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Leprosy Review

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

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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.

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Editorial

VOLUNTARY DONOR AGENCIES IN ANTILEPROSY WORK: PRESENT CONTRIBUTION AND PROBABLE FUTURE*

For 10 years or more, those engaged in antileprosy work have been aware of the possibilities offered by multi-drug therapy (MDT). It has been commonplace to speak in the abstract of rapid change. Now the reality of that change, with both its successes and its limitations, is becoming evident.

Today we are faced by a debate which, although at times tendentious, at least results from success. Just what are the tasks remaining in leprosy, and what are their scale? What is the time-frame in which we need to think? And who will support and undertake the continuing work?

Voluntary donor agencies, such as those in membership of ILEP, the International Federation of Anti-leprosy Associations, come to that discussion with a particular perspective, the traditional vision of not-for-profit charitable organizations in liberal democracies: to seek support for the needy, and to fill gaps in provision.

It must be stressed that this article discusses only the role of voluntary *donor* agencies, and does not deal with the extremely important contribution made by local associations in endemic countries. They are often the local partners of the donor agencies discussed here; and it is frequently they who do the real work in the field.

The financial contribution

The contribution of not-for-profit associations from industrialized countries in the field of leprosy has been and continues to be remarkable. Indeed, compared with other areas of support to developing countries, it is probably unique, for in leprosy work, it is voluntary agencies, not governments, that are by far the largest source of external funding.

During 1993, ILEP Members expected to provide approximately $75 million dollars in grants. Total funds for leprosy from not-for-profit agencies will have been somewhat higher than this but ILEP, with 20 members based in 15 countries, does include all the

* The author is General Secretary of the International Federation of Anti-Leprosy Associations (ILEP). It must be stressed, however, that the views expressed here are personal, are not a statement on behalf of ILEP, and do not commit that Federation or its member-associations in any way.

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major charitable bodies interested in leprosy. Only 3 or 4 of its members receive significant co-financing from their own governments. So, even taking account of the new World Bank soft loan for the Indian National Leprosy Eradication Programme, ILEP support far outweighs what is provided directly for antileprosy work by donor government sources.

The main intergovernmental organization concerned with leprosy, the World Health Organization (WHO), provides technical advice and consultants for governments, not funds for operational activity. Through the Tropical Diseases Research (TDR) programme, it does make some funding available for research. A part of the funds for both TDR and the general leprosy programme of WHO is provided by some Members of ILEP.

Coordination of support

ILEP is also unique among networks of voluntary donor agencies for the quality of financial and operational coordination between its members. The initial impetus for the Federation was and remains the desire of members to ensure that their funds are used wisely with the greatest possible benefit for people with leprosy.

That means avoiding wasteful duplication of funding but yet collaborating when necessary. Approximately one-third of all projects supported by members receive funds from more than one association. At the same time members are jealous of their own autonomy and each decides independently how and for what they wish to give support.

Thus, over the 27 years of its existence, the Federation has developed a set of tools to ensure coordination while retaining individual autonomy. Members meet once every 6 months to share news and discuss joint funding. For each project and most countries, a single member is appointed as 'coordinator' to be the channel for contact with all supporting members. Through an information network based on central registration of projects and standardized reporting systems (the infamous A, B and C Questionnaires!), members know what each other is supporting and how projects are progressing. In addition the Medical Commission ensures coordination of medical advice on matters of common interest.

This all sounds fine, but this structure is also feeling the impact of the success of MDT. To some degree, the system of coordinators presumes a geographical division of responsibilities between the members. Yet now, as attention increasingly focuses on the relatively small number of countries that have large numbers of people with leprosy, it is more common to see several member-associations operationally active in the same country. In such cases, members have a considerable need for enhanced working cooperation on the ground, in addition to their financial coordination. This is especially true regarding their relationship with national programmes and governments.

Public health, targets and the humanitarian imperative

For the most part, money given out by ILEP Members has been collected from the general public. As such, it is an expression of humanitarian concern by a great number of individual donors in many countries. There can be a temptation to discuss such generosity

in sentimental terms but it has very practical implications for the present debate about continuing needs in antileprosy work.

Individual donors put trust in the agencies to which they give. They expect their monies to have some direct positive impact on the lives of individual leprosy patients. In other words there are assumptions at play which are antithetical to a purely public health approach.

While individual donors are likely to be encouraged that their money will help in some way to 'reduce leprosy', they are also likely to be ill at ease if the greatest good for the greatest number is achieved at the detriment of particular individuals. This dichotomy is implicit in the differing statements of target adopted by ILEP and by WHO in response to the success that was seen by the late 1980s to be possible with MDT.

During 1988–90 an Expert Group of the ILEP Medical Commission, anxious to accelerate the use of MDT, looked at what could be recommended as basic, rather than optimum, conditions for MDT implementation, after what was already a decade of experience worldwide. To their technical proposals,[1] they added the idea that ILEP Members adopt a concerted time-specific strategy for MDT implementation.

This led in June 1990 to acceptance by members of their target of *MDT for all by the Year 2000*. It is notable on two counts. First, reflecting the hesitation of autonomous associations to be formally committed to common action, it is more a strong statement of determined intent than a fully fleshed-out coordinated strategy. Second, it follows the humanitarian imperative so important to members and the donors to whom they are responsible. It speaks of bringing a good to *everybody* who should benefit.

A year later the World Health Assembly, the governing body of WHO and an organ of governments, adopted what at first glance appears to be the similar target of *Elimination of leprosy as a public health problem by the year 2000, defined as the reduction of prevalence to a level below 1 case per 10 000 population*.[2] It differs, however, in significant ways. It is more managerial in its attempt to define a precise measurable target, and in the systematic way in which it has been pursued by WHO. It is more political in offering governments a dramatic achievement within a relatively short space of time.

Above all, however, it is less ambitious. It limits the horizon to 'leprosy as a public health problem' and defines that problem arbitrarily at a level which, while by no means easy to reach, can be seen as a practical possibility. There is an underlying assumption, difficult for the traditional humanitarian to accept, that there will still be people with leprosy whose problems either need not be seen as significant or who must be left to a later stage and further targets.

When is a case not a case?

Given the humanitarian viewpoint, a further difficulty, to which voluntary agencies have become more sensitive, is the definition of a case of leprosy now in use. When in 1988 the WHO Expert Committee on Leprosy, in its Sixth Report,[3] limited the definition to *a person showing clinical signs of leprosy . . . and requiring chemotherapy* there was little reaction. It seemed to be a straightforward, if somewhat tautological, working definition.

Today we see the practical implications in radically revised global and country statistics on leprosy. Progress toward the elimination target as seen in the statistics is rapid only partly because of the undoubted impact of MDT. It is also because all those people

who are released from treatment, but who remain affected by damage from the disease, no longer fall within the definition of a case.

The Sixth Committee Report did go on to recommend that projects should maintain not only lists of the cases requiring chemotherapy but also lists of those *who have deformities and disabilities due to past leprosy* when released from surveillance and treatment. Sadly, this further recommendation has been largely overlooked. Now, for the most part, patients once released from chemotherapy surveillance are lost as far as any formal records are concerned.

In the days of lifelong monotherapy, the distinction was irrelevant. Today it is taking us time to adjust to a view of leprosy-affected people in two groups: a, those requiring MDT; and b, those requiring support for the physical and social sequelae of the disease. The definitions and statistics focus our attention on the first. Yet surely the second must also be of public concern?

Progress toward the ILEP target of MDT for all

ILEP figures are always based on returns (the ILEP B Questionnaire) from supported projects giving patient data as at 31 December of the year in question. Data at the end of 1992 show that MDT coverage in member-supported projects had reached 64%, an increase of 4% from 1991.[4] This continues a steady rise since 1984 when coverage was only 8%. MDT coverage for newly-detected cases is even better, reaching 79% during 1992.

At project level, it is interesting to see that out of the 204 projects reporting over 500 patients under chemotherapy, only 41 had less than 50% MDT coverage. In all, 127, or 62%, were using MDT for over 75% of their registered patients. Perhaps inevitably, it is the largest projects that still have furthest to go; 5 out of the 11 with over 10 000 patients are below 50% MDT coverage.

These figures suggest that attainment of the ILEP target by the year 2000 in projects currently supported by members is by no means impossible. The target of *MDT for All*, however, was quite consciously phrased in more ambitious terms. It was always understood that it implied further action to help bring MDT to additional areas and projects not yet supported by members. That remains a considerable challenge.

Global MDT coverage, as reported by WHO in mid-1993, was 49%.[5] Thus there are still significant numbers of people who are known to control programmes but are not yet receiving MDT. Furthermore, WHO estimates of the total number of people with leprosy suggest there is still a gap of around 760 000 undetected cases.[5]

ILEP Members are helping to overcome these gaps, first through support to numerous national programmes in order to bring complete leprosy control coverage to those countries. Such support may often be for drugs or training rather than the total programme costs. Given that governments in most countries have now accepted responsibility for leprosy control, this is a growing feature of support by voluntary donor agencies. Funding of numerous independent projects continues, but increasingly within the framework of national programmes.

Second are new initiatives, especially in India. In March 1993, 9 members, recognizing the challenge still to be faced in the country which has two-thirds of all registered patients, committed themselves to increasing their involvement. This has already led to additional drug grants, undertaking of 'AMPLE' register cleaning and rapid survey exercises in a

number of districts, and cooperation in provision of training for staff in districts which are to begin MDT implementation once the World Bank loan begins to flow.

The continuing load

Associations such as those in ILEP have long accepted the opportunities offered by MDT—to reduce drastically the bacteriological load and thus the pool of transmission, and to prevent disabilities by early cure. They have and continue energetically to support implementation of MDT.

Many, however, have always been reluctant to put all their eggs in that basket. They have never forgotten their original humanitarian concern for the whole patient. Today, around two-thirds of support by ILEP Members goes to leprosy-control programmes, often including care and rehabilitation components. Some 7% goes specifically to rehabilitation programmes.

For member-associations the recent ILA Congress (Orlando, September 1993) was significant for its debates and state-of-the-art lectures reflecting heightened awareness of the continuing tasks in leprosy, even if the year 2000 targets are achieved. Members took note that action will still be needed and financial support required for:

—Those difficult places which will not have reached the target of MDT for all or the target of prevalence of 1 per 10 000 by the year 2000: countries with civil war, geographically inaccessible regions, and those parts of major leprosy countries that have a weak health service infrastructure.

—Ensuring detection and treatment of the new cases which will continue to appear. Even if our optimism is proved right and transmission is being drastically reduced by the present implementation of MDT, new cases will continue to appear for years to come. Indeed ILEP figures show a considerable *rise* in new cases over the last few years (1992: 196 000; 1991: 156 000; 1990: 107 000).
And, of course, a global prevalence rate of 1 per 10 000 will still mean half a million people.

—Ensuring the care of disabilities, physical rehabilitation, and social re-integration of patients. Prevention of disabilities is now accepted as a normal part of any effective leprosy control programme *while patients are under MDT treatment.* Much more problematic is the question of who could or should provide any further care for the 30% or so of leprosy-affected people who are either directly left with disabilities or are at risk of developing deformities due to loss of sensation. Even with the most optimistic view of the successes to be achieved with MDT, it must be assumed that at least the present generation of patients so affected will require some care throughout their lifetime. That in turn means maybe a futher 30–40 years of significant demand on health services.

Action on disability: are targets possible?

The target of MDT for All remains valid for the first two concerns just cited. Action on disabilities and the social needs of patients, however, calls for fresh targets and fresh clarity about the tasks to be undertaken.

In a sense these are the historical concerns of voluntary agencies in leprosy. Long before a cure for the disease was known, there were projects providing support to the individual sufferer. Nonetheless, there is much still to be made clear as we move into the next era of leprosy work.

When talking of leprosy-affected people beyond those needing MDT, what are the numbers? The WHO estimate published in 1992[6] talks of '2–3 million' people having disabilities as a result of leprosy. The ILEP Medical Commission commenting on that estimate,[7] considered the real figure for people with Grade 2 disability could be twice as high, so 4–6 million.

These are large crude guesstimates of very real chronic human problems. Before even thinking of targets for action, we need a much more sophisticated picture of what numbers of people with what kinds of problem are to be found where.

Next, collection of such data presumes that there is something which can be done. A great attraction of MDT is that relatively simple actions produce consistently positive and evident results: the patient gets better. To have similarly simple effective tools in disability care would be a great help and permit development of genuine 'disability control' programmes.

It is probably in the area of footwear protection that we come closest to simple widely accepted recommendations, but even here there are those who question the necessity and efficacy of footwear provision. Initiatives such as the Prevention of Sole Wounds Study, a joint project of ILEP Members, which is due to report its results in the near future, are small steps in the right direction.

Then, perhaps, the greatest question—who or which services should respond to the continuing needs of leprosy-affected people? Voluntary agencies are likely always to respond to calls for support from projects offering rehabilitation or a social service to a group of individuals. There is, however, a danger of thinking in terms of vertical programmes and unfairly providing to ex-leprosy patients services that are just as necessary to other people with disabilities.

A framework for looking at this problem was offered by Dr H. Srinivasan in his state-of-the-art lecture at Orlando[8] when he spoke of the need to *transfer the technology of re-enablement* from specialized leprosy programmes while they still exist, to the staff of primary health care services, as well as to the patients themselves and their families. While this may well be the way forward, it poses a major challenge to voluntary donor agencies. It suggests a pattern of funding that is relatively alien.

Supporting systems or projects: the dilemma of associations

The humanitarian impetus is ill at ease with broad impersonal systems. Associations look for warm close relationships with the projects and initiatives they fund. This is possible with small local projects; it is more difficult with large government-run programmes. Yet Srinivasan's 'transfer of technology' conjures up images of large programmes training many thousands of PHC workers through short, frequently repeated courses. The personal dimension for both donor and recipient is diluted, if not lost.

The same difficulty exists as regards the future of leprosy control work under conditions of low prevalence. Here again commentators such as Dr P. Feenstra,[9] who himself is a member of the ILEP Medical Commission, suggest that antileprosy work will

be based on general health workers at the periphery, with support from doctors at district level; and only at the national or regional level will there be staff possessing specialist knowledge of leprosy to provide a referral service.

The probability is that the response of voluntary donor agencies such as those within ILEP will be to support pilot programmes, initiatives by local associations, and specialist referral services with which they can maintain a close-working relationship. Grants to enable a government to deliver some standard service will be less common. When they do occur, it is likely to be for discrete identifiable parts of the broader programme, such as drugs or training.

A lasting commitment to leprosy

What is clear, however, is the continuing commitment to leprosy of those voluntary donor associations which have traditionally specialized in the disease. Inevitably, there has been serious thought in recent years, both inside individual associations and within ILEP as a network, about the long-term future.

It is noticeable that a number of members have concluded with a re-affirmation of their commitment to leprosy work. Others, by broadening the statement of purpose in their constitutions, have opened a window to future work in areas such as tuberculosis, dermatology, or general rehabilitation. In all such cases, however, they have stressed that activity in other fields must be linked with, or at least assist, their antileprosy work.

It is interesting that a recent consultation with members regarding the possible need for changes to the Federation as such, met with an overwhelming response to the effect that no need for change is necessary at present. The continuing tasks in leprosy are perceived by member-associations as so great that the coordination function of ILEP will be needed by them for the foreseeable future.

There is some danger, however, that associations which are not leprosy-specialized to start with will withdraw from supporting antileprosy activity. This has been seen with a couple that have left ILEP in recent years; and with other generalized Third World development agencies whose involvement in leprosy has been reduced or given no priority for growth. If attention is given only to the figures of declining prevalence due to MDT, even people and organizations with practical leprosy involvement may come to think that there is little left to do.

Nonetheless, there is little danger that humanitarian associations long-focused on leprosy will disappear from the scene. The oldest ILEP Member, The Leprosy Mission International, celebrates its 120th anniversary in 1994. It and its colleagues in ILEP will be around for a good few years yet. Indeed, it is probably fair to say that there will be voluntary agencies active in support of people with leprosy long after governmental bodies such as WHO have moved on to other organizational and political priorities.

Together with governments, WHO, and local associations, voluntary donor agencies seek to grasp the opportunity offered today by MDT. With their humanitarian origins and purpose, however, they do not forget that at the end of the day it is the stigma of deformity, not the bacterium, which is the human tragedy of leprosy.

In many fields, it is the traditional role of voluntary associations to fill gaps, to respond to needs that official bodies have not yet recognized or been able to deal with. Leprosy is no different. Voluntary support for antileprosy work will continue. In time there may be

links with other medical issues, but the commitment to leprosy will not disappear. As attention moves from MDT implementation to continuing care and social rehabilitation, it is voluntary donor agencies that will be in the forefront, together with their local partners in endemic countries.

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Type 1 reaction, neuritis and disability in leprosy. What is the current epidemiological situation?

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Summary Type 1 reaction is one of the major causes of nerve damage in leprosy patients leading to disabilities of varying severity. Though this complication of leprosy has been extensively described, we still know very little of its natural history and of the factors which may predispose to it. This paper examines the descriptive and analytic epidemiology of these reactions in leprosy. We find that they vary greatly in clinical expression, time of onset, duration and severity, which has important implications for the way they are handled in the context of leprosy-control programmes. We review the various risk factors that have been suggested over the last 30 years and the evidence of their utility in identifying 'high-risk' patients is assessed. We then review the specific aspects of neuritis and disability in leprosy and examine the contribution of Type 1 reaction to leprosy-associated disabilities. The prospects for early detection and prevention of Type 1 reaction are examined in the light of current knowledge, both at research and at the leprosy control level.

Introduction

Leprosy causes disability through damage to peripheral nerves, resulting in a loss of nerve function, which may affect seriously the future health and livelihood of leprosy patients. Nerve damage can occur across the entire spectrum of the disease, either as a chronic or as an acute phenomenon, and is sometimes responsible for real clinical emergencies. Type 1 reaction (T_1R) is generally accepted to be one of the major causes of nerve damage in leprosy, leading to disabilities of varying severity.[1–4] Though this complication has long been recognized, little is yet known of its natural history and of the risk factors which may favour it. During the 1980s much emphasis was placed on the antimycobacterial aspects of leprosy treatment, but rather less on the problem of nerve damage, though its prevention is extremely important in order to avoid permanent disability. In this regard, knowledge of the epidemiology of T_1R and identification of potential risk factors should be of benefit to leprosy control programmes (LCP).

Two main forms of reactional states have been described, usually called Type 1 and Type 2 reactions.[2,3] Type 1 reactions are characterized by episodes of increased

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inflammatory activity in skin and/or nerves of patients with borderline leprosy, whose immunological status is unstable.[2] They are associated with a delayed type cellular hypersensitivity (DTH) to *Mycobacterium leprae* antigens. Type 2 reaction, or erythema nodosum leprosum (ENL), will not be discussed here. This reaction occurs mainly in lepromatous leprosy, usually after more than 1 year of treatment, and involves systemic symptoms. The underlying mechanism is thought to be primarily humoral, related to an Arthus phenomenon (Type II of the classification of Gell and Coombs).[2,3]

Description

Though Type 1 reaction is a well-known complication of leprosy, which has been discussed extensively in the literature, no agreement has yet been reached on its definition and nomenclature.[1–3] There have been 2 types of T_1R described, the so-called 'upgrading' and 'downgrading' reactions.[2,3,5] 'Upgrading' reactions are associated with a rapid increase in the cell-mediated immune (CMI) response to *M. leprae* antigens and a decrease in bacterial load, and are interpreted as a shift across the leprosy spectrum towards the tuberculoid end. Conversely, 'downgrading' reactions are thought to be related to a partial loss of cellular immunity and a shift towards the lepromatous pole, though this is still disputed by some authors.[6] In fact, the signs and symptoms accompanying upgrading and downgrading reactions are often clinically similar and may even be undistinguishable.[7] Furthermore, the term 'reversal' has been used either as a synonym of T_1R or to designate the 'upgrading' form of T_1R. In this review, the term T_1R is used to include both upgrading and downgrading forms.

Clinically, T_1R is characterized by episodes of increased inflammatory activity in skin lesions and/or nerves.[7,8] Skin lesions become swollen and flare up. New lesions may develop. In addition, oedema may occur in the face, the hands or the feet. Inflammation in the nerves causes pain and functional impairment, which can lead to various degrees of disability, such as facial paralysis, claw hand, foot drop or anaesthesia. The nerves most at risk are the ulnar, the facial and the common peroneal nerves.[9] It is widely agreed that the gravity of T_1R is related to the degree of nerve involvement.[10] Neuritis can present in different ways: it may sometimes be dramatically acute, constituting a medical emergency,[11] or it may be insidious and painless ('silent neuritis'),[12] leading to disability without prodromes ('quiet nerve paralysis').[13] In the latter situation, changes in sensory or motor function are not readily apparent and can be detected only by repeated nerve function assessments (sensory and motor testing).

Histologically, features of T_1R vary according to the underlying leprosy type and the severity of the reaction. Ridley and Radia described four stages.[14] In brief, the main feature of T_1R is an influx of mononuclear cells associated with an oedema, leading to a distortion of the surrounding tissues and to compression of nerves. At a later stage, host cells change to an epithelioid form and there is formation of giant cells. The final stage is characterized by fibrosis.

Immunologically, T_1R is associated with an increase in the CMI response to mycobacterial antigens. This was shown experimentally by Rees & Weddel,[15] who succeeded in producing T_1R in thymectomized irradiated lepromatous mice, 1 to 2 weeks after a transfusion of syngenic lymphocytes. Godal[5] confirmed these findings in human patients by demonstrating an increase in lymphocyte transformation test (LTT) response

to whole *M. leprae* antigens during T_1R. Later, Barnetson *et al.*,[16] using whole and sonicated *M. leprae* as antigens for LTT, found that nerve and skin reactions in borderline leprosy patients are associated with responses to different antigens. Though these findings await confirmation, it has been suggested that in reactions involving nerves, cytoplasmic antigens are released which have previously been hidden within Schwann cells, while in reactions involving skin, there is an equivalent release of surface antigens from macrophages. Several investigators have tried to determine the various T-cell subsets involved in T_1R. It has been shown that a redistribution of the suppressor/cytotoxic subgroups occurs during T_1R, with a rise in the T_{CD4+}/T_{CD8+} ratio.[17] Interferon gamma (INF-γ) produced by the CD4+ cells has been shown to have some role in upgrading reactions through recruitment of monocytes and activation of macrophages.[18] Recently it has been reported that anti-PGL-1 IgM seropositivity was associated significantly with subsequent manifestation of T_1R among 41 borderline leprosy patients in Nepal.[19]

The epidemiology of T_1R

Knowledge of the natural history of T_1R is limited, because not many appropriate epidemiological studies have been carried out. A major problem has been the difficulty of achieving a consistent and commonly agreed case-definition of T_1R.[1–3,6–9] In fact, most authors give a clinical and/or histological description of T_1R but few of them have given a clear case-definition. According to Ridley,[2] a reaction is usually defined as an acute episode occurring in the otherwise chronic course of the infection, which appears to have an allergic basis. He further stated that downgrading and upgrading reactions were associated with a change in CMI. Later, Waters *et al.*[3]
given to the 'episodes of significant inflammation occurring in leprosy which are the result of infection with *M. leprae* and are not due to secondary infection, trauma, etc. Case-definitions used in various studies differ according to the type of clinical signs and symptoms considered (whether dermatological or neurological), their relative importance and the means of diagnosis (Table 1). This variation can be explained by the absence of any 'gold standard' for the definitive diagnosis of T_1R. In addition, as has been reported by several authors, it can be very difficult to distinguish between relapse in paucibacillary patients and late T_1R on clinical and histological grounds.[20–22] For all these reasons, it is difficult to provide accurate estimates of T_1R incidence.

Several factors must be considered in evaluating the frequency of T_1R: the method of case-ascertainment (hospital or population-based leprosy control programme), the type of study (retrospective, prospective or cross-sectional), the type of treatment (dapsone monotherapy, multi-drug therapy), the duration of follow-up and the geographic area (Table 2). Major referral centres generally report higher frequency of T_1R than do leprosy control programmes, and most retrospective data accumulated over many years give general figures which do not take into account the variations in recruitment, diagnosis and treatment.

There are very few reports on the frequency of T_1R during the dapsone monotherapy era. Because of the length of treatment (5 years or more for paucibacillary patients and life-long for multibacillary patients), T_1Rs were reported to occur either 'at registration' or 'during treatment'. For some authors, any evidence of increased activity in lesions occurring during treatment was considered a reaction, whereas after treatment it was

Table 1. Summary of case-definitions of T_1R used in studies giving estimates of T_1R frequency in leprosy

Study	Definition of T_1R
Zaire[24]	Inflammation of one or more nerves and/or inflammation of existing skin lesions and/or peripheral oedema
Malawi[20]	• Any tender enlarged nerve • (Renewed) inflammation in the skin lesions • Recent paresis/paralysis
India[26]	Sudden and abrupt appearance of erythema, swelling and tenderness in the whole of the existing lesion(s), with or without the appearance of new lesion(s) with similar signs of inflammation
Nepal[19]	Acute neuritis that presents with the tender enlargement of a peripheral nerve trunk associated with partial or complete loss of motor or sensory function
Malawi[25]	Renewed inflammation in previously existing skin lesions and/or signs of neuritis
India[28]	Any of the following: • new erythema of existing skin lesions • new erythematous skin lesions without features of ENL • new acute neuritis • results of histopathology
Ethiopia[29]	Any of the following: • pain or tenderness in one or more nerves with or without nerve function loss • change in VMT <6 months • change in ST <6 months

considered a relapse. In a retrospective assessment of 100 patients examined for T_1R in 1976 in Ethiopia, it was found that 51 presented at registration with a T_1R and one-third developed a T_1R in year 1 of treatment, though the way in which the cases were selected for the study is not clear.[23]

One of the effects of introducing short-course multidrug therapy (MDT) in the treatment of leprosy has been that T_1Rs now commonly occur *during* and *after* completion of treatment. Thus, in a therapeutic trial of 3 different treatment regimens of various duration (including DDS, rifampicin and clofazimine) in Zaire, 20 out of 335 PB patients (6%) developed an episode of T_1R within 1 year after starting treatment. Among MB patients (BI $\geqslant 2$ at any site), 18 out of 280 (6·4%) were in T_1R at time of registration, and 115 (41·1%) developed a T_1R during treatment, 16 of them after stopping rifampicin intake at 26 weeks.[24] In Malawi, 503 new PB patients (BI $\leqslant 1$ at all sites) from 2 different areas (301 in central Malawi and 202 in the Karonga District) were recruited in a study to evaluate the WHO–MDT regimen. Among the 301 self-reporting patients recruited in the central region, 8 (2·6%) were in 'marked T_1R' at registration, 5 (1·7%) developed a T_1R during treatment and 12 (3·9%) after treatment.[20] After 4 years follow-up of the whole cohort, 17 out of 499 (3·5%) were reported to have developed T_1R, 15 of them within the first 12 months after completion of treatment.[25] In India, among 95 PB patients treated with MDT, 9% developed T_1R in year 1 after completing treatment.[26] Unfortunately, the data collected from these various studies and reports are not comparable, as different classification of leprosy cases and different definitions and diagnostic criteria of T_1R were used.

There is a general agreement among authors that T_1Rs particularly occur in borderline (BT to BL) leprosy.[2,3,8] As can be seen in published reports and studies, the risk of T_1R appears to be a function of leprosy classification (Table 2). In Addis Ababa, of 692

Table 2. Summary of published estimates of T_1R frequency in leprosy

Study	No of patients/type of leprosy		No of T_1R (%) Before treatment	During treatment	After treatment	Follow-up duration	Total
Ethiopia[23]				< 1 year DDS	> 1 year DDS	NS	
	BT	50	30	19	1		
	BB	13	9	3	1		
	BL	37	12	13	12		
Zaire[24]	PB	325	—	20	(6)	NS	20 (6)
	MB	280	18 (6·4)	115	(41)		133 (47·5)
India[26]	PB (2 regimens)						
	reg 1	95	0	0	9 (9·5)	12 months	
	reg 2	95	0	7 (7·3)	0	12 months	
Malawi[20]	PB	503					
	• LCP*	301	8 (2·6)	5 (1·7)	12 (3·9)	12 months	25 (8·3)
	• Karonga†						
	A	162	—	—	0 (0)		
	S	40	3 (7·5)	2 (5)	3 (7·5)		8 (20·0)
Malawi[25]	PB (LCP + Karonga)						
		499	—	—	17 (3·5)§	4 years	17 (3·5)
Malawi‡	PB	1013		24 (2·4)		NS	
	MB	119		12 (10·1)			
India[28]	TT	77		3 (3·8)		5 years	
	BT	218		25 (11·5)			
	BB	3		3 (100)			
	BL	67		10 (14·9)			
	LL	123		3 (2·4)			
	Other	6		—			
	Total	494		44 (8·9)			
Ethiopia[27]	BT	304		60 (19·7)		1 year	
	BL	249		105 (42·2)			
	LL	99		10 (10·1)			
	Total	692		175 (25·3)			
Ethiopia[29]	BT‖	216	6 (2·8)	22 (10·2)	17 (7·9)	1 year	45 (20·8)
	BL¶	266	13	103	—		116 (43·6)
	LL	109	0	21	—		21 (19·2)

* LCP: Leprosy control programme: all self-reporting patients.
† Karonga district. A: actively detected; S: self-reporting.
‡ personal communication.
§ Of which 15 reactions occurred during the first 12 months after MDT.
‖ cohort 07/87–07/88.
¶ cohort 07/87–12/88.
NS—non specified.

new patients registered in 1989, 175 (25%) developed a T_1R: 60 out of 304 (19·7%) BT leprosy cases, 105 out of 249 (42%) BL and 10 out of 99 (10·1%) LL cases;[27] no BB cases were identified. A retrospective assessment of all leprosy cases who attended a leprosy centre in Hyderabad, India, during 1985 found that, overall, 44 out of 494 (10·9%) patients were reported to have developed T_1R. Estimates varied according to classification: 3/77 (3·8%) TT, 25/218 (11·4%) BT, 3/3 (100·0%) BB, 10/67 (14·8%) BL, and 3/123 (2·4%) LL leprosy cases.[28] Due to differences in the classifications employed (either clinical, bacteriological or histopathological) and in the method of recruitment of patients (surveys, self-reporting cases, actively detected cases), data are not comparable between studies and it is difficult to estimate whether or not the risk of developing T_1R is strictly dependant upon the histological type of leprosy.

Type 1 reactions can be diagnosed at different times in the course of leprosy: at time of leprosy diagnosis, during treatment and after completion of treatment:

1. At time of leprosy diagnosis; some patients who were never before diagnosed or treated may present to LCPs for the first time in a stage of reaction. In Hyderabad, among the 44 cases of T_1R diagnosed during 1 year, 21 (47·5%) were new leprosy patients presenting for the first time.[28] In the clinical trial in Zaire, 18/280 (6·4%) MB patients were diagnosed with T_1R at their recruitment into the trial.[24] In Addis Ababa, among 216 new BT patients diagnosed during 1 year, 6 (2·8%) presented with T_1R at time of leprosy diagnosis and among 266 BL patients who started MDT during a period of 18 months, 13 (4·9%) were in T_1R at time of leprosy diagnosis. In Malawi, 8/301 (2·6%) self-reporting paucibacillary patients were in T_1R at registration. As noted in Malawi, patients actively detected at the early stage of the disease and rapidly put under treatment are less likely to seek care than are patients with unknown or untreated leprosy who suffer from pain or acute neurological disorder or from an inflamed and painful patch on the skin.[20] Poor and passive case-finding is likely to result in a higher number of T_1Rs at registration than is active case-finding. The percentage of cases in reaction at time of leprosy diagnosis thus reflects case-finding activities.

2. The occurrence of T_1R *during* and *after* treatment varies according to the background leprosy type and to the type of treatment. It varies also with the quality of follow-up, which is likely to be closer in clinical trials and epidemiological studies than in general LCPs. Among the 44 cases diagnosed in Hyderabad in 1985, 42·5% developed a T_1R while under chemotherapy and 5% after chemotherapy.[28] In the clinical trial in Zaire, the time of onset of T_1R among PB patients receiving 3 regimens of various duration (1 single dose, 10 weeks or 12 months duration) ranged from 16 to 32 weeks after the beginning of treatment.[24] In Addis Ababa, among the 216 new BT patients diagnosed over 1 year, 22 (10·2%) developed a T_1R during the 6 months course of MDT, and 17 (7·9%) within the first year after treatment.[29] Similarly, among the 266 BL patients who started MDT during a period of 18 months, 70 (26·3%) developed T_1R during the first year and 33 (12·4%) during the second year of MDT. In Malawi, among the 499 PB patients followed-up after WHO–MDT, 14 (2·8%) developed T_1R within the first 6 months of treatment.[25] These findings are consistent with the report of Rose and Waters,[9] that the majority of T_1R in BT patients develop within the first 6 months of treatment, but that some reactions may develop up to 3 years thereafter. In BB leprosy, T_1R usually starts within a few weeks or months after commencing MDT. In BL leprosy, T_1R is said to occur within 1–12 months after starting MDT, but may also occur in the second, third or

even the fourth year.[9] In summary, the period of greatest risk of T_1R among patients not in reaction at time of diagnosis is the first 6–12 months of treatment. The temporal distribution of T_1Rs according to leprosy classification in the sub-cited studies and reports is shown in Figure 1.

The duration of T_1R varies with both the histological type and the treatment of leprosy, ranging from a few months (3–9) in BT patients to more than a year or even several years in BL or subpolar lepromatous patients.[3,9] The situation is complicated by the possibility of recurrent episodes of T_1R, occurring particularly at the time of tailing off corticosteroid treatment. In the retrospective study carried out in Hyderabad, 14 out of the 44 patients with T_1R developed further recurrent episodes: 7 had 1 recurrent reaction, 1 had 2, 2 had 3, 3 had 4 and 1 had 5.[28] Recurrent episodes occurred up to 40 months after the initial reaction, but most occurred during the first 6 months after the initial episode. Whether these were related to reduced dosage of prednisolone or were new episodes is not clear. Such recurrent reactions pose a problem as some patients may become dependent upon steroid therapy.

The search for risk factors

In 1985, WHO identified prevention of disability as one of the three main objectives of leprosy control, in addition to treatment and rehabilitation of patients.[21] In this context, given that T_1R is thought to be responsible for much of the disability and deformity in leprosy, LCPs were encouraged to focus on early detection and treatment of T_1Rs, in order to prevent nerve damage. It was then logical to try to identify the factors (whether clinical, histological or immunological) which might predict the occurrence of T_1R in individual leprosy patients. Several risk factors have been suggested over the past 20 years, some of them well documented, but most based only on case reports (Table 3). Numerous studies have been carried out on the immunological and molecular aspects of T_1R, but no specific molecular mediator has been identified, and there is as yet no simple test allowing confident prediction of T_1R risk in a patient newly diagnosed with leprosy. We review here the available evidence relating to specific risk factors.

BCG VACCINATION

It was long considered that the development of lepromatous disease in patients infected with *M. leprae* reflected some antigen-specific deficiency in the host's ability to mount an effective cellular response to the bacilli. Attempts were thus made to boost the immune system by injection of antigens of specific or related micro-organisms. Several authors investigated the use of BCG in the immunotherapy of lepromatous and borderline lepromatous patients—and some of them reported reactions among the recipients of the therapy. Thus, Montestruc[30] and Wade[31] reported episodes of acute inflammation in lesions of lepromatous and tuberculoid patients after BCG vaccination. Similarly, Floch[32] reported the occurrence of tuberculoid lesions in children 1–3 months after receiving BCG vaccination. Later, Convit *et al.*[33] developed a vaccine against leprosy containing 6×10^8 heat-killed *M. leprae* together with BCG, injected intradermally in several sites. Among 531 patients with LL, BL and Mitsuda negative IL leprosy, 78 of 227 (34%) LL patients and 52 out of 77 (68%) BL patients developed a T_1R. This was

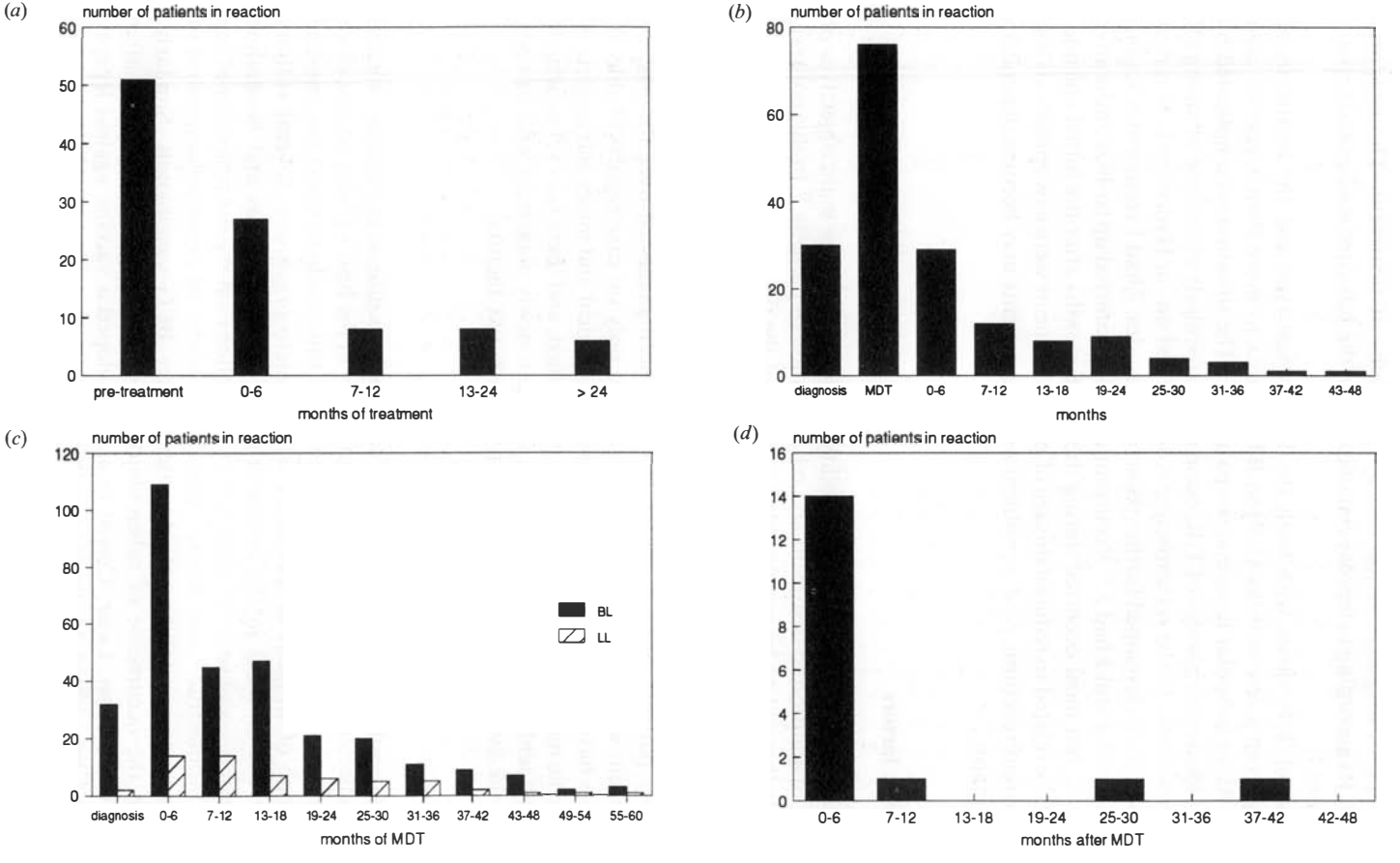

Figure 1. Temporal distribution of Type 1 reactions before, during and after treatment in various studies and reports.

(a) 100 borderline patients treated with DDS in Ethiopia;[23]
(b) BT patients treated with MDT between July 1987 and December 1992 in Ethiopia during and after MDT;[29]
(c) BL and LL patients treated with MDT between July 1987 and December 1992 in Ethiopia;[29] and
(d) Cohort of 499 patients treated with MDT followed over 4 years in Malaŵi.[25]

Table 3. Proposed risk factors for occurrence of T_1R in leprosy

Author	Source	Risk factor	Observation
Floch[32]	Case-report	BCG	Tuberculoid lesions in children 1–3 months after BCG vaccination
Montestruc[30]	Case-report	BCG	Reaction in arrested lepromatous cases after BCG vaccination
Wade[31]	Case-report	BCG	Reaction after BCG vaccination in patients with tuberculoid leprosy
Lawson[34]	Textbook	Pregnancy and the puerperium	'Acute reactive state' in women with leprosy after delivery
Ridley[2]	Article	Treatment	Risk of upgrading reactions in patients with borderline leprosy under treatment and of downgrading reactions in untreated patients
Jopling[37]	Textbook	Treatment	Risk of upgrading reactions in patients with borderline leprosy during the first 6 months to 1 year of treatment. Downgrading reactions in untreated patients
Rose[35]	Case-report	Pregnancy and lactation	Adverse reactions in 7 women with untreated borderline leprosy 3 weeks to 4 months after delivery
Duncan[12]	Prospective study	Pregnancy	Pregnancy is associated with first appearance of signs and symptoms of leprosy and with relapse in cured patients. 52/119 women with leprosy presented 85 episodes of neuritis during pregnancy and after delivery (mainly 9–12 months)
Hastings[8]	Textbook	• Vaccination • Treatment (upgrading reactions) • Tuberculosis • Intercurrent infection • Trauma • Stress	
Boerrigter[20]	Prospective study	Stage of disease at detection	Risk of late T_1R is higher among self-reporting patients (with generally more advanced disease) than among actively detected patients
Bryceson[7]	Textbook	• Pregnancy and lactation • Vaccination • Intercurrent infection • Psychological stress	
Rose & Waters[9]	Editorial	• Pregnancy and lactation • Intercurrent infection • BCG • Treatment (MDT)	Pregnant women with leprosy are prone to develop T_1R 4–12 weeks after delivery
Roche[19]	Prospective study	Seropositivity to anti-PGL-1 IgM	Seropositivity to anti-PGL-1 antibodies is significantly associated with subsequent manifestation of T_1R in 136 patients with newly diagnosed borderline leprosy

accompanied by an important reduction in the bacterial population within active lesions and was considered by the authors to demonstrate an increase in CMI. Most patients experienced the reactions during the first 6 months following immunotherapy.

PREGNANCY AND THE PUERPERIUM

Several reports indicate that pregnancy and the puerperium are associated with an increased risk of T_1R in leprosy.[34] In 1974, Rose described 7 cases of adverse reactions occurring 2 weeks to 4 months after delivery in women with borderline leprosy.[35] On the basis of a report that maternal lymphocyte responses to PHA and PPD antigens were depressed during pregnancy and returned to normal at delivery or shortly afterwards,[36] Rose suggested that T_1R may have been precipitated by a return of CMI competence following pregnancy.

In a prospective study of 119 women with leprosy followed during pregnancy and for 2 subsequent years in Ethiopia, 52 women presented 85 episodes of neuritis during pregnancy and the puerperium (0·7 episodes per patient).[12] In this study neuritis was classified as 'overt' (pain and/or tenderness of nerves) or 'silent' (impairment of motor and/or sensory function without nerve pain or tenderness) and was related either to T_1R, ENL or to 'deterioration of patients' leprosy status'. Data on the timing of neuritis in relation with pregnancy were not clearly presented, but it was reported that among the 45 women with BL leprosy, 21 (47%) developed 35 episodes of neuritis, 3 during pregnancy and 14 during the first year after delivery. Among the 40 women with BT/TT leprosy, 16 (40%) developed 24 episodes of neuritis, 6 of them during pregnancy. 'Overt' neuritis was reported to occur before delivery and during the first 12 months after post-partum, whereas silent neuritis occurred at all stages, but mainly after 6–9 months post-partum, though there was no evidence for a significant difference. The absence of obvious clinical signs alerting the patient (and the doctor) might have played a role in the late appearance of the latter form. Unfortunately, as no non-pregnant controls were followed-up, the relative risk of neuritis associated with pregnancy could not be calculated.

CHEMOTHERAPY

The influence of antileprosy drugs on T_1R risk has long been a subject of debate. For many years, chemotherapy was considered a risk factor for the 'upgrading' form of T_1R, which was thought to occur only in treated patients, whereas the 'downgrading' form was supposed to occur mainly in untreated patients.[2,3,37,38] Despite several attempts to measure and compare the respective effects of various antileprosy drugs on T_1R, the situation still appears to be complex.[24,39,40] It is difficult to evaluate whether the risk of T_1R is different with MDT or with dapsone monotherapy. In addition, the impossibility of distinguishing clinically between upgrading and downgrading forms makes it difficult to assess this aspect of the effect of treatment.

The introduction of short-course MDT has had a complicating effect on the occurrence of T_1R in that PB patients on short-term regimens could experience reactions several months *after* treatment, thereby posing the difficult problem of differentiating between PB relapse and late T_1R.[3,20,22,41] Unfortunately, as no proper clinical trial comparing DDS against MDT with a long-term follow-up was carried out before

launching MDT, we lack information on the patterns of T_1R in relation to different chemotherapy regimens. At present, it is only possible to address this issue with historical studies using very cautious criteria. Thus, a study in Malawi which compared patients diagnosed before 1981 and treated with dapsone monotherapy with patients diagnosed later and treated with WHO–MDT, found evidence that reactions were less frequent and occurred earlier in the MDT recipients (J. M. P. Pönnighaus & R. Wilson, personal communication). In Ethiopia, an increase of the number of patients with T_1R has been observed since the implementation of WHO–MDT,[22,27] but this should be interpreted with caution, as those are crude numbers (not rates) and data on T_1R during the dapsone monotherapy era were likely to be incomplete. The increase in reaction cases observed in this study might well be related to increased ascertainment in recent years.

OTHER RISK FACTORS

Several other potential risk factors have been mentioned in the literature, though without formal studies: intercurrent infection, in particular tuberculosis,[7,8] stress, trauma (psychological and physical)[8] and oral contraception.[35] The little evidence on these associations is based more on anecdotal reports or hypotheses than on hard data.

HIV infection has been reported to cause several peripheral neuropathy syndromes, and there was some concern that HIV associated neuropathy might be confused with or exacerbate leprosy neuritis.[42] There are reports that neuritis might be more severe in co-infected people[43] and that 'new skin lesions and lepromin anergy' during treatment occur more frequently in HIV-positive than in HIV-negative leprosy patients,[44] but these reports appear to be poorly documented or poorly controlled and await further investigation.

Some authors have tried to identify simple clinical factors which could allow prediction of T_1R in patients with leprosy. In a retrospective study of 1226 PB leprosy patients, Hogeweg *et al.*[45] identified 26 (2·1%) patients with lagophthalmos—24 had signs and symptoms compatible with T_1R and among those 22 had a patch of more than 3 cm around the eye or the malar region. The authors concluded that facial nerve damage was more likely to occur in patients developing T_1R with an inflamed patch on the face. Unfortunately, the chronology of events in these patients is not clear and, as no appropriate controls were identified, no relative risk could be calculated.

The mode of detection plays an important role in the reported frequency of T_1R in leprosy. In a follow-up study of PB patients treated with WHO–MDT in 2 different areas in Malawi, Boerrigter *et al.* found that the risk of T_1R during the year after registration was higher among self-reporting than among actively detected patients.[20] Self-reported patients were also found to be more likely to have palpable enlarged nerves at intake than were the actively detected patients.

The quest for risk factors includes the identification of biological markers which could allow anticipation of T_1R in patients with leprosy. In a prospective study of 136 borderline leprosy patients treated with MDT in Nepal, Roche *et al.*[19] found that seropositivity to anti-PGL-1 antibodies, assessed with an ELISA assay, was associated significantly with subsequent manifestation of T_1R. This association was strongest in patients who were both anti-PGL-1 antibody seropositive *and* lepromin positive. The authors suggested that patients who are both lepromin and anti-PGL-1 positive at the time of diagnosis should be monitored closely during the first 6 months of chemotherapy

as they are at high risk of developing T_1R. This study shows that it might be possible to find markers to identify persons at risk of developing T_1R, but further work is needed to clarify the relationship and to assess the respective effects of age, sex, smear positivity and leprosy classification. The question also arises of the feasibility of such tests to detect patients at risk under field conditions and whether these results could ever warrant a systematic testing of 'high-risk' leprosy patients.

The impact of T_1R in leprosy: neuritis and disability

NEURITIS: THE IMPORTANCE OF EARLY DETECTION OF NERVE DAMAGE

M. leprae has the unique characteristic of entering peripheral nerves and multiplying within Schwann cells. The response of the tissue to this invasion is extremely variable:[4] it can be minimal with no functional changes in the nerve or it may be very extensive, resulting in nerve destruction and complete loss of function. Literally 'inflammation of the nerves, neuritis is usually defined as 'pain and/or tenderness in the nerves'.[46] Neuritis and nerve damage are, however, not synonymous: there can be neuritis with little or no evidence of nerve damage and, conversely, nerve function can deteriorate in the absence of nerve pain or tenderness.[4]

Neuritis is the most important and serious aspect of T_1R which, if not treated, carries the risk of irreversible disability and deformity.[27] According to Pearson,[46] nerve damage in T_1R is the result of the host's immune response to the presence of antigenic material derived from the leprosy bacilli within the nerves. For Job,[4] 'much of nerve destruction takes place during the reactive phases of leprosy', due to the combined effects of increased intraneural pressure caused by the inflammatory process within the nerve and extensive intraneural vascular changes.

There is great variation in clinical presentation of neuritis, from 'quiet nerve paralysis'[13] or 'silent' neuritis[12,47] to acute 'overt' neuritis,[12] with apparently similar risk of disability, but the respective importance of motor and sensory dysfunction may vary according to the type of nerve involved. Little is known of the distribution and outcome of these different forms. In the study of neuritis in pregnant women in Ethiopia, among the 85 episodes of neuritis occurring during pregnancy or lactation, 74 episodes were followed by persistent nerve damage: 29 showed motor loss only, 12 sensory loss only, and 33 developed mixed motor and sensory loss.[12] Silent neuritis appeared to occur more frequently than overt neuritis and to cause more damage to sensory nerves than to motor nerves, though the difference was not statistically significant.

It is generally reported that nerve damage can be reversed if treatment is given early enough, e.g. within 6 months of onset.[27] It is therefore important in leprosy control programmes to *detect* signs of neuritis (either overt or silent) *early* in order to increase the chances of recovery and to prevent disability. Patients with overt neuritis usually report to clinics because of obvious symptoms (pain, tenderness or acute function loss), but the main problem lies in patients who slowly develop a progressive function loss without any patent signs of neuritis, i.e. 'silent neuritis'.[12,13] In this situation, nerve damage can be detected only by repeated testing of nerve function.

The signs and symptoms of neuritis include pain, tenderness and nerve enlargement. Their assessment is, however, subjective and liable to variation, and the ability of such

assessments to measure changes in nerve function over time is limited. Several tests have been developed to grade and monitor motor and sensory function:

Motor function

Goodwin[48] developed in 1968 a voluntary motor test (VMT) for leprosy patients, based on the MRC scale of strength.[49] This test was subsequently reviewed by several authors.[50–52] While there is a general agreement on the type of muscles to be tested, several scales have been proposed to grade the muscular strength. The most frequently used is the MRC scale, which grades muscular strength on a 5-point scale, but simpler 3- or 4-point scales have also been devised, mainly for field use[53] (Appendix 1).

Sensory function

Various methods have been developed to test the different aspects of sensory function.[52] The most commonly used are those based on nylon monofilaments[54–56] or on a ball-point pen.[57] The 2 methods are not strictly comparable because the nylon filaments test the sensory response to an increasing range of determined forces, whereas the ball pen tests the response to a single stimulus. Though the latter method is less standardized, many authors prefer to use it, especially in the field, because of its simplicity and low cost, in contrast to the nylon monofilaments which are more complicated to use and more expensive.

In order to follow accurately the evolution of a patient during or after chemotherapy, and to enable an early detection of nerve function loss (especially in the absence of visible clinical signs), tests have to be repeated regularly. The need for continued monitoring of nerve function implies the use of a repeatable and reliable test. Variability between observers must be kept to a minimum in order to allow comparability of the results when tests are performed by different observers.[58] This implies careful training and ongoing supervision of leprosy workers involved in nerve examination. Studies are still needed to evaluate the repeatability of these tests and to assess intra- and inter-observer variation, in order to identify which tests are the most practical and least liable to variation when used on successive measurements.

DISABILITY IN LEPROSY AND ITS ASSOCIATION WITH T_1R

The public health importance of leprosy is a function of the disabilities associated with the disease. Most leprosy disability follows damage to peripheral nerves and is a consequence of anaesthesia, dryness of skin and/or muscular paralysis, in various combinations.[7] The importance of disabilities in the control of leprosy from the human, social and economic point of view was recognized long ago.[59] Despite this, few studies have tried to measure the risk of disability in patients with leprosy and the burden of disability attributable to leprosy in general populations, let alone the relationship between T_1R and disability in leprosy.

Most of the published estimates of disability related to leprosy are prevalence figures (percentages of leprosy cases with disability, sometimes called 'disability rates'), but the definitions of disability and the criteria used for classification are often unclear (Table 4).

Table 4. Definition, classification and estimates of disability frequency in various studies (see text)

Author	Type of study	Definition of disability	Classification of disability	Frequency estimates of disability	Comments
Martinez-Dominguez[59]	Population surveys	No	WHO scale (1960)[60]	Nigeria: 23·4% Cameroon: 37·6% Thailand: 41·5%	— % dis. higher in males *vs* females — % dis. increases with age — % dis. higher in lepromatous *vs* nonlepromatous group
Srinivasan & Nordeen[61]	Population survey (males > 15)	No	Social/physical deformity scale	165/465 = 33·5% (all disabilities)	— % dis. increase with age and duration of disease — % dis. higher in lepromatous *vs* nonlepromatous group
Smith[62]	General population survey	No	Disability Index (DI-2)[63]	292/931 = 31%	—% dis. higher in males *vs* females —% dis. increases with age —% dis. varies with type of leprosy
Reddy[64]	Population survey (6 villages)	No	Disability Index (DI-2) WHO scale (1970)[68]	31/191 = 16·2%	—% dis. higher in males *vs* females — % dis. increases with age — % dis. higher in agricult than students
Sehgal[65]	Retrospective assessment (patients seen in an urban leprosy centre)	No. Both deformity/ disability used	WHO scale (1960)[60] VMT, ST	105/350 = 30%	— % dis. higher in males *vs* females — % dis. higher in young *vs* old age group — % dis. higher in PB *vs* MB and develop earlier
Keeler[66]	Retrospective assessment	No	No	2/335 = 0·6%	29% patients lost to follow-up, migrated, discharged or dead
Pönnighaus[67]	Retrospective cohort study	No	3 groups: mild, moderate, severe. Correspondence with WHO scales given	—during treatment: 2·9/1000 py —after treatment: 8·0/1000 py	— % dis. at registration increases with age —DR higher in males than females —DR higher in passively *vs* actively detected patients —DR higher after than during treatment

Note: DR = disability rate; % dis. = percentage of patients with disability.

Some of the reports come from leprosy institutions or hospitals where patients are highly selected and do not reflect the situation in the general population. When measured in population surveys, the estimates give only a global picture of disability in leprosy populations, as all types of disability (old and new, mild and severe) are counted together and the time of onset of disability in relation to leprosy diagnosis and treatment is generally not taken into account.

More than 20 years ago, Martinez-Dominguez *et al.* carried out random population surveys of leprosy in various countries and gave estimates of percentages disabled ranging from 23·4% in Nigeria to 41·5% in Thailand,[59] using the WHO scale for grading physical disabilities resulting from leprosy.[60] In a cross-sectional population survey in South India, Srinivasan & Nordeen[61] found 165 out of 465 male leprosy patients (35·5%) with a 'disability of some kind', either physical, social or combined. Disability was not clearly defined, but the authors set up a scale to grade each particular deformity of the hands and feet. In all these studies, the proportion of leprosy patients with disability was shown to increase with age, duration of disease and treatment, and was higher towards the lepromatous end of the spectrum. In another population survey in South India, 292 out of 931 leprosy cases (31%) were found disabled,[62] using a Disability Index based on the 1960 WHO scale,[63] but no further information on the severity of disabilities was given. Other studies using population surveys or retrospective assessment methods found disability rates between 16% and 30%.[64,65] A retrospective assessment of 473 leprosy patients presenting without disability at time of diagnosis between 1971 and 1976 in Trinidad and Tobago, reported an incidence of disability after starting chemotherapy of 0·6% (2/473), but almost a third of these patients (138) could not be re-examined in 1978, due to migration, lost to follow-up, discharge or death.[66]

Some authors have tried to estimate the risk of disability in leprosy populations using retrospective cohort studies. In Malawi, Pönnighaus *et al.* reviewed data from 1654 confirmed leprosy patients examined between 1973 and 1987 in the Karonga district.[67] They graded disability of face, hands and feet together as minor, moderate and severe, to form a general disability score for each patient. They found that the proportion of leprosy patients with disability increased with age at registration. The disability rate was higher in males than in females and in self-reported compared to actively detected patients. Calculating the incidence rate of disability within this population, the authors found that the risk of acquiring a new disability in leprosy patients with no disability at registration was higher after treatment (8/1000 person years) than during treatment (2·9/1000 person years, $p < 0{\cdot}02$).

In their study in 1966, Srinivasan & Nordeen[61] raised the possibility that 'DDS given under field conditions' might be associated with disability in leprosy populations. Subsequently, Radhakrishna and Nair,[68] in a retrospective study of 5746 leprosy patients without deformity at registration and treated with dapsone, found that the incidence of deformity over a 5-year period increased significantly with regularity of drug collection. In a linked case-control study, they found that mean regularity of drug collection in deformed patients *before the development of any deformity* was significantly higher than the mean regularity in matched controls (leprosy patients without deformity). They concluded that a causal link between regularity of dapsone collection and the development of deformity could exist. Unfortunately, there was no definition or classification of 'deformity' in this study, and we do not know if this term includes only the physical alterations (claw hands, foot-drop, etc.) or if it includes also the common

physiological damages of leprosy (alteration of sensory and/or motor function). Furthermore, the gravity of the deformities was not specified and we do not have any information on the 30% defaulters, which casts some doubt on case-selection and ascertainment: those patients might have defaulted due to a severe disability, whereas patients who regularly collected their drug could have done it because of mild disability. The history of reactions among patients with and without deformity was not known, and, as we have seen earlier, chemotherapy has been suggested to increase the risk of reaction in leprosy. Lastly the authors admitted that 'other' factors might be operating to lead to deformity, and they proposed further investigation on this issue.

In most studies disability or deformity are thus not clearly defined and the use of different criteria or grading scales make the estimates difficult to compare (Table 4). The wide variation in published estimates of disability in leprosy can be explained by the absence of a commonly-agreed definition of disability, the differences between the various classification systems employed and the frequent confusion between disability (alteration of function) and deformity (alteration of shape). Generally, disability and deformity are assessed using WHO scales, first proposed 30 years ago to classify disability in relation to leprosy[60] and subsequently revised twice.[69,70] These scales, however, do not differentiate between disability and deformity, which are assembled in the same grading system. Despite both revisions, the WHO disability scales have been subject to numerous criticisms: it has been pointed out that very significant changes can occur in the extent of disability without any change in the disability grades.[53] There was also some concern that changes over time in the grades could be related to changes in method or area of testing rather than to real physical changes, as neither the method nor the testing areas were standardized.[57] Several modifications of the WHO scales have been proposed,[51,57,71] but there is as yet no general agreement on the definition and classification of disability.

To measure the burden of disability due to leprosy in endemic areas and to allow comparability of data, there is a need for a clear definition and a standard classification of disability. In 1980, the World Health Organization developed an International Classification of Impairment, Disability and Handicap (ICIDH),[72] which gave an independent classification system for each of these 3 conditions and related the impact of illness with subsequent disorders according to the following model:

Disease → Impairment → Disability → Handicap

Distinct definitions and classifications have been developed for each of these terms:

Impairment (I code): '[in the context of health experience], an impairment is any loss or abnormality of psychological, physiological, or anatomical structure of function'.

Disability (D code): '[. . .] a disability is any restriction or lack (resulting from impairment) of ability to perform an activity in the manner or within the range considered normal for a human being'.

Handicap (H code): '[. . .] a handicap is a disadvantage for a given individual, resulting from impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual'.

One of the advantages of this classification is that it offers a progressive gradation of the disorders which may arise as a consequence of illness: impairment represents disturbance at the organ level (thus including deformity), disability represents distur-

bance at the level of the person (limit in function or ability) and handicap reflects the individual's interaction with and his adaptation to the environment. These definitions avoid the confusion between disability and deformity[73] and allow differentiation between what is observable by the physician and what is experienced by the patient. Some authors have started to examine their potential application to leprosy.[73,74]

Theoretically, the use of a standard classification of disability (such as the ICIDH) should facilitate the measurement of the prevalence of disability in leprosy populations and comparisons between data from different areas. It should also be possible to estimate in general populations the proportion of disability related to leprosy in comparison to that attributable to other diseases, e.g. trauma, diabetes, tropical neuropathies, for various degrees of severity. One of the difficulties in such studies will be that of differentiating between 'new' and 'old' disabilities, if the time of onset of disability in relation to leprosy diagnosis and treatment is not taken into account.

The part of disability experienced by a population which is directly attributable to leprosy might be expressed in terms of a 'population attributable risk %' (PAR%) or 'population attributable fraction',[75] which in theory measures the reduction in disabilities which could be achieved at population level if adequate measures were taken to prevent the disabilities attributable to leprosy. The PAR% can be calculated in 2 ways: either by measuring the risk of disability in a leprosy endemic population (r_t) and the risk of disability in leprosy-free population (r_o), or else by measuring the prevalence of leprosy in a leprosy-endemic area (p), the risk of disability among leprosy patients (r_i) and the risk of disability in comparable individuals without leprosy (r_o):

$$\text{PAR}\% = (r_t - r_o)/r_t = p(\text{RR}-1)/[p(\text{RR}-1)+1], \qquad \text{where} \qquad \text{RR} = r_i/r_o.$$

Though simple in theory, there are major obstacles to the estimation of the contribution of leprosy to disability in any population through calculation of the PAR% statistic:

1. Types of disease-attributable disability differ greatly according to the diseases concerned: for example, at population level, leprosy is likely to be responsible for most of the claw hands, but would contribute very little to blindness, which is more likely, in developing countries, to be related to onchocerciasis, trachoma or vitamin A deficiency. Similarly, most foot-drop and claw toes would be attributable to leprosy, whereas most leg paralysis would be attributable to poliomyelitis or to spine traumas.

2. Disability is an insidious event in leprosy, and the time lag between the onset of leprosy and leprosy-attributable disability is extremely variable. It is therefore difficult to estimate at a given time how much of the problem could be avoided by prevention, as a substantial proportion of present leprosy-associated disabilities is probably related to leprosy which appeared several years ago, when diagnosis and treatment were different from what they are today. Consequently, the estimation of the effect of disability prevention would require follow-up lasting several years. As a contrast, contribution of car accidents to disabilities could readily be calculated and used to plan and assess a disability prevention programme, because of the short time span between such accidents and consequent disabilities.

3. The risk of disability in individuals with and without leprosy might in theory be estimated using a cohort study design, but the follow-up of such a cohort would be long and the study difficult to undertake. Another approach to the problem would be to use a

case-control study design, in which the cases are disabled individuals, the controls are non-disabled individuals and the exposure leprosy, in order to estimate in general populations the relative risk (RR) of disability related to leprosy. This would reduce the problem of the long time span between leprosy and disability but, as noted above, the RR is likely to vary greatly according to the type of disability. In addition, the cause of disability will depend heavily on the method of recruitment of cases, especially in countries where leprosy control is still run vertically (as traumas and diabetes, for instance, will be overrepresented in public hospitals, and disabled leprosy patients will be found mainly in leprosy rehabilitation centres).

The contribution of leprosy to the disability load in general populations is thus difficult to measure and may not be readily interpretable. The same logic can, however, be applied to estimate, *within* leprosy patient populations, the proportion of leprosy-related disabilities *attributable to* T_1R, which could thus be avoided by preventing T_1R in this population. We can illustrate the method with the data collected in Malawi by Boerrigter *et al.*,[25] who followed 503 PB leprosy patients during and after WHO–MDT. Among 499 patients followed up for 4 years, 17 developed an episode of T_1R. The risk of developing new disabilities was significantly higher among patients who experienced a severe T_1R after completion of MDT than among those who did not ($RR = 19{\cdot}33$, $p < 0{\cdot}003$). Assuming that p (proportion of cases with history of reaction in the population) is equal to 17/499 ($= 0{\cdot}035$), and using the above formula, the percentage of disability due to T_1R in leprosy in this population (PAR%) can be estimated as 38%. In other words, in this population of PB leprosy cases, more than a third of the leprosy-related disabilities which occurred within the 4 years after completion of WHO–MDT was attributable to T_1R and could have been avoided if T_1R were totally prevented. Further useful information on this issue could be obtained by estimating the PAR% of disability due to T_1R according to age, sex, leprosy type and treatment. This information could be obtained using case-control studies in areas where criteria used for the diagnosis of T_1R, the classification of disabilities and the chronology of events have been carefully recorded. A potential difficulty is that of attributing disability to T_1R, particularly in patients who experienced several episodes of T_1R or other complications of leprosy, including ENL. With clear definitions and diagnostic criteria, the respective influence of T_1R (whether single or recurrent), of ENL, or of neuritis (carefully defined) on disability in leprosy could be estimated using either cohort or case-control studies, keeping in mind the limitations of these methods. This would allow estimation of the risk of T_1R in leprosy, and would allow calculation of the burden of disabilities attributable to reactions in a leprosy patient population. In addition, such studies would help to determine the risk factors for T_1R and would give useful information on the pathogenesis of neuritis in leprosy.

Conclusion

Data accumulated over the past 20 years show that Type 1 reactions vary greatly in terms of clinical expression, time of occurrence, duration and consequences. This variation reflects the instability of the immune response to *M. leprae* antigens in patients with borderline leprosy. Because of this variation, it is important to base studies upon strictly defined case-definitions and diagnostic criteria.

The public health impact of leprosy is related to disabilities, which are themselves a multi-factorial consequence of nerve damage. Though nerve damage has been described by Job as an 'ever-present serious complication of all forms of leprosy',[4] the relations

between nerve damage, neuritis, T_1R and disability are still not clear. The relationship of neuritis to Type 1 or Type 2 reaction is in particular need of clarification, as appropriate treatments are different. It is in this context that a sound knowledge of T_1R in leprosy (definition, pathogenesis, diagnosis) is necessary, in order to evaluate its impact on disability. As discussed above, the contribution of T_1R to the overall disability burden can in theory be estimated through the calculation of PAR% statistics. This type of information as well as information on incidence, time of onset, duration and risk factors can most accurately be obtained through a cohort study. However, given the long duration of follow-up required to collect appropriate data on nerve damage and on disability and the trends in leprosy incidence today (which is decreasing almost everywhere in the world),[76] the feasibility of cohort study designs is questionable. Alternative methods, such as case-control studies, should thus be considered, bearing in mind their constraints and limitations.

In most leprosy-control programmes, the problem of T_1R is considered at the level of its consequences in terms of nerve damage and disability. The emphasis is on early detection of nerve damage by regular testing of nerve function during and after leprosy treatment—a mandatory complement of MDT. This approach should be feasible everywhere, provided that leprosy workers have been properly trained to perform these tests and are regularly supervised. Early detection of nerve damage is dependant upon the frequency with which tests are performed, which is a function of the number of contacts between the patients and the leprosy-control programme. This poses the problem of logistic constraints in remote areas, and emphasizes the need to ensure good patient compliance.

Another perspective at LCP level is that of predicting the occurrence of T_1R in patients with leprosy at the time of diagnosis and during treatment, through the identification of specific risk factors. Though several risk factors have been recognized and proposed over the last 20 years, mainly based on repeated observations and reports, no controlled studies have been carried out and we still lack the means to predict reactions confidently enough to prevent them. Further studies on the epidemiology and risk factors associated with T_1R in leprosy would provide a better knowledge of the natural history, predictability and preventability of this phenomenon.

With the recent WHO commitment to eliminate leprosy 'as a public health problem by the year 2000,[77] there are strong arguments to plan for the integration of leprosy control into general health services and/or combined programmes.[78] In this context, MDT delivery becomes the responsibility of general health care workers, who will be in charge of the follow-up of patients and will thus be responsible for prevention of disability. These general health care workers will need to be trained in all aspects of leprosy control, including detection of neuritis and assessment of nerve damage, emphasizing that treatment of leprosy entails more than MDT alone.[79] At the same time, the integration of leprosy into general health services will lead to an appreciation of leprosy as just one of many causes of impairment, disability and handicap in these populations.[80]

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APPENDIX 1

Scales used in voluntary motor testing

1. MRC SCALE:

The examiner first demonstrates the correct movement to the patient, and then asks him to repeat it spontaneously. If the patient is able to perform the full range of the demonstrated movement, he is asked to hold it against resistance. According to the result, the examiner grades the movement as follows:

— Grade 5: Full range of movement against resistance
— Grade 4: Full range of movement but less than normal resistance
— Grade 3: Full range of movement but no resistance
— Grade 2: Partial range of movement with no resistance
— Grade 1: Perceptible contraction of the muscle not resulting in joint movement
— Grade 0: Complete paralysis

2. 'SRMP' SCALE

The same procedure applies, with the following scale:

— **S**trong: Full range of the movement against resistance
— **R**esistance reduced: Reduced range of the movement against resistance
— **M**ovement reduced: Range of spontaneous movement reduced
— **P**aralysis: No spontaneous movement

3. 'SWP' SCALE:

As before, but with a 3-point scale:

— **S**trong: Full range of the movement against resistance
— **W**eak: Weak movement against or without resistance
— **P**aralysis: No spontaneous movement

APPENDIX 2

Sensory testing

1. NYLON FILAMENTS (adapted from Bell-Krotoski 1956)

Semmes–Weinstein graded nylon monofilaments are used on specific sites of the hands and feet. Each filament is applied slowly to bending, held for 1·5 seconds and lifted slowly while the patient's eyes are closed or otherwise averted. Each filament is applied 3 times in each tested area. Each time, the patient is asked to point out the stimulated area. If the patient points at least twice within 2 cm of the stimulated point, the response is judged correct for that filament. The lightest filament (number 5) is applied first. If it is felt, the number 5 is recorded in the blank corresponding to the touched area. If this is not felt, the next heavier filament is tried (number 4), and so on for the remaining filaments. If no filament is felt, a zero is placed in the blank, showing complete anaesthesia in this area.

Various nylon filaments are used for the hands and feet in leprosy centres worldwide, but the most used are:

— hands: g
- Number 5: 0·2
- Number 4: 2·0
- Number 3: 4·0
- Number 2: 10·0
- Number 1: 300·0

— feet:
- Number 3: 2·0
- Number 2: 10·0
- Number 1: 300·0

2. BALL-POINT PEN (Watson 1953)

A ball-point pen is applied on specific sites of the hands and feet, allowing a denting of 1 mm during 2 sec, while the patient's eyes are closed. He/she is asked to point the stimulated area with the finger. The ball pen is applied 3 times on each site. If the patient responds to at least 2 out of the 3 applications within 2 cm on a specific site, the response is correct and coded 1, otherwise 0.

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Réaction de Type I, névrite et infirmité dans la lèpre. Où en est la situation épidémiologique?

C. Lienhart et P. E. M. Fine

Résumé La réaction de Type I est une des principales causes de lésion nerveuse chez les lépreux entrainaut à des infirmités de gravité diverse. Bien que cette complication de la lèpre ait été largement décrite, nous connaissons encore très peu son histoire naturelle et les facteurs qui peuvent y prédisposer. Cet article examine l'épidémiologie descriptive et analytique de ces réactions dans la lèpre. Se apparaît qu'elles varient largement dans leur tableau clinique, le moment de leur apparition, leur durée et leur gravité, ce qui a des implications importantes sur la façon de les traiter dans les programmes de contrôle de la lèpre. Nous examinons les divers facteurs de risques qui ont été suggérés au cours des 30 dernières années et les preuves de l'utilité de ces facteurs pour l'identification des patients à haut risque. Nous examinons ensuite les aspects spécifiques de la névrite et de l'infirmité dans la lèpre et nous recherchons la contribution de la réaction Type I aux infirmités associées à la lèpre. Les perspectives pour le dépistage précoce et la prévention de la réaction Type I sont examinées à la lumière de nos connaissances actuelles, au niveau de la recherche et du contrôle de la lèpre.

La reacción de Tipo 1, neuritis y deshabilidad en la lepra. ¿Cuál es la situación epidemiológica actual?

C. Lienhardt y P. E. M. Fine

Resumen La reacción de tipo 1 es una de las causas principales del daño causado a los nervios de los leprosos que resulta en minusvalidez de severidad variable. Aunque se ha descrito extensamente esta complicación de la lepra, se conoce muy poco de sus antecedentes naturales y de los factores que puedan acentuarlo. Esta publicación examina la epidemiología descriptiva y analítica de esta reacciones en la lepra. Establecimos que varían mucho en carácter clínico, iniciación, duración y severidad, lo que tiene implicaciones importantes sobre la manera de que se manejan en el contexto de los programas de control de la lepra. Se han evaluado los varios factores de riesgo que se han sugerido durante los últimos 30 años y las pruebas que existen para la identificación de pacientes más expuestos al riesgo. Luego estudiamos los aspectos específicos de la neuritis y la deshabilidad en la lepra y examinamos la contribución de la reacción de tipo 1 a las deshabilidades asociadas con la lepra. Se examinan las posibilidades de una detección y prevención tempranas de la reacción de tipo 1 en vista de los conocimientos actuales, tanto en las investigaciones como en el nivel del control de la lepra.

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T lymphocyte reactivity of leprosy patients and healthy contacts from a leprosy-endemic population to delipidified cell components of *Mycobacterium leprae*

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Summary In this study, we measured *in vitro* proliferative responses of peripheral blood mononuclear cells from both leprosy patients across the clinical spectrum and also healthy contacts from a leprosy-endemic population to delipidified cell components of *Mycobacterium leprae* (DCC) and Dharmendra lepromin. Dharmendra lepromin was poor in inducing *in vitro* T cell proliferation in all the study groups, even though it elicited marked *in vivo* skin test reaction in tuberculoid leprosy patients and healthy contacts. In contrast, Dharmendra preparation of BCG induced marked T-cell response in tuberculoid as well as bacterial index negative lepromatous patients. DCC induced a significantly higher lymphoproliferative response than Dharmendra lepromin in all study groups. A significant positive correlation was observed between the lymphoproliferative responses to DCC and BCG. The present study, based on a large number of leprosy patients and healthy contacts, clearly demonstrates that DCC, depleted of glycolipids and lipopolysaccharides, is a good antigenic preparation for evaluating T-cell reactivity to *M. leprae*.

Introduction

Although leprosy continues to be a major public health problem in many parts of the world,[1] WHO envisages that vigorous implementation of multidrug chemotherapy will decrease the prevalence of the disease to a negligible level by the year 2000;[2] also research to develop an antileprosy vaccine that will interrupt the transmission of the disease is

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0305-7518/94/065034+11 $01.00

being vigorously carried out.[3] Most individuals in leprosy-endemic areas develop a strong cellular immunity to *Mycobacterium leprae* and do not develop the disease,[3,4] and only a small minority become susceptible to the infection, and the reasons for their failure to develop a protective immunity against *M. leprae* are poorly understood.[5,6] An ideal antileprosy vaccine must be capable of inducing protective immunity against *M. leprae* in these individuals.[3] Prospective antileprosy vaccines, such as killed *M. leprae* and BCG, either alone or in combination, and 2 other closely-related mycobacteria, namely ICRC bacillus and *Mycobacterium w*, are currently undergoing field trials.[7] These vaccines were initially selected for their immunotherapeutic potential in leprosy patients before being used for clinical trials in apparently healthy individuals in a leprosy-endemic population.[3]

Many studies have demonstrated that *M. leprae* inhibits T-cell responses both *in vitro* and *in vivo*.[7–15] Certain cell surface components of *M. leprae*, such as phenolic glycolipid-I (PGL-I), lipoarabinomannan (LAM) and lipopolysaccharide, were shown to inhibit T lymphocyte proliferation[15–19] as well as interferon-γ (IFN-γ)-mediated activation of macrophages[20–22] *in vitro*. However, because it is not known how these immunomodulatory components of *M. leprae* in the vaccine preparations would influence the development of immunity to leprosy following vaccination, attempts have been made to remove these inhibitory substances from *M. leprae* to render it more immunogenic. Several studies have demonstrated that cell walls of *M. leprae* depleted of lipids, glycolipids and carbohydrate antigens induced strong T-cell proliferative responses,[23–27] induced IL-2 and IFN-γ synthesis,[28] augmented the killing of phagocytosed live *M. leprae* inside the macrophages,[29] elicited pronounced delayed type hypersensitivity reactions in sensitized guinea-pigs and tuberculoid leprosy patients,[27] and protected mice against leprosy bacilli.[30]

In this study, we evaluated the antigenicity of delipidified cell components of *M. leprae* (DCC, referred to previously as delipidified cell wall, DCW) by measuring the *in vitro* T lymphocyte reactivity to this in a large number of healthy contacts and leprosy patients across the disease spectrum, taken from a leprosy-endemic population in southern India. For comparison, the lymphoproliferative response to BCG and Dharmendra lepromin and the skin test reaction to the latter were also simultaneously measured.

Materials and methods

ANTIGENS

The Dharmendra preparation of *M. leprae* was generously supplied by Dr U. Sengupta, Central Jalma Institute for Leprosy, Agra, India. The BCG (Danish strain 1331) was kindly provided by The Director, BCG Vaccine Laboratories, Madras, India. It was subjected to Dharmendra treatment[31] and suspended in phosphate-buffered saline at a concentration of 10^7 bacilli per ml. Delipidified cell components of *M. leprae* (DCC) were prepared as described previously.[24] (Briefly, the pellet fraction of *M. leprae* sonicate extract was washed 3 times with chloroform:methanol (2:1). The residual material was further delipidified by extensive treatment with acetone and then with ethanol:ether (1:1). The final residue was suspended in saline and the protein concentration was determined.)

CELL CULTURE REAGENTS

Metrizoate sodium, Hanks's balanced salt solution, powdered culture medium, RPMI 1640 and penicillin-streptomycin mixture were purchased from Sigma Chemical Co., USA. Ficoll 400 was purchased from Pharmacia, Sweden.

BLOOD SAMPLES

Blood samples from leprosy patients, healthy family contacts (HFC) and healthy hospital contacts (HHC) were collected from a leposy hospital (Voluntary Health Services, Leprosy Project) located at Sakthinagar in the Periyar District, Tamil Nadu, India. The population covered by this leprosy control unit had a prevalence rate of 15·32 per 1000 at the beginning of this study (April 1989) and is covered by multidrug chemotherapy. Leprosy patients were classified clinically and bacteriologically[32] into polar lepromatous (LL), borderline lepromatous (BL), midborderline (BB), borderline tuberculoid (BT) and polar tuberculoid (TT) patients. HFC were healthy individuals living in the household of leprosy patients. Healthy hospital staff who had been exposed to leprosy patients for between 1 and 10 years were classified as HHC. We studied 162 samples, which had been collected from 96 leprosy patients (33 LL, 13 BL, 11 BB, 27 BT and 12 TT), 52 HFC and 14 HHC. Untreated and treated patients, under MDT for between 2 and 228 weeks, were included. LL and BL patients were grouped together and segregated into bacterial index (BI) positive (LBI+) and BI negative (LBI−) lepromatous patients. Patients with reactions were excluded from this study. We took 16 healthy noncontact (HNC) samples from students of the School of Biological Sciences, Madurai Kamaraj University, who had not had any habitual contact with leprosy patients even though they live in an endemic area. The study subjects were selected randomly without any bias towards age or sex. However, individuals below 12 years and above 70 years of age were not included. Each subject donated about 20 ml of venous blood into heparinized vacutainers (Vacuette; Griener, Germany).

LYMPHOPROLIFERATIVE ASSAYS

Peripheral blood mononuclear cells (PBMC), separated over a Ficoll-metrizoate density gradient,[33] were washed and suspended at a concentration of 1×10^6/ml in RPMI 1640 containing penicillin (100 U/ml), streptomycin (100 μg/ml) and 10% foetal calf serum (FCS) or normal human AB serum. Cultures with 10^5 cells in 200 μl final volume were stimulated with optimal concentration of PHA-P (10 μg/ml), Dharmendra lepromin (5×10^5 bacilli per ml), DCC (10 μg/ml) or BCG (5×10^5 bacilli/ml). The antigens are not cytotoxic at the concentrations used. Triplicate cultures in 96 well flat-bottom microtitre plates (Nunc, Denmark) were incubated at 37°C in a humidified atmosphere of 5% CO_2—95% air. Mitogen cultures were stimulated in FCS-containing medium for 3 days while antigen cultures were stimulated in human AB serum containing medium for 6 days. During the final 16 hr of the culture period, 0·5 μCi of ^{3}H-thymidine (Bhabha Atomic Research Center, Bombay, India, specific activity 6·7 Ci/mmol) was added to each well. Cultures were harvested onto glass fibre filters and the radioactivity incorporated was measured by a liquid scintillation counter (LKB Wallac, Sweden).

The results are expressed as ΔCPM (mean CPM of stimulated cultures − mean CPM

Table 1. *In vitro* lymphoproliferative responses to PHA-P, Dharmendra lepromin, delipidified cell components of *M. leprae* (DCC) and Dharmendra preparation of *M. bovis* BCG

Study groups	PHA-P	Dh. Lepromin	DCC	Dh. BCG
LBI+	31,028 ± 2,677† (51)‡	124 ± 129 (29)	3,149 ± 1,011* (33)	7,588 ± 1,335 (55)
LBI−	24,163 ± 2,167 (19)	275 ± 149 (8)	2,218 ± 1,008 (11)	10,981 ± 1,470 (19)
BB	25,426 ± 3,633 (13)	1,079 ± 712 (8)	4,258 ± 1,937 (11)	6,536 ± 2,233 (17)
BT	27,274 ± 2,570 (26)	1,938 ± 1,010 (7)	11,291 ± 4,911 (7)	13,908 ± 1,782 (36)
TT	21,722 ± 2,898 (16)	2,389 ± 1,168 (12)	6,843 ± 2,688 (5)	11,749 ± 2,424 (14)
HFC	32,208 ± 2,891 (53)	1,530 ± 1,024 (23)	8,499 ± 1,900* (52)	11,734 ± 1,660 (58)
HHC	36,825 ± 6,146 (16)	3,776 ± 3,627 (5)	14,192 ± 3,620* (14)	20,484 ± 5,171 (17)
HNC	40,825 ± 4,897 (14)	2,962 ± 1,583 (9)	13,197 ± 2,485* (16)	26,342 ± 5,478§ (15)

* Mean response significantly higher than that to Dharmendra lepromin within the group ($p < 0.05$).
† Mean ± SE of ΔCPM values.
‡ Number of individuals studied.
§ Mean response significantly higher than that of all other study groups ($p < 0.05$).

of control cultures) or stimulation index (SI = mean CPM of stimulated cultures/mean CPM of control cultures). Based on the range of response observed and the published literature, responses were considered positive when the SI was more than 3·0 and ΔCPM was more than 5000 for all antigens, and was more than 10,000 for PHA-P.

LEPROMIN SKIN TEST

A lepromin skin test was performed on the same day that blood samples were collected for lymphoproliferative assays. Indurations developed in response to intradermally inoculated Dharmendra lepromin (0·1 ml) were recorded 21 days postinoculation (late lepromin reaction).

STATISTICAL ANALYSIS

The Student's *t*-test and regression analyses were carried out using the EPISTAT statistical package.

Results

LYMPHOPROLIFERATIVE RESPONSE

PBMC from all groups of leprosy patients, healthy contacts and noncontacts showed poor *in vitro* proliferative response to Dharmendra lepromin (Table 1). None of the lepromatous patients responded to Dharmendra lepromin and, even in the other study groups only a small proportion of individuals showed any responsiveness (Figure 1). On the other hand, DCC induced a markedly higher proliferative response than Dharmendra lepromin in all the study groups (Table 1). Discernible gradation was observed in the proportion of responders to DCC, increasing from the lepromatous to tuberculoid pole (Figure 1). Such a gradation was not observed for the mitogenic response to PHA-P, which was uniformly high among the various study groups, including the lepromatous patient groups.

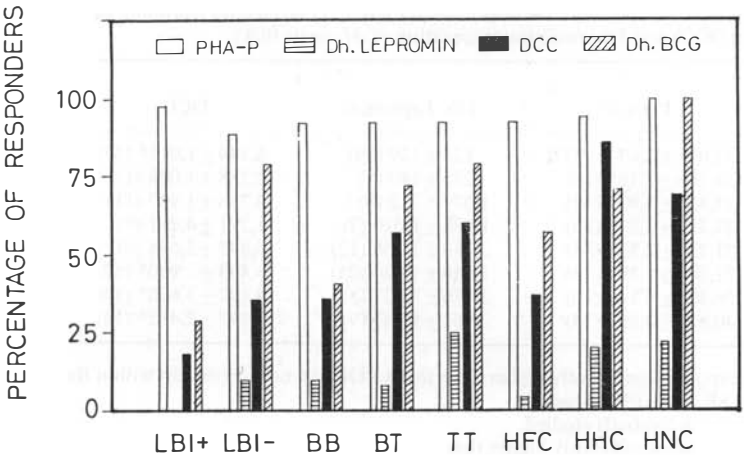

Figure 1. Proportion of responders to PHA-P, Dharmendra lepromin, DCC and Dharmendra preparation of BCG in *in vitro* lymphoproliferative assays. Responses were considered positive when SI was more than 3·0 and ΔCPM values were more than 10,000 for PHA-P and more than 5,000 for all antigens.

In contrast to Dharmendra lepromin, Dharmendra preparation of BCG induced good proliferative response in all groups of leprosy patients, contacts and noncontacts (Table 1). HNC showed significantly higher responses than all the other study groups. Interestingly, the proportion of BCG responders was significantly higher among LBI− patients than LBI+ patients (Figure 1). It should be noted that responses to DCC and BCG were markedly low among HFC compared to HHC, while their responses to PHA-P were comparable (Table 1).

Analysis of the pooled data from all study groups revealed a significant positive correlation between the responses to DCC and BCG (Figure 2). Almost all responders to DCC responded to BCG as well (45/51). About 40% of the subjects did not respond to both DCC and BCG, and the majority of these individuals belonged to lepromatous and BB patients (Table 2). A considerable proportion of HFC also failed to respond to both. In contrast, the majority of the HHC responded to both the antigens. Strikingly, 23 out of

Table 2. Comparison of the lymphoproliferative responses to BCG and DCC in leprosy patients, healthy contacts and non-contacts

Study groups	N*	Percentage of BCG R DCC R	BCG R DCC NR	BCG NR DCC R	BCG NR DCC NR
LBI+	28	18	7	4	71
LBI−	3	33	67	0	0
BB	9	22	22	11	45
BT/TT	9	56	22	0	22
HFC	47	30	23	2	45
HHC	14	64	14	22	0
HNC	11	82	18	0	0

* N = number of individuals studied in each group. Responders (R) and non-responders (NR) are defined in Figure 1.

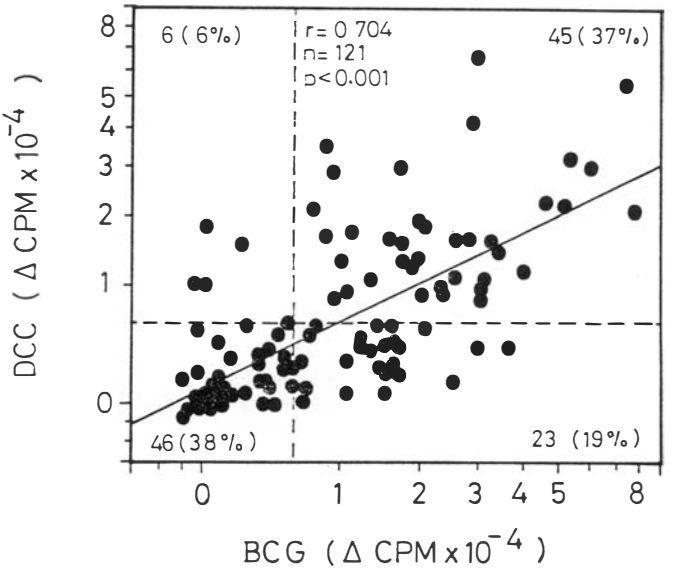

Figure 2. Correlation between the responses to DCC and BCG. Data from all leprosy patient groups, healthy contacts and noncontacts were pooled and the correlation between the responses to DCC and BCG was evaluated by regression analysis. Vertical and horizontal dashed lines bisecting the *x* and *y* axes represent the cutoff values for positive response to BCG and DCC, respectively (for details see Fig. 1). For each plot, the number and the percentage (in parentheses) of individuals within each quadrant are mentioned. *r*, correlation coefficient; *n*, total number of subjects studied; *p*, significance level of the correlation.

Table 3. Skin test response to Dharmendra lepromin in leprosy patients and healthy contacts

		Late lepromin reaction					
Study groups	(N)†	Diameter (mm): Score	0 (−)	<3 (±)	3–5 (+)	6–10 (++)	>10 or Ulcer (+++)	Percentage of responders*
LBI+	(41)		41	—	—	—	—	0
LBI−	(10)		10	—	—	—	—	0
BB	(13)		11	1	—	1	—	8
BT	(20)		8	—	1	7	4	60
TT	(17)		2	—	2	9	4	88
HFC	(60)		20	1	16	17	6	65
HHC	(12)		5	—	1	4	2	58

We inoculated 0·1 ml of Dharmendra lepromin intradermally in the forearm. The induration was measured after 21 days. Based on the diameter of induration, scores are defined arbitrarily. Skin testing was not done on healthy noncontacts.

† (N) = number of individuals tested in each group. Values given are number of individuals in each category.

* Responders are defined as individuals who developed indurations measuring > 3 mm in diameter.

68 BCG responders did not respond to DCC (Figure 2) and these subjects were represented in all groups of leprosy patients, HFC, HHC and HNC (Table 2).

IN VIVO SKIN TEST REACTION TO DHARMENDRA LEPROMIN

Despite its failure to induce *in vitro* lymphoproliferative response uniformly in all groups of leprosy patients and healthy controls, Dharmendra lepromin elicited a marked late lepromin reaction in tuberculoid patients and healthy contacts (Table 3). Lepromatous

Table 4. Comparison of the *in vivo* response to Dharmendra lepromin and *in vitro* response to DCC

Skin test response to Dharmendra lepromin:		R	R	NR	NR
Lymphoproliferative response to DCC:		R	NR	R	NR
Study groups	(N)*		(percentage)		
LBI+	(33)	0·00	0·00	18·18	81·82
LBI−	(5)	0·00	0·00	12·50	87·50
BB	(11)	0·00	9·09	36·36	54·55
BT	(7)	28·57	14·29	28·57	28·57
TT	(5)	60·00	40·00	0·00	0·00
HFC	(50)	22·00	40·00	16·00	22·00
HHC	(12)	41·67	16·67	41·67	0·00

* N = Number of individuals tested in each group. Responders (R) and non-responders (NR) are defined in Table 3 and Figure 1.

patients, irrespective of their BI status, and BB patients did not develop a skin test reaction to Dharmendra lepromin.

Analysis of the data revealed that in a considerable proportion of individuals among all study groups (except TT) who failed to mount lepromin reaction *in vivo*, DCC elicited a positive lymphoproliferative response (Table 4). Conversely, among tuberculoid patients and healthy contacts a significant proportion of individuals did not respond to DCC *in vitro*, but developed a lepromin reaction *in vivo*.

Discussion

Various preparations of *M. leprae*, such as whole bacilli, Dharmendra lepromin, sonicate extracts and cell wall components have been used in *in vitro* assays to measure T lymphocyte reactivity to the antigens of *M. leprae* in leprosy patients and healthy contacts.[9,34–38] Recent investigations have demonstrated that PGL-I and LAM which accumulate on the surface of *M. leprae* are the major immunomodulatory components capable of inhibiting both T cell proliferation[16–19] and macrophage activation and effector functions.[20,21] In fact, LAM has been shown to inhibit the transcription of IL-2 gene in T lymphocytes[39] and IFN-γ inducible genes in mononuclear phagocytes.[40] Most individuals exposed to leprosy bacilli in endemic areas overcome the adverse effects of these components and develop strong cellular immune responses and protective immunity to the pathogen.

In the present study involving a large number of leprosy patients and healthy contacts, we observed that Dharmendra lepromin induced poor *in vitro* lymphoproliferation in all study groups though others have shown reactivity in tuberculoid patients and healthy contacts.[9,34] In contrast, Dharmendra preparation of BCG induced proliferation of PBMC from all groups including the BI negative lepromatous patients, indicating that Dharmendra treatment[31] of mycobacteria by chloroform and ether *per se* does not affect the antigenic constituents. The fact that Dharmendra lepromin induced marked skin test reactions in tuberculoid patients and healthy contacts argues against any loss of antigenic material in the preparation, as well as against the lack of immunological reactivity in the

study subjects towards *M. leprae*. Earlier studies from our laboratory have demonstrated that Dharmendra lepromin inhibited T cell proliferative responses of normal subjects to mitogens and antigens, and this was associated with the downregulation of CD2 expression on T lymphocyte surface.[13,14] However, DCC did not modulate CD2.[41] Presumably, the immunomodulatory components of *M. leprae* present in Dharmendra lepromin would obscure the stimulatory effect of its antigenic constituents. In contrast to Dharmendra lepromin, whole bacilli have been shown to elicit a T cell proliferative response in tuberculoid patients.[35] Therefore, it is likely that the immunomodulatory components are more exposed on Dharmendra lepromin than whole bacilli by limited treatment with organic solvents. However, induction of marked skin test reactions by Dharmendra lepromin suggests that the immunomodulatory components are either diluted out or degraded *in vivo*, and the antigenic components released slowly from the intact bacilli elicit a strong late lepromin reaction.

DCC induced a significantly higher level of lymphoproliferative response than Dharmendra lepromin in all groups of leprosy patients, healthy contacts and non-contacts. A significant positive correlation observed between the responses to DCC and BCG reflects the close antigenic similarity between *M. leprae* and *M. bovis* BCG. However, about 20% of the subjects belonging to all study groups responded to BCG but not to DCC, indicating that responsiveness to BCG is not always associated with a positive response to DCC. This is probably due to the qualitative and quantitative differences in the antigenic composition of DCC and BCG, as much as the variability in the immune response of an individual.

Our results show that DCC is indeed a better antigenic preparation than Dharmendra lepromin for measuring the T lymphocyte response to *M. leprae*. In fact, DCC induced a lymphoproliferative response even in those individuals who failed to show an *in vivo* skin test reaction to Dharmendra lepromin. On the other hand, a positive skin-test response to Dharmendra lepromin in the absence of demonstrable T cell reactivity to DCC *in vitro* could be explained by a very low frequency of T lymphocytes reactive to *M. leprae* in the peripheral circulation which could have been recruited to the inoculation site over the period of 21 days. It has also been demonstrated that purified cell wall preparations of *M. leprae* induced more pronounced skin test reactions than lepromin in tuberculoid leprosy patients.[27] Depletion of lipids and carbohydrates has rendered DCC more antigenic, presumably by relieving the immunomodulatory effects on antigen-presenting macrophages and effector T lymphocytes. Though the immunomodulatory components present in whole *M. leprae* preparations used for vaccination are likely to be cleared by catabolic processes, they can delay the induction of specific immunity, especially at doses given for vaccination compared to that used for skin testing. Therefore, until the immunogenic constituents of *M. leprae* are defined at molecular level, delipidified antigenic preparations of *M. leprae* would be ideal alternatives to whole bacilli in leprosy vaccination strategies.

Acknowledgments

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Réactivité aux constituants cellulaires délipidifiés de *Mycobacterium leprae* des T-lymphocytes de malades lépreux et de contacts sains appartenant à une population où la lèpre est endémique

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Résumé Nous avons mesuré la prolifération *in vitro* des mononucléaires du sang périphérique en réponse à la présence des constituants cellulaires délipidifiés de *Mycobacterium leprae* (DCC) et de la lépromine Dharmendra chez, d'une part, des lépreux choisis dans tout le spectre clinique et, d'autre part, des contacts sains pris dans une population où la lèpre est endémique. La lépromine Dharmendra a provoqué une médiocre prolifération des cellules T *in vitro* dans tous les groupes de l'étude, bien qu'elle ait suscité *in vivo* une réaction nette au test cutané dans les cas de lèpre tuberculoïde et chez les contacts sains. Par contre, la préparation Dharmendra de BCG a provoqué une réponse nette des cellules T tant chez les malades lépromateux tuberculoïdes que chez ceux à indice bactériel négatif. DCC a provoqué une lymphoprolifération significativement plus élévée que la lépromine Dharmendra chez tous les groupes de l'étude. Nous avons observé une corrélation positive significative entre les réponses à DCC et BCG. Cette étude, basée sur un grand nombre de malades lépreux et de contacts sains démontre clairement que DCC, après élimination des glycolipides et des lipopolysaccharides, constitue une bonne préparation antigénique pour évaluer la réactivité des cellules T à *M. leprae.*

La reactividad de T Linfocitos de los pacientes leprosos y contactos sanos de poblaciones con lepra endémica, a los componentes de células delipidificadas de *Mycobacterium leprae*

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Resumen En este estudio, se midieron las respuestas proliferatives de las células mononucleares hemáticas periféricas tanto de los pacientes leprosos con una extensa gama clínica, como de los contactos sanos de poblaciones con lepra endémica, a los componentes de células delipidificadas de *Mycobacterium leprae* (DCC) y Dharmendra lepromin. El Dharmendra lepromin tenía poca efectividad para inducir proliferación de células T in vitro en todos los grupos estudiados, aunque provocó una reacción dérmica in vivo en los leprosos tuberculoides y en los contactos sanos. En cambio, la preparación Dharmendra de BCG indució una respuesta definitiva de células T en los pacientes tuberculosos además de en los pacientes lepromatosos con índice bacteriano negativo. DCC indució una respuesta lainfoproliferativa significativamente mayor que el Dharmendra lepromin en todos los grupos estudiados. Se observó una correlación positiva significativa entre las respuestas linfoprolifertivas al DCC y el BCG. Este estudio, basado en un gran número de leprosos y contactos sanos, demuestra claramente que DCC, con reducido glicolípidos y lipopolisacaridos, es una buena preparación antigénica para la evaluación de la reactividad de células T a *M. leprae.*

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A randomized clinical trial of two single-dose treatments for paucibacillary leprosy

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Summary We compared 2 single-dose regimens for the treatment of paucibacillary leprosy in a randomized clinical trial in Zaïre. The regimens were : C2 (rifampicin 40 mg/kg and 1200 mg clofazimine once) and C4 (rifampicin 40 mg/kg, clofazimine 100 mg, DDS 100 mg and ethionamide 500 mg once). An analysis of the results of patients enrolled between May 1987 and December 1988, with a maximum follow-up of 4 years, is presented. A total of 622 patients were enrolled and 14 paucibacillary and 1 multibacillary relapses occurred. The overall paucibacillary relapse rate was 2·4 per 100 person years. This relapse rate was higher for older patients as well as for patients with 3 or more lesions. The probability of cure at 3 years is 0·816 for C2 and 0·823 for C4, the difference not being statistically significant. The probability of cure at 3 years with either regimen is higher for patients with 1 or 2 lesions (0·872) than for patients with 3 or more lesions (0·787), and it is higher for patients with a bacterial index of 0 (0·831) than for patients with a bacterial index of 1 (0·699). These results are compared to other studies. We also discuss the potential of single-dose treatment regimens for paucibacillary leprosy.

Introduction

In a previous study on the treatment of paucibacillary (PB) leprosy it was discovered that a single dose of rifampicin (RMP) 40 mg/kg bodyweight resulted in unacceptable cure and relapse rates in patients with a BI = 1 and was therefore unsuited for wide-scale application.[1]

We report here an analysis of a randomized clinical trial of 2 single-dose treatments for PB leprosy. The objective of the trial was to evaluate, in terms of probability of cure, relapse rate, and development of disabilities 2 single-dose regimens for the treatment of PB leprosy. An additional objective was to assess the influence of other factors (age, sex,

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histological type, bacterial index (BI) and number of lesions) on probability of cure, relapse rate and development of disabilities.

Patients and methods

The trial was approved by the authorities within the Ministry of Health of the Republic of Zaïre and conducted under the auspices of the Bureau National de la Lèpre. Patients were recruited from 11 leprosy treatment units in 3 regions in Zaïre between May 1987 and December 1988. All of these units have outreach activities. Staff at these units are paramedical workers with extensive experience in leprosy control. They are supervised on a regular basis (at least twice a year) by 1 medical officer per region. Patients presenting to these units' clinics were diagnosed and classified on clinical grounds. Only new patients were eligible for inclusion in the study. A slit-skin smear was obtained from at least 3 sites and examined at the unit's laboratory facilities. Patients diagnosed as having PB leprosy were fully informed on the treatment to be received. After the patient's consent, a 6-mm or, rarely, a 4-mm punch biopsy was taken from the most active looking lesion. Some patients refused a biopsy, including the patients who had a single facial lesion. Skin biopsies were fixed either in a 10% formalin solution or in FMA fixative[2] and sent to the Leprosy Laboratory, Institute of Tropical Medicine, Antwerp, Belgium, together with a clinical information form. During the initial clinical examination, each patient's skin lesions were indicated on a body chart. The disability grading was according to the recommendations of the WHO's expert committee in 1977[3] using a 4-grade system. Development of disabilities was analysed for those who were free of disability at enrollment. The patients' ages were either taken from their identity cards or estimated.

The regime the patients undertook was chosen randomly from either treatment. If there was a serious clinical doubt as to whether the patient really suffered from PB leprosy, we waited for the result of a skin biopsy and the patient was randomized when he or she re-presented to the clinic after the reception of the histopathology result.

The 2 single-dose treatment regimens (adult doses) were:

C2: 40 mg/kg RMP and 1200 mg clofazimine (CLO).
C4: 40 mg/kg RMP, 100 mg CLO, 100 mg DDS and 500 mg ethionamide (ETH).

All drugs were swallowed in the presence of the staff.

Patients were entered in the study if both the following conditions were fulfilled: a BI of no more than 1 at any site either in the slit-skin smear or the sections for histopathology, and a histopathological pattern of either TT or BT leprosy.[4]

All histological preparations were examined by a single examiner (SRP). Indeterminate cases were excluded, because there is considerable controversy concerning their significance.[5]

Data are available for up to 4 years for patients enrolled during 1987 but only for up to 3 years for the majority of patients enrolled during 1988. A follow-up examination was done 1 year after the date of treatment, consisting of the same procedures as the initial examination, with the exception of the taking of a skin smear (unless clinically indicated) and a biopsy, as previous research had shown that only a small proportion (18–39%) of patients would have achieved histopathological cure 1 year after the start of treatment.[6] At 2 years after the treatment, a biopsy was included in the follow-up examination. As a

rule, follow-up biopsies were taken from the same lesion from which the initial biopsy was taken. However, if this lesion had disappeared at follow-up, and other lesions were still present or new lesions had appeared, the follow-up biopsy was taken from these lesions. If histology had shown no evidence of leprosy at 2 years, no biopsy was taken at 3 years unless there were clinical reasons for doing so, e.g. reappearance of old lesions or appearance of new lesions. If, on the other hand, there were histological signs of leprosy at 2 years, a biopsy was taken at 3 years. Similar rules were applied for the follow-up examination at 4 years. The criterium for cure was the disappearance of histological lesions at year 2 or 3 if the patient did not have a 'no leprosy' biopsy at year 2.

PB relapses are defined as patients who show histological evidence of leprosy after having shown no histological evidence of leprosy in a previous biopsy. As the first follow-up biopsy is taken at 2 years, a patient can only be at risk of PB relapse from year 2 onwards. Multibacillary (MB) relapses are defined as patients who show a BT of 2 or more in either skin smear or sections for histopathology at any time during the follow-up period.

Statistical analysis was performed using survival analysis techniques: the Kaplan–Meyer estimate of survival, Peto's formula for calculation of 95% confidence intervals and the logrank test for comparison of the survival function.[7,8] The χ^2 test with continuity correction was used for the comparison of proportions. Confidence intervals for single proportions were based on the normal approximation to the binomial distribution. Relapse rates were calculated using as a denominator the person years since treatment. Significance testing and confidence intervals for relapse rates were based on the normal approximation to the Poisson distribution. The confidence interval for a rate of 0 was taken from *Tabulae Scientificae*.[9] Relative risks and 95% confidence intervals for development of disabilities were calculated with Epi-Info.

Results

Randomization resulted in 317 patients receiving C2 and 305 patients receiving C4. Their characteristics are shown in Table 1.

The patients are approximately equally distributed over both regimens in the number of skin lesions (<3 versus $\geqslant 3$), histopathological classification (BT versus TT), BI as found in the tissue sections (1 versus 0), age and sex. Age is unknown for 173 patients (28%), as some of the participating units failed to communicate this information.

A total of 8 patients died before the projected follow-up examination at 2 years from causes unrelated to leprosy. A total number of 187 (30%) patients have so far not been assessed and are therefore considered as lost to follow-up. Tables 2 and 3 give their characteristics at intake, and according to treatment regimen, respectively. There is no difference in losses to follow-up between both treatment regimens. Patients aged 0–39 are more likely to be lost to follow-up (33%) than patients aged 40–79 (22%): $0{\cdot}05 > p > 0{\cdot}025$.

Estimates of the probability of cure at 2 and 3 years of follow-up are given in Table 3 for both regimens. A Kaplan–Meyer estimate of noncure at 3 years was calculated assuming that patients who were not assessed at 2 years (but were assessed at 3 years) had the same probability of non-cure at 2 years as those patients who were assessed at both 2 and 3 years. The difference in probability of cure between C2 and C4 is not significant (log rank test $= 0{\cdot}24$ and $p > 0{\cdot}5$).

Table 1. Distribution of patients according to treatment regimen

	Regimen C2		Regimen C4	
	N = 317	(%)	N = 305	(%)
Sex				
male	144	(45·4)	118	(38·7)
female	170	(53·6)	184	(60·3)
unknown	3	(0·9)	3	(1·0)
Age group				
0–19	55	(17·4)	41	(13·4)
20–39	64	(20·2)	64	(21·0)
40–59	96	(30·3)	86	(28·2)
60–79	22	(6·9)	21	(6·9)
unknown	80	(25·2)	93	(30·5)
Number of skin lesions				
1 or 2	136	(42·9)	129	(42·3)
3 or more	181	(57·1)	176	(57·7)
Bacterial index				
0	296	(93·4)	283	(92·8)
1	21	(6·6)	22	(7·2)
Histopathological classification				
BT	287	(90·5)	284	(93·1)
TT	30	(9·5)	21	(6·9)

Disability scores for C2 and C4 were compared for 6 sites (left and right eyes, hands and feet) and no significant differences were observed, either between the 2 regimens or between different follow-up times.

The overall probability of cure for patients treated with either C2 or C4 is 0·723 (95% CI: 0·701–0·746) at 2 years while it is 0·820 (95% CI: 0·784–0·856) at 3 years. No differences in probability of cure were observed according to age group (log rank $\chi^2 = 0{\cdot}27$ and $p > 0{\cdot}5$ for 0–39 vs 40–79 years of age) or according to sex (log rank $\chi^2 = 1{\cdot}10$ and $p > 0{\cdot}25$). Table 4 gives the estimates of the probability of cure with 95% confidence intervals at 2 and 3 years according to histopathological classification, number of lesions and BI. Patients with BT leprosy have a smaller probability (81%) of being cured at 3 years than have TT patients (91%), but the observed difference is not significant ($p > 0{\cdot}1$). Patients with $\geqslant 3$ skin lesions have a smaller probability (79%) of being cured at 3 years than have patients with < 3 skin lesions (87%). The observed difference is significant at the 90% level but not at the 95% level. The log rank test χ^2 is 3·82 resulting in $0{\cdot}1 > p > 0{\cdot}05$. Finally patients with a BI = 1 have a smaller probability (70%) of being cured at 3 years than have patients with a BI = 0 as found in the tissue sections (83%). This difference is significant at the 95% level. (The log rank test χ^2 is 4·15 and $0{\cdot}05 > p > 0{\cdot}025$.)

A boy who was 13 years old on enrollment as a patient in 1988 experienced a relapse of MB leprosy. He had an initial negative skin smear, a histopathological pattern of BT leprosy with a BI = 0, had more than 3 lesions and received the C4 regimen. Relapse was diagnosed 25 months after receiving treatment; histopathology showed a pattern of BB with a BI = 3; the skin smear result was 4/4/1. The patient had been diagnosed as having

Table 2. Characteristics at intake of patients lost to follow-up

	Patients lost to follow up	
	N	(%) of total
Regimen		
C2	94	(30)
C4	93	(30)
Age group		
0–19	33	(34)
20–39	41	(32)
40–59	38	(21)
60–79	12	(28)
unknown	63	(36)
Sex		
male	83	(32)
female	99	(28)
unknown	5	
Histopathological classification		
BT	171	(30)
TT	16	(31)
Bacterial index		
0	180	(31)
1	7	(16)
Number of skin lesions		
1 or 2	91	(34)
3 or more	96	(27)

between 50 and 100 flat, hypopigmented, ill-defined skin lesions. The clinical picture was obscured by onchocerciasis lesions. The earlobes were possibly enlarged. Unfortunately, another skin smear was not taken after this smear proved negative. The initial skin biopsy had been taken from a large lesion on the thigh. During the follow-up examination at 1 year, all lesions attributable to leprosy had apparently disappeared, while there were still onchocerciasis lesions. During the follow-up examination at 2 years, multiple small lesions were present on the trunk, the back, the upper arms and the face; the earlobes were clearly enlarged with formation of nodules. Chemotherapy for MB leprosy was started as soon as the diagnosis was made.

Paucibacillary relapses occurred in 14 patients: their characteristics as well as an estimate of the relapse rate per 100 person years (PY) at risk are listed in Table 5.

The overall relapse rate (for both C2 and C4) was 2·4 per 100 PY (95% CI: 1·1–3·7). The relapse rate was not significantly different between regimens C2 and C4 (3·3 and 1·6 respectively per 100 PY), between males and females (2·0 and 2·7 respectively per 100 PY), between BT and TT histopathological classification (2·6 and 0·0 respectively per 100 PY) nor between BI = 1 and BI = 0 (5·9 and 2·2 respectively per 100 PY). There was, however, a significant difference in relapse rate between age groups: patients aged 0–39 had a relapse rate of 0·5 per 100 PY while patients aged 40–79 had a relapse rate of 4·8 per 100 PY ($z = 2{\cdot}47$; two-tailed $p = 0{\cdot}014$). Between patients with 1 or 2 lesions (relapse rate of 0·4 per

Table 3. Characteristics of patients lost to follow-up, according to treatment regimen

	Regimen C2		Regimen C4	
	N = 94	(%)	N = 93	(%)
Sex				
male	41	(44)	42	(45)
female	51	(54)	48	(52)
unknown	2	(2)	3	(3)
Age group				
0–19	22	(23)	11	(12)
20–39	18	(19)	23	(25)
40–59	19	(20)	19	(20)
60–79	5	(5)	7	(8)
unknown	30	(32)	33	(36)
Number of skin lesions				
1 or 2	50	(53)	41	(44)
3 or more	44	(47)	52	(56)
Bacterial index				
0	91	(97)	89	(96)
1	3	(3)	4	(4)
Histopathological classification				
BT	87	(93)	84	(90)
TT	7	(7)	9	(10)

Table 4. Probabilities of cure at 2 and 3 years according to treatment regimen, to histopathological classification, number of skin lesions and bacterial index

	At 2 years P (95% C.I.)	At 3 years P (95% C.I.)
Regimen C2	0·701 (0·668–0·735)	0·816 (0·768–0·865)
Regimen C4	0·746 (0·716–0·776)	0·823 (0·769–0·878)
Histopathological classification		
BT	0·715 (0·691–0·739)	0·812 (0·773–0·851)
TT	0·821 (0·765–0·878)	0·906 (0·833–0·980)
Number of skin lesions		
1 or 2	0·770 (0·739–0·800)	0·872 (0·825–0·919)
3 or more	0·690 (0·658–0·722)	0·787 (0·736–0·837)
Bacterial index		
0	0·740 (0·718–0·763)	0·831 (0·794–0·868)
1	0·533 (0·419–0·648)	0·699 (0·550–0·849)

Table 5. Characteristics of 14 paucibacillary relapse cases and estimated relapse rates per 100 PY

	N	Total	Relapse rate per 100 PY
All	15	582	2·5 (1·3–4·0)
Regimen			
C2	9	276	3·3 (1·1–5·4)
C4	6	306	1·9 (0·7–4·0)
Age group			
0–39	2	217	0·9 (0·1–3·5)
40–79	10	209	4·8 (1·8–7·8)
unknown	3	156	1·9 (0·0–4·1)
Sex			
male	6	252	2·3 (0·8–4·9)
female	9	330	2·7 (0·9–4·5)
Histopathological classification			
TT	0	41	0·0 (0·0–9·0)
BT	15	541	2·7 (1·7–4·9)
Bacterial index			
0	13	548	2·3 (1·2–4·0)
1	2	34	5·9 (0·0–14·0)
Number of skin lesions			
1 or 2	1	273	0·4 (0·0–1·1)
3 or more	14	309	4·5 (2·4–7·6)

100 PY) and patients with 3 or more lesions (relapse rate of 4·2 per 100 PY), the difference in relapse rate was also significant ($z = 2·71$; two-tailed $p = 0·007$).

Patients who received the C4 regimen were 1·6 times more likely to develop disabilities as compared to those on C2, but this difference was not significant ($p = 0·2$) (Table 6).

Patients 40–79 years old were 5 times more likely to develop disabilities as were patients aged 0–39 ($p = 0·001$). Patients with 1 or 2 lesions were far less likely to develop disabilities as were patients with 3 or more lesions (RR = 6·9; $p = 0·00002$). None of the 26 TT patients developed disabilities, while 12% of 304 BT patients did; the difference is not statistically significant, however ($p = 0·1$). This is in line with observations made in previous studies.[1,6,14]

Discussion

CHOICE OF THE STUDY REGIMENS

The choice of the 2 regimens was based on the previous experience in the same collaborating units with a single-dose regimen consisting only of a single dose of 40 mg/kg rifampicin[1]: patients who received this regimen were estimated to reach histological cure at 2 years in 53–54% of patients and at 3 years in 65–85% of patients.

It is obvious that if a single-dose regimen is to be effective, (an)other drug(s) should be

Table 6. Development of disabilities in initially disability-free patients

		Disabilities at FU			
	N	N	(%)	RR	(95% CI)
Overall	330	37	(11·2)		
Regimen					
C2	173	15	(8·7)		Reference
C4	157	22	(14·0)	1·6	(0·9–3·0)
Sex					
female	200	21	(10·5)		Reference
male	129	16	(12·4)	1·2	(0·6–2·2)
Age group					
0–39	121	4	(3·3)		Reference
40–79	120	20	(16·7)	5·0	(1·8–14)
Number of skin lesions					
1 or 2	150	4	(2·7)		Reference
3 or more	180	33	(18·3)	6·9	(2·5–19)
Bacterial index					
0	307	32	(10·4)		Reference
1	23	5	(21·7)	2·1	(0·9–4·8)
Histopathological classification					
TT	26	0	(0·0)		Reference
BT	304	37	(12·2)	∞	*

added to the RMP. A study at the Institut Marchoux in Bamako in multibacillary patients found monthly doses of 1200 mg CLO to be quite effective in inhibiting the growth of *Mycobacterium leprae*.[10]

The C2 regimen, consisting of 40 mg/kg RMP and 1200 mg of CLO, was therefore tried. The control regimen should ideally have been either the previously studied regimen (in order to show that the addition of 1200 mg CLO does or does not have an effect) or the MDT regimen as recommended by the WHO study group in 1982.[12] The WHO recommended regimen was rejected because of the expected low accessibility of the new patients; indeed the bulk of new patients were expected to come from remote clinics, where a monthly visit by the units' staff would not be possible. The previously-studied regimen of 40 mg/kg RMP as a single dose should therefore have been the control regimen in this setting. There was, however, opposition from some of the staff of the collaborating units to this, because there was already some evidence that this regimen was slightly less effective when compared to the regimen consisting of 1500 mg rifampicin once followed by 1 year of daily DDS.[9] On the other hand, the advantage of a single-dose regimen was recognized by all the staff. The C4 regimen was therefore proposed as it is reported here.

RELAPSE RATE

As we stressed in our previous publications[1,6,15] a major difficulty in evaluating therapeutic studies in PB leprosy is to differentiate relapses from reversal reactions. In all

Table 7. Probability of cure at 3 years after start of treatment for various treatment regimens for PB leprosy

Regimen	Probability of cure at 3 years from start of treatment (%)
RMP 1500 mg once + DDS 100 mg daily for 1-year [1]	69–81
idem [6]	83–89
RMP 40 mg/kg once [1]	65–85
DDS 100 mg daily for 3 years [14]	68
RMP 8 weekly doses of 900 mg [14]	66
RMP 10 weekly doses of 900 mg [6]	91–96
RMP 10 weekly doses of 600 mg [6]	90–93
RMP 12 weekly doses of 900 mg [14]	68
RMP 600 mg daily + DDS 100 mg daily for 6 days [14]	78
RMP 600 mg monthly + DDS 100 mg daily for 6 months [14]	72
RMP 40 mg/kg + clofazimine 1200 mg once (C2)	82
RMP 40 mg/g + clofazimine 100 mg + DDS 100 mg + ethionamide 500 mg once (C4)	82

our previous studies as well as in this one, we have chosen for 'the worst hypothesis' and counted all reappearances of histopathological lesions as relapses, although at least some of these could be reversal reactions. Furthermore, the present study was interrupted at an early stage, with a mean follow-up of 1·5 years, which may be too early to detect all relapses.

In addition to the 14 PB relapses, a single MB relapse occurred. It seems possible that the patient already had features of MB leprosy on enrollment in 1988. Chopra *et al.* observed 4 MB relapses among 11,095 PB patients released from control.[11] Both Boerrigter *et al.*[13]
follow-up studies of PB leprosy patients who received either the WHO recommended regimen or a modification of this.

The PB relapse rate was higher for C2 (3·3 per 100 PY; 95% CI: 1·1–5·4) when compared to C4 (1·6 per 100 PY; 95% CI: 0·2–3·1); but the difference was not significant. It may be concluded that the addition of a high dose (1200 mg) of CLO to a single high dose (40 mg/kg) of RMP is no better in terms of relapse rate than the addition of conventional single doses of CLO (100 mg), DDS (100 mg) and ethionamide (500 mg) to the same single high dose of RMP. Boerrigter *et al.*[13]
PY (95% CI: 3·4–11·4) for WHO–MDT and reviewed reported relapse rates from other publications, ranging from 7 to 120 per 1000 PY. The overall relapse in the present study, 24 per 1000 PY (95% CI: 11–37) is within that range, but formal comparison is unjustified as widely different methodologies were used in these studies. In our earlier studies, using the same methodology, relapse rates of 0·0 to 1·0 per 100 PY[1] and 1·3 to 5·2 per 100 PY[9] for a single high dose of RMP followed by 1 year of daily dapsone, a relapse rate of 2·0 to 2·4 per 100 PY[9] for 10 weekly doses of RMP and a relapse rate of 1·3 to 3·6 per 100 PY[1] for a single high dose of RMP were reported.

PROBABILITY OF CURE

The probability of cure at 3 years is 81·6% for C2 and 82·3% for C4, the difference between both regimens not being significant. Even though no formal statistical comparison is possible with other regimens, these figures do compare favourably to 9 other regimens which were studied with the same methodology[1,6,15] as is shown in Table 7.

The regimen recommended by the WHO Study Group, studied with the same methodology, yielded a probability of cure of 72% at 3 years.[15]

A recent study from India in patients with a single lesion, using similar methodology as we used in the present study, compared WHO/MDT to daily DDS: good or excellent results (as assessed by histopathology 2·5 years after starting therapy) were obtained in 80% of patients on WHO–MDT and in 91% of patients on daily DDS: the difference was not significant due to the small numbers of patients (25 and 23, respectively).[16] Our estimate of cure at 3 years for patients with 1 or 2 lesions, treated with either C2 or C4, was 87%. Like the relapse rates, the probability of cure also varies with the immunological spectrum (Table 4): it was significantly higher for patients with 1 or 2 lesions (as compared to patients with 3 or more lesions) and patients with a BI = 0 (as compared to patients with a BI = 1); the difference between TT and BT was not significant.

VALUE OF SKIN SMEAR RESULTS

In its most recent report, the WHO Expert Committee recommended that 'Any case . . . showing smear positivity will be classified as MB for purposes of multidrug therapy programmes',[17] because it was realized that patients with a BI = 1 did not fare as well on the recommended regimen for PB leprosy as patients who had a BI = 0. We have made the same observation here for both regimens under study: the probability of cure at 3 years was 83% for patients with a BI = 0, while it was 70% for patients with a BI = 1 ($p < 0{\cdot}05$). However, these figures relate to the BI as determined in the histopathological sections. In our study only 1 patient out of 36 with a BI of 1 in the sections for histopathology for whom local skin smear results are available had a skin smear result of 1, while the remaining 35 had a skin smear result of 0. Histopathology is the more sensitive method as isolated bacilli are often situated in nerve twigs and therefore often missed when taking a skin smear.

EFFECTIVENESS OF TREATMENT REGIMENS

In terms of effectiveness, single-dose treatments for PB leprosy can be more or less effective than the WHO recommended regimen, depending on the accessibility of the patients. This can be illustrated with a numerical example looking at hypothetical probabilities of cure at 3 years (PC3). Let us assume PC3 to be 90% for regular patients on the WHO recommended regimen and 60% for irregular patients (including patients who collect just 1 out of the recommended 6 doses) on the WHO regimen. Let us assume PC3 to be 80% for all patients on a single-dose treatment (there can be no irregular patients with a single-dose regimen). The overall probability of cure at 3 years will depend on the proportions of patients who would be regular and irregular on the WHO recommended regimen. Let us assume that in an urban situation with good coverage by the drug delivery system, the proportions of regulars and irregulars are 90% and 10%, respectively. Here $(90\% \times 90\%) + (10\% \times 60\%) = 87\%$ of patients would be cured at 3 years with the WHO regimen. Let us consider on the other hand a rural area which has difficult roads and a rainy season that blocks most of them for about 3 months every year, and assume that in this area the proportions of regulars and irregulars are 50% and 50%, respectively. Here $(50\% \times 90\%) + (50\% \times 60\%) = 75\%$ of patients would be cured at 3 years with the WHO regimen. In both situations 80% of patients would be cured at 3 years with the single-dose

regimen. In this hypothetical example, the WHO regimen would perform better than the single-dose regimen in an urban area, but the opposite would be true in a rural area. In an unpublished study of attendance to the WHO regimen in Kinshasa, Zaïre, 31 (22%) out of 139 new PB patients were considered a treatment compliance risk and were therefore not given the WHO recommended regimen, while another 19 (14%) were irregular (i.e. they did not take their 6 doses within 9 months). Irregularity is most probably worse in rural areas. Considerations of this kind should be borne in mind when interpreting cure rates and relapse rates from published studies, where patients who failed to compete the regimen are not included in the results. It is also likely that routine control programmes achieve lower compliance rates than research programmes do.

Finally a possible disadvantage of single-dose treatment might be that reversal reactions, particularly in areas that are inacessible, remain undetected and untreated, possibly causing severe disabilities.

Conclusions and recommendations

The most effective single-dose treatment for PB leprosy has still not been found. However, 3 classes of drugs have emerged as candidates for inclusion in multiple drug regimens for leprosy in recent years. Several fluoroquinolones have been found to be active against *M. leprae*[18]: ofloxacin has been studied the most, but because the serum half-life is only 6 hours,[19] while it is 11 hours for fleroxacin,[20] fleroxacin may be a better option for a single-dose regimen. Clarithromycin and minocycline are bactericidal against *M. leprae* and have extended serum half-lifes.[21,22] These drugs could be particularly suited for combined therapy with rifampicin, as they all have a different mode of action.

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Un essai clinique randomizé de deux traitements par dose unique de la lèpre paucibacillaire

S. R. Pattyn, P. Ghys, L. Janssens, K. Tshilumba, L. Kuykens, N. Karibushi et P. Denis

Résumé Nous avons comparé 2 posologies à dose unique pour le traitement de la lèpre paucibacillaire dans un essai clinique randomizé au Zaire. Les posologies étaient: C2 (rifampicine 40 mg/kg et clofazimine 1200 mg en une prise) et C4 (rifampicine 40 mg/kg, clofazimine 100 mg, DDS 100 mg et éthionamide 500 mg en une prise). Nous présentons une analyse des résultats sur les malades enrôlés entre mai 1987 et décembre 1988, avec un suivi maximum de 4 ans. Un total de 622 malades ont été enrôlés et 14 rechutes paucibacillaires et une multibacillaire ont été observées. Le taux global de rechutes paucibacillaires a été de 2,4% par 100 personnes/années. Ce taux de rechute a été plus élevé chez les patients les plus âgés ainsi que chez ceux qui avaient 3 lésions ou plus. La probabilité de guérison à 3 ans est 0,816 pour C2 et 0,823 pour C4: la différence n'est pas significative. La probabilité de guérison à 3 ans avec les 2 posologies est plus forte pour les malades avec 1 ou 2 lésions (0,872) que pour les malades avec 3 lésions ou plus (0,787) et également pour les malades avec un index bactérien de 0 (0,831) que pour les malades avec un index bactérien de 1 (0,699). Ces résultats sont comparés à ceux d'autres études. Nous discutons aussi du potentiel d'un traitement à dose unique dans les lèpres paucibacillaires.

Un ensayo clínico aleatorio de dos tratamientos de dósis única para la lepra paucibacilar

S. R. Pattyn, P. Ghys, L. Janssens, K. Tshilumba, L. Kuykens, N. Karibushi y P. Denis

Resumen Comparamos dos regímenes de dósis única en el tratamiento de la lepra paucibacilar, en un ensayo clínico aleatorio en Zaire. Los regímenes fueron: C2 (rifampicina 40 mg/kg y 1200 mg clofazimina una vez) y C4 (rifampicina 40 mg/kg, 100 mg clofazimina, 100 mg DDS y 500 mg etionamida una vez). Se presenta un análisis de los resultados de los pacientes registrados entre mayo 1987 y diciembre 1988, con un control posterior máximo de 4 años. Se registró un total de 622 pacientes y se observaron 14 relapsos 14 paucibacilares y 1 multibacilar. La tasa de relapso paucibacilar fue 2,4 por persona-año. Esta tasa de relapso fue más elevada en el caso de los pacientes más viejos, como también en el caso de pacientes con 3 o más lesiones. La probabilidad de una cura en 3 años es 0,816 en el caso de C2, y 0,823 en el de C4, y la diferencia no es significativa. La probabilidad de una cura en 3 años con cualquiera de los dos regímenes es mayor para los pacientes con 1 o 2 lesiones es (0,872), que cuando hay 3 o más lesiones (0,787), y es mayor para pacientes con un índice bacterial de 0 (0,831) que para pacientes con un índice bacterial de 1 (0,699). Se comparan estos resultados con los de otros estudios. También discutimos el potencial de regímenes de tratamiento con una dosis única en la lepra paucibacilar.

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The effect of footwear on sensory testing in leprosy

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Summary The aim of this study was to identify the effect of footwear on sensory testing in leprosy. This was achieved by using 3 methods of sensory testing within 1 district of East Africa. We included 72 leprosy patients and 36 controls (nonleprosy patients) in the study and these were subdivided into 2 groups, depending on whether they normally wore shoes or went barefoot. The methods used were the WHO sensory test, graded monofilaments and the biothesiometer. The results showed significant differences in the threshold levels between both groups of patients with the biothesiometer and monofilaments, demonstrating the importance of having separate values when screening for leprosy and assessing which patients are at the most risk of developing ulcers. The importance of having quantitative methods of testing was also demonstrated, as only then can the results be sufficiently standardized to identify the at-risk groups and also be sufficiently sensitive to differentiate between shoe wearing and nonshoe wearing patients.

Introduction

Plantar ulceration is the most common serious disability in leprosy,[1] and therefore is of temendous economic importance. This is usually caused by a 'previous ulcer', and the prevention of this first ulcer must be a priority in any leprosy programme. Injuries sustained by the misuse of anaesthetic limbs may cause or lead to ulceration. This can be avoided by educating patients in the care of anaesthetic parts and by protecting the anaesthetic feet with shoes. However, the patient must first recognize and acknowledge their lack of normal sensation and unfortunately many patients are unwilling to admit to being abnormal. Therefore a great deal of interest, concern and time on the part of the medical worker, combined with the ability to define a high risk group quickly and accurately, is needed in order to best use the limited resources available.

The sensory testing of nerve damage has been demonstrated to be a much more reproducible and therefore a more reliable method in comparison to voluntary muscle

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testing.[2] Several studies demonstrate a relationship between sensory loss and the risk of plantar ulceration.[3] It is agreed that loss of light touch is not really a disability, but if a patient cannot localize a firm touch, he is liable to suffer frequent injury; this is known as loss of 'protective sensation'. The purpose of this study was to use 3 different methods of sensory testing in order to define high risk groups, that is patients who have lost protective sensation, between shoe wearing and nonshoe wearing groups of the population.

Several studies have compared the sensitivity of vibratometry, Semmes–Weinstein filaments, 265 Hz tuning fork, biothesiometer, light touch, pin-prick and 2-point discrimination. Vibratometry and the Semmes–Weinstein filaments have been found to be the most effective methods of measuring sensory deficit in the hand and foot.[4–6] This study therefore uses vibratometry and monofilaments in conjunction with the standard WHO pencil stimulus. The WHO test is a commonly-used method in the Third World and the 1970 WHO expert committee on leprosy states 'the failure to localise firm touch is a useful sign that the patient is now in danger from mechanical injury and burns'.[7] The graded pressure sensitive monofilaments were based on the Semmes–Weinstein filaments,[8] a method of proven value in mild nerve damage[9] which is used in the USA. There are reports of their use in the Third World,[4,9] but they are not routinely used on patients. Finally the biothesiometer, an electrical vibration meter which quantifies vibration sensation, is only of experimental use in leprosy, although it is widely used in diabetes.

The idea of this study came from the work done by Hammond & Klenerman,[4] in which they assessed protective sensation in the foot using Semmes–Weinstein filaments and a biothesiometer. They noted that the average values for their controls and the level of protective sensation calculated with the Semmes–Weinstein monofilaments did not differ significantly from the results of Birke & Sims[3] despite the fact that most of Hammond & Klenerman's controls were accustomed to barefoot walking. The aim of this study was to use 3 similar methods of testing within 1 distinct of East Africa, but to differentiate between the shoe and nonshoe wearing members of this population, the idea being that if there is a different level of protective sensation within these 2 groups, then knowledge of this difference would improve the practical value of sensory testing.

Method

PATIENTS AND MATERIALS

The leprosy patients used in this study were a mixture of inhabitants of Kindwitwi Leprosy Village and those being treated in the surrounding Rufiji delta by the village outreach programme. These were divided into 2 groups: those who once had, or were suffering from plantar ulcers and those who had never suffered plantar ulceration. A history of ulceration was determined by physical examination, medical records and patient interviews. We excluded anyone uncertain as to whether they had suffered plantar ulceration, known diabetic mellitus sufferers, and anyone with any other skin disease or foot pathology. A control group was drawn up, matched for age and sex, using noninfected individuals from Kindwitwi.

Each of these 3 groups was then subdivided into those who wore shoes and those who never had. In order to qualify as a 'shoe-wearer', the individual must have worn shoes continually at least 5 years before they were diagnosed as having leprosy, or in the case of the controls, for at least 5 years.

The materials used were a ball-point pen for the WHO standard sensory test; a set of 4 graded pressure-sensitive filaments calibrated to bend slightly when forces of 0·5 g, 2 g, 5 g and 10 g, respectively, were applied, mounted on wire handles;[8] and a battery-run biothesiometer with a fixed frequency of 120 Hz and an amplitude range of 0–25 micrometres.

General considerations

To minimize any fear on the part of the patient, no session lasted for more than 20 minutes, so concentration was maintained throughout. The history and examination were carried out in a quiet room with a local doctor as an interpreter. When the patient was comfortable, a brief history was taken detailing age, sex, disease type, duration, treatment, history of past and present ulceration, and history of footwear. We also ensured that the patient had no other foot problems unrelated to leprosy. The examination was then begun. We demonstrated the tests to the patient, and when the subject was certain he or she understood them, the patient was blindfolded and the tests carried out in succession—4 sites on the sole of the foot were selected; the plantar surface of the big toe, and the first, third and fifth metatarsal heads. These were chosen because they are the commonest sites of ulceration.[3]

Testing methods

WHO STANDARD SENSORY TEST

This was described by the WHO expert committee on leprosy in their 4th report in 1970.[7] To test for insensitivity the examiner uses a point of a pen or pencil. The pressure applied is firm enough to dimple the skin but not enough to move feet or toes; the foot must be supported during testing. The blindfolded patient must point to the place where he or she has been touched. A 'positive' WHO test is the ability to point accurately (within 2 cm) to the point of dimpling in all 4 positions, a 'negative' test is the inability to do so in 1 or more positions.

GRADED PRESSURE SENSITIVE MONOFILAMENTS

The filaments were applied in ascending order perpendicular to the skin at an approximate rate of 1 sec touch, 1 sec hold and 1 sec lift, the force being sufficient to bend the thread slightly. The patient then touches the point where the thread had been felt, not having been informed of the moment when the stimulus was delivered; 1–3 individual stimuli were delivered in each, enough for the tester to be confident that the thread had been felt or not. It is best to test the sites in random order, each area being touched once at a time, returning later to a site if there was doubt the first time. A single site should not be touched several times in quick succession.[8] The threshold at each site was taken as that filament at which the subject could accurately and reproducibly detect the site of pressure stimulus. The highest threshold from the sites was taken as the 'foot threshold'. If the 10-g filament was not detected at any site the test was recorded as negative for that foot.

Table 1. Number of feet examined in each group

	Shoe wearers	Nonshoe wearers
Controls	Group A ($n=36$)	Group B ($n=36$)
With leprosy but no ulcers	Group C ($n=36$)	Group D ($n=32$)
With leprosy and ulcers	Group E ($n=36$)	Group F ($n=40$)

BIOTHESIOMETER

The probe was held lightly on each site and the amplitude of vibration gradually increased from zero until the individual first noticed the sensation. This was repeated 3 times at each site and the mean calculated. The 'foot amplitude' was taken as the mean of the 4 sites, with those subjects unable to feel maximum vibration being given an arbitrary value of 25 micrometers (the maximum amplitude).

Results

The number of patients involved in each group are shown in Table 1.

BIOTHESIOMETER

Figure 1 demonstrates that in the shoe-wearing population, if the biothesiometer is used with a threshold value of 4 mV, leprosy can be indicated, and the results suggest that if it was used as a screening test it would be very effective and efficient, producing no false positives and only approximately 2·5% false negatives (Table 2).

In the nonshoe wearing population, Figure 2 demonstrates that if this same threshold value of 4 mV was used there would be a very high false positive rate of almost 14%, but if the value of 5 mV was used there would be no false positives and only approximately 2% false negatives.

In trying to find a protective sensation level the results again show a difference between the shoe and nonshoe wearing populations. In the nonshoe wearing population there is a protective level of 14 mV with 94% of leprosy patients without ulcers being able to feel it

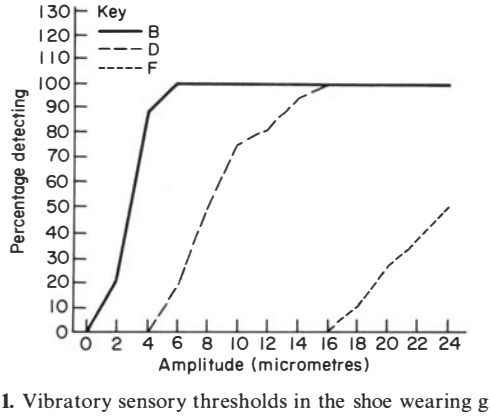

Figure 1. Vibratory sensory thresholds in the shoe wearing groups.

Table 2. Number of feet in each group responding to particular vibratory levels

	Biothesiometer reading (micrometres)	
Group classification	Felt 4 or below	Felt 5 or below
A	36	36
C and E	2	11
B	31	36
D and F	0	2

and 100% of patients with ulcers being unable to feel it (Table 3). In the shoe wearing population the value of 10 mV was found to be a cut-off for the majority of patients with 83% of patients without ulcers being able to feel it and 14% of patients with ulcers being able to feel it (Table 4).

GRADED PRESSURE SENSITIVE MONOFILAMENTS

In the shoe wearing population the 0·5 g monofilament could be used as an effective screening test, with a combined false positive and false negative rate of only 6·9%. It would, however, be unreasonable to use this monofilament value on the bare footed population as the combined false positive, false negative rate would be over 37·5%, which is clearly impractical. However, the 2 g monofilament would not be effective either as too many people would be missed, and so it would appear that for the bare footed population a monofilament value between 0·5 and 2 g is needed.

This test does not demonstrate any clear protective sensation levels in either of the population groups studied, probably because of its limited sensitivity.

WHO STANDARD SENSORY TEST

The WHO test failed to demonstrate any clear values for either a threshold for leprosy or a protective sensation level. This demonstrates the limitations of having a simple positive/

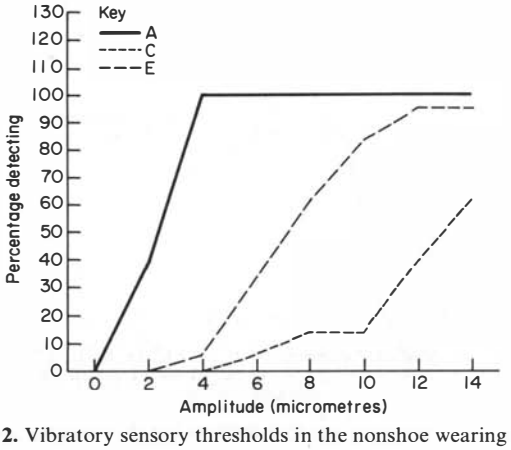

Figure 2. Vibratory sensory thresholds in the nonshoe wearing groups.

Table 3. Protective sensation level for nonshoe wearing population

Group	Felt 14 or below	Felt 21 or below
D	30	32
F	0	18

Table 4. Protective sensation level for shoe wearing population

Group	Felt 10 or below
C ($n=36$)	30
E ($n=36$)	5

Table 5. Number of feet in each group responding to each monofialment

Group	Felt (0·5 g)	Felt (2 g)	Felt (5 g)	Felt (10 g)
A	36	36	36	36
B	24	36	36	36
C	4	21	33	36
D	3	14	21	25
E	1	12	12	20
F	0	3	4	10

Table 6. Responses of each group to the WHO test

Group	WHO test positive (%)	WHO test negative (%)
A	100	0
B	100	0
C	97	3
D	94	6
E	56	44
F	55	45

negative test in comparison to a graded response, and the former is clearly not sensitive enough for this form of testing.

Discussion

In this study we have compared the use of the 3 methods of sensory testing in the shoe wearing and nonshoe wearing populations. We found that although the WHO test is very simple, cheap and quick, because it is not graded in any way its use is very limited, an observation that has already been demonstrated.[4]

The monofilaments clearly demonstrated differences between the shoe wearing and

barefoot populations. Due to the limited range and size of the divisions in the monofilaments we used, however, they did not demonstrate specific values that could be used in screening. This we feel could be remedied by using a more finely divided set of monofilaments within the range (0·5–5 g) and also increasing their upper limit.

The biothesiometer, although expensive (costing around $400[10]) was by far the most useful test. It demonstrated threshold values and protective sensation values for both groups of patients, the values being different between the groups. The values are all of practical use with sensitivity levels ranging from 70 to 100% and specificity levels ranging from 83 to 100%.

Leprosy is feared mainly because of the hideous deformities and crippling disabilities that it leads to in some patients. The real goal of leprosy programmes all over the world is to prevent these disabilities and deformities by arresting the spread of leprosy. Disability prevention is one of the major objectives, but although much is being done indirectly by the eradication of leprosy, this is of little help to those who already suffer from this disease. Several reasons have been put forward to explain why disability prevention is not always an integral part of leprosy programmes: it requires individual attention compared to the mass programmes of drug treatment, it is a lifelong commitment because the anaesthesia remains for life despite treatment, specific expertise is required, and disability prevention requires informed and active co-operation between health carers and the patient.[11]

The key in all these factors is time. Time is a very valuable commodity, particularly in the Third World and it is very important that carers use it efficiently. This is achieved (as has been expressed before) by selecting an 'at risk' group of patients on which to direct resources. However, this is only of use if it is done accurately, and it would appear that when studying sensation loss in the feet, grouping all leprosy patients together regardless of footwear is as inaccurate as prescribing a single standard dose of medication to all patients irrespective of their age or sex. This study has demonstrated that threshold values and protective sensation values for sensation loss can be found and used in leprosy patients, but for these values to be effective different values have to be found and used for shoe wearing and nonshoe wearing patients. There is a need for a more detailed study using a larger cohort to be carried out to discover exactly what those values are for each of the various tests used in sensation loss. Our study shows that it may also be necessary to develop some of the tests to increase their sensitivity.

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L'effet des chaussures sur les tests sensoriels dans la lèpre

C. J. Stratford et B. M. Owen

Résumé L'objet de cette étude était d'identifier l'effet des chaussures sur les tests sensoriels dans la lèpre. Pour cela nous avons utilisé 3 méthodes d'exploration sensorielle dans un district d'Afrique de l'Est. L'étude portait sur 72 malades lépreux et 36 témoins (malades non lépreux), subdivisés en 2 groupes selon qu'ils portaient habituellement des chaussures ou qu'ils allaient pieds nus. Les méthodes utilisées étaient le test sensoriel de WHO, les filaments calibrés et le biothésiomètre. Les résultats ont révélé des différences significatives entre les seuils dans les 2 groupes de malades avec le biothésiomètre et les monofilaments, démontrant ainsi l'importance d'avoir des valeurs séparées pour le dépistage de la lèpre et pour la détermination des patients les plus à risque de développer un ulcère. L'importance des méthodes quantitatives a été également démontrée, car c'est seulement ainsi que les résultats peuvent être suffisamment standardisés pour identifier les groupes à risque et également, être assez sensibles pour différencier entre les malades portant des chaussures et ceux marchant pieds nus.

El efecto del calzado sobre les pruebas sensorias

C. J. Stratford y B. M. Owen

Resumen El propósito de este estudio es identificar el efecto del calzado sobre las pruebas sensorias del calzado. Esto se logró mediante tres métodos de pruebas senorias en un distrito de Africa del Este. Incluimos en el estudio 72 pacientes leprosos y 36 pacientes de control (no leprosos) y se dividieron en dos grupos, dependiendo de si normalmente se ponían zapatos o si iban descalzos. Los métodos utilizados fueron la prueba sensoria OMS, monofilamentos graduados y el biotesiómetro. Los resultados indicaron diferencias significativas de los niveles umbrales entre ambos grupos de pacientes con el biotesiómetro y con los monofilamentos, demostrando la importancia de la exploración para la lepra y evaluando cuáles pacientes tienen más riesgo de desarrollar úlceras. También se demostró la importancia de los métodos de prueba cuantitativos porque solamente entonces se puede normalizar la identificación de los grupos con riesgo para que sea suficientemente sensible para diferenciar entre los pacientes que se ponían zapatos y los que iban descalzos.

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Understanding the attitude of multidisciplinary teams working in leprosy

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Summary This study investigated the attitude of health personnel who were working for the National Leprosy Eradication Programme (NLEP) in India to their leprosy patients. These personnel were studied individually and as homogeneous groups so that comparisons were possible within and among the groups, and between the groups in different regions who were conducting similar health programmes, with a difference in length of between 1 and 5 years.

The sample population was the NLEP employees of 2 state governments, consisting of 8 health professional groups. A questionnaire was developed for each of these groups to elicit information on 5 aspects of the relationships with their patients.

The main outcome of the study was that two-thirds of the personnel tested possessed the 'minimum desirable' interaction with their patients. The quality of their relationships differed only among work specialities, but was consistent within the same speciality in different regions; this pattern was unchanged after 5 years of a multidrug (MDT) programme. A further analysis showed that although they possessed a caring attitude towards patients from low socioeconomic classes, a domineering attitude towards these same patients was also prevalent. Analysis according to speciality revealed that laboratory technicians had the highest 'desirable attitude' (74·67%) and health educators had the lowest (57·5%), while the rest of the team members fell in between. The stigma shown towards leprosy was higher among doctors when compared to the rest of the team members.

Discussion is based on the performance, overall and in each of its 5 facets, of each the professional groups with reference to their job descriptions and with similar studies undertaken earlier.

Introduction

A brief survey of relevant literature shows that the stigma attached to leprosy and the discrimination against those suffering from it have been well documented.[1–4] Bijlevd and his research team at the Royal Tropical Institute in Amsterdam[1,5–7] and Kumar and his team at CLTRI, India[8–10] have done extensive studies on the expectations of leprosy patients of medical teams in Indonesia, Kenya and India. In recent years tremendous

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advances have been made in understanding leprosy. Our own investigations have shown that leprosy health professionals in India have appreciated these advances and are equipped with adequate knowledge.[11] Therefore it is reasonable to expect them to be free from discriminatory bias. A study of the attitudes of paramedical workers in leprosy concluded that a good working environment and job accomplishments are essential for an appropriate attitude towards leprosy patients.[12] A study of Nigerian nurses has shown that because they knew little about leprosy they had an aversion to sufferers of this disease.[13] The National Leprosy Eradication Programme in India (NLEP) is a nationwide programme, employing 24,474 people (in 1987).[14] At district level it is organized into Leprosy Control Units (LCUs), Survey–Education–Treatment Centres (SETs) and Temporary Hospitalization wards. The NLEP is wholly funded by the Government of India and all aspects of care are given free to patients. Health personnel of the NLEP routinely undertake case finding, diagnosis, treatment, health education and rehabilitation.

A brief account of the whole survey in which the analysis of 'the attitude of the multidisciplinary teams to leprosy patients', is a part, is as follows: In 1987, the working environment of the NLEP personnel was investigated. A questionnaire was developed for this purpose which tested 4 major variables, (1) organizational behaviour, (2) human relations, (3) job satisfaction and (4) higher orders need strength. These were further subdivided into 19 variables (Table 2). (Details on most of these variables have been published already[15–17] and are also in the process of publication.[11,18] In this paper an attempt has been made to elaborate only the 'health team–leprosy patients relationship' which was one of the variables tested (no. 17 in Table 2), and, at the same time, to correlate it with a few of the other 18 variables in this survey.

This variable was chosen because the establishment of a close rapport with the patient and counselling are essential features of the NLEP work. Therefore attitudes of the personnel involved while directly dealing with leprosy patients affects the quality of the care given, and ultimately the efficacy of the programme itself.[19]

OBJECTIVES OF THIS STUDY ARE AS FOLLOWS:

1 to investigate the attitude to leprosy patients of the health personnel of the NLEP, as homogeneous groups;
2 to compare attitudes within and among the groups; and
3 to investigate whether attitudes changed as the programme evolved in 2 different regions while conducting similar programmes.

Personnel and methods

PERSONNEL STUDIED

We studied health professionals employed in the NLEP in India. For uniform data collection and adequate representation, cluster sampling was done. We chose 2 districts as clusters, 1 from Andhra Pradesh (AP) state and another from Tamil Nadu (TN) state; all health personnel working in the NLEP of both these districts were included in the study. These 2 districts were chosen because in one the MDT programme had started only 1 year before the data collection of this study, whereas in the other, the MDT had been in

Table 1. Demographic details of the personnel participated in the study

Health personnel numbers	No. of posts	No. participated in study	State they belong to		Mean age range (in years)	Sex		Response rate in %
			AP	TN		M	F	
1 Doctor	22	21	5	16	42 (5/6)	21	0	98·4
2 Nurses	23	23	8	15	36 (1/2)	0	23	100
3 LTs	15	15	4	11	32 (1/3)	13	2	100
4 HEs	8	8	2	6	45	8	0	100
5 PTs	14	13	3	10	38	11	2	95·5
6 Pharm.	5	5	0	5	35 (1/3)	5	0	100
7 PMWs	234	230	94	136	33	230	0	98
8 NMSs	45	41	17	24	45	41	0	90·5
Total/Mean	366	356	133	223	35	329	27	96·1

operation for over 5 years. This kind of variation will help in understanding the different attitudes between year 1 and year 5.

The health personnel of the NLEP in a district consisted of 1 doctor, 2 nurses, 3 nonmedical supervisors (NMSs), 4 health educators (HEs), 5 leprosy paramedical workers (PMWs), 6 physiotherapy technicians (PTs), 7 laboratory technicians (LTs), and 8 pharmacists (Pharm). They formed the total sample population (N: 366), of whom 356 participated in the study (a 96·1% response rate). The reason for a 3·9% nonresponse was due mainly to their nonavailability during data collection. The other characteristics of the sample population are shown in Table 1.

METHOD OF ASSESSMENT

The data was collected using an attitude scale developed by the researcher. The subjects in this study were only assessed by means of a questionnaire, which tested the subject's responses to 5 facets of patient–care relationships, which are:

1 a supportive or prejudiced attitude towards patients;
2 a participative or domineering attitude towards patients;
3 their attitude towards handling stigmatizing aspects in leprosy care;
4 a committed or undercommitted attitude to leprosy patient care; and
5 their attitude towards caring for patients from a low socioeconomic class.

These facets are described in detail in the 'Discussion' section of this paper, and were chosen after nondirective interviews and informal group discussions with a spectrum of health personnel, as described by Moser,[20] during a pilot analysis of the NLEP organizational climate by the author (unpublished data). There was also patient feedback in establishing these facets.

The questionnaire contained statements corresponding to each of the 5 facets. The statements, each loaded with 1 facet, were modified according to the job description of the subject interviewed. For example, while testing attitudes towards handling stigmatizing aspects in leprosy care (Facet 4), pharmacists were given a statement regarding medicine dispensing to disfigured leprosy patients, while statements on ulcer care were given to doctors. This was done to make questions more relevant to the work of the person tested.

The questionnaire was conducted in the interviewer's presence, but it was completed by the interviewee and all results were confidential.

The scoring system for this questionnaire was adapted from the modified Likert scale response of Vasudeva.[21] It consisted of a 6-point response: strongly agree (SA); agree (A); mildly agree (MA); mildly disagree (MD); disagree (D) and strongly disagree (SD). The 6-point response was chosen to eliminate the 'not sure' response, as there were reports that the 'not sure' response can lead to difficulty and controversy in the interpretation of behavioural studies.[22] The 6-point response system used in this study makes the subject either reject or accept the statement.

We presented 3 of the 5 statements in the questionnaire to imply negative discrimination and the remaining 2 to imply positive discrimination (Table 3). The scoring for the 2 positive statements were: SD-0, D-1, MD-2, MA-3, A-4 and SA-5. The scores to the responses for negative statements were SD-5, D-4, MD-3, MA-2, A-1 and SA-0. The intercorrelation of facets to this variable with other variables was $r = +0{\cdot}002$. The internal consistency of the attitude scale was obtained by correcting r with the KR-21 formula, $r = 1{\cdot}00$.[23]

Table 2. Coefficient ranking of variables

Number of Variable	N	Mean	S.D.	Coefficient of variations	Rank
1 Skill development	356	3·09	0·52	16·82	1
2 Autonomy	356	2·95	0·62	21·01	2
3 Interdepartmental relations	356	2·95	0·63	21·36	3
4 Skill variety	356	3·03	0·66	21·78	4
5 Organisational commitment	356	3·06	0·67	21·90	5
6 Organisational climate	356	2·84	0·63	22·18	6
7 Technical satisfaction	356	2·74	0·66	24·09	7
8 Skill utilisation	356	2·77	0·69	24·91	8
9 Interaction of health professionals with administration staff	356	2·49	0·63	25·30	9
10 Job significance within the organisation	356	2·71	0·69	25·46	10
11 Adjustment pattern to the nature of work	356	2·43	0·62	25·51	11
12 Job significance within the community	356	2·57	0·68	26·46	12
13 Adjustment pattern to the disease	356	2·30	0·59	25·65	13
14 Pay satisfaction	356	2·70	0·72	26·67	14
15 Promotion satisfaction	356	2·91	0·78	26·80	15
16 Supervisory behaviour	62	2·83	0·76	26·86	16
17 Health Professionals–leprosy patients relationship	356	2·58	0·71	27·52	17
18 Subordinates description of supervisors behaviour	356	2·39	0·67	28·03	18
19 Doctor–Paramedical Relationships	356	2·43	0·72	29·63	19

STATISTICS USED

(a) The mean of the scores obtained by each person for all the 19 variables was calculated, and the coefficient of variation was computed for priority ranking (Table 2).
(b) A 'two-tail' test was used for analysing the significance of difference in responses between both states.
(c) The overall attitude of the individual professional group was analysed with the assistance of a bar diagram.

Table 3. Frequency of responses by total sample in each facet

Facet no.	Bias of statement	Frequency of response							Desirable attitude	
		0	1	2	3	4	5	Total	Score >15·0	Percent (%)
1	Negative	49	107	81	40	70	9	356	237	66·57
2	Negative	42	132	16	26	100	36	352	190	53·98
3	Negative	33	72	19	54	146	28	352	228	64·77
4	Positive	31	98	52	18	105	49	353	181	51·27
5	Positive	158	14	25	3	18	9	355	325	91·27
Overall percentage of the total sample with score									>15·0	65·57

(d) Similarly, the overall attitude of the individual professional group's response to each facet tested was analysed with the assistance of a graph.

Results

1 The scores obtained for each factor of the questionnaire were totalled. A score of 15 or above was considered to indicate a 'desirable attitude' in the person tested under the presumption that the positive urge overwhelmed the negative inner feelings. The results of such tabulation are shown in Table 3. According to these criteria, 65·54% of the personnel tested had a 'minimum desirable attitude'.

2 An analysis of the responses to each facet shows the lowest range on facet 2 (in Fig. 1, range 20–57%) indicating a domineering attitude of health personnel towards their patients, and the highest range in caring attitude towards patients from a low socioeconomic class (range 86–100%: facet 5 in Fig. 1).

3 Further analysis (Table 2) of 19 work-related attitudinal variables ranked according to the mean score, standard deviation and coefficient of variations show that health professionals' attitude with leprosy patients ranked 17th in the total of 19 variables (N = 356; Mean = 2·58; SD = 0·71; Coefficient of variations = 27·52). (The remaining 18 variables are briefly summarized in the 'Introduction' section of this paper.)

4 Overall 'desirable attitudes' in relationships with patients by different health professionals were calculated. Laboratory technicians had the highest score (74·67%), and the health educators had the lowest score (57·5%) while the rest of the team members ranged in between (Fig. 2). The PMWs are promoted to NMSs on seniority basis. Both these professional groups shared the same overall attitude towards patients (NMSs 65·85% and PMWs 65·09%) (Fig. 2).

5 An analysis of the data was made to discover whether there was a change in attitude over time in both regions, i.e. in the region where MDT had been in practice for 5 years compared to the region where the programme had been initiated only 1 year previously. The analysis was done using the 2-tail test for obtaining the level of significance for the difference between both groups. The results show no such significant difference (Table 4). The quality of the relationship between health personnel and leprosy patients differed only between specialities on the basis of their work, but remained consistent in different regions, and this pattern is still seen even after 5 years.

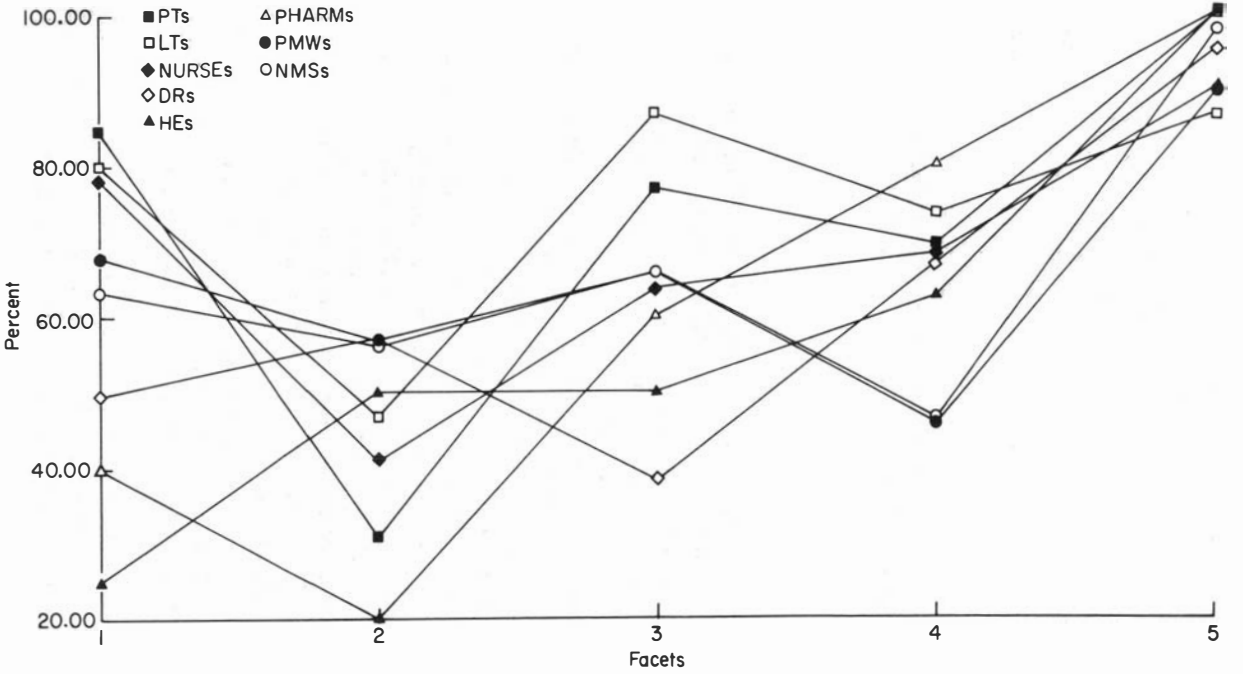

Figure 1. Percentage achieving 'desirable attitude' in each facet.

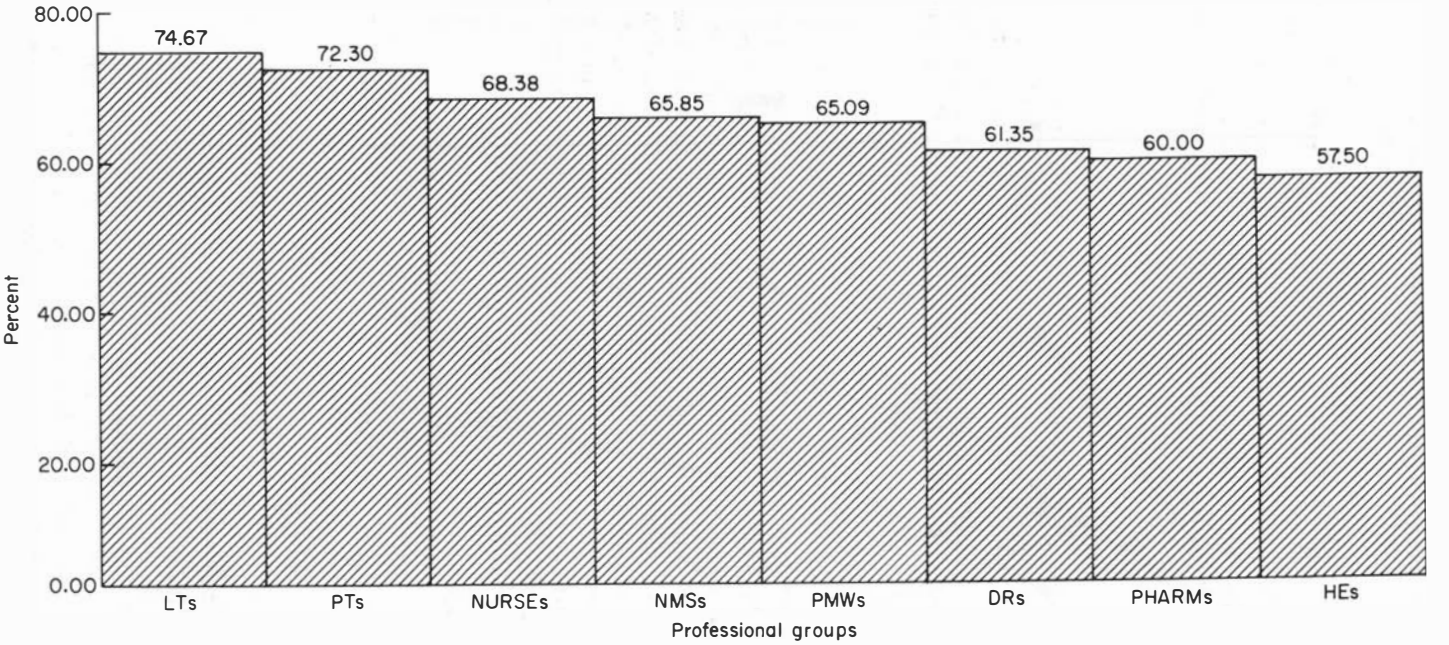

Figure 2. Percentage achieving 'desirable attitude' in total score.

Table 4. Scores by programme duration

Duration of programme (years)	N	Mean	SD	SEr	F	P	Separate variance estimate t	df	2-tail *p*	Significant/ Not significant
1	133	2·60	0·660	0·075	1·24	0·180	0·46	301·17	0·644	N.S.
5	223	2·57	0·740	0·049						

* Significance level of F value is small. Therefore separate variance 2-tail probability estimate used.

Discussion

The main finding of this study is that the attitude of two-thirds of the NLEP personnel to their patients is in the 'desirable' range, and one-third is not, which is a significant proportion. It appears that this is the prime reason for the low ranking of the relationship of the health personnel with leprosy patients that appears in Table 2. Based on the results of this study, the pattern of group dynamics experienced by the NLEP is explained as follows:

COMMAND GROUPS

Careful observation of Table 2 shows that the lower 4 rankings (16–19) are related to interactions between health personnel at the leader–subordinate level, e.g., health personnel with leprosy patients, doctors with paramedical staff and supervisors with subordinates. On the other hand, interdepartmental relationships are observed in the highest ranking rows (1–3). Similarly, the interaction of health professionals with administrative staff is observed in the upper middle ranking rows (4–9). Both these observations indicate that outgroup bias does not adversely affect the interaction between members of different groups within the programme, provided the leader–subordinate relationship does not exist.

PROFESSIONAL GROUPS

An analysis of each facet based on the performance of each professional group has been used to compare their attitude within and across the groups. The findings are as follows:

Supportive or prejudiced attitude

A supportive attitude is the inclination of the team to understand the emotional (affective) disposition of the patient, e.g., anxiety, depression and anger, and the willingness to show empathy. A prejudicial attitude is the failure to appreciate the patient's emotional problems.

Physiotherapy technicians had the highest supportive attitude while nurses were third on the list. By the nature of their work, these professionals have a limited number of patients to take care of per day and they spend more time with individual patients compared to all the other professionals in this study. Because of the chronic nature of these deformities (e.g. recurrent ulcers), the same patients are seen and known by these

personnel over a period of several years, therefore a better rapport is developed with these patients and, because the patients are aware of the chronic nature of their deformities, there is little or no pressure by these patients on the personnel to cure these deformities within a specific period of time, so the patient population shows less aggressiveness to these personnel. Laboratory technicians also scored very highly in this factor, despite the fact that they have very limited opportunity to interact with patients.

Participative or domineering attitude

If health personnel allow the patient some leeway to decide on his treatment procedure, it indicates a participative attitude. Expecting a patient to think and act exactly as the health professional does, indicates a domineering attitude. This study demonstrates that this is the only facet in which most of the team members have scored low (Fig. 1), indicating that a domineering attitude towards patients is significantly high.

The organization itself is perhaps the cause of it. In the NLEP, antileprosy care is given free; a seller–customer type of interaction does not take place when treatment is given free and this places the patient more at the mercy of various health personnel. Such a situation can easily lead to a considerable number of health workers adopting an authoritarian attitude. It is interesting to note that doctors, the team leaders, had a much less domineering approach than the personnel of all the other deciplines. Professional ethics are emphasized more in medical education than in the other 6 disciplines researched in this study, resulting in a better inculcation of these ethics to their professional life.

Attitudes in handling the stigmatizing aspects in leprosy care

Societies' aversion to leprosy and its deformities have been documented in the past.[1–4] The analysis of this facet of the study was to determine whether or not the multidisciplinary team shared the same negative feelings.

The results demonstrated that while 50% of allied health professionals did not share this aversion, approximately two-thirds of the doctors did. The historical reasons for fear about leprosy cannot be the cause of this as doctors are more aware of the rational scientific facts of leprosy than the allied health personnel.

A study has proved that from a very early stage in their education, medical students possessed a conservative attitude towards certain issues,[24] and another study has demonstrated that doctors have unrecognized prejudices about chronic illnesses because they are not easily curable.[25] Deformities in leprosy are chronic in nature and it is not surprising that doctors working in leprosy may have an unrecognized prejudice. Another study stated that the medical profession may hold attitudes and values which are representative of only a minority of society.[26] It is derived from empirical evidence which shows that physicians are mainly drawn from a narrow stratum of the population. This study pointed out that medical students in Britain are almost exclusively drawn from the Registrar General's Social Classes 1 and 2 (that is mainly the business and professional classes), while most of their patients are likely to come from social class 3 to 5 (composed mainly of manual workers).[26] However, how this relates to the situation in India has not been established. If these facts are relevant to the Indian situation it demonstrates that the stigma is high among doctors in comparison to the rest of the specialities despite progress and change in medical knowledge.

Committed or undercommitted attitude

The commitment of the team members refers to an effective attachment to the kind of job the personnel are doing. Bijleveld[7] stated that there was a lack of commitment among the PMWs in many countries. This statement still holds good for PMWs and NMSs, as is demonstrated by this study when the scale of overcommittedness to undercomittedness is applied (facet 3 in Fig. 2).

Interestingly, PMWs and NMSs are highly rewarded groups of workers in terms of monetary benefits and promotions,[16,17] and their self-image has significantly increased from its rather low status in the 60s to that of a moderate status job.[16,17] The job description of PMWs includes demanding activities, such as preclinic drives, taking the patients to the clinics, keeping patient absenteeism at the clinic at the lowest level possible, screening the general public and schoolchildren for leprosy, and record work. The senior PMWs are promoted to NMSs and they supervise the abovementioned activities of the PMWs.

Their working hours are in the very early or latter part of the day, so the work characteristics and environment are stressful. A study has shown that individuals who work in stressful and demanding situations may develop emotional exhaustion.[27] In turn, this may be the cause of a less committed attitude. Both these professional groups form the largest number of team members in the NLEP (Table 1) and as they have responsibility for the major share of leprosy control activities,[28] their commitment to their work must be enhanced.

Caring for patients from a low socioeconomic class

Leprosy patients are mostly from the lower socioeconomic and educational classes.[29] Earlier studies have shown that different socially disadvantaged groups, like women and black patients, receive inferior care to that provided for their respective counterparts.[30] This is not the case now in leprosy (facet 5 in Fig. 1). However, the abovementioned study was done in a general hospital where multiracial groups were treated, whereas this study was carried out in a vertical programme in which only leprosy patients were treated, so a further study is essential in an environment where leprosy is treated along with other diseases. Nevertheless, this result illustrates that almost all the professional groups (86–100%) had no problem in caring for patients from a low socioeconomic class (facet 5 in Fig. 1). It certainly reveals that leprosy personnel do understand more about the social and cultural differences between themselves and their patients.

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Comment comprendre l'attitude envers leurs malades des équipes multidisciplinaires travaillant sur la lèpre?

R. Premkumar, K. Satish Kumar et S. L. Dave

Résumé Cette étude examine l'attitude envers leurs malades lépreux du personnel de santé travaillant pour le programme national d'éradication de la lèpre (NLEP) aux Indes. Ce personnel a été étudié individullement et par groupes homogènes de façon à permettre les comparaisons à l'intérieur du groupe et entre les groupes, et, d'autre part, entre les groupes de différentes régions poursuivant des programmes de santé similaires, pendant des périodes allant de 1 à 5 années.

L'échantillon de population était constitué d'employés du NLEP de 2 gouvernements d'état, soit 8 groupes de personnel de santé. Nous avons établi un questionnaire pour chacun de ces groupes pour obtenir des informations sur 5 aspects de leur relations avec leurs malades.

La principale observation a été que les deux tiers du personnel examiné possédaient le 'minimum désirable' d'interéaction avec leurs malades. La qualité de leurs relations variait seulement avec les spécialités du travail, mais restait constante dans la même spécialité dans des régions différentes; ce tableau n'avait pas changé après 5 ans d'un programme de thérapeutique multidrogue (MDT). Une analyse supplémentaire a montré que, bien que le personnel ait une attitude attentionnée envers les malades des classes sociales inférieures, une attitude opprimante envers ces mêmes malades était également répandue. L'analyse par spécialité a révélé que les techniciens de laboratoire arrivaient les premiers pour 'l'attitude désirable' (74,67%) et les éducateurs de santé les derniers (57,5%), le reste de l'équipe se plaçant entre les deux. Le préjudice contre la lèpre était plus fort chez les médecins que chez les autres membres de l'équipe.

La discussion est basée sur les performances, globales et dans chacune des 5 facettes de l'enquête, de chaque groupe avec référence à leur rôle professionnel et aux études similaires menées auparavant.

Comprendiendo la actitud de los equipos multidisciplinarios a sus pacientes leprosos

R. Premkumar, K. Satish Kumar y S. L. Dave

Resumen Este estudio investigó la actitud a sus pacientes leprosos del personal de sanidad que trabaja en el Programa Nacional para la Eradicación de la Lepra (NLEP), en India. Se estudió el personal, como individuos o en grupos homogéneos para poder efectuar comparaciones en y entre grupos, y entre los grupos de regiones diferentes que realizaban programas similares, con una diferencia de duración de entre 1 y 5 años.

La muestra de la población fue los empleados del NLEP de 2 gobiernos de estado consistiendo de 8 grupos de profesionales de sanidad. Se desarrolló un cuestionario para cada uno de estos grupos para extraer información sobre 5 aspectos de sus relaciones con sus pacientes.

El resultado principal del estudio fue que dos tercios del personal examinado tenía la interacción 'mínima deseable' con sus pacientes. La calidad de sus relaciones diferia según la especialización de su trabajo, pero era uniforme para la misma especialización en regiones diferentes; esta conclusión permaneció constante después de 5 años de un programa multidroga (MDT). Un análisis posterior indicaba que tenían una actitud humanitaria a las clases socio-económicas bajas, y al mismo tiempo una actitud dominante a los mismos pacientes. Un análisis que tomaba en cuenta la especialización reveló que los técnicos de laboratorio tenían la 'actitud deseable' más elevada (74,67%), y los educadores de sanidad tenían la más baja (57,5%), y los demás miembros del equipo presentaban un valor intermedio. El estigma hacia la lepra fue mayor entre los médicos que entre los demás miembros del equipo.

La discusión está está basada en la actuación, total y dividida en 5 características, de cada uno de los grupos profesionales con referencia al tipo de trabajo y a los estudios similares realizados antes.

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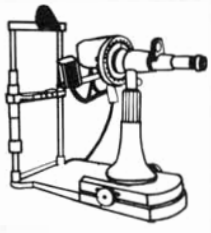

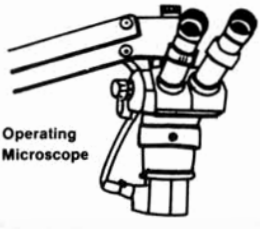

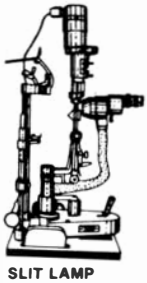

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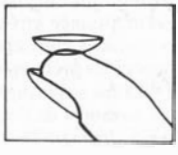

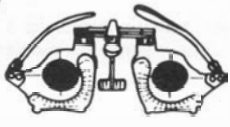

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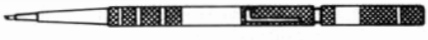

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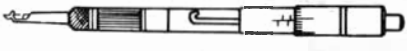

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Editorial Notice

As you are probably aware the donations made to most charities have been much reduced in recent years, so it has become necessary to cut the production costs of *Leprosy Review*.

The principal changes are the reduction in the number of pages published per annum. For this reason Teaching Materials and the News and Notes sections do not appear in this issue, and in future issues these sections will be much reduced. Other measures that will be taken are the ceasing of translation of the summaries into French and Spanish from the June issue onwards; and also the provision of free offprints will cease with this issue.

Nevertheless, we trust that you will continue to find the *Journal* a useful and informative publication.