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Leprosy Review

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

British Leprosy Relief Association
LEPRA

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

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

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Editorial

SURGICAL REHABILITATION

Leprosy would be easy to cure if it was only a disease of the skin but its seriousness comes from the fact that it is also, and mainly, a disease of peripheral nerves. Even if medication can ensure bacterial cure, many leprosy patients continue to develop incapacities[5–67] from which these questions arise: why are they always located in the extremities? what is the pattern of these deformities and mutilations? and which problems can be partly solved by reconstructive surgery?

Because technical requirements and the training of surgeons varies from country to country the aim is not to define the best surgical treatments or techniques but to develop concepts and techniques which enable as many leprosy patients as possible to be treated with the means that are available in their country. In relation to the aim of 'Health for all by the year 2000', I would like to think that by the year 2000 all leprosy patients will have the benefit of the medical means available in the environment where they live.

Patterns of deformities in leprosy

CLASSIFICATION OF THE DISTAL SITES OF DEFORMITIES

The pathogenesis of leprosy neuritis is based on the destruction of *Mycobacterium leprae* in nerve trunks causing inflammatory and immunological phenomena, with cellular and oedematous infiltration, resulting in the swelling of nerve trunks; this produces a form of 'hypertrophic' neuritis. At the same time, the epineurium thickens and becomes rigid leading to a mechanical internal compression. Certainly this enlargement is seen in anatomical regions in which nerve trunks lie superficial, in the limb, just under the skin, where tissues are occasionally below body temperature, a factor contributing to the damaging reaction which takes place.[33] But in these superficial regions, the swollen nerve trunks pass through unyielding osteofibrous tunnels, as Guadagnini[49] has shown. These tunnels are normally moulded around nerve trunks of normal size. When there is nerve involvement, steroid treatment and rest by splinting are sometimes not enough to suppress the immunological and inflammatory response in the nerve and to relieve the intraneural tension by decreasing oedema and inflammation. Then the element of superadded mechanical external compression determines the site of the functional deficit of nerve trunks—these compression sites are:[8–49]

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The ulnar nerve: at the elbow, under the epitrochlear–olecranon ligament and under the arch formed by the flexor carpi ulnaris muscle origin, producing claw hand;
the median nerve: at the wrist, under the carpal ligament, producing opponens function loss; both ulnar and median nerve damage producing palmar hand sensory loss;
the lateral popliteal nerve: at the knee, under deep fascia behind the neck of the fibula and under the arch formed by the peroneus longus muscle origin, producing foot drop;
the tibialis posterior nerve and the origin of plantar nerves: at the ankle, under the flexor retinaculum and at the entrance of the plantar tunnels, producing clawed toes and particularly sole sensory loss;
the facial nerve: in temporalis tunnel and/or above the zygomatic arch and across the fascia of the parotid gland, producing facial paralysis and particularly lagophthalmos which is often the cause of corneal ulcers.

Involvement of the radial nerve is very rare (3 cases of 438 ulnar nerve involvements in a series recorded in 1979).[27] Evidence of these external compressions has been shown by lipiodal neurographies[10] and recently both external and internal pressure of median nerve have been measured by computerized microcaptors.[42] The clinical signs of nerve involvement are: thickening, tenderness or pain, sensory impairment with abnormal sensation such as a burning feeling and numbness.

Nerve trunk damage will produce the following:

Pain (in reactional neuritis, severe neuralgic pain may cripple patients overnight), nevertheless, it is not always associated to the other clinical signs;
Sweating loss, in the area of the nerve;
Motor loss of which the resulting disabilities are few: claw fingers and thumb opposition loss, foot drop, clawing of toes and lagophthalmos. Thus, only a few techniques will be necessary to correct these deformities and the surgeon can use multiple muscles innervated by median or radial nerve at the forearm or by posterior tibialis nerve at the calf, which will never be paralysed—this is the opposite of poliomyelitis paralysis in which there are a lot of deformities and therefore corrective techniques;
Sensory loss: It extends to the nerve trunk's distribution, most often without patches; it is different from the limited sensory loss of patches which is very superficial and may occur anywhere in the body.

PATHOGENESIS OF ULCERS AND MUTILATIONS

Because of sensory loss of hands or soles of the feet, the leprosy patients do not feel pain due to trauma, high or repetitive moderate stress, burns or infection. They continue to use a wounded and infected limb without sensation and subject it to stress in spite of infection. This leads to skin wounds, ulcers, damage and infection of soft tissues, joints and bones and then to absorbence, which months or years later, causes gradual 'spontaneous' amputation of fingers, toes, or parts of hands and feet. All this condemns patients to repeated dressings (the cost of which is considerable), for many years, before undergoing the so called 'required' surgical amputations.

In addition to these deformities and disabilities which are the consequence of leprotic neuritis, the deformities directly caused by infection with *M. leprae* are few: Flat nose, loss of eyebrows, specific ocular lesions (iridocyclitis, cataract) gynecomastia.

Place of surgery in the care of deformities

There are two aims—to restore the most important lost anatomical functions and to correct the appearance of leprosy patients.

RECONSTRUCTIVE SURGERY

Motor paralysis

Reconstructive surgery can correct most of the deformities due to motor paralysis. The limbs should be kept mobile and preoperative exercises are necessary to prevent joints becoming stiff or to reduce stiffness, particularly in the fingers and ankles. The skin must be free of ulceration or contracture (if there are contractures after exercises and splintage, skin—plasty or full thickness skin graft may be necessary).

All the techniques used for the correction of traumatic paralysis give similar mechanical results for leprosy paralysis, provided that the surgeons are experienced in these techniques and in their indications.[8–22] The only, but very important, difference is that in leprosy, hands and feet often have definitive sensory loss.

Hand deformities

Claw fingers: The paralysis of the intrinsic muscles of the hand leads to claw hand; this deformity makes grasp and pinch movements difficult, and adapted tools, large handles or grip aids are useful, although often not available. Surgery can restore motor function loss and also correct the appearance (which is a cause of social rejection). Because of sensory loss all accurate finger movements must not always be restored (e.g. finger spacing or abduction of the index finger, partially restored by transfer in the radial edge of the first phalanx, become awkward and it is better to restore a 'bidigital hand', that can grasp objects between the thumb and the four fingers acting together, by fixing the transfer in the ulnar side of the index).[8–21,25–32] Furthermore, excessive prehension strength is to be avoided because it affects the trophicity of extremities submitted to repetitive stress.[33]

Possible postoperative complications should be known, the most frequent of which is 'intrinsic plus' hypercorrection, it is due to the too powerful action of the transfer[25–32] and to the loss of the strong antagonist action on the 2nd phalanx of the FDS tendon disinserted. It should also be acknowledged that the FDS is a very active anterior ligament of the PIP joint, as described in 1961,[25] and this explains why hypercorrection can occur after a simple disinsertion of the FDS as after the lasso operation, or even after slackening of the FDS as in flexor pulley advancement.[22]

Many operations can be used and the choice is made according to the training of the surgeon in hand reconstructive surgery, also to the degree of joint stiffness, time of procedures, postoperative exercises needed and the technical requirements. Here are the operations currently performed.

Intrinsic reactivation procedures: these operations use tendon transfer in such a way as to simulate the paralysed intrinsic muscles.

Transfer to the lateral band of the expansion of interossei

Stiles–Bunnell's operation was the first used. A flexor digitorum sublimis tendon is

transferred to the expansion of its own finger.[25–31] It does give very good results but the use of a powerful muscle to replace a weak intrinsic muscle of a mobile finger can result in overcorrection, which develops into a postoperative 'intrinsic plus' deformity. To prevent this, Bunnell & Littler have proposed to use only one tendon sublimis for the four fingers.

Fowler's operation:[45] the transfer of extensor proprius of the index and 5th fingers divided in two strips is not easy to perform because of the insufficient length of the transferred tendon to allow a good suture. It may however be useful to correct failure of another operation.

Brand's operation[32] uses an extensor carpi radialis lengthened with a many-tailed free tendon graft. This procedure uses either dorsal, interosseous route or carpal tunnel route and gives very good results. But this operation is a long process and to add a new tendon through the carpal tunnel may produce median nerve compression.

Giraudeau's operation:[48] the flexor carpi radialis is lengthened with fascia lata using the carpal tunnel route after the opening of the carpal ligament. It provides good results.

Transfer to the tendon of interossei

Palande's operation[59] uses the extensor carpi radialis longus lengthened with fascia lata and fixes the strip on the tendon of interossei; a complementary transfer of a tail to the hypothenars aims at a better restoration of a reversed metacarpal arch.

Transfer in the pulley

Zancolli's lasso operation:[71] the FDS tendon is removed from its insertion on the medial phalanx in order to be sutured to itself after making a loop through the proximal pulley of flexor sheath. It provides only an independent proximal interphalangeal flexion (PIP) then extensor tendons can extend PIP and DIP joint. Results are good and this simple procedure needs only a palmar incision; but the removal of the tendon sublimis that is a strong anterior ligament of the PIP has given intrinsic plus deformity in rare cases. To prevent this complication:

Boucher has proposed the use of only one tendon for two fingers;
Van Droogenbroeck uses only a slip of tendon sublimis;
Palande uses tendon flexor carpi radialis longus lengthened with fascia lata.

Chevallard's operation:[43] In a simpler manner, Chevallard[15] sutures the FDS tendon directly to the pulley by non-resorbable thread without any section of FDS tendon. Of all the procedures this is the quickest to perform.

Passive stabilization of metacarpo phalangeal joint (MCPJ): The restriction of MCPJ hyperextension allows the extensor tendon to extend PIP and DIP joints.

Tenodesis: free tendons are used to prevent MCPJ hyperextension; Srinivasan uses tenodesis[63] from extensor (in the dorsum of the hand) to extensor (in the first phalanx) passing volar to the deep transverse metacarpal ligament.

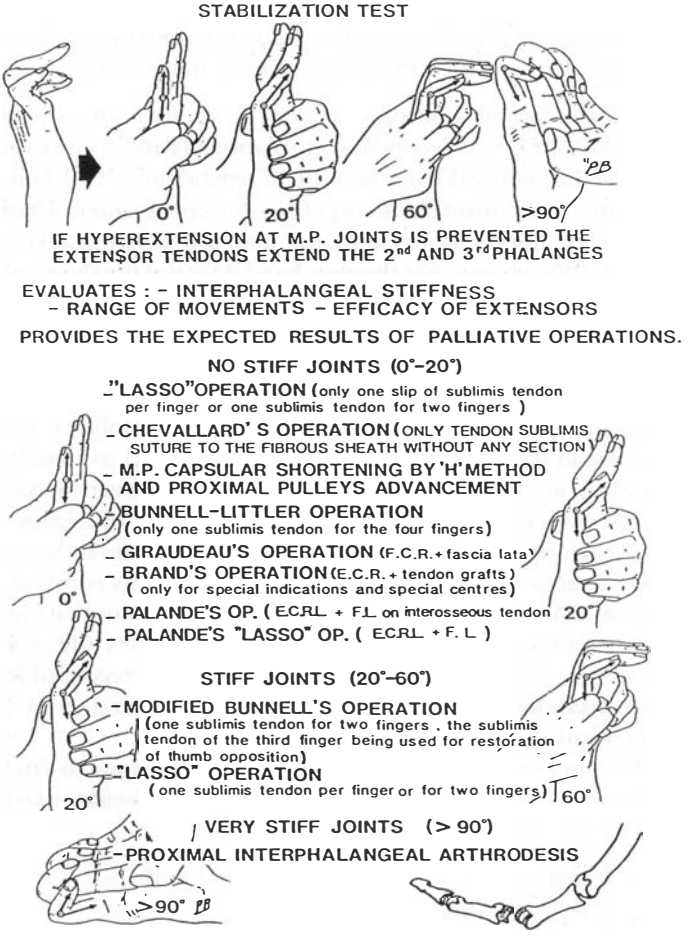
Zancolli's capsulorraphy:[69,70] the shortening of anterior capsule of MCPS to restrict its extension is performed using either a U shaped capsular incision or an orange quarter resection or a transosseous fixation. These procedures correct the clawing but cannot restore the sequence of flexion of fingers. The procedure of capsular-shortening is simplified by an H-shaped capsular incision[8,9,22] and an added accurate pulley advancement[8,9,25] restores a normal closing sequence of fingers.

Dermodesis: Srinivasan uses shortening of palmar skin[64] to reduce MCPJ hyperexten-

sion associated with the pulley advancement procedure; this is a very simple and safe procedure. All these interventions demand a 10–15° MCPJ flexion at rest which some patients do not accept.

Proximal interphalangeal arthrodesis. Exceptionally indicated in very stiff flexion of fingers it allows the flexor a pinch or a little grasp movement.

Conditions of the hand: The finger joints should be as mobile as possible; passive and active exercises will prevent or cure joint stiffness.[1] The extensor system must be normal. In endemic areas, general surgeons must often undertake operations for leprous claw hand without very special hand surgery training and the techniques must be simple.[8] For more than 30 years, to help them in indications for palliative surgery of claw hand, I have taken into account four levels of PIP joint stiffness, which enables one to propose a simple therapeutic scheme, based on the stabilization test.[7,8,15,20,25] This test evaluates: interphalangeal stiffness; range of movements; efficacy of extensors. The indications are related to the degree of stiffness and give consistently good results, as shown by the comparative recording of 222 hand operations.[22]



Reconstruction of thumb opposition: The aim is to provide an abductor–rotator of the thumb. Many operative procedures could be used but the two most widely performed are:

Flexor digitorum sublimis transfer: first proposed by St Bunnell, there are a variety of routes to the thumb. My choice[8–14] is a modified Thompson's operation with FDS of the middle finger passed around the ulnar border of the palmar aponeurosis at the lower border of the carpal ligament; one tendon strip is then passed over the dorsum of the metacarpal head and attached to the adductor insertion; the other tendon strip is attached to both the extensor tendon of the thumb at the middle of the first phalanx and to the abductor pollicis brevis so as to prevent its undesirable secondary slipping, and probably acts as a tenodesis preventing MCPJ hyperextension. Nevertheless this very good procedure uses a FDS tendon and, when there is no finger joint stiffness, intrinsic plus deformities can be induced.

Extensor indicis proprius transfer: a modified and simplified procedure[11] of Burkhalter's operation uses EIP rerouted directly around the ulnar side of forearm and attached both to the extensor tendon of the thumb at the middle of the first phalanx and to abductor pollicis brevis. This procedure gives good opposition of thumb but the associated claw thumb is not always corrected and this transfer must be completed by transfer of the distal radial half of flexor pollicis longus to extensor pollicis longus at the middle of proximal phalanx, or by a PIP arthrodesis if there is stiff joint.[11]

Of course, after reconstructive surgery, extremities remain anaesthetic. Unfortunately, perhaps in 25–30% of cases, secondary mutilations (with preservation of restored function) will occur in the operated hand because of sensory loss.[8,15,21] This has prompted a discussion of the value of reconstructive surgery in the leprosy hand, Faget & Mayoral[46] in 1944 argued that claw hand reduces activities and will thus preserve the hand from trauma. In fact, Brand[33] has shown that the claw hand does not use the whole of its palmar surface for carrying heavy objects but only the tip of the fingers; this represents a pressure ten times as strong as the pressure exerted on a normal hand. This misuse of the finger tips is for Brand one of the most important causes of finger absorption because of subcutaneous necrosis leading to scarring. When motor function of an anaesthetic hand has been restored, 'this hand will wrap the fingers around the object, so that all of the surface of the fingers and palm surrounds as much of the object as possible. In this way, the actual strain of bearing the weight of the object is spread over the surface of all the fingers and not only over the surface of the tip of the finger of a claw hand'. Health education[5,55,67] and teaching how to prevent or to treat any injuries or burns[66] is necessary so that minor injuries cannot become major 'disasters'; but this is not always effective. Long ago, Anaxogore said: 'man is intelligent because he has a hand'; it could also be said that 'the leprosy patient will preserve his hand and his extremities if he is intelligent', and this is observed in almost 60–70% cases. In my practice I have recorded leprosy patients who have had no disabilities or mutilations for 19 years and even 24 years after reconstructive surgery of the hand.

Clawed toes: To suppress the exposure of the tip of the toes to friction strains or ulceration and stress of the sole over the prominent metatarsal heads, two procedures are generally used with good results:

Flexor-extensor transposition, if the toes are without stiffness.

Arthroplasty of PIP joint, when there is stiffness.

Foot drop

Double tendon transfer, a technique proposed by Carayon in 1953,[40] seems to be the best way to correct the paralysis of the dorsiflexors and the evertors of the foot.[6] Using an interosseous route, the transfer of the tibialis posterior tendon into the tibialis anterior tendon corrects varus and drop foot, while the transfer of the flexor digitorum communis tendon into both the extensor hallucis tendon and the extensor digitorum tendons completes correction of varus and drop foot and also gives active extension of toes and eversion of the foot. This procedure is performed exclusively in the leg above the ankle, far from any possible recently healed plantar ulcer. This double transfer will then give more strength than the single tendon transfer of tibialis posterior. When there is stiffness of the ankle with inability to passive preoperative dorsiflexion, a lengthening of tendo Achillis must be performed.

Single tendon transfer of tibialis posterior, first proposed by Watkins in 1954, nevertheless is better known and most frequently performed, using either interosseous or circumtibial route, as proposed by Ober[56] in 1953, with many procedures of distal insertion.

Triple arthrodesis (of subtalar, talonavicular and calcaneo-cuboid joints) a technique that is rarely used now because its action is passive, and thus will deteriorate; the postoperative immobilization for 5 months is too long; and there are risks of bone infection and of nonunion.

Lagophthalmos: To insure the cornea is covered during sleep there are two techniques:

Lateral tarsorraphy, of half the orbital margin, is a simple technique, easy to perform by non-specialized surgeons.

Active muscle transplant[3–35] uses a fascicle of temporalis muscle and is a technique for specialized surgeons when the cornea is sensitive.

Timing of palliative surgery

Operate when patterns of paralysis are stable: no increasing paralysis; no recovering muscle function; before severe stiffness develops; without an episode of reaction; 6 months after the beginning of MDT. Surgery should be undertaken 6–12 months after the onset of paralysis.

Strategy and tactics

Reconstructive surgery needs experienced surgeons, but in the surgical treatment of motor paralysis a delay in surgery of some weeks does not matter if joint stiffness is prevented,[2,5,8,66] with the exception of corneal ulcers for which temporary tarsorraphy may be needed as an emergency. The first possibility is to send these patients to the nearest place where a competent surgeon can operate on them.[8] The second is to ask a surgeon experienced in reconstructive surgery to come to the hospital for a limited period of time[15] to operate on the patients who have been assembled, and at the same time teach a less experienced surgeon of the local hospital how to operate on

SENSORY LOSS

Because sensory loss is the main complication of leprosy and the cause of most mutilations, attempts to restore sensation are of great interest.

A neurovascular skin island pedicle graft[53] transfers sensation from a relatively unimportant part of the hand to an insensitive area where a protective sensation is necessary. This technique is rarely possible because of widespread sensory loss.

Nerve grafts: cutaneous nerves usually used for autografts are not available because of their frequent involvement by the disease. Gye[50] and McLeod[54] have used grafts from fresh cadavers, freeze-dried, irradiated and immunosuppressive agents; out of 23 nerve allografts, McLeod had only 2 good results with ulnar nerves (graft lengths were from 7 cm for a median nerve to 31 cm for a cubital nerve). The problems encountered were the large length of autografts which are necessary and the difficulty of determining exactly where the nerves are affected proximally and distally. Nevertheless, other research trials are needed to correct this important disability.

PLASTIC COSMETICS SURGERY

Usual operations

Reconstruction of the nose: Replacement of the scarred mucosa by skin graft and support of the ridge of the nose by bone graft.[3–33]

Gynecomastia: Removal of the enlarged gland by circum areolar incision.

Exceptional operations

Reconstructive surgery of the paralysed hand does not correct wasting of interosseous muscle, particularly between thumb and index metacarpal. In some countries or for some leprosy patients this interosseous wasting remains an obvious stigma of the disease. Three procedures have been performed to mask this wasting: Dermis graft,[5] injectable liquid silicone[44] and silastic implant.[68] Nevertheless, we can say that today it is an 'unnecessary luxury' operation, even if it has a psychological effect.

SURGICAL CARE OF ULCERS AND INFECTION OF EXTREMITIES

Hand

Pulp and bone infection and necrosis may extend to the synovial sheaths in the palm or the forearm. As for non-leprosy patients, they need incisions and drainages and sometimes amputations. Palmar ulcers may need skin flap.

Foot

Plantar ulcers are one of the most disabling deformities. They lead to infection of deep tissues, joints and bone, which need incision, drainage, sequestrectomy, metatatarsectomy, metatarsophalangeal joint excision and finally distal and then proximal amputations. These amputations are a disaster in endemic countries because of the lack of special footwear or artificial limbs.

Treatment of plantar ulcers: at the 13th International Leprosy Congress in the Hague in 1988, 23 panels reported good results in many treatments used for the healing of plantar ulcers (casting, zinc, collagene, hydrocolloid, epidermal skin, graft, island, flaps . . .) but it is well known that the biggest problem in insensitive foot is not the healing of plantar ulcers which can very often heal by rest (bed rest or plaster cast) and anything else, but always by rest, even if sometimes the healing time is shortened by some days. The problem is how to prevent their recurrence.

Curative plastic surgery: Excision—suture, local island flaps (sometimes with skin of a toe from which infected bone and joint has been removed) can shorten the healing time but recurrences are frequent. To prevent recurrence some procedures try to suppress the mechanical factor of ulcers.

Modification of elective high pressure sites of the sole. It is well known that plantar ulcers occur under prominent bones either anatomical, as tubercle of the base of the fifth metatarsal and of the calcaneus or secondary to deformities as metatarsal heads, exposed by clawed toes, or lateral border of a varus drop foot (in 1960 a record of 1049 plantar ulcers[51] showed that 78% occur under metatarsal heads or in the tip of the toes, 8% under the tubercle of the base of the fifth metatarsal and 12% under great calcaneal tubercle).

Protective footwear: the aim is to distribute the weight over the maximum area of plantar insensitive skin, to relieve the insensitive and/or scarred areas from weight bearing and to be moulded on deformed and even shortened feet.[24–66] This is obtained by using an insole of microcellular rubber or of plastazote which can be moulded. The footwear should be produced in large numbers, at a low cost, and if possible sold to all people in the market, then modified (insole) by a local shoe-maker. It should also be acceptable to the patients, without identifying them as suffering of leprosy. From the three designs of footwear—for feet with ulceration and shortening, for insensitive feet with some deformity and for insensitive but not deformed feet, the latter is the design which can satisfy all the required conditions. Thus, cost effectiveness should give priority to the provision of footwear to the greater number of insensitive but not deformed feet.

Corrective surgery for deformities.[8,47,51,61]

Correction of claw toes: it prevents ulcers under metatarsal heads and also in the tip of the toes.

Correction of foot drop: it prevents ulcers on the lateral side of the foot.

Removal of bony prominences:[8,15] Plantar calcaneus tubercle: its removal enlarges the plantar weight-bearing surface of calcaneus and lowers the pressure per unit on the skin of the heel.

Tubercle of the base of the fifth metatarsal: its removal suppresses high pressure when this tubercle has excessive size.

Metatarsal heads: even if the healed ulcers under them will not recur after their removal, the weight-bearing surface is deplaced proximally under the tip of the remaining metatarsal bone. So it seems to be not a very logical procedure except when there is infection of joint or protrusion of a single metatarsal head. If not, correction of the claw-toes is the choice.

Prophylactic surgical tibial nerve decompression. After Reginato published his paper in 1962, I have performed this decompression which prevents the occurrence or recurrence of plantar ulcers even when they are long standing. The results were published in 1969,[8,28] 1976[29] and 1979;[30] in some cases partial sensory recovery occurred. The best results[23] were observed in patients with only insensitive sole of the foot or a first ulcer healed. Therefore

it would be particularly judicious to look for plantar sensory loss and to take into account 'grade 1' particularly in every case of reaction. Of course, this decompression cannot secure improvement or healing of superinfected tissues and bones. The healing of long standing plantar ulcers without any clinical sensory recovery was explained by the simultaneous decompression of posterior tibial vessels and by the section of local sympathetic nerve supply to the artery when the nerve is separated from the artery.

Nevertheless 'nerve decompression does not rule out the need for corrective operations: removal of prominent bones, palliative surgery of foot drop or claw toes'[8–28] (and the provision of standard or protective footwear).

Palande in 1975,[58] Van Droogenbroeck in 1977, Pandya in 1978, Kumar in 1985, and others, have also published their results.

THERAPEUTIC SURGERY

Surgical nerve decompression

Sometimes medical treatment is not sufficient to improve nerve involvement or nerve damage, even if nerve rest by suitable splint or plaster cast has been used. To prevent definitive nerve damage and thus deformities and mutilations, it is clear that surgery can suppress the superadded mechanical external and internal compression as first proposed by Guadagnini[49] in 1953.

There are differences of opinion concerning its usefulness: perusal of literature shows that this nerve surgery has been done for a long time by many authors, with good results; but many others have reported good results with the medical treatment only and they consider the indications for neurolysis have been much reduced. Nevertheless, it may be observed that medical treatment only may have drawbacks: consumption of analgesics may be excessive, mainly because of neuritic pain. This consumption is rarely taken into account in published studies; corticosteroids regimens are not yet well defined. Steroid treatment needs frequent and prolonged hospitalization interfering with the individuals' ability to lead a normal life; large doses lead to serious morbidity; they have their own side-effects and many patients develop dependancy. It is well known that long-standing corticosteroid regimens may favour stress fractures, delayed wound healing and increase of susceptibility to other infections such as tuberculosis. But in leprosy there are no studies about its impact on decalcification of bones, stress fractures and the super-infection of wounds and ulcers. Thalidomide also has side-effects in addition to its teratogenic effect and to procure thalidomide very often raises difficulties. Failures of thalidomide with relapses has led to the use of cyclosporine A, which has significant side-effects and thalidomide itself may produce sensory polyneuropathy. In some published cases (but how many are unpublished?) of corticosteroid treatment, sometimes prolonged for more than 1 or even 2 years, there was no recovery and if nerve surgery is then performed, it is useless. In some of these cases, in which pain was finally relieved, we might say that medical treatment would have eventually improved it in time, but decreased pain is not necessarily an indication of improvement of the nerve, because pain may decrease as nerve function decreases.[15,17,18] In these cases, earlier surgical nerve decompression might give recovery and therefore shorten the duration of corticosteroid treatment of neuritis. Indeed, some 'good' results of MDT in a country where experienced surgeons are available, have recently been published 'with no disability noted of more than grade 1'.

What will be the evolution of these grade 1 disabilities, 3 or 5 years later? Because disabilities in anaesthetic limb extremities may appear after many months or years, these 'grade 1' cases should be seen at regular intervals for follow-up examination, for at least 2 years after release from MDT.[5–67]

However, many therapists still have doubts about the efficiency of nerve decompression. They think it is not possible to determine whether nerve surgery will give better results than medical treatment alone. There are two main explanations for their doubts: (1) Although for more than 30 years good results of nerve surgery in leprosy have been reported by many authors, these authors have not had the same data and methods of evaluation (a prospective study about nerve surgery needs to be made in large centres). (2) Sometimes, quite sincere therapists, who have asked surgeons for nerve decompression, have thought an immediate result of surgical decompression was a failure because they did not appreciate that recovery is not immediate. When there is partial function loss, early decompression may give rapid recovery in some weeks. Usually, however, recovery duration is longer than that observed after nerve suture: one millimetre advancement from the decompression site every day. This duration is longer for ulnar nerve than for median nerve[8–12] and in many cases there are possibilities of late recovery, $1\frac{1}{2}$ or 2 years after. But in leprosy, lesions are not uniform, some fasciculi only compressed may recover after decompression, while other destroyed fasciculi do not recover; and recovery is not as regular or as predictable as after nerve suture or after decompression of an entrapment neuropathy.

Strategy and tactics: To give good results, nerve surgical decompression has to be made before nerve damage becomes definitive (the sooner the decompression the earlier the recovery), and in hyperacute painful neuritis or in reversal neuritis, time-lag range may be a few days or weeks. Thus, in many cases, time must not be lost. To make this surgery possible in the field (where, even now, relatively unskilled staff use only clinical findings to classify patients but where sometimes a surgeon is available in a nearby district hospital), it is necessary: (1) to use a standard technique:[8,12,13] it could be external decompression with tunnel opening, and internal decompression by longitudinal incision of the sheath in its superficial aspect over the swelling with medial and lateral resection of a quarter of the thickened sheath. (In 1957 and 1962 Carayon[37,38,41] proposed internal decompression by fascicular endoneurolysis and for him, 'endoneural liberation is the essential step', nevertheless this is a neurosurgical procedure for specialized surgeons in specialized centres[39] and it is not adapted to technical field conditions.) (2) To have simple indications:[8,12,17,18] the right time to operate would be the time after which acute pain and/or sensory and motor loss go on or grow worse after the beginning of medical anti-inflammatory treatment associated with splinting. (Time lag range: 8–10 days for hyperacute painful neuritis; 8–10 weeks for reversal neuritis and 8–10 months for ENL neuritis.) As I have proposed for many years,[16] this implies a neurological examination which is easy to do, rapid but reliable, liable to be often repeated, to look for clinical aggravation. Simpler indications could be: hyperacute neuritis with intractable pain, and/or first plantar ulcer (which is evidence of plantar sensory loss).

No postoperative worsening of paralysis was found but recovery of the whole of sensitivity cannot be obtained in all cases (the later we operate the less recovery we get) but rate of recovery can often be 40 to 60% and this protective sensitivity is very important to prevent disabilities and mutilations. The medical treatment must be continued. This easily carried out decompression surgery is not a luxury at all, it must be done whenever it is

possible, it avoids occurrence of mutilations, is cheaper than repeated dressing on a life-long basis. And even if a surgeon would only operate on leprosy patients with hyperalgic reactional neuritis or with first recent ulcer, when medical treatment is not sufficient, these cases constitute half the indications.

Conclusion

Surgery does not claim to be the first priority in the treatment of leprosy patients. Nevertheless, in leprosy, many problems can be partly solved by surgery and when a surgeon is available in the environment in which the disabled patient lives, reconstructive, cosmetic, salvage and therapeutic surgery can give better results, earlier, and often be cheaper than a lifetime of dressings and physiotherapy. Indeed, even if what I wrote in 1969 at the end of my paper relating to francophone Africa about leprosy surgery[8] was a little enthusiastic it holds true now.

'Owing to the very limited number of specialized leprosy surgery centres, to the budgetary difficulties of the hospitalization, these leprosy patients have to be treated on the spot by non-specialized surgeons of the district. In other words, we need simple and quick techniques, not needing long hospitalization, or significant postoperative re-education, enabling us to treat a greater number at less cost. As a conclusion, we can see that a surgeon able to carry out some neurolyses, using only four simple and efficient interventions of palliative surgery, can thus prevent or cure deformities in 90% of (recent) leprosy patients and bring them back to a normal life'.

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Evaluation of gelatin particle agglutination assay for the detection of anti-PGLI antibodies. Comparison with ELISA method and applicability on a large scale study using blood collected on filter paper

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Summary Given the technical difficulties of the ELISA method, a gelatin particle agglutination test (MLPA) has been developed recently for the detection of anti-PGLI antibodies. The purpose of this study was to compare these 2 tests. MLPA was found to be less specific than ELISA (91% versus 98%, $\chi^2 = 66{\cdot}8$, $p < 0{\cdot}001$). The sensitivity of both tests was of 95% for the diagnosis of multibacillary patients. In the case of paucibacillary patients. MLPA was found to be less sensitive than ELISA (21% versus 35%, $\chi^2 = 6{\cdot}98$, $p > 0{\cdot}01$). The agreement between the 2 tests for a positive or a negative result was satisfying (85% to 100%), except for the weakly seropositive individuals (71%). The correlation between OD obtained with ELISA and antibody titre obtained with MLPA was statistically significant ($r = 0{\cdot}70$, $p < 0{\cdot}001$). Conversely to ELISA, MLPA was not applicable on blood samples absorbed on filter paper without a serious loss of sensitivity. In conclusion, this study demonstrated that the MLPA test can only reliably detect anti-PGLI antibodies in multibacillary cases.

