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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

LEPROSY CONTROL THROUGH GENERAL HEALTH SERVICES AND/OR COMBINED PROGRAMMES

1. Introduction

CONCEPT OF INTEGRATION

In most countries where leprosy is endemic, activities aimed at controlling the disease first began as vertical programmes. A vertical programme is organized from national level down to operational level and is separate from the other health services, having its own specialized staff and clinics. Since the implementation of multidrug therapy (MDT), however, integration of leprosy control into the general health service has gained much wider acceptance. To a great extent this is based on the best utilization of resources, because with the declining number of registered leprosy cases, vertical programmes have become less cost-effective. The basic justification for integration, however, is the principle of equity: all members of a community including leprosy patients should have access to optimal health care, consisting of general, continuous and comprehensive care. Such care can only be provided by multipurpose, permanent and decentralized health services. General health care means that a patient receives care for all common health problems, whereas the vertical services only provide care for specific health problems. Continuous health care implies the permanent, daily accessibility of the services, contrary to the intermittent availability of vertical services, e.g. monthly clinics. Comprehensive health care means that the patient is cared for by staff who know the personal history and (family) background of the patient.

Integration means that leprosy control activities become the responsibility of the general health service, i.e. a multipurpose, permanent and decentralized health service, that is as close to the community as possible. Integration does *not* mean that specialized elements should disappear from the health service. On the contrary, a specialized component must be available within the general health service at the central and intermediate levels for planning and evaluation, the provision of training, technical supervision, advice, referral services and research.

RATIONALE OF INTEGRATION

In 1966 the WHO Expert Committee on Leprosy, in its Third Report, stated: 'The role of the leprologist is mainly to give technical advice and guidance and to train personnel.

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Executive functions in the field should be performed by properly trained public health doctors and paramedical personnel. In countries with leprosy campaigns and concurrently existing general health services, their progressive convergence and ultimate merging must be sought to comply with the accepted view that all problems and programmes in the health field are so interdependent that they must be considered together.'[1] Stanley Browne also wrote in 1972: 'There is no medical reason why leprosy should maintain its splendid isolation from the rest of medicine. Leprosy cannot demand special medical consideration or special legislative measures . . . and does not require a separate service.'[2]

The issue of integration of leprosy control into the general health services has undergone a revival associated with two important developments of the 1980s:

—the international acceptance of the primary health care (PHC) approach, urging decision-makers, in keeping with the principle of equality, to acknowledge that leprosy control should be the integral responsibility of community-based general health services,[3] and
—the introduction of MDT, which has dramatically shortened the duration of the treatment.

Based on the significant progress made with MDT and the consequent reduction in the disease prevalence as well as to the increased priority accorded to leprosy control by several countries, the World Health Assembly, during its 44th meeting in May 1991, adopted in a resolution the goal of attaining the elimination of leprosy as a public health problem by the year 2000. Elimination is defined as reaching a prevalence below one case per 10,000 population.[4] In order to achieve this goal, to which the Member States of the WHO have committed themselves, MDT should be applied to virtually all cases within the next few years. It is obvious that for this purpose the general health services, which usually provide better coverage of the population than vertical programmes, must be involved.[5]

A fourth consideration is becoming increasingly important that is strongly related to the above arguments in favour of integration (equity, cost-effectiveness and coverage), i.e. the sustainability of the leprosy services. After the successful implementation of MDT the prevalence of leprosy will be strongly reduced. In most countries it will not be feasible to maintain a costly vertical service under such conditions. The only way of sustaining leprosy services at their necessary operational level is incorporation with other health services.

2. Limitations of vertical leprosy control programmes

The previous limited levels of achievement in leprosy control may be blamed partially on the limitations inherent to vertical programmes. The main and most frequently reported problems associated with a vertical approach are presented in Table 1.[3,6] These limitations, most of them interrelated, hinder an optimal relationship between the leprosy services and the community. Poor accessability results in delayed self-reporting by leprosy patients and reduced compliance with chemotherapy. Although not all of these limitations occur in every vertical leprosy control programme, in many situations most of them demonstrate the need to integrate leprosy control into the general health service.

Table 1. Limitations of vertical leprosy control programmes

1	Insufficient coverage of populations.
2	Lack of comprehensive health care.
3	Lack of continuous health care.
4	Lack of general health care.
5	Inefficient use of resources (finances, equipment, manpower).
6	Reinforcement of the stigma attached to leprosy.
7	Dependence on donor agencies.

3. Obstacles to integration

Although the need for integration is widely recognized, actual progress has been slow in many countries, and even where integration has been implemented, vertical characteristics often remain. A wide variety of (transitional) mixtures exist between fully vertical control programmes and completely integrated programmes.

Many reasons have been suggested as possible explanations for the slow progress of integration. The most prominent problems that hamper integration are indicated in Table 2.[3,6]

The factors related to commitment mainly concern the resistance to change among various groups at different levels of the health system. These problems should be solved by an adequate explanation of the concept, rationale and benefits of integration. Unacceptable legislation concerning leprosy should be identified and repealed wherever it exists. The problems relating to planning and evaluation can be prevented by carefully planning the process of integration (Section 5). The problems relating to implementation can be prevented by adequate preparation and training of the general and previous vertical staff and, especially in the earlier stages, by intensive supervision.[7] It should be clearly explained that the additional workload for the general health staff is only marginal (generally about 1–2%).[5]

4. Combination of vertical programmes

The combination of vertical control programmes, such as for leprosy and tuberculosis, should not be confused with integration. The combination of vertical programmes is often considered as an intermediate step towards integration. This may be questioned as, in principle, such combined vertical programmes are subject to the same limitations as vertical programmes for leprosy alone. Apart from the limitations of vertical programmes mentioned in Section 2, there are additional risks and pitfalls related to the combination of leprosy control and other services within a single vertical programme:

—a tendency to isolate the other services, e.g., general health staff may not feel responsible any more for the treatment of common skin diseases, such as scabies, if a separate vertical dermatological service operates in the area; and
—the stigma associated with leprosy may have a negative influence on the implementation of the other components of the programme.

Table 2. Obstacles to integration

Commitment	
1	A lack of political commitment to leprosy control and/or integration.
2	If leprosy has a low prevalence, the disease may not have a high priority in general health services.
3	Specialized vertical staff may not accept that multipurpose health workers can deal adequately with leprosy, and being afraid of losing their jobs, often do not support integration.
4	The stigma attached to leprosy reinforces the common belief among health workers, politicians, administrators and the community that leprosy is a special disease which should be treated by a special service.
5	Because of the stigma leprosy patients may not accept care from health workers who are members of their own communities.
6	Leprosy patients may not accept care from general health workers as they prefer to be seen by 'specialists'.[7]
7	Some donor agencies prefer to support vertical programmes with autonomous infrastructures.
8	In some countries legislation still prohibits full acceptance of leprosy patients by health services and other service agencies.
Planning and evaluation	
9	Inadequate planning of the process of integration (often too hurried).
10	Conflict between the interests of specialists, who demand a wide range of data for monitoring and evaluation and those of the general health service administrators, who wish to simplify information systems.
Implementation	
11	Inadequate administrative support.
12	The infrastructure and/or managerial capacity of the general health services may be less adequate than that of the (previous) vertical leprosy control programme.
13	General health workers may not have adequate knowledge, skills and motivation. This is mainly due to a combination of poor training, inadequate technical supervision and because multipurpose workers see relatively few leprosy patients.
14	After integration, resources for leprosy control may be decreased as a result of priority setting (structural adjustment programme); this may lead to a worsening of operational performance.
15	General medical staff may be reluctant to do the additional work required for the care of patients with a chronic disease which needs long-term treatment (health education, retrieval of absentees, ulcer care, etc.).

However, the combination of vertical programmes has a number of advantages as indicated in Table 3.

The combination of vertical programmes has already been established in several countries, such as the combination of leprosy control with tuberculosis control, e.g., Tanzania and Zambia. Apart from an epidemiological similarity, leprosy and tuberculosis have common essential operational features for their control.[9,10] Because of these operational similarities this combination appears to be appropriate, within the above-mentioned limitations.

In other countries vertical leprosy control services are implemented in combination with the dermatological services, e.g., Brazil, Guyana and China. Usually the combined leprosy and dermatological services have developed from vertical leprosy programmes adopting the care for skin diseases in order to decrease the stigma associated with the leprosy programme. As skin clinics are more acceptable than specific leprosy clinics, the combination results in earlier case-finding and improved treatment compliance.[11] In Kenya the leprosy services are combined in a single programme with the dermatological and tuberculosis services.

The combination of vertical programmes shares many of its advantages with integration. However, the shared advantages are of a greater magnitude with integration

Table 3. Advantages of combined vertical programmes

More efficient

1 Supervision for both diseases can be implemented by the same persons, reducing the costs of salaries and transport.
2 The same applies for laboratory services and health education activities.
3 Training of health staff involved in leprosy control and other control programmes (supervisors as well as peripheral staff) can be combined, reducing the number of staff to be trained, the overall time needed for training and, consequently, the costs of training.

Increased coverage

4 Combined programmes may exist in areas where one or both of the diseases may have too low a prevalence to justify the existence of specialized monovalent staff.[8]
5 The vertical programmes may benefit from each other's existing services network (staff, health service facilities, etc.).

Better sustainability

6 After successful implementation of MDT the number of leprosy patients will be considerably reduced. Specialized, monovalent leprosy services would, for reasons of cost-effectiveness, not be justified any more. Combination of leprosy control with another vertical disease control programme would help to sustain leprosy expertise.

Increased acceptance

7 Combined programmes may result in better acceptance of leprosy patients as well as leprosy workers by other health staff and the community, thus creating more opportunity for future integration.

Availability of sources of finance

8 Other vertical programmes may benefit from the existing voluntary external resources for leprosy work, (e.g., funds, transport, equipment etc).

than with the combination of vertical programmes, e.g., integration will generally result in better coverage and greater reduction of stigma. As, moreover, the combination of vertical programmes is subject to most of the limitations of vertical programmes for leprosy alone, the integration of leprosy control into the general health service is more preferable than combining with another vertical programme. Within the integrated services, however, the specialized technical leprosy component can be combined with that for other diseases. This integrated programmes combination reinforces most of the advantages, therefore an additional increase in efficiency and an extra impact on sustainability can be expected. In view of the declining prevalence of leprosy, this strategy of combining specialized components which are integrated into the general health service appears to be the best possible option for leprosy control programmes. It can already be observed in many countries where combined vertical programmes are carried out that the programmes are not strictly vertical anymore but are, more or less, integrated at the peripheral level of the health services, where general health workers are involved in the detection and treatment of leprosy.

5. Planning integration of leprosy control into the general health services

The change from a vertical to an integrated programme is far from easy. The process must be carefully researched and planned and must be appropriate for the specific local

situation of an area. A situation analysis should identify which obstacles to integration are important under the specific local conditions (Section 3). The plan of action for integration should clearly indicate how these problems are to be solved. Adequate resources should be made available. If the process is hurried and staff and patients are not properly prepared, the quality of patient care and the confidence of patients in the services as well as their willingness to cooperate will deteriorate. If the process is too slow, those who want to negate the achievement of integration by delay will be given the opportunity to do so, and the process is likely to fail by default. It should be realized from the beginning that it may take many years before the patients, community and staff will have fully accepted the new situation.

In addition to the identification of the obstacles and their solutions the following considerations are vital in the planning and implementation of integration:

—It is crucial that staff and public accept leprosy patients' use of general health facilities and that the leprosy patients themselves should be willing to attend these facilities. This can only be achieved by intensive staff training and adequate health education.

—A prerequisite for integration is the existence of an adequately functioning general health service infrastructure. Where this does not yet exist, the vertical programme should, for the time being, be continued. However, it should be explored to what extent the vertical leprosy control programme could be used to strengthen the general health service infrastructure.[2,12]

—In integrating leprosy control into general health services equity and quality of care for leprosy patients should be assured. This implies that in any country the leprosy service should be of the *same* quality level (not less, but also not more) as the services for other health problems.[5]

—The process of integration requires careful and adequate planning in advance, and needs to be introduced step-by-step (phasing in place, time and activities). An outline for the planning of the integration process is provided in the Report on the WHO Consultation on Implementation of Leprosy Control through PHC.[6] There is no universally acceptable blueprint for all steps in the transition process. Each country should develop its own strategy, but individual countries using the outline should be able to work out an effective plan of action that is appropriate for their own specific situations.

—It is not possible to identify uniform, globally applicable criteria and standards to indicate when vertical programmes should be integrated. This will have to be decided against the background of the specific situation in each country. Under high-prevalence conditions, for example, it is probably justified that the vertical programme continues until the backlog of patients still registered for dapsone monotherapy have been screened and after the vast majority of the cases have been administered MDT. In general, about 1 year for research and planning the process of integration and at least 6 months for training (including sensitization to the needs of patients) of general and supervisory staff will be required before integration can be implemented.

—It is better that health-related activities are undertaken by adequately-trained workers at the most peripheral possible level of the health service. In high and medium endemic areas peripheral general health staff should be capable of diagnosing and treating leprosy under the technical supervision of specialized workers stationed at the intermediate level. Under low-prevalence conditions general health staff should have

sufficient knowledge and awareness of leprosy in order to identify and refer suspect cases to the centralized, specialized staff for diagnosis and initiation of MDT. This should be guaranteed through appropriate training and regular follow-up during supervisory visits.

—A specialized component must be available within the general health service at the central and intermediate levels for planning and evaluation, the provision of training, technical supervision, advice, referral services and research. Depending on local conditions (e.g., prevalence of leprosy, availability and level of training of various echelons of health staff), each country should decide at which level of the health system such specialized support should be available and whether this should be combined with specialized components for other diseases.

—The tasks of both the multipurpose staff and the specialized staff should be well defined and laid down in a national leprosy control manual. Leprosy control tasks, specified for the respective levels of the health system, are presented in the report of the WHO Consultation on the Implementation of Leprosy Control.[6] This outline requires adaptation to the specific local situations in the various countries.

—Most vertical programmes have detailed recording and reporting systems. With integration, however, the system needs simplification to allow for appropriate data collection by peripheral multipurpose health workers. Only data directly linked to decision-making should be routinely collected.

—Systematic management training, geared to planning, monitoring and evaluation of integrated leprosy control programmes, is needed for intermediate-level health services managers.

—The incorporation of leprosy control into the curricula of medical faculties and paramedical schools is essential for the successful operation of leprosy control as an integrated part of the general health services and to sustain leprosy expertise within the health services.

