high proportion of patients emigrating prior to or just as treatment finishes is of concern, both for completion of treatment and the detection of late reaction or relapse. The Western Samoan treatment programme has the same problem, with the frequent movement of patients to American Samoa, New Zealand and Hawaii.[7]

While WHO MDT has generally been shown to speed up clinical improvement[3] the rate of fall of BI does not differ significantly between various drug regimens, presumably because BI measures both dead and viable organisms, which are eliminated by a process unrelated to antimicrobial treatment.[17] We found the most rapid rate of BI fall in the group with prior interrupted treatment. This was the group with the longest duration of previous treatment and it is this long duration of treatment which is the likely reason for the rate of fall being the most rapid of the 3 groups. (This is not an argument in support of interrupted treatment!)

Active lesions persisted at the end of treatment in 9% (1 of 11) with PBD, at the lower end of incidences between 4·3% and 27·8% quoted elsewhere.[17] We elected to continue treatment until lesions were clinically inactive.[13] Our treatment for MBD is conservative, treating up to 2 sets of negative skin smears taken 12 months apart.

Our single patient who relapsed had extensive initial clinical disease, though with a negative BI. Following this episode in 1984, we treated patients with extensive BT disease and BI = 1+ or B = 0, with 2 years MB MDT, contrary to the then current official recommendations[1] though in line with, but still more stringent than, recent recommendations.[3] This early decision may well have decreased our relapse rate. We have followed up insufficient numbers after completion of WHO MD MDT to enable us to predict relapse. However, we have seen no relapses so far in the 23 patients we have been able to follow up who took WHO MB MDT after prior treatment.

In conclusion we have found WHO MDT well accepted, and our experience of reactions and relapse, within the limits imposed by small numbers, is similar to others.

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References

[1] WHO Study Group. *Chemotherapy of leprosy for control programme.* Technical Report Series 675. WHO: Geneva, 1982.
[2] Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five group system. *Int J Lepr*, 1966; **34:** 255–73.
[3] WHO Expert Committee on Leprosy. *Sixth report.* Technical Report Series, No. 768. WHO: Geneva, 1988.
[4] Ponnighaus IM, Boerrigter G, Fine PEM, Ponnighaus JM, Russell J. Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malaŵi. *Lepr Rev*, 1990; **61:** 366–74.

[5] WHO collaborating centre for the epidemiology of leprosy. *Global evaluation of the introduction of multidrug therapy*. Leprosy Epidemiological Bulletin No. 6. Brussels: January 1991.
[6] Mastro TD, Redd SC, Breiman RF. Imported leprosy in the United States, 1978 through 1988: an epidemic without secondary transmission. *Am J Public Health*, 1992; **82:** 1127–30.
[7] Paksoy N, Levi V. Preliminary assessment of multidrug therapy in leprosy patients in Western Samoa. *NZ Med J,* 1989: **102:** 589–91.
[8] Montreewasuwat N, Peerapakorn S. Leprosy situation in Thailand. *South-East Asian J. Trop. Med. Public Health*, 1988; **19:** 515–17.
[9] Suite M, Edinborough NB. A second report on multidrug therapy for leprosy in Trinidad and Tobago. *Lepr Rev*. 1989; **60:** 288–99.
[10] Rangaraj M, Rangaraj J. Experience with multidrug therapy in Sierra Leone: clinical, operational and managerial analysis. *Lepr Rev*, 1986; **57** Suppl 3: 77–91.
[11] Noordeen SK, Lopez Bravo L, Daumerie D. Global review of multidrug therapy (MDT) in leprosy. *WHO Statistics Quarterly,* 1991; **44:** 2–15.
[12] Byrd SR, Gelber RH. Effect of dapsone on haemoglobin concentration in patients with leprosy. *Lepr Rev*, 1991; **62:** 171–8.
[13] Powell RD, De Gowin RL, Bennett Eppes R, McNamara JV, Carson PE. The antimalarial and hemolytic properties of 4,4′-diaminodiphenyl sulfone (DDS). *Int J Lep*, 1967; **35:** 590–667.
[14] Jopling WH. Side effects of antileprosy drugs in common use (Editorial). *Lepr Rev,* 1983; **54:** 261–70.
[15] Mason GH, Ellis-Pegler RB, Arthur JF. Clofazamine and eosinophilic enteritis. *Lepr Rev*, 1977; **48:** 175–80.
[16] Rose P. Reversal reactions in leprosy and their management (Editorial). *Lepr Rev*, 1991; **62:** 113–21.
[17] Ji B, Grosset JH. Recent advances in the chemotherapy of leprosy (Editorial). *Lepr Rev*, 1990; **61:** 313–29.

Les effets de la chimiothérapie de l'organisation mondiale pour la santé (oms) sur la lèpre importée à Auckland, Nouvelle Zélande, 1983–90

J. Cornwall, G. Cameron et R. B. Ellis-Pegler

Résumé De janvier 1983 à décembre 1990 à Auckland, Nouvelle Zélande, 87 malades—28 cas de maladie paucibacillaire (PBD) et 59 cas de maladie multibacillaire (MBD)—ont commencé la thérapeutique multidrogue (MDT) de l'OMS.

Tous étaient des immigrées venant des îles du Pacifique (65) ou d'Asie (22). Au total 57 malades avient déjà reçu des régimes non-OMS, quelques uns continuellement, mais souvent de façon intermittente, pendant de nombreuses années; 30 malades ont eu seulement MDT de l'OMS. En décembre 1990, 50 avaient terminé le traitement, avec 1 rechute et 1 réaction tardive, les deux chez des malades avec PBD traités seulement avec MDT de l'OMS. Il n'y a eu aucune rechute chez les malades traités par MDT de l'OMS après un traitement antérieur contre la lèpre.

Chez les multibacillaires, les réactions lépreuses de type II ont été moins nombreuses (16%) chez ceux traités seulement par MDT de l'OMS que chez ceux traitées continuellement avant 1983 par d'autres régimes (64%). Les réactions lépreuses de type I ont été observées chez 20% environ des deux groupes. L'index bactérien a baissé plus vite chez ceux qui avaient eu un traitement antérieur prolongé débutant avec MDT de l'OMS que chez ceux dont le traitement MDT de l'OMS constituait la première chimiothérapie antilépreuse.

En général, nous avons constaté que MDT de l'OMS était bien supporté et le taux d'observance était bon, mais 13 malades (15%) ont quitté Auckland avant la fin du traitement et 6 (7%) pendant la période du suivi.

Los efectos de la quimioterapie de la Organización Mundial de la Salud sobre la lepra importada, en Auckland, Nueva Zelandie, 1983–90

J. Cornwall, G. Cameron y R. B. Ellis-Pegler

Resumen Se comenzo la quimioterapia de la Organización Mundial de la Salud (OMS) entre enero 1983 y diciembre 1990 en Auckland, Nueva Zelandia, sobre 87 pacientes (28 paucibacilares (PBD) y 59 multibacilares (MBD)).

Todos eran inmigrantes de las Islas del Pacifico (65) o de Asia (22). Un total de 57 pacientes ya habían realizado regímenes OMS por muchos años, algunos de forma continua, pero a menudo intermitente; 30 pacientes recibieron tratamiento multidroga OMS solamente. En diciembre 1990, 50 habián completado el tratamiento, con una recaída y una reacción retardada, ambos casos en pacientes con PCB tratados con MDT OMS solamente. No hubieron recaídas entre los tratados con MDT OMS después de un tratamiento posterior para la lepra.

En los casos con MBD, las reacciones leprosas de tipo II erán menos comunes (16%) en los tratados solamente por MDT OMS que en los que habían sido tratados continuamente antes de 1983 con regímenes más antiguos (64%). Se presentaron reacciones leprosas de tipo I en un 20% de ambos grupos. El índice bacteriano bajó con más rapidez en los que habían tenido un tratamiento anterior prolongado que comenzaban MDT OMS que los que comenzaban MDT OMS como su tratamiento inicial contra la lepra.

En general, nuestra opinión es que MDT OMS ha sido bien aceptado y la conformidad ha sido buena, pero 13 pacientes (15%) abandonaron Auckland antes de completar el tratamiento, y 6 (7%) durante el estudio posterior.

Lepr Rev (1993) **64,** 250–254

Further observations on MDT blister–calendar packs in vertical leprosy eradication programmes—a multicentre study (Phase II)

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Summary To improve operational efficiency as well as to improve patient compliance in leprosy programmes, DANIDA introduced blister–calendar packs (BCP) to deliver MDT in 4 MDT districts in India in 1987. An objective study (Phase II) involving 343 patients in a trial group (BCP group) and 253 patients in a control group (loose drug group) showed no significant difference in compliance rates for self-administered doses between the 2 groups.

Hence, while assessing the use of BCPs in leprosy programmes, other operational benefits like safe storage, easy transportation, easy drug accounting and safe preservation at home are to be considered. These aspects were followed up from Phase I of the study.

Introduction

An important factor that ensures the success of the MDT programme is obtaining maximum treatment compliance, especially for self-administered drugs. Many factors influence patients' compliance, including a continuous and regular supply of all 3 drugs and easy methods of preserving these drugs at home without damage or loss. Drug delivery in a socially acceptable and attractive form is an additional factor that influences patients' compliance. Easy storage, ease of transportation without any loss or damage, easy accounting and preparation for clinics at control unit level are also factors that could influence the efficiency of the MDT programme in general.

DANIDA is assisting the National Leprosy Eradication Programme (NLEP) in India in 4 districts, with 1 unit in Orissa, 1 in Tamilnadu and 2 in Madhya Pradesh. As an

§ The study was done by the first author during his assignment with DANIDA-DANLEP, New Delhi.

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alternative strategy of drug delivery, to overcome the operational problems and to improve patients' as well as programme workers' compliance, we introduced BCPs (which are manufactured by Pharmanova AS Copenhagen) to all MB and PB patients, with the objectives described in an earlier paper on Phase I of this multicentre study.[1]

The Phase II trial was designed to study the patients' compliance for self-administered drugs of MDT by comparing patients in the same locality who received blister calendar packs with patients who received loose drugs. The study was carried out between 1987 and 1989.

Material and methods

MDT is delivered through a circuit plan, as described by NLEP, India.[2] (A circuit consists generally of 2 subcentres with 2 paramedical workers (PMW) who serve a population of 40,000.) We selected 8 subcentres randomly from 4 districts which have been entered into the MDT programme—Salem district in Tamilnadu state, Cuttack district in Orissa state, and Durg and Rajnandagaon districts in Madhya Pradesh state. In each circuit, a single subcentre was selected for the trial group (BCP), while the other was selected for the control group (loose drugs).

All the MB and PB patients of both sexes were included from these subcentres except patients under 14 and over 50 years of age, as their compliance is likely to be influenced by other factors, such as parents administering drugs to their children and older patients being helped by other family members. The customary visits (Preclinic motivation visit) usually made to remind the patients of the day pulse clinics were held did not take place in these subcentres to eliminate the influence of the paramedical workers' visits.

Patients who attended regularly for the monthly supervised pulse dose were visited once every 2 months by the paramedical worker in charge of the sector for tablet/capsule count and for collection of urine samples for the DDS test without a prior warning. Urine samples were collected at home on 3 occasions, at 2 monthly intervals, 7 days after the last pulse dose and 7 days before the next pulse dose. The tablet/capsule count took place at the time of urine collection. The urine samples were coded and sent to RRE Society, Bombay, for performing a quantitative test[3] (Dapsone/Creatinine ratio) as well as a qualitative test (Tile Test method).[4] The results were decoded at the end of the study.

—The result was considered positive or regular by quantitative test when the Dapsone/Creatinine ratio ranged between 17·8 and 135·0 on an intake of 100 mg dapsone daily.[5]
—The qualitative test was considered positive when the urine was pink.[4]
—The tablet/capsule count was considered 'Correct' when the number of dapsone tablets/clofazimine capsules on the day of the count tallied with the date of issue.
—Tablet/capsule count was considered 'Wrong' when the number of dapsone tablets/clofazimine capsules remaining on the day of the count did not tally with the date of issue.

The paramedical workers, non-medical supervisors and medical officers were given intensive training in the field to carry out this study effectively. A simple data collection form was designed to feed data into the computer at the DANLEP office, New Delhi.

Results and Discussion

Table 1. Number of leprosy patients in the study

Group	No. of patients		
	MB	PB	Total
Trial	197	367	564
Control	187	266	453

A total of 1017 adult male and female patients were included in this study. However, due to operational problems, urine samples could not be collected from all the patients on 3 occasions at regular intervals in the routine leprosy eradication programme.

On all 3 occasions, no significant difference was observed between trial and control groups regarding their compliance for intake of self-administered drugs. The compliance rate ranged between 86–94% in the trial group and 83–95% in the control group.

Dapsone tablet/clofazimine capsule results were available from all the 564 patients in the trial group and from 453 patients in the control group for the 3 occasions. The tablet/capsule counting method was followed to observe compliance for self-administered drugs. The compliance rate ranged between 86–91% in the trial group and 87–89% in the control group. No significant difference was observed between the 2 groups. All these patients were regular for monthly supervised pulse doses throughout the 6 months of the study period.

In DANIDA MDT districts, other intervention techniques such as community participation were also attempted to improve the compliance rate for drug intake. This may have contributed to the compliance of both the study and control groups.

A similar study was undertaken in an urban area where no other interventions such as community participation were undertaken in order to improve compliance rates. The results did not show any significant difference between patients using BCPs and loose

Table 2. Compliance rate by urine test method*

Frequency	Trial group			Control group		
	Total	Positive	Negative	Total	Positive	Negative
I	343	296	47	253	209	44
	%	86	14	%	83	17
II	265	250	15	164	141	23
	%	94	6	%	86	14
III	134	126	8	55	52	3
	%	94	6	%	95	5

* By quantitative and qualitative test of urine samples.

Table 3. Compliance rate by tablet/capsule count method

	Trial			Control		
Frequency	Total	Correct	Wrong	Total	Correct	Wrong
I	564	484	80	453	396	57
	%	86	14	%	87	13
II	564	488	76	453	401	52
	%	87	13	%	89	11
III	564	515	49	453	399	54
	%	91	9	%	88	12

drugs.[6] It therefore could be inferred that apparently BCP does not improve patients' compliance.

However, Phase I of this study[1] (performed in the same 4 districts) showed that patients receiving BCPs preferred them to loose drugs because, for example, the BCPs are attractive and easier to handle, carry and preserve. Similarly leprosy control unit field workers reported that BCP was easier to prepare for clinics, and to dispense and transport the drugs and to prepare monthly drug accounting lists. The time required to prepare a pulse clinic for between 50 and 100 patients was less than 1 hour with BCPs but was about 3–5 hours with loose drug counting and packing.

Thus, while evaluating the use of BCPs in mass leprosy eradication programmes, it would be advisable to consider the operational advantages of this alternative system of drug delivery.

BCPs may be even more useful for integrated leprosy control programmes where primary health care personnel (such as medical officers and multipurpose workers) are involved in drug delivery. Staff working in these programmes would value a simple and quick method of drug delivery and drug accounting.

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References

[1] Revankar CR, Sorensen Birte H, Kielstrup RW, Multicentre Study Group. Delivery of MDT through blister–calendar packs in leprosy eradication programmes—multicentre field study (Phase I). *Lep Rev*, 1989; **60:** 135.

[2] Government of India, *Guidelines for multidrug treatment in endemic districts 1986*. Published by Leprosy Division, DGHS, New Delhi.

[3] Ellard GA, Gammon PT, Harris JM. The application of urine tests to monitor the regularity of dapsone self-administration. *Lepr Rev*, 1974; **45:** 224.

[4] Irudayaraj PS, Lourdumary, Aschoff M, Balkrishnan S. A comparison of screening tests for dapsone in urine. *Lepr India*, 1983; **55:** 528.
[5] Naik SS, Ganapati R. Regularity of dapsone intake by leprosy patients attending urban treatment centre. *Lepr India,* 1977; **49:** 207.
[6] Revankar CR, Dhamale CB, Ganapati R. Experience of multi-drug therapy blister calendar packs in an urban leprosy control programme in Bombay. Letter to Editor, *Lepr Rev*, 1991; **62:** 336.

Lepr Rev (1993) **64,** 250–254

Nouvelles observations sur le conditionnement de MDT sous emballage monoalvéolaire daté dans les programmes verticaux d'éradication de la lèpre—une étude multicentrée (Phase II)

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Résumé Pour améliorer l'efficacité opérationnelle des programmes contre la lèpre en même temps que l'observance du traitement par le patient, DANIDA a introduit les emballages à alvéoles datées (BCP) pour distribuer MDT dans 4 districts MDT des Indes en 1987. Une étude objective (Phase II) comprenant 343 malades dans un groupe d'essai et 253 dans un groupe témoin (drogue en vrac) n'a pas révélé de différence significative entre les deux groupes dans les taux d'observance pour les médicaments administrés par le malade lui-même.

Par conséquent, lorsqu'on évalue l'usage de BCP dans les programmes anti-lèpre, on doit considérer les autres avantages opérationnels, tels que sécurité du stockage, facilité du transport, facilité de la compatibilité du médicament et sécurité de la conservation à la maison. L'étude de ces aspects continue la Phase I du programme.

Observaciones adicionales sobre los empaques blister–calendario en los programas verticales de eradicación de la lepra—un estudio multi-centro (Fase II)

C. R. Revankar, Nivedita Gupta, Birte H. Sorensen, S. S. Naik y El Grupo de Estudio Multi-centro

Resumen Para mejorar la eficacia operativa además de mejorar la conformidad por los pacientes de los programas contra la lepra, DANIDA introdujo empaques blister-calendario (BCP) para realizar MDT en 4 distritos MDT de India, en 1987. Un estudio objetivo (Fase II) con 343 pacientes en un grupo de prueba (grupo BCP) y 253 pacientes en un grupo de control (grupo de droga al granel), no indicó una diferencia significativa de los niveles de conformidad para las dósis autoadministradas entre los dos grupos.

Por lo tanto, aunque evaluamos el uso de BCPs en los programas contra la lepra, se considerarán otros beneficios operativos como almacenamiento seguro, facilidad de transporte, control de la droga, y preservación segura en domicilio. Se continúan estos aspectos de la Fase I del estudio.

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Trigeminal neuralgia—a presenting feature of facial leprosy

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Summary Trigeminal neuralgia is a well recognized clinical entity. However, it has not been reported to mimic leprosy or vice versa. Of the 3 cases reported here, 2 initially presented with neuralgic symptoms similar to that seen in trigeminal neuralgia and later developed borderline lesions on the face. The 3rd case demonstrated a tingling sensation along with firm and palpable supraorbital nerve (a branch of trigeminal nerve), and a very early skin lesion on the face pointed to the need to consider neuritic type leprosy before concluding the final diagnosis of a disease like trigeminal neuralgia which calls for a different therapeutic approach.

Introduction

Many workers support the theory that leprosy starts with the appearance of an indeterminate patch on the skin and then progresses to the other serious forms or types.[1] Neuritic leprosy is the only type which appears without passing through this stage. However, some recent reports say that even neuritic cases have been seen to develop borderline skin lesions in the course of the disease.[6]

Various syndromes associated with nerve lesions have been considered or compared with leprosy, either at the time of making a differential diagnosis, or they have been known to occur during the course of leprosy.

In the first group, scalenus anterior syndrome, cervical rib syndrome and meralgia paraesthetica are the commonest.

In the second group the most frequently occurring clinical entity is lagophthalmos due to the involvement of the facial nerve trunk or its branches supplying the orbicularis oculi.[7] Less frequently occurring cranial nerve involvements are bulbar palsy type syndrome[8] and the loss of taste sensation due to the combined effects of facial, trigeminal and glossopharyngeal nerves.[9] Melkersson syndrome, a rarely seen clinical entity which is manifested by a recurrent facial paralysis, recurrent and eventually permanent facial

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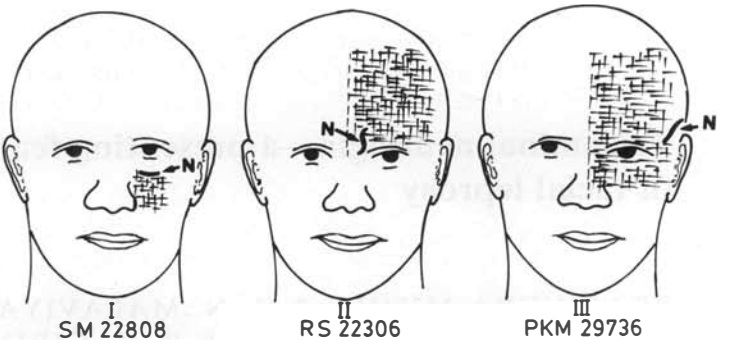

Figure 1. Location of facial lesions in different patients.

(especially confined to lips) oedema and less constantly, plication of the tongue, has also been described, and this could be due to leprosy, at least in the Far East.[10]

Trigeminal neuralgia occurs in the elderly and middle aged, and consists of an excruciating paroxysm of pain in the gums, lips, cheek and chin, and, very rarely, in the distribution of the ophthalmic division of the 5th nerve. The pain seldom lasts more than a few seconds but may be so intense that the patient winces. The paroxysms frequently occur day and night for several weeks at a time. The cause of this clinical entity is unknown, although occasionally it is a manifestation of multiple sclerosis or herpes zoster. Very rarely a tumour or vascular anomaly in posterior fossa causes irritative lesion in the nerves, which is symptomatically indistinguishable from that of trigeminal neuralgia.

The text-book picture of trigeminal neuralgia does not include paralysis of muscles supplied by the 5th nerve.

Case reports (Figure 1)

1. S.H., a 25-year-old Muslim male, complained of tingling in a small area of his left cheek, intermittently for 3 months. In the area of irritative symptoms no visible patch or nerve thickening was noticed. Slit skin smear for *M. leprae* and lepromin reaction was negative. A provisional diagnosis of Trigeminal neuralgia was made. At the time of the 2nd examination (12 months later), a raised infiltrated patch with anaesthesia along with thickened infraorbital branches on the same side was noticed. A clinical diagnosis of BT leprosy was made and later confirmed by histology of the lesion.

2. R.J., a 27-year-old Hindu male, under treatment for neuritic leprosy , had developed a cutaneous lesion 12 months before and had paraesthetic symptoms (tingling) on pressing the left side of the forehead. On examination the supraorbital branch of the left trigeminal nerve was found palpable and firm. On pressing this the patient complained about the tingling. There was a faint hypopigmented patch on the left side of the forehead which gradually became more demarcated. The patient responded to a course of multidrug therapy supplemented with oral steroids. Histology of the lesion confirmed BT leprosy.

3. P.K.M., a 30-year-old Hindu male, presented with a sudden onset of an erythematous

patch on the left side of the forehead, which covered the area demarcated by hairline above and nasolabial fold below, midline of the face, medially and laterally, and most part of the left eyebrow laterally. On the same side the zygomatic branch of facial nerve was thick. This patient gave a history of having suffered with trigeminal neuralgia 8 years ago which had recovered partially without treatment. He had paralysis of the muscles which are supplied by the motor division of the trigeminal nerve.

He was treated as a case of cerebro-vascular abnormality. After 2 months the lesion was found to be erythematous, firm, smooth and oedematous. Its margins sloped. The left ear was red, slightly itchy and edematous. The cornea was dry and corneal sensations were decreased. There was lacrimation, sialorrhoea and rhinorrhoea, but the patient was unable to feel the discharge due to anaesthesia, indicating sensory loss on the left side. Sensation for modalities like temperature and touch were reduced and impaired in the area innervated by ophthalmic and maxillary divisions of the trigeminal nerve. However, impairment of these modalities in mandibular division was doubtful. Taste sensations were partially affected though the left side of the oral cavity was anaesthetic.

The muscles supplied by the left trigeminal nerve were wasted. Muscle power in massater, pterygoid and temporalis were graded 3, 2 and 1, respectively. There was no weakness in the muscles supplied by the facial nerve.

In slit skin smears from facial lesions and ear lobules, *Mycobacterium leprae* were absent. Blood, urine analysis, skull X-ray and CAT scan were within normal limits. Tests for VDRL and LE cells were negative.

The patient was diagnosed as suffering with borderline tuberculoid leprosy.

Discussion

In the 1st case a provisional diagnosis of trigeminal neuralgia was made. Even in the 2nd, paraesthetic symptoms suggested the same diagnosis but there were enough signs to diagnose leprosy. In the 3rd case, even though the first diagnosis of trigeminal neuralgia had been made 8 years before, there is enough information to support the belief that those manifestations could have been an early presentation of leprosy.

Trigeminal neuralgia is a sensory affliction and impairment of motor functions is not documented. In leprous neuritis it is common to find damage to the motor functions resulting in paresis or complete paralysis of the muscles supplied by the affected nerve.

Neurological manifestations of preclinical leprosy deserve more attention. As early as 1964, Cochrane had observed that the early lesion may be preceded by vague paraesthetic or neurological symptoms.[11] To quote him, 'I am convinced that the first definite evidence of disease is seen in the appearance of an area of anaesthesia. This definite sign may be preceded by vague subjective symptoms such as tingling.' He further observed that the time gap between the onset of the 1st sign and diagnosis of leprosy can vary from 2 to 20 years. A recent study by us (under communication) also supports the above views.[12]

The cases reviewed here give enough information to support the view that trigeminal neuralgia-like symptoms may be due to leprosy, and before diagnosing a patient as suffering from trigeminal neuralgia, leprosy should also be considered, particularly if the patient has a family history of leprosy or he or she lives in a leprosy endemic area.

References

[1] Dharmendra. Indeterminate group. Vol. 1. Bombay: Medical Publishing House, 1978; 44–7.
Noordeen SK. Epidemiology of (Poly)neuritic type of leprosy. *Lepr India*, 1972; **Vol. XLIV(2):** 90–6.
Chacko GJG. *Evolution of pathological lesions in leprosy patients and their immunological significance.* Proceedings of Indo U.K. symposium on leprosy. April 1986, 82–9. Central JALMA Institute publication, Agra, India.

[4] Shenoi SD, Padhee A. Polyneuritic leprosy changing in borderline tuberculoid (BT). *Ind J Lepr*, 1990; **62:** 363–4.

[5] Talwar S, Jha PK, Tiwari VD. (1992) *Neuritic leprosy epidemiology and therapeutic responsiveness* (abstract). XVII Biennial Conference and the workshop of Indian association of leprologists; abstracts of scientific papers FC 38.

[6] Brajendra Mishra, Mukherjee Ashok, Girdhar A, Husain S, Malaviya GN, Girdhar BK. Neuritic leprosy: further progression (under communication).
Diwan VS. A survey of deformities in leprosy (with special reference to face). *Lepr Rev*, 1962; **33:** 225–64.
Ishihara S. Bulbar palsy appearing in leprosy patients. *La Lepro*, 1967; **36:** 199 (Japanese: adapted from English summary).

[9] Malaviya GN, Ramu G. Loss of taste sensation over the tongue in leprous facial palsy—a case report 1981; **53**(4): 656–9.

[10] Maurice Victor, Adams RD. Diseases of cranial nerves. In: *Harrison's Principles of Internal Medicine.* Eighth edn, p. 121. Tokyo: Blakiston Publication; McGraw Hill; Kogakusha Ltd, 1977.

[11] Cochrane RAG. *Leprosy in Theory and Practice.* London: John Bristol & Co, 1964; 251.

[12] Brajendra Mishra, Mukherjee A, Girdhar Anita, Husain Sajid, Malaviya GN, Girdhar BK. Evolution of early lesions in leprosy *Lepr. Rev*, 1993; **64:** 259–66.

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Névralgie du trijumeau—un élément caractéristique de la lèpre de la face

BRAJENDRA MISHRA, G. N. MALAVIYA, A. GIRDHAR, S. HUSAIN ET B. K. GIRDHAR

Résumé La névralgie du trijumeau est une entité clinique bien connue. Cependant, on n'a pas rapporté d'observation où elle imite la lèpre ou vice-versa. Des trois cas rapportés ici, deux présentaient au début des symptômes névralgiques similaires à ceux que l'on observe dans la névralgie du trijumeau, et ont développé par la suite des lésions borderline de la face. Dans le troisième cas, une sensation de picotement accompagnée d'un nerf sus-orbital ferme et palpable—une branche du nerf trijumeau—et un début de lésion cutanée de la face évoquent une lépre de type névritique qu'il faut envisager avant de porter un diagnostic de maladie du genre névralgie du trijumeau qui demande un traitement différent.

La neuralgia trigeminal—una característica diagnóstica de la lepra facial

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Resumen La neuralgia trigeminal es una entidad clínica bien reconocida. Sin embargo, no se ha informado que imita la lepra, ni viceversa. De los tres casos informados aquí, dos inicialmente presentaron síntomas neurálgicas similares a las que se observan en la neuralgia trigeminal, y posteriormente desarrollaron lesiones dudosas en la cara. En el tercer caso, una sensación de hormigueo y una zona firme y sensible entre la supraorbital, es decir una rama del nervio trigeminal, y una lesión muy temprana de la cara, indica la necesidad de pensar en lepra de un tipo neurítico, antes de decidir en un diagnóstico de una enfermedad como neuralgia trigeminal, que requiere un tratamiento terapéutico diferente.

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Evolution of early lesions in leprosy

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Summary We observed 29 patients presenting with vague peripheral neurological symptoms for 6 months or more. During this period, 16 developed clinical leprosy, 3 developed borderline tuberculoid leprosy and the other 13 developed neuritic leprosy. Of these 13 cases 11 subsequently developed skin lesions similar to those seen in indeterminate and in borderline tuberculoid leprosy. Based on the above observations, an attempt has been made to explain the evolution of early lesions of leprosy.

Introduction

Clinical leprosy is diagnosed by the presence of 2 of the 3 cardinal signs—hypopigmentation and/or infiltration of the skin, nerve thickening and/or anaesthesia and the presence of *Mycobacterium leprae* in skin or nerves. By the time 2 cardinal signs appear the leprosy lesions are well established. Can leprosy be diagnosed earlier than this?

It has been postulated that a hypopigmented patch, with or without anaesthesia, may not be the first clinical event in the course of the disease. There may be some preceding neurological symptoms which go unnoticed because of their insidious onset and vague appearance.

At present most diagnoses of leprosy, especially those made in the field, are based on clinical observations, and laboratory tests are used to provide additional supportive evidence in order to confirm the clinical diagnoses.

Taking into consideration the above, we undertook the present work, and selective patients attending the outpatient department at CJIL Agra were observed for about $2\frac{1}{2}$ years.

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Material and methods

For this study we selected 29 people who voluntarily presented with certain neurological symptoms which they believed could probably be due to leprosy. These patients visited us more or less regularly over a long period, and could therefore be followed-up and included in the study, because it is difficult to study patients properly who present for some vague symptoms but stop coming after 1 or 2 visits. As a result a common denominator for the cases used in our study could not be established. Their neurological symptoms were localized to a particular site of the body and there was no clinical evidence of leprosy.

They were thoroughly examined in order to rule out leprosy or any other disease likely to be responsible for their symptoms. The 29 patients we selected for our study had an area of numbness or tingling, a sense of burning or heaviness or formication and incomplete or complete anaesthesia. They did not have any local or regional nerve thickening, hypopigmented or erythematous, raised or flat skin lesions.

Patients who had one or more of the above symptoms, along with associated nerve thickening, were diagnosed as cases of neuritic leprosy. When this was diagnosed the subjects were examined in good daylight to rule out any cutaneous lesion of leprosy.

The cases developing cutaneous manifestations were those who had one or more of the above symptoms along with ill- or well-defined, flat or raised, hypopigmented or infiltrated, single or multiple skin lesions.

Smear examinations were done from both ears and at least one from the site of the above-mentioned symptoms. Lepromin (Dharmendra) 0·1 ml, intradermal was given and the reaction was read after 24–48 hours. Erythema over 10 mm in diameter was considered as a positive reaction to lepromin. Biopsies were taken for histology in some cases. It was very difficult to convince our patients to undergo biopsy at the stage 'Under observation' because they were new to hospital and apparently there was nothing in the skin, therefore the majority of the biopsies could only be performed in later parts of the study.

All 29 cases kept under observation were given a placebo to ensure their regular visit. The moment the diagnosis of leprosy was made on clinical grounds, patients were put under appropriate antileprosy therapy consisting of dapsone 100 mgs daily and Rifampicin 600 mgs once a month.

VISIT SCHEDULE

Patients usually visited at monthly intervals, but some of the cases reported a week earlier or later.

OBSERVATIONS

1. *Symptomatology*

All 29 cases had neurological symptoms which included impaired/altered sensation (in 24) and paraesthetic symptoms (in 7). Some of the cases had more than a single symptom. Slit skin smear examinations were done in 25 cases and all were negative for *M. leprae*. Lepromin status was examined in 17 cases and of these only 4 cases had a positive Mitsuda reaction and the remaining 13 were negative.

2. *Histology*

We performed 16 biopsies on 11 patients at various stages of the disease. Of the 16 biopsies, 2 were performed on the areas of sensory impairment at the stage of 'under observation'. At the stage of 'Neuritic leprosy' 5 biopsies were performed and, finally, at the stage of 'Leprosy with cutaneous lesions' 9 biopsies were performed. Biopsies could be grouped as follows (see Table 1).

Group I

We performed 2 biopsies at the stage of 'Under observation', both obtained from the area of sensory impairment in cases 9 and 12. In case 9 there was no evidence of leprosy; however, on follow-up this case developed mononeuritic leprosy, followed by the appearance of an indeterminate lesion (proven histologically). In case 12, the skin showed BT histology at the stage of 'Under observation' (without any visible skin lesion) and on follow-up this case also developed mononeuritic leprosy and afterwards progressed to histologically proven clinical TT skin lesion (Table 1).

Group II

We performed 5 biopsies at the stage of 'Neuritic leprosy'. Two biopsies were performed on the anaesthetic skin, in case 1 there was no evidence of leprosy and in case 2 non-specific changes were seen. 3 nerve biopsies on cases 1, 7 and 8 revealed BT/I, I/BT and BT histology, respectively, and 2 of these mononeuritic cases, 7 and 8, later developed histologically proven BT skin lesions. Case 1, another suffering from neuritic leprosy, demonstrated BT histology in nerves but no evidence of leprosy in skin biopsy (Table 1).

Group III

We performed 9 biopsies at the stage of 'Cutaneous leprosy' obtained from the cutaneous lesions and in all, except case 11, (cases 3, 4, 6, 7, 8, 9, 10 and 12), there was total concordance for disease. However, in case 11 non-specific changes were seen in clinical BT skin lesion (Table 1).

EVOLUTION OF EARLY LEPROSY LESIONS

The 29 cases we followed up to study altered sensation for between 6 months and $2\frac{1}{2}$ years showed the following pattern (Figures 1 and 2):

(a) There was no change in 13 patients, and 1 had been suffering from anaesthesia in both upper limbs.
(b) Cases 1 and 2 while under observation progressed to the stage of mononeuritic leprosy.
(c) Cases 3, 4 and 5 while under observation developed borderline tuberculoid lesions in skin, without passing through the stage of 'Neuritic leprosy'; case 4 in this group at the stage of 'Under observation' showed symptoms similar to those seen in trigeminal neuralgia in an area inervated by the infraorbital branch of the trigeminal nerve. Later this patient developed a BT lesion exactly at the site of the initial symptom. In cases 3 and 5 lesions appeared at sites where it was difficult to palpate the cutaneous nerve.

Table 1. Evolution of early lesions in leprosy

S. No.	Name	Age	Sex	Duration of altered sansation on first visit (months)	Smear examination	Lepromin	Under observation Histology		Period for developing neuritic from stage of U.O.		Neuritic Leprosy			Transition period for change of nuritic to cutaneous leprosy		Leprosy with cutaneous manifestation	
											Clinical	Histology					
							Nerve	Skin	Months	Days	Monopoly	Nerve	Skin	Months	Days	Clinical	Histology
1	SL	65	M	—	−Ve	−Ve	—	—	22	15	M	BT/I	NE	—	—	—	—
2	MA	35	M	14	—	—	—	—	9	07	M	—	NSC		—	—	—
3	MV	35	M	12	−Ve	−Ve	—	—	—	—	—	—	—	5	10	MBT	BT
4	SH	24	M	5·5	−Ve	+Ve	—	—	—	—	—	—	—	1	00	BT	T
5	PR	35	M	—	—	—	—	—	—	—	—	—	—	0	28	BT	—
6	GD	16	F		−Ve	−Ve	—	—	3	28	M	—	—	7	05	BT	I
7	MN	18	M	36	−Ve	−Ve	—	—	3	15	M	I/BT	—	1	03	BT	BT
8	RN	40	M	—	−Ve	—	—	—	0	28	M	BT	—	2	00	BT	BT
9	GR	25	M	—	−Ve	+Ve	—	NE	6	00	M	—	—	0	19	I	I
10	RS	50	M	—	—	—	—	—	0	23	M	—	—	1	07	BT	I
11	RNS	40	M	—	−Ve	−Ve	—	—	5	25	P	—	—	0	20	BT	NSC
12	RH	34	M	4	−Ve	−Ve	—	I/BT	12	00	M	—	—	8	08	BT	I/BT
13	SR	25	M	36	—	—	—	—	4	20	M	—	—	0	23	BT	—
14	AS	25	M	24	−Ve	—	—	—	11	00	M	—	—	17	17	BT	—
15	NN	45	M	—	−Ve	—	—	—	23	00	M	—	—	4	11	BT	—
16	MU	35	M	—	−Ve	—	—	—	0	23	M	—	—	1	03	BT	—

NE: No evidence of leprosy, NSC: Nonspecific changes, MBT: Macular BT, NEUR: Neuritic Leprosy, UO: Under Observation, MONO: Mononeuritic, POLY: Polyneuritic, I: Indeterminate, BT: Borderline Tuberculoid.

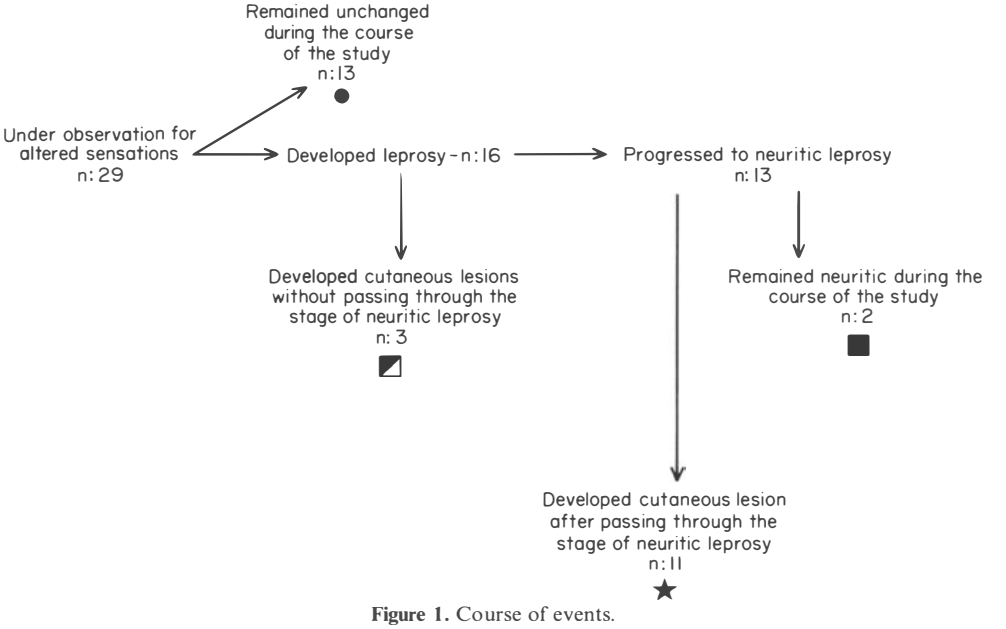

Figure 1. Course of events.

(d) In this category cases 6–16 'Under observation' passed through the stage of 'Neuritic leprosy' and later on developed BT lesions; 1 of these had multiple patches.

TIME FRAME FOR THE EVOLUTION OF EARLY LEPROSY LESIONS

The period the altered sensation had lasted in all the patients when they first visited the hospital varied from 2 to 30 months, averaging 18 months (A). The length of time taken to develop 'Neuritic leprosy' during the stage of 'Under observation' in hospital was also variable. The average period for 11 cases was about 5 months and 9 days (B), 2 cases (at serial numbers 1 and 15) being excluded because of their very high values. The average transition period from the stage of 'Neuritic leprosy' to 'Leprosy with cutaneous lesions' was calculated in a similar fashion and is 4 months and 2 days (C). Thus it can be said that after noticing the altered sensation the average time taken to develop cutaneous leprosy is 27 months and 11 days (A (18 months) + B (5 months and 9 days) + C (4 months and 2 days)).

The treatment was started once a definite clinical diagnosis of leprosy was made. This means that on average it took 4 months and 2 days for cutaneous lesions to appear following development of neuritic leprosy under treatment.

Discussion

The early diagnosis of leprosy has become a subject of great importance for the success of the leprosy eradication programme. Nowadays efforts are being made to diagnose leprosy

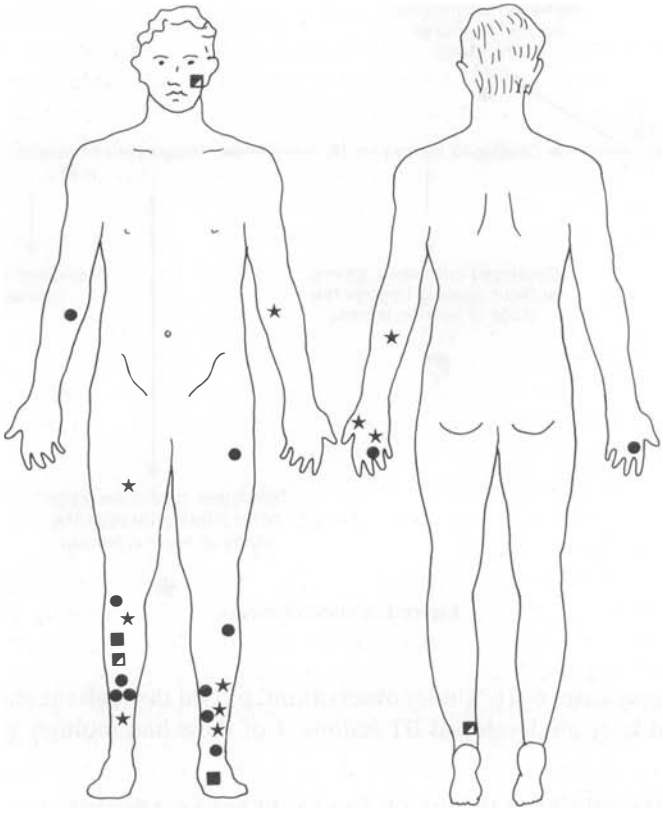

Figure 2. Site of the lesions. (Not depicted in figure:

1 case had anaesthesia on both upper limbs. 1 case developed multiple nerve trunk involvement and multiple cutaneous lesions.)

Legends:

● Remained unchanged during the course of the study. ■ Remained neuritic during the course of the study. ★ Developed cutaneous lesion after passing through the stage of neuritic leprosy. ◩ Developed cutaneous lesions without passing through the stage of neuritic leprosy.

early with the help of immunological and biochemical tests, but these tests are not 100% accurate and doubts have been expressed about their efficacy.[1] The interpretation of these tests is difficult in suspected cases where the results could be expected to be of greatest help. The tests are also available only at selected centres; therefore for field workers the early diagnosis of leprosy is likely to remain clinical. Efforts have been made in the present work to understand the significance of some of the neurological symptoms in the context of the early diagnosis of leprosy.

For all practical purposes, and as generally agreed, the earliest clinically manifest lesion of leprosy is a flat macule with slight hypopigmentation, ill-defined margins and questionable sensory impairment. This concept is well-accepted and propagated by others.

It is probably easier for both physician and patient to recall events in reference to an

observed episode. A visible skin patch is such an episode in the natural history of leprosy and is likely to be the reason for the popularity of the above concept. In contrast, it is difficult to recall some vague neurological manifestation in reference to a long and variable time period and then correlate this with leprosy lesions appearing at a later date after a period varying from a few months to many years. This is even more likely when these neurological symptoms are insidious and observed infrequently for a varying period and are therefore easily forgotten or overlooked.

The importance of these neurological symptoms before the diseases manifest has been observed by Cochrane.[2] He writes: 'I am convinced that the first definite evidence of disease is seen in the appearance of an area of anaesthesia. This definite sign may be preceded by vague subjective symptoms such as tingling'. He further observed that between the onset of the first sign and the diagnosis of leprosy there was a gap of between 2 and 20 years. In the present study the interval between the onset of neurological symptoms and the definitive clinical diagnosis of cutaneous leprosy averaged about 27 months and 11 days.

In the present study no correlation of the symptomatic state or manifest disease could be established with factors like age, sex, immune status and bacteriological examination. Histologically, of the 11 cases biopsied, disease was confirmed in 9.

As happens in many other diseases all those who are infected do not necessarily develop the disease. Accordingly, in the present study of 29 cases only 16 developed the disease, with the remaining 13 remaining stationary. This period of observation—considering the long incubation period of leprosy—was short, especially when it is accepted that a leprosy granuloma can remain incipient without clinical manifestations.

A similar transition to that observed in the present work, from 'Neuritic' to 'Leprosy with cutaneous manifestations' has been observed by Noordeen[3]—1 case; Chacko[4]—2 cases; Shenoi & Padhee[5]—1 case and by Talwar *et al.*[6]—8 cases, covering the total spectrum except BL/LL.

The transition period from the stage of 'Neuritic leprosy' to 'Leprosy with cutaneous lesions' has been observed in the present study, with an average of 4 months 2 days. Similar observations have been made by us in another series of 16 cases with an average transition period of 3 months 8 days (under communication).[7] A transition time of 2–6 months has been observed by Talwar *et al.*[6]

The events which trigger such changes remain illusive and raise the following questions:

1 Is neuritic leprosy an early form of cutaneous leprosy which, under the influence of some factors as yet unknown, remains stationary for a varying period?
2 Is the appearance of a skin patch an outcome of immunological upgrading or downgrading?
3 What is the potential of neuritic leprosy with lepromatous histology, negative smear and lepromin negativity to progress to cutaneous lepromatous leprosy?
4 Probably the answer can be obtained if neural and cutaneous biopsies are available for comparison.

In this preliminary study, a definite sequence of vague neurological symptoms (prodromal stage?) and the subsequent development of manifest disease—i.e. first neuritic and later cutaneous, has been observed. Cochrane suggested this possibility and mentioned it in his book.[2]

Some questions need answering. As observed in the present study, is there a definite sequence of paraesthetic prodromal symptoms prior to the development of neuritic leprosy transforming further in at least a proportion of the cases to cutaneous forms in the field situation as well? And can leprosy be diagnosed on the strength of these symptoms? This subject requires some long-term studies at least in contacts of known leprosy cases with such symptoms. Some of these can be subjected to neural and cutaneous histology for understanding the natural history of the disease. In hyperendemic areas people with these neurological symptoms can be placed under surveillance for at least 5 years.

References

[1] Dharmendra. *Indeterminate group*, Volume 1. Bombay: Kothari Medical Publishing House, 1978, pp. 44–7.
[2] Cochrane, RG. *Leprosy in Theory and Practice*, Cochrane RG, Davey TF (eds). London: John Bristol and Company, 1964, p. 251.
[3] Noordeen SK. Epidemiology of (Poly)neuritic type of Leprosy. *Lepr India*, 1972; Vol. **XLIV,** No. 2: 90–6.
[4] Chacko GJG. *Evolution of pathological lesions in leprosy patients and their immunological significance*. Proceedings of Indo–U.K. symposium on leprosy, April 17–10, 1986; 82–89.
[5] Shenoi SD, Padhee A. Polyneuritic leprosy changing in borderline line tuberculoid (BT). *Ind J Lepr*, 1990; **62:** 363.
[6] Talwar S, Jha PK, Tiwari VD. Neuritic leprosy epidemiology and therapeutic responsiveness. *Lepr Rev*, 1992; **63:** 263–8.
[7] Brajendra Mishra, Mukherjee Ashok, Girdher Anita, Husain Sajid, Malaviya GN, Girdher BK. Neuritic leprosy: further progression (under communication).

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Evolution des lésions précoces dans la lépre

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Résumé Nous avons observé 29 malades qui présentaient de vagues symptômes neurologiques périphériques pendant 6 mois ou plus. Au cours de cette période, 16 ont manifesté une lèpre clinique: 3 une lèpre borderline tuberculoïde et les 13 autres une lèpre névritique; d'autre part, 11 ont manifesté par la suite des lésions cutanées similaires à celles observées dans les lèpres indéterminées et borderlines tuberculoïdes. Sur la base de ces observations, nous essayons d'expliquer l'évolution des lésions précoces de la lèpre.

Evaluación de las lesiones tempranas en la lepra

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Resumen Hemos observado 29 pacientes con síntomas neurológicos periféricos inciertos por 6 meses o más. Durante este período, 16 desarrollaron lepra clínica, 3 lepra tuberculoide incierta, y los restantes 13 lepra neurítica, y 11 pacientes posteriormente desarrollaron lesiones dérmicas similares a las que se observan en la lepra tuberculoide incierta. Basándose en estas observaciones, se ha tratado de explicar la evolución de las lesiones tempranas en la lepra.

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Human immunodeficiency virus and leprosy—type 1 reactions, nerve damage and steroid therapy: 'a case report'

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Summary In this study a 28-year-old female with both BL leprosy and HIV infections is discussed. Her clinical progress was followed until she completed MDT. During this period she developed recurrent reactional episodes, nerve damage and intercurrent illnesses—some of which might have been due to steroids.

Introduction

There is very little information on the interaction between the human immunodeficiency virus (HIV) and leprosy, especially concerning the clinical progress of leprosy. A report from Zambia has described some clinical observations on 10 leprosy patients suffering from HIV.[1] This paper describes the clinical progress of a BL patient who received and completed the WHO recommended MDT regimen.

CASE REPORT

M.J., a 28-year-old Ugandan female market vendor, presented at a leprosy clinic we were holding with a 3-month history of multiple skin lesions.

Examination revealed her to be in good general condition, with skin lesions clinically compatible with borderline lepromatous (BL) leprosy. The posterior tibial and radial cutaneous nerves showed thickening bilaterally and were non-tender. There was no evidence of peripheral neuropathy. On slit skin smear, the highest bacteriological index (BI) was 2 (left ear lobe).

She agreed to take part in an ongoing study that required screening for HIV antibodies. After we had counselled the patient, an HIV test was done, and she tested positive on both the HIV check (Dupont) and Wellcozyme HIV Recombinant test.

The patient was put on Dapsone 100 mg once daily, Clofazimine 50 mg once daily and Rifampicin 600 mg with Clofazimine 300 mg once monthly (supervised).

She presented with a type 1 reaction 4 months after onset of MDT with swelling of the skin lesions on the trunk and upper limbs, with no nerve tenderness or peripheral neuropathy. She was hospitalized and put on prednisolone 40 mg once daily which cured

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the skin irregularities. This treatment was maintained for 2 weeks and for the following 6 weeks she was weaned off steroids. The highest BI during this episode was 1 (left ear lobe). The patient was subsequently discharged in good general condition.

She was re-admitted 2 months after discharge suffering from a type 1 reaction having had swelling of the facial lesions for 1 week. On examination, she had a weakness of the left obicularis oculi muscle and a bilateral weakness in abducting the little finger. There was no nerve tenderness, but she had developed diarrhoea a few days after her discharge which had persisted up to the time of her re-admission. Further examination revealed oral candidiasis, with genital and axillary sores. Her general condition had deteriorated. Prednisolone 40 mg once daily was recommenced, and the facial swellings then subsided. After 4 weeks of this treatment there was no improvement in the weakness of her little fingers or the left arbicularis oculi. Then she developed a bilateral weakness in opposition of the thumb. Steroids were slowly tapered off. The BI during this episode was 0. The patient received the proper treatment for her other disorders , and clinically improved. She was discharged and continued with MDT from her local clinic. She has since been in and out of hospital with a recurrence of genital sores, oral candidiasis and fevers. The patient has completed 24 doses of MDT and the BI has remained negative. She is currently under surveillance.

Discussion

After earlier reports by Lamfers, suggesting a possible association between HIV and leprosy,[2] it has not been uncommon to have to treat patients suffering from both conditions. In one major study, Ponnighaus *et al.*[3] have demonstrated that HIV infection is probably not a risk factor for clinical leprosy *per se*. However, the information on clinical progress in patients who are also HIV infected is still minimal. A multibacillary patient whose lesions subsided quickly under anti-leprosy therapy has been described by Kennedy *et al.*[4]

In this case, response to chemotherapy (MDT) *per se* appears satisfactory, with a decline of the BI from 2 to 0 after $7\frac{1}{2}$ months.

Perhaps the relapse of the Type 1 reaction in this patient was caused by the inadequate course of steroids which only lasted for 6 weeks. However, the possibility of recurrent reactional episodes of type 1 among these patients with an increased incidence of nerve damage compared to non HIV patients has to be borne in mind.

It is possible that the steroid therapy given during the first episodes of reversal reaction speeded the onset of oral and genital candidiasis with which the patient presented on re-admission. However, steroids should probably be given in symptomless HIV positive patients if this is indicated by the clinical manifestations.

The fact that the steroid treatment only had a disappointing response in the patient's functional nerve recovery might also be due to the inadequate prednisolone course. On the other hand, this could just as likely be due to a necrotizing vasculitis in the peripheral nerves by the neurotrophic HIV.[5]

This is the first multibacillary leprosy patient in Uganda who completed the WHO recommended MDT regimen and is HIV positive, albeit with an on/off intermittent illness.

Acknowledgments

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References

[1] Vreeburg AEM. Clinical observations on leprosy patients with HIV infection in Zambia. *Lepr Rev*, 1992; **63:** 134–40.
[2] Lamfers EJP, Bastiaans AH, Mravunac M, Rampen FHJ. Leprosy in the acquired immunodeficiency syndrome. *Ann Intern Med*, 1987; **107:** 111–12.
[3] Ponninghaus JM, Mwanjasi LJ, Fine PEM, Shaw M, Turner AC, Oxborrow SM, Lucas SB, Jenkins PA, Sterne JAC, Bliss L. Is HIV infection a risk factor for leprosy? *Int J Lepr*, 1991; **59:** 221–3.
[4] Kennedy C, Chin A Lien RAM, Stolz E, van Joost T, Naafs B. Leprosy and human immunodeficiency virus infection; a closer look at the lesions. *Int J. Derm,* 1990; **29:** 139–40.
[5] Patki AH. Some possible interactions of *M. leprae* and HIV in the peripheral nerves. *Int J Lepr*, 1991; **59:** 331–2.

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Virus de l'immunodéficience humaine et lèpre—réactions du type I, atteintes du nerf et thérapeutique aux stéroïdes: rapport d'un cas.

R. Bwire et H. J. S. Kawuma

Résumé Dans cette étude, nous discutons le cas d'une femme agée de 28 ans atteinte à la fois de lèpre BL et d'infection par HIV. Son évolution clinique est suivie jusqu'à la fin du traitement MDT. Au cours de cette période, elle a présenté des poussées réactionnelles recurrentes, une atteinte du nerf et des maladies intercurrentes dont certaines pourraient être dûes aux stéroïdes.

El virus de la inmunodeficiencia humana y la lepra—Reacciones de Tipo 1, Daños de los nervios y la terapia de esteroides: Estudio de un caso

R. Bwire y H. J. S. Kawuma

Resumen Se discute el caso de una mujer de 28 años con infecciones de lepra y VIH. Se ha seguido su progreso clínico hasta completar MDT. Durante este período, desarrolló reacciones recurrentes, daños de los nervios y enfermedades intercurrentes, algunas de las cuales podrían ser debidas a los esteroides.

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Squamous cell carcinoma in plantar ulcers in leprosy. A case control study

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Summary The objective of this case-control study was to identify factors associated with the development of squamous cell carcinoma (SCC) in plantar ulcers of leprosy patients. We examined 2 matched groups consisting of leprosy patients with and without SCC in a plantar ulcer.

No correlations were found between the development of SCC and race, profession, place of origin, duration of leprosy, the type and duration of leprosy chemotherapy, presence of bone involvement and type of ulcer care treatment given. The only statistically valid finding was that the duration of the ulcer was significantly lower in the group with malignant change. In this group there was an apparently higher use of pesticides, the difference being not of statistical significance.

It is concluded that factors other than ulcer duration need to be looked for, in order to identify factors influencing malignant change in plantar ulcers of leprosy patients.

Introduction

Squamous cell carcinoma (SCC) has been described as a complication of chronic, usually plantar, ulcers in leprosy patients. Recently we reviewed 38 consecutive cases of SCC in ulcers of leprosy patients presenting at the McKean Rehabilitation Centre in Northern Thailand for ulcer care.[1] It was found that the incidence rate of SCC in the group at risk (leprosy patients with disability grading 1 and 2)[2] was 0·79:1000 per year. The age group most commonly involved was that of 60 to 69 years and the classification specific incidence rate was highest among BT patients (2·02:1000 per year).

SCC in leprosy patients has been reported from various countries around the world. Most articles concern individual case reports. The incidence rates found in the Northern Thailand study appear to be higher than those found in, for example, India, a country with a large leprosy population. During the past 30 years only relatively small numbers of cases have been reported from India,[3,4] and not many epidemiological details are available. This impression of low incidence was confirmed when a postal survey was done among 27 centres in India belonging to The Leprosy Mission (unpublished data). It was

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estimated that the incidence rate of SCC was at least a factor 10 less than found in the Northern Thailand study.

The objective of this study was to identify factors that were possibly associated with the development of SCC in plantar ulcers of leprosy patients. The method used was a case-control study.

Methods

The selected 'cases' were leprosy patients admitted to the McKean Rehabilitation Centre (Chiang Mai, Northern Thailand) between 1985 and 1991 and diagnosed with SCC in plantar ulcers. Those patients who were still alive in 1991 (so that additional information could be obtained from them personally), from whom sufficient data was available and for whom suitable 'controls' could be found were included in the study.

'Controls' were selected from leprosy patients with plantar ulcers but without (a history of) SCC, who during the same period presented at the Centre or one of the associated out-patient clinics. The 'controls' were matched for age-group (10-year groupings, 20–29, etc.), sex and leprosy classification.

Information obtained included general personal data, leprosy history and therapy, duration of ulcer(s) and evidence of bone involvement (osteo-myelitis). Special attention was given to the type of ulcer treatment received, in particular whether herbal or traditional medications were used. A final question concerned the use of pesticides and other chemicals in farming work.

The objective was to have 3 'control' patients for each case of SCC.

Results

The 'case' group of patients with SCC consisted of 17 individuals; 6 females (35%) and 11 males (65%). The average age was 60 ± 10 years. Included in the 'control' group were 50 patients; 17 females and 33 males. The average age was 61 ± 10 years. Distribution of the leprosy classification for both groups was as follows: BT: 53%, BL: 29% and LL: 18%. All but 5 patients were ethnic Thai. The remaining 5, all in the 'control' group, were from 5 different ethnic backgrounds common in Northern Thailand. The large majority of patients were farmers or involved in farming work. All patients in both groups showed evidence of bone involvement and (previous) osteomyelitis. History of other diseases gave no additional information.

A summary of the main results is given in Table 1. Comparing the 2 groups, it appears that there are no significant differences ($p > 0{\cdot}05$) between the place of origin (leprosy colony versus independent living), the average duration of leprosy, the type and duration of leprosy chemotherapy and the use of herbal or traditional medicine as opposed to conventional ulcer treatment. Between the 2 groups, there is a significant difference ($p < 0{\cdot}05$) in the duration of the ulcers. The average duration in the 'control' group is 26 ± 12 years. In the 'case' group, this duration is 15 ± 11 years. There is also an apparent, but not significant ($p = 0{\cdot}06$) difference in the use of pesticides in farming work.

Table 1. Summary of the main results from the case-control study of squamous cell carcinoma (SCC) in plantar ulcers of leprosy patients

	'Case' group (with SCC) ($n=17$)	'Control' group ($n=50$)
From leprosy colony or village	12 (71%)	37 (74%)
Average duration of leprosy	36 ± 8 years	35 ± 11 years
Leprosy chemotherapy:		
* Dapsone monotherapy	17 (100%)	48 (94%)
* Multidrug therapy (MB and PB)	3 (18%)	15 (30%)
Duration leprosy chemotherapy	19 ± 12 years	18 ± 11 years
Duration of ulcer(s)	15 ± 11 years	26 ± 12 years
Use of herbal/traditional medicine in ulcer treatment	1 (7%)*	4 (8%)
Use of pesticides or chemicals in farming work	4 (29%)*	4 (8%)

* In 3 cases no answer obtained.

Discussion

Squamous cell carcinoma is known to be an occasional complication of long-standing ulcerative conditions such as venereal granulomas, syphilis, lupus vulgaris, lupus erythematosus, chronic ulcers, osteomyelitis sinuses, old burn scars and hidradenitis suppurativa. A number of environmental carcinogens acting on the skin have been identified, including sunlight, ionizing radiation, (medicinal) arsenic and chemical agents, especially those derived from coal (tar) and mineral oil.[5] It is assumed that scar tissue in particular is abnormally susceptible to the effects of these agents.

In this case-control study no associations between the development of SCC and factors concerning race, profession, place of origin, duration of leprosy, type and duration of leprosy chemotherapy, presence of bone involvement and type of ulcer care treatment were found. The only significant difference between the 2 groups was the duration of the ulcer. It appeared that the average duration of the ulcer in the group with SCC is shorter than the 'control' group. This, in fact, is surprising. It was previously assumed that duration of ulceration is a main factor in the development of SCC.[1] From the present data it is clear that factors other than just duration of ulceration determine the event of SCC.

The possibility of pesticide use (a known risk factor for SCC in the skin) as a contributing factor to the development of SCC in plantar ulcers of leprosy patients, is suggested from this study. In Thailand pesticides are readily available and used excessively. The various chemical compounds, including known carcinogens, come under many different brand names and often in cocktails. The patients concerned in this study were not able to recall the contents of pesticides they used.

There remains the question why SCC in plantar ulcers of leprosy patients seems to occur more frequently in Northern Thailand than in other countries. Tumour registry statistics in 1989 of the province Chiang Mai in Northern Thailand shows that skin cancer (all types) comes last in the list of the 10 leading sites of cancer.[6] The age standardized rate (ASR) is 0·047/1000 in males and 0·054/1000 in females. Of all skin cancers at any site on the skin, 40% were due to SCC. The incidence rate of SCC in chronic ulcers of leprosy patients from the same geographical area was 0·79/1000, a factor 10 higher. The incidence

of non-melanocytic skin cancer (mainly consisting of SCC) in Thailand is very small compared to countries such as Australia where this group is the most common type of cancer diagnosed (95,000 new cases estimated per year).[7] This is obviously related to excess sun exposure on light-skinned Caucasians. Sun exposure as a cause of skin cancer is very rare in the darker coloured Thai population. Considering this, there is no reason to assume that Thai are genetically more susceptible to SCC on their skin than are, for example, Caucasians.

It can therefore be concluded that further research is needed to identify the factors that influence malignant change in plantar ulcer of leprosy patients.

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References

[1] Richards JH, Smith TC. Squamous cell carcinoma in chronic ulcers in leprosy: a review of 38 consecutive cases. *Lepr Rev*, 1991; **62:** 381–8.
[2] WHO Expert Committee on Leprosy. *Sixth report*. Technical Report Series, No. 768. WHO: Geneva, 1988.
[3] Srinivasan H, Desikan KV. Cauliflower growths in neuropathic plantar ulcers in leprosy. *J Bone Joint Surg*, 1971; **53:** 123–32.
[4] Sane SB, Mehta JM. Malignant transformation in trophic ulcers in leprosy: a study of 12 cases. *Ind J Lepr*, 1988; **60:** 93–9.
[5] Squamous cell carcinoma of the skin. In: *Textbook of Dermatology*. Rook A. *et al*. (eds). London: Blackwell Scientific Publications, 1986: 2431–7.
[6] Tumor Registry Cancer Unit. *Statistical Report 1989*, Volume 12. Chiang Mai: Faculty of Medicine, Chiang Mai Univesity, Thailand.
[7] Armstrong BK. The epidemiology and prevention of cancer in Australia. *Aust N Z J Surg*, 1988; **58:** 179–87.

Carcinome à cellules squameuses des ulcères plantaires dans la lèpre. Étude controlée

J. H. Richardus et T. C. Smith

Résumé L'objet de cette étude controlée était d'identifier les facteurs associés au développement de carcinome à cellules squameuses (SCC) dans les ulcères plantaires de lépreux. Nous avons examiné deux groupes similaires composés de lépreux avec ou sans SCC dans an ulcère plantaire.

Aucune relation n'a été observée entre le développement de SCC et la race, la profession, le lieu d'orogine, la durée de la lèpre, le type et la durée de la chimiothérapie antilépreuse, la présence d'une atteinte osseuse et le type de soins donnés à l'ulcère. Le seul résultat ayant une valeur statistique a été l'observation que la durée de l'ulcère était raccourcie de façon significative dans le groupe à évolution maligne. Dans ce groupe, l'usage de pesticides était apparemment plus élevé, mais la différence n'avait pas de signification statistique.

Nous en concluons que, pour identifier les facteurs qui influencent l'évolution maligne des ulcères plantaires des lépreux, il faut chercher ailleurs que dans la durée de l'ulcère.

Carcinomas de célula escamosa (SCC) en las úlceras plantares. Un estudio de control de caso

J. H. Richardus y T. C. Smith

Resumen El propósito de este estudio de control de caso era identificar los factores asociados con el desarrollo del carcinoma de célula escamosa (SCC) en las úlceras plantares de los pacientes leprosos. Se examinaron 2 grupos equivalentes que consistían de pacientes con y sin SCC en una úlcera plantar.

No se encontraron correlaciones entre el desarrollo de SCC y la raza, profesión, origen, duración de lepra, el tipo y duración de la quimioterapia contra la lepra, la presencia de implicación ósea, ni el tipo de tratamiento de la úlcera. El único resultado de validez estadística fue que la duración de la úlcera era significativamente menos en el grupo de cambio maligno. En este grupo, parecía que había un uso más importante de pesticidas, aunque la diferencia no era significativa.

Se concluye que hay que buscar otros factores que la duración de las úlceras para identificar factores que influyen los cambios malignos de la úlceras plantares en los pacientes leprosos.

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Letters to the Editor

PGL-I ANTIBODY IN HIV INFECTED PATIENTS

Sir,

Following up the issue discussed at the Nairobi meeting, Kenya, in December 1987, on 'Interrelations of Tropical Diseases and HIV infection', sponsored by TDR and GPA,[1] we refer to a serological study in a group of 437 Cuban HIV infected patients. Their HIV infection was diagnosed by ELISA and confirmed by Western blot and all of them were in-patients at the AIDS hospital in Havana.

The control group was 313 blood donors without HIV infection (tested by ELISA) and without any known contact with leprosy (individual interview) and was also age-matched to the HIV infected patients.

An indirect ELISA was performed, according to the method described by González-Abreu *et al.*,[2] with sera separated from venous blood obtained from individuals of both groups. The antigen used was ND-A-BSA, obtained by courtesy of Dr V. Verez, Faculty of Chemistry, University of Havana, Cuba.

Among the 437 HIV infected patients, 65 (14·9%) had Optical Density (O.D.) readings higher than the established cut-off value (0·200). This figure was significantly higher (χ^2, $p = 0{\cdot}05$) than that observed in the control group, where only 4 (1·3%) individuals were classified as seropositive. This result is worth noting if compared to that of a seroepidemiological study conducted in a leprosy endemic area, where 13,970 individuals from the general population were tested for PGL-I antibody. In this endemic area, only 3·03% of the tested individuals showed O.D. readings above the cut-off value. It is also noteworthy that O.D. readings higher than 0·400 in the HIV infected group were ten-fold (3·20%) those in the endemic population (0·33%) (Table 1).

None of the patients who showed O.D. readings higher than the cut-off value have developed any clinical signs of leprosy so far. It is true that few reports of a direct association between HIV

Table 1. Ranges of O.D. readings observed among HIV (+) patients, blood donors and endemic population

D.O ranges	HIV patients (%)[1,2]	Blood donors (%)[1,2]	Endemic population (%)[1]
<0·200	372 (85·12)	309 (98·7)	13547 (96·7)
0·200–0·299	33 (7·55)	3 (0·96)	273 (1·94)
0·300–0·399	18 (4·11)	1 (0·32)	104 (0·74)
> =0·400	14 (3·20)	—	46 (0·33)
> =0·200	65 (14·87)	4 (1·27)	423 (3·02)

(1) $\chi^2 = 217{\cdot}481$ 6 gl $p = 5{\cdot}390 \times 10^{-12}$.
(2) $\chi^2 = 40{\cdot}649$ 3 gl $p = 4{\cdot}409 \times 10^{-10}$.

infection and leprosy have been published, but it is recommended that workers remain vigilant, because the effects of HIV infection in a leprosy endemic area might be quite unexpected.[3] It has been suggested that HIV-induced immunosuppression might increase the prevalence of multibacillary forms of leprosy,[4] but, because of the long incubation period of leprosy, patients could die from other HIV-associated causes before leprosy becomes clinically apparent.

All these arguments are of great importance in relation to the results observed in this study, because if these patients are really infected with *Mycobacterium leprae* they might become a silent source of infection in their environment.

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References

[1] Tropical Disease and HIV Infection; UNDF–World Bank–WHO, Kenya, 1987. *Lepr Rev*, 1988; **59:** 279.
[2] González-Abreu E, Mora N, Perez M, Pereira M, Perez J, González AB. Serodiagnosis of leprosy in patients' contacts by enzyme-linked immunosorbent assay. *Lepr Rev*, 1990; **61:** 145–50.
[3] Turk JL, Rees RJW. Aids and leprosy. *Lepr Rev*, 1988; **59:** 193–4.
4 Ponnighaus JM, Mwanjasi LJ, Fine PEM, Shaw MA, Turner AC, Oxborrow SM, Lucas SB, Jenkins PA, Sterne JAC, Bliss L. Is HIV Infection a risk factor for leprosy? *Int J Lepr*, 1991; **59:** 221–8.

SIDE-EFFECTS OF ISOPRODIAN COMPARED WITH WHO-MDT IN RURAL NEPAL

Sir,

In the past, we have used Isoprodian (ISO) (which is a combination preparation containing 50 mg DDS, 175 mg prothionamide and 150 mg isoniazide per tablet), fairly extensively as an anti-leprosy treatment in our field programme, both with and without rifampicin 600 mg on clinic visits, so we thought that detailing our experience with the use of ISO might be of some use to your readers.

The problem we face in Nepal is patients who live too far away from their treatment unit to attend monthly or even bi-monthly for WHO-MDT, so they usually remained on DDS monotherapy. In the past quite a few patients have been treated with ISO, apparently without many problems. So in 1989, when we were considering what to do with the 'monotherapy problem', we considered ISO as a possible alternative for 'remote patients'. However, because a recent study on long-term compliance with prothionamide suggested that only 50% of the doses may be ingested due to the gastro-intestinal side-effects (GIS) of the drug,[1] we decided that we should first try to study the occurrence of any side-effects in Nepali patients before using ISO on a large scale. A study was set up in our Ghorahi referral centre that included patients who had previously been on DDS monotherapy because they lived too far away and any new patients who registered during the study period (1989).

Methodology

In total 106 cases were admitted to the study. Their mean age was 38 (range 11–74, Standard Deviation (SD) = 14·3): 90 were male, 16 were female; 87 patients were classified as MB, 19 as PB. The criteria for MB/PB classification have been discussed at length in reference 2. In all, 37 cases had

Table 1. MB/PB classification of study patients

Classification	Isoprodian	WHO MDT	Total
MB	40	47	87
PB	3	16	19
Total	43	63	106

been previously treated with DDS monotherapy (average duration 58 months, SD = 47 months) and the remaining 69 were new, previously untreated cases. The patients ($n = 63$) that could be motivated to attend the clinic at least once every 2 months were put on WHO-MDT according to their MB/PB classification. The remaining 43 (40·6%) were put on an ISO regimen according to their classification as follows (Table 1):

* PB: Isoprodian 2 od for 1 year.
* MB: Isoprodian 2 od, clofazimine 50 mg od and rifampicin 900 mg stat (supervised) at every clinic visit, for 3 years.

In the ISO group the patients had to walk an average of 23 hours (SD = 17·9) to get to the clinic; in the WHO-MDT group this average was 13 hours (SD = 10·8). At every clinic visit patients had a blood sample taken for PGL-1 serology (on filterpaper), and a DDS urine spot test was done. Patients were examined for signs of jaundice and asked about symptoms of GIS. Patients with a recent history of jaundice, a positive bilirubin urine test, indications of renal failure or gastric ulcer and all pregnant women were excluded from the study. Patients with a positive stool test for parasites received appropriate treatment. Patients were instructed to take their ISO tablets at bedtime with food.

Results

At the time of this evaluation, after an average follow-up time of $3\frac{1}{2}$ years, 14 patients (32·5%) in the ISO treatment group and 13 patients (20·7%) in the WHO-MDT group were lost to follow-up (Figure 1). Of the remaining patients, 32 have been released from treatment and 46 continue on treatment. Of 226 DDS urine spot tests that were done to monitor treatment compliance, 79 (35%) were negative, 1 was doubtful and 147 were positive. There was no difference between the 2 treatment groups in the proportion of tests that were negative ($p = 0{\cdot}7$, χ^2 test), (Figure 2).

During 262 follow-up examinations no episodes of jaundice were found. No mention was made of GID during these examinations, except for 5 patients in the ISO group who had to stop taking Isoprodian due to severe GIS; 4 patients were changed over successfully to a regimen that did not contain prothionamide or isoniazid; 1 patient defaulted after stopping ISO due to severe GIS and 1 patient in the WHO-MDT group finished 24 doses of MB-MDT despite recurrent abdominal pain and nausea. The Relative Risk of developing severe (= persistant, despite symptomatic treatment) GIS when taking Isoprodian as compared to WHO-MDT is 7·33 (95% confidence limits: 0·89–60·53, $p = 0{\cdot}039$, 2-tailed Fisher's exact test).

Discussion

For patients unable to attend regularly for supervised WHO-MDT, Isoprodian seems an attractive alternative. It combines 2 effective anti-leprosy drugs conveniently in 1 tablet. The possible gastro-intestinal side-effects of prothionamide are well known and the risk of hepatitis has especially been found to be dose-related.[3] This may explain why doses of 125 mg and 250 mg daily were found to be acceptable to Indian patients by Stanley *et al.*[4] The same group of investigators found symptoms of 'moderate or severe GIS' in 'a third of the patients' in a compliance study using Isoprodian

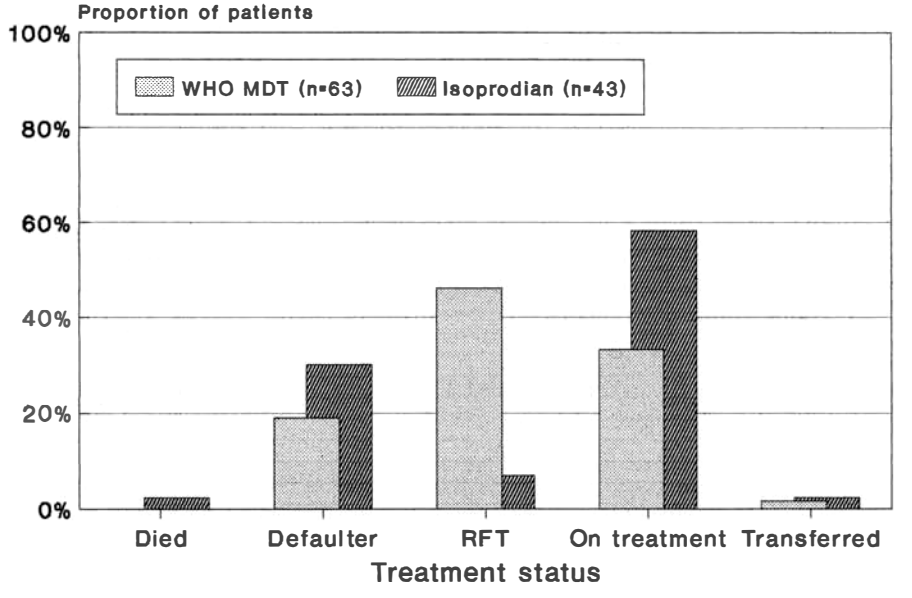

Figure 1. Treatment status of study patients after $3\frac{1}{2}$ years follow-up.

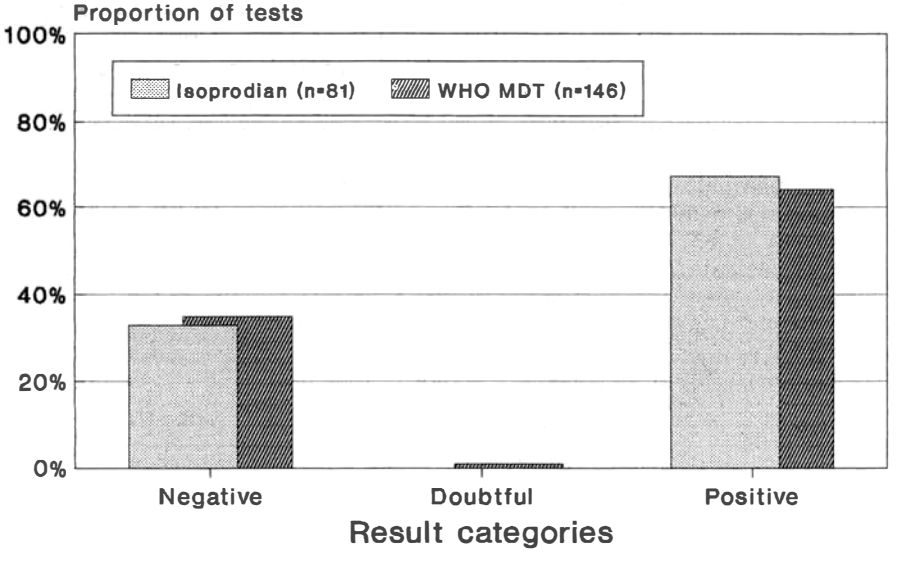

Figure 2. DDS urine spot-test results.

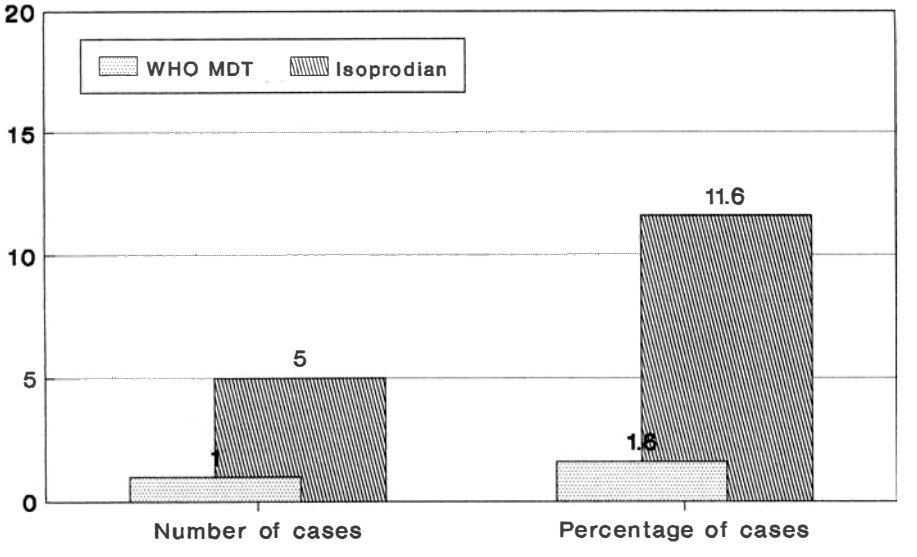

Figure 3. Gastro-intestinal side-effects (severe).

(prothionamide 350 mg daily).[1] GIS appeared to be responsible for the fact that 25% of the patients failed to complete the study. It could well be that this is also the explanation for the high drop-out rate (25%) in this study, but no definite conclusions can be drawn as the defaulter rate was high in both treatment groups and none of the defaulters could be followed up by home visits. The high defaulter rate is, in our experience, quite common among patients living far away from the clinic they attend. In 5 patients (9·3%) of the ISO group the regimen needed to be changed due to severe GIS. These patients were changed over to WHO-MDT, but with rifampicin only at clinic visits, but 1 patient defaulted before the alternative treatment could be started. There is no explanation as to why mild or moderate GIS was not reported. The low compliance of 65% found with the DDS spot test did not seem related to ingestion of prothionamide, as it was similar in both treatment groups.

This study seems to confirm the recommendation of Ellard *et al.*[1] that prothionamide (Isoprodian) should be prescribed only to patients who can be properly monitored. We have decided to treat patients who can not frequently attend the clinic with unsupervised WHO-MDT in blister calendar packs rather than with Isoprodian.

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References

[1] Ellard GA, Kiran KU, Stanley JNA. Long-term prothionamide compliance: a study carried out in India using a combined formulation containing prothionamide, dapsone and isoniazid. *Lepr Rev*, 1988; **59:** 163–75.
[2] van Brakel WH, de Soldenhoff R, McDougall AC. The allocation of leprosy patients into paucibacillary and multibacillary groups for multidrug therapy, taking into account the number of body areas affected by skin, or skin and nerve lesions. *Lepr Rev*, 1992; **63:** 231–46.
[3] Pattyn SR, Groenen G, Janssens L, Kuykens L, Mputu LB. Treatment of multibacillary leprosy with a regimen of 13 weeks duration. *Lepr Rev*, 1992; **63:** 41–6.
[4] Stanley JNA, Pearson JMH, Ellard GA. Ethionamide, prothionamide and thiacetazone self-administration. Studies of patient compliance using isoniazid-marked formulations. *Lepr Rev*, 1986; **57:** 9–18.

COMMENT: PERSISTENCE OF *MYCOBACTERIUM LEPRAE* IN THE PERIPHERAL NERVES OF MULTIDRUG-TREATED LEPROSY PATIENTS

Sir,

The paper by Shetty *et al.* (*Lepr Rev*, 1992; **63:** 329–36) entitled 'Persistence of *Mycobacterium leprae* in the peripheral nerves of multidrug-treated leprosy patients' points to the need for very sensitive techniques for the detection and monitoring of nerve damage in treated patients, preferably well before clinical signs and symptoms are evident.

Low *et al.*[1] described a new approach to the detection of autonomic abnormalities of neuropathic origin based on the use of laser Doppler velicometry to detect changes in fingertip blood flow following deep inspiratory gasp or cold challenge to the contralateral limb. We have found this technique to be a reliable and reproducible way of detecting and quantitating impairment of autonomic reflexes in newly-diagnosed leprosy patients with no obvious deformity.[2,3] In addition, autonomic reflexes, particularly those elicited by contralateral cold challenge, were impaired in an unexpectedly high proportion of apparently healthy, fully treated, ex-leprosy patients. There are obviously several explanations for such dysautonomia in treated patients but persisting bacterial antigen or viable bacteria could well be a principal cause.

It would therefore be of great interest to apply the technique of laser Doppler velicometry together with histological studies on the persistence of *M. leprae* in peripheral nerves after completion of MDT in order to determine whether this technique could provide a non-invasive indication for the need of further therapy. At present, the equipment is somewhat cumbersome and costly but, provided that there is a demand for such equipment, it could be simplified and miniaturized for easy field use.

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References

[1] Low PA, Neumann C, Dyck PJ, Fealey RD, Tuck RR. Evaluation of skin vasomotor reflexes by using laser Doppler velicometry. *Mayo Clin Proc*, 1983; **58:** 583–92.
[2] Beck JS, Abbot NC, Samson PD, Butlin R, Grange JM, Cree IA, Forster A, Khan F. Impairment of vasomotor reflexes in the fingertips of leprosy patients. *Journal of Neurology, Neurosurgery and Psychiatry*, 1991; **54:** 965–71.
[3] Abbot NC, Beck JS, Samson PD, Butlin CR, Brown RA, Forster A, Grange JM, Cree IA. Impairment of fingertip vasomotor reflexes in leprosy patients and apparently healthy contacts. *Int J Lepr*, 1991; **59:** 537–47.

COMMENT: 'THE ALLOCATION OF LEPROSY PATIENTS INTO PAUCIBACILLARY AND MULTIBACILLARY GROUPS FOR MULTIDRUG THERAPY, TAKING INTO ACCOUNT THE NUMBER OF BODY AREAS AFFECTED BY SKIN, OR SKIN AND NERVE LESIONS'

Sir,

I have read with interest the article entitled: 'The allocation of leprosy patients into paucibacillary and multibacillary groups for multidrug therapy, taking into account the number of body areas affected by skin, or skin and nerve lesions', by W. H. van Brakel *et al.*, Lepr Rev, 1992; **63:** 231–46.

Concerning their comparison of the body area system with the score system I described based on the findings in Ethiopian patients[1] (which was in fact not introduced in Ethiopia), I should like to make the following comments:

—As stated in my article, in the score system only those whose clinical classification was confirmed by skin smear results were included (clinically PB with negative skin smears and clinically MB with positive skin smears).

—In my example of 6 clinical signs, a total score cut-off point of up to 10 for PB classification and more than 10 for MB classification resulted in an over-classification as MB of 10·5% of PB patients and an under-classification as PB of 4·9% of MB patients (table 12 of my article).

—The conclusion that the 4·9% false-negative proportion in the Ethiopian system might have been much higher in reality, if patients had been classified on histological findings instead of skin smears, is incorrect. The correct conclusion is that, if nerve biopsies had been examined, a proportion of those classified as PB would in fact have been MB cases, and hence the proportion of patients over-classified as MB will be less than 10·5%.

—It is clinically debateable whether PB patients with a PB histology picture in the skin should be considered MB cases while the nerve histology reveals a BI compatible with MB leprosy. It has been demonstrated that the BIs in skin and nerve biopsies taken from patients at the same time can vary in possibly 50% of cases.[2,3] The nerves may contain a bacterial density of up to 1000 times that of skin. The significance of this finding for the classification of patients is not known.

It is unfortunate that the system using body areas gives a high proportion of cases over-classified as MB. Findings similar to the 61% over-classification in the BC3 system were observed in Ethiopia using the number of skin lesions. If patients with more than 5 skin lesions are classified as MB, 58% of PB patients will be over-classified.[1] It appears that if a single parameter is used for classification of patients, the specificity is low. With such a considerable MB over-classification, it could be argued that all patients should be treated as MB. In my opinion, for patient related, operational and financial reasons, a system of classification which results in over-classification of more than about 25% of PB patients is not acceptable.

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References

[1] Becx-Bleumink M. Allocation of patients to paucibacillary or multibacillary drug regimens for the treatment of leprosy—a comparison of methods based on skin smears as opposed to clinical methods—alternative clinical methods for classification of patients. *Int J Lepr*, 1991; **59:** 292–303.

[2] Ridley DS, Lucas SB. The use of histopathology in leprosy diagnosis and research. *Lepr Rev*, 1989; **60:** 257–62.

[3] Ridley DS, Ridley MJ. Classification of nerves is modified by the delayed recognition of *Mycobacterium leprae*. *Int J Lepr*, 1986; **54:** 596–606.

COMMENT: 'RESULTS OF SURGICAL PROCEDURES FOR THE CORRECTION OF FOOT-DROP AND OF LAGOPHTHALMUS DUE TO LEPROSY'

Sir,

As an ophthalmologist with a special interest in ocular leprosy, I was struck by the results of temporalis muscle transposition (TMT) surgery in 'Results of surgical procedures for the correction of foot-drop and of lagophthalmus due to leprosy' by Weber *et al.* (*Lepr Rev*, 1992; **63:** 255–62).

Such retrospective studies are understandably hampered by missing data preoperatively, and a lack of selection criteria for surgery, which makes a final evaluation difficult. Nevertheless, the study shows that it is highly useful to reflect on follow-up data of surgical procedures.

The purpose of the fairly complicated TMT surgery, to be followed by extensive physiotherapy, is to achieve a kind of 'spontaneous regular blinking', whereas other types of lid surgery for lagophthalmus aim only at protection of the eye by the narrowing of the lid gap and acceptable cosmesis. It is therefore unfortunate that the authors, at their final examination, do not mention 'spontaneous regular blinking', nor whether the eyes were closed during sleep. It is well-known that these functional results after TMT are often disappointing.

Corneal anaesthesia is considered a contra-indication for TMT surgery, because patients with loss of corneal sensation do not feel any urge to blink. It is therefore surprising that 19 out of 33 eyes with lagophthalmus (57%) had anaesthetic corneas at the time of evaluation. It is questionable whether the corneal anaesthesia could have developed secondarily, due to persisting exposure after the TMT procedure. The comment 'closing slowly' in 4 eyes probably means that although the patients could close their eyes with effort, the eyes in daily life were continuously open and exposed.

It is equally surprising that 5 eyes (15%) were found to be blind (WHO definition of visual acuity of $<0{\cdot}05$). One wonders if blindness due to corneal ulcer or opacity was already present preoperatively or developed after surgery, due to lack of blinking and persistent exposure. The latter seems more probable as no sensible surgeon would do such elaborate surgery on already blind eyes.

Altogether, although the lid gap on intentional closing was $\leqslant 2$ mm in the majority of the patients the final results were poor, with 15 eyes having corneal opacities, corneal ulcer or keratitis, of which 5 of these were blind.

The authors rightly state that 'patients should only stay away from work or should be cared for in hospitals as short a time as possible'. The results of TMT, as mentioned above, therefore do not seem to justify the complicated surgery and intensive physiotherapy required. A possible exception could be made for young, intelligent, and highly motivated patients with a large lid gap but clear corneas with good corneal sensitivity. Temporalis transfer procedures remain indicated for the correction of lower facial palsy[1] in which no ready alternatives are available, but again only in highly motivated and intelligent patients.

Ophthalmologists consider simple mechanical narrowing of the lid gap as the treatment of choice for established lagophthalmus (lid gap of > 5 mm). This is relatively simple surgery which can be taught to people with limited surgical experience and does not require physiotherapy. It can be done on an outpatient basis, if necessary. There is a great variety in procedures, for example tarsal strip procedures,[2,3] ectropion correction by wedge excision[4] or, in basic circumstances, by simple tarsorraphy.[5]

However, the same kind of follow-up study is urgently needed on the results of treatment of lagophthalmus by lid surgery alone.

Furthermore, all patients with lagophthalmus should be encouraged to wear sunglasses for additional protection and, if reasonable, to use artificial tears and ointment at night.

Above all, all efforts should be aimed at identifying patients with a reversal reaction in the face

and an early lagophthalmus of less than 6 months duration, for treatment with a course of systemic steroids as for RR, in order to prevent or restore the facial palsy.[6]

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References

[1] Warren G. Facial palsy—a leprosy surgeon's viewpoint. *Austr New Zeal J Opthalmol*, 1990; **18:** 257–66.
[2] Anderson RL, Gordy DD. The Tarsal Strip Procedure. *Arch Ophthalmol*, 1979; **97:** 2192–6.
[3] Collin JRO. *A manual of systemic eyelid surgery*. 2nd ed. Edinburgh: Churchill Livingstone, 1989, pp. 131–2.
[4] Fox SA. *Ophthalmic Plastic Surgery*. New York: Grune & Stratton, 1976, pp. 296–7.
[5] Fox SA. *Ophthalmic Plastic Surgery*. New York: Grune & Stratton, 1976, p. 217.
[6] Kiran KU, Hogeweg M, Suneetha S. Treatment of recent facial nerve damage with lagophthalmos, using a semistandardized steroid regimen. *Lepr Rev*, 1991; **62:** 1501–54.

Lepr Rev (1993) **64,** 284–285

Book Reviews

***Clinical Leprosy*. Virendra N. Sehgal** (Third Edition 1993)

This small textbook has been written for medical practitioners and undergraduates from the standpoint of leprosy in India.

A brief chapter on epidemiology summarizes the distribution of leprosy in India. The clinical features and the histopathology of the various forms of leprosy are well described, following the Indian Classification (with the addition of 'histoid leprosy'), and both are illustrated by black and white photographs.

A major deficiency is the omission of any description of the techniques of clinical examination necessary to reach a diagnosis, and of the precise details of how to test for the loss of sensation in a skin lesion, how to palpate peripheral nerves and assess enlargement and tenderness and how to take a skin smear by the 'slit and scrape' method. Concerning this last, the statement (p. 4) that 'smears are prepared from scrapings from a skin infection of the lesion' is most confusing. The staining procedure described is the hot method, the cold method is not mentioned. It is recommended that a minimum of 7 sites be examined.

The clinical features and treatment of reactions are covered rather briefly and insufficient emphasis is given to the importance of early diagnosis and early treatment of neuritis in Type 1 reactions.

It is surprising that in such a recent publication deformities and disabilities are described under the now superseded 5-Grade WHO system.

In the chapter on therapy, the antileprotic drugs in common use are described, with their dosage and side-effects. The inclusion of amithiozone is of doubtful value and no evidence is given for the statement that monthly rifampicin and the WHO-recommended schedule for multibacillary leprosy may predispose to drug resistance, persisters and relapse. The newer drugs are listed briefly.

One chapter is devoted to the reprinting *in toto* of the ILEP Medical Commission's useful and practical recommendations on the Basic Requirements for Implementation of MDT (1989). Another gives a concise review of drug resistance, persisters and relapse, somewhat marred, however, by the inclusion of the now outdated U.S. Public Health Service Drug Regimens.

Chapters on Urban Leprosy and Prevention and Control are specifically related to the Indian situation, though the view expressed in favour of segregation is controversial.

There are a number of typing errors and misprints, the most confusing being in the grading of the lepromin test (pp. 6 and 7).

Regretfully, this book cannot be recommended for use outside India.

H. W. Wheate

Published by Jaypee Brothers Medical Publishers (P) Ltd., New Delhi. 198 pages, 10 Appendices. Price Rs. 125.00.

***Leprosy: diagnosis and management*. Dr C. K. Job, Dr A. J. Selvapandian and Dr C. K. Rao**

This little book on leprosy is unashamedly Indian in its approach and is thus a useful corrective to a number of other small books on leprosy which tend to stress the African experience and viewpoint.

It is written for busy medical practitioners and enquiring students so that they can obtain an understanding of the disease and the basic essentials of management. Nevertheless, the title is misleading, as the book proceeds from history through epidemiology, pathogenesis, immunology and complications on to diagnosis and management of the disease and its several medical, surgical and rehabilitative sequelae. The need for the normal appearance of the patient to counteract stigma is stressed. In such a small book, it is clearly necessary to be a little dogmatic but generalizations have been kept to a minimum and statements are usually in line with current thinking.

In the absence of any references, it is a pity that there are no suggestions for further reading other than two large textbooks of leprosy.

I found it interesting that although the Ridley–Joppling classification had generally been accepted, the 5 other systems variously used in India still needed a discussion and the Job and Chako modification which omits mid-borderline disease seems to hold sway.

Immunology is rather narrowly confined to the lepromin test and antibody tests without a clear account of their usefulness in practice. Some comment on the genetics of susceptibility and the role of the HLA system might have enlivened this chapter. The interesting discussion of the variations on treatment regimes recommended by the World Health Organization ends with a description of the Indian preference which takes account of the difficulty experienced in distinguishing between persistent activity and immunological reactivity in Indian patients. I wonder if trivalent antimonials are really still used for reactional states in India now that Chloroquine and corticosteroids are so widely available.

Excellent accounts of disease of the eye, nose and peripheral nerves are followed by a succinct account of the Indian approach to control and the management of deformities. The ordinary practitioner might like more emphasis on the need for education of the patient but he will find the practical attitude for the management of plantar ulcers useful. A fuller account of the pathogenesis of these ulcers would have made it clear that plantar ulcers are always full depth.

This book undoubtedly provides a useful introduction to the disease in India but the enquiring student will need to look beyond it if he is to gain an understanding of pathogenesis and the basis of chemotherapy, for example, or to obtain a glimpse of the advances made by contemporary science in the several disciplines that go to make up a study of leprosy.

Anthony Bryceson

Lepr Rev (1993) **64,** 286–288

Teaching Materials and Services; News and Notes

'Tuberculosis and leprosy; evidence for interaction of disease'

The above is the title of a contribution by Keith Manchester in *Human paleopathology; current syntheses and future options*, eds D. J. Ortner & A. C. Aufderheide, 1991, and published by the Smithsonian Institution Press, Washington. This paper, '. . . seeks to review the history of tuberculosis and leprosy in antiquity and to consider the historic changing patterns within the concept of modern epidemiology and immunology'. The author, who has published extensively on the paleopathology of leprosy, reviews the bacteriology, immunology and epidemiology of the disease and then proceeds to review its history, with particular reference to findings in skeletons from burial sites. The concluding sections deal with the interaction between leprosy and tuberculosis through the ages, including a consideration of the influence of increasing urbanization on the latter and the possibility that the decline of leprosy may, at least to some extent, be linked to immunological and other changes due to the persistence of tuberculosis. There are 63 references. (Dr Keith Manchester's address is: 66 Pollard Lane, Bradford, Yorkshire BD2 4RW, UK.)

Compact Disc of Leprosy Literature 1913–1991: Leprosy Research Foundation, USA

A copy of this compact disc has been supplied by Dr Ray Foster, a trustee of the Leprosy Research Foundation. It is accompanied with instructions on its content and use, which 'represents the culmination of 10 years' work collecting, keying-in and down-loading the world's scientific literature on leprosy. The CD-ROM (read only memory) is a collection of 41,168 citations from 2874 books and journals. About half of the citations have abstracts; 8148 of the pre-1984 Tropical Disease Bulletin abstracts can be found in no other computer format except in the 1913–1991 leprosy compact disc ROM. This CD-ROM is being made available at the price of $20.00 (to cover postage and handling) to any who would like to obtain it.

A folio with the disc gives full details of terminology, method of use and content. Contact: Dr Ray Foster, Leprosy Research Foundation, 11588 Lawton Court, Loma Linda, CA 92354, U.S.A.

Graves Educational Resources, change of address:

Please note that all orders for the purchase, hire or subscription of Graves programmes should be made to: Graves Medical Audiovisual Library, Concord Video & Film Council, 201 Felixstowe Road, Ipswich IP3 9BJ. Telephone: 0473 726012/715754; Fax: 0473 274531

After 1 April information relating to the sale, hire and subscription hire of our audiovisual programmes will be available from Ipswich.

The payment of invoices issued from Chelmsford should also be made to this address.

All enquiries other than those relating to the supply of audiovisual programmes should be made to Graves Educational Resources at the address below:

Graves Educational Resources, 220 New London Road, Chelmsford, Essex CM2 9BJ, UK. Phone: 0245 283351; Fax: 0245 354710.

India: Report of the 4th Independent Evaluation of the National Leprosy Eradication Programme

This Report gives a full account of the objectives, methodology observations, conclusions and recommendations of the 4th Independent Evaluation of the NLEP, which covered 24 of the states/union territories in December 1991. Copies are available from the Leprosy Division, Directorate of Health Services, Ministry of Health, New Delhi 110001, India. (See also, 'National Strategy for the Elimination of Leprosy in India' by B. N. Mittal, *Ind. J. Lepr*, **64,** 513–20.)

Learning for health

The following is taken from the Editor's letter:

Welcome to *Learning for Health*. This is the first issue of a newsletter that will be published every 6 months. We hope our readers will find it informative and useful. The Education Resource Group of the Liverpool School of Tropical Medicine works in teacher training for health workers, training in health education/promotion and human resource development. *Learning for Health* will reflect these interests, and is for anyone working in these areas, particularly in developing countries. It is not an academic journal. Instead it will emphasize practical ideas to be used in our everyday situations, and the style will be simple and easy-to-read.

Learning for Health will not tell you what to do. One of the words which will often come up in these pages is 'facilitator'. This word literally means 'enabler', or someone who makes things easier. We may think of a teacher as someone who addresses a problem, gives the right answers and lays down correct actions. On the other hand a facilitator enables the learners first to sort out what the problem is, then agree for themselves how the problem should be tackled in their own situation. Jan Ritchie's article 'Communicating the Paradox' illustrates this, especially the story at the beginning.

You can contribute to *Learning for Health* through any of our regular features. One of these is CHESS, or Community Health Education Support Service, which gives ideas on practical problems people write to us about. We welcome your enquiries. We would also like readers to write to us with their responses to the problems raised, which we can reprint in a Letters page.

Another regular feature is the 'Reviews' section, where again we welcome your contributions. Perhaps you have read a book, seen a video, or used a teaching aid which was especially useful. You can either review it yourself (we would need to see the item being reviewed too) or tell us about it so that someone else can review it.

There is also a regular 'Notes and News' section, so if you have announcements about training courses, conferences, new publications, or news items of interest, please let us know.

Address: Education Resource Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK.

Liverpool School of Tropical Medicine, UK

The Liverpool School of Tropical Medicine, a registered charity affiliated to the University of Liverpool, is one of the few postgraduate centres of excellence in the world in the field of tropical medicine and its allied disciplines. Its principal, inter-related functions are research, teaching, and consultative activities. The School is extensively involved in national and international programmes to control tropical disease and to develop effective health care systems. It has links with health ministries, universities and research institutions worldwide. The School has well-equipped, modern teaching and research facilities. There are 3 general lecture theatres, the largest of which accommodates 144 students, as well as several seminar rooms. The Dagnall Laboratory, equipped with a video microscope and overhead colour television monitors, provides bench space for up to 80 students and there are several smaller teaching and research laboratories. Teaching methods and course content are continuously evaluated and importance is attached to small group teaching wherever possible. The School also houses a computer laboratory and most courses include training in the use of computers, and statistical and epidemiological methods.

The School offers a number of courses leading to University of Liverpool degrees and diplomas, a series of School Certificate Courses and a number of Short Courses. Research facilities and training leading to the degree of MPhil or PhD can be offered in most major disciplines relating to tropical health. Current research covers the spectrum from molecular biology to health systems and operational field research. All tuition in the School is provided in English and students whose native language is not English must possess a suitable English Language qualification. For those wishing to improve their level of English, the English Language Unit in the University can provide full-time language tuition to overseas students prior to commencement of study as well as continuing part-time language support. English classes are also available for students' families.

Enquiries: Liverpool School of Tropical Hygiene, Pembroke Place, Liverpool L3 5QA, UK.

Need for social science inputs in leprosy eradication. Ninth Erwin Stindl Memorial Oration 1992

The above oration was given by Dr A. M. Kurup, Chief Research Scientist at the Centre for Social Science Research on Leprosy, Gandhi Memorial Leprosy Foundation, Wardha, India. This talk was given in the Grecaltes Training Centre, Calcutta on 30 January 1992, and is now printed in a 40-page booklet, and is available from Grecaltes (price US$5 or 30 rupees).

The 3 sections of the lecture relate to: (1) health and society; (2) the social complications of leprosy; and (3) social science research. The first section is a general introduction with statements about the concepts of health and disease; the next outlines the size of the leprosy problem, its social and economic consequences, the patients' concept of cure and difficulties of treatment compliance.

The author brings together recommendations for social science research and these are listed in the third section. These recommendations have been made by various international bodies or working groups during the past 10 years. The areas already investigated take up half a page whilst the recommendations cover 8 pages, indicating that much remains to be done. The Centre for Social Science Research in Wardha, India is one of the few centres where training and research are being carried out.

In places, this lecture contains long sentences and the sociological terminology make comprehension difficult for the non-sociologist. There are numerous typographical errors.

Catalogue: WHO publications on tropical diseases, 1993

This catalogue provides bibliographic and descriptive information for 50 WHO publications focused on the prevention and control of tropical diseases. Publications are grouped according to the following topics:

- malaria,
- schistosomiasis,
- filariasis,
- trypanosomiasis,
- the leishmaniases,
- leprosy,
- tuberculosis,
- AIDS,
- intestinal parasitic infections,
- model prescribing information,
- laboratory methods,
- travel medicine,
- vector control.

In view of the magnitude of human suffering caused by tropical diseases, many of these books concentrate on strategies for prevention and control, emphasizing methods that are feasible, effective, affordable, and acceptable to communities. Some addressed to physicians and nurses, serve as clinical guides to the diagnosis and management of disease. Others, intended for health planners, provide comprehensive reports on virtually every practical or technical factor that needs to be considered when designing national policies for control. Still others set out training materials that can help health professionals acquire new skills or do a better job, even when conditions are primitive and resources scarce.

Regardless of topic, all publications participate in the larger WHO objective of using the tools of pragmatism, developed during more than 40 years of experience and backed by the best scientific knowledge, to pursue the visionary goal of better health for all.

Further enquiries: WHO Publications, Distribution & Sales, 1211 Geneva 27, Switzerland.