Introduction

A specific phenolic glycolipid, the PGLI, has been isolated from *Mycobacterium leprae*[1] and it was demonstrated that most of the multibacillary leprosy patients displayed high titres of IgM anti-PGLI.[2] Numerous studies have been undertaken to evaluate the usefulness of this serology for the diagnosis or the prognosis of leprosy,[3–6] and for seroepidemiological studies.[7,8] Indirect ELISA was the method classically used. Given the technical difficulties for untrained personnel to apply this method, a gelatin particle agglutination test (MLPA) on microtiter plates has been developed recently.[9] The agglutination test as compared to ELISA assay, is usually rapid and simple to perform. The aims of this work are first to compare and study the correlations between ELISA and

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MLPA tests for the diagnosis of leprosy, and secondly to define the applicability of the MLPA test on blood samples collected on filter paper.

Methodology

SERA TESTED

Negative controls

They were composed of 414 healthy Polynesian individuals without known contact with leprosy patients and 32 healthy persons from a nonendemic country.

Leprosy patients

We have tested the sera from 44 leprosy patients before treatment. According to the Ridley–Jopling scale they were classified as 21 multibacillary patients (4 BL, 17 LL) and 23 paucibacillary patients (7 I, 6 BT, 8 TT, 2 N).

Household contacts

A total of 262 household contacts were selected for this study. Using the ELISA method, 109 of them were seronegative and 153 were seropositive. These latter subjects were classified in 3 groups according to their antibody level: OD492 nm [0·200–0·300] for 66, [0·300–0·600] for 66 and [$>$ 0·600] for 21 of them.

The sequential sera from 6 contact's subjects who further developed leprosy (4 I, 1 BT, 1 LL) were also tested.

ANTI-PGLI ELISA TEST

The conventional indirect ELISA method for the detection of human IgM antibodies has been described in a previous study.[10] The antigen used was the chemically synthesized trisaccharide NTP conjugated to bovine serum albumin kindly supplied by Dr T Fujiwara.[11] The sera were screened at 1/250 dilution and the positives were semiquantitated by two-fold dilutions. The threshold of ELISA test was 0·200 OD according to previous studies on Polynesian sera.[12]

PARTICLE AGGLUTINATION TEST MLPA

The MLPA kits in which the gelatin particles were sensitized with NTP antigen (Fujirebio Inc, Japan) were kindly supplied by the WHO Regional Office for the Western Pacific. The protocol of the test was according to the manufacturer's specification. A negative control was achieved with unsensitized gelatin particles at 1/16 final dilution of each serum. All the sera were screened with sensitized particles at 1/32 final dilution and a semiquantitative test using two-fold dilutions was conducted for the positive sera. The antibody titre was expressed as the highest dilution giving a positive pattern. The interpretation of the agglutination pattern was according to the manufacturer's criteria: negative (no agglutination or inconclusive agglutination), positive (complete agglutina-

tion). Because of the subjective analysis on the degree of agglutination, the sera were coded.

MLPA on blood collected on filter paper

Blood obtained by pricking the finger-tip was absorbed on Whatman No. 1 paper cards with 5 mm diameter precut discs (Serobuvard, Laboratoire LDA, France).[13] The processing of these samples was as followed: four paper discs per patient were eluted overnight into 100 microlitres of MLPA diluent, which is the minimum volume required to immerse the discs. According to the volume of blood absorbed on the filter, the final dilution of the sera for MLPA test was 1/25 for the control with unsensitized particles and 1/50 for the screening with sensitized particles.

STATISTICAL ANALYSIS

The agreement rate between MLPA and ELISA in detecting positive and negative subjects was calculated as follows: number of positive results + number of negative results by the 2 methods/total number sera tested $\times 100$. The correlation between ELISA and MLPA was calculated according to the least square method and the χ^2 method was used to compare percentages.

Results

SPECIFICITY FOR SERODIAGNOSIS OF LEPROSY

All of the 32 sera from healthy subjects living in nonendemic countries were negative both in ELISA and MLPA (100% of the agreement rate). The results of the 414 healthy Polynesian subjects are reported in Table 1 and the agreement rate for this group was 86%.

The specificity of MLPA and ELISA was 91·5% and 98%, respectively, when considering healthy Polynesian as negative controls ($\chi^2 = 66{\cdot}8$, $p < 0{\cdot}001$).

Table 1. Comparison between MLPA and ELISA tests for detecting anti-PGLI antibodies in negative controls and patients

Group	No. of serum specimens	No. of specimens with test result				% Agreement rate
		$E^+ M^+$	$E^+ M^-$	$E^- M^+$	$E^- M^-$	
Polynesian negative controls	414	8*	1	27†	378	86
Multibacillary patients	21	20‡	0	0	1	100
Paucibacillary patients	23	5§	3	0	15	82

E, ELISA; M, MLPA.
* MLPA titre = 32 × 4 and 64 × 4.
† MLPA titre = 32 × 15, 64 × 10 and 128 × 2.
‡ MLPA titre = 64 × 1, 128 × 7, 256 × 4, 512 × 3, 1024 × 1, 2048 × 2 and 8192 × 2.
§ MLPA titre = 32 × 4 and 64 × 1.

SENSITIVITY FOR SERODIAGNOSIS OF LEPROSY

The results obtained in using the 2 tests on patients' sera are found in Table 1. For the multibacillary patients the agreement rate was 100% between the 2 tests and the sensitivity 95% for both tests. For the paucibacillary patients the agreement rate was 82% and sensitivity was 21% for MLPA and 35% for ELISA ($\chi^2 = 6{\cdot}98$, $p < 0{\cdot}01$).

DETECTION OF ANTI-PGLI IN HOUSEHOLD CONTACTS

A total of 262 selected contacts displaying a large range of antibody level were tested. The agreement rates between the 2 tests according to the different antibody level obtained by ELISA are reported in Table 2. A significant correlation was obtained between the MLPA titres and the optical density obtained in ELISA ($r = 0{\cdot}70$, $p < 0{\cdot}001$).

The sequential sera from 6 contacts who developed leprosy (1 LL, 1 BT, 4 I) could be tested by ELISA and MLPA. The results are reported in Table 3. The agreement rate between MLPA and ELISA was 81%.

APPLICABILITY OF MLPA FOR BLOOD SAMPLES COLLECTED ON FILTER PAPER

A total of 130 pairs of sera and blood absorbed on filter paper was tested with MLPA. Using the sera, 58 individuals (45%) were seronegative and 72 (55%) were seropositive. Using whole blood collected on Whatman paper, 109 (84%) were seronegative and 21 (16%) were seropositive. These latter individuals represented only 29% of the subjects found seropositive using the serum.

Discussion

The objectives of this study were to compare the gelatin particle agglutination test MLPA and the standard indirect ELISA test for the detection of anti-PGLI antibodies, and to evaluate the applicability of MLPA on blood samples collected on filter paper.

For the serodiagnosis of leprosy patients, MLPA was found to be less specific than

Table 2. Agreement between MLPA and ELISA for 262 contacts subjects presenting different anti-PGLI levels as determined by ELISA. Coefficient correlation $r = 0{\cdot}70$ ($p < 0{\cdot}001$)

ELISA activity OD_{492}nm	Number sera tested	MLPA +	MLPA −	Agreement rate (%)
$< 0{\cdot}200$ (−)	109	16*	93	85
[0·200–0·300] (+)	66	47†	19	71
[0·300–0·600] (+)	66	62‡	4	94
$> 0{\cdot}600$ (+)	21	20§	1	95

* MLPA titre: 32×9, 64×4, 128×3.
† MLPA titre: 32×29, 64×16, 128×2.
‡ MLPA titre: 32×20, 64×35, 128×7.
§ MLPA titre: 64×6, 128×12, 256×2.

Table 3. MLPA and ELISA in sequential sera from 6 contacts who developed leprosy

Subject	Months before diagnosis	ELISA OD_{492}nm	MLPA titre	Type of leprosy developed
1	24	0·601 (+)	(+) 64	
	0	1·374 (+)	(+) 256	LL
2	27	0·003 (−)	(−)	
	13	0·215 (+)	(+) 32	
	3	0·500 (+)	(+) 32	
	0	0·634 (+)	(+) 32	BT
3	23	0·180 (−)	(−)	
	0	0·346 (+)	(−)	I
4	8	0·348 (+)	(+) 64	
	0	0·327 (+)	(+) 64	I
5	16	0·189 (−)	(−)	
	10	0·188 (−)	(+) 32	
	0	0·390 (+)	(+) 32	I
6	43	0·189 (−)	(−)	
	16	0·147 (−)	(+) 64	
	0	0·150 (−)	(−)	I

ELISA ($\chi^2 = 66{\cdot}8$, $p < 0{\cdot}001$). However, it is noteworthy that more than half of the false positives using MLPA (15/27) that were negative in ELISA, had low antibody titre equal to 32. The positive pattern may be due to some biophysical peculiarities in some sera, that resulted in a non-specific agglutination of the particles. The sensitivity was 95% for both tests when considering the multibacillary patients but for the paucibacillary patients, ELISA (35%) was more sensitive than MLPA (21%) ($\chi^2 = 6{\cdot}98$, $p < 0{\cdot}01$). The paucibacillary patients generally display a very low level of anti-PGLI antibodies that cannot be detected by MLPA. Anyhow, for these latter patients the PGLI is not a suitable antigen for serodiagnosis. The specificity of MLPA can be improved to 96% if its cut-off is fixed at 64 instead of 32, but in that case the sensitivity for detecting the paucibacillary form of the disease drops to 4% as it remained at 95% for the multibacillary form.

The agreement rate for positive or negative results between MLPA and ELISA was as good for patients as for contacts and ranged from 71% to 100%. In general the concordance was the lowest for the individuals who were weakly positive in ELISA. The correlation between the MLPA titres and OD in ELISA was highly significant ($r = 0{\cdot}7$, $p < 0{\cdot}001$).

Because the agglutination test is rapid and easy to perform, it may constitute an interesting assay for large scale serological studies. Blood collected on filter paper has been used successfully in ELISA for the detection of anti-PGLI antibodies.[13] In this connection, we compared the results of MLPA obtained with the serum and with blood eluted from filter paper. The agreement rate obtained was fair (61%) and only 29% of the positive individuals were found positive using filter paper. Because the titres were much lower when using blood absorbed on filter paper than when using serum obtained by venepuncture, the weakly positive subjects turned out to be negative. This may be explained by an inefficient elution of antibodies from the paper discs. This technical

problem has proved difficult to overcome as, conversely to ELISA, a high concentration of sera is needed for MLPA and thus the volume of diluent used is too small to ensure a complete antibody elution. However, according to whether the prerogative of the test for a precise use is specificity or sensitivity, one can raise the cut-off, i.e. the screening dilution of the sera, and consequently use a larger volume of diluent for soaking the filter paper discs.

The usefulness of the detection of anti-PGLI has been extensively evaluated for the serodiagnosis of patients, the subclinical diagnosis among contact population, or the monitoring of patients during chemotherapy. The conclusions of these studies were that anti-PGLI assay can be used as an additional tool for the diagnosis of multibacillary patients, and also as an alternate tool to the BI determination for the surveillance of multibacillary patients after treatment. In countries where the implementation of such a test is planned and where the technical facilities are too limited for setting up the ELISA method, the agglutination MLPA test may be a good substitute.

In conclusion, in spite of a lower specificity and sensitivity of MLPA for the detection of paucibacillary patients than ELISA, the agreement and the correlation between the 2 tests were satisfying. This study demonstrated that the MLPA test can only reliably detect the anti-PGLI antibodies in multibacillary patients and conversely to ELISA, MLPA was not applicable on blood absorbed on filter paper without a serious loss of sensitivity.

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L'évaluation de la réaction d'agglutination de particules sur un support gélatineux pour la détection des anticorps anti-PGLI. Comparaison avec la méthode ELISA et son application dans le cadre d'une étude à grande échelle utilisant du sang recueilli sur papier filtre

SUZANNE CHANTEAU, J-L CARTEL, J P BOUTIN ET J ROUX

Résumé Compte tenu des difficultés de la méthode ELISA, une réaction d'agglutination de particules sur un support gélatineux (MLPA) a récemment été mis au point pour détecter les anticorps anti-PGLI. Cette étude avait pour objectif de comparer ces 2 tests. MPLA était moins spécifique que le test ELISA (91% par rapport à 98%, $\chi^2 = 66{,}8$, $p < 0{,}001$). La sensibilité des deux tests était de 95% pour le diagnostic des patients pluribacillaires. Dans le cas des patients paucibacillaires, le MLPA était moins sensible que le test ELISA (21% par rapport à 35%, $\chi^2 = 6{,}98$, $p > 0{\cdot}01$). La concordance des résultats positifs et négatifs entre les deux tests était satisfaisante (85% à 100%) sauf pour les individus légèrement séropositifs (71%). La corrélation observée entre la DO (densité optique) obtenue par la méthode ELISA et le titre d'anticorps obtenu par la méthode MLPA était significative sur le plan statistique ($r = 0,70$, $p < 0{,}001$). Contrairement à ELISA , MLPA ne s'appliquait pas aux prélèvements sanguins absorbés sur papier filtre sans une perte importante de sensibilité. Donc, cette étude a prouvé que le test MLPA ne décelait les anticorps anti-PGLI avec efficacité que dans les cas des patients pluribacillaires.

Evaluación del ensayo de aglutinación de particula en gelatina para le detección de anticuerpos anti-PGLI. Comparición con el método ELISA y su aplicabilidad en estudios de gran escala usando sangre recogida en papel filtro

SUZANNE CHANTEAU, J-L CARTEL, J P BOUTIN Y J ROUX

Resumen Debido a las dificultades técnicas del método ELISA, se ha desarrollado recientemente un test de aglutinación de particula en gelatina (MLPA) para la detección de anticuerpos anti-PGLI. El propósito de este estudio fue comparar estos dos tests. Se encontró que el MLPA era menos específico que ELISA (91% versus 98%, $\chi^2 = 66{,}8$, $p < 0{,}001$). La sensibilidad de ambos tests fue de 95% para el diagnóstico de pacientes multibacilares. En el caso de pacientes paucibacilares, se encontró que el MLPA era menos sensibile que ELISA (21% versus 35%, $\chi^2 = 6{,}98$, $p > 0{,}01$). La concordancia entre los dos tests para un resultado positivo o negativo fue satisfactorio (85% a 100%), excepto para los individuos seropositivos débiles (71%). La correlación entre OD obtenida con ELISA y el grado de anticuerpo obtenido con MLPA fue estadisticamente significativo ($r = 0,70$, $p < 0{,}001$). En forma inversa a ELISA, el MLPA no fue aplicable a muestras de sangre que estaban impregnadas en papel de filtro sin que hubiera una pérdida seria en la sensibilidad. En conclusión, este estudio demostró que el test de MLPA puede detectar anticuerpos anti-PGLI en forma segura solamente en casos multibacilares.

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Soluble interleukin-2 receptors: levels in leprosy, and during and after Type 1 (lepra) and Type 2 (ENL) reactions

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Summary Twenty-five patients with Type 1 (lepra) and Type 2 (ENL) reactions, were assayed for SIL-2R in serum—before and after treatment for their acute condition—and the results were compared with 10 normal healthy adults and 20 patients of leprosy *per se*. Classification of each subject into different leprosy groups, and into various types and subtypes of reactions, was done according to standard criteria, prior to inclusion into the study. Detailed statistical evaluation of the data revealed significantly higher levels of SIL-2R in all leprosy patients, as compared to normal controls, with higher levels in the multibacillary groups as compared to the paucibacillary group. SIL-2Rs appeared higher in Type 1 upgrading reaction than in other forms of reaction, though this was not statistically significant.

There was no significant change in levels following treatment and clinical remission.

Introduction

'Soluble' interleukin-2 receptors (SIL-2R), are part of the alpha polypeptide subunit (55 Kd) with low affinity to IL-2, that are released from the cell membrane of activated immunocompetent cells under certain conditions, *in vitro*[1] and *in vivo*.[2,3] The role of this molecule in modulation of immune mechanisms is still unsettled although its 'potential' in down-regulating immune activation is well recognized.[4] In addition to malignancies,[3] AIDS[5] and autoimmune diseases, SIL-2R has been studied in leprosy patients *per se* with intriguing findings.[6,7] The SIL-2R values were raised across the spectrum and did not vary significantly between the various clinical bacilliferous groups, while paucibacillary cases had significantly different values, falling somewhere between that of the normal healthy adults and the multibacillary clinical groups. However, in a few patients who were

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diagnosed to have 'reversal reaction', extremely high serum levels of the polypeptide were obtained.[6]

Since the immunopathogenic mechanisms in reactions of leprosy continue to be an enigma, it was thought worthwhile to investigate the levels of SIL-2R during reactions, and after clinical remission following the conventional treatment.

Materials and methods

CLINICAL MATERIAL

The study group consisted of 25 patients, of Type 1 (lepra) and Type 2 (ENL) reactions of leprosy. The primary diagnosis in each case was made by the criteria described by Ridley & Jopling,[8] with modifications as suggested by Sehgal.[9,10] Accordingly the patients were grouped into borderline–tuberculoid (BT), borderline–borderline (BB), borderline–lepromatous (BL) and lepromatous (LL). Reactions were classified into either Type 1 (lepra) or Type 2 (ENL) reaction based on well-recognized clinical, bacteriological immunological and histopathological criteria.[11] Patients having Type 1 (lepra) reaction were further subclassified into upgrading (reversal) or downgrading subtypes.[11,12] Care was taken to differentiate the former from relapse and the latter from downgrading *per se*[13] (Tables 1 and 2).

In addition to multidrug therapy,[14] patients with Type 1 reaction were treated with chloroquine phosphate in tablet form (250 mg IP), 1 tablet orally three times a day for 1 week, followed by 1 tablet twice daily for 1 week, and subsequently 1 tablet per day until the clinical subsidence of reaction. Patients with neurological symptoms were, in addition, given a tablet of prednisolone 20–40 mg per day orally, in divided doses, along with suitable nursing and physiotherapy.[15] Patients with Type 2 reaction on the other hand, were treated with prednisolone 40–80 mg per day orally, in addition to augmented doses of clofazimine (150–300 mg per day in divided dosages) until clinical signs of reaction subsided. Corticosteroids were then gradually reduced, in a stepwise manner,

Table 1. Age in years of subjects/patients in various clinical groups as compared to that in normal healthy controls

	Leprosy groups	No. of subjects/patients	Age (in years)		
			Mean	95% Confidence limits	
				Lower	Upper
1	Normal healthy controls	10	27·7	24·5	31·4
2	Normal BT controls	10	28·4	23·0	35·0
3	Normal BL controls	4	31·5	18·3	54·2
4	Normal LL controls	6	32·9	23·7	45·5
5	BT upgrading (Type 1)	4	39·8	23·2	68·5
6	BB upgrading (Type 1)	2	42·4	27·2	66·2
7	BB downgrading (Type 1)	3	26·0	12·9	52·3
8	BL downgrading (Type 1)	5	37·1	34·1	40·4
9	BL Type II (ENL)	2	35·5	18·7	67·4
10	LL Type II (ENL)	9	33·4	26·5	42·0

Table 2. Soluble interleukin-2 receptor in the various clinical groups, and before and after treatment for reactions

Unit—U/L

	Leprosy groups	No. of subjects/patients	Before treatment			After treatment		
			Mean	25% Confidence limits		Mean	95% Confidence limits	
				Lower	Upper		Lower	Upper
1	Normal healthy controls	10	296	186	470	—	—	—
2	Normal BT controls	10	482	295	786	—	—	—
3	Normal BL controls	4	865	673	1111	—	—	—
4	Normal LL controls	6	663	563	780	—		—
5	BT upgrading (Type 1)	4	897	318	2526	1119	652	1920
6	BB upgrading (Type 1)	2	1243	806	1917	1332	812	2186
7	BB downgrading (Type 1)	3	795	486	1302	608	256	1441
8	BL downgrading (Type 1)	5	727	549	963	664	389	1131
9	BL Type II (ENL)	2	587	507	679	724	484	1082
10	LL Type II (ENL)	9	747	672	830	734	653	826

and finally withdrawn, followed by a reduction in dosages of clofazimine to the standard MDT regime.[14,15]

Venous blood samples were collected before starting antireactional treatment and when clinical signs of reaction had abated. The sera was stored, after separation at room temperature, in glass containers at $-65°$ to $-70°$C (Forma Scientific deep-freeze).

Other investigations undertaken for all the patients included chest X-rays, haematological profile, blood sugar and urea, serum creatinine, liver enzymes, serum proteins acute phase treactants (alpha-1-antitrypsin and C-reactive protein) and lymphocyte adenosine deaminase activity.

SIL-2R ESTIMATION

SIL-2R estimation was performed using a commercially obtained ELISA kit (CELL-FREE Interleukin-2 receptor test kit; CK1020; T-cell Sciences Inc., Cambridge, MA 02139, USA), from Hysel India Ltd. This kit included SIL-2R standards, anti-1L-2R coating antibody, anti-IL-2R HRP conjugated antibody, sample diluent, substrate diluent, OPD (o-phenylene diamene) substrate, buffered hydrogen peroxide, buffer, blocking diluent and surfactant. The assay was carried out according to the manufacturers instructions after bringing the test samples gradually to room temperature. The optical readings were taken on an automatic ELISA reader (TITERTEK) at 490 nm. A standard curve was plotted on a graph paper from the mean of readings obtained from the supplied standard solutions. The concentration of SIL-2R in the test samples were determined from the mean optical readings and the standard curve, and expressed as arbitrary units per ml.

CONTROLS

Twenty patients with leprosy, derived from varous groups of leprosy,[8–10] not having any

clinical evidence of reaction, along with 10 normal healthy adult volunteers formed the controls for the study (Tables 1 and 2).

STATISTICAL METHODS

In view of the variability with respect of age and SIL-2R, observations were transformed to log values to achieve variance stability and normality. Analysis of variance (one way classification) was done to test for the significance of variation amongst the different clinical groups including normal healthy controls, and, finally, homoscedastic leprosy groups were pooled and subjected to weighted analysis of variance, as described by Welch.[16] Individual and other sensible comparisons were done through linear contrasts.[17] Significance of rise/fall after treatment was tested by '*t*' test for paired samples.

Results

The age of all the patients, including normal healthy controls was 33 ± 9 (mean $\pm$ SD) years, varying from 18 to 56 years. The age distribution of each of the clinical groups has also been given in Table 1. There was no evidence of significant ($p > 0{\cdot}05$) variation in age amongst the leprosy groups thus indicating that the groups were not significantly heterogeneous with respect to age.

Of the total patients studied 21·8% were females. Few of the clinical groups did not have females. It was assumed that the low number of females in the other groups would have little effect on the study variables.

Table 2 gives the mean levels of SIL-2R in the age groups of leprosy, along with their 95% confidence limits. Mean SIL-2R level in BT patients (not in reaction) was observed to be higher, though not significantly, as compared to that in normal healthy controls ($p > 0{\cdot}05$). SIL-2R levels were significantly higher in the other clinical groups (normal BL controls, normal LL controls, and other reaction groups) as compared to the BT group and the normal healthy controls ($p < 0{\cdot}05$). SIL-2R values did not vary significantly before and after treatment in any of the test clinical groups.

On pooling together the data obtained from all patients with reactions into Type 1 upgrading group, Type 1 downgrading and Type 2 reaction groups, irrespective of primary disease classification, the mean SIL-2R level of Type 1 upgrading reaction appears higher than any of the other groups and is significant by the Students' '*t*' test. However, on weighted analysis by the abovementioned method(s), no statistical significance could be established.

Discussion

The SIL-2R molecule, 10 Kd less in size as compared to the alpha polypeptide subunit from which it is derived,[1] has been studied and characterized.[4,18] Although the 'potential' of this molecule in immune regulation is well recognized, studies in different diseases have yet to prove its role in down-regulating IL-2 mediated immunological responses. Furthermore, *in vitro* studies to establish requirements for production of SIL-2R[19–22] and

its affinity for IL-2,[4,23,24] though supportive of the above hypothesis, have failed to establish the exact mechanism or role SIL-2R plays in the immune pathways.

Reactions in leprosy continues to be a poorly delineated phenomenon, perhaps unparalleled by any other infectious disease. While it is a well-recognized clinical entity, with well accepted immunological and histopathological criterias,[12] the mechanisms are far from clear (why some patients develop reactions while others do not? What determines whether a patient with Type 1 reaction will upgrade or downgrade? What determines clinical subsidence of reaction?) and remain to be elucidated.

Though, from the results, no firm conclusion can be made regarding sex and age in reactions, indirect evidence that the clinical groups have an homogenous age representation, was obtained by the lack of significant age variation between the various groups.

SIL-2R values in the various test groups did not vary significantly from those obtained from the bacilliferous leprosy patients (without reaction), after detailed weighted analysis of the individual groups. BT patients (not having reaction) were all paucibacillary and had significantly lower SIL-2R ($p < 0{\cdot}05$). On pooling the data to form larger groups of patients with Type 1 (downgrading) or (upgrading), and Type 2 (ENL) reactions, Students' '*t*' test revealed significantly higher levels of SIL-2R receptors in Type 1 upgrading reaction, both before and after treatment, as compared to all the other groups (with or without reactions). Interestingly, Tung *et al.*[6] had highlighted similar findings earlier, in their maiden report. The apparent higher values in Type 1 upgrading reactions are not borne out by statistical analysis, due to large variation in individual SIL-2R readings relative to the sample sizes giving large standard deviation. However, it is tempting to speculate that the apparent difference of higher SIL-2R levels, between Type 1 upgrading reaction and other forms of reaction, is due to its unique immunopathogenesis.

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The lack of significant differences in the test groups before and after treatment until clinical remission (some with corticosteroids) is intriguing, and is contrary to an earlier report of precipitous fall in SIL-2R levels following corticosteroid therapy.[6] It would appear that SIL-2R levels remain unaffected by corticosteroids, even in Type 1 reactions, a finding identical to that of Scollard *et al*,[25] in suction induced blisters, over representative skin lesions.

It is now known that SIL-2Rs are secreted in a wide variety of clinical and laboratory situations.[1–3, 5–7, 20,22] Furthermore, all cells which manifest receptors for IL-2 are potential

'secretors' of SIL-2R.[19] Though SIL-2R binds IL-2 efficiently, this bindings is of low affinity and considerably high concentrations would be necessary for it to significantly block the action of IL-2, and cause down-regulation of IL-2 mediated responses. These levels are reportedly not obtained *in vitro* but may occur transiently *in vivo*, at least near the site of release.[24] However, the contradictory finding of reduced SIL-2R after immunotherapy for allergy,[26] may support the view that SIL-2Rs are a 'non-specific' secretory 'by-product' of intrinsic down-regulation by immunocompetent cells, following any alteration in a state of immunological 'balance'.[1]

In leprosy, reactions are an accepted manifestation of acute immunological 'imbalance', with changes in CD4+ cell activity and/or numbers.[25] Raised SIL-2R values in reactions should then reflect the immunological instability. The lack of significant variation obtained perhaps underscores the inherent unstable immunity in patients manifesting leprosy *per se*. Further, the lack of change in SIL-2R levels following treatment and clinical subsidence of reaction points towards the absence of any role of SIL-2Rs in 'stabilizing' the immunological 'imbalance' that exists in these states.

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Récepteurs solubles interleukine-2: les types de lèpre et les réactions pendant et après le type 1 (lepra) et le type 2 (ENL)

V N Sehgal, S N Bhattacharya, Y Shah, V K Sharma et C K Gupta

Resumé Vingt-cinq patients présentant des réactions de type 1 (lepra) et de type 2 (ENL) firent l'objet d'un essai (SIL-2R dans du sérum) avant et après le traitement de leurs symptômes aigus et les résultats furent comparés avec ceux de 10 adultes sains normaux et 20 patients souffrant de lèpre *per se*. La classification de chaque sujet en différents groupes de lèpre et en différents types et sous-types de réactions fut fait selon des critères normaux avant le début de l'étude. Les évaluations statistiques détaillées des données révèlent des niveaux considérablement plus élevés de SIL-2R chez tous les lépreux comparés aux groupes témoins normaux, les groupes pluribacillaires ayant des niveaux plus élevés que les groupes paucibacillaires. Les récepteurs SIL 2Rs apparaissent en nombre plus élevé dans la réaction plus poussée de type 1 que dans les autres réactions quoique leur signification sur le plan statistique ne soit pas importante.

Les niveaux n'avaient pas fort changé à la suite d'un traitement ou d'une rémission clinique.

Receptores solubles de interleucina-2: niveles en la lepra y, durante y después de las reacciones tipo 1 (lepra) y tipo 2 (ENL)

V N Sehgal, S N Bhattacharya, Y Shah, V K Sharma y C K Gupta

Resumen Veinticinco pacientes con reacciones tipo 1 (lepra) y tipo 2 (ENL) fueron estudiados por SIL-2R en suero, antes y después del tratamiento de su condición aguda y los resultados se compararon con 10 adultos de salud normal y con 20 pacientes con lepra *per se*. Le classificación de cada sujeto en diferentes grupos de leprosos, y en varios tipos y subtipos de reacciones fue hecha de acuerdo a criterios estándar, previo a la inducción en el estudio. La evaluación estadística detallada de los datos reveló niveles elevados significativos de SIL-2R en todos los pacientes leprosos, comparados con los controles normales, con niveles más elevados en los grupos multibacilares comparado con el grupo paucibacilar. Los SIL-2R aparecieron más elevados en la reacción tipo 1 mejorada que en las otras formas de reacción, aunque esto no fue estadísticamente significativo.

No hubo cambios significativos en los niveles posteriormente al tratamiento y remisión clinica.

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Does Convit vaccine (BCG + *Mycobacterium leprae*) afford protection against biochemical changes in renal brush border membrane in experimental leprosy?

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Summary Renal functional status in *Mycobacterium leprae* infected mice can be best studied by examining the enzymatic status of brush border membrane vesicles from proximal convoluted tubule. The role of vaccination in modulation of the renal status brought by the disease has been studied using this technique. The characteristic marker enzymes of renal brush border membrane—namely alkaline phosphatase, leucine aminopeptidase and γ-glutamyl transpeptidase decreased significantly ($p < 0{\cdot}01$) in due course in *M. leprae* infection over a period of 9 months. The combined vaccine (BCG + *M. leprae*) may have a protective effect on renal abnormalities only in the initial stages of infection as indicated by a significant rise in enzymatic levels. However, no significant ($p > 0{\cdot}05$) protective effect of vaccine was found in a more advanced disease state after 9 months in infected mice.

Introduction

Renal involvement is a frequent finding in leprosy.[1–3] A number of trials of vaccination have been conducted in humans[4,5] to assess its protective value in the disease. Significant rates of skin test conversions have been reported 3 months after vaccination with BCG alone and with two consecutive doses of killed *Mycobacterium leprae* with or without BCG.[6] Vaccination studies have also been carried out in animal models of leprosy particularly in mice[4,7,8] since this animal can be easily obtained and handled.

Earlier studies elucidated the histopathological and immunological status of the kidneys in leprosy subjects.[9,11] These criteria do not in themselves explain the complete renal pathogenesis or indicate the state of infection at which the renal impairment actually starts; these parameters also do not pick up damage at the cytochemical level. In a recent

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study, significant enzymuria was detected in untreated multibacillary leprosy patients[12] which may reflect the level and extent of renal damage. We planned to study the onset and alterations in renal brush border membrane (BBM) enzymes also in a mouse model of leprosy at different time periods of experimental infection. It may be possible also to examine the role of vaccination in the modulation of renal impairment in the mouse model using renal BBM enzymes as the biochemical markers for the detection of insult to kidneys.

Materials and methods

SOURCE OF *M. LEPRAE*

The *M. leprae* were isolated from skin biopsies taken from lepromatous leprosy patients with a BI ranging from 4+ to 6+ and a MI of more than 1%. The bacteria were counted and an inoculation of 1×10^4 acid fast bacilli (AFB) was used for mouse footpad infection.

MICE

Outbred lacca strain of Swiss albino mice each weighing 20–25 gm (3–4 weeks old) were used for the study.

VACCINATION

The vaccine preparation was made by mixing BCG (BCG, Vaccine Laboratory, Guindy, Madras) and armadillo derived *M. leprae* (Dr R J W Rees, Immunology of Leprosy (IMMLEP) Bank) at the concentration of 1×10^5 and 3×10^6 AFB per mouse, respectively.[4,14]

IMMUNIZATION OF MICE

Each mouse was injected subcutaneously with 30 μl of vaccine preparation in the left hind footpad. Three weeks later a booster dose of the vaccine was injected using 10 times diluted mixed vaccine preparation.[15] A week later, the mice were given *M. leprae* infected in the right hind footpad subcutaneously.[4] Control animals received 30 μl of normal saline injections simultaneously. The animals were thus challenged with *M. leprae* 4 weeks after the primary vaccination dose.

LEPROSY

Leprosy infection was assessed by the footpad bacterial counts[16] at different time intervals ranging from 0 to 9 months during the course of infection.

EXPERIMENTAL DESIGN

A total of 150 Swiss albino mice (lacca strain) obtained from the central animal house of

the Postgraduate Institute of Medical Education and Research, Chandigarh, India, were divided into the following three groups:

(i) NC (normal controls);
(ii) NIC (normal infected controls);
(iii) NIV (normal infected and vaccinated).

PREPARATION OF BRUSH BORDER MEMBRANE VESICLES (BBMV)

The BBMV from the renal cortex were prepared by the method of Malathi[17] and the quality was checked as described by Turner & Moran.[18]

ENZYME ASSAY

Alkaline phosphatase was assayed by the method of Bergmeyer,[19] leucine aminopeptidase was assayed by the method of Goldberg & Rutenberg.[20] The method of Naftalin[21] was used to determine the activity of γ-glutamyl transpeptidase. The substrate concentration was standardized and used for each enzyme assay throughout the study. One enzyme unit is defined as μ mole of substrate hydrolysed per minute per mg protein under standard assay conditions and the enzymatic activities are expressed as Mean $\pm$ SD. Protein was estimated by the method of Lowry.[22]

Results

The BBMV prepared from the renal cortex of *M. leprae* infected mice were employed for the assessment of kidney function during the course of experimental leprosy and the role of vaccination in preventing/reverting the impairment caused by the infective agent. The normal infected (NIC) and vaccinated (NIV) groups were compared with the NC group. The hydrolytic enzymes characteristic of BBM studied included alkaline phosphatase (AP), leucine aminopeptidase (LAP) and γ-glutamyl transpeptidase (γGT).

The activities of alkaline phosphatase estimated from the BBMV from vaccinated (NIV) and infected (NIC) groups of mice were compared with controls (NC) as given in Figure 1. No significant difference in enzymatic activities was found between the groups at zero time. However, a significant decrease ($p < 0{\cdot}01$) in enzymatic activity was found at 1 month in the NIC group, the fall was more pronounced from 3 to 9 months post-infection when compared with the NC group. The NIV group of mice showed a significant rise ($p < 0{\cdot}001$) in the enzymatic activity compared to the NIC group at 1 month post-infection and this increase persisted up to a 3 month period of infection. However, after 6 months of infection, there was no significant ($p > 0{\cdot}05$) difference between NIV and NIC groups. In the 9 month post-infection group, there was a significant fall ($p < 0{\cdot}01$) in enzymatic activity both in the infected (NIC) and vaccinated (NIV) groups when compared with the control group (NC).

Figure 2 depicts the activities of leucine aminopeptidase in vesicle preparations from the three groups of animals described earlier. Here also there was a significant fall in the enzymatic activity after 1 month of infection to 9 months post-infection (NIC group), whereas the enzymatic activities in the BBMV of NIV group were significantly increased

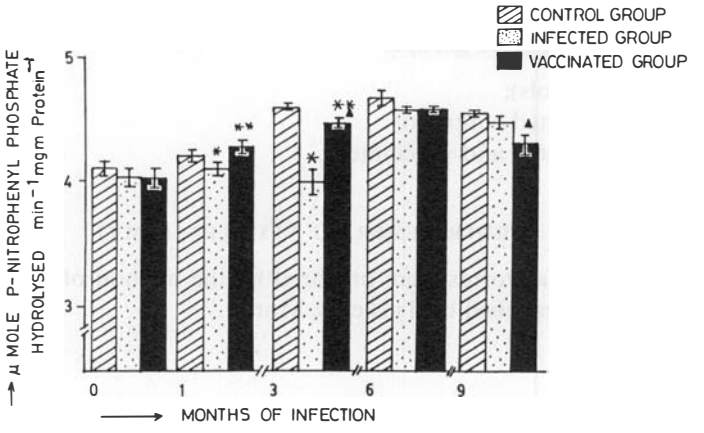

Figure 1. Activities of alkaline phosphatase in control, infected and infected-vaccinated groups of mice killed at 0, 1, 3, 6 and 9 month intervals. Values are represented as Mean ± SD. The level of significance is *, $p < 0{\cdot}001$ control *vs* infected group; **, $p < 0{\cdot}001$ infected *vs* infected-vaccinated group; *, $p < 0{\cdot}001$ control *vs* infected-vaccinated group.

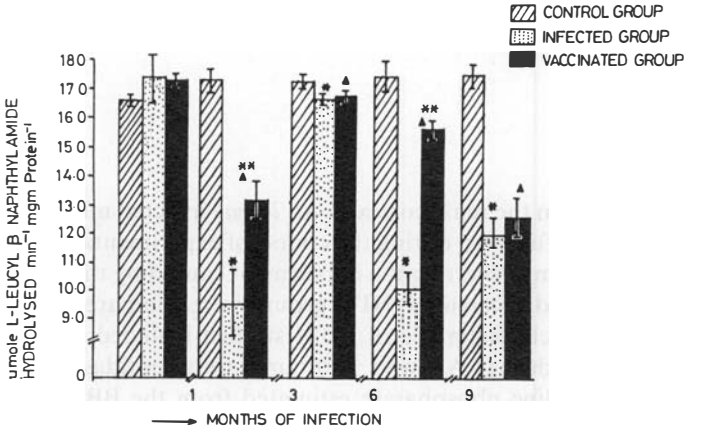

Figure 2. Activities of leucine aminopeptidase in the control, infected and infected-vaccinated groups of mice sacrificed at 0, 1, 3, 6 and 9 month intervals. Values are represented as Mean ± SD. The level of significance is: *, $p < 0{\cdot}001$ control *vs* infected group; **, $p < 0{\cdot}001$ infected *vs* infected-vaccinated group; †, $p < 0{\cdot}001$ control *vs* infected-vaccinated group.

after 1 to 6 months post-infection. At 3 months and 9 months post-infection, no significant difference ($p < 0{\cdot}05$) was found between the NIC and NIV vaccinated group of animals.

Figure 3 demonstrates the activities of γ-glutamyl transpeptidase in vesicle preparations of the three groups. A similar pattern was observed with this enzyme also, i.e. a significant fall in the activity occurred following *M. leprae* infection up to 9 months post-infection in comparison to control animals. A significant rise ($p < 0{\cdot}01$) in the enzymatic activity in the vaccinated group in comparison to NIC group was seen. It is evident from Figure 3 that there is no significant difference ($p > 0{\cdot}05$) between the vaccinated group and

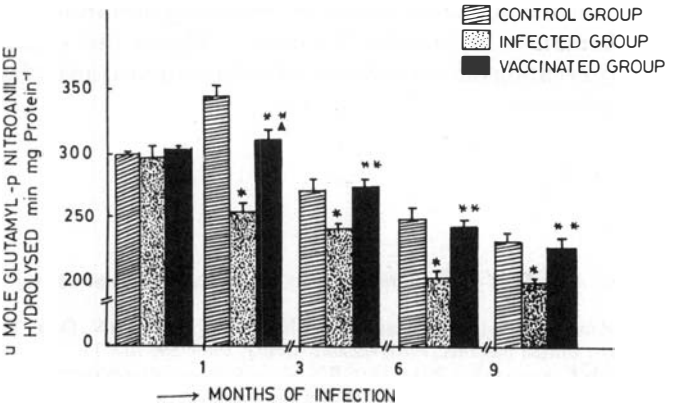

Figure 3. Activities of γ-glutamyl transpeptidase in the control, infected and infected-vaccinated groups of mice sacrificed at 0, 1, 3, 6 and 9 month intervals. Values are represented as Mean ± SD. The level of significance is: *, $p < 0{\cdot}001$ control *vs* infected group; **, $p < 0{\cdot}001$ infected *vs* infected-vaccinated group; †, $p < 0{\cdot}001$ control *vs* infected-vaccinated group.

control group at 3 months and the post-infected group followed up to 9 months, an indication of the protective effect of the vaccination during the study period.

Discussion

Laboratory animals, as experimental models of diseases, can be used for the early detection of the onset of the disease. Accepted markers of disease are abberations in the histopathological and immunological parameters, but reflect the disease process at a very advanced stage. Complete renal structural and functional status cannot thus be evaluated by the existing parameters. Establishment of biochemical parameters for the early detection of the disease would be appropriate. It has been found that BBM enzymes are altered much earlier during the disease compared to histopathological alterations and hence can be used as markers for the early detection of the disease. The BBMV can also be used for the study of the role of vaccination in modulation of the renal status brought about by the disease.

A significant fall in the enzymatic activities of all three BBM enzymes during the course of experimental *M. leprae* infection in mice from 1 to 9 months is an indication of gradual damage of the renal proximal tubule membrane compared to the control group of animals. These observations are in agreement with the earlier histopathological,[11,23] immunological[10,24] and functional alterations[11,25] in the kidneys in human subjects.

The significant difference in the activity of the enzymes studied in NIC and NIV groups may have the following implications: the biochemical alterations across renal BBM are specific to *M. leprae* infection as these could be reversed by giving the vaccination mixture of BCG and *M. leprae*. The vaccination may have a protective effect on the renal impairment brought about by leprosy only in the initial stages and no significant protective effect was found in the advanced disease state in the 9-month infected group of animals. It is likely that the combined BCG and *M. leprae* vaccine

prevents the formation of immune complexes by disturbing the ratio of antigen : antibody required for the formation of immune complexes. Hence the vaccine may have a preliminary role in preventing the immune complex deposition at an initial stage when the antigen load is not in excess.

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Le vaccin convit (BCG + *Mycobacterium leprae*) offre-t-il une protection contre les changements biochimiques de la bordure en brosse de la membrane rénale dans le cas de la lèpre expérimentale?

M Kohli, N K Ganguly, S Kaur, K S Chugh, V K Sharma et S R Bhushnurmath

Résumé La meilleure méthode d'examen de la fonction rénale des souris infectées par le Mycobacterium leprae est d'étudier l'état enzymatique des vésicules du bord en brosse de la membrane du tube contourné proximal rénal. Cette technique a été utilisée pour déterminer le rôle de la vaccination dans la modulation de la fonction rénale atteinte par la maladie. Les enzymes marqueuses caractéristiques de la membrane à bord en brosse à savoir la phosphatase alcaline, la leucine-aminopeptidase et la gamma-glutamyl transpeptidase avaient fort baissé ($p < 0,01$) après un certain temps dans le cas d'une infection causée par le *M. leprae*, au cours d'une période de 9 mois. Le vaccin combiné (BCG + *M. leprae*) peut avoir une action protectrice contre les anomalies rénales uniquement en début d'infection comme l'indique l'elévation importante du nombre d'enzymes. Cependant, chez les souris infectées, le vaccin n'avait aucun effect protecteur notable ($p > 0,05$) 9 mois plus tard, lorsque la maladie avait évolué.

¿Puede dar protección la vacuna Convit (BCG + *Mycobacterium leprae*) en contre de los cambios bioquimicos en la membrana renal de borde en cepillo en la lepra experimental?

M Kohli, N K Ganguly, S Kaur, K S Chugh, V K Sharma y S R Bhushnurmath

Resumen El estado funcional renal en los ratones infectados con *Mycobacterium leprae* puede ser mejor estudiado examinando el estado enzimático de las vesículas de la membrana de borde en cepillo del túbulo contorneado proximal. Se ha estudiado, usando esta técnica, el papel que juega la vacuna en la modulación del estado renal ocasionado por la enfermedad. Las enzimas marcadoras características de la membrana renal de borde en cepillo, llamadas fosfatasa alcalina, leucina aminopeptidasa y gamma-glutamil transpeptidasa disminuyeron significativamente ($p < 0,01$) en debido curso en la infección con *M. leprae* durante un período de 9 meses. La vacuna combinada (BCG + *M. leprae*) puede que tenga un efecto protector sobre las anormalidades renales solamente en las etapas iniciales de la infección indicado por un aumento significativo de los niveles enzimáticos. Sin embargo, no se encontró un efecto protector significativo ($p > 0,05$) de la vacuna en estados de enfermedad más avanzados después de 9 meses en ratones infectados.

Lepr Rev (1991) **62,** 276–279

The susceptibility testing of 13 strains of *Mycobacterium leprae* to rifampicin and the determination of minimal effective dosage

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Summary By use of the mouse footpad technique, the susceptibility testing of 13 strains of *Mycobacterium leprae* to rifampicin (RFP) and the determination of minimal effective dosage (MED) were carried out. Among these strains of *M. leprae*, 8 were obtained from previously untreated multibacillary leprosy patients and 5 from relapsed leprosy patients without using RFP previously. The results showed that the MED of all strains to RFP were $\leqslant 0{\cdot}001\%$ FRP in the diet, 5 strains being equal to 0·001%, $5 \leqslant 0{\cdot}0001\%$, $2 \geqslant 0{\cdot}0003\%$ and $1 \leqslant 0{\cdot}0003\%$. The results indicated that the MED value of RFP could be lower than that of other reports. Because the critical concentration of RFP for assessment of RFP-resistant strains is not well established a further study would be worthwhile. The results of the determination of sera RFP concentrations in mice administered the RFP diet were identical with that of Holmes' report. Five of the 13 strains also showed that the growth of bacilli were suppressed by 10 mg/kg RFP using the gavage method.

Introduction

Since Opromolla firstly used rifampicin (RFP) to treat patients in 1963, the bactericidal activity of RFP for *M. leprae* was confirmed by many researchers.[1–3] So far this drug has been used for leprosy in almost every country. With the development of the mouse footpad technique, it has become possible to estimate the minimal effective dosage (MED) of this drug. However, the critical concentration of RFP is not as well established as that of dapsone (DDS),[4] so that the finding of RFP-resistance could be very difficult, particularly low degree resistance. For studying the sensitivity of *M. leprae* to RFP and the determination of MED suppressing *M. leprae* growth, we collected 13 strains of *M. leprae* from the skin lesions of patients with multibacillary leprosy in leprosaria. This paper reports the activity of RFP against these strains of *M. leprae* and MED in the experiments of mouse footpad.

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Materials and methods

SOURCE OF *M. LEPRAE*

A total of 13 strains of *M. leprae* were isolated, of which 8 strains were obtained from previously untreated multibacillary leprosy patients and 5 from relapsed leprosy patients without using RFP previously. The specimens were taken by skin biopsy or by the scrape method.

MOUSE FOOTPAD TECHNIQUE

The mouse footpad technique for drug susceptibility testing was as described previously.[5,6] The CFW-strain mice were used in all studies. Inoculation of $1{\cdot}0 \times 10^4$ in both hind footpads was employed. For each of the strains one group of $10 \sim 12$ mice served as untreated control and groups treated ($6 \sim 8$ mice each) were divided into groups of 0·003, 0·001, 0·0003 and 0·0001% RFP per 100 g diet. At the same time 5 out of the 13 patient strains were also taken up with 10 mg/kg RFP once a week by gavage. The drugs were given by the continuous administration method. In the untreated control group *M. leprae* from both rear footpads were harvested at $5 \sim 6$ months after inoculation, at intervals of 1–2 months, until the average number of bacilli per footpad was observed to be at least 5×10^5. At this time the remaining control mice and all treated mice were killed and harvested. Some experiments were observed for 12 months after inoculation.

DETERMINATION OF SERUM RFP CONCENTRATIONS IN SOME GROUPS OF MICE

Estimation of the concentrations of RFP in the sera of some groups of treated mice was done. The method of determination was described previously by Holmes & Hilson using an agar diffusion technique for microbiological assay.[7]

Results

The results of RFP susceptibility testing and minimal effective dosage in 13 strains of *M. leprae* are summarized in Table 1. The results showed that the MED of all strains to RFP were $\leqslant 0{\cdot}001\%$ RFP diet, including 5 strains being equal to 0·001%, $5 \leqslant 0{\cdot}0001\%$, $2 \geqslant 0{\cdot}0003\%$ and $1 \leqslant 0{\cdot}0003\%$. Five strains of *M. leprae* (patient strain Nos 7, 8, 11, 12 and 13) investigated were also suppressed by 10 mg/kg RFP dosage once a week by gavage in the experiments. The concentrations of RFP in the sera of mice receiving 0·001, 0·003% RFP diet were $0{\cdot}13 \sim 0{\cdot}38$ μg/ml and $0{\cdot}5 \sim 1{\cdot}6$ μg/ml. The average level of RFP concentration was 0·21 μg/ml and 0·87 μg/ml respectively.

Discussion

The first publication by Jacobson & Hastings[8] reported a case of a RFP-resistant leprosy patient treated with RFP alone. The evidence was obtained by experiment of mouse footpads. The strain of the *M. leprae* inoculated grew in the footpads of mice which were given 0·001, 0·01 and 0·03% RFP in the diet. However the organism was inhibited in the

Table 1. RFP-susceptibility test and MED in 13 strains of *M. leprae*

Patient strain No.	RFP in the mouse diet (g%)					RFP (*gavage*) 10 mg/kg	MED (g/100g)
	0	0·0001	0·0003	0·001	0·003		
1	8/8*	6/8	4/7	0/6	0/6	ND	0·001
2	8/8	3/6	4/6	0/6	0/7	ND	0·001
3	8/8	0/8	0/6	0/6	0/6	ND	⩽0·0001
4	8/8	0/6	0/6	0/6	0/7	ND	⩽0·0001
5	11/11	6/8	6/8	0/8	0/6	ND	0·001
6	8/8	0/6	0/6	0/6	0/6	ND	⩽0·0001
7	10/10	3/6	ND	0/6	0/6	0/8	⩾0·0003
8	7/7	0/6	0/6	0/7	0/6	0/8	⩽0·0001
9	10/10	5/5	4/8	0/7	0/7	ND	0·001
10	8/10	0/8	0/6	0/8	0/6	ND	⩽0·0001
11	7/8	7/8	4/6	0/7	0/6	0/8	0·001
12	7/8	ND	0/7	0/7	0/6	0/6	⩽0·0003
13	10/10	6/8	ND	0/8	0/8	0/6	⩾0·0003

Multiplication of *M. leprae*: $\geqslant 10^5$ *M. leprae* per footpad.
* No. mice showing multiplication of *M. leprae*. No. mice harvested.
ND, not done.

mice administered 0·06% RFP diet. As the critical concentration of RFP was not well established, detecting low degree resistance of *M. leprae* was directly influenced. The MED values of RFP reported by experts are variable. Rees *et al.*[9] showed that 5 strains of *M. leprae* were suppressed by 0·0025% RFP diet. Holmes & Hilson reported 3 strains to MED of RFP, in which 2 strains were 0·001% and one strain was 0·0003%, they suggested that 0·001% RFP was the available value for measurement of RFP-resistant organism. Thereafter, Holmes[10] also reported results of RFP MED for 8 strains of *M. leprae* which were taken from previously untreated lepromatous leprosy patients. Six of the 8 strains were suppressed by 0·001% RFP in the diet, the remaining 2 strains were 0·0003% and 0·003% RFP. Devasundaram *et al*[11] presented that the growth of several strains were inhibited by 0·001% RFP diet, but some strains were not. A report[12] in China showed that the growth of *M. leprae* in the footpads of mice was suppressed by 0·0001% RFP in the diet, and 0·001% RFP exhibited significantly bactericidal activity. The results mentioned above were similar to ours which indicated that MED of RFP for all 13 strains of *M. leprae* were ⩽0·001% and the majority of these strains were <0·001%. It is possible that MED level of RFP was lower than that of other countries. In addition, 5 of the 13 strains were also inhibited by 10 mg/kg RFP (equal to 0·0005% RFP) once a week by gavage. Shepard[2] reported that no antileprosy activity to 0·001 and 0·0001% RFP for *M. leprae* were observed. However, the bactericidal action was found using 0·01% RFP in the diet. Guelpa-Lauras *et al.*[13] reported 9 cases of RFP-resistant leprosy. The evidence was obtained by experiments of mouse footpad, which multiplication of *M. leprae* were found in mice administered 10 mg/kg RFP once a week by gavage. The data mentioned above suggested the MED values of RFP differ among the reports.

The studies have been performed to determine sera RFP concentrations in some groups of treated mice infected with *M. leprae*, the results were similar to that of Holmes' report, which showed that the RFP concentrations in the diet were correct.

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Etude de la sensibilité de 13 souches du bacille de Hansen *Mycobacterium leprae* à la rifampicine et détermination d'une dose minimale efficace.

WANG HEYING, LI WENZHONG, YE GANYUN, YU LINCHONG ET SHI MEIQIN

Résumé Une étude de sensibilité à la rifampicine (RFP) de 13 souches du *Mycobacterium leprae* fut menée sur le coussinet plantaire de la souris ainsi que la détermination d'une dose minimale efficace (MED). Parmi ces souches du *M. leprae*, 8 furent obtenues de patients pluribacillaires non traités précédemment et 5 de lépreux récidivant qui n'avaient pas été traités à la RFP. Les résultats ont prouvé que la MED de toutes les souches sensibles à la RFP étaient $\leqslant 0{,}001\%$ de RFP dans l'alimentation, 5 souches étant égales à 0,001%, $5 \leqslant 0{,}0001\%$, $2 \geqslant 0{,}0003\%$ et $1 \leqslant 0{,}0003\%$. Les résultats indiquaient que la valeur de la MED de la RFP pouvait être inférieure à celle indiquée dans d'autres rapports. Etant donné que la concentration critique de RFP permettant d'évaluer les souches résistantes à la RFP n'est pas bien connue, une autre étude s'avèrerait utile. Les résultats de la détermination des concentrations de sérums RFP chez les souris ayant reçu un régime de RFP étaient identiques à ceux du rapport de Holmes. Une élévation du nombre des bacilles avait été supprimée dans 5 des 13 souches en administrant 10 mg/kg de RFP par gavage.

El test de susceptibilidad de 13 cepas de *Mycobacterium leprae* a la rifampicina y la determinación de la dosificación efectiva mínima.

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Resumen Se llevó a cabo el test de la susceptibilidad a la rifampicina (RFP) y la determinación de la dosificación efectiva mínima (MED) en 13 cepas de *Mycobacterium leprae* mediante el uso de la técnica del cojincillo del pié de ratón. Entre estas cepas de *M. leprae*, 8 fueron obtenidas de pacientes leprosos multibacilares no tratados previamente y 5 de pacientes leprosos con recaída sin haber usado RFP previamente. Los resultados mostraron que la MED de todas las cepas a RFP fue de $\leqslant 0{,}001\%$ de RFP en la dieta, 5 cepas siendo iguales a 0,001%, $5 \leqslant 0{,}0001\%$, $2 \geqslant 0{,}0003\%$ y $1 \leqslant 0{,}0003\%$. Los resultados indicaron que el valor de MED de RFP sería menor que lo informado por otros trabajos. Debido a la concentración crítica de RFP para la valoración de las cepas resistentes a RFP no está bien establecido si vale la pena un estudio posterior. Los resultados de la determinación de las concentraciones de RFP en el suero en ratones administrados con dieta con RFP fueron idénticos a aquellos informados por Holmes. Cinco de las 13 cepas mostraron también que el crecimiento de los bacilos fue detenido con 10 mg/kg de RFP usando el método de gavaje.

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The activity of rifabutin against *Mycobacterium leprae*

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Summary Minimal effective doses of rifabutin and rifampicin were determined in *Mycobacterium leprae* isolated from skin biopsies of newly diagnosed, previously untreated lepromatous leprosy patients. Rifabutin was more potent than rifampicin. Our previous report that rifabutin was fully active against rifampicin-resistant *M. leprae* could not be confirmed. Examination of two strains of rifampicin-resistant *M. leprae* from elsewhere, and a repeat experiment on our original strain of rifampicin-resistant bacilli, showed full cross-resistance between rifampicin and rifabutin. A clinical trial in three newly diagnosed, previously untreated lepromatous patients showed that rifabutin has rapid bactericidal activity.

Introduction

Several members of the ansamycin group of antimicrobials have been found to be very active against *M. leprae*.[1–3] Rifampicin is the best known of this group and considerable experience in the use of this drug for the treatment of leprosy has accumulated in the past 15 years.[4] It is the only one of the antileprosy drugs currently available that is rapidly bactericidal for *M. leprae* and it is now considered a standard drug worldwide for the treatment of all types of leprosy in combination with other drugs.[5]

Rifabutin (LM427) is a newer member of the ansamycin group whose activity against *M. leprae* has been demonstrated in the mouse footpad and whose minimal effective dose is several times lower than that of rifampicin.[6] Rifabutin has been used extensively to treat *M. avium-intracellulare* infections in patients with acquired immune deficiency syndrome and it appears to be safe and well tolerated.[7]

We have extended our earlier studies of the minimal effective dose of rifabutin in mouse footpad infections with *M. leprae*,[1] further studied the activity of rifabutin against rifampicin-resistant *M. leprae* in mouse footpads,[6] and we undertook a small clinical trial of rifabutin to measure the rapidity of onset of its bactericidal activity against *M. leprae*.

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Materials and methods

DETERMINATIONS OF MINIMAL EFFECTIVE DOSES

Seven consecutive skin biopsies from patients with untreated lepromatous leprosy with a bacterial index (BI) of 4+ or greater and a morphological index (MI) of 1% or greater which were received for routine drug sensitivity studies were used for mouse footpad inoculations. The methods for inoculation, harvest, and bacterial enumerations were those of Shepard[8] and Shepard & McRae.[9] Dapsone (Sigma Chemical Co., St Louis, MO), clofazimine (Geigy, Buffalo Grove, IL), rifampicin (Sigma), and rifabutin (Farmitalia Carbo Erba, Milan, Italy) were mixed in powdered mouse food (Purina Mills, St Louis, MO) at the concentrations indicated and fed continuously. Diets were prepared fresh at weekly intervals and stored at 0–4°C. BALB/c mice were locally bred from breeding stock (Harlan Sprague Dawley, Indianapolis, IN, or Charles Rivers Breeding Labs, Wilmington, MA, or Bantin and Kingman, Fremont, CA), The animals had access to water *ad libitum*.

RIFABUTIN ACTIVITY AGAINST RIFAMPICIN-RESISTANT STRAINS OF *M. LEPRAE*

The activity of rifabutin was tested in continuous feeding experiments on three different occasions against rifampicin-resistant bacilli. In 1983 rifabutin was tested against a mouse footpad passaged strain of *M. leprae* (#3026) isolated originally in 1977 from a patient with rifampicin-resistant disease.[6] Additional mouse footpad passaged, rifampicin-resistant strains were shipped at 0–4°C as amputated mouse footpads from Paris to Carville from the laboratories of Drs Grosset and Guelpa-Lauras.[10] These strains grew in mice given rifampicin 10 mg/kg by gavage at weekly intervals. Finally the Carville passaged strain (#3026) was retested in 1986. The Carville strain had been passaged in mice continuously fed 0·01% w/w dietary rifampicin. We have tested well over 250 isolates of *M. leprae* from leprosy patients' skin biopsies for drug sensitivities in mouse footpad infections. With the exception of the cases of rifampicin resistance which we have reported,[6,11] all these isolates were completely inhibited by 0·01% dietary rifampicin prepared and administered as outlined above.

CLINICAL BACTERICIDAL ACTIVITY

After giving informed consent three male patients aged from 21 to 49 years with borderline lepromatous or lepromatous leprosy entered the study. All three patients had a BI of at least 4+ and a MI of 1% or more. All were new, previously untreated cases. The patients were hospitalized and all medications were given under supervision. Routine haematological studies, blood chemistries, and urinalysis were done prior to, and on days 2 and 14 of the study. Each patient had baseline skin smears from 12 sites and a skin biopsy for histopathology. Punch skin biopsies for baseline mouse footpad viability and drug sensitivities were performed and four repeat biopsies for mouse footpad viabilities (growth of bacilli detected within 12 months after a footpad inoculum of 5000 bacilli) were done on days 1, 3–6, 7 and 14 after beginning rifabutin. Baseline drug sensitivities were determined in mice fed 0·01%, 0·001% and 0·0001% dapsone, 0·001% clofazimine, 0·01% rifampicin and 0·001%, 0·003%, 0·0001% and 0·00003% rifabutin.

Two patients were given rifabutin 300 mg daily for 14 days and the third patient was given a single dose of 300 mg on day 1 of the study. The rifabutin doses were given without regard for meals since meals do not appear to affect the drug's absorption.[7]

Results

DETERMINATIONS OF MINIMAL EFFECTIVE DOSE

The results from 7 consecutive isolates of *M. leprae* are summarized in Table 1. The minimal effective dose of rifampicin varied from 0·001% to less than 0·00003% w/w in the diet and that of rifabutin varied from 0·0001% to less than 0·00003%. In the isolates which permit comparison, rifabutin seems to be at least 3-fold more potent than rifampicin in mice.

RIFABUTIN ACTIVITY AGAINST RIFAMPICIN-RESISTANT STRAINS OF *M. LEPRAE*

In 1984 we reported that rifampicin-resistant *M. leprae* strain #3026 grew in mice fed 0·01% dietary rifampicin but no growth was seen in mice receiving rifabutin 0·001% to 0·00003% in the diets.[6] This strain was inoculated into mice on 26 July 1983 for this experiment. The bacilli had been passaged in mice continuously fed 0·01% w/w dietary rifampicin since November 1978. They had been passaged in drug-free mice from January 1977 to November 1978. The details of the results of this experiment in 1983 are given in

Table 1. Minimal effective doses of rifampicin and rifabutin against *M. leprae* in mice. Values are the number of acid-fast bacilli per footpad counted as a pool of four footpads

Treatment (continuous)	Isolate						
	B3651	B3657	SI24	SI26	H59	B3661	B2448
Controls	$6{\cdot}12 \times 10^5$	$7{\cdot}56 \times 10^5$	$7{\cdot}97 \times 10^5$	$6{\cdot}20 \times 10^5$	$6{\cdot}04 \times 10^5$	$1{\cdot}09 \times 10^6$	$6{\cdot}43 \times 10^5$
Dapsone (%)							
0·01	N.G.*	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
0·001	$7{\cdot}77 \times 10^4$	N.G.	N.G.	N.G.	N.G.	N.G.	$5{\cdot}52 \times 10^5$
0·0001	$2{\cdot}87 \times 10^4$	N.G.	N.G.	N.G.	$3{\cdot}60 \times 10^4$	N.G.	$9{\cdot}16 \times 10^5$
Clofazimine (%)							
0·001	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
Rifampicin (%)							
0·01	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
0·001	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
0·0001	$1{\cdot}44 \times 10^5$	$2{\cdot}00 \times 10^4$	N.G.	N.G.	$5{\cdot}44 \times 10^5$	N.G.	N.G.
0·000,03	$1{\cdot}76 \times 10^5$	$1{\cdot}60 \times 10^4$	N.G.	N.G.	$8{\cdot}58 \times 10^5$	N.G.	N.G.
Rifabutin (%)							
0·001	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
0·0003	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
0·0001	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.	N.G.
0·000,03	$7{\cdot}75 \times 10^5$	N.G.	N.G.	N.G.	$6{\cdot}72 \times 10^5$	N.G.	N.G.

* N.G. = No growth detected.

Table 2. The activity of rifabutin against rifampicin-resistant *M. leprae* strain No. 3026 inoculated in 1983*[6]

Treatment (continuous)	No.+/ Total	AFB/Footpad ($\times \pm$SEM)‡
Controls	6/6	$8{\cdot}34\ (\pm 0{\cdot}65) \times 10^5$
Rifampicin (%)		
0·01	6/6	$1{\cdot}76\ (\pm 0{\cdot}46) \times 10^5$
0·001	2/5	$1{\cdot}92\ (\pm 1{\cdot}27) \times 10^5$
0·0001	5/6	$3{\cdot}07\ (\pm 0{\cdot}87) \times 10^5$
0·000,03	5/6	$1{\cdot}89\ (\pm 0{\cdot}16) \times 10^5$
Rifabutin (%)		
0·001	0/6	$< 1{\cdot}6 \times 10^4$
0·0003	0/6	$< 1{\cdot}6 \times 10^4$
0·0001	0/6	$< 1{\cdot}6 \times 10^4$
0·000,03	0/6	$< 1{\cdot}6 \times 10^4$

* Inoculated 7/26/83, harvested 2/10/84.
‡ Means of positive footpads only.

Table 3. The activity of rifabutin against rifampicin-resistant *M. leprae* strains No. 83004 and No. 82026 from Drs Grosset and Guelpa-Lauras

Treatment (continuous)	Isolate			
	No. 83004*		No. 82026†	
	No.+/Total	AFB/Footpad ($\times \pm$SEM)‡	No.+/Total	AFB/Footpad ($\times \pm$SEM)
Controls	5/6	$2{\cdot}39\ (\pm 0{\cdot}46) \times 10^5$	5/6	$6{\cdot}18\ (\pm 2{\cdot}16) \times 10^5$
Dapsone				
0·01	0/6	$< 1{\cdot}6 \times 10^4$	0/6	$< 1{\cdot}6 \times 10^4$
0·001	6/6	$2{\cdot}59\ (\pm 0{\cdot}57) \times 10^5$	6/6	$1{\cdot}81\ (\pm 0{\cdot}79) \times 10^5$
0·0001	6/6	$5{\cdot}94\ (\pm 0{\cdot}95) \times 10^5$	6/6	$7{\cdot}34\ (\pm 1{\cdot}29) \times 10^5$
Clofazimine (%)				
0·001	0/6	$< 1{\cdot}6 \times 10^4$	0/6	$< 1{\cdot}6 \times 10^4$
Rifampicin (%)				
0·01	6/6	$9{\cdot}53\ (\pm 2{\cdot}72) \times 10^5$	6/6	$1{\cdot}79\ (\pm 0{\cdot}74) \times 10^5$
0·001	4/6	$5{\cdot}26\ (\pm 1{\cdot}93) \times 10^5$	6/6	$1{\cdot}31\ (\pm 0{\cdot}13) \times 10^6$
0·0001	6/6	$9{\cdot}35\ (\pm 2{\cdot}50) \times 10^5$	6/6	$1{\cdot}49\ (\pm 0{\cdot}18) \times 10^6$
0·000,03	6/6	$1{\cdot}05\ (\pm 0{\cdot}22) \times 10^6$	6/6	$2{\cdot}74\ (\pm 0{\cdot}49) \times 10^6$
Rifabutin (%)				
0·001	6/6	$3{\cdot}86\ (\pm 1{\cdot}37) \times 10^5$	6/6	$3{\cdot}71\ (\pm 0{\cdot}86) \times 10^5$
0·0003	6/6	$4{\cdot}58\ (\pm 1{\cdot}34) \times 10^5$	6/6	$2{\cdot}29\ (\pm 0{\cdot}82) \times 10^5$
0·0001	6/6	$8{\cdot}41\ (\pm 1{\cdot}93) \times 10^5$	6/6	$1{\cdot}04\ (\pm 0{\cdot}13) \times 10^6$
0·000,03	6/6	$4{\cdot}10\ (\pm 1{\cdot}51) \times 10^5$	6/6	$1{\cdot}71\ (\pm 0{\cdot}17) \times 10^6$

* Inoculated 3 February 1986, harvested 19 November 1986.
† Inoculated 3 February 1986, harvested 8 January 1987.
‡ Means of positive footpads only.

Table 2. Our interpretation of these results was that rifabutin was fully active against this rifampicin-resistant strain of *M. leprae*.

On 28 August 1985 we received two *M. leprae* strains from Drs Grosset and Guelpa-Lauras which had been found to be rifampicin-resistant in their laboratory.[10] Unfortunately these two strains (#82061 and #82073) did not grow in our control mice, presumably due to loss of viability during shipment. A further shipment was received on 30 January 1986. These strains (#83004 and #82026) were viable and were tested against various doses of dapsone, clofazimine, rifampicin, and rifabutin. The results are presented in Table 3. Clearly there was full cross-resistance between rifampicin and rifabutin in these two strains of *M. leprae*.

We then re-examined our strain #3026 which had remained in passage in mice continuously fed 0·01% w/w dietary rifampicin. The mice were inoculated on 1 December 1986 when the results with strain #83004 became available, and the experiment of 26 July 1983 was repeated. The results are given in Table 4. In contrast to the 1983 results, rifabutin now showed no activity in doses up to 0·001% w/w dietary concentrations against this rifampicin-resistant strain of *M. leprae*.

CLINICAL BACTERICIDAL ACTIVITY

The results of the clinical study are summarized in Table 5. The sensitivity pattern in the pretreatment biopsy in patient No. 1 showed full sensitivity to all drugs in all concentrations studied except for growth in the two lowest rifabutin levels of 0·0001% and 0·00003%. Patients No. 2 and No. 3 showed full sensitivities to all drugs in all concentrations tested. In patient No. 1, inoculation of 5000 bacilli became noninfectious for mice 4–7 days after starting rifabutin. In patients No. 2 and No. 3, 5000 bacilli became noninfectious within 24 hr of a single dose of 300 mg of rifabutin.

Table 4. Repeat drug sensitivity studies with Carville No. 3026 strain of rifampicin-resistant *M. leprae* inoculated 1986*

Treatment (continuous)	No. +/Total	AFB/Footpad (x+SEM)†
Controls	6/6	$7{\cdot}33\ (\pm 1{\cdot}70) \times 10^5$
Rifampicin (%)		
0·01	6/6	$2{\cdot}29\ (\pm 0{\cdot}38) \times 10^5$
0·001	6/6	$9{\cdot}24\ (\pm 1{\cdot}87) \times 10^5$
0·0001	6/6	$6{\cdot}87\ (\pm 0{\cdot}90) \times 10^5$
0·000,03	4/4	$5{\cdot}88\ (\pm 0{\cdot}74) \times 10^5$
Rifabutin (%)		
0·001	6/6	$1{\cdot}12\ (\pm 0{\cdot}12) \times 10^6$
0·0003	6/6	$7{\cdot}19\ (\pm 1{\cdot}31) \times 10^5$
0·0001	2/2	$5{\cdot}19\ (\pm 3{\cdot}59) \times 10^5$
0·000,03	6/6	$1{\cdot}22\ (\pm 0{\cdot}43) \times 10^6$

* Mice inoculated 1 December 1986, harvested 21 October 1987.

† Means of positive footpads only.

Table 5. Clinical mouse footpad studies

	Patient		
	1	2	3
Rifabutin dose	300 mg daily	300 mg daily	300 mg single dose
Average BI*	4·7	4·0	4·5
Footpad results—AFB/FP†			
Pretreatment	9×10^5	2×10^5	6×10^5
Day 1	5×10^4	0	0
Day 4	6×10^4	0	0
Day 7	0	0	0
Day 14	0	0	0

* BI = Bacterial index.
† AFB/FP = Acid-fast bacilli per footpad.

Discussion

As measured by minimal effective dose determinations in mice, rifabutin is highly active against *M. leprae* and is more potent than rifampicin.

We are unable to offer a satisfactory explanation for our inability to repeat our observation of rifabutin sensitivity of the rifampicin-resistant *M. leprae* isolate No. 3026. The 1983 data (Table 2) appeared satisfactory, although in retrospect the lack of uniform takes or growth at the lower dosage levels of rifampicin are unusual. We have rechecked all records and found no evidence of technical errors. The technical and animal caretaker personnel are very experienced and reliable.

The primary effect of the rifamycins is inhibition of DNA-dependent RNA polymerase. Mutations of a single amino acid in the enzyme diminish or completely abolish the ability of rifamycins to bind to RNA polymerase, resulting in drug-resistant organisms.[12] One could speculate that rifabutin acted on the rifampicin-resistant *M. leprae* isolate No. 3026 at a site other than DNA-dependent RNA polymerase in 1983. There is evidence that rifabutin can inhibit the biosynthesis of DNA in a rifampicin-resistant mutant of *M. tuberculosis* H37Rv.[12] One could further speculate that another mutation occurred between 1983 and 1986 in this strain, resulting in rifabutin resistance at this site of action also. We have no evidence for such a biologic explanation, just as we have no evidence for a technical explanation for these findings.

We undertook a trial of rifabutin in a small number of leprosy patients to measure its bactericidal activity and to compare the results with similar trials previously carried out with rifampicin by Levy *et al.*[13] and the rifampicin trial at Carville in the early 1970s. In these studies, single doses of 600–1500 mg of rifampicin and daily doses of 600 mg and 300 mg were given to newly diagnosed lepromatous or borderline lepromatous patients and a series of skin biopsies were obtained for mouse footpad studies. Single doses of 600 mg of rifampicin or more resulted in loss of growth of 5000 *M. leprae* in almost all of the mouse footpads within 3 to 5 days. Daily rifabutin, in doses of 300 mg, similarly prevented the growth of 5000 of the patients' *M. leprae* within 1 to 7 days.

The results obtained in these 3 patients indicate a level of bactericidal activity of

rifabutin against *M. leprae* which is comparable to that observed with rifampicin. The clinical study is too small to adequately define the role of rifabutin in the treatment of leprosy, but it suggests that rifabutin could have a role similar to rifampicin.

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L'activite de la rifabutine vis-à-vis de *Mycobacterium leprae*

L J Yoder, R R Jacobson et R C Hastings

Résume Des doses minimales efficaces de rifabutine et rifampicine furent détectées dans de *Mycobacterium leprae* isolé par biopsies cutanées chez des patients non traités, récemment diagnostiqués comme souffrant de lèpre lépromateuse. La rifabutine était plus efficace que la rifampicine. Il n'a pas été possible de confirmer notre rapport précédent sur l'efficacité totale de la rifabutine vis-à-vis de *M. leprae* résistant à rifampicine. L'examen des deux souches de *M. leprae* résistantes à la rifampicine provenant d'une autre source et une seconde expérimentation sur la souche originale de bacilles résistants à la rifampicine a révélé une résistance croisée totale entre la rifampicine et la rifabutine. Un essai clinique effectué sur trois patients non traités et récemment diagnostiqués comme souffrant de lèpre lépromateuse indiquait que l'activité bactéricide de la rifabutine était plus rapide.

La actividad de la rifabutina en contra del *Mycobacterium leprae*

L J Yoder, R R Jacobson y R C Hastings

Resumen Las dosis efectivas mínimas de rifabutinay rifampicina fueron determinadas en *Mycobacterium leprae* aislados de biopsias de piel de pacientes leprosos lepromatosos, no tratados previamente y con diagnóstico reciente. La rifabutina fue más potente que la rifampicina. Nuestro informe previo de que la rifabutina era completamente activa en contra del *M. leprae* resistente a la rifampicina no pudo ser confirmado. El estudio de dos cepas de *M. leprae* resistentes a la rifampicina de otro lugar, y una repetición del experimento en nuestra cepa original de bacilo resistente a la rifampicina, mostró una resistencia cruzada completa entre rifampicina y rifabutina. Un ensayo clínico en tres pacientes lepromatosos no tratodos previamente y con diagnóstico reciente, mostró que la rifabutina tiene una actividad bactericida rápida.

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Risk of relapse among non-lepromatous patients released from treatment after dapsone monotherapy

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Summary Information on 14,625 non-lepromatous patients released from treatment after dapsone monotherapy and followed up to a maximum of 15 years at the ILEP project, Dharmapuri, India, was analysed to study the pattern of relapses. The overall relapse rate was 5/1000 person years. Males had a higher relapse rate than females. The risk of relapse increased with age, number of lesions and duration of treatment. The risk for relapse remained constant over several years after release from treatment. Even though the absolute risk for relapse after MDT may be different, the pattern of relapses and the factors affecting it may be similar to what has been shown in this study.

Introduction

With the introduction of multidrug therapy the prevalence of leprosy cases requiring treatment has reduced in many endemic districts of India. Paucibacillary cases are being maintained under surveillance for 2 years after treatment, for the early diagnosis of treatment failures, relapses and reactions. There are also a large number of non-lepromatous patients who have been released from treatment after dapsone monotherapy. At present there is very little information on their long term risk for relapse. Further, identification of factors which modify the risk for relapse following dapsone monotherapy, may facilitate the planning of follow-up procedures for patients released after MDT. With this in view a historical cohort study was carried out at the ILEP Leprosy Control project at Dharmapuri, Tamil Nadu, India, to measure the relapse rates among non-lepromatous patients treated with dapsone monotherapy and factors affecting the risk for relapse.

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Background information

The ILEP programme at Dharmapuri was started in 1968 by the Damien Foundation. It was covering a population of 1 million when the project was handed over to the Government of Tamil Nadu in 1985. Throughout this period the unit had maintained a high level of efficiency in leprosy control work and documentation. The population covered by this unit was essentially rural. The control work was based on the guidelines suggested by the National Leprosy Control Programme. Cases were classified into 'N', 'N?L' and 'L', according to the practice prevalent at that time. 'N' included TT and early BT cases and 'N?L' included the more advanced BT and BB. BL and LL cases were put under 'L'. Apart from this, bacteriologically negative cases with macular lesions were classified as 'I'. This probably included a wide range of cases. Polyneuritic cases were classified as 'P'.

Until 1971 dapsone was administered in gradually increasing doses up to a maximum of 300 mg per week for adults; children received half that dose. From 1972 this practice of gradually increasing the dose was given up and the maximum dose was increased to 400 mg per week. From 1975 the dose of dapsone was further increased so that the adults received a maximum of 700 mg per week. Patients were declared inactive when the lesions had disappeared, or when a previously raised lesion had become macular or wrinkled in the absence of any evidence of neuritis.

After inactivity, non-lepromatous patients were maintained on the same dose of dapsone for a period of $1\frac{1}{2}$ to 5 years, wherever possible, before being declared as released from treatment (RFT). These patients were indefinitely followed up during the annual 'known case verification'. The treatment cards contained all the relevant information including details regarding relapses. The criteria for relapse were the following:

(a) Evidence of recurrence of activity in the old lesion;
(b) Appearance of a new lesion;
(c) Evidence of new nerve involvement.

All relapses were seen and confirmed by a medical officer.

Methodology

All non-lepromatous patients released from treatment from 1968 to 1985 were included in the study. Those who were known to have left the area or died were excluded. The individual treatment cards were reviewed carefully and information regarding personal characteristics, nature and extent of the disease, number of weeks of treatment, date of RFT and date of relapse (if relapsed) were extracted. The duration of treatment was calculated from the information on the number of weeks for which treatment was administered to the patients. The information was fed into a computer and analysed using SPSS PC.

Relapse rates were calculated as

$$= \frac{\text{No. of relapses} \times 1000}{\text{No. of person years of follow-up}}.$$

Cases were assumed to have been released from treatment uniformly throughout the year, thus contributing on average half a person year of observation each, during the calender year of RFT. Risk of relapse and cumulative risk for relapse were calculated using the actuarial method. Since cases who had died or left the area were excluded from the study, all the withdrawals were due to censoring caused by the study. Hazard ratios for relapses were calculated based on Cox's proportional hazards model using EGRET.

Results

Of the 14,889 records examined 264 had to be excluded due to incompleteness of information. The remaining 14,625 patients had been followed up for a maximum period of 15 years (mean = 5·2 years; SD = 3·3 years) after RFT. There were 387 relapses during 75,916·5 person years of follow-up giving an overall relapse rate of 5·1/1000 person years.

As shown in Table 1 the relapse rates were lowest for the 'N' type (4·6/1000 per year). 'N?L' and polyneuritic cases had similar relapse rates. Indeterminate cases had the highest relapse rates (24/1000). The differences in relapse rates between 'N' and other types were statistically significant ($P < 0·05$). Relapse rate among males was 80% higher than that among females (Table 2) ($P < 0·001$). Relapse rates appeared to increase with age at diagnosis until 30 years (Table 3). After that the relapse rate showed a fall. A similar trend was noticed when relapse rates were analysed according to age at RFT (Table 4). Relapse rate tended to increase with duration of treatment (Table 5). When the relapse rates were examined according to the three different periods with different treatment schedules, no significant differences were noticed (Table 6).

Relapse rates increased with the number of patches at the time of diagnosis (Table 7).

Table 1. Relapse rates according to type of leprosy

Type	No. of cases	Person years of follow-up	Relapse	Rate/1000 PY
N	13,395	71,620·5	331	4·62
N?L	727	1,509·5	20	13·24
Polyneuritic	459	2,619·5	32	12·21
I	44	167·0	4	23·95
	14,625	75,916·5	387	5·1

Table 2. Relapse rates by sex

Sex	No. of patients	Person years	No. of relapses	Rate/1000 PY	*P*
Female	7,085	38,092·5	139	3·65	<0·001
Male	7,540	37,824·0	248	6·56	
	14,625	75,916·5	387	5·1	

Table 3. Relapse rates by age at diagnosis

Age in years	No. of patients	Person years	No. of relapses	Rate/1000
1–10	2,564	15,616	40	2·56
11–20	2,264	12,325	72	5·84
21–30	2,285	11,553·5	86	7·44
31–40	3,203	16,343·5	112	6·85
41 & above	4,309	20,078·5	77	3·83
	14,625	75,916·5	387	5·1

Table 4. Relapse rates by age at RFT

Age at RFT	No. of patients	Person years	No. of relapses	Rate/1000
1–10	480	3,751·0	7	1·87
11–20	3,237	19,508·5	65	3·33
21–30	1,758	8,551·0	62	7·25
31–40	2,605	13,795·5	104	7·54
41 & above	6,545	30,310·5	149	4·92
	14,625	75,916·5	387	

Table 5. Relapse rates by duration of treatment

Duration of treatment in years	No. of patients	Person years	No. of relapses	Rate/1000	*P*
Up to 3	7,616	43,413·0	174	4·0	<0·05
4–5	4,047	19,398·5	107	5·5	<0·01
6 & above	2,962	13,105·0	106	8·1	
	14,625	75,916·5	387		

Table 6. Relapse rates according to the period of registration

Period of registration	Person years	No. of relapses	Relapse rate	*P*
1968–1971	49,821·5	255	5·1	NS
1972–1974	14,691·0	82	5·6	NS
1975–1984	11,404·0	50	4·4	
	75,916·5			

Table 7. Relapse rates by number of patches

No. of patches	No. of patients	Person year	No. of relapses	Rate/1000*
1	6,797	38,062·5	127	3·34
2–3	3,872	21,026·0	96	4·57
4–6	1,513	7,089·0	52	7·34
7–10	736	3,094	28	9·05
> 10	1,248	4,025	52	12·92
	14,166†	73,297·0	355	

* χ^2 for trend = 89·3; $P < 0·001$.
† 459 polyneuritic cases were excluded from this analysis.

Graph 1 shows the cumulative risk of relapse according to the number of patches. For patients with more than 10 patches the probability of relapse by the 7th year was 10%.

The annual risk of relapse after RFT was stable at around 5/1000 during the first 7 years. There was a slight decrease in the relapse rate after 7 years (Table 8). This fall is to be expected since there were hardly any cases with more serious forms of disease who had been followed up for more than 7 years.

The effect of the number of patches, duration of treatment and age at diagnosis on the risk for relapse were examined by doing survival analysis using Cox's proportional hazards model for males and females separately (Appendix I & II). The relative risk for relapse increased with the number of patches and duration of treatment as seen in the univariate analysis. However, the relative reduction in the risk for relapse after age 30, seen in the univariate analysis, disappears when adjustments are made for the number of patches and duration of treatment. Thus the risk for relapse tends to increase with the age of the patient at detection. The pattern was similar when age at RFT was entered into the model instead of age at detection.

Table 8. Risk of relapse by year of follow-up

Years after RFT	No. starting the period	Relapse	Withdrawals during the year	Risk/1000	Cumulative probability of relapse/1000
1	14,625	64	1,385	4·59	4·6
2	13,176	78	1,393	6·25	10·8
3	11,705	66	1,476	6·02	16·7
4	10,163	50	1,361	5·27	21·9
5	8,752	40	1,891	5·12	26·9
6	6,821	33	1,581	5·47	32·3
7	5,207	27	1,085	5·79	37·9
8	4,095	11	1,072	3·091	40·9
9	3,012	9	563	3·30	44·1
10	2,440	4	485	1·82	45·9
11	1,951	3	1,085	2·13	47·9
12	863	2	511	3·30	51·0
13	350	—	285	—	—
14	65	—	61	—	—
15	4	—	—	—	—

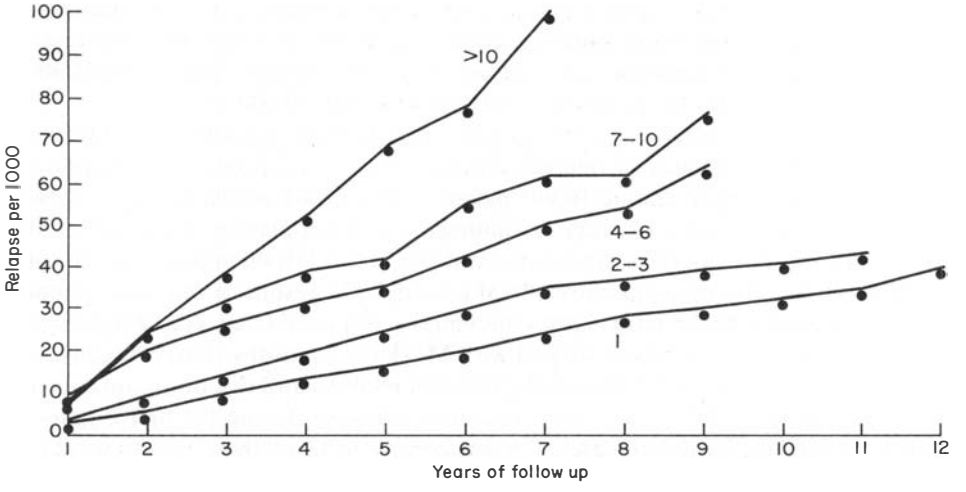

Figure 1. Cumulative risk of relapse (per 1000) according to year of follow-up by number of patches.

Discussion

The annual risk of relapse following RFT appears to remain steady for 7–9 years at about 5 per 1000. Jesudasan[1] studied relapse rates according to the time after RFT and reported the relapse rates to be about 13/1000 for the first 2 years and about 5/1000 subsequently. The design of that study varied from the present one, in that, there was a one time special verification of all RFT cases. Neelan[2] had reported that relapse after RFT remained the same over the first $4\frac{1}{2}$ years of follow-up. This study suggests that the phenomenon of relapse occurs relentlessly for fairly long periods after releasing from treatment which is incompatible with the concept of median incubation period of $3\frac{1}{2}$ years suggested by Pattyn.[3]

The finding that the males had a higher rate of relapse was similar to what has been reported by Jesudasan. One possible reason for this could be differential surveillance. On the other hand this finding is consistent with the reduced risk of disease and higher rate of remission[2] that women seem to enjoy.

The striking association between the risk for relapse and the number of patches is consistent with the findings from other studies.[1,2]

The effect of age on the relapse rate could be a function of the severity of the disease, since with increasing age at detection the severity also increases incipiently. Similarly the duration of treatment could be a surrogate for severity of disease. Patients whose lesions took a longer time to resolve could have received longer duration of treatment. Thus it appears possible that the duration of time taken for the resolution of lesions may be related to the risk of relapse.

The overall absolute risk for relapse per year is only about 5/1000 in this group and could be considered a conservative estimate. Maintaining all patients under active surveillance may not be cost effective. On the other hand it may be worthwhile following up individuals with multiple lesions since the risk of relapse is quite high even if they have had prolonged treatment.

Though, these results are based on the analysis of secondary data, they should reflect the load of relapses that occur during routine field work. It is difficult to estimate the proportion of dapsone-resistant cases among them. An average control unit of 400,000 population in a hyperendemic district may have about 10,000 known cases of non-lepromatous leprosy, released after treatment with dapsone monotherapy. One should expect to get about 50 cases of relapses annually from this population. Chopra *et al.*[4] reported 21 relapses from among 10,995 patients treated with paucibacillary regime and followed up to a maximum of 4 years. Assuming that this population yielded about 21,000 person years of follow-up the relapse rate would be about 1/1000 person years of follow-up, which is lower than the one shown by this study. The results of our study cannot be directly compared with the information on relapses, obtained from a careful prospective follow-up of paucibacillary cases treated with MDT for 6 months. This is because of the difficulties one may face in distinguishing between relapses and reactions and because of the well-known fact that risk for these reactions is higher during the first 2 years after initiation of treatment. In the case of monotherapy most of these events would have occurred during therapy and not after release from treatment. Similarly, frequent and careful follow-up may yield a larger number of events related to changes in the nature and extent of the patches which, probably would be missed, during routine surveillance.

Even though there is a problem of comparing absolute rates of relapses between a historical cohort study and a concurrent cohort study, the pattern of relapses and the factors that modify the risk of relapse are likely to be similar for both those treated with monotherapy and MDT. Further, as shown in this study, the risk of relapse may remain constant over a long period of time after releasing from treatment.

Acknowledgments

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Appendix I

Effect of age, number of patches and duration of treatment on risk for relapse (Cox's proportional hazards model)—males

Term	Hazard ratio	95% Confidence bounds	
Age			
0–10	1·000*	—	—
11–20	1·142	1·059	1·231
21–30	1·251	1·154	1·357
31–40	1·306	1·209	1·410
> 40	1,440	1·340	1·547
NOP			
1	1·000*	—	—
2–3	1·007	0·9511	1·067
4–6	1·162	1·071	1·261
7–10	1·270	1·142	1·411
> 10	1·710	1·566	1·868
Treatment			
< 3 years	1·000*	—	—
4–5 years	1·357	1·281	1·438
> 6 years	1·391	1·299	1·490

* Reference category; NOP: Number of patches.

Appendix II

Effect of age, number of patches and duration of treatment on risk for relapse (Cox's proportional hazards model)—females

Term	Hazard ratio	95% Confidence bounds	
Age			
0–10 years	1·000*	—	—
11–20 years	1·181	1·079	1·294
21–30 years	1·253	1·152	1·363
31–40 years	1·232	1·142	1·328
> 40 years	1·363	1·267	1·467
NOP			
1	1·000*	—	—
2–3	1·020	0·9646	1·079
4–6	1·139	1·050	1·236
7–10	1·200	1·063	1·355
> 10	1·568	1·415	1·737
Treatment			
< 3 years	1·000*	—	—
4–5 years	1·508	1·422	1·600
> 6 years	1·580	1·468	1·700

* Reference category; NOP: Number of patches.

Risque de recidives chez les patients non-lepromateux chez qui le traitement a ete arrete apres une monotherapie par la dapsone

T D Pandian, Jayaprakash Muliyil et Claire Vellut

Résume Les données relatives à 14·625 patients non-lépromateux chez qui le traitement a été arrêté après une monothérapie à la dapsone et suivis pendant un maximum de 15 ans dans le cadre du projet ELEP à Dharmapuri en Inde, furent examinées pour déterminer le profil des récidives. Le nombre total des récidives était de 5/1·000 personnes par an. Le nombre de récidives chez les hommes était plus élevé que chez les femmes. Le risque de récidive augmentait avec l'âge, le nombre de lésions et la durée du traitement. Le risque de récidive restait constant plusieurs années après la fin du traitement. Quoique le risque absolu de récidive après *MDT* puisse être différent, le profil des récidives et les facteurs déterminants peuvent être semblables à ceux mentionnés dans cette étude.

Riesgo de recaída en los pacientes no lepromatosos liberados del tratamiento de monoterapia con dapsona

T D Pandian, Jayaprakash Muliyil y Claire Vellut

Resumen La información de 14·625 pacientes no lepromatosos liberados del tratamiento de monoterapia con dapsona y seguidos hasta un máximo de 15 años fue analizada en el proyecto ELEP, en Dharmapuri, India, para estudiar el modo de desarrollo de las recaídas. La tasa de recaída en conjunto fue de 5/1000 años personas. Los hombres tuvieron una tasa de recaída más alta que las mujeres. El riesgo a la recaída aumentó con la edad, número de lesiones y duración del tratamiento. El riesgo de recaida permaneció constante durante varios años después de la liberación del tratamiento. Aún cuando el riesgo de recaída absoluto después de *MDT* puede ser diferente, el modo de recaídas y los factores que lo afectan pueden ser similares a los que se han mostrado en este estudio.

Lepr Rev (1991) **61,** 297–302

Immunological upgrading with combined immunotherapy and chemotherapy in a lepromatous leprosy patient: a case report

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Summary Immunotherapy with *Mycobacterium w* was given, in addition to standard multidrug therapy (MDT) to a lepromatous leprosy (LL) patient with a bacteriological index (BI) of 6. After 15 months of treatment this patient attained bacteriological negativity and clinical inactivity. Histopathologically the patient upgraded to borderline-tuberculoid at 12 months, and at 15 months showed features of nonspecific infiltration in the dermis. The rapid immunological upgrading seen in the patient is highlighted in this paper.

Introduction

Lepromatous leprosy patients show anergy to react against *Mycobacterium leprae* and its multiplication in skin and peripheral nerves is virtually unchecked as there is an absence of host cell-mediated immunity (CMI).[1] This case report forms part of a large scale ongoing phase II/phase III clinical trials to evaluate the immunotherapeutic and immunoprophylactic potential of an antileprosy vaccine, *Mycobacterium w (M.w)*. The study is designed to investigate if immunotherapy in the form of a vaccine, based on a cross-reactive mycobacterium, given as an adjunct to chemotherapy is able to induce host CMI and reverse the host anergy to *M. leprae*. Early results of the immunotherapeutic trials with this vaccine have already been reported.[2,3] This case highlights a patient with an initial bacteriological index (BI) of 6 who upgraded immunologically to borderline-tuberculoid (BT) and then was completely cleared of bacilli and granuloma in a period of less than 24 pulses of MDT.

Case report

A 55-year-old male patient came with complaints of lesions on trunk and limbs, loss of sensation in hands and feet and a trophic ulcer on the left foot of 18 months duration. He

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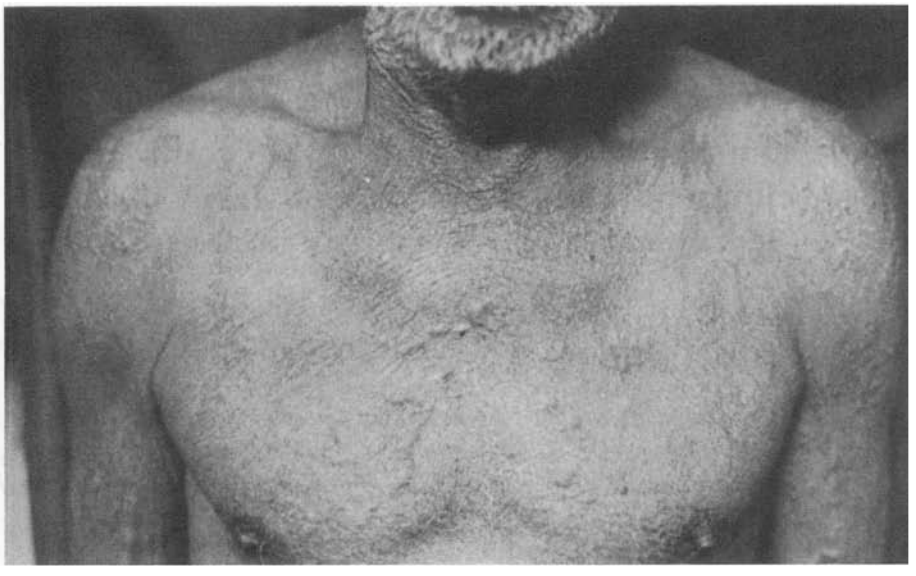

Figure 1. Erythematous papulonodular lesions over the chest.

had no previous history of treatment. On examination the patient had papulonodular lesions and erythematous plaques over the face, chest and back and coarse infiltration over the rest of the body (Figure 1). All nerve trunks were bilaterally involved—moderately thick but not tender. The patient had glove and stocking loss of sensation. Slit smears from both eyebrows, earlobes and from two patches on the lower back gave a

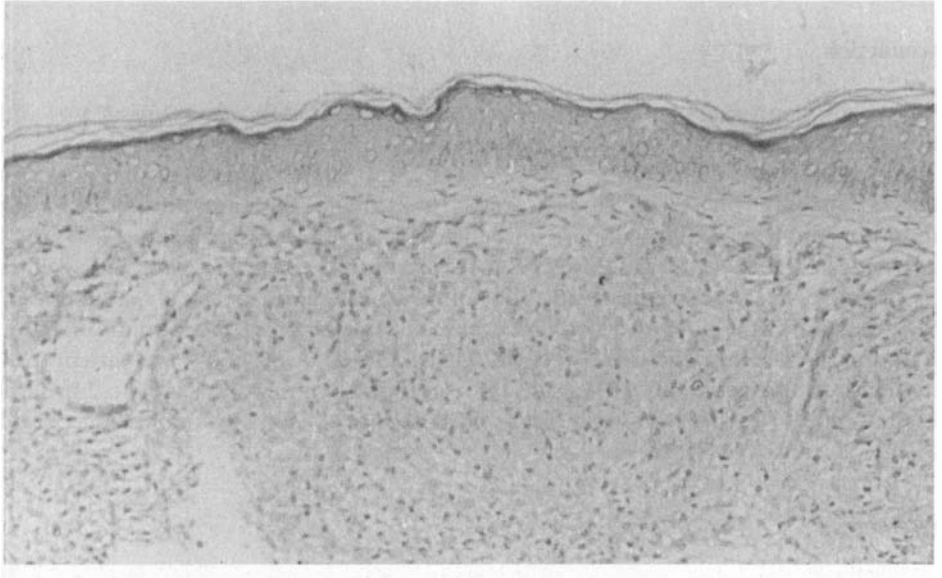

Figure 2. Photomicrograph showing macrophage granuloma in dermis with sparing of sub-epidermal zone. Lymphocytes are scanty and randomly distributed. This lesion had a BI of 5+ on the Ridley scale. (H/E ×600)

cumulative BI of 6 (Ridley's logarithmic scale). Clinical diagnosis of subpolar lepromatous leprosy was made. This was confirmed histopathologically (Figure 2). Lepromin A (supplied by WHO) testing was done. The late Mitsuda reaction at 21 days was negative.

Clinical scoring was done every 6 months using Ramu's score.[4,5] In this scoring system the body is divided into 7 regions, i.e. face, head and neck, right and left upper limbs, chest and abdomen, back and buttock, and right and left lower limbs. Each region is independently scored. A score of one is given to predominantly macular lesions, two to diffuse infiltration, three to few papules or plaques and four to predominantly papulonodular lesions. A score of one to four is thus given to each of the 7 regions. This patients cumulative initial score was 22. The patient was administered a standard multidrug regimen (MDT)[6].

In addition to chemotherapy, the patient received vaccine containing 1×10^9 killed *M.w* in 0·1 ml normal saline (0·85% NaCl) as first dose, followed by 5×10^8 killed bacilli as subsequent doses given intradermally (i.d.) at 3 monthly intervals. After 2 doses of vaccine and 4 months of regular treatment, the patient defaulted in attending the clinic due to personal problems. After a 7-month lapse, the patient reported to the clinic presenting with a mild Type 1 upgrading reaction. During this period the patient denied having taken any antileprosy treatment. The spot test for dapsone (DDS)[7] in urine was negative. The patient was then reviewed for his clinical, bacteriological, histopathological and immunological status. The patients BI had fallen to 2·33, and he had histopathologically upgraded to BL. The lepromin reaction was 5 mm at this time and clinical improvement was evidenced by a decrease in clinical score to 15. The patient was managed on nonsteroidal anti-inflammatory drugs (NSAID).

At the end of 12 months of treatment and 4 doses of vaccine, the patient showed notable clinical (Figure 3) and bacteriological improvement. His BI had fallen to 0·66 and his clinical score was 5. Histopathologically there was an upgrading to BT (Figure 4) and a

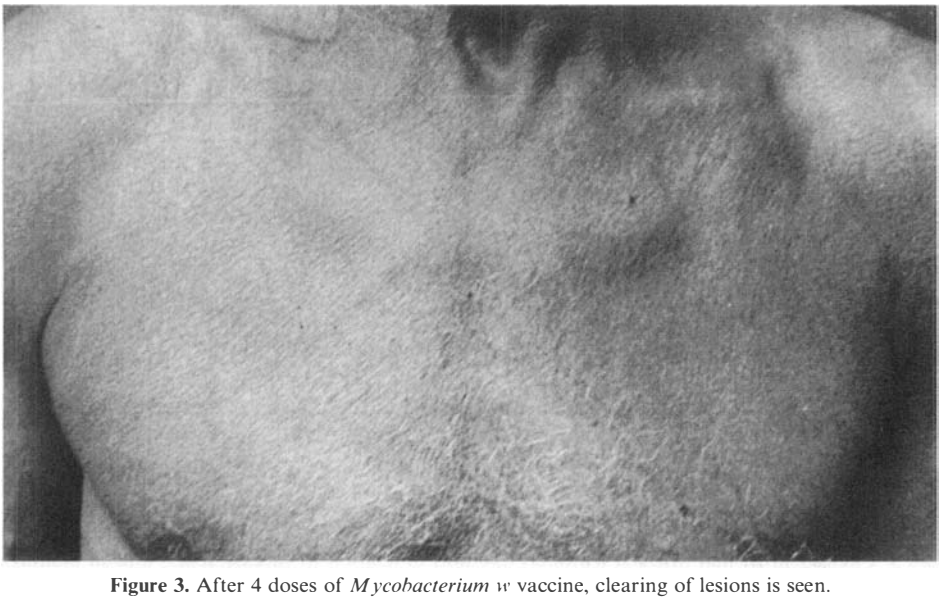

Figure 3. After 4 doses of *Mycobacterium w* vaccine, clearing of lesions is seen.

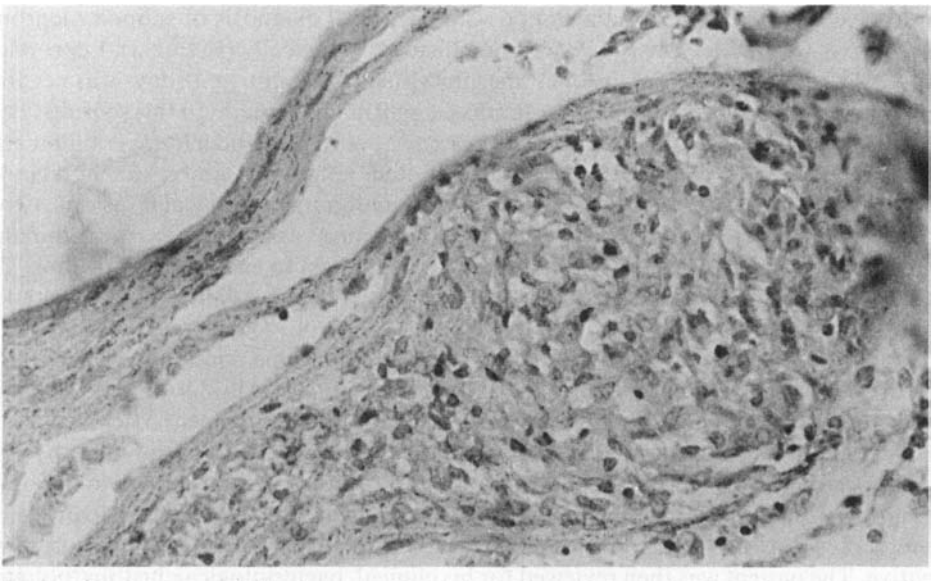

Figure 4. Photomicrograph from a biopsy taken at the end of 12 months treatment showing a small granuloma within the arrectores pilorum muscle. The cells comprising the granuloma were epithelioid cells, scattered lymphocytes and ill formed giant cells. This was the only granuloma seen in the entire section. No bacilli were found in the lesion at this stage. (H/E ×1320).

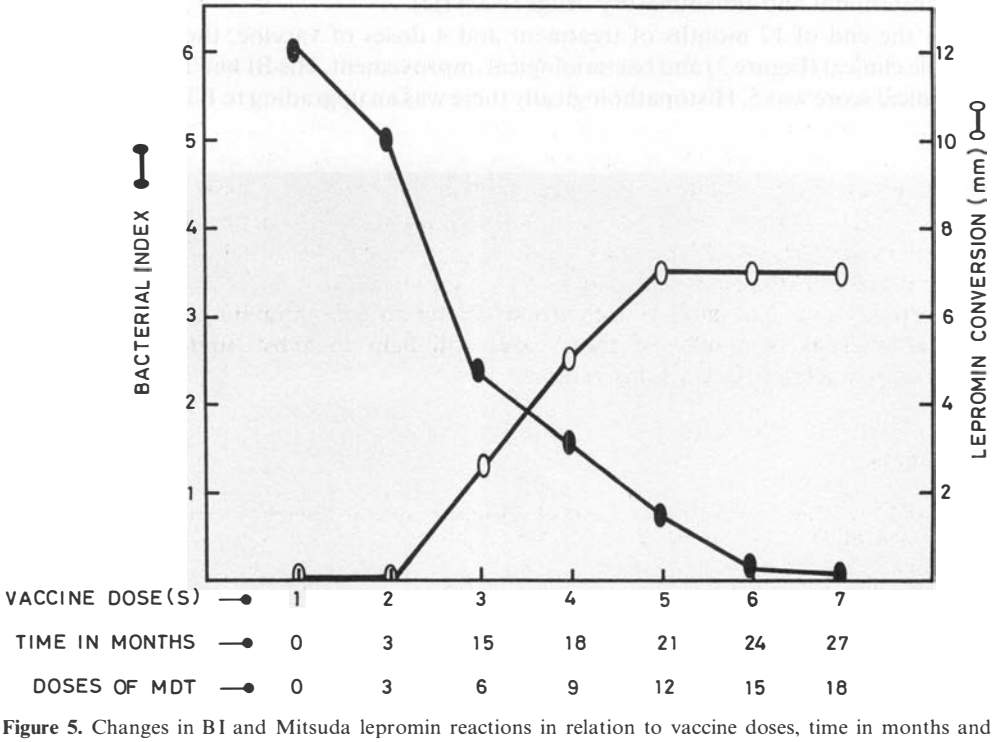

Figure 5. Changes in BI and Mitsuda lepromin reactions in relation to vaccine doses, time in months and treatment status.

lepromin reaction showed 7 mm induration (moderately positive). After a further period of 3 months of therapy, the patient reached a stage of both bacterial and clinical inactivity. Biopsy from the same skin site revealed only sparse infiltration in the dermis with no evidence of granuloma or AFB. Repeat slit-skin smears over the next 2 months were also negative. In October 1989 this patient was released from treatment after completing 24 pulses. Case progression in terms of lepromin conversion and bacterial fall is given in Figure 5.

Discussion

This case report highlights the immunological upgrading of an LL patients after receiving *M.w* vaccine.

The reports with MDT alone show that in multibacillary (MB) cases, the mean BI fall is between 0·6 and 1·0 unit per year[8]. It is well documented that patients on chemotherapy do not upgrade immunologically and remain lepromin negative at the end of therapy despite bacteriological negativity.[9,10]

This particular case demonstrated a rapid fall in BI (from 6 to 0 in less than 24 months), showed a Mitsuda lepromin conversion (from negativity to 7 mm positivity) and went through a gradual histopathological upgrading from LL to BL to BT and then showed complete subsidence of disease without any undesirable side-effects including nerve damage. Convit *et al.* have reported immunological upgrading with a vaccine containing killed *M. leprae* and live BCG. They observed histological upgrading in 71% patients and soluble antigen (SA) conversion in 38% active LL and BL patients.[11,12] Kaplan *et al.* have shown faster rates of BI fall in sites locally injected with interleukin-2.[13] Deo *et al.* have used ICRC bacillus as an immunotherapeutic vaccine. The vaccine has shown to engender lepromin conversion and clinical upgrading in lepromatous patients.[14]

The mechanisms of action of *M.w* are as yet unclear. The *in vitro* and animal experimental studies indicate presence in *M.w* of antigens cross-reactive with *M. leprae*.[15,16] These antigens were found immunogenic in nature as they evoked DTH type of reaction in both LL and TT patients, when administered intradermally.[17,18] *M.w* has also shown a good DTH response locally at the vaccination site.

Currently over 320 patients are enrolled in the on going immunotherapeutic trials. Further analysis of results of these cases will help to substantiate the beneficial immunotherapeutic effects of this vaccine.

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Amélioration de l'immunité suite à une immunothérapie combinée à une chimiothérapie chez les patients LL: une observation

S A Zaheer, N R Suresh, H K Kar, A K Sharma, A Mukherjee, R Mukherjee et G P Talwar

Résumé Un patient lèpre lépromateuse (LL) dont le indíce bactériologique (BI) était de 6 a subi une immunothérapie au Hansen *Mycobacterium w* à la suite d'un traitement par associations médicamenteuses. Après 15 mois de traitement, il y avait négativité des examens bactériologiques et absence de symptômes chez ce patient. Sur le plan histopathologique, le patient a progressé vers la tuberculoïde dimorphe 12 mois, et à 15 mois, il présentait des caractéristiques d'infiltration dermique non-spécifique. L'amélioration rapide de l'immunité de ce patient est discutée dans le présent article.

Mejoramiento inmunológico con inmunoterapia y quimioterapia combinada en un paciente LL: Informe de un caso

S A Zaheer, N R Suresh, H K Kar, A K Sharma, A Mukherjee, R Mukherjee y G P Talwar

Resumen A un paciente leproso lepromatoso (LL) con un indíce bacteriológico (BI) de 6, se le dió inmunoterapia con *Mycobacterium w* en adición a la terapia estándar de multidroga (MDT). Después de 15 meses de tratamiento, este paciente alcanzó negatividad bacteriológica e inactividad clínica. Este paciente mejoró histopatológicamente y llegó a estar sólo en el límite de la tuberculosis después a los 12 meses de tratamiento y a los 15 meses mostró signos de infiltración no-específica en la dermis. Se destaca en este trabajo el rápido mejoramiento inmunológico visto en el paciente.

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Is bacteriological examination by skin smear necessary in all paucibacillary leprosy patients in mass control programmes?

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Summary Skin smear bacteriological examination results of 11,255 paucibacillary leprosy patients from 8 leprosy control units under the National Leprosy Eradication Programme (NLEP) in South India and the Outpatient Department (OPD) of the Central Leprosy Teaching & Research Institute (CLT&RI), Chengalpattu, between 1987 and 1989 were collected and analysed. Only 0·05% of the smears from leprosy control units and 2·49% from the OPD of CLT&RI were found to be positive. Not a single smear from indeterminate, tuberculoid and pure neuritic types of leprosy out of 8263 examined was found positive under field conditions. The relevance of carrying out routine bacteriological examination in mass leprosy control programmes is discussed.

Introduction

Leprosy patients of all types are being grouped into paucibacillary (PB) and multibacillary (MB) for treatment purposes with the advent of multidrug therapy (MDT). Indeterminate (I) and tuberculoid (T) under the Madrid classification, indeterminate (I), tuberculoid (TT) and borderline–tuberculoid (BT) leprosy in the Ridley–Jopling classification whenever diagnosed clinically or histopathologically, with a bacteriological index of $<2+$ on the Ridley–Jopling scale at any site were included in the PB leprosy group[1]. Indeterminate, tuberculoid, borderline–tuberculoid (BT) and pure neuritic (PN) leprosy patients are grouped under PB as per consensus classification of the Indian Association of leprologists 1981[2]. However, it was recommended that any case belonging to I, TT or BT leprosy groups according to the Ridley–Jopling classification with skin-smear positivity will be classified as MB for the purpose of MDT Programmes.[3] The guidelines under NLEP in India also states that all skin-smear positive patients irrespective of their clinical classification should be brought under MB MDT. As a result, it becomes absolutely necessary to carry out the bacteriological examination of all leprosy cases detected before giving them treatment. Most of the textbooks on leprosy state that skin-smear results are seldom positive in I and TT types which form the bulk of PB cases.[4–7]

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There is no literature on the extent of positivity of skin smears of patients who are I, TT, BT and PN under field conditions in mass programmes on a large scale and at routine examinations in out-patient departments (OPD) in leprosy institutions. An attempt has been made in this paper to find out the above information and analyse it as to the relevance of routine bacteriological skin smear examination in PB leprosy patients in mass control programmes.

Materials and methods

Under NLEP in India, on detection of the new leprosy cases activity or passively, they are confirmed and classified clinically by medical officers. A smear examination is then carried out for allocation to either PB or MB MDT regimens. Some of the medical officers working in leprosy control units in Krishna, Cuddappah and Chittoor Districts in Andhra Pradesh State were requested through their district leprosy officer to furnish information relating to bacteriological examination results of newly detected PB leprosy patients (I, TT, BT & PN) for the years 1987, 1988 and 1989 through a format sent to them. The medical officers were personally briefed and requested to collect information by examining individual patient care-cards of all new cases detected during the period under reference. They were specifically told to include all such I, TT, BT, and PN cases receiving MB treatment in the data furnished by them. The same information has been collected from the Field Operational Area and OPD of CLT&RI for the above period. Similar information from a leprosy control unit in Tamil Nadu State has been collected from the database which has been computerized as a part of an on-going in-depth evaluation of MDT project in the Institute. The units were picked up as per operational convenience and to render data of reasonable validity. The smears were collected from a minimum of 3 sites and read on the Ridley–Jopling scale as per NLEP guidelines by a trained laboratory technician at each of the centres reported. A limited cross-check of about 5% smears was reported by one unit (Machilipatnam) on the smear examination at the District Leprosy Office of Krishna District with no variation of results. All the units mentioned above have been implementing MDT projects since 1987.

Results

Information collected from 8 leprosy control units (including the field operational area of the Institute) and the OPD of CLT&RI were summarized in Table 1.

Out of the 12,686 new cases detected/reported between 1987 and 1989, in 11,255 (88·7%) patients the slit-skin smear bacteriological examination has been carried out. Coverage of examination ranged from 58·6% in the CLT&RI field area to 100% in a number of the centres (Pileru, Palamaner, Produturu & OPD of CLT&RI).

The total positive cases were 39 (0·35%) of the total examined cases. The positivity in various centres ranged from 0% in several units to 2·49% in OPD of CLT&RI. In all the field units positivity was reported as 0% except in Pileru and Palamaner units where the positivity was 0·25% and 0·29% respectively.

Table 1. New PB cases detected skin smears examined and positive cases in different centres, 1987–89

S.no.	Name of the leprosy control unit	Indeterminate			Tuberculoid			Borderline–tuberculoid			Pure neuritic			Total		
		R	E	P	R	E	P	R	E	P	R	E	P	R	E	P
1	Nuzvid	15	6 (40·0)	0	1025	1014 (98·9)	0	572	433 (75·7)	0	11	6 (54·5)	0	1623	1459 (89·9)	0
2	Machilipatnam	1188	962 (81·0)	0	1314	1012 (77·0)	0	406	260 (64·0)	0	202	147 (72·8)	0	3110	2381 (76·6)	0
3	Assisi	10	4 (40)	0	989	706 (71·4)	0	19	19 (100)	0	1	1 (100)	0	1019	730 (71·6)	0
4	Pileru	0	0	0	698	698 (100)	0	417	417 (100)	3 (0·72)	63	63 (100)	0	1178	1178 (100)	3 (0·25)
5	Palamaner	18	18 (100)	0	450	450 (100)	0	206	206 (100)	2 (0·97)	23	23 (100)	0	697	697 (100)	2 (0·29)
6	Proddutur	225	225 (100)	0	1651	1651 (100)	0	29	29 (100)	0	34	34 (100)	0	1939	1939 (100)	0
7	Nammakkal	0	0	0	1106	1035 (93·6)	0	261	244 (93·5)	0	2	2 (100)	0	1369	1281 (93·6)	0
8	CLT&RI field area	2	2 (100)	0	350	200 (57·1)	0	33	22 (66·7)	0	4	4 (100)	0	389	228 (58·6)	0
9	Subtotal	1458	1217 (83·5)	0	7583	6766 (89·2)	0	1943	1630 (83·9)	5 (0·31)	340	280 (82·4)	0	11,324	9893 (87·4)	5 (0·05)
10	CLT&RI outpatient	97	97 (100)	2 (2·06)	281	281 (100)	4 (1·42)	984	984 (100)	28 (2·85)	0	0	0	1362	1362 (100)	34 (2·49)
11	Grand total	1555	1314 (84·5)	2 (0·15)	7864	7047 (89·6)	4 (0·06)	2927	2614 (89·3)	33 (1·26)	340	280 (82·4)	0	12,686	11,255 (88·7)	39 (0·35)

R, registered; E, examined; p, positive; Figures in brackets are percentages.

POSITIVITY AND TYPE OF DISEASE

All types of PB leprosy cases except PN showed positivity ranging from 0·06% in TT to 1·26% in BT when results from all cases were taken together. However, the smears from I, TT & PN from all LCUs (including field operational area of CLT&RI) were reported negative. Only 2 LCUs out of the 8 reported positivity and they were 0·25% and 0·29% in Pileru and Palamaner respectively. The positivity of smears from OPD of CLT&RI ranged from 1·42% in TT cases to 2·85% in BT cases.

TYPE DISTRIBUTION OF SKIN SMEAR EXAMINED CASES

Of the 11,255 cases examined for skin smear bacteriology 11·7%, 62·6%, 23·2% and 2·5% belonged to I, TT, BT and PN respectively. The proportion of different types ranged from 0 to 40·4%, 20·6% to 96·7%, 1·5% to 72·2% and 0 to 6·2% in different centres for I, TT, BT and PN respectively.

BACTERIOLOGICAL INDEX (BI) OF POSITIVE CASES (Table 2)

Of the 39 positive cases, the BI at any one site was more than 1+ on Ridleys scale in only 11 cases (28·2%). All the cases with a BI of more than 1+ belonged to the BT group.

DISCUSSION

Skin smear bacteriological positivity in the PB group of leprosy patients has been reported as high as 21·8% with a BI of 1+ on Ridleys scale.[8] However, it was reported in

Table 2. BI of positive cases

	Type			
BI*	I	TT	BT	Total
1+	2	4	22	28 (71·8)
2+	—	—	7	7 (17·9)
3+	—	—	4	4 (10·3)
Total	2 (5·1)	4 (10·3)	33 (84·6)	39 (100)

* Maximum bacteriological index at any examined site.

Figures in brackets are percentages.

the same study that relapses could not be correlated with the initial bacteriological status using three different drug regimens including the WHO recommendation, at $3\frac{1}{2}$ years follow-up. Interobserver variation in reading the smears as negative while actually they are positive and vice versa has also been reported to the extent of 5·6% and 2·3% respectively.[9] The weakness and shortcomings in laboratory services are by no means new; they have been continuously identified over 20 years in numerous publications in leprosy and tuberculosis literature and this situation is unlikely to improve to the desired standards.[10] Organizing bacteriological examination of skin smears of all cases has been identified as a bottleneck by successive independent evaluation teams in India.[11–13] The bulk of the new leprosy cases detected (70–80%) belong to the PB group. In the present analysis, about 22·2% were found to be of the BT type. Under field conditions, it is only 0·31% of BT type and 0·05% of all types of the PB group that were found to be bacteriologically positive and none of the I, TT and PN group were positive. It is evident from the observations of successive independent evaluation team reports that perhaps it is almost impossible to improve the laboratory services in a mass control programme. The question is, with the very low positivity rates that are obtained above under field conditions, whether it would be worthwhile to carry out routine skin-smear examination in the PB group of leprosy patients in a mass control programme? It appears, perhaps, that it is not necessary to do skin smear bacteriology as a routine in all new PB group of patients, except BT type, especially when they are clinically confirmed by a medical person before commencement of treatment. Even under ideal conditions such as the OPD of CLT&RI, which can not be produced in field laboratories, the overall positivity was only 2·49%. Surveillance after release from treatment with MDT regimen is more or less mandatory for a period of 2 years in all control programmes. As such even those few cases which should have received MB MDT, had the bacteriological positivity been detected before commencement of treatment, could be taken care of during the surveillance period by way of detecting signs of clinical activity of the disease and instituting necessary MB treatment.

At present a lot of time is being spent by laboratory technicians on collection and examination of skin smears of PB leprosy patients, with a limited purpose served considering the effort involved, since nearly 70% to 80% of the new cases belong to this group. Further, if this routine examination is given up, they may well spend their time on bacteriological examination of MB cases, where it is actually needed for monitoring response to chemotherapy and deciding the time of release from treatment (RFT). Other advantages in giving up this routine examination are:

1 the saving of resources;
2 possibly better compliance of patients to clinic attendance;
3 saving the patients from unnecessary inconvenience due to pain; and
4 preventing the patients from possible exposure to AIDS, hepatitis B etc., due to faulty sterile techniques.

Conclusion

Skin smear bacteriological examination is perhaps not necessary in the PB group of newly detected leprosy patients (except the BT group) as a routine in a mass control programme when the clinical confirmation of diagnosis is made by a medical person.

There are several advantages if the above examination is given up, without jeopardizing the interests of the individual patient seriously.

Further analysis using more extensive data would be useful in identifying which of the BT cases would need smear examination with reference to clinical features.

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L'examen bactériologique par la méthode des frottis cutanés est-il nécessaire chez tous les patients lépreux paucibacillaires dans le cadre des programmes de contrôle à grande échelle?

P S Rao V Ekambaram, B N Reddy, P Krishamoorthy, S K Suresh Kumar et A Dutta

Résumé Entre 1987 et 1989 furent recueillis et analysés les résultats de l'examen bactériologique par frottis cutanés de 11.255 lépreux paucibacillaires provenant de 8 centres de contrôle de la lèpre dans le cadre du Programme national d'Eradication de la Lèpre (NLEP) dans le sud de l'Inde et des consultations hospitalières extemes OPD de l'Institut central de Recherche et d'Enseignement de la Lèpre (CLT&RI) à Chengalpattu. Seuls

0,05% des frottis provenant des centres de contrôle de la lèpre et 2,49% provenant des consultations hospitalières externes du CLT&RI se sont avérés positifs. Aucun fottis du type lèpre indéterminée, LT ou purement névritique provenant des 8263 patients examinés ne s'est avéré positif sur le terrain. L'importance des examens bactériologiques de routine dans le cadre des programmes de contrôle de la lèpre à grande échelle est discuté.

¿Es el examen bacteriológico del frotis de piel necesario en todos los pacientes leprosos paucibacilarios en los programas de control en masa?

P S Rao, V Ekambaram, B N Reddy, P Krishnamoorthy, S K Suresh Kumar y A Dutta

Resmuen Se recolectaron y analizaron los resultados de los exámenes bacteriológicos de los frotis de piel de 11.255 pacientes leprosos paucibacilarios de 8 unidades de control de lepra bajo el Programa Nacional de Erradicación de la Lepra (NLEP) en el Sur de la India y el Departamento de Pacientes Ambulatorios (OPD) del Instituto Central de Investigación y Enseñanza de la Lepra (CLT&RI), Chengalpattu, entre 1987 y 1989. Sólo el 0,05% de los frotis de las unidades de control de la lepra y el 2,49% de OPD de CLT&RI fueron encontrados ser positivos. Ni siquiera un frotis de lepra de tipo indeterminado, tuberculoide o puramente Neuritico de 8263 casos examinados se encotró que era positivo en las condiciones de estudio. Se discute la relevancia de llevar a cabo exámenes bacteriológicos de rutina como una rutina en los programas de control de la lepra en masa.

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Fluorescein diacetate and ethidium bromide staining to determine the viability of *Mycobacterium smegmatis* and *Escherichia coli*

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Summary The ability of the fluorescein diacetate and ethidium bromide fluorescent staining method to assess the percentage of viable bacterial cells in suspension was compared with the plate counting method. *Mycobacterium smegmatis* and *Escherichia coli* bacterial cell suspensions were incubated at 60°C. At different time intervals samples were taken and the percentage of viable cells in each sample was assessed by the fluorescent staining method and compared with the plate counting method. The fluorescent staining method showed a positive correlation with the plate counting method. However, the viable counts by the plate counting method were lower than the staining method when incubated at 60°C, indicating a lag period in the decay of enzymes after bacterial death. Hence, the fluorescent staining technique can be used to assess the trend of bacterial death rather than to assess the exact number of viable bacilli.

Introduction

Fluorescein diacetate (FDA) was used to determine the viability of mammalian cells.[1] It is a nonpolar, nonfluorescent fatty acid ester and passes readily into living cells where it is hydrolysed by esterases to yield polar, fluorescent fluorescein, if the membrane integrity is intact. The fluorescein rapidly accumulates inside the cells resulting in green-stained cells when viewed under fluorescent microscope.

Ethidium bromide (EB) enters cells whose cell membrane integrity is altered and intercalates with double stranded nucleic acid to form a red-orange fluorescent complex.[2]

Both FDA and EB were combined into a single assay and used to measure the viability of *M. smegmatis* and *M. phlei*.[3] It has been suggested th t FDA:EB staining procedure can be used to assess the viability of *M. leprae*.[4–6] In the present study, the FDA:EB

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staining procedure is compared with the time honoured plate counting method to assess the percentage of viable *M. smegmatis* and *Esch. coli* cells in suspension.

Materials and methods

Kvach & Veras's (1982) procedure was adopted to prepare single cell *M. smegmatis* suspension.[3] The single cell suspension was placed in a bath of water at 60°C. At 0 min, 20 min and 50 min, samples were taken and used for FDA:EB staining, plate counting (serially diluted suspensions were plated on Dubos agar medium, incubated at 37°C and colonies counted after 72 h) and calculating the total number of cells. (Ten micro litres of the serially diluted single cell suspensions were smeared in a fixed area on a microscopic slide and stained using the Ziehl–Neelsen method. The number of bacilli in the circled areas were counted and from this the total number of bacilli in the undiluted suspension was calculated.)[7]

The percentage of viable cells using the plate counting method was calculated by the following formula:

$$\text{Percentage of viable cells by plate counting method} = \frac{\text{Coloney count/ml, in undiluted cell suspension}}{\text{Total number of cells/ml, in undiluted sample}} \times 100.$$

Esch. coli was grown in nutrient broth at 37°C. The cell suspension was kept in a bath of water at 60°C. Samples were taken at 0 min, 30 min and 60 min and used for FDA:EB staining, calculating the number of cells (as described earlier except that a simple staining with dilute carbol fuchsin was done instead of acid-fast staining) and plate counting (serially diluted suspensions were plated on nutrient agar plates and colonies were counted after overnight incubation at 37°C).

FDA:EB working solution was prepared as per the procedure of Kvach & Veras.[3] A working solution of 0·5 ml of FDA:EB was added to 1·0 ml of *Esch. coli*/*M. smegmatis* single cell suspension and incubated for 10 min at room temperature. A wet mount was prepared and viewed under a dark field fluorescent microscope. B223 as the primary filter and G247 as the secondary filter were used. A total number of 200 red and green cells were counted. Green cells were considered as live and red cells as dead. Percentage viability by this procedure was calculated using the formula mentioned below:

$$\text{Percentage of viable cells by staining procedure} = \frac{\text{No. of green cells}}{\text{Total No. of cells counted}} \times 100.$$

Results

M. smegmatis incubated at 37°C for 48 hr showed $90 \pm 5\%$ (mean $\pm$ standard deviation of three experiments) green cells by staining and $83 \pm 10\%$ viable cells by plate counting. There were $20 \pm 7\%$ and $5 \pm 2\%$ green cells after heating for 20 min and 50 min respectively at 60°C. The plate counting showed $0{\cdot}001 \pm 001\%$ and 0% viable cells after heating at 60°C for 20 min and 50 min respectively (Figure 1).

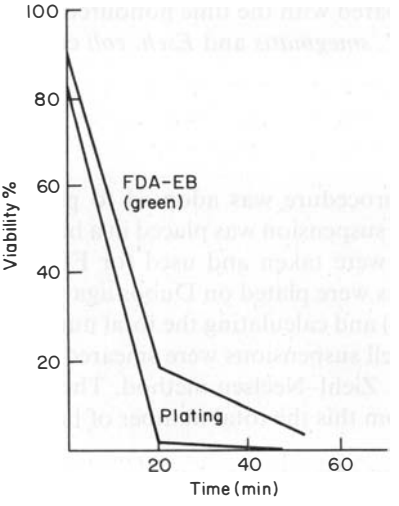

Figure 1. Percentage of viable *M. smegmatis* cells (at 60°C) detected by FDA:EB staining (green cells) and the plate counting method.

Esch. coli grown overnight showed 90 ± 6% green cells by staining and 85 ± 7% viable cells by plate counting. After heating at 60°C for 30 min, 46 ± 5% green cells were seen by staining while the plate counting showed 0·003 ± 0·002% viable cells. After 60 min at 60°C, there were 20 ± 7% green cells whereas no bacterial colony (0%) was seen in the plate (Figure 2).

Autoclaved samples of both *Esch. coli* and *M. smegmatis* showed 0% green cells.

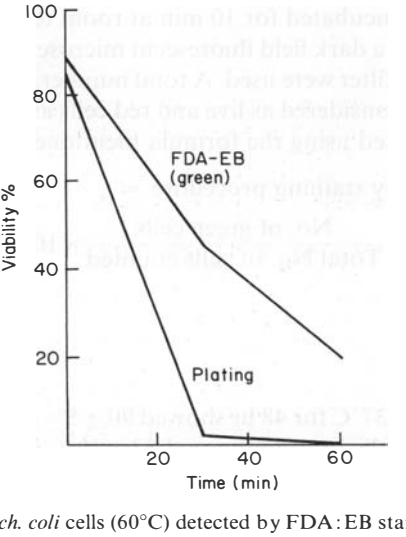

Figure 2. Percentage of viable *Esch. coli* cells (60°C) detected by FDA:EB staining (green cells) and the plate counting method.

Discussion

In *M. smegmatis*, the percentage of green cells decreased when they were heated for longer duration (90%, 20% and 5% at 0 min, 20 min, and 50 min respectively at 60°C). This corresponds with the decrease in percentage of viable cells seen in plate counting (83%, 0·001% and 0% at 0 min, 20 min, and 50 min respectively at 60°C).

Similarly, the percentage of green *Esch. coli* cells decreased with increase in duration of heating (90%, 46% and 20% at 0 min, 30 min and 60 min respectively at 60°C). This corresponds positively with the decreasing percentage of viable cells seen in plate counting (85%, 0·003% and 0% at 0 min, 30 min and 60 min respectively 60°C). Thus the decreasing percentage of green cells correspond with decrease in viability (as seen from plate counting). Yet the correlation is not absolute. The percentage of green cells is always higher (7–20% and 5–45% in *M. smegmatis* and *Esch. coli* respectively) than that expected by plate counting. A similar observation has been made by others.[3,8]

Kvach & Veras have suggested that the higher percentage of green cells as compared to colony forming units could be due to bacterial cell clumping and adherence of some bacteria to the L-shaped glass rod used to spread the suspension on plates.[3]

In our study, the bacterial suspensions were spread over the plate by simple tilting and rotation of plates and we did not use a L-shaped glass rod. When the bacterial suspensions were autoclaved (121°C for 15 min) all the cells became red and not even a single green cell was seen. But at a lower temperature (60°C) more green cells than expected were seen. Thus the persistance of some green cells is probably related to the inactivation of enzyme rather than clumping or adherence of bacteria to the L-shaped glass rod.

Our study clearly shows that the enzyme responsible for the fluorescent staining remains active for sometime after the death of bacilli and supports the similar view expressed by Katoch *et al.*[9] The fluorescent technique thus appears to be useful mainly in assessing the reduction of viability rather than true quantitation of viable cells. This needs to be kept in mind when assessing the viability of mycobacteria from clinical samples.

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La coloration au diacetate de fluorescéine et bromure d'éthidium pour determiner la viabilité de *Mycobacterium smegmatis* et d'*Escherischia coli*

V Jayapal, K M Sharmila, G Selvibai, S P Thyagarajan, S Shanmugasundaram et S Subramanian

Sommaire La capacité de la méthode de coloration au diacetate de fluorescéine et bromure d'éthidium pour estimer le pourcentage de céllules bactériennes viables en suspension a été comparée avec la méthode de compte des colonies sur plaque. Des suspensions de céllules de *Mycobacterium smegmatis* et d'*Escherischia coli* ont été incubées à 60°C. Aux différents intervalles de temps des échantillons ont été pris et le pourcentage de céllules viables estimé sur chaque échantillon par la méthode de coloration fluorescente. Le résultat obtenu a été comparé à la compte des colonies sur plaque. La méthode de coloration fluorescente a montré une corrélation positive avec la méthode de compte sur plaque. Néanmoins, la valeur obtenue pour la recompte des colonies viables sur plaque a été moins élevée que chez la méthode de coloration après incubation à 60°C, ce qui indique un décalage entre la morte des bactéries et la détérioration des enzymes. D'ou la méthode de coloration fluorescente peut être utilisée pour estimer les tendances dans le dépérissement des bactéries plutôt que pour le calcul exacte du nombre de bacilles viables.

Coloración a base de diacetato de fluoresceíne y bromuro de etidio para determinar la viabilidad de *Mycobacterium smegmatis* y de *Escherichia coli*

V Jayapal, K M Sharmila, G Selvibai, S P Thyagarajan, S Shanmugasundaram y S Subramanian

Resumen Se comparó el método de coloración a base de diacetato de fluoresceína y bromuro de etidio para calcular el porcentaje de células bacterianas viables en suspensión con el método de cuenta de colonias sobre placas. Se incubaron a 60°C suspensiones de células bacterianas de *Mycobacterium smegmatis* y de *Escherichia coli*. Se tomaron muestras a intervalos de tiempo distintos, se calculó el porcentaje de células viables en cada muestra por el método de colorantes fluorescentes y se comparó el resultado al obtenido por el método de cuenta de colonias sobre placas. Se halló una correlación positiva entre los resultados obtenidos por ambos métados. No obstante, la cuenta de células viables por el método de cuenta de colonias sobre places resultó inferior a la cuenta obtenida por medio del método de colorantes (llevándose la incubación a cabo a 60°C). Esto sugiere que existe un periodo de retraso tras la muerte de las bacterias hasta iniciarse el deterioro de las enzimas. Por lo tanto, el método de coloración fluorescente puede utilizarse más bien para evaluar las tendencias del decaimiento de las bacterias que para calcular el número exacto de bacilos viables.

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SPECIAL ARTICLE

ALERT-India 1981–89: nine years' experience of leprosy control in the slums of Bombay

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Summary Bombay has a population of about 8 million people, one-half of whom live in slums. In 1981, ALERT-India started its first leprosy control project in N, S and T Wards of Greater Bombay Municipal Corporation covering an area of 122 sq km in the north-eastern suburbs of Vidhyavihar, Ghatkopar, Vikhroli, Kanjurmarg, Bhandup and Mulund, with a total population of 1,100,000 according to the 1981 census. In the 9 years of operation, over 12,000 patients have been registered and treated and of these 7425 have been released from treatment, having satisfactorily completed courses of chemotherapy. However, over 1000 cases are still identified every year by house-to-house or school surveys, or by self-reporting, including a considerable percentage in children. The origin, development, staff structure, operational procedure, administration and recording system of ALERT-India are described in detail, with emphasis on what has been accompolished with purely outpatient facilities, using paramedical workers, all of whom have received inservice training from Government recognized training centres for their specific tasks. The account includes a brief description of an expansion of the organization's work into townships in New Bombay, where preliminary surveys in 1988 confirmed the presence of leprosy cases and the need for treatment facilities. The discussion addresses: 1, the better use of the large volume of statistical information which has been collected by ALERT-India during the past 9 years, with emphasis on its value in assessing the impact on the control programme and modifying future policy; 2, the need to radically examine the present policy of survey, *versus* an 'education campaign approach' with regard to increasing early case-detection and self-reporting; 3, the establishment of a central coordinating body for leprosy control in Bombay to exchange information, coordinate efforts and formulate a future plan of action, the latter in association with the National Leprosy Eradication Programme; and 4, the development of a health education resource centre in association with the Bombay Municipal Corporation.

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Introduction

ALERT-India was founded in October 1978. The letters stand for 'Association for Leprosy Education, Rehabilitation and Treatment' and this organization in India should not be confused with the All-Africa Leprosy and Rehabilitation Training Centre, also called ALERT, in Addis Ababa, Ethiopia. ALERT-India is registered under Acts of 1860 and 1950; it is a registered charity with audited accounts and donations are exempt from tax. The main financial support up to 1984 was from OXFAM (UK); from 1985 onwards it came from the Damien Foundation (Belgium) and other ILEP agencies such as the Associazione Italiana Amici de Raoul Follereau (Italy), Institute Fame Pereo (Canada) and the Association Francaise Raoul Follereau (France). The Damien Foundation is the ILEP Coordinator in India for finance and technical supervision. Its main objective is the eradication of leprosy, but the full list of subsidiary objectives as formulated and adopted by the Founder Members in October 1978 is as follows:

1 To detect early and infectious cases of leprosy in the community and reach the goal of total case detection through intensive surveys.
2 To treat every person diagnosed as suffering from active leprosy with adequate case-holding.
3 To create leprosy consciousness among the sections of the community through intensive health education programmes.
4 To work ardently towards total prevention of dehabilitation and promote sociopsychological and economic rehabilitation of leprosy patients in the milieu of the community.
5 To undertake and promote study and research in leprosy and related sciences.

To reach these objectives, three phases were envisaged.

Phase One

1 The establishment of a control programme and personnel to implement it; and
2 Bringing the maximum area under the Urban Leprosy Control Programme of the Association.

These would entail undertaking the following activities:

(a) conducting on-going surveys (house-to-house) in the project areas;
(b) progressively establishing treatment centres in surveyed areas;
(c) carry out a widespread programme of education particularly towards removal of existing deep-rooted prejudice and bias against the disease and its victims;
(d) setting up the office and records system (data collection, tabulation, analysis and control);
(e) establishment of a laboratory and a physiotherapy centre;
(f) publicising ALERT's aims, objectives and involvement, gaining community goodwill and cooperation at large, and the mobilization of local resources.

Phase Two

1 Establishment of a mini-hospital for special cases together with a full-fledged physiotherapy (physical rehabilitation centre); and

2 Health education Centre;
3 Undertake and promote study and research.

Phase Three

1 Implementing the economic, occupational, rehabilitation programmes;
2 Promotion of an Urban Training Centre (woefully lacking) and the establishment of a social research wing to promote the cause of eradication. Depending upon the progress made, funds available and the situation then prevailing, it will quite likely be possible to dovetail the phases into each other and thereby implement the programme more expeditiously and effectively.

Board of management

ALERT-India has a Board of Management of 9 members, most of whom have been on the Board since at least 1983; some were in fact founders of the Association. Some are medically qualified and experienced in leprosy, others have backgrounds in community or social work, education, nursing or administration. The Board is the legal body responsible for the Association and the overall policy decisions/directives and sanctions. The Chief Executive is an Ex-officio member of the Board of Management. Project planning, implementation and day-to-day administration are delegated to the Chief Executive, who carries out tasks through his team of officers and field staff. He also acts as Project Holder for the sponsoring agencies on behalf of the Association and as the 'Reporting Trustee' to the Governments and their departments.

Buildings, offices, clinics

The main administrative office is convenient to the centre of Bombay and is used by the Chief Executive and office staff. For field work and administration, two large rooms were acquired in 1985 in an industrial block in the heart of the control area, Vikhroli. This 'Project Office' includes a laboratory for slit-skin smears, storeroom, office accommodation, a teaching or meeting area and space for the reception and treatment of patients at a weekly clinic.

The project area

The area allocated is that of the three wards N, S and T as shown in Figure 1. These wards include the areas known as Vidyavihar, Ghatkopar, Kanjurmarg, Bhandup and Mulund. The estimated population of the three wards is 1,500,000. For administrative purposes the whole target area has been divided into 18 zones, each of which has one paramedical worker in charge, who carries out a full range of control activities, including surveys, case-detection, follow-up and health education, he also assists the medical officer during weekly visits to each zone. A field supervisor is responsible for the performance of 4 to 5 paramedical workers, and he in turn is supervised by the Project Officer, who is also

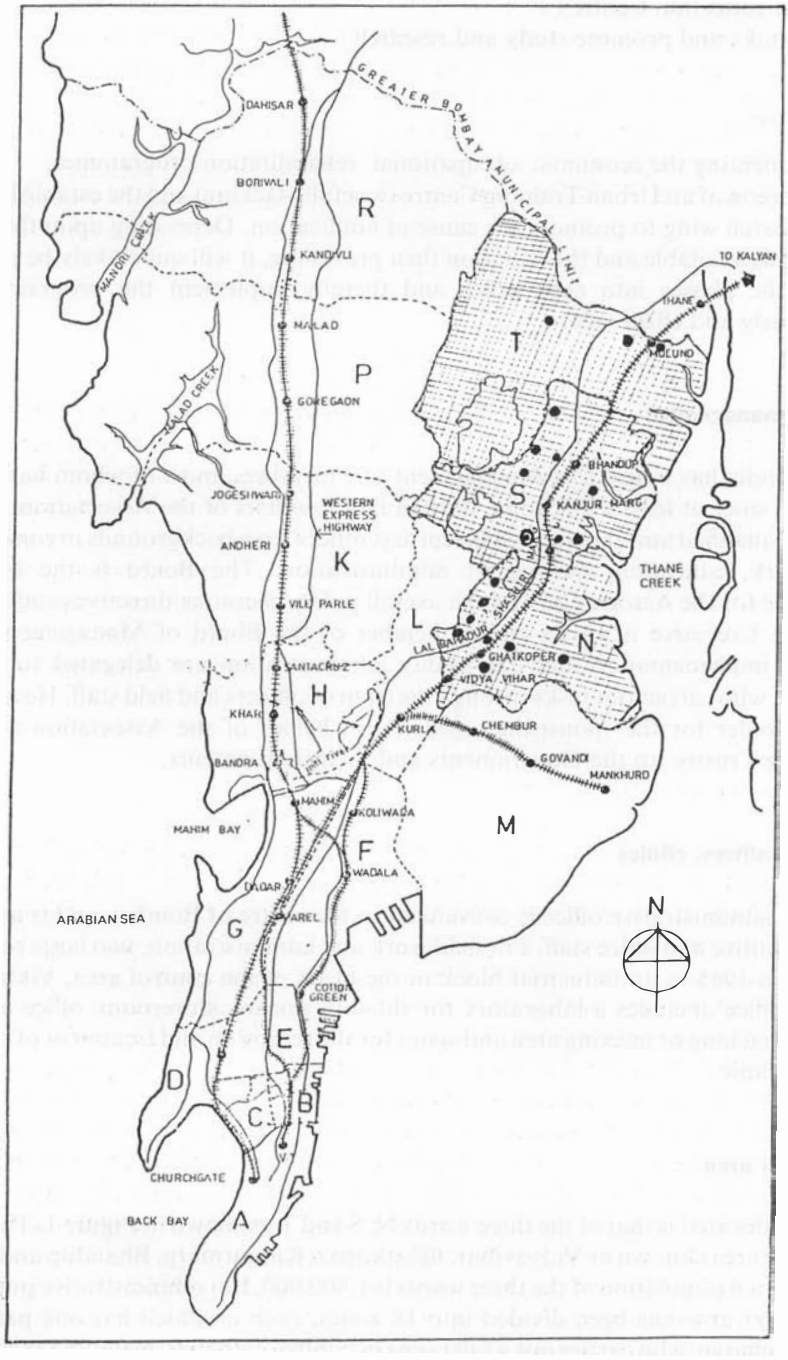

Figure 1. Map of Greater Bombay; total population 8 million. The letters A–H, K–N, P, S and T refer to 'wards' of Greater Bombay, of which N, S and T (shaded ara) are the control areas for ALERT-India. The area of the 'New Bombay Townships', in which programmes will be set up by ALERT-India in 1990, are to the right of Thane Creek, i.e. inland, towards the East.

responsible for the planning and execution of the control programme as a whole. The medical officers are ultimately accountable for the proper implementation of all technical and professional aspects of the programme and are directly responsible for the diagnosis and treatment of all patients. Every 3 months there is a general meeting of the entire staff, including health educators and the social worker to discuss problems and to review progress. Once yearly a general self-evaluation is carried out by field workers and officers, using a questionnaire, and the outcome discussed at a meeting, chaired by the Chief Executive.

Staffing

This includes: 1, the Chief Executive (with qualification in social welfare administration); 2, two full-time medical officers (one of them functioning as the Project Officer); 3, four field supervisors (trained paramedical workers); 4, twenty paramedical workers, all of whom have had inservice training with ALERT-India and in Government recognized training centres; 5, one smear technician; 6, one physiotherapist; and 7, one social worker (female; with a degree in social work), one driver and one typist. One paramedical worker is responsible on average, for about 50,000 people, with four field supervisors for 20 paramedical workers. Fifteen out of the 20 paramedical workers are already trained as health educators and the rest will complete their training in health education in 1991.

Control policy and field activities

These follow essentially conventional lines, as laid down (and used widely in India) by the National Leprosy Control (now Eradication) Programme in 1954.[1] This is based to a large extent on the principle of 'survey education and treatment'. Surveys have been carried out in this project in: 1, the general population; 2, contacts of known cases and 3, schools. In addition, a considerable number of cases are referred from private practitioners and others are apparently entirely self-reporting. Through the 9 years of operation, the approximate percentages of cases found in the above categories are: 1, 37%; 2, 16% and 3, 12%. From the 18 zones referred to above in the three wards of this project, one is still to be surveyed, but in the others surveys have been completed on a door-to-door basis, identifying slum colonies, one room tenements and lower middle-class housing societies in each zone of the project area. These teams examine 80% of the population in every cluster. Anyone familiar with conditions in the slums of Bombay will readily agree that this is neither complete nor satisfactory as a basis for 'survey' and it is likely that the teams fail to contact some members of the community, including those who leave the house early to go to work, even if visits are repeated. It has also to be appreciated (see Discussion) that the population is to some extent 'shifting' due to employment opportunities in the City or in villages which defy monitoring. All survey activity has been accompanied, from the early years of the work of ALERT-India, by intensive health education, using verbal communication, leaflets and pictures of early leprosy, and the attempts which have been made to assess its value will be discussed below.

Treatment

Nineteen clinics are scattered throughout the project area and they are held weekly, each patient receiving medication for 4 weeks at a time, on the occasion of attendance for supervised drugs. The regimens followed are those advised by the World Health Organization (WHO) in 1982[2] (not those of the National Leprosy Eradication Programme) and the criteria for the grouping of patients for pauci or multibacillary regimens are also those of WHO, with the following modifications: 1, All patients with less than 4 lesions are treated as pauci-bacillary; 2, all patients with 10 or more lesions are treated as multi-bacillary, regardless of bacteriological findings (i.e. even if negative); 3, all cases with between 4 and 9 lesions, and less than 3 nerves involved, are treated as paucibacillary; and 4, all cases with more than 4 lesions and more than 3 nerves involved are treated as multibacillary. Pure neuritic cases with only 1 or 2 nerves involved are treated as paucibacillary and those with multiple nerves involved as multibacillary, but only after thorough examination and assessment by a medical officer. The periods of treatment are also essentially those advised by WHO, with the following modifications:

1 All paucibacillary cases are allowed a maximum of 9 months to complete the course of 6 supervised doses.
2 If a medical officer confirms that there is clinical activity on completion of the 6 months course, treatment may be continued for a further 6 months.
3 Triple drug therapy for multibacillary cases should be completed within 36 months, or continued until smears are negative and or clinical inactivity, whichever is the longer.
4 In certain cases, however, at the discretion of the medical officer, treatment for multibacillary cases has been stopped after 40 supervised doses, regardless of bacteriological positivity.

It is important to note that multiple drug therapy is given only to patients who are able to give an address or contact point; who understand what is needed by way of monthly attendances and daily, unsupervised treatment; and who agree to keep in touch with the programme for the necessary period of time. Unless these criteria are met ALERT-India, in common with other agencies doing leprosy work in Bombay, has not used multiple drug therapy. These patients are either given a supply of dapsone 100 mg to take daily, with a prescription or a letter introducing them to the health services in another part of India, if they intend to leave Bombay. This policy, developed because of the danger of issuing expensive and potentially toxic drugs to patients who might never appear again, is judged now to be increasingly unacceptable, and alternative strategies to ensure that all patients presenting with active leprosy, especially if multibacillary, receive multiple drug therapy, are under discussion (see Research).

Drug supplies and distribution

Dapsone, clofazimine and rifampicin are supplied loose in stock bottles or plastic containers and made up into 1-month supplies (in the case of dapsone and clofazimine) for dispensing to patients. Blister packs, already widely used in some other parts of India, have not been used in this project, nor to our knowledge, in other parts of Bombay. Their

use in the future, especially if advantages in compliance are demonstrated by trials, has not however, been ruled out. Based on personal interviews with patients, pill counts, occasional checks of the urine for dapsone and assessment of the clinical and bacteriological results, our impression is that compliance to prescribed medication is satisfactory.

Planning, monitoring and evaluation

From the earliest stages of work, attention has constantly been given to the yearly development of a 'plan of work', identifying priority areas for attention, writing specific objectives and drawing up a monthly timetable of work for all members of the team. Monthly progress and work reports have been in use throughout, including specific suggestions for the improvement of work performance. Quarterly reviews and reports are made by the Project Officer, including an analysis of achievements (or failures) in priority areas. Half yearly and yearly evaluations are made by the Chief Executive, including an analysis of the overall achievements of the Association, based on the set objectives. Of particular importance are the operational assessments which have been carried out every 3 years by an external team (usually 3 or 4 experts in the field of leprosy control), to assess the quality of work, achievements and overall plan of action, whilst at the same time making proposals for changes, corrections and improvements for the future.

Referral of reactions, complications, cases requiring hospitalization

It is of interest that the need to refer patients for any of these reasons has been remarkably low. It has in fact been necessary to refer patients for severe reactions or other serious complications on less than 100 occasions, during the 9 years of the programme. We have been fortunate to have excellent contact with the staff and facilities of the Vimala Dermatological Centre, to whose physicians we are extremely grateful. Patients stay in hospital for a minimum of time needed and then return to our care. The entire element of 'removal' to an isolated leprosarium has thus been avoided by an almost totally outpatient approach and this may have contributed to the high level of interest and cooperation by patients and the community.

Laboratory services for slit-skin smears

Facilities for taking smears are available in all 19 clinics of the project area. Sites are selected either by a medical officer or by the next most highly experienced paramedical worker available. Smears are taken and fixed by a laboratory technician or a paramedical worker trained in this procedure. Until the end of 1985, patients with less than 4 lesions were not routinely smeared, unless requested for some special reason. The present policy is that all cases are smeared prior to starting treatment, the only exception being children with a single lesion on the face. Appropriate instructions have been issued to Medical Officers concerning the possibility that multibacillary patients, who are partially (and perhaps inadequately) treated, or relapsing, may present with less than 4 lesions. Once

fixed, labelled and dated, smears are sent to the 'Project Office' in Vikhroli, where one laboratory has been maintained through the years for the staining, examination and reporting of all smears, in accordance with advice given in a recent publication on the subject,[3] to the effect that selection and taking may be peripheral, but the staining and interpretation should be centralized and constantly under supervision. The bacteriological index (BI) only is recorded, not the morphological index (MI) or any other index. One technician has been trained at the Schieffelin Leprosy Research and Training Centre in Vellore, South India. It has been possible only during the last 2 years to organize reliability or comparability checks with other centres in India, but medical officers check approximately 5% of smears on a random basis. Particularly in view of the recent recommendations by WHO[4] that the finding of a positive BI at any site means that the patient should receive the multibacillary regimen (3 drugs for a minimum of 2 years), all slides with a BI of 1 will be double checked by a medical officer from now on.

Records, registers and reports

In recent years, following recommendations made by independent consultants, the number of registers and reports has been considerably reduced, but it is still necessary to supply them for three different agencies: 1, ALERT-India itself; 2, the Government of Maharashtra; and 3, the International Federation of Anti-Leprosy Associations (ILEP) in London. (The OMSLEP recording system has not been used.) The forms in use for ALERT-India for clinical details, smear reports, survey findings, contact examinations, etc., are entirely conventional and relatively easy to complete, but the monthly progress report for the Government is a lengthy and somewhat complicated document of 24 pages, which is time consuming for the health staff concerned, but nevertheless obligatory for administrative purposes. The ILEP Questionnaire or Form BG called for over 150 separate items of information, and although these are for the most part readily available from other sources and the form is required only once a year, it is clear that health staff are generally being asked to allocate an unreasonable amount of working time to the completion of these and other forms. Our belief is that the most important items which require recording are: 1, the total number of patients registered; 2, the number on multiple drug therapy; 3, the number who have satisfactorily completed it and been released from treatment; and 4, the proportion of new and currently registered cases with significant disability.

Healthy contact survey examination

As far as possible all contacts of index cases are examined once yearly, except contacts of multibacillary cases, who are examined every 6 months. The total number of contacts examined between 1981 and the end of 1989 was 48,060 from which 1189 cases (2·4%) have been diagnosed as having leprosy and treated.

School surveys

To date 249,122 school children have been examined, all between the ages of 5 and 15

Table 1. ALERT-India 1981–89: population covered, new cases detected and prevalance rate per thousand

	Population covered	New cases detected	%	PR/1000
1 Door to door survey among slums, chawls and housing colonies	461,628	4150	37	8·9
2 School survey among municipal, private, primary and secondary school	249,122	1348	12	5·4
3 Contact examination of known cases	48,060	1189	11	24·7
4 Health contact examinations	—	586	5	—
5 Voluntary/referals and others	—	3946	35	—
Total		11,219	100	

years. The case detection rates per thousand in recent years have been as follows: 1, 1984—4·16; 2, 1985—4·66; 3, 1986—9·79; 4, 1987—6·4; 5, 1988—4·2; and 6, 1989—5·7. The overall prevalence of new cases among school children was 5·4 per 1000.

Rehabilitation

This term appears in the title of ALERT and in the 'Plan of Action' of 1978, but in the sense of mental and physical rehabilitation of disabled patients to enable them to find gainful occupation, it has not been possible to develop this activity with much effect. Although this has been largely due to lack of trained staff, premises and equipment, it became clear after only a few years of experiences that it is extremely difficult, probably unrealistic, to rehabilitate patients in a community where there is already unemployment amongst healthy people, or to train them for useful work in remote villages, if they intend to return home. In the more general sense, we continue to teach disability prevention and self-care by patients, but incline increasingly to the view that the treatment of seriously disabled patients and their rehabilitation should be undertaken by agencies which have the staff, expertise and premises, and who are prepared to integrate leprosy patients with those disabled from other causes.

Public reactions to house-to-house and other forms of survey

We had anticipated opposition and refusal to allow health staff to enter houses and examine occupants, but this occurred on only a very small number of occasions. A second visit, once confidence has been established, usually meets with complete success. We attribute such good relations to: 1, the careful orientation of staff before they embark on this kind of work, to ensure that they proceed diplomatically and with respect for the privacy and convenience of others; and 2, the fact that the slum populations of Bombay are now more than used to visitors, students and health or social workers of various kinds;

Table 2. ALERT-India 1981–89: yearly case detection, child and disability rates, smear positive cases

	1981	1982	1983	1984	1985	1986	1987	1988	1989	Total
1 Total cases detected in each year (Annual) (new & old cases)	847	1416	1615	1019	1921	2038	1018	1094	1088	12,056
2 New cases among the above	847	1313	1517	964	1875	1831	896	988	988	11,219
3 Percentage of new cases	100	92	94	94·6	97·6	89·8	88	90·3	90·8	93
4 Child cases among the new cases	213	402	627	266	349	586	285	440	326	3494
5 Percentage of child cases (new cases)	25	30·6	41·3	27·5	18·6	32	31·8	44·5	33	31
6 Deformed (Grade 2 & 3) cases among new cases	45	47	76	42	76	85	35	40	47	493
7 Percentage of deformed cases (new cases)	5·3	3·5	5	4·3	4	4·6	3·9	4	4·7	4·4
8 Smear positive cases among new cases	28	76	97	54	132	165	94	78	74	798
9 Percentage of smear positive cases (new cases)	3·3	5·7	6·3	5·6	7	9	10	7·8	7·4	7

Table 3. ALERT-India 1981–89: total of registered cases, chemotherapy, cases released from treatment or lost to control

	1981	1982	1983	1984	1985	1986	1987	1988	1989	Total*
1 Total cases registered (new & old) (Annual)	847	1416	1615	1019	1921	2038	1018	1094	1088	12,056
2 Total cases put on MDT	1	55	149	132	1126	1434	1052	1022	1019	5990
%	0·12	3·8	9·2	13	58·6	70	103	93	94	49·6
3 Total cases put on dapsone monotherapy	846	1361	1466	887	795	604	—	72	69	6066
%	99·8	96·2	90·8	87	41·4	30	—	7	6	50·4
4 Total cases on MDT released from treatment (RFT)	—	2	53	58	180	1270	1006	727	882	4178
5 Total cases released from control (RFC) including some on dapsone monotherapy	—	1	13	44	139	394	1611	723	322	3247
6 Total cases lost to control (deletions)	8	164	198	172	423	573	620	313	355	2826†

* The figures in this column have to be interpreted in the light of the fact that 15% of all cases are still on MDT or monotherapy at the time of writing this report.

† Anecdotally, information from social workers in ALERT-India and other agencies working in leprosy control in Bombay, indicates that many of these patients have transferred to other parts of the City and re-registered for treatment.

once assured that the enquiry has nothing to do with legal matters, they are in general highly cooperative. Female staff work in pairs and appear to be able to carry out their duties with complete safety.

The personal health record of staff in ALERT-India

In the 9 years of operation in the slum areas described, often under conditions of great heat and without facilities for washing, etc, it is notable that we have had a low incidence of viral or other illnesses in doctors or paramedical workers. This is despite frequent contact with people suffering from measles, typhoid, dysentery, hepatitis, influenza, respiratory infections of various kinds, including active tuberculosis. During the 9 year period only one case of leprosy (pauci bacillary) has been diagnosed in an employee. Part-time or voluntary workers have included male and female students in their teens, none of whom has contracted a significant illness to our knowledge.

Research

ALERT-India has always been open to liaison with medical schools, universities and scientists, but with priority for operational and 'field-based' research on urban leprosy control and the extraordinary sociological conditions which prevail in the slum conditions of the project area. Pressure of work and lack of time have to a considerable extent precluded adequate attention to such research but we have had many visitors from different parts of the world and in 1987–88 data was collected by Dr Atul Vadher (Department of Experimental Psychology, Oxford University) which will contribute to a thesis on social and psychological aspects of leprosy in relation to compliance to prescribed medication.[5] More recently, Dr Nigel Crook (Department of Economic and Political Studies, School of Oriental and African Studies, The University of London) has completed a final assessment of a study of the 'educational campaign method' which started in Maharashtra Nagar in early 1986, which is due for publication in the near future.[6] Another study of sociological and population data in the New Townships of Vashi and Turbhe, with a preliminary estimate of the number of leprosy cases in those areas, has been submitted for publication.[7]

At least two other subjects calling for operational research remain and they are both of potentially great importance to the immediate plan of action. The first concerns the disconcertingly large number of patients who present, or are discovered to have leprosy in ALERT-India, but who are unable to give an undertaking that they will be in the area long enough to take a course of multiple drug therapy. Some of these are transient or visiting; others intend to return to their villages in the near future; others are unable to give an address or point of contact for supervision and follow-up, or are judged for a variety of reasons to be unlikely to pursue daily self-medication and monthly attendances for a reasonable period of time. To deny these patients any form of treatment or to give them dapsone monotherapy is an unacceptable policy which is now under intensive review in this organization. There are, however, good reasons for concluding that this problem (which occurs in slum programmes in several other parts of India) cannot be solved without consultation between ALERT-India, all other agencies working in leprosy

control in Bombay, the Ministry of Health of Maharashtra and probably also the national Leprosy Eradication Programme of India. Meanwhile, we have outlined a pilot research programme to: 1, identify the patients concerned in greater detail; 2, define the sociological and other reasons which impede safe implementation of multiple drug therapy; and 3, propose solutions.

The second subject concerns the remarkably large number of private practitioners in the N, S and T wards of this project and the likelihood that many more will settle in the New Townships in the coming years. The potential of private practitioners in Bombay in cae-detection and referral for treatment has already been shown to be considerable and it is now our intention to compile a comprehensive list of all practitioners in the area and to invite their cooperation, whilst at the same time carefully respecting their right to receive and treat patients as they see fit, and any element of professional confidence which may be involved. This enquiry will include information on the controversial question: 'Does the acceptance and treatment of leprosy patients in private practice enhance, or damage, the reputation of the doctor and the numbers of patients who come for consultation?'

Discussion and future plans

The registration of over 12,056 cases in a period of 9 years, followed by the release from control of over 7425, after completion of satisfactory courses of treatment, would appear to be a significant contribution towards the control of leprosy in the urban slums of this project. The disease has obviously been arrested in a large number of individuals; nerve damage has been prevented; relapse rates are low and there is at least a possibility that we have reduced the pool of infectious/contagious cases. There remain, however, a number of disconcerting aspects to this work, including the fact that we continue to register about 1000 new cases each year, but have little knowledge of their source of infection, whether within the project area or from some other part of Bombay (or India). We are also uncertain about the cost-effectiveness of our approach to case-detection and treatment. Survey can be laborious, time-consuming and expensive and it is notorious for the 'discovery' of cases who are unlikely to accept the diagnosis of leprosy and attend well for treatment. Broadly based educational campaigns, using all kinds of media, have been found by Ganapati[8] and others to have advantages over routine survey and it is to be hoped that the study already referred to in Maharashtra Nagar will contribute further information in this area.

Under **Treatment** it has already been pointed out that a considerable number of patients with active leprosy do not, for a variety of reasons, receive multiple drug therapy and this is a matter of considerable concern which points to the need for some kind of central or coordinating body amongst the agencies working in leprosy control in Bombay. It should not be impossible to analyse and overcome the operational and other obstacles which give rise to this situation, whilst at the same time reviewing working methods, report forms, records and other matters of mutual interest to the 10 agencies concerned.

As already indicated, ALERT-India is now entering a new phase of work in the Townships of New Bombay and this may point to the urgency of making sure that baseline data are properly assembled and that data from the main project areas is analysed to greater advantage. We aim to educate the public and prevent disability through early case detection and chemotherapy. To do this effectively, we have to

constantly keep in mind the need to study not only the disease and the drugs available for treatment, but also the complex and challenging pattern of society in the slums where we work.

Acknowledgments

We are grateful to Dr Claire Vellut, Ms Simone Liegeois, Dr M S Nilakanta Rao, Dr D Lobo and Mr M S Mehendale for permission to use information recorded by them in their Second and Third Operational Assessments of ALERT-India, Bombay, 1987 and 1990.

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ALERT-India 1981–89: Une expérience de 9 ans du contrôle de la lèpre dans les taudis de Bombay

AA Samy, J Mancheril, K P Manek et A C McDougall

Résumé Bombay a une population d'environ 8 millions d'habitants dont la moitié vit dans des taudis. En 1981, ALERT-India commença son premier projet de contrôle de la lèpre dans les quartiers N, S et T de la municipalité du grand Bombay d'une surface de 122 km carré dans les faubourgs nord-est de Vidhyavihar, Ghatkopar, Vikhroli, Kanjurmarg, Bhandup et Mulund dont la population totale s'élève à 1.100.000 habitants d'après le recensement effectué en 1981. Au cours des neuf années d'activités, plus de 12.000 patients ont été enregistrés et soignés dont 7425 chez qui le traitement a été arrêté ayant terminé avec succes un traitement complet de chimiothérapie. Toutefois, plus de 1000 cas sont encore identifiés chaque année par des enquêtes à domicile ou dans les écoles ou par notification volontaire et comprennent un grand nombre d'enfants. La création, le développement, le personnel, les méthodes de travail, l'administration et la méthode d'enregistrement utilisée par ALERT-India sont décrits en détail. L'accent est mis sur les résultats obtenus uniquement en consultations hospitalières externes avec l'aide des paramédicaux qui ont tous reçu une formation spécifique en cours d'emploi dans des centres de formation reconnus par le gouvernement. Le rapport inclut une brève description de l'essor des activités de l'organisation dans les banlieues de New Bombay où les enquêtes préliminaires effectuées en 1988 confirmaient l'existence de lépreux et la nécessité de dispensaires. Les questions abordées sont les suivantes: 1, l'emploi plus judicieux des données statistiques recueillies par ALERT-India au cours des 9 dernières années soulignant leur importance sur l'évaluation de l'impact du programme de contrôle et sur l'évolution des politiques futures; 2, la nécessité de comparer en détail le programme actuel d'enquêtes au système de campagnes éducatives afin de promouvoir le dépistage des cas précoces et les notifications

volontaires; 3, la création d'un organisme central de coordination pour le contrôle de la lèpre à Bombay permettant l'échange d'information, la coordination des efforts et la formulation de plans d'action futurs en association avec le Programme National d'Eradication de la Lèpre; 4, la création d'un centre de ressources en matière d'éducation sanitaire avec la Municipalité de Bombay.

ALERT-India 1981–89: Nueve años de experiencia en el control de la lepra en los barrios pobres de Bombay

A A Säamy, J Mancheril, K P Manek y A C McDougall

Resumen Bombay tiene una población de alrededor de 8 millones de personas, de las cuales la mitad vive en barrios probres. En 1981, ALERT-India inició su proyecto de control de la lepra en los distritos N, S y T de la Corporación Municipal de Gran Bombay cubriendo un área de 122 km cuadrados en los suburbios del nor-este de Vidhyavihar, Ghatkopar, Vikhroli, Kanjurmarg, Bhandup y Mulund, con una población total de 1.100.000 de acuerdo con el censo de 1981. En los 9 años de operación, más de 12.000 pacientes han sido registrados y tratados y de éstos 7425 han sido liberados del tratamiento, habiendo completado en forma satisfactoria cursos de quimioterapia. Sin embargo, más de 1000 casos son todavía identificados cada año en las encuestas casa por casa o en las escuelas o por auto informe, incluyendo un porcentaje considerable de niños. Se describe en detalle el origen, el desarrollo , la estructura del personal, los procedimientos operacionales, la administración y el sistema de registro de ALERTA-India, con énfasis en lo que se ha logrado con facilidades para pacientes ambulatorios solamente, usando trabajadores paramédicos, todos los cuales han recibido entrenamiento, durante su funcionamiento, de centros de entrenamiento reconocidos por el Gobierno por sus tareas específicas. El informe incluye una descripción breve de una expansión del trabajo de la organización hacia los pueblos en Bombay Nueva, donde las encuestas preliminares en 1988 confirmaron la presencia de casos de leprosos y la necesidad de facilidades para su tratamiento. La discusión propone: 1, el mejor uso del gran volumen de información estadística que ha juntado ALERTA-India durante los 9 años pasados, con énfasis en su valor de evaluar el impacto del programa de control y de modificar la política futura; 2, la necesidad de examinar radicalmente la política de encuesta presente, *versus* un 'enfoque de campaña educacional' con miras a aumentar la detección temprana de casos y el auto-informe; 3, el establecimiento de un cuerpo coordinador central para el control de la lepra en Bombay para intercambiar información, coordinar esfuerzos y formular un plan de acción futuro, este último en asociación con el Programa Nacional de Erradicación de la Lepra; y 4, el desarrollo de un centro d recursos para la educación en la salud en asociación con la Corporación Municipal de Bombay.

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SPECIAL ARTICLE

A multi-media approach to health education*

R C FRIEDERICKS
Development Communication Productions Kathmandu, Nepal

Many health and development agencies around the world concentrate on providing services, training personnel, supplying materials, etc., and overlook the part communication plays in their activities. Many books and manuals available on development issues do not address communications. Yet it is so much a part of their activities that it is taken for granted. But a close look at the communication and the information components of a programme can be beneficial for the success of the whole project.

Every kind of health or development activity is information related or dependent in some way.[1] These information components can and should be identified. Successful programmes are the ones that are involved with and aware of the people they serve. They are set up to pass on materials and technology that are appropriate to the situation and are oriented to giving away information.

Most of the information components involved in development or health education communication can be summarized in 'prime or key messages' which are relatively easy to transfer.[2] It is sometimes assumed that communication brings about change in peoples lives. Health education by itself can not make a difference because along with health education there must be an infrastructure of clinics, medical personnel and medicines. Only a better mix of information and human, physical and material sources can bring about substantial changes.[3]

People must have access to material resources as well as to information. Communication must lead to awareness and to feasible action. Using the radio to inform all pregnant women to go to the nearest hospital at the first sign of labour will not be helpful to a woman living 10 days walk from a hospital. To use a commercial example, it is frustrating to many young people living in the remote hills of Nepal to continually hear messages on the radio encouraging them to enjoy some commodity which is not available in their district.

Therefore information must be appropriate to the availability of services and materials where the information is distributed. These considerations help communicators define the information that is essential and produce messages that are most helpful to the people.

* Paper presented at a Health Education Seminar sponsored by the International Nepal Fellowship, Pokhara, Nepal on 23 March 1990

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Variety of media

Media can be categorized into basic and extended media.[4] Basic media are those which communicate ideas in the basic environment; person to person, person to group, group discussions, classroom lectures, or even large public meetings where public address systems are used. Extended media, on the other hand, are those media which extend time and space; books, other printed materials, films, audio cassettes, television, and even the telephone. In the basic media situation various extended media can be incorporated such as posters, flashcards, slides, audio cassettes, and other visual aids which help focus attention or expand the impact of the message.

No one media is better than another. Each media has its function, and each one is useful for a specific purpose. Combining them often increases their usefulness. Commercial advertising has used every possible medium and has often lead the way in the field of communication.[5] Many of the principles and techniques of developmental communication have been borrowed from commercial advertising.

Multi-media approach

One of the principles discovered was that in order to reach every possible target group it was necessary to use as many media as possible. The same product will be advertised in many magazines targeted for different audiences, radio programmes of many kinds, TV ads during many different kinds of programmes, and then, of course, in brochures, posters, bill boards along highways and on buses. The general public is assaulted with images and phrases about the product. Through this the public is informed, whether it wants to be or not, of the product and its qualities.

Similar approaches have been successfully used for health education. In India over the last few years, WHO and other funding agencies have given about $20 million for the national EPI (immunization) programme. A full 10% of this, $2 million, was spent on communication. The mass media was used, extension workers equipped with visual aids were dispatched, posters, bill boards, leaflets, were all produced and distributed. This approach was so successful that there has been a tremendous demand for immunization throughout India, almost more than the EPI programme can handle.[6]

In Nepal the Nun Chini Pani (oral rehydration) campaign used a similar multi-media approach. Radio, television, demonstrations by extension workers in village squares and schools were carried out throughout the country. Posters, memory cards, leaflets, and many other items, each giving the directions for making the oral rehydration solution with household items were distributed. At the end of the 3 year campaign 85% of the population of Nepal had heard the message, 57% could repeat the ingredients, and 25% had actually used it. Of those who had heard the message it was reported that 60% had heard it on the radio.[7]

Though radio may have been the original source of hearing about oral rehydration for 60% of the population, it is likely that their understanding of the message and ability to repeat or use the information was reinforced through other media such as the mobile teams who actually demonstrated the mixing of the ingredients, or from posters, leaflets or other materials.

In both cases mentioned above, it was determined that success was due to continuous,

rather than sporadic, repetition of simple messages over a long period of time using all available media. The campaigns were based on solid research into local needs, beliefs, attitudes, knowledge and practices. Interpersonal channels of communication were by far the most important because of personal contact and an opportunity to actually demonstrate or answer questions. Posters, the radio and television were the most effective in creating awareness. Radio and TV messages lent authority to the teams who came to villages to talk and demonstrate and helped mould public opinion and create a receptive attitude. Personal visits and demonstrations imparted the actual techniques or encouraged the decision making process toward trial and use of the oral rehydration solution or immunization of children.

Health and development programmes need to take a careful look at how they are communicating. Many rely only on basic media. Others use extended media as an aid or in some cases in place of basic media. A poster may be put up on a clinic wall and the staff may assume that their health education obligation has been met. Are staff trained well enough in communication skills to be effective basic communicators? Are doctors, nurses, fieldworkers, and extension workers trained as effective basic communicators? Are they able to effectively use extended media?

Basic media, if used correctly, is extremely effective for person to person contact. It is effective in the clinic with a patient or in the waiting room, in the village square or in a school. Mobile teams or travelling drama groups are likewise effective with person to person contacts. The use of audio/visual materials, which are helpful in attracting large crowds, can be turned into a basic media situation by having a discussion afterwards.

Distribution of printed materials has not proven effective in Nepal. This is due to the difficulty of carrying and distributing the material and the low literacy rate in rural areas. Visual literacy, though easy to teach, is limited primarily to those who are already literate.[8] This limits the effectiveness of visual aids and posters.

The Leprosy Control Programme in Nepal made significant changes in early case finding and attitude change across Nepali society. Though the problem of leprosy has not been solved, it may be safe to assume that the level of success achieved has been due to the medical infrastructure available in many parts of the country and to the continuous repetition of simple messages:

(1) leprosy can be cured . . .
(2) the early signs of leprosy are . . .
(3) treatment can be found at . . .

These messages have been repeated by healthworkers in the field, by printed materials distributed among community leaders who are often literate, and over the radio. It has been found that during and after periods of radio broadcast of these messages, case finding significantly increased.[9]

A strategy for the nineties?

If each programme commits itself to serious analysis of its communication components it will be able to identify the key messages it has to offer the people it serves. Simplicity is essential. It is also essential that the message be relevant. For example, a key message for a TB programme might be 'TB can be cured if treatment is taken regularly for a year'. This

kind of message can be repeated through various media and is relevant to the entire population, both for those who have TB and for those who are in danger of getting the disease. This message can be repeated over the radio to create awareness and add authority to the healthworker. A leaflet can provide details to those who can read and want to know more. The messages should be based on realistic objectives related to actual local conditions and possibilities.

It will be discovered that many programmes share the same essential key messages, although there may be variations due to local culture and language. A consistent approach to communicating these key messages is necessary. All health and development programmes would be better off if they could pool their efforts to 'sell' nutrition, sanitation, TB control or whatever. Sharing creative ideas will preclude waste, amateurish production efforts, and the 're-invention of the wheel'.

Identifying key messages and designing them for the various media requires a central resource. This resource would need to assume a role in co-ordinating the identification of key messages, research and design for appropriate communication strategies, and the production of materials at a national or regional level for various health and development programmes. The mandate of such a resource centre would be the effective utilization of communication as a powerful tool for health and development.

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Obituaries

DR DHARMENDRA 1900–91

Dr Dharmendra, the most senior Indian leprologist, who was very well known throughout the world as an eminent scientist died peacefully on 10 March 1991, aged 91. He carried to his credit 60 years of continuous work in leprosy, during which he played a prominent role in shaping the leprosy programmes in India.

Dr Dharmendra was born on 1 February 1900 in Lahore. He took a medicine degree in 1928, and subsequently a Diploma in Bacteriology at London University. He did most of his research work at the school of Tropical Medicine, Calcutta, where he worked with Dr Ernest Muir. He joined the Institute as a junior scientist in 1928 and gradually rose to the position of Head of Department, working there till 1955. It was during this period that he carried out his famous work of preparing purified lepromin, which is now called Dharmendra lepromin. Most-widely used in India and other countries. Dharmendra lepromin produces both early and late reactions in skin testing. As a proponent of Indian classification of leprosy, Dr Dharmendra strongly defended and advocated it at all international congresses.

Dr Dharmendra held several important positions in India. When the National Leprosy Control Programme was planned in 1955 Dr Dharmendra was chosen as its first Director, and he laid the foundation for the control work, which has now grown to a mammoth size. When the Central Leprosy Teaching and Research Centre was started, Dr Dharmendra was appointed as its first Director in 1957. He built up the Institution from scratch to an internationally recognized centre. He served there until his retirement in 1966. Subsequently he continued his work there as an Emeritus Scientist with the Indian Council of Medical Research.

The name of Dr Dharmendra has been closely linked with the *Indian Journal of Leprosy* from the time of its inception. He was the Editor of the Journal for almost 40 years with a few short breaks; and even during these breaks he maintained a close link with the Journal. Finally with the October 1989 issue of the Journal he retired at 90 years of age; only because he was physically unable to carry on any longer. The Journal was indeed Dr Dharmendra's 'baby' which he had carefully nurtured from 1938. Dr Dharmendra was also the author of a textbook on leprosy, and several small booklets, pamphlets and health education material.

In appreciation of his work, Dr Dharmendra received several honours including the title 'Padmashree' from the Government of India, the Damien-Dutton Award and the International Gandhi Award. Dr Dharmendra has left an indelible mark on the history of Indian leprology.

K V DESIKAN

THACHAKKADU NATESA JAGADISAN 1909–91

Professor Thachakkadu Natesa Jagadisan born on 2 October 1909 was an outstanding man who had a worldwide influence on the care given to those suffering from leprosy, a disease he developed when he was 10 years old. His father had just died, having been a victim of the post-war influenza epidemic. C. K. Rao writes, 'Having neither resources nor resourcefulness, the little Jagadisan was in a lonely prison of fear for he had heard people say the most fearful things about leprosy and thought himself doomed to be one of those wretches he saw in the streets; the abandoned victims of the disease.

Fortunately, Jagadisan's leprosy was quiescent and he was able to take his Honours Degree in English Language and Literature in 1930 and teach for 11 years, having married Asanambal when a schoolboy of 14.

In April 1934 Minakshi was born. Sadly she had infantile convulsions which developed into epileptic fits and, in her 'teens, brain fever. She became completely dependent on others for everything. In his later years Jagadisan was worried who would look after her, but fortunately she predeceased her mother and father.

A second daughter, Sulochana was born in August 1937 and she brought lasting joy and gladness to her father, especially by giving birth to Sankaran a very much loved and able grandson currently studying in the UK. In 1938 Natarajan was born, but Jagadisan's only son was destined for a very short life and died of pneumonia in August 1942, a year which became a turning point in the Professor's life. Not only did he have to face the death of his son but also the humiliation of being refused a lecturership at a college in Trichinopoly because of his leprosy, despite a medical certificate from Dr Robert Cochrane certifying that, 'he is non-infective and is no danger to the public'.

The decision, in Jagadisan's own words caused neither disappointment nor sadness. He was already, 'familiar with the wild fear and prejudice of people towards leprosy and the consequent social injustice to which the innocent sufferers are subject'. However, it did start Jagadisan on the road to fulfilment and international fame. Now he knew that his life's work was to educate people in the simple facts of leprosy so that it would be viewed as a disease and not dreaded as a social disgrace.

Once again Cockrane helped by giving Jagadisan a post in the Madras branch of the British Empire Leprosy Relief Association, BELRA, as the Honorary publicity officer, in 1943. The Sir Dorabji Tata Trust provided a modest stipend which, 'secured me life without anxiety in which to serve a sacred and dear cause'. In 1945 he became the Honorary Secretary of the same organization.

Following political developments, the Hind Kusht Nivaran Sangh (HKNS), took over, in 1950, the assets and liabilities of the Indian Council of BELRA which had been set up in 1925. The Minister for Health for India, Amrit Kaur, offered Jagadisan the post of Secretary, a job which 'needs courage and patience and few have that sympathy in the same measure as one like you who has suffered and serves'. Jagadisan became the organizing secretary of the HKNS, a post he held until 1970.

Jagadisan needed to become more actively involved in leprosy work and as a result of a meeting he and Cockrane had with Mahatma Gandhi on the 8 February 1945 the Kasturba Kushta Nivaran Nilayam was approved and through immense effort and drive on Jagadisan's part set up at Malavanthangal. The nearest railway station was 10 miles away, so having left Madras early in the morning Jagadisan, his wife and two children arrived by bullock cart late in the evening. It was a thrilling moment for all the villagers when at midnight on the 15 August 1947 Jagadisan first hoisted the Indian national flag in this remote village. Mahatma Gandhi shared Jagadisan's confidence that leprosy could be conquered and when asked to open the Kasturba Kushta Nivaran Nilayam replied 'Get someone to open it, opening a hospital is not a big matter but I shall come to close it'.

In spite of dedicated work and great support, Gandhi was not able to carry out his wish. The

results however speak for themselves, in 1945 the overall prevalence of leprosy in the area was 48 per 1000 and in 1987 only 3 per 1000! Not content with providing modern drugs for the 100 or more villages, Jagadisan also arranged dental and eye treatment for the area.

Jagadisan's influence was much wider and by maintaining his position as Honorary Advisor for BELRA, now LEPRA, in India he travelled the length and breadth of India vetting requests for support. He was particularly interested in children's work as he saw this as very important. Jagadisan's advice and integrity could always be relied upon and he quickly developed a very wide network of friends in the leprosy field, especially those in the charity world. He was never at a loss to find someone or some organization to help a deserving cause.

Despite the increasing difficulties caused by his leprosy, Jagadisan travelled widely in the cause of leprosy and took an active part, not only in many Leprosy Conferences in India from 1947 to the XII International Congress held in New Delhi in 1984, but also in international leprosy congresses held in Madrid, Tokyo, Rio de Janeiro, and London. He had friends everywhere and was much sought after as a speaker and writer on his pet subject.

Many awards came his way in later years, but the one he treasured most was the International Gandhi Award for Distinguished work in Leprosy given in 1988. In presenting the award The President of India, Mr R. Venkataraman, concluded his presentation speech by saying:

> 'Professor Jagadisan, in presenting you this Award, I am not just placing it in a Gandhian's hands, but through them, at the feet of the Master, whose name it bears.'

It was in fact a stroke of fortune, not only for Jagadisan but also for the cause of leprosy, that he caught leprosy in his youth. His life, which started with so many setbacks, was truly one of 'fulfilment through leprosy'.

G F HARRIS

HENRY E HOBBS, FRCS, DOMS, DO
1910–1990

Henry Hobbs died on 3 October 1990 aged 80. He was formerly consultant ophthalmic surgeon to the Royal Free Hospital and Maida Vale Hospital for Nervous Diseases and honorary consultant to Moorfields Eye Hospital in London. An obituary notice in the *British Medical Journal* stated that during his working life ophthalmology matured as a surgical specialty and scientific discipline and that he played a significant part in this. His contributions were numerous and he had a particular interest in glaucoma, the use of lasers in diabetic retinopathy, the retinotoxicity of chloroquine and the ocular complications of leprosy.

I should like to give further details on this latter fact. Henry Hobbs was the honorary ophthalmic consultant to the Hospital and Homes of St Giles for sufferers from leprosy at East Hanningfield, Essex for 24 years and during that time he had the care of a very considerable number of patients with ocular complications of all degrees of severity. He was a most kind and courteous man and showed meticulous care in his examination, treatment and follow-up of all his patients over the years. He published several articles in leprosy journals on the blinding lesions of leprosy and he introduced the simple pen–torch illuminated loupe, which has been of great help in the diagnosis of uveitis to many leprologists working under field conditions. He was always willing to give time to train doctors in the detailed examination of the eyes in leprosy. He paid visits to several centres abroad, in particular Sungei Buloh, Malaysia and Chikankata, Zambia to make surveys and to assist and train the local workers in the management of eye conditions. In his last working year he cooperated in a joint investigation into the ocular histopathology of animals experimentally infected with *Mycobacterium leprae* and *M. lepraemurium*. His work was always of the highest standard and he will be remembered with affection and gratitude by many people.

D J HARMAN

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Letters to the Editor

EXPERIENCE OF MULTIDRUG THERAPY BLISTER-CALENDAR PACKS IN AN URBAN LEPROSY CONTROL PROGRAMME IN BOMBAY

Sir,

Blister–calendar Packs (BCP) have been used as an alternative method of dispensing multidrug therapy (MDT) in a DANIDA assisted National Leprosy Eradication Programme in a few districts in India since 1987. The preliminary observations made so far are in favour of using the packs in leprosy programmes.[1,2] To make further observations in a metropolitan city leprosy programme, blister–calendar packs were used in the Bombay Leprosy Project on a small scale and the following observations were made.

A total of 235 leprosy patients (MB, 54; PB, 181) were considered separately for studying the compliance of the intake of self-administered doses of MDT. Fifty patients who were previously under MDT with loose capsules and whose urine test results for dapsone were available were taken as a control (group A). Subsequently, the same group was given BCP MDT treatment (group B). Additionally 185 new patients were also given BCP MDT treatment (group C). Urine samples were collected during the mid-period of two pulse doses by paying surprise home visits. For 3 consecutive months urine was tested qualitatively for dapsone. The urine test results of 50 patients from group B were compared with their earlier results during loose capsule treatment (group A). The compliance rate ranged between 78 and 96% in group B which was the same as when they had received loose capsule treatment. In group C the compliance rate ranged between 70 and 96%. This indicated that MDT delivery through BCP did not influence the intake of self-administered doses.

However, other operational advantages like ease of drug accounting, storage and dispensing were confirmed by the administers. The patients also confirmed that BCP were easier to look after at home and more convenient to carry while travelling. The last tablet reminded patients about clinic day.

While considering the application of BCPs, operational advantages of this alternative delivery should be given more consideration than the increase in patients' compliance for self-administered doses.

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STATUS OF THE MULTIBACILLARY LEPROSY PATIENTS TREATED WITH COMBINED REGIMENS OF 1 YEAR DURATION, AFTER A MEAN FOLLOW-UP OF MORE THAN 5 YEARS

Sir,

In *Lepr Rev*, 1989; **60:** 109–17 and 118–23 the results of two studies concerning two treatment regimens in multibacillary leprosy were published. These studies concerned, respectively, 919 patient years of follow-up with a mean of 4·29 years and 1121 patients with a mean of 3·8 years. Most of these patients have been further followed and some patients lost to follow-up during the previous years have been re-examined in 1989 or 1990. One relapse case has been diagnosed.

We therefore would like to present the data concerning these two studies as of October 1990.

Regimen 8-44 RED: rifampicin (RMP) 600 mg, ethionamide (ETH) 500 mg and dapsone (DDS) 100 mg daily (except Sundays) for 8 weeks, followed by RMP 600 mg once a week with ETH 500 mg and DDS 100 mg daily for 44 weeks. DDS was replaced by CLO in patients harbouring DDS-resistant organisms.

Results are as follows:

Follow-up (years)	No. of patients seen	Person years of follow-up (cumulative)	No. of relapses	Confidence interval for 0 or 1 relapse per 100 person years	No. of late reversal reactions (%)
1	214	214	—	0–1·73	—
2	211	425	—	0–0·87	4 (1·80)
3	203	628	—	0–0·61	2 (0·98)
4	198	826	—	0–0·46	3 (1·5)
5	184	1010	—	0–0·37	5 (2·7)
6	151	1161	—	0–0·37	2 (1·3)
7	86	1247	—	0–0·30	—
8	21	1268	1	0–0.50	—

The mean follow-up is now 5·9 years. One relapse occurred in Anjouan, 98 months after the end of therapy and was diagnosed clinically and confirmed by the bacteriological and histological examinations. The *Mycobacterium leprae* strain has been inoculated into mouse foot-pads, results are not yet available. Reversal reactions are diagnosed when lesions show clinical activity in the absence of bacteriological and histopathological evidence of relapse, and reside spontaneously. The mean and median interval between the end of treatment and appearance of a reversal reaction was 40 months.

Regimen RED/D: daily (except Sundays) supervised, RMP 600 mg, ETH 500 mg, DDS 100 mg during 6 months, followed for 6 months by daily, unsupervised DDS 100 mg.

RED/ED: identical with RED/D during the first 6 months, but followed for 6 months by daily unsupervised ETH 500 and DDS 100 mg.

REC/C: identical with RED/D, but DDS replaced by CLO 100 mg.

REC/EC: identical with RED/ED, but DDS replaced by CLO 100 mg.

No relapses were observed.

Results for all patients combined are as follows:

Follow-up (years)	No. of patients seen	Person years of follow-up (cumulative)	Confidence interval for 0 relapse per 100 person years	No. of late reversal reactions (%)
1	296	296	0–1·27	4 (1·30)
2	279	575	0–0·66	7 (2.50)
3	263	838	0–0·45	8 (3·00)
4	242	1080	0–0·37	4 (1·60)
5	204	1284	0–0·30	3 (1·40)
6	140	1424	0–0·20	—
7	61	1485	0–0·20	—
8	17	1502	0–0·19	—

The mean follow-up is now 5·07 years. No relapses were diagnosed. The mean interval between the end of treatment and the appearance of a reversal reaction was 41 months, median 38 months.

Results for regimens RED/D and REC/C combined are as follows:

Follow-up (years)	No. of patients seen	Person years of follow-up (cumulative)	Confidence interval for 0 relapse per 100 person years
1	147	147	0–2·43
2	138	285	0–1·31
3	129	414	0–0·92
4	116	530	0–0·74
5	98	628	0–0·61
6	71	699	0·0·53
7	33	732	0–0·45
8	10	742	0–0·44

Results for regimens RED/DE and REC/CE combined are as follows:

Follow-up (years)	No. of patients seen	Person years of follow-up (cumulative)	Confidence interval for 0 relapse per 100 person years
1	149	149	0–2·43
2	141	290	0–1·23
3	134	424	0–0·92
4	126	550	0–0·68
5	106	656	0–0·57
6	69	725	0·0·53
7	28	753	0–0·49
8	7	760	0–0·49

We wanted to show these results because the mean duration of follow-up is now above 5 years for both studies, and to emphasize once more that it is possible to stop treatment in multibacillary leprosy when the BI is still positive, and, since the relapse rate is so low, it is probably possible to treat multibacillary leprosy for a shorter period of time than 1 year. However, at present,

ethionamide should be replaced by other drug(s) that were unknown when the above studies were undertaken.

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COMMENT: LEPROSY DEFORMITIES: EXPERIENCE IN MOLAI, NIGERIA

Sir,

I read with interest the paper by B B Iyere, 'Leprosy deformities: experience in Molai Leprosy Hospital, Maiduguri, Borno State, Nigeria', (*Lepr Rev*, 1990; **61:** 171–9).

Lagophthalmos was tested in this article by asking the patient to close his/her eyes as tightly as possible . . . if there was a lid gap, it was recorded as lagophthalmos. This procedure however will lead to an underestimation of lagophthalmos. 'Generally the delicate palpebral fibres fail before the stronger orbital ones, thus a patient may sleep with the cornea exposed, yet can close the lids by voluntary effort'.[1] 'In milder degrees the patient may be able to close the eyes by voluntary effort, while they may remain open in sleep, but in the more pronounced degrees even forcible squeezing becomes ineffective and the eyes remain permanently unclosed'.[2]

It is therefore recommended to test for lagophthalmos by asking the patient to close his/her eyes mildly, as in sleep and then to observe and measure the lid gap in millimetres.

Any gap of ≥ 1 mm is considered to be lagophthalmos. In the case of a gap in mild closure of ≥ 5 mm or if the lower part of the cornea is exposed during mild closure eyelid surgery is recommended for better closure and protection of the eye.

To test for lid weakness, if there is no gap on mild closure, the patient can be asked to close his/her eyes as tightly as possible, while the examiner tries to pull the eyelids gently apart.

From the results mentioned in the article: eyelid weakness was found in 2·7% of the males and 17·6% of the females, whereas the lagophthalmos found is more or less alike, 2·2 and 3·1% respectively, one may wonder if the women for cultural or physical reasons may have given less resistance towards forced opening of the eyelids than the men. In my experience eyelid weakness and lagophthalmos occur alike in both sexes.

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COMMENT: A LOOK AT WORLD LEPROSY

Sir,

Recommending multibacillary (MB) drug regimes to erstwhile MB cases, who for decades have been smear negative following prolonged periods of dapsone monotherapy is a debatable issue

despite consensus among many leprologists and widespread compliance. WHO recommendations have been brought to light in your special article (*Lepr Rev* 1991; **62:** 72–86). Though these were made under 'very special circumstances' and were directed 'primarily towards leprosy control' it does not clarify many issues. What of the individual who has had no signs of activity whatsoever, no clinical or bacteriological evidence of leprosy for at least 10 years and has further received many years of dapsone monotherapy prior to achieving smear negativity? Am I right in understanding that in such an unsuspecting individual instead of stopping his therapy, we administer two other drugs for 24 months? While I concede that there may be epidemiological reasons for this, where is the definitive clinical indication? Also does lepromin negativity by itself warrant therapy? Clofazimine therapy while relatively well tolerated may still occasionally result in abdominal emergencies. Skin discolouration is also unacceptable to many and this in itself has become a stigma of late. Rifampicin too has its well known hepatic and renal side-effects.

There being no clear clinical indication to commence fresh therapy in such situations I would prefer to stop monotherapy and have regular yearly reviews of these patients for life. I must concede that this is applicable only to 'special settings' like ours where most such treated MB cases live in a colony, a stone's throw from our base hospital and who are not likely to abscond. If it is 'persisters' that one is concerned about a compromise could still be made by choosing the WHO's PB MDT regimen to eradicate them, thus avoiding the addition of a third drug. At least under such 'special circumstances', clinicians must have the freedom to assess individual cases on their own merit and choose an appropriate line of management. I personally feel that directives from governmental and other authorities should not infringe on the rights of individual clinicians to pursue a rational line of management, at least in special situations. Also the ethical question of giving new drugs to apparently healthy individuals while at the same time avoiding negligence remains to be answered. What would be your (or the author's) advice for situations like this?

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V K EDWARD

REPLY: RECOMMENDING DRUG REGIMENS TO SMEAR NEGATIVE MB CASES AFTER PROLONGED DAPSONE MONOTHERAPY

Sir,

The question of how to deal with dapsone-treated smear-negative multibacillary patients was discussed in the WHO Expert Committee on Leprosy. *Sixth Report* (WHO Technical Report Series No. 768, 1988) which made the recommendation that, where resources permit, such patients should be given MDT for two years. It is this recommendation that is referred to in my paper. The reason for giving MDT is to prevent relapse which occurs at the rate of about 2% of patients per year. While the recommendation of the Expert Committee is generally for leprosy control programmes with the proviso 'where resources permit', in individual instances judgements may have to be made on the basis of the specific local situation. In a wider context, it is pertinent to point out that one of the factors making leprosy control successful through MDT possible is the application of standard treatment regimens and procedures rather than individualized treatment approaches.

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S K NOORDEEN

COMMENT: CLOFAZIMINE-INDUCED LYMPHOEDEMA

Sir,

In the light of a previous observation reported on clofazimine-induced lymphoedema[1] we would like to report our observations on 75 patients who are being treated at the Leprosy Mission Hospital, Shahdhara, Delhi.

Seventy-five patients were seen at random from June to December 1990 as they presented to the regular outpatient clinic for their monthly check-up and antileprosy treatment. Seventy-two of them had been on multidrug therapy (MDT) for paucibacillary or multibacillary leprosy for some length of time.

The patients were aged between 10 and 55 years, with a mean age of 30 years for males and 29 years for females. The types of leprosy seen among these patients were as follows: of the 60 male patients 26 had lepromatous leprosy, 28 had borderline–lepromatous leprosy, 5 had borderline–tuberculoid leprosy and 1 had tuberculoid leprosy. Among the 15 female patients 4 were lepromatous, 8 were borderline–lepromatous and 3 were borderline–tuberculoid.

None of these patients had any cardiovascular, renal, hepatic, filarial or nutritional disease prior to or after commencement of MDT.

Forty-five of these patients had pedal oedema, which we have found to be varied in nature and of possibly different aetiology. On clinical assessment and on reviewing their histories, the following observations were made:

1 Of these patients, 9 had either plantar ulcers or some foot deformity on the same foot on which the oedema was observed. This could possibly imply that the oedema in these patients might have been aggravated by the plantar ulcer or foot deformity.
2 Pedal oedema in both feet before starting MDT was present in 16 patients. Four of these patients were definite that the oedema had subsided after the onset of therapy. This could possibly imply that the oedema in these patients was a consequence of the disease process itself. Two of the 16 patients developed oedema of the hands after MDT was started, though there was no evidence of either Type I or Type II reaction.
3 Two patients with plantar ulcers on one foot had developed oedema of the opposite foot after MDT was started. This could have been due to a compensation in the stance, trauma, or clofazimine.
4 History of recurrent ENL was given by 8 patients who had been on steroids. One of these patients had also been on long-term steroids for ulnar neuritis. There is a possibility that in these patients the pedal (peripheral) oedema could be due to steroids.
5 What interested us the most was that there were 10 patients at least who did not have any pedal oedema before MDT, but who subjectively and symptomatically complained of a development of oedema of the feet after the onset of therapy. One patient showed oedema more in one foot than the other, though there was no obvious pathology of the foot.

It appears to us that the pattern of pedal oedema in these 10 patients was similar to that of the patients reported earlier.[1] We would like to suggest that the pedal oedema in these 10 patients could be due to a lymphatic stasis produced by clofazimine in the lymphatic channels.

Clofazimine has been shown to be deposited in the lymph nodes by various histopathologists,[2 4] and such deposition was considered to be responsible for abdominal pain.[5] One report also mentions the development of persistent ard generalized oedema in a patient who was given clofazimine 100 mg daily, with prednisolone 10 mg.[6]

We intend to follow up these patients who have been studied in a randomized and retrospective manner. Radiological and biochemical studies are also being planned. But we would certainly be interested in receiving comments from leprologists, pathologists, pharmacologists or others on the

possibility of clofazimine-induced lymphoedema, and we would also like to know if similar reports or observations have been made in any other centre.

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Lepr Rev (1991) **62,** 343–345

Book Reviews

Guido Groenen *La lépre en pratique.*

This book is written for district medical officers who are in charge of the overall health problems in the district and for whom leprosy is also one of their responsibilities.

The author has successfully used simple language and therefore the book reads very easily. One has the impression that it is a compilation of notes prepared for a course in leprosy and edited in bookform. There are very many cross-references from one paragraph to the other, e.g. see 5.8.3.1., see 5.8.3.2.

The book consists of 7 chapters, 5 appendices followed by a very practical and adequate bibliography mentioning the most important and recent publications on leprosy and its control which are available in French, and a list of addresses where these publications can be obtained.

Chapter 1, bacteriology; Chapter 2, immunology; Chapter 3, epidemiology: the term 'infection' is not well defined and the treatment of all existing cases is discussed under primary prevention, which in fact is a secondary prevention. Chapter 4, signs and symptoms. Here most of the signs and symptoms which may occur in leprosy regardless of the classification, are given a short description. After reading this chapter, it is still impossible to make a diagnosis of leprosy, which is handled in the following chapter. The distinction between primary and secondary deformities is somewhat mixed up.

Chapter 5, management of patients is the main part of the book (131 pp.). It covers quite a number of subjects, after a short introduction there follows case-detection, how to examine a patient, diagnosis and classification (Jopling), treatment (WHO), reactions, rehabilitation and eye lesions. As a whole this chapter is excellent. Definitions and decisions to be taken are short and clear and contain many practical details useful under field conditions. Under bacteriological examination, it is a pity that the sequence in which the smears have to be put on the slide is not stressed: first smear on the far end from the number or the other way round. The author warns, under classification, that 'tuberculoid leprosy' is not synonymous with paucibacillary (PB), but in a few occasions tuberculoid is used where it should be PB. Reversal reactions are mentioned as 'réaction type 1', 'réaction réverse' or 'réaction d'inversion'.

The use of only one term may avoid possible confusion. In differential diagnosis, a short description of the most common African diseases is given, together with the differences from leprosy and suggestions for their treatment. This latter point is a very welcome idea. Rehabilitation deals mainly with the treatment of deformities in the field as far as possible.

Chapter 6, health education in leprosy; Chapter 7, planning of a leprosy control programme. This chapter is intended for a more senior level: central or provincial. It is a short summary of a few publications mentioned in the bibliography.

The Appendixes refer mainly to practical techniques in the laboratory, rehabilitation, eye examination and treatment, suggestions for documents which need to be kept and the day-to-day management of the project. The explanation and example on how to calculate the drug requirements for a certain period, so that there is no shortage and wastage of drugs, is very practical.

In summary it is a very practical and adequate book for people in the field who have to deal with leprosy and it deserves widespread distribution in French-speaking Africa.

J A Cap

Published by Damien Foundation, rue Stévin 16-B-1040 Brussels, Belgium, 1990. $3.00

***Leprosy*, Third Edition. Anthony Bryceson and Roy E. Pfaltzgraff**

This excellent handbook should prove of value not only to medical students and doctors in leprosy endemic countries but also to workers in other fields who require a basic introduction to that aspect of the subject which impinges on their own discipline.

The first four chapters provide a sound scientific introduction, the clear description of the clinical features following on logically from the masterly chapter on Clinical Pathology.

Diagnosis is dealt with comprehensively, with due note being taken of the pitfalls presented by other skin conditions common in the tropics.

The chapter on treatment summarizes the properties of the various drugs in common use and more particularly those constituting the WHO-recommended multi-drug regimens. It emphasizes the importance of early recognition and prompt treatment of reactional conditions and the associated neuritis and stresses the need for education of the patient both as to compliance with the prescribed therapy and as to the prevention of disability.

The basic elements of immunology are presented clearly and simply and related to the clinico-pathological spectrum of leprosy and to reactions. Matters on which there is controversy or difference of opinion among the experts are identified so that the result is a generally acceptable consensus.

A short chapter on the management of reactions is of practical value both to the hospital doctor and to the field worker. The observation that 'Early diagnosis and treatment and energetic management of reactional states should prevent the development of all disabilities' deserves wide publicity. The authors' experience that clofazimine is of value in the treatment of Type 1 reactions is not shared by all workers, but otherwise the measures advocated are those generally recommended.

The complications due to nerve damage are well described and are illustrated by some particularly good photographs and clear diagrams. At the outset it is emphasised that 'Prevention of nerve damage needs to be constantly stressed as the single most important aspect of leprosy management and one that is often neglected', and the authors proceed to do this in the following chapters on the Eye in Leprosy, Physical Rehabilitation (which includes much of great practical value in the prevention and management of plantar ulceration) and Social, Psychological and Vocational Rehabilitation.

The final chapters cover Experimental Leprosy, with a historical review as well as an up-to-date account of recent advances; Epidemiology, in which the authors aim to provoke thought and further study by posing relevant and important questions, rather than to provide answers unsupported by firm data; and Leprosy Control which reviews the principles and the methods currently in operation, their achievements and their limitations, and concludes with a timely call for the development of practical measures for primary prevention.

Almost inevitably there are a few typographical errors but these do not detract from the high quality of the presentation. Readers whose first language is not English will find the text readily understandable and will appreciate the didactic style. Many will find the list of references for 'Further Reading', given at the end of each chapter, especially helpful.

Hopefully, this Third Edition will enjoy even greater popularity than its predecessors.

Harold W Wheate

Published by Churchill Livingstone, Edinburgh, 1990. 256 pp; £9.95; ISBN No 0 443 03373 0.

The Indian Leprologists Look Back

A questionnaire was sent to 22 Indian leprologists of international reknown and the replies, tape-recordings, received from 16 of them comprise this interesting collection of informal, personal reminiscences. The group includes clinicians, surgeons, epidemiologists and research workers. The brief accounts of their work and achievements, as well as their varied perspectives on present trends in leprosy control and their hopes for the future, constitute a historical summary of leprosy work in India during the past 40 years. At the same time they give us an insight into the personalities and motivation of some of the best known leprologists of our day.

The book has been produced most economically (financial support from three leprosy voluntary organizations is acknowledged) to make it available to all grades of leprosy workers in India as a means of encouragement and indeed of inspiration. However, it should have a wider appeal and is warmly recommended as light reading by all involved in leprosy control and the care of leprosy patients.

Harold W Wheate

Acworth Leprosy Hospital Society for Research, Rehabilitation and Education, Wadala, Bombay-400 031, India. Price Rs. 25/–.

Lepr Rev (1991) **62,** 346–348

Teaching Materials and Services

Hesperian Foundation; a book on disabled village children

Over 50 million children in the world are seriously disabled. It is sometimes argued that in poor countries, rehabilitation services are too expensive or require too much skill to be included in 'primary health care'. But experience in many countries shows that effective low-cost rehabilitation can and should be a basic part of primary care. Often the best programmes emerge when disabled persons and their families organize and run their own programmes.

Disabled Village Children has grown out of Project PROJIMO, a community-based rehabilitation programme in western Mexico run by disabled villagers. Experts from many countries in many fields of rehabilitation have helped in creating and revising the book. Five years in the making, the book has been developed with financial support from UNICEF, OXFAM, the Public Welfare Foundation, and several other private foundations.

Disabled Village Children is a 'reference book' that gives simplified but detailed information on almost every aspect of disability and rehabilitation. It includes information normally only available to professionals (therapists, doctors, brace makers, wheelchair builders, rehabilitation engineers), but in simple, clear English, with many pictures. This allows concerned persons with little schooling to understand basic concepts, to provide effective assistance, and to make appropriate aids at low cost, using local resources. 672 pages.

Price: $11.00 post paid in the USA; $9.00 each for 12 or more copies.

Special price for orders from and paid for by a poor country: $7.00 each for 1–11 copies; $6.00 each for 12 or more copies, this includes postage. Apply: Hesperian Foundation, PO Box 1692, Palo Alto, CA 94302, USA.

Leprosy—teaching and learning materials in French

A booklet in French, describing the full range of material available in the French language, is now available from: Association Francaise Raoul Follereau, 31 rue de Dantzig, BP 79, 75722 Paris Cedex 15, France. The material is classified as follows: basic texts, general information, epidemiology, clinical dermatology, laboratory work, treatment (MDT), surgery/rehabilitation and health education and a numerical system indicates which items are most suitable for health workers at different levels.

Leprosy—basic information and management in Bengali

The above book has been translated by Dr D S Chaudhury, Calcutta and is available from him at Greater Calcutta Leprosy Treatment and Health Education Scheme, 23 Market Street, Calcutta 700 087, India.

(This booklet is also available in English, French and Spanish. An Indonesian translation is in progress.)

Facts for Life; UNICEF, WHO, UNESCO

The health of children in the developing world could be dramatically improved if all families were empowered with today's essential child health information. The information has now been brought together in *Facts for Life*, published by UNICEF, WHO and UNESCO in partnership with many of the world's leading medical and children's organizations.

Facts for Life is a challenge to communicators of all kinds—politicians, educators, religious leaders, health professionals, business leaders, trade unions, voluntary organizations, and the mass media. It is for all those who can help to make its contents part of every family's basic stock of child-care knowledge.

Facts for Life is a practical contribution to the evolving primary health care movement. Intended principally for the developing world, its national and international versions bring together today's essential family information on maternal and child health care. That information—about birth-spacing, safe motherhood, breastfeeding, weaning and child growth, immunization, diarrhoeal diseases, respiratory infections, domestic hygiene, malaria and AIDS—could now enable most families in the developing world to make significant improvements in their own and their children's health. *Facts for Life* is therefore an aid to achieving the first level of primary health care–a well-informed community.

Address: UNICEF, DIPA, Facts for Life Unit, 3 UN Plaza, New York, NY 100017, USA.

School of Medical Education, New South Wales, Australia

The World Health Organization Regional Training Centre for the Western Pacific Region and the Centre for Medical Education Research and Development were established in 1973 at the University of New South Wales through a Tripartite agreement between the World Health Organization, the Commonwealth Government and the University of New South Wales. Their primary goal was to assist in raising the standards of health care through the advancement of education for the health professions. That goal has broadened to encompass the training of all those involved in health development. In September 1983 Council of the University approved a Faculty of Medicine resolution to upgrade the Centre to a School of Medical Education. The School trains teaching staff for the health professions, managers of health services, and those working with health development in the community, assists organizations responsible for education and training programmes, provides consultant services and conducts research.

The school operates at Faculty level within the University of New South Wales Medical School, at the national level in collaboration with various institutions within Australia, and at the regional level in collaboration with the World Health Organization as the WHO Regional Training Centre in the Western Pacific Region.

The WHO Regional Training Centre receives an annual grant from the Commonwealth Department of Community Services and Health. WHO provides per capita funds for sponsored students. The Centre also receives funds through tuition fees, consultants' fees and contractual arrangements with various organizations.

The academic programme within the University includes a Master's degree course in Health Personnel Education by coursework or research, advanced study and research in the field of health personnel education and health development leading to the degree of Doctor of Philosophy, a series of intensive courses on specific educational topics, and a seminar programme.

A Master's degree Course in Public Health in now also offered in conjunction with the Schools of Health Services Management and Community Medicine.

In 1991 a Master/Graduate Diploma of Clinical Education will be introduced within the School. This will be a specialized post-graduate course designed for professional upgrading of clinicians.

Within Australia and the Region, consultant services are provided to teaching institutions, government departments and professional associations seeking assistance with educational management problems.

Applied research and evaluation studies are undertaken with a view to improving the quality of education for health personnel and its relevance to health care needs. Continuing evaluation of the School's own teaching programme and consultant services aims to ensure their relevance to the diverse needs of clients and students.

Address: School of Medical Education, University of New South Wales, PO Box 1, Kensington, NSW, Australia 2033.

CONTACT

CONTACT is the periodical bulletin of the Christian Medical Commission (CMC), a sub-unit of the World Council of Churches (WCC). It is published six times a year in English, French, and Spanish. Selected issues are also published in Portuguese in Geneva, Kiswahili in Kenya and Tanzania, and Arabic in Egypt. Present circulation exceeds 35,000.

CONTACT deals with varied aspects of the community's involvement in health and seeks to report topical, innovative, and courageous approaches to the promotion of health and integrated development. A complete list of back issues is published in the first annual issue of each language version. Articles may be freely reproduced, providing that acknowledgement is made to *CONTACT*, the bi-monthly bulletin of the CMC/WCC.

Address: CMC/WCC, PO Box 2100, CH-1211, Geneva 2, Switzerland.

Appropriate Health Resources and Technologies Action Group: AHRTAG

AHRTAG's Disability Unit was established in 1981, and is concerned with improving the quality of life for disabled people in developing countries and supports the integration of disabled people within their communities.

The Unit has a wide range of information and materials for tackling practical issues; workshop materials, appropriate technology aids and equipment.

The Disability Unit organizes seminars and workshops in collaboration with local organizations as an effective way of exchanging ideas.

The Unit also produces a free international newsletter called *Community Based Rehabilitation*, which offers a link for disabled people, exchange for ideas and practical information point for people with disabilities and people working with them.

AHRTAG produces various publications for disabled people which include: *We can Play and Move; Simple Aids for Daily Living; Personal Transport for Disabled People* and *Alternative Limbmaking*.

For any further information about AHRTAG's work and resources please contact: AHRTAG, 1 London Bridge Street, London SE1 9SG.

TALC: Teaching Aids at Low Cost

TALC has developed a wide range of books, booklets accessories and colour transparency sets with text, covering diagnostic, preventive and curative aspects of tropical health and disease, with particular attention to children, but including a great deal of information which is valuable in adult medical practice. The cost of any item is remarkably low, and still lower for applicants from developing countries. A complete subject and price list, together with details for ordering and despatch are available from: TALC, PO Box 49, St Albans, Herts AL1 4AX, England.

Programme for International Training in Health (INTRAH)

The Program for International Training in Health (INTRAH) of the University of North Carolina at Chapel Hill, USA has compiled a List of Free Materials in Family Planning and Maternal and Child Health, 1990. Recognizing that health professionals require reference and training materials to do their jobs effectively and to keep up-to-date in their fields, INTRAH has devised this list (in English and French) of materials available free of charge from health agencies around the world.

Information about how to obtain the list is available from INTRAH at the following addresses:

Catherine Murphy,
Training Materials Officer,
INTRAH,
208 N. Columbia Street,
Chapel Hill, NC 27514,
USA

Pauline Muhuhu, Director,
INTRAH/Angelphone,
P.O. Box 55699,
Nairobi, Kenya.

Pape Gaye, Director,
INTRAH/Francophone,
B.P. 12357,
Lomé, Togo.

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News and Notes

TDR call for applications for support of research training

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), established in 1976, has two objectives:

(1) research and development of new tools to control the TDR target diseases: malaria, filariasis (including onchocerciasis), African trypanosomiasis and Chagas disease, leishmaniasis, schistosomiasis and leprosy;
(2) strengthening of research capabilities in countries where these diseases are endemic.

As an important way to achieve its second objective, TDR provides funding to train research workers from disease-endemic countries. TDR support enables research workers to acquire research skills related to one or more of the TDR target diseases or in a discipline related to these diseases, such as molecular and cell biology, immunology, entomology, parasitology, epidemiology, clinical pharmacology, and the social sciences. Applications relating to product development and molecular entomology are also welcome. Funding is available for opportunities in established training programmes for studies leading to a doctoral level degree, or for an individualized post-graduate programme in a centre which conducts research in tropical diseases. Support for Masters level courses will be considered in exceptional cases.

The maximum duration of TDR support for research training is three years. Those eligible to apply for research training include:

- staff members of (i) institutions currently receiving one of the TDR institution strengthening grants, and (ii) other institutions where TDR support for such grants came to end two to three years ago;
- scientists from other institutions who are already engaged in research or committed to doing research on one or more of TDR's target diseases, and whose home institution is equipped with required research facilities;
- staff members of Ministry of Health disease control services who are involved in planning, executing and evaluating disease control programmes related to TDR's target diseases;
- scientists who have had appropriate post-graduate training in epidemiology, social sciences, and other field-oriented subjects and who require practical, hands-on (postdoctoral) training in a research project or suitable institution doing field research in one of TDR's target diseases;
- scientists with post-graduate research training who have been actively involved in clinical, field or laboratory research in one of TDR's target diseases for a minimum of five years and who now want to spend a period of time in a suitable research centre or laboratory to upgrade their skills or to carry out specialized experiments or data analyses.

Address: Dr J A Hashmi, Special Programme for Research and Training in Tropical Diseases, WHO, 1211 Geneva 27, Switzerland.

African Medical and Research Foundation (AMREF)

The following is extracted from the current AMREF brochure:

Good health is a state which very few of us achieve, though we all aspire to it and consider it our due. In many parts of Africa however, it is bad health that is taken for granted. World Health

Organization statistics show that poor nutrition and lack of clean water are the cause of 80% of ill health.

AMREF, the African Medical & Research Foundation, founded in 1956 by Sir Archibald McIndoe together with two of his former pupils, Sir Michael Wood and Dr Tom Rees, is dedicated to changing this. As well as providing better medical care, AMREF is working to assist rural communities to improve social conditions. AMREF is particularly concerned that the health education and medical provision it offers are based on a sound knowledge of the customs, habits and associated beliefs of the people with whom it is working. The aim is for maximum participation of the community in its own health programmes. So AMREF collaborates with governments, developing health education through the training of African staff who are able to introduce change to their own people in a sensitive and appropriate way.

AMREF supports workshops where local people are employed to build homes and hospitals for the community. Projects to provide clean water and improved agricultural facilities are also part of the Foundation's work.

AMREF has responded to the challenge of Africa's vast distances and the isolation of its many tiny rural communities by developing a travelling health service. The Clinical Service has mobile ground units that visit the more remote areas in Kenya, Tanzania and Uganda, carrying out immunisation programmes, teaching programmes and general health care. This works as a cost effective alternative to specialist medicine which is often less appropriate and unobtainable in these poorer rural areas. Maternal Child Health Clinics are one of our major concerns where health workers, chosen by the community, teach the local people about nutrition, family-planning and sanitation.

To supplement these projects, AMREF trains local staff:

- recruiting suitable local people to form an integrated rural health service;
- providing refresher and extension courses;
- preparing teaching materials to be used in the classroom and as manuals;
- distributing a range of publications, audio-visual materials, and making regular radio broadcasts in Swahili and English.

Address: AMREF, 11 Waterloo Street, Clifton, Bristol BS8 4BT, England.

Action in International Medicine (AIM), UK

The following is extracted from the *Observer* newspaper, 4 April 1991:

British doctors are planning international action to stop millions of avoidable deaths in the Third World. A radical new group, supported by 68 medical colleges and academies worldwide, will formally launch its declaration of aims in Toronto in August.

'Any doctor who does not have a conscience about the millions of people who do not have access to medical care of any kind is not a full member of the profession', said Sir Gordon Wolstenholme, former director of the Ciba Foundation and motivating force behind the new group.

Sir Gordon hopes the organization, Action in International Medicine (AIM), will complement the work of the World Health Organization rather than compete with it.

As it is not tied to any government, it is hoped that AIM will prove to have greater flexibility and be considerably less bureaucratic and bothered by red tape.

The group has helped to establish three projects in the Third World, in Brazil, Zambia and Malaysia to train doctors in community and general medicine. Their training will enable them to run district hospitals, providing basic surgery and obstetrics and out-patient clinics to treat diabetes and high blood pressure and deal with paediatrics.

'We are not trying to whip up people to go and practice in the Third World, but to help raise standards and improve the basic training of local people. There is no point in going out and doing 5000 operations unless, when you come away, you leave doctors there better able to do the operation themselves.

'We want to see centres established to train doctors in general practice. Many developing countries provide good training in specialist fields, but are not good at producing the generalist who can cope with the health needs of the general population.

'In many countries, doctors who have just qualified have to work for two or three years in a district hospital to pay the government back for their training. But these hospitals are under-resourced and because the doctors have just qualified and are totally inexperienced, they usually hate it and leave as soon as they can.

'We feel that the best doctors should be put in these district hospitals and these jobs should be made more attractive.'

Address: Sir Gordon Wolstenholme, AIM, Windeyer Building, 46 Cleveland Street, London W1P 6DB, England.

Implants of levonorgestrel for contraception

The following is extracted from a report 'At arms length' in the latest *IDRC Reports*, Volume 18, No. 4, 18:

'NORPLANT capsules are the first contraceptive implants to become available for general use. NORPLANT has been approved in 15 countries and is currently being reviewed by the Food and Drug Administration (FDA) in the United States. It is estimated that close to half a million women are using, or have used, the implant worldwide, and the numbers are increasing rapidly.

The contraceptive part of NORPLANT is not new. The thin rubber capsules contain small doses of a synthetic hormone called levonorgestrel, a substance used in oral contraceptives for years.

What is new is the method by which the contraceptive is delivered: a continuous release of controlled amounts of hormone into the woman's body for a period of up to 5 years.

The development of NORPLANT is a fascinating and surprising story; fascinating, because it demonstrates how complex, costly, and fraught with hazards the process of developing a contraceptive can be. It is surprising because, despite the cost of over $20 million and 25 years of research, NORPLANT was not developed by one of the multinational pharmaceutical giants, but by the Population Council, an international non-profit organization based in New York.

Wayne Bardin, a vice-president of the Population Council, became involved with the project 10 years after it began. "There was a great deal of opposition to implants from population experts who were convinced that women would never accept the methods", he said. "Even I had some doubts". But the experts were wrong.

From the very beginning, the Council never had difficulty attracting volunteers to test the new contraceptive.

As is often the case in research and development, the creation of NORPLANT required a small measure of chance. It is just possible, for example, that if the Population Council's Dr Sheldon Segal had not had lunch one day in 1965 with a representative of the Dow Corning Corporation, the implant might never have been developed. Over lunch the conversation turned to Silastic, a polymerized silicone rubber material used by Dow Corning in artificial heart valves and other medical implant devices.

To Segal, Silastic material suggested another possibility—a contraceptive implant. If dyes and other liquids slowly dissolved through the Silastic implant, hormones, he reasoned, could also slowly release from the capsules into the body. He began to test his idea that same day in his laboratory on female rats. The concept was workable.'

UNICEF—Facts and figures, 1990

The above brochure gives an account of UNICEF's work in various parts of the world, together with a wealth of factual information under the headings of health, economy, immunization, demography, maternity, education, literacy, mortality, nutrition, water and sanitation. Address:

UNICEF Headquarters, UNICEF House, 3 UN Plaza, New York, NY 10017, USA. (UNICEF has regional offices in Australia, Columbia, Cote d'Ivoire, India, Japan, Jordan, Kenya and Thailand.)

Leprosy control: role of medical institutions—seminar held in Bombay, India

The above seminar was held in December 1990 and was sponsored by the Bombay Leprosy Project and PSM Department, LTM Medical College, Sion, Bombay. The report carries accounts of the talks given by Dr P S N Reddy, Dr C R Revankar, Dr Jerajani and Dr (Mrs) Shantha Sankaranarayanan. The views expressed are of interest to those who still struggle with the problem of persuading medical schools in leprosy-endemic countries to ensure that students receive appropriate training and clinical experience in leprosy. It would appear that India has made more progress in this endeavour than most other countries. The opening paragraphs of Dr Jerajani's contribution include the interesting observation that, '. . . leprosy is an integrated part of dermatology . . .' and that the Indian Association of Dermatologists and Venereologists has changed its title to include leprosy.

Blister–calendar packs for MDT in the Philippines

Following the use of locally-produced blister–calendar packs for multidrug therapy for leprosy in the Philippines in a pilot trial 1985–88, the National Leprosy Control Programme has used packs produced by Ciba-Geigy, on over 39,000 cases. Blister–calendar packs have also been used for tuberculosis in the Philippines (see Valeza FS & McDougall, AC, Blister–calendar packs for the treatment of tuberculosis, *Lancet*, 13 January 1991.

Antileishmanial effects of clofazimine and other antimycobacterial agents

The following is the authors' summary of a recent publication with the above title by Evans AT, Croft SL, Peters W in *Ann Trop Med Parasitol*, 1989; **83:** 447–54—'In the search for more effective alternatives to the presently used antileishmanial drugs, the activity of the major groups of antimycobacterial compounds has been examined, both *in vitro* and in animal models of infection. *In vitro*, clofazimine was the most effective compound tested, with a mean ED_{50} of 2·3 mg l^{-1} against *Leishmania mexicana amazonensis*, 1·4 mg l^{-2} against *L. donovani* and 0·5 mg l^{-1} against *L. major*. Other active compounds were the thiosemicarbazone thiambutosine and salinazid, a derivative of isoniazid. Isoniazid itself was inactive and rifampicin only partially active. *In vivo*, only clofazimine displayed significant activity, and it was most effective against cutaneous infections. It is considered that antimycobacterial activity is in general a poor predictor of antileishmanial potency.'

Reversal reactions and relapse after multidrug therapy, Hyderabad, India, 2-day workshop, December 1991

Dhoolpet Leprosy Research Centre is organizing a 2-day workshop cum training programme on reversal reactions and relapse after multidrug therapy (MDT) in leprosy on 9–10 December 1991 at Hyderabad. It is anticipated that over 200 doctors involved in leprosy will attend. Participants from the UK and Holland have also confirmed their participation. The subjects covered include: clinical aspects of relapse and reaction after MDT and their management; immunology and immunopathology of reversal reactions; other aspects of leprosy neuritis, other neuropathies; and application of PCR techniques.

The proposed panel of lecturers include: Dr Arundathi, Dr M J Colston, Dr Kumar Jesudasan, Drs Mr & Mrs Katoch, Dr Diana Lockwood, Dr B Naffs, Dr Indira Nath, Dr S K Noordeen, Dr D Palande, Dr P S Rao, Dr G Rarau and Dr Patricia Rose.

For further information: Dr J N A Stanley, Dhoolpet Leprosy Research Centre, Karwan, Hyderabad 500 006, India. *Tel*: 0842 43236.

Instructions to Authors

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

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

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

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