—Health systems research directed to decision-making at the operational level is essential to ascertain cost-effective and optimal strategies for achieving early case detection, full MDT coverage and adequate patient management by integrated leprosy control programmes. This includes the identification of the most peripheral level of the health services to which individual tasks in the field of leprosy control can be effectively delegated and the identification of optimal methods for promoting intersectoral co-operation and community participation in leprosy control under specific local conditions.

—Non-governmental organizations supporting leprosy control must be involved in the planning process. They will continue to be important partners with governments in integrated leprosy control programmes, although not directly responsible any more for the implementation of the programme. Their contribution will be mainly required in the fields of technical assistance, training and reorientation of health personnel for integration, provision of teaching and learning materials, supplies of drugs, logistic support and social and physical rehabilitation.

6. Conclusion

Because MDT has proven effectiveness and the member states of the WHO have accepted

the goal of the elimination of leprosy by the year 2000, it is mandatory that all leprosy patients in need of chemotherapy receive MDT as soon as possible. In most countries where the disease is endemic, this objective cannot be achieved through vertical programmes. Full utilization will have to be made of the existing general health service. Integrated leprosy control programmes have advantages over the intermittent and mono-purpose services of vertical programmes, which, moreover, in many situations reinforce the stigma attached to the disease. In reality, it has already been shown in several integrated programmes that leprosy control can be effectively implemented by general health services.[3,5,6,12] Although the day-to-day patient management and recording and reporting will become the task of general health staff, specialized services must be maintained within the integrated programme at central and intermediate levels, and particularly under low prevalence conditions the integrated specialized leprosy component should be combined with similar services for other diseases, such as tuberculosis.

There *must* be an adequately functioning general health service infrastructure before integration. Where integration is not yet possible, vertical services may still be appropriate but, depending on local conditions, and mainly for the purpose of efficiency, consideration may be given to combining the vertical leprosy service with other vertical health programmes. This should only be accepted as a temporary solution within the framework of a well-planned transition towards full integration.

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References

[1] WHO Technical Report Series, No. 319, 1966 (*WHO Expert Committee on Leprosy*: Third Report).
[2] Browne SG. The integration of leprosy into the general health services. *Lepr Rev*, 1972; **43:** 16–20.
[3] Feenstra P, Tadele T. A broader scope for leprosy control. *World Health Forum*, 1988; **9:** 53–8.
[4] Noordeen SK. Elimination of leprosy as a public health problem. *Lepr Rev*, 1992; **63:** 1–4.
[5] Yuasa Y. MDT for all; target oriented leprosy control programme in the 1990s. *Int J Lepr*, 1991; **59:** 624–38.
[6] WHO. *Report of the consultation on implementation of leprosy control through primary health care*. WHO, Geneva, 1986. (WHO/CDS/LEP/86.3).
[7] Warndorf DK, Warndorf JA. Leprosy control in Zimbabwe: from a vertical to a horizontal programme. *Lepr Rev*, 1990; **61:** 183–7.
[8] Varkevisser CM, Risseeuw CI, Bijleveld I. *Integration of combined leprosy and tuberculosis services within the general health care delivery system, Western Province, Kenya.* Royal Tropical Institute, Amsterdam, The Netherlands, 1977.
[9] Fine P. Leprosy and tuberculosis, an epidemiological comparison. *Tubercle*, 1984; **65:** 137–53.
[10] De Rijk AJ. Combining tuberculosis and leprosy services in one programme. *Ethiop J Health Dev*, 1984; **1:** 37–43.
[11] Ryan TJ. Dermatology—Global planning in relation to leprosy management. *Lepr Rev*, 1990; **61:** 209–12.
[12] Buchmann H. *Leprosy control services as an integrated part of primary health care programmes in developing countries.* German Leprosy Relief Association, Würzburg, Germany, 1978.

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Editorial

HUMAN IMMUNODEFICIENCY VIRUS AND LEPROSY

From the earliest reports of what has since become the pandemic of human immunodeficiency virus (HIV) infection, a close association between HIV infection and a previously uncommon mycobacterial disease—that due to infection with *Mycobacterium avium* complex (MAC)—was evident.[1] Then and since, clinically significant disease due to MAC is restricted to HIV-positive people in industrialized countries. Later it was realized that *M. tuberculosis* is associated with HIV infection to the extent that, in sub-Saharan Africa, tuberculosis is clinically the most important opportunistic disease in HIV-positive people.[2] A significant proportion of the population there is latently infected with *M. tuberculosis*, and it is thought that HIV infection, by its progressive destruction of cell-mediated immunity, permits the reactivation of tuberculous lesions.

What about *M. leprae* and HIV? In Africa, which today has the greatest number of HIV-infected people of all the continents, leprosy is still relatively common. Further, India has the greatest number of known cases of leprosy in the world, and appears to be on the rising curve of an HIV epidemic potentially as significant as that in Africa.[3] So, an interaction between the two infections could be important. In fact, despite expectations,[4–7] little interaction has been observed.

The potential interactions and complications are many. HIV infection could:

1 increase the probability of infection with *M. leprae*;
2 increase the probability of clinical leprosy developing in a dually infected person;
3 alter the clinical pattern of leprosy;
4 alter the response to antileprosy chemotherapy.

Similarly, prior infection with *M. leprae*—latent or as clinical leprosy—might:

5 increase the probability of acquiring HIV infection;
6 alter the temporal cadence of HIV infection and progression to AIDS;
7 alter the clinical patterns of HIV-associated opportunistic diseases.

There are other potential interactions:

8 leprosy might confound HIV serology;
9 HIV-associated neuropathy might be confused with or exacerbate leprosy neuritis;
10 neuropathy due to antiretroviral chemotherapy might be confused with leprosy;
11 nonleprosy mycobacterioses in HIV-positive people might be confused diagnostically with leprosy;

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12 national policies on BCG vaccination might be amended because of endemic HIV infection;
13 slit-skin smear taking could spread HIV infection;
14 leprosy workers may become increasingly involved with the problems of HIV counselling.

The first 11 propositions listed above will be briefly discussed here; the last 3 have been considered elsewhere.[8–10]

The studies presented to date on propositions 1–7 are either case reports[11–16] or cross-sectional surveys, usually of leprosy patients,[4,17–26] and rarely of patients with AIDS.[27] A few contain longitudinal data on clinical development[11,14,15,26] and some describe the histopathology of the leprosy lesions.[11–15,21,25]

Propositions 1 and 5: *M. leprae* and HIV are reciprocally promoting

That HIV and *M. leprae* infections each might reciprocally increase the probability of later infection with the other is, on theoretical grounds, unlikely. For example, unlike many sexually transmitted diseases, leprosy seldom causes genital ulcer and is rarely, if ever, transmitted by sexual contact. Meticulously selected control groups would be needed to pursue these propositions, and not least, a sensitive and specific test for preclinical infection with *M. leprae* would be required, which currently does not exist. If a cross-sectional study of patients with leprosy shows a higher HIV-seroprevalence than among comparable nonleprosy patients, it could indicate that leprosy promotes the acquisition of HIV infection. It could also, and more probably, indicate that HIV infection predisposes to development of clinical leprosy.

Propositions 2, 3 and 4: Clinical, therapeutic and epidemiological associations between leprosy and HIV

Early studies of leprosy patients in Africa found prevalences of HIV-positivity ranging from 0%[17] to 30%[18], the latter higher than in controls. More recent studies, involving more than 100 people per group, have not found significant differences in HIV prevalence between leprosy patients and control nonleprosy subjects.[22–25] The reason for these discrepancies is not faulty HIV serology (see below) but the selection of cases and appropriate controls. Leprosy patients examined in hospital are often self-reporting and unrepresentative of patients diagnosed in the field (the majority of leprosy cases). They usually have more severe leprosy disease, and may have other nonleprosy ailments that are associated with HIV infection. Further, immigrant leprosy patients may have higher HIV prevalences than resident patients. These and other confounding factors in such epidemiological studies are discussed in a recent study from Malawi.[25]

One early expectation was that HIV infection would, through immunosuppression, increase the ratio of multibacillary to paucibacillary cases of leprosy. The relevant studies—all from Africa where paucibacillary leprosy is more frequent than multibacillary—all found no such change associated with HIV.[20,22,24–26]

Related to this is the expectation that bacillary relapse might be frequent in HIV-

positive, treated leprosy patients. The published case reports detailing response to therapy all indicate resolution of skin lesions at the normal rate.[11,13–16] Relapse has been noted once, in a lepromatous patient with a CD4+ T-lymphocyte count of 121/mm^3, but the only documentation is 'a bacterial index of 1+ on the scale of Ridley'.[12] Concerning leprosy reactions in HIV-positive patients, an abstract from Haiti described HIV-positive treated tuberculoid leprosy patients who developed 'new skin lesions and lepromin anergy' on treatment, at a greater frequency than HIV-negative patients.[20,27] Whether the 'new skin lesions' were delayed hypersensitivity reactions or bacterial relapses is unclear. A possible reversal reaction was reported in an HIV-positive patient treated for 'pure cutaneous leprosy' who 5 years later developed mononeuritis multiplex with tuberculoid skin histology; there were no acid-fast bacilli and the lepromin test was positive.[12] No case of erythema nodosum leprosum (ENL) in an HIV-positive patient has been reported.

A potentially important clinical difference is described from Zambia. Out of 82 new leprosy cases seen in a hospital (8 HIV-positive), 'active neuritis' was equally frequent at presentation in HIV-positive and -negative groups (50%). On standard management, with steroids, the HIV-positive group had less good recovery of nerve function. However, the numbers were small, and the selection of controls was erratic.[26]

One case report details the histopathology and immunocytochemical studies of a leprosy skin lesion in an HIV-positive patient.[14] The histology was multibacillary BL leprosy, about half the lesional T-cells were CD4+ (despite a depressed blood CD4+ T-lymphocyte count of 300/mm^3), and there was no local interferon-gamma production as judged by absence of HLA-DR staining of the epidermis above the lesion. Unfortunately, this and the other single case reports do not really provide much illumination since it is not evident how representative they are of local case material. Conversely, case reports that show strikingly unusual features of leprosy in an HIV-positive patient might indicate a route for further research. These are still awaited.

Concerning lepromin tests, most of the large surveys have not included them in evaluation. Whilst the study from Haiti found that the HIV-positive tuberculoid leprosy patients who developed new lesions on chemotherapy became lepromin negative,[20] other reports note 4 co-infected patients with positive lepromin tests, 1 of whom had a CD4+ T-lymphocyte count of only 12/mm^3.[12,13,16]

Most of the studies on HIV and leprosy concern HIV-1 infection. HIV-2 infection is mainly restricted to West Africa, and also causes AIDS.[28] Determined rates of HIV-2 infection in patients with leprosy were described in 2 studies. In Mali, HIV-2 and dual HIV-$\frac{1}{2}$ infection occurred at the same prevalence in leprosy patients (both paucibacillary and multibacillary) as in nonleprosy controls.[24] Similarly, although the figures are not given, HIV-2 was found at expected prevalences in leprosy patients in Senegal and the Côte d'Ivoire.[28]

Finally, a survey of hospitalized patients with AIDS in Burundi found 4 patients with leprosy (all female, representing 6% of those studied); no further data are provided.[27]

Propositions 6 and 7: leprosy may influence the course of HIV disease

Several authors have suggested that *M. leprae* infection may accelerate the course of HIV infection.[20,22,29] The argument is that many mycobacterial infections induce cell secretion of tumour necrosis factor (TNF-α). Whilst TNF-α is important in granuloma formation,

it promotes production of HIV in monocytes and lymphocytes, hence increasing the cytopathic effects of HIV, reducing CD4+ T-lymphocyte levels and causing a more rapid progression to AIDS.[30] Case reports quote a range of blood CD4+ T-lymphocyte counts at presentation with leprosy in HIV-positive patients: 12, 121, 300, and 350 per mm^3.[12–15] A few studies indicate deaths—from AIDS-defining conditions such as tuberculosis or HIV encephalopathy—following diagnosis and treatment of leprosy.[11,14,26] Generally there is little published information on HIV-related sequelae in *M. leprae*/HIV co-infected people. None of this confirms or refutes the propositions. In order to do this the following studies would be needed:

natural history studies of leprosy patients with and without HIV infection;
2 analyses of cytokine expression and HIV replication (ideally) or surrogate markers of HIV expression (such as β_2-microglobulin) in leprosy patients and controls; [30]
3 proper evaluation of mortality with determination of the causes of death. This may require autopsy and is not easy—for example whilst the fact of increased mortality in tuberculosis patients with HIV-infection compared with HIV-negatives is well known, the actual causes of death are still unclear.[31,32]

Proposition 8: leprosy and HIV serology

Some early studies reported false-positive HIV serology in leprosy patients[24]. Four percent of sera from Indonesian patients with leprosy were HIV-positive on screening tests including ELISA, although Western blots were negative;[33] 5% of leprosy patients in Zaire also gave false-positive ELISAs.[17] This suggested that antibody cross-reactions could reduce the specificity of HIV serology in leprosy patients (particularly lepromatous) in tropical countries. This was the case with the first generation HIV ELISAs used in Africa, being affected by malaria antibodies.[34] Potentially confusing bands on Western blots in patients with tuberculosis and leprosy have also been reported.[35] However, a larger study in Malawi examining several HIV-serotesting strategies found no excess of problematic sera from leprosy compared with nonleprosy patients. Moreover, most of the problems in the leprosy group were in tuberculoid rather than lepromatous patients, the former having low leprosy specific antibody titres.[36] With the recent HIV tests, false-positive serology due potentially to leprosy is effectively eliminated.

Propositions 9 and 10: neuropathy, HIV and leprosy

HIV itself is a cause of several peripheral neuropathy syndromes including distal symmetrical neuropathy, mononeuritis multiplex, and autonomic neuropathy.[37,38] No reports of such neuropathies clinically mimicking leprosy have yet appeared. Histologically these neuropathies may show perivascular intra-neural inflammation, sometimes necrotizing vasculitis,[39] but not granulomatous inflammation (nor, of course, acid-fast bacilli). By in-situ hybridization, HIV can be demonstrated in inflammatory cells in the endoneurium and epineurium.[39]

It has been suggested that HIV and *M. leprae* may enhance each other so causing a more fulminant neuritis than is seen in HIV-negative leprosy patients.[26,40] The limited

histopathological studies on leprosy neuritis in Malawian patients have not shown any difference between HIV-positives and negatives.[21] The Malawi survey, moreover, found that all the incident leprosy patients who had disability (indicating severe neuritis) were HIV-negative.[25] Again, this emphasizes the importance of studying large numbers of patients with appropriate controls. Although theoretically possible, such an intraneural interaction awaits further support.

Antiretroviral chemotherapy with the dideoxynucleoside analogues ddI and ddC has been associated with a reversible distal sensory neuropathy.[38] This is unlikely to be a clinical problem in poor, leprosy-endemic countries given the high costs of these drugs.

Proposition 11: non-leprosy lesions resembling leprosy

The non-specific rashes that, in Africa, are commonly associated with HIV-infection[21,41] are unlikely to be clinically confused with leprosy. A potential histological confusion is of multibacillary mycobacterial histiocytosis in immunosuppressed patients (due usually to a MAC infection), resembling lepromatous leprosy and even a histoid.[42,43] One case report documents a retroperitoneal lymph node in an HIV-positive patient containing *M. scrofulaceum* and showing histology similar to lepromatous leprosy lymphadenitis.[44]

Summary and conclusions

In summary, clinical leprosy does not appear to be more frequent in HIV-positive than in HIV-negative people in areas where both infections are endemic. There is no evidence that the paucibacillary to multibacillary distribution of patients is altered by HIV infection. There are reports that neuritis is more severe in co-infected people, and that reversal reactions (or, at least, new lesions) may be more frequent after therapy; but these reports are either poorly documented or poorly controlled.

In several ways, this lack of expected leprosy is similar to the patterns of other low-virulent infections in HIV-positive patients in the tropics, such as MAC infection, *Pneumocystis carinii* and cytomegalovirus infection.[45] Despite the presence of the agents in the environment and/or in the human host, they are infrequently encountered clinicopathologically.[46,47] This is in marked contrast to their importance in industrialized countries. One explanation, as yet unproven, is that HIV-positive patients in the tropics do not live long enough in states of severe immunosuppression to develop these infections. Perhaps the same applies to *M. leprae* infection, whose incubation period can be measured in decades and whose clinical course may evolve over years, in contrast to the common reactivation of latent, virulent *M. tuberculosis* infection with its high morbidity.

There may also be an analogy between leprosy and infection with *Plasmodium falciparum*, *Strongyloides stercoralis* and *Entamoeba histolytica*: these infections are controlled (or at least influenced) by cell-mediated immunity and, theoretically, should be more frequent in HIV-positive people than HIV-negatives. In fact they are not, and leprosy may be regarded as another 'missing infection in AIDS'.[48] As noted previously, 'the immunology of leprosy is once again not as we thought it would be'.[8]

The cynic might conclude that further investigation of associations between leprosy and HIV infection are a waste of time and money, given the epidemic status of HIV

infection and AIDS and the comparative unimportance, demographically, of leprosy. In the future, national leprosy control programmes may well have some of their previous government funding diverted to AIDS control programmes. A lack of interest would be short-sighted. With greater case numbers, and especially if survival with HIV infection lengthens, there may be some perceptible changes in the local clinical cadences of leprosy associated with HIV. More representative studies of CD4+ T-lymphocyte counts in HIV-positive and HIV-negative leprosy patients, with follow-up evaluations during treatment, should be done. These should also be correlated with lepromin test results. Coupled with laboratory studies of the cellular interactions between HIV and *M. leprae*—using immunocytochemical techniques on lesions and (*pace* tuberculosis) studies of HIV expression and cytokines—such research will provide valuable information on this still-mysterious host–parasite relationship called leprosy.

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References

[1] Collins FM. *Mycobacterium avium*-complex infections and development of the acquired immunodeficiency syndrome: casual opportunist or causal co-factor? *Int J Lepr*, 1986; **54:** 458–474.
[2] De Cock KM, Soro B, Coulibaly IM, Lucas SB. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA*, 1992; **268:** 1581–1587.
[3] Kaur A, Babu PG, Jacob M, et al. Clinical and laboratory profile of AIDS in India. *J Acq Immune Def Synd*, 1992; **5:** 883–889.
[4] Daumerie D, Castelli F, Pizzocolo G, Carosi G. HIV and leprosy: a hypothetical mutual interference. *2nd Int Symp AIDS Africa*, 1987; TH-78:(Abstract)
[5] Morrow RH, Colebunders RL, Chin J. Interactions of HIV infection with endemic tropical diseases. *AIDS*, 1989; **3 suppl 1:** S79–S87.
[6] Gormus BJ, Murphey-Corb M, Martin LN, *et al*. Interactions between simian immunodeficiency virus and *Mycobacterium leprae* in experimentally inoculated rhesus monkeys. *J Infect Dis*, 1989; **160:** 405–413.
[7] Turk JL, Rees RJW. AIDS and leprosy. *Lepr Rev*, 1988; **59:** 193–194.
[8] Fine PEM. Reflections on the elimination of leprosy. *Int J Lepr*, 1992; **60:** 71–80.
[9] WHO. Guidelines for personnel involved in collection of skin smears in leprosy control programmes for the prevention and control of possible infection with HIV. *Lepr Rev*, 1987; **58:** 207–208.
[10] Ponnighaus JM, Oxborrow SM. Counselling HIV positive leprosy patients. *Lepr Rev*, 1991; **62:** 105.
[11] Lamfers EJP, Bastiaans AH, Mravunac M, Rampen FHJ. Leprosy in the acquired immunodeficiency syndrome. *Ann Intern Med*, 1987; **107:** 111–112.
[12] Janssen F, Wallach D, Khuong MA, et al. Association de maladie de Hansen et d'infection par le virus d'immunodéficience humaine. Deux observations. *Presse Med*, 1988; **17:** 1652–1653.
[13] De Truchis P, Balloul H, Fegueux S, Matheron S, Saimot AG, Coulaud JP. Lèpre au cours de l'infection VIH. *4th Int Conf Afr AIDS*, 1989; **198**:(Abstract)
[14] Kennedy C, Chin A, Lien RAM, Stolz E, van Joost T, Naafs B. Leprosy and human immunodeficiency virus infection; a closer look at the lesions. *Int J Dermatol*, 1990; **29:** 130–140.
[15] Raguin G, Reymond JL, Vabres P, Salmon D, Brion JP, Vilde JL. Association infection à VIH et lèpre. *Presse Med*, 1991; **20:** 478.
[16] Serra M, Padilha-Gonçalves A, Rachid-de-Lacerda MC, Basílio-de-Oliveira CA, Pinto CA, Rais-de-Sá MO. Treatment of dermatological manifestations in developing countries—practice, efficacy and cost aspects. *8th Int Conf AIDS*, 1992;**PoD 5773**:(Abstract)
[17] Dazza MC, Larouz' B, Aktar L, Mabika WA, Bantu S, Brun-Vezinet F. High prevalence rate of unconfirmed HIV-1 ELISA in African patients with leprosy. *4th Int Conf AIDS*, 1988; 5543.(Abstract)
[18] Meeran K. Prevalence of HIV infection among patients with leprosy and tuberculosis in rural Zambia. *Br Med J*, 1989; **298:** 364–365.
[19] Péan C, Pape JW, Deschamps MM, Dambreville M. Prévalence et évolution de l'infection au VIH chez les lépreux en Haiti. *Int J Lepr*, 1989; **57:** FP 018, S306-S307.(Abstract)

[20] Péan C, Pape JW, Deschamps M-M, Dantreville M, Johnson WD. Natural history of *M.leprae* and HIV infection. *5th Int Conf AIDS*, 1989; Th.B.P.70.(Abstract)
[21] Lucas SB. Dermatopathological aspects of HIV disease in Africa. *4th Int Conf Afr AIDS*, 1989; 164.(Abstract)
[22] Leonard G, Sangare A, Verdier M, et al. Prevalence of HIV infection among patients with leprosy in African countries and Yemen. *J Acq Immune Def Synd*, 1990; **3:** 1109–1113.
[23] Tekle-Haimanot R, Frommel D, Tadesse T, Verdier M, Abebe M, Denis F. A survey of HTLV-1 and HIVs in Ethiopian leprosy patients. *AIDS*, 1991; **5:** 108–110.
[24] Tounkara A, Fofana Y, Diabate M, Sangare D. Etude de la seroconversion anti-VIH chez les lépreux lépromateux au Mali. Enquête préliminaire. *Med Afr Noire*, 1991; **38:** 89–91.
[25] Ponnighaus JM, Mwanjasi LJ, Fine PEM, et al. Is HIV infection a risk factor for leprosy? *Int J Lepr*, 1991; **59:** 221–228.
[26] Vreeburg AEM. Clinical observations on leprosy patients with HIV-1 infection in Zambia. *Lepr Rev*, 1992; **63:** 134–140.
[27] Standaert B, Kocheleff P, Kadende P, et al. Acquired immunodeficiency syndrome and human immunodefiency virus infection in Bujumbura, Burundi. *Trans R Soc Trop Med Hyg*, 1988; **82:** 902–904.
[28] De Cock KM, Odehouri K, Colebunders RL, et al. A comparison of HIV-1 and HIV-2 infections in hospitalized patients in Abidjan, Cote d'Ivoire. *AIDS*, 1990; **4:** 443–448.
[29] Miller RA. Leprosy and AIDS: a review of the literature and speculations on the impact of CD4+ lymphocyte depletion on immunity to *Mycobacterium leprae*. *Int J Lepr*, 1991; **59:** 639–644.
[30] Wallis RS, Vjecha M, Amir-Tahmasseb M, et al. Influence of tuberculosis on human immunodeficiency virus (HIV-1): enhanced cytokine expression and elevated β2-microglobulin in HIV-1 associated tuberculosis. *J Infect Dis*, 1993; **167:** 43–48.
[31] Abouya YL, Kassim S, Ackah A, et al. Prospective cohort study of pulmonary tuberculosis patients with HIV infections in Abidjan, Côte d'Ivoire. *6th Int Conf Afr AIDS*, 1991; **WA 203:**(Abstract)
[32] Nunn P, Brindle R, Carpenter L, et al. Cohort study of HIV infection in tuberculosis patients, Nairobi, Kenya: analysis of early (6 months) mortality. *Am Rev Respir Dis*, 1992; **146:** 849–854.
[33] Nuti M, Defelici A, von Axel-Castrelli, Roscigno G. False HIV positivity in leprosy. *Int J Lepr*, 1989; **57:** PO 350, p.S366.(Abstract)
[34] Biggar RJ, Gigase PL, Melbye M, et al. ELISA HTLV III retrovirus antibody reactivity associated with malaria and immune complexes in healthy Africans. *Lancet*, 1985; **2:** 520–523.
[35] ShivRaj L, Patil SA, Girdhar A, Sengupta U, Desikan KV, Srinivasan H. Antibodies to HIV-1 in sera from patients with mycobacterial infections. *Int J Lepr*, 1988; **56:** 546–551.
[36] Shaw M, Turner AC, Blackwell JM, Fine PEM, Ponnighaus JM. Setting up HIV serology for the Karonga prevention trial in Malawi. *Lepr Rev*, 1991; **62:** 87–104.
[37] Budka H, Wiley CA, Kleihues P, *et al.* HIV-associated disease of the nervous system: review of the nomenclature and proposal for neuropathology-based terminology. *Brain Pathol*, 1991; **1:** 143–152.
[38] Simpson DM, Wolfe DE. Neuromuscular complications of HIV infection and its treatment. *AIDS*, 1991; **5:** 917–926.
[39] Gherardi R, Lebargy F, Gaulard P, Mhiri C, Bernaudin JF, Gray F. Necrotizing vasculitis and HIV replication in peripheral nerves. *N Engl J Med*, 1989; **321:** 685–686.
[40] Patki AH. Some possible interactions of *M.leprae* and HIV in the peripheral nerves. *Int J Lepr*, 1991; **59:** 331–332.
[41] Colebunders RL, Mann JM, Francis H, et al. Generalized papular pruritic eruption in African patients with human immnodeficiency virus infection. *AIDS*, 1987; **1:** 117–121.
[42] Cole GW, Gebhard J. *Mycobacterium avium* infection of the skin resembling lepromatous leprosy. *Br J Dermatol*, 1979; **101:** 71–74.
[43] Wood C, Nickoloff BJ, Todes-Taylor NR. Pseudotumour resulting from atypical mycobacterial infection: a 'histoid' variety of *Mycobacterium avium-intracellulare* complex infection. *Am J Clin Pathol*, 1985; **83:** 524–527.
[44] Delabie J, De Wolf-Peeters C, Bobbaers H, Bilbe G, Desmet VJ. Immunophenotypic analysis of histiocytes in AIDS-associated *Mycobacterium scrofulaceum* infection: similarities with lepromatous leprosy. *Clin Exp Immunol*, 1991; **85:** 214–218.
[45] Lucas SB, Hounnou A, Beaumel A, et al. The pathology of adult HIV infection in Abidjan, Côte d'Ivoire. *8th Int Conf AIDS*, 1992; **PoB 3751**:(Abstract)
[46] Wakefield AE, Stewart TJ, Moxon ER, Marsh K, Hopkin JM. Infection with *Pneumocystis carinii* is prevalent in healthy Gambian children. *Trans R Soc Trop Med Hyg*, 1990; **84:** 800–802.
[47] Morrissey A, Aisu TO, Falkinham JO, Eriki PP, Ellner JJ, Daniel TM. Absence of *Mycobacterium avium* complex disease in patients with AIDS in Uganda. *J Acq Immune Def Synd*, 1992; **5:** 477–478.
[48] Lucas SB. Missing infections in AIDS. *Trans R Soc Trop Med Hyg*, 1990; **84 Suppl 1:** 34–38.

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In leprosy the presence of mycobacteria in the nerve is an essential factor in the cycle and spectrum of *Mycobacterium leprae* infection

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Summary A total of 220 untreated leprosy patients who underwent parallel skin and nerve biopsies are included in this study, which is intended to evaluate the extent of previously reported differences in bacillary load between skin and nerve lesions in leprosy and to describe the response of peripheral blood lymphocytes to *Mycobacterium leprae* antigens in such patients.

In 161 patients out of the 220, the skin and nerve biopsies were diagnostic for leprosy. When patients were grouped according their skin and nerve lesions, the 3 groups observed were (1) paucibacillary skin and nerve lesions; (2) multibacillary skin and nerve lesions, and (3) paucibacillary skin and multibacillary nerve lesions. There was no observation of a group of patients with multibacillary skin and paucibacillary nerve lesions. In all patients with multibacillary nerve lesions, regardless of the type of skin lesions, a low response of peripheral blood lymphocytes to *M. leprae* was consistently noted. These results suggest that the bacillary load in the nerve is certainly one of the factors determining the immunological spectrum observed in leprosy.

Introduction

Leprosy manifests itself as a spectrum from lepromatous to tuberculoid forms and affects skin and nerve. The number, distribution, appearance and bacillary load of the skin lesions are used as the main criteria for the classification of the disease. Tuberculoid patients have few skin lesions, in which *M. leprae* are rare (paucibacillary), while lepromatous patients generally have numerous skin lesions in which organisms are abundant (multibacillary). However, studies have shown differences between the bacillary load in the skin and nerves.[1,2,3,4] Indeed there are patients who are classified as a paucibacillary case with regard to their skin lesion but who present with a high bacillary load in the nerves.

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Our work is intended to evaluate, in Ethiopian patients, the extent of the difference in bacillary load between the skin and the nerve and to describe these patients' T-cell response to *M. leprae*.

Materials and methods

PATIENTS

A total of 220 untreated leprosy patients who underwent parallel skin and nerve biopsies between January 1987 and June 1990 at ALERT are included in this study. The biopsies were performed and examined at AHRI. All biopsied nerves were radial cutaneous nerves of the hand. The skin and nerve biopsies were routinely processed and sections were stained with haematoxylin & Eosin and TRIFF reagents.

The skin lesions were classified according to the Ridley–Jopling criteria.[5] The nerve lesions were classified as paucibacillary or multibacillary neuritis on the basis of the bacillary index (BI). The logarithmic scale used to determine the BI of smears was applied for tissue sections. A BI > 2 was considered as a multibacillary case.[6]

LYMPHOPROLIFERATIVE ASSAY (LPA)

LPA were performed for a few patients randomly selected from each group. LPA were realized in the presence of *M. leprae* (batch numbers CD 106, provided by Dr R. J. W. Rees, N.I.M.R., Mill Hill, London; through the WHO/TDR IMMLEP project) or tuberculin purified protein derivative PPD (obtained from the Tuberculin Department, Statens Serum Institut, Copenhagen, Denmark).

The isolation and culture of mononuclear cells were performed according to the methods of Closs *et al.*[7] and Reitan *et al.*[8] Briefly 15×10^4 mononuclear cells per well were incubated in RPMI 1640 with 5% Normal Human Serum for 6 days with 10 μg of sonicated *M. leprae* or 10 μg of PPD or as control 10 μg phytohaemagglutinin (Sigma).

Results of LPA's are expressed as the mean count per minute (cpm) of triplicate wells and the degree proliferation induced by each antigen (Δcpm) as cpm of stimulated culture minus cpm of unstimulated control cultures. Our result are expressed as Δcpm of *M. leprae* stimulated cultures/Δcpm of PPD stimulated culture. Presentation of the results in this manner using PPD as internal reference circumvents the problem of interassay variations obtained when reporting results as absolute cpm.

Table 1. Grouping of patients

Group	Classification of lesions	No. of Patients	Percent
I	Indeterminate skin and Paucibacillary nerve (IS, PN)	27	16·7
II	Indeterminate skin and Multibacillary nerve (IS, MN)	37	22·9
III	Borderline tuberculoid skin and Paucibacillary nerve (BTS, PN)	46	28·5
IV	Borderline tuberculoid skin and Multibacillary nerve (BTS, MN)	9	5·7
V	Borderline lepromatous or Lepromatous lepromatous skin and Multibacillary nerve (LS, MN)	42	26·0

Table 2. LPA Results

Group	Type of skin and nerve lesions association	No. of patients tested for LPA	Mean Δcpm *M. leprae* ± SD Δcpm PPD
I	Indeterminate skin paucibacillary nerve (IS, PN)	3	60 ± 1
II	Indeterminate skin multibacillary nerve (IS MN)	4	5·75 ± 3·1
III	BT skin paucibacillary nerve (BTS, PN)	3	54·3 ± 5·1
IV	BT skin multibacillary nerve (BTS, MN)	9	9 ± 3·2
V	BL or LL skin multibacillary nerve (LS, MN)	3	6 ± 2·7

Results

In 18 out of the 220 patients neither the skin nor the nerve was diagnostic for leprosy. In 27 patients only the skin biopsy was diagnostic for leprosy while in 14 patients the diagnosis of leprosy was made solely on the nerve biopsy.

In the remaining 161 patients both the skin and nerve biopsies were diagnostic for leprosy. The grouping of these 161 patients is presented in Table 1.

LPA results are presented in Table 2. In groups I (ISPN) and III (BTS, PN) the ratio of Δcpm *M. leprae*/Δcpm PPD was approximately 50% while in the other groups this ratio was less than 13%.

Discussion

We found 5 types of association of skin and nerve involvement, but none were observed presenting with multibacillary skin and paucibacillary nerve lesions. This finding confirms the previous reports that describe a higher bacillary load in the nerve than in the skin in individual patients.[2,9]

Results of LPA are informative and a trend is apparent. Specifically, in patients presenting with multibacillary nerve lesion, regardless of the BI in the skin lesion, a low response of peripheral blood lymphocytes to *M. leprae* was consistently noted. In group V (patients who were unambiguously lepromatous cases), the low lymphocyte response to *M. leprae* was consistent with their classification.[9,10] In group IV (patients who were BT with smear negative skin lesion and multibacillary nerve lesion), a low lymphocyte proliferative response was surprising as this is inconsistent with the classification based on skin lesion. As anticipated, group III (cases with paucibacillary skin and nerve lesion), displayed a substantial lymphocyte reactivity in the presence of *M. leprae* compared to group II, group IV and group V, all having in common multibacillary nerve lesion.

Bjune[11] has raised pertinent questions as to why so many BT patients have LPA response to *M. leprae*. Various reasons have been given[11,12] and from our study one explanation may be added. The patients who have BI = 0 in skin lesion and who have low LPA response to *M. leprae* could be those who have a high bacillary load in their nerve lesion. The low responsiveness to *M. leprae* antigens of the patients with indeterminate

skin lesion and multibacillary nerve lesion (group II) is similar to that in patients with primary neuritic leprosy, as reported by Nath and colleagues.[13]

Do the above observations deserve consideration regarding the type of multidrug therapy (MDT) to be prescribed for leprosy patients? Kaur *et al.*[9] have raised the question 'do patients with multibacillary neural lesion require the WHO MDT multibacillary regimen for proper management?'. These authors feel that long-term MDT may not be necessary since the total bacillary count is less than 10 in patients with negative skin lesion and heavy bacterial load in the nerve. However, we do not share this opinion. At ALERT our policy is to prescribe a WHO multibacillary MDT regimen for all patients with paucibacillary skin lesion but with multibacillary nerve lesion.

The existence of leprosy patients classified as paucibacillary on the basis of their skin lesion but who should be considered as multibacillary for treatment purposes has been stressed by different authors.[14,15] Reddy[16] raised this issue and advocated a uniform long-term MDT regimen for all leprosy patients, regardless of classification. The above-mentioned points of view and concepts may be addressed in a different way in the common condition of a leprosy control set-up where nerve biopsy facilities are not available. This approach may be based on the importance to be given to the lepromin test. Thus a patient diagnosed as presenting a paucibacillary leprosy but having a negative lepromin test would benefit from long-term MDT regimen.

The hospital-based study described in this paper examined only a limited number of patients, but allowed us to emphasize 2 main questions. First, our results suggest that the bacillary load in the nerve (paucibacillary or multibacillary) is certainly one of the factors determining the immunological spectrum of the disease; it has been observed that patients with multibacillary nerve lesion have low LPA response regardless of their BI in skin lesion. Secondly a heavy bacillary load in the nerve may act as a reservoir of bacilli which allows a relapse to occur; or this may allow the disease to continue due to insufficient treatment.[17]

In order to more fully answer these questions a larger prospective study in which multiple immunological parameters are to be assessed is in progress.

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Reference

[1] Srinivasar H, Rao KS, Iyer CGS. Discrepancy in the histopathological features of leprosy lesions in the skin and peripheral nerve. *Lepr India*, 1982; **54:** 275–86.

[2] Nilsen R, Mengistu G, Reddy BB. The role of nerve biopsies in the diagnosis and management of leprosy. *Lepr Rev*, 1989; **60:** 28–32.

[3] Nilsen R, Mshana RN, Negesse Y, Mengistu G, Kana B. Immunohistochemical studies of leprous neuritis. *Lepr Rev*, 1986; **57:** *Suppl* 2, 177–87.

[4] Yemane Berhan T, Negesse Y. Relapse rates in paucibacillary leprosy. WHO regimen versus initial classification. Abstract P. 118, VI World Congress of Dermatology: Tropical, Geographic and Ecologic—Rio de Janeiro, April 29–May 3, 1989.

[5] Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five group system. *Int J Lepr*, 1966; **34:** 255–73.
[6] Negesse Y. Leprous neuritis, classification of leprosy and multidrug therapy (letter). *Int J Lepr*, 1988; **56:** 329–30.
[7] Closs O, Reitan LJ, Negassi K, Harboe M, Belehu A. *In vitro* stimulation of lymphocytes in leprosy patients, healthy contacts of leprosy patients and subjects not exposed to leprosy. *Scand J Immunol*, 1982; **16:** 103–15.
[8] Reitan LJ, Closs O, Belehu A. *In vitro* lymphocyte stimulation in patients with lepromatous and borderline tuberculoid leprosy. The effect of dapsone treatment on the response to *M. leprae* antigens, PPD and non-mycobacterial stimulants. *Int J Lepr*, 1982; **50:** 455–67.
[9] Kaur G, Girdhar BK, Girdhar A, Malaviya GN, Mukherjee A, Sengupta U, Desikan KV. A clinical study of neuritic leprosy patients. *Int J Lepr*, 1991; **59:** 385–91.
[10] Godal T, Mykestad B, Samuel DR, Myrvang B. Characterization of the cellular immune defect in lepromatous leprosy: a specific lack of circulating *M. leprae* reactive lymphocytes. *Clin exp Imm*, 1971; **9:** 821–31.
[11] Bjune G. Variation of *in vitro* lymphocyte responses to *M. leprae* antigen in borderline tuberculoid patients. *Int J Lepr*, 1980; **48:** 30–9.
[12] Bjune G, Barnetson R, StC, Ridley DS, Kronvall G. Lymphocyte transformation test in leprosy; correlation of the response with inflammation of lesions. *Clin exp Imm*, 1976; **25:** 85–94.
[13] Nathl, Narayanan RB, Sathish M, Ahuja GK, Singh R. Selective loss of *M. leprae* responsiveness of circulating lymphocytes in primary neuritic leprosy. *Lepr Rev*, 1981; **52:** 79–89.
[14] Bernardi CDV, Gerbase AC, Fereira J, Pino GD, Bakos L. Operational classification in Hansen's disease control. Abstract in *Int J Lepr*, 1984; **52:** Suppl 1: 741.
[15] Jesudasan K, Christian M. Risk of paucibacillary leprosy patients released from control relapsing with multibacillary leprosy. *Int J Lepr*, 1985; **53:** 19–21.
[16] Reddy NBB. Why classify leprosy patients into paucibacillary and multibacillary group? *Lepr Rev*, 1987; **58:** 89.
[17] Stoner GL. Importance of the neural predilection of *M. leprae* in leprosy. *Lancet*, November 10, 1979; 994–6.

Dans la lèpre, la présence de mycobactéries dans le nerf est un facteur essentiel dans le cycle et le spectre de l'infection par *Mycobacterium leprae*

YOHANNES NEGESSE, KASSA BEIMNET, TIVADAR MIKO, ASSEFA WONDIMU ET TEBEBE YEMANE BERHAN

Résumé Deux cent vingt lépreux non traités qui ont eu des biopsies parallèles de la peau et du nerf sont inclus dans cette étude qui a pour but d'évaluer l'importance des différences signalées auparavant entre la charge bacillaire des lésions cutanées et celle des lésions nerveuses dans la lèpre et de décrire la réponse des lymphocytes du sang périphérique aux antigènes de *M. leprae* chez ces patients.

Chez 161 patients sur les 220, les biopsies cutanées et nerveuses ont amené à un diagnostic de lèpre. Lorsque les patients ont été répartis suivant leurs lésions cutanées et nerveuses, on a observé les trois groupes suivants: (1) lésions cutanées et nerveuses paucibacillaires; (2) lésions cutanées et nerveuses multibacillaires et (3) lésions cutanées paucibacillaires et lésions nerveuses multibacillaires. On n'a pas observé de groupe de patients avec des lésions cutanées multibacillaires et nerveuses paucibacillaires. Chez tous les patients portant des lésions nerveuses multibacillaires, quel que soit le type des lésions cutanées, on a constamment noté une faible réponse des lymphocytes du sang périphérique à *M. leprae*. Ces résultats suggèrent que la charge bacillaire dans le nerf est certainement un des facteurs déterminant le spectre immunologique observé dans la lèpre.

En los casos de lepra, la presencia de *Mycobacterium* en el nervio es un factor imprescindible en el ciclo y gama de infección por *Mycobacterium leprae*

YOHANNES NEGESSE, KASSA BEIMNET, TIVADAR MIKO, ASSEFA WONDIMU Y TEBEBE YEMANE BERHAN

Resumen Doscientos veinte pacientes con lepra sin tratar que fueron sometidos a biopsias en paralelo de piel y neural, participaron en este estudio cuya intención fue evaluar las diferencias informadas anteriormente de la carga bacilar entre lesiones de la piel y neural en la lepra, y describir la respuesta de los linfocitos hemáticos periféricos a los antigenos *Mycobacterium leprae* en tales pacientes.

En ciento sesenta y un pacientes de los doscientos, las biopsias de piel y neurales fueron positivos para la lepra. Cuando se agruparon los pacientes de acuerdo con las lesiones de piel y neurales, los tres grupos fueron (1) lesiones de piel y neural paucibacilares; (2) lesiones de piel y neural multibacilares; (3) lesiones de piel paucibacilares y neural multibacilares. No se encontró un grupo de pacientes con lesiones de piel multibacilares y neural paucibacilares. En todos los pacientes, sin tener en cuenta el tipo de lesión de la piel, se notó una respuesta baja de los linfocitos hemáticos periféricos de *M. leprae*. Estos resultados sugieren que ciertamente la carga bacilar de los nervios es uno de los factores que determina la gama immunológica de la lepra.

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Concurrent skin and nerve histology in leprosy and its role in the classification of leprosy

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Summary Concurrent skin and nerve histology was evaluated in 60 leprosy patients (25 BT, 28 BL and 7 LL). The twin aims were to study the comparative histology and the usefulness of nerve histology in the classification of the disease. In BT patients, clinical and histological classification was in agreement in 11 (44%) skin and 17 (68%) nerve biopsies. Concurrent skin and nerve histology was in consonance in 14 (56%) BT patients, while in 6 (24%) patients, only nerve histology was helpful in the classification of the disease, the skin histology being non-specific. Nerve histology was classified as BL in 3 (12%) BT patients, the skin histology was non-specific.

In the BL group, the histology of 23 (82·4%) nerve biopsies correlated with the clinical classification, in contrast to skin histology which correlated with clinical assessment in 19 (68%) patients only. In the LL patients, the histology of nerve correlated with the clinical classification in 5 patients (71·4%), compared to histology of the skin in 4 (57%) patients only. The GF was higher in the nerves than in the skin throughout the leprosy spectrum (BT, BL, LL); the difference was, however, marginal in BL leprosy. The average bacteriological index (BI) was higher in nerves (4+) compared to that of skin histology and slit skin smears (3+) in BL leprosy. There was, however, no difference in the BI of the slit skin smears, skin and nerve biopsies in lepromatous leprosy.

It is inferred that the neural histology is often more useful than skin histology in the classification of leprosy patients ($p < 0{\cdot}01$) and it correlates better with clinical classification, particularly in the borderline tuberculoid disease. The neural histology gave a better idea about the bacterial load in the BT, BL patients. It is proposed that bacteriologically negative patients clinically and histologically classified as BT, but with nerve histology more consistent with BL, should be considered multibacillary for purposes of therapy.

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Introduction

Although the main parameters for the diagnosis and classification of leprosy are related to the skin, leprosy is primarily a disease of the peripheral nerves. The clinical diagnosis of leprosy is largely based on characteristic skin lesions in association with thickened nerves and the presence of anaesthesia. Demonstration of acid fast bacilli (AFB) in slit skin smears (SSS), and histopathology of the skin are commonly used to confirm the diagnosis and classification of the disease. The histopathology of the skin lesions usually provides adequate information about the type of leprosy. The role of neural histology in diagnosis and classification of leprosy has been recently highlighted.[1] In the majority of the cases the lesions in the nerves were found to be more bacillated than the skin, and persisted after the skin lesions had regressed.[2–4]

The present study was undertaken to compare the histopathology of skin and nerves in the biopsies taken simultaneously, its correlation with the clinical classification, and to ascertain the usefulness of neural histology in the classification and selection of a therapeutic regimen.

Classification of leprosy is not only important for a better understanding of the disease but also for treatment purposes. The concept of multibacillary leprosy was established with an idea of formulating its therapeutic strategy.

This paper mostly highlights the role of neural pathology in the treatment policy of leprosy in general and borderline tuberculoid leprosy in particular. There are two distinct clinical subsets of BT leprosy, one group is close to TT (TTs − BT) with few skin lesions and few thickened nerves and much intact CMI and SSS − ve, while the other group is close to BB (BB − BT), with multiple lesions ($\geqslant 10$), multiple thickened nerves, much compromised CMI and SSS + ve. Using WHO–1988 guidelines, there is no difficulty in treating the patients of BT who are SSS + ve from skin, but the real problem is selecting the treatment for BT patients who are SSS − ve. Though they are SSS − ve and histopathology of the skin shows nonspecific changes and no AFBs, many of them frequently show specific granuloma and AFBs in their nerves. According to WHO guidelines, we are probably undertreating these BT patients, who may be a potential source of resistance and relapse. In view of their SSS negativity there is no other monitoring guideline to measure the adequacy of *WHO-PBR* in these subsets of BT leprosy. Therefore, histopathology of nerves is certainly an important tool in monitoring the treatment of this group of patients.

Materials and methods

We selected 60 consecutive untreated patients with leprosy from the leprosy clinic held at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. We used the Ridley–Jopling classification of leprosy.[8] A lepromin test was done in all 60 patients, using Dharmendra antigen.[9] All the patients were subjected to parallel skin and nerve biopsies. Full thickness skin biopsies were taken from infiltrated plaques, fixed in Zenker's formalin and stained with haematoxylin & eosin and Fite–Faraco stain for lepra bacilli. The biopsies were studied for the location and type of cells composing the granuloma, the presence or absence of subepidermal free zone, the destruction of nerves and appendages, and the presence of AFBs. The histology was classified into the 5

conventional groups, TT, BT, BB, BL and LL. The granuloma fraction (GF), which is the fraction of the dermis occupied by granuloma in a section observed under low power objective expressed decimally, was also determined.[10]

Nerve biopsies were performed from thickened, purely sensory nerves, such as radial cutaneous ($n=51$), sural ($n=2$) greater auricular ($n=2$), or other cutaneous nerves in the proximity of skin lesions ($n=3$). Ulnar nerve biopsy ($n=2$) was obtained during open drainage of nerve abscesses. Fixation and staining of the nerve biopsy specimens was undertaken in the same way as for skin biopsies. Apart from the cellular morphology, the GF was determined by estimating the fraction of nerve tissue occupied by granuloma. We used the histopathological criteria laid down by Ridley for the nerve biopsy classification of leprosy.[11]

The data was analysed using Chi-square to study the role of neural histology in leprosy classification and its correlation with the clinical classification.

Results

The 60 patients studied included 25 BT and 35 BL/LL patients (28 BL, 7 LL). All BT patients were slit smear negative. The BL patients had a mean bacteriological index (BI) of 3+ and lepromatous patients had BI of 4+ and above. All BL/LL patients were lepromin negative. The demographic details of the patients are shown in Table 1.

BORDERLINE TUBERCULOID LEPROSY

In the clinically BT patients there were 25 skin biopsies; 11 were classified as BT, 3 as TT; the skin histology could not be classified in the remaining 7 biopsies as they showed only nonspecific features. Of the 25 nerve biopsies studied, 17 showed features of BT, 3 were TT, 3 had BL histology and 2 showed nonspecific neuritis. The difference between the skin and nerve histology classification was highly significant ($p<0{\cdot}01$).

Clinico-histological Correlation

In the BT patients, the neural histology correlated with clinical classification in 17 (68%) patients, compared to skin histology which was consistent in 11 (44%) patients only. The

Table 1. Demographic details of 60 patients

Characteristic	Type of leprosy	
	BT	BL/LL
Number of patients	25	35
Mean age in years (range)	26 (16–42)	36 (16–62)
Sex	20 M, 5 F	29 M, 6 F
Mean duration in months (range)	8 (6–24)	24 (6–48)
Number of patches (range)	3·6 (1–10)	Innumerable
Lepromin	All + ve (2+ to 3+)	All negative
Bacteriologic indices (BI/MI)	No AFB	3·2+ (3+ to 4+)

Table 2. Neural histology in BT leprosy

Tissue	No. of patients studied	Number classified			Number not classified
		BT	TT	BL	
Skin	25	11	3	0	11
Nerve	25	17	3	3	2

Neural *vs* skin histology = $p < 0{\cdot}02$.
Classified *vs* not classified = $p < 0{\cdot}01$.

neural histology was helpful in the classification of the disease spectrum in 23 (92%) patients, whereas dermal histology was only significant in 14 (56%) patients (Table 2, $p < 0{\cdot}02$). The difference became even more significant if 2 BT patients who were not confirmed by skin or nerve biopsy are excluded from the analysis ($p < 0{\cdot}01$).

The analysis of parallel skin and nerve histology in the BT group showed concordance in 14 patients (11 BT, 3 TT). In all, 6 nerve biopsies were classified as BT and 3 as BL; however, the skin histology showed nonspecific features in these patients.

The mean granuloma fraction (GF) was higher in the nerves (0·38) than in the skin biopsies classified as BT (0·19). Lymphocytes and epithelioid cells were more abundant in nerves compared to skin. Caseation was present in 8 nerve biopsies. AFBs were demonstrated in 8 nerve biopsies whereas no acid-fast bacilli were demonstrated in slit skin smears and skin biopsies.

BORDERLINE LEPROMATOUS AND LEPROMATOUS LEPROSY

Of the 28 clinically BL patients, the skin biopsy was classified as BL in 19, BB in 2 and in the remaining 7 the histology was nonspecific. Of the 28 nerve biopsies in this group, 23 were classified as BL, one as BB and in 4 neuritis was nonspecific. The mean granuloma fraction was 0·5 in nerve biopsies compared to 0·4 in skin biopsies. The average BI in skin biopsies was similar to skin slit smear results (3+). However, the BI in the nerve biopsies was higher, with a mean of 4+. There was no statistically significant difference in the skin and nerve histology as regards the correlation with clinical classification in BL and LL patients (Tables 3 and 4). The skin and nerve histology showed almost similar features.

Table 3. Neural histology in BL leprosy

Tissue studied	Number of patients studied	Number classified			No. not classified
		BL	LL	BB	
Skin	28	19	0	2	7
Nerve	28	23	0	1	4

Skin *vs* neural histology = $p > 0{\cdot}05$.
Classified *vs* not classified = $p > 0{\cdot}05$.

Table 4. Neural histology in lepromatous leprosy

Tissue studied	Number of patients studied	Number classified			Number not classified
		LL	BL	BB	
Skin	7	4	2	0	1
Nerve	7	5	2	0	0

Neural *vs* skin histology $= p > 0{\cdot}05$.
Classified *vs* not classified $= p > 0{\cdot}05$.

The granuloma fraction was, however, higher in the nerves (0·7) than in the skin biopsies (0·5). All specimens of nerve and skin biopsies were positive for AFB, and there was no difference in the mean BI at either site.

Discussion

Though the Ridley–Jopling classification is widely accepted, its histological component refers only to skin with the presumption that there may be no significant difference in the classification in the skin and neural histology. However, discrepancies have lately been brought out showing that many nerve biopsies show histological grading lower than the skin.[1,2]

The value of the study of neural histology in the diagnosis of doubtful cases of leprosy was documented by Nilsen *et al.*[1] who found it to be diagnostic of leprosy in one-third of patients when skin histology showed nonspecific features. The significance of neural histology in the classification of leprosy is less well documented. Mukherjee & Mishra[13] found neural histology to be more useful in the classification of leprosy in one-third of patients, in whom skin had indeterminate or nonspecific features. The skin and nerve histology was found to be qualitatively similar when granuloma was well developed at both sites. Similarly in the present study, neural histology was found to be significantly better in classifying leprosy, especially in the borderline tuberculoid group, as nonspecific changes were less frequent in the nerves ($p < 0{\cdot}01$; Table 2). The difference was, however, not significant in the BL-LL spectrum. Ridley & Ridley,[12] in a study of concurrent skin and nerve histology in 42 patients, found similar features for purposes of classification in the polar forms of leprosy (TT, LL). We observed similar histological findings in skin and nerves in lepromatous leprosy. We did not have clinically diagnosed TT patients. However, 3 patients with TT histology in skin showed similar features in the nerves.

Caseation in the histopathological sections of nerves is well documented in TT and BT leprosy. Ridley[11] considered it to be more indicative of subpolar tuberculoid leprosy (TTs). Foci of caseation necrosis were large in some of the nerves we studied, the nerves were irregularly thickened and nodular, and the findings were considered to be suggestive of nerve abscess. Caseation was not seen in the corresponding skin biopsies, indicating that delayed hypersensitivity to *Mycobacterium leprae* antigen was better manifest in nerves in these patients.

The relevance of lower immunological grading and heavy bacterial load in the nerves is debated.[1,14] Nerves are protected sites for *M. leprae* and allow unhindered multiplication of bacilli in early stages of infection. The discrepancy in the skin and nerve histology was explained by the delayed recognition of *M. leprae* antigen which allows a build up of antigen within the nerves.[12] Nilsen *et al.*[1] classified patients with a bacterial index of more than 2+ in their nerves as multibacillary. Negesse[14] suggested that patients clinically and histologically diagnosed as tuberculoid, in whom nerve histology showed a BI of more than 2+, might be classified as having dimorphic leprosy. We agree with Nilsen *et al.*[1] and propose that such patients be classified as multibacillary on the basis of combined skin and neural histology, and treated with multibacillary drug regimens. This may reduce the incidence of relapse because the number of bacilli harboured in the nerves may be better tackled with MB type of MDT. Ridley & Ridley[12] concede that nerve histology might be of prognostic value in individual patients. There is need for further studies to compare the relapse rate of paucibacillary patients classified after study of concurrent skin and nerve histology and comparing them with therapy decided on the basis of skin histology findings alone. The skin histology will continue to be a standard tool in the confirmation of the diagnosis and classification of leprosy. The neural histology, whenever feasible, will give more information about the exact classification and immunological spectrum of the patient. Neural histology will be of use in classifying leprosy patients when skin histology is indeterminate or nonspecific.

References

1 Nilsen R, Mengistu G, Reddy BB. The role of nerve biopsies in the diagnosis and management of leprosy. *Lepr Rev*, 1989; **60:** 28–32.

2 Antia NH, Pandya NU. Qualitative histology and quantitative bacteriology in various tissues of leprosy patients. *Lepr Rev*, 1976; **47:** 175–83.

3 Srinivasan H, Rao KS, Iyer CAS. Discrepancy in the histopathological features of leprosy lesions in the skin and peripheral nerve. *Lepr India*, 1982; **54:** 275–86.

4 Haimanot RT, Mshana RN, McDougall AC, Andersen JG. Sural nerve biopsy in leprosy patients after varying period of treatment: Histopathological and bacteriological finding in light microscopy. *Int J Lepr*, 1984; **52:** 163–70.

5 Ridley DS. *Skin biopsy in Leprosy*. Ciba-Geigy Ltd. Basle (Switzerland), 1977, 39–40.

6 Katoch K, Ramanathan U, Natarajan M, Bagg AK, Bhatia AS, Saxena RK, Ramu. Relapse in paucibacillary patients treatment with three short regimens containing rifampicin. *Int J Lepr,* 1989; **57:** 458.

7 Kaur S, Sharma VK, Basak P, Kaur I. Paucibacillary multidrug therapy in Leprosy. $7\frac{1}{2}$ years experience. *Ind J Lepr*, 1992; **64:** 1563–61.

8 Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five group system. *Int J Lepr*, 1966; **34:** 255–73.

9 Dharmendra. Studies of the lepromin test. A bacillus antigen standardised by weight. *Lepr India*, 1942; **14:** 122–9.

10 Ridley DS. *Skin biopsy in leprosy*. Basel Documenta Geigy, 1985, 59.

11 Ridley DS. *Pathogenesis of leprosy and related diseases*. London: Wright, 1988; 168–71.

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

13 Mukherjee A, Misra RS. Comparative histology of skin and nerve granulomas in leprosy patients. *Lepr Rev*, 1988; 177–80.

14 Negesse Y. Leprous neuritis, classification of leprosy and multidrug therapy. *Int J Lepr*, 1988; **56:** 329–30.

Histologie simultanée de la peau et du nerf dans la lèpre et son rôle dans la classification de la lèpre

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Résumé L'histologie simultanée de la peau et du nerf a été déterminée chez 60 patients atteints de lèpre (25 BT, 28 BL, et 7 LL). Le double but du projet était d'étudier l'histologie comparée et l'intérêt de l'histologie du nerf dans la classification de la maladie. Chez les patients BT, la classification clinique et histologique concordaient dans 11 (44%) biopsies de la peau et 17 (68%) biopsies du nerf. L'histologie simultanée de la peau et du nerf s'accordaient dans 14 (56%) des patients BT, tandis que chez 6 (24%) patients, seule l'histologie du nerf était utile pour la classification de la maladie, la biopsie de la peau n'étant pas spécifique. L'histologie du nerf a été classée en BL chez 3 (12%) des patients BT, la biopsie de la peau n'était pas spécifique.

Dans le groupe BL, l'histologie de 23 (82,4%) biopsies du nerf correspondait avec la classification clinique, par contre, la biopsie de la peau ne correspondait au tableau clinique que chez (68%) patients. Chez les patients LL, l'histologie du nerf correspondait avec la classification clinique chez 5 (71,4%), comparé à l'histologie de la peau chez 4 (57%) patients seulement. Le GF était plus élevé dans les nerfs que dans la peau sur tout l'ensemble de la lèpre (BT, BL, LL), la différence était pourtant marginale dans la lèpre BL. L'index bactériologique moyen (IB) était plus élevé dans les nerfs (4+) que dans l'histologie de la peau et les frottis de peau fendue (3+) dans la lèpre BL. Il n'y avait pourtant pas de différence dans les IB des frottis de peau fendue, les biopsies de peau et de nerf dans la lèpre lépromateuse.

En conclusion, l'histologie du nerf convient mieux que l'histologie de la peau à la classification des patients lépreux ($p < 0{,}01$) et correspond mieux à la classification clinique, en particulier dans la maladie borderline tuberculoïde.

L'histologie du nerf a donné une meilleure idée de la charge bactérienne chez les patients BT et BL. Nous proposons que les patients à bactériologie négative, diagnostiqués par la clinique et l'histologie comme BT, mais avec une histologie du nerf correspondant mieux à BL soient considérés comme multibacillaires pour le choix du traitement.

La histología concurrente de la piel y neural en la lepra y su papel en la classificación de la lepra

SURRINDER KAUR, VINOD K. SHARMA, PRASANTA BASAK, INDERJEET KAUR Y BISHAN D. RADOTRA

Resumen Se evaluó la histología concurrente de la piel y neural en 60 pacientes con lepra (25 BT, 28 BL y 7LL). El objetivo doble fue el estudio de la histología comparativa y la utilidad de la histología neural para la clasificación de la enfermedad. En los pacientes BT, la clasificación clínica e histológica correspondía con 11 (44%) biopsias de la piel y con 17 (68%) neural. La histología de la piel y neural concurrentes concordaba con 14 (56%) de los paciente BT, pero en 6 (24%) de los pacientes solamente la histología neural ayudaba en la clasificación de la enfermedad ya que la histología de la piel no era específica. La histología neural fue clasificada de BL en 3 (12%) de los pacientes BT, y la histología de la piel no era específica.

En el grupo GL, la histología de 23 (82,4%) de las biopsias neurales correlacionaba con la clasificación clínica, comparada con la histología de la piela que correlacionaba con la evaluación clínica en 19 (68%) de los pacientes. En los pacientes LL, la histología neural correlacionaba con la clasificación clínica en 5 casos (71,4%), comparada con la histología de la piel de los 4 (57%) pacientes. El GF fue más elevado en el caso neural que en el de la piel por toda la gama de la lepra (BT, BL, LL); sin embargo, la diferencia era muy pequeña en el caso de la lepra BL. El índice bacteriológico medio (BI) fue más en la histología neural (4+) que en la histología de la piel y frótis de la piel cortada (SSS) (3+) en la lepra BL. Sin embargo, no había diferencia entre el BI de los frótis de la piel cortada, y las biopsias de la piel y neural en la lepra lepromatosa.

Se concluye que la histoloía neural es más adecuada que la histología de la piel para la clasificación de los pacientes leprosos ($p < 0{,}01$) ye que correlaciona mejor con la clasificación clínica, especialmente en los casos tuberculoides dudosos.

La histología neural presenta una mejor idea de la carga bacteriana en los pacientes BT, BL. Se propone que los pacientes con un diagnóstico clinico e histológico BT, pero con una histología neural más consistente con BL, deberán ser considerados casos multibacilares para los propósitos terapéuticos.

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Pilot study to determine acceptability and ability of heat-killed *Mycobacterium leprae* plus BCG (HKML+BCG) vaccine to induce skin test conversion

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Summary Although local reactions, including erythema, induration and ulcers, appeared in every patient after the injection of the combined HKML+BCG vaccine, they were accepted by the patients. There was no tendency for the local reaction to become aggravated after repeated vaccination. However, systemic reactions, mainly iridocyclitis and complaint of numbness of the fingers and toes, became quite common after the 5th vaccination and therefore significantly reduced the acceptability of vaccine by injection. It seems that repeated vaccination might activate the iridocyclitis, but the relationship between the complaint of numbness and vaccination has not been well established. Neither typical ENL nor reversal reaction had been observed throughout the trial.

A significant proportion of patients converted to SMLA positivity after repeated vaccination. However, it seems the positive status was not stable as many of them reverted to negative after the following vaccination. After the 7th vaccination, the positive conversion rate to SMLA-I was 45% and to SMLA-II was 35%. After the 8th vaccination, 66·7% of patients converted to Mitsuda reaction positive, which has been confirmed by histopathological examination. Nevertheless, further follow-up is required in order to determine whether or not such conversion will be of a long duration.

The reactions to SMLA-I and SMLA-II were associated but only correlated at a moderate level. Overall, the positive conversion rate to SMLA-I was significantly higher than that to SMLA-II after repeated vaccination. Neither the early reaction nor the late (Mitsuda) reaction of the lepromin test were correlated to either SMLA reaction.

The repeated vaccination of HKML+BCG vaccine did not affect the weakly-positive anti-PGL-1 *Mycobacterium leprae* antibody level seen in the skin-smear negative lepromatous patients participating in this study.

Introduction

Immunotherapy represents a potential approach of stimulating specific cell-mediated immune responsiveness to *Mycobacterium leprae*, which is lacking in patients with

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multibacillary leprosy, especially near the lepromatous pole. If successful, immunotherapy might accelerate the removal of persisting viable organisms, thereby reducing the rate of relapse after stopping chemotherapy, and facilitate clearance of the dead organisms, thus reducing the frequency and severity of ENL. To date, only a limited amount of information is available on potential immunotherapeutic treatment. Convit and his colleagues have claimed the therapeutic efficacy of a vaccine consisting of heat-killed *M. leprae* (HKML) plus BCG.[1]

The objectives of the project are: 1, to assess the acceptability to the patients of repeated vaccination with the combined (HKML + BCG) vaccine as a first step to independently evaluate its therapeutic effects; and 2, to assess the efficacy of the (HKML + BCG) vaccine in terms of conversion of the negative response to soluble *M. leprae* skin test antigen (SMLA) and Mitsuda lepromin among skin smear-negative lepromatous patients.

Materials and Methods

PATIENTS

A total of 30 leprosy patients, 23 male and 7 female, with an age range from 32 to 63 years, were selected for the trial. All of them had been diagnosed, confirmed by histopathology, as BL or LL leprosy with Mitsuda reaction negative (<3 mm), and treated with chemotherapy at least 5 years before the trial; the initial BI was at least 3+ or more according to the Ridley–Jopling scale but the patients had become skin smear-negative with no active lesions after effective chemotherapy, and showed no response (0 mm) to both types (Rees and Convit) of SMLAs in skin-test during the preliminary screening of the trial. Before the first vaccination 22 out of the 30 cases were PPD (RT 23, 2 TU/0·1 ml) positive. Antileprosy chemotherapy was continued during the trial.

SKIN TEST ANTIGENS AND VACCINES

In order to avoid the batch-to-batch variation in potency, the same batches of antigens/vaccines including both types (Rees and Convit) of SMLA, PPD (RT 23, 2 TU/0·1 ml, Copenhagen), Mitsuda lepromin, HKML (armadillo-derived, 3×10^9 AFB/ml, IMMLEP *M. leprae* Bank, London) and lyophilized BCG (Institut Pasteur, Paris) were used throughout the trial. They were obtained through the arrangement of the THELEP Steering Committee, WHO.

SKIN-TESTS, BLOOD SAMPLE COLLECTIONS AND VACCINATIONS

According to the protocol, all the patients received (HKML + BCG) vaccine every 3 months for a total of 8 vaccinations. The patients were skin-tested with both SMLAs 3 days before each vaccination. PPD was tested as well, as long as the induration in response to PPD was 9 mm or less. A blood sample was collected for PGL-1 antibody assay at the time of each skin testing. Both SMLA and PPD were injected strictly intradermally in a volume of 0·1 ml each, and each new injection was given 2 cm distal to the previous one. The results were read 72 hr after the injections. The reading of the skin-

testing was made 'blindly' by 2 independent assessors and the results were communicated independently to a 3rd person.

If both results were similar (within 1 mm) the results were recorded; if the 2 results differed by more than 1 mm, the assessors re-read the skin reactions independently until they reached the same result. Each vaccine dose, in a total volume of 0·3 ml, consisted of 6×10^8 AFB of HKML and 0·2 mg of BCG to those patients with induration of 9 mm or less in response to PPD, or 0·02 mg of BCG to those with induration of 10 mm or more in response to PPD. Each dose was injected strictly intradermally, and divided equally in 3 different sites (deltoid areas). At the end of the trial, i.e. after the 8th vaccination, the patients were administered a skin test with Mitsuda lepromin, and the early reaction (72 h after the injection) and late or Mitsuda reaction (4 weeks after the injection) to lepromin were measured, and in some cases biopsy was taken from the site where Mitsuda reaction was thought to be positive.

M. LEPRAE ANTIBODY ASSAY

As mentioned above, blood samples were collected at the time of each skin test and the sera was preserved in a deep freezer ($-75°C$). The ELISA technique was used to measure the IgM and IgG antibodies against the conjugate of natural trisaccharide component of PGL-1 of *M. leprae* and bovine serum albumin (BSA) (NT-O-BSA).

MONITORING FOR SIDE-EFFECTS AND ACCEPTABILITY TO THE VACCINATION

During the course of the trial, patients were interviewed and examined regularly and frequently for side-effects, including local and systemic adverse reactions, and acceptability to the vaccination. In fact, since all these patients were hospitalized due to various reasons for the duration of the trial, such interviews and examinations were very convenient. The patients had the right to refuse to continue the vaccination and skin-testing if they felt that the reaction, either local or systemic, was unacceptable.

Results

ACCEPTABILITY TO THE PATIENTS OF REPEATED VACCINATION WITH HKML + BCG

Local reactions

Various degrees of local reaction occurred even after the first vaccination. Usually from day 2 after vaccination, patients felt itching at the site of injection together with erythema and induration of a diameter of 10 mm or more, and 7 to 10 days later, in every patient an ulcer appeared near the centre of the induration. During the following month, the ulcer produced a scab, followed by reformation of an ulcer. In some patients, this cycle was repeated several times. In most cases, it took 45–60 days before the ulcer was healed. Occasionally, ulcers might continue until the next vaccination. The diameters of the ulcers ranged from 3 to 7 mm. As shown in Table 1, there was no tendency for the ulcers to become larger and the length of ulceration did not last longer during the course of

Table 1. The diameters (mm) of vaccination ulcers

Vaccination							
1st	2nd	3rd	4th	5th	6th	7th	8th
5·1 ± 1·1 (n = 30)	4·4 ± 0·8 (n = 30)	4·4 ± 0·7 (n = 30)	4·3 ± 0·7 (n = 29)	4·2 ± 0·6 (n = 22)	4·1 ± 0·4 (n = 14)	4·0 ± 0·4 (n = 21)	4·0 ± 0·4 (n = 21)

repeated vaccination. In general, the local reactions were accepted by the patients and none of them refused the vaccination because of local reactions.

Systemic reactions

Up to the first 3 vaccinations, no definite systemic reaction had been observed. However, after the 4th vaccination, 2 patients had a fever, of approximately 38°C, together with a painful swelling of the axillary lymph node. After the 5th vaccination, 8 patients (26·6%) developed iridocyclitis and 5 patients (16·6%) complained of numbness of the fingers and toes but without significant positive signs. The patients who developed iridocyclitis did not have any other signs of leprosy reaction and all of them had similar episodes before vaccination. It is likely that repeated vaccinations might activate the iridocyclitis. Numbness of the fingers and toes (apart from the hypertrophy of cervical vertebra) was confirmed by X-ray examination in 1 patient. In the other 4 patients these symptoms could not definitely be attributed to vaccination despite the fact that the complaint gradually disappeared within 6 months after stopping the vaccinations. Because of these adverse reactions, only 14 patients (46·6%) received the 6th vaccination. The acceptance rate, as shown in Figure 1, was increased somewhat at the 7th and 8th vaccination after palliative treatment was given. Because of systemic reactions only 12 patients (40%) had completed the 8 vaccinations and another 7 (23·3%) had accepted 7 vaccinations. However, neither typical ENL nor reversal reaction had been observed throughout the trial.

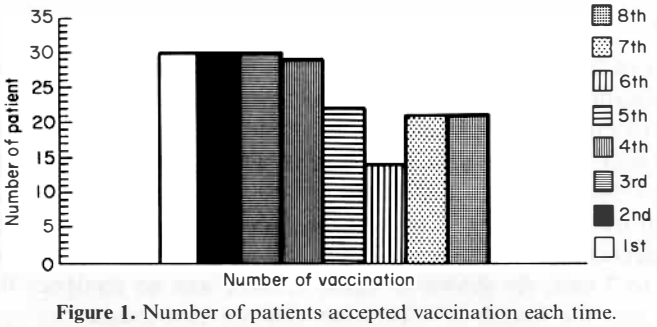

Figure 1. Number of patients accepted vaccination each time.

Table 2. SMLA Skin-test reactions (mm) before and after each vaccination

Case no.	Before		First		Second		Third		Fourth		Fifth		Sixth		Seventh	
	I*	II†	I	II	I	II	I	II	I	II	I	II	I	II	I	II
1	0	0	7	0	10	0	10	0	12	0	0	0	7	7	7	7
2	0	0	0	0	5	0	15	8	0	0	0	0	0	0	3	0
3	0	0	0	0	0	0	10	10	12	12	10	7	12	8	12	10
4	0	0	0	0	0	0	5	5	7	0	0	0	2	5	ND	ND
5	0	0	0	0	0	0	0	0	0	0	0	0	4	2	5	5
6	0	0	0	0	3	3	0	0	7	0	0	0	3	0	7	5
7	0	0	0	0	0	0	0	0	0	0	0	0	7	4	5	4
8	0	0	5	6	13	15	13	15	14	12	10	15	14	12	15	12
9	0	0	0	0	10	5	10	5	12	0	6	8	8	6	7	4
10	0	0	0	0	10	5	3	3	0	5	0	0	12	10	16	12
11	0	0	0	0	0	0	10	8	ND	ND	ND	ND	0	0	7	3
12	0	0	0	0	0	0	0	0	0	10	ND	ND	12	8	12	8
13	0	0	0	0	20	17	14	12	ND	ND	ND	ND	ND	ND	ND	ND
14	0	0	0	0	0	0	0	0	12	13	ND	ND	6	6	ND	ND
15	0	0	0	0	0	8	3	7	10	8	8	7	15	10	10	10
16	0	0	0	0	13	10	10	8	10	8	ND	ND	ND	ND	ND	ND
17	0	0	12	13	15	15	13	14	11	10	ND	ND	ND	ND	ND	ND
18	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND
19	0	0	0	0	0	0	8	0	5	0	ND	ND	4	4	10	8
20	0	0	0	0	8	8	6	6	ND	ND	ND	ND	ND	ND	ND	ND
21	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
22	0	0	0	0	0	0	0	6	0	0	ND	ND	6	0	0	0
23	0	0	0	0	6	7	12	14	8	8	ND	ND	6	7	10	8
24	0	0	0	0	0	0	8	6	ND	ND	ND	ND	10	8	ND	ND
25	0	0	0	0	0	5	10	12	ND	ND	ND	ND	ND	ND	ND	ND
26	0	0	0	0	8	5	8	9	0	0	7	5	9	8	8	10
27	0	0	0	0	5	3	0	0	11	8	8	4	10	8	10	8
28	0	0	0	0	0	0	6	8	2	2	ND	ND	0	0	8	8
29	0	0	0	0	10	10	12	12	ND	ND	ND	ND	10	10	8	11
30	0	0	0	0	0	0	6	6	5	0	ND	ND	12	10	12	10
Positivity‡ rate (%)																
	0		3·3		26·7		41·4		40·9		15·4		39·1		45·0	
		0		3·3		16·7		24·1		22·7		7·7		21·7		35·0

* Rees antigen.
† Convit antigen.
‡ Induration ⩾ 10 mm.

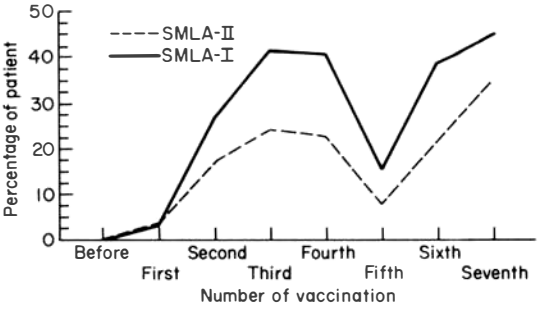

Figure 2. Positive conversion rates to both SMLAs.

SKIN-TEST CONVERSION TO PPD AND SMLAS

PPD test

There were 22 patients who were PPD-positive before the 1st vaccination. Among the 8 patients who were PPD-negative at the beginning of the trial, 3 converted to positive after the 1st vaccination, 4 converted after the 2nd vaccination, and the 8th remained PPD-negative after the 3rd, also his last, vaccination.

SMLA tests

As mentioned above, 2 types of SMLA were used. SMLA-I refers to Rees antigen and SMLA-II refers to Convit antigen. A significant proportion of the patients converted to a positive reaction after repeated vaccinations, 45% to SMLA-I and 35% to SMLA-II after the 7th vaccination. In fact, conversion to SMLA occurred in a certain proportion of patients after the 2nd vaccination. As shown in Table 2 and Figure 2, the conversion rates had reached the plateau after the 3rd vaccination. Although the conversion rates to both antigens had significantly reduced after the 5th vaccination, i.e. immediately before the 6th vaccination, this was probably due to the fact that 9 out of the 16 patients who had refused the 6th vaccination and SMLA tests were positive already to at least one SMLA antigen either after the 3rd or the 4th vaccination. A total of 21 (70%) patients were converted to SMLA-positive at least once to at least one antigen during the course of the trial: 7 (Case Nos 1, 2, 9, 11, 19, 24 and 27) became positive only to SMLA-I antigen; 1 (Case No. 6) became positive to SMLA-II; and 13 (Case Nos 3, 8, 10, 12, 13, 14, 15, 16, 17, 23, 25, 29 and 30) were positive to both antigens. However, many of them reverted to negative during the following tests. For instance, among the 20 patients who received skin tests after the 7th vaccination, 13 (Case Nos 1, 2, 3, 8, 9, 10, 11, 12, 15, 23, 27, 29 and 30) had been converted to SMLA-positive to at least a minimum of one antigen after the previous vaccinations, and 7 (Case Nos 1, 2, 9, 11, 12, 23 and 29) became negative again after the 7th vaccination. Therefore, it seems that the positive status to SMLA was not stable. Table 3 presents the pooled data from all the SMLA skin test result after vaccinations. Although the responses to SMLA-I and to SMLA-II were not independent ($\chi^2 = 62{\cdot}67$, $p < 0{\cdot}001$), the correlation between them, as measured by the ϕ coefficient,[2] was only 0·63, indicating that the correlation was only moderate. In fact, the pooled data

Table 3. Association between skin test reactions to SMLA-I and SMLA-II

		SMLA-I		
		+	−	Total
SMLA-II	+	28	3	31
	−	22	114	136
Total		50	117	167

$\chi^2 = 62{\cdot}67$, $p < 0{\cdot}001$.

Table 4. SMLA skin-test reactions (mm) after the seventh vaccination and Early and Late (Mitsuda) lepromin reactions (mm) after the eighth vaccination

Case no.	SMLA-test reaction		Lepromin reaction	
	SMLA-I	SMLA-II	Early reaction	Mitsuda reaction
1	7	7	0	0
2	3	0	0	0
3	12	10	3·5	3·5
4*	ND	ND	0	5·5
5	5	5	0	0
6*	7	5	0	5
7	5	4	0	0
8	15	12	5	0
9*	7	4	4·5	5·5
10*	16	12	4	7·5
11	7	3	8	0
12	12	8	12·5	5
15	10	10	0	5·5
19	10	8	0	6·5
22	0	0	7·5	5
23	10	8	0	7
26	8	10	9·5	6·5
27	10	8	11·5	3·5
28	8	8	4	6
29	8	11	7	0
30	12	10	5·5	4
Positivity† rate (%)				
	45·0	35·0	9·5	66·7

* Biopsy was taken from the site of Mitsuda reaction.

† Induration ⩾ 10 mm for SMLA and early reaction of lepromin, and nodule ⩾ 3 mm for Mitsuda reaction.

also indicated that the positive rate (29·9%) to SMLA-I was significantly higher than the positive rate (18·6%) to SMLA-II ($p < 0{\cdot}05$).

Skin test conversion to lepromin after the 8th vaccination

Lepromin was tested in 21 patients after the 8th vaccination and the results of early and late (Mitsuda) reactions are presented in Table 4, together with their reactions to both

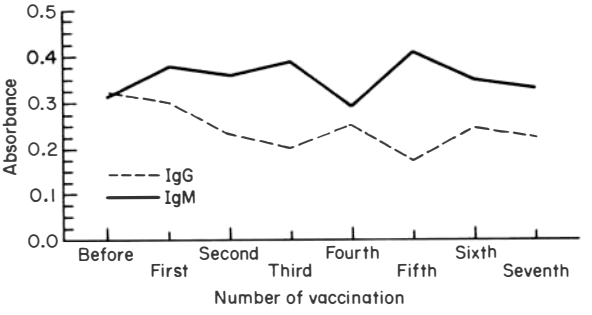

Figure 3. Levels of *M. leprae* antibody before and during vaccination.

SMLA antigens after the 7th vaccination. Only 2 (9·5%) patients were early reaction positive to lepromin, whereas 14 (66·7%) were Mitsuda reaction positive. Calculated by Fisher's exact test, the p value was 0·19 between early reaction versus SMLA-I reaction, 0·41 between early reaction versus SMLA-II reaction, 0·054 between Mitsuda reaction versus SMLA-I reaction and 0·35 between Mitsuda reaction versus SMLA-II reaction. Therefore, neither the early reaction nor the Mitsuda reaction of lepromin test were correlated to either SMLA-I or SMLA-II reaction.

Skin biopsy was taken for histopathological examination from the lepromin injected site of 4 patients (Case Nos 4, 6, 9 and 10) who showed positive Mitsuda reaction. Dr K. V. Desikan of the Leprosy Histopathological Centre, Mahatma Gandhi Institute of Medical Science, Wardha, India 'blindly' examined the biopsy slides, and all the histopathological findings were consistent with positive Mitsuda reaction.

The profile of anti-PGL-1 M. leprae *antibody during vaccination*

In our laboratory, the normal range, in terms of absorbance (A490), of IgM and IgG antibody against NT-O-BSA among non-leprosy contacts is $\leqslant 0{\cdot}28$ and $\leqslant 0{\cdot}15$, respectively. As shown in Figure 3, despite the fact that all the patients were skin-smear negative after effective treatment, the mean absorbance of their IgM and IgG antibody was slightly higher than normal values before vaccination. Since the profile remained basically the same throughout the whole period of the trial, it seems that the repeated vaccinations of (HKML+BCG) vaccine did not stimulate anti-PGL-1 *M. leprae* antibody production over the 2-year interval.

Discussion

Today leprosy is believed to be a cell-mediated immune deficiency disease. Even if multibacillary leprosy is cured following a routine treatment with any of the different effective antileprotic drugs, this deficiency is not repaired—the lepromin test is continuously negative, and some viable bacilli still exist in the host, but stopping the chemotherapy might lead to relapse of the disease, and the antigen which dead bacilli release might induce an immune reaction that is harmful to the host.

Early in the 1950s Schujman reported that after vaccination with BCG, the lepromin test converted to positive among the clinically subsided, skin smear-negative lepromatous patients, but this vaccination did not effect the protective immunity.

In 1957, Indian scholars separated a culturable AFB (ICRC bacteria) from LL patients which could induce the cell-mediated immune response to the leprosy bacilli among laboratory animals and humans. After separation from LL patients in 1969, multifamilial culture *in vitro*, γ-ray inactivation and finally intracutaneous injection at the dosage of 0·1 ml (50–90 μg bacilli), 55·7% LL and 91% BB–BL converted to lepromin test positive, and 5 out of 46 cases showed reversal reaction.

In addition to ICRC bacteria, Indian scholars used a heat-killed vaccine named W bacillus, an atypical, quick growing bacillus that had been separated from the sputum of tuberculotic patients. They selected 32 BL–LL leprosy patients, who had negative skin-smears after chemotherapy, and intracutaneously injected normal saline containing 5×10^7 bacilli and 20 cases converted to lepromin test positive after 4–6 weeks, and the positivity lasted beyond 6–11 months.

In the 1970s, Convit *et al.* claimed that the combined vaccine (consisting of HKML plus BCG) was both acceptable and effective as a treatment for leprosy patients, but it is unclear how the combined vaccine activates the protective immunity of the lepromatous leprosy. Recently immunological study has confirmed that the mechanism was complicated. *In vitro* T-lymphocytes of the lepromatous patients lack a normal response to leprosy bacilli, and the deficiency of interleukin-II may be a factor, related to the activation of the suppressor cells. Lepromatous patients have a normal response to BCG, so the immunotherapy acts like a source supplying interleukin-II, a pathway making good the deficiency of the patients. Also, the macrophages activated by BCG might be changed noticeably in managing and passing the antigen, which produce effective protective cell-mediated immune reaction.

Since 1990 we have selected 30 patients for the trial who had a combined vaccine of HKML plus BCG, and all skin-smear negative after the treatment of MDT. There were 8 injections in the trial. The main local skin reaction was a tolerable ulceration, but systemic reaction, including iridocyclitis, and a numbness of fingers and toes, gradually increased after the 5th injection. The iridocyclitis had obvious opthalmological manifestation, but the latter had no objective positive signs, although the patients complained of numbness. All the complaints subsided after antisymptomatic treatment. During the trial, neither ENL nor reversal reaction was found.

After the 8th injection, 66·7% cases converted to Mitsuda reaction positive. Histopathological examination showed tuberculoid infiltration surrounding the vessels in deep reticular stratum, which demonstrated that specific cell-mediated immune response to leprosy bacilli was repaired and reinforced among two-thirds of patients in the trial. Combined chemotherapy plus vaccine injection might facilitate the clearance of the leprosy bacilli in the host, reduce relapse and shorten the duration of skin-smear negativity.

Acknowledgment

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express their gratitude to Dr K. V. Desikan for his assistance in histopathologic confirmations of the Mitsuda reactions.

References

[1] Convit, J, Aranzazu, N, Zuniga, M, Ulrich, M, Pinardi, ME, Castellazzi, Z, Alvarado, J. Immunotherapy and immunoprophylaxis. *Lepr Rev*, 1983; **54** (Special Issue): 47S–60S.
[2] Fleiss H. Sampling method I: Naturalistic or cross-sectional studies. In *Statistical methods for rates and proportions*, Second edition, Wiley Interscience, pp. 59–60.
[3] Shujman, S. Subsequent evolution of the induced Mitsuda reaction in clinically and bacteriolocally lepromatous cases. *Int J Lepr*, 1956; **24** 51–56.
[4] Convit J, Ulrich, M, Aranzazu N, Castellanos, PL, Pinardi, ME, Reyes, O. The development of a vaccination model using two microorganisms and its application in leprosy and leishmaniasia *Lepr Rev*, 1986; **57** Suppl 2: 263–273.

Une étude pilote pour déterminer l'acceptabilité du vaccin tué par la chaleur de *Mycobacterium leprae* plus BCG (HKML + BCG) et son aptitude a faire virer la cuti-réaction

CHEN ZAI-LING, TANG QUAN-GUI, WANG ZAI-MING ET CHEN JIAKUN

Résumé Bien que des réactions locales, comprenant érythème; induration et ulcères, soient apparues chez tous les patients après l'injection du vaccin combiné HKML + BCG, cette injection a été bien acceptée par les patients. Il n'y a pas eu tendance à l'aggravation des réactions locales après des vaccinations répétées. Pourtant, la fréquence des réactions systémiques, en particulier l'irido-cyclite et celle des patients se plaignant d'engourdissement des doigts et des orteils ont augmenté après la 5ème vaccination et ont réduit l'acceptabilité de la 6ème injection. Il semble que la vaccination répétée puisse activer l'irido-cyclite, mais la correlation entre la plainte d'engourdissement et la vaccination n'a pas été prouvée. Ni ENL typique ni réaction de réversion n'ont eté observés au cours de cet essai.

Une proportion significative des patients sont devenus SMLA-positifs après la vaccination répétée. Pourtant, il semble que cette positivité ne soit pas stable car beaucoup d'entre eux sont redevenus négatifs après la vaccination suivante. Après la 7ème vaccination, le taux de positivation à SMLA-I a été de 45% et à SMLA-II de 35%. Après la 8ème vaccination, 66,7 des patients sont devenus positifs à la réaction de Mitsuda, ce qui a été confirmé par examen histopathologique. Mais il faudra continuer à suivre ces patients pour déterminer si cette conversion sera de longue durée ou passagère.

Les réactions à SMLA-I et SMLA-II ont été associées mais la corrélation était d'un niveau moyen. Au total, la positivation à SMLA-I a été sensiblement plus élevée que celle à SMLA-II après la vaccination répétée. Ni la réaction précoce ni la réaction tardive au test de la lépromine (Mitsuda) n'a présenté de corrélation avec l'une ou l'autre des réactions à SMLA.

La vaccination répétée au vaccin HKML + BCG n'a pas modifié le taux d'anticorps anti-PGL-I *Mycobacterium leprae* faiblement positif observé chez les patients lépromateux à frottis de peau négatif participant à cette étude.

Un estudio piloto para establecer la aceptabilidad y habilidad de *Mycobacterium leprae* matados por calor más vacuna BCG (HKML + BCG) para inducir conversión de la prueba dérmica

CHEN ZAI-LING, TANG QUAN-GUI, WANG ZAI-MING Y CHEN JIAKUN

Resumen Aunque reacciones locales, incluyendo eritema, induración y úlceras, aparecieron en todos los pacientes después de la inyección de vacuna (HKML + BCG), aquellas fueron aceptados por los pacientes. No hubo tendencia para que se agrave la reacción local después de repetir la vacunación. Sin embargo, las reacciones sistémicas, principalmente iridociclitis y quejas de adormecimiento de los dedos de las manos y pies, eran bastante comúnes despues de la 5a. vacunación y, por lo tanto, reducen la aceptabilidad de vacunación por inyección significativamente. Parece que la vacunación repetida puede activar la iridociclitis, pero no se ha establecido bien la relación entre el adormecimiento y la vacunación. Durante el estudio no se observó una ENL típica ni una reacción inversa.

Una proporción significativa de pacientes cambiaron a positividad SMLA después de vacunación repetida. Sin embargo, parece que el estado positivo no era estable ya que muchos de ellos revirtieron a negativo despues de la vacunación siguiente. Después de la 7a. vacunación, el nivel de conversión positiva a SMLA-I fue 45%, y a SMLA-II 35%. Después de la 8a. vacunación, 66,7% de los pacientes convierteron a una reacción Mitsuda positiva, confirmada por un examen histopatológico. No obstante, será necesario un estudio posterior para establecer si la conversión será de largo plazo.

Las reacciones a SMLA-I y SMLA-II estaban asociadas, pero solamente correlacionaban en un nivel moderado. En total, el nivel de conversión positiva a SMLA-I era significativamente más alta que la conversión a SMLA-II después de vacunación repetida. Ni la reacción anterior ni la posterior (Mitsuda) de la prueba de lepromina correlacionaban con las reacciones SMLA.

La vacunación repetida con vacuna (HKML + BCG) no afectó el nivel de anticuerpos anti-PGL-1 de *Mycobacterium lepræ* observado en los pacientes lepromatosos con smear de la piel negativo.

Lepr Rev (1993) **64,** 128–135

Survey for secondary dapsone and rifampicin resistance in Cuba

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Summary A total of 1211 Cuban multibacillary leprosy patients treated for at least 5 years were clinically and bacteriologically examined. They were being treated according to a 2-phase monotherapy regimen with RMP first and DADDS afterwards. On skin-smear examination 50 patients were found positive, of which 9 showed a BI of 3+ or higher at any site. With regard to the clinical status the only cases found with clinical signs of relapse were 5 out of 7 long-standing patients with BI of 4+ and 5+. A 6th patient of this high BI group who showed a good clinical condition, except for a heavy infiltration of both earlobes, was receiving a second RMP course when examined and biopsied for this research. These 9 patients were biopsied and susceptibility tests to RMP and DDS performed. The results showed that in 1 case the *Mycobacterium leprae* were resistant to both drugs; the organisms from 2 other patients were susceptible to RMP but low-grade resistant to DDS. Those from another patient were susceptible to RMP and fully resistant to DDS. In 3 other cases the bacilli did not multiply in any of the mice but 1 of these strains was from the patient taking a second RMP course, therefore this strain might also be susceptible to RMP and resistant to DDS. In the last 2 cases multiplication was only observed in 2 of the controls and in 1 of the 0·0001% DDS treated mice; therefore, these experiments were not conclusive, and the AFB recovered were inoculated into fresh mice to repeat the tests but these failed to multiply.

Introduction

Multidrug therapy (MDT) has recently been implemented for the treatment of all Cuban leprosy patients. Between about 1962 and 1977, in Cuba chemotherapy of leprosy had consisted exclusively of dapsone (DDS) monotherapy, but in 1977[1] this treatment

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strategy was drastically modified by the introduction of a 2-phase therapeutic regimen consisting of (a) treating all registered patients, whatever the duration of prior DDS treatment, with a course of 600 mg daily rifampicin (RMP) monotherapy in skin-smear positive patients for 6 months and in skin-smear negative patients for 3 months, the RMP course being followed by acedapsone (DADDS), 225 mg once a month, for an indefinite length of time in the case of the skin-smear positive patients and for 5 years in the case of the skin-smear negative patients, provided the lesions were cleared up and (b) giving the same therapeutic regimen to all patients detected thereafter. The drug intake for both RMP and DADDS was controlled by only having trained health personnel administer drugs to the patients throughout the country.

According to Lechat (M. Lechat, WHO/OPS Consultant. Report on a mission to Cuba. Nov. 8–15, 1984), when considering only the multibacillary types of the disease, the Cuban leprosy patients constitute a very heterogeneous group, which include:

1. Pre-1977 patients, who had been treated with DDS monotherapy for an indetermined time before 1977, and were still skin-smear positive at the initiation of RMP and harbouring DDS resistant bacilli. The post-RMP treatment with DADDS in these patients would have been ineffective. If RMP is not 100% effective in killing the DDS resistant bacilli, these patients would sooner or later present with a relapse. The time of onset of the relapse would, however, be delayed due to the reduction in bacillary load caused by RMP.
2. The same patients as (1) above but harbouring DDS sensitive bacilli. The post-RMP treatment with DADDS would have been effective to clean up the bacilli, provided the patient had not developed secondary resistance during the prolonged course of DADDS.
3. Pre-1977 patients who had been previously treated with DDS monotherapy for an indetermined time, and were skin-smear negative at the initiation of RMP, but possibly harbouring *M. leprae* 'persisters'. RMP followed by DADDS would have been effective to prevent relapse as long as treatment was maintained.
4. Post-1977 patients treated with RMP with no previous treatment with DDS. Some of them may have primary DDS resistance if infected before 1977. If infected after 1977 they may have primary DDS and/or RMP resistance.

A study was conducted to search for secondary DDS and RMP resistance, the results of which are reported herein.

Materials and methods

From April 1987 through May 1989, before MDT implementation, a total of 1211 leprosy patients residing in 7 Cuban provinces were seen. Of these, 992 were classified as lepromatous, 180 as dimorphous and 39 as indeterminate, according to the Madrid classification (Table 1). These indeterminate patients were found skin-smear positive when diagnosed. They all had begun treatment at least 5 years before and were receiving the prescribed DADDS therapy, apart from a patient who had intolerance to the drug. Their clinical records were abstracted, dermatological examination performed and skin-smears taken from both earlobes, both elbows and 1 or 2 other skin sites where active or residual lesions were observed.

Those patients with a Bacteriological Index (BI) of 3+ or higher were biopsied, the

Table 1. Distribution of patients according to sex and leprosy type

	Type			
Sex	Lepr.	Dimorph.	Indet.	Total
Male	662	85	20	727
Female	370	95	19	484
Total	992	180	39	1211

Table 2. Distribution of patients diagnosed before 1977 according to the year of diagnosis

Year	Number	Skin-smear + (1977)	Skin-smear + (study)
Before 1936	6	1	0
1936–40	8	1	0
1941–45	29	3	1
1946–50	53	10	0
1951–55	44	10	3
1956–60	66	13	5
1961–65	149	34	2
Sub-Total	355	72	11
1966–70	186	42	7
Sub-Total	541	114	18
1971–76	233	84	3
Total	774	198	21

specimens carried immediately in vacuum flasks immersed in wet ice to the laboratory in Havana where their bacilli were recovered and inoculated into the right hind footpad of groups of normal female BALB/C mice in a dose of 10^4 organisms per footpad. The procedures employed for recovery of *M. leprae* from biopsy specimens, inoculation into footpads, harvests, smearing on to microscope slides, fixation and staining of smears and counting of acid fast bacilli (AFB) were the same as those described by Shepard,[2,3] with minor modifications. For each specimen 50 mice were inoculated and then divided into 5 groups of 10 mice each; 1 group was left as control and given a normal diet, 3 other groups were fed DDS at a concentration of 0·01 g, 0·001 g and 0·0001 g per 100 g of powdered food, respectively, and the 5th group was administered RMP in a dosage of 10 mg per kg of body weight once a week by oesophageal cannula (gavage). Beginning 8 months after inoculation, 1 control mouse was killed at 2–3-month intervals (except for cases 15, 247 and 1211 which were all killed 14 months after inoculation) and their footpads harvested. When at least 1 of the controls reached the level of 5×10^5 AFB all mice were killed and counts were performed. The criterion for multiplication was the recovery of at least 10^5 AFB per footpad harvested.

Table 3. Distribution of patients diagnosed after 1976 according to the year of diagnosis

Year	Number	Skin-smear + (when diagnosed)	Skin-smear + (study)
1977	46	28	0
1978	49	34	2
1979	56	37	1
1980	59	43	3
1981	73	53	5
1982	64	42	4
1983	68	52	9
1984	22	14	5
Total	437	303	29

Results

Table 2 shows that 774 patients were diagnosed (and began treatment) before 1977, and of these 198 (25·5%) were still skin-smear positive when the RMP treatment started in that year. The proportion of these latter patients diagnosed in the period 1966–70 (42/186–22·5%), and therefore treated with DDS monotherapy for 7–11 years, was slightly, but not significantly, higher ($p > 0{\cdot}005$, Hypothesis test for 2 proportions) than that in those diagnosed before 1966 (72/355–20·2%) and significantly lower ($p < 0{\cdot}001$, Hypothesis test for 2 proportions) than that in the group of 1971–76 (84/233–36·0%), who had not been treated with the drug for more than 6 years. Of all pre-1977 patients, 21 (2·7%) were found skin-smear positive when examined for this investigation.

The number of patients detected between 1977 and 1984 (and therefore starting treatment with RMP) was 436, among whom 302 (69·2%) were found skin-smear positive at the time of diagnosis. When examined for this study 29 (6·6%) of these post-1977 patients were positive (Table 3). Thus 50 out of 1211 (4·1%) multibacillary patients treated for at least 5 years were found skin-smear positive. The BI values observed are shown in Table 4. The majority showed a BI of only 1+ or 2+. Only 9 patients were observed with a BI equal to or above 3+, and therefore eligible for mouse footpad inoculation. Of these latter, the 2 patients with a BI of 3+ had received treatment for 5 and 6 years, respectively, while those 7 patients with BI of 4+ and 5+ were all diagnosed and started treatment before 1969.

With regard to the clinical status, the only cases found with clinical signs of relapse were 5 of the 7 long-standing patients with BI of 4+ and 5+. A 6th patient in this high BI group who showed a good clinical condition, except for a heavy infiltration of both earlobes, was receiving a second RMP course, prescribed by his consultant dermatologist on account of his persistently high BI, when examined and biopsied for this research. The 7th patient was carefully examined by the dermatologist co-ordinating the research team at the time of the biopsy, and, remarkably, no single clinical sign of relapse was observed.

The results of the susceptibility test to RMP and DDS of the *M. leprae* obtained from the 9 eligible patients are summarized in Table 5. In 3 instances (patients 15, 247 and 1211) no multiplication was observed in any mice, but patient 247 was taking a 2nd course of

Table 4. Bacteriological Index values observed among 50 skin-smear positive patients

Year of diagnosis	Bacteriological Index				
	1	2	3	4	5
1941–45				1	
1946–50					
1951–55	1	1			1
1956–60	2	1		1	1
1961–65	2				
1966–70	2	2		3	
1971–75	3				
1976–80	5	1			
1981–84	12	9	2		
Total	27	14	2	5	2

Table 5. Results of the susceptibility tests to DDS and RMP of 9 patients with BI of 3+ or higher

Patient	Control	g dapsone/100 g of food			RMP 10 mg/Kg
		0·0001	0·001	0·01	
15	0/9	0/4	ND	ND	0/4
247	0/9	0/4	ND	ND	0/4
447	6/6	5/5	6/9	3/8	7/8
656	9/9	10/10	9/9	6/6	0/8
684	3/4	5/5	0/8	ND	0/7
736	8/8	5/6	0/9	ND	0/8
905	0/6	1/8	0/8	0/8	0/8
967	2/6	0/9	0/8	0/7	0/6
1211	0/10	0/4	ND	ND	0/4

RMP at the time of the biopsy, therefore his strain might be susceptible to RMP and resistant to DDS since his BI was 5+ 11 years after the commencement of the 2-phase therapy. The strain from patient 447 was found to be resistant to both RMP and all 3 different concentrations of DDS in the diet. In patient 656 the organisms were fully resistant to DDS but did not multiply in any of the RMP treated mice. In patients 684 and 736 only the controls and the mice treated with the lowest DDS concentration were positive, thus indicating a low-degree of DDS resistance. In the last 2 cases (patients 905 and 967) multiplication was only observed in 2 of the controls (Patient 967) and in 1 of the 0·0001% DDS treated mice (Patient 905), therefore these experiments were not conclusive and the AFB recovered were inoculated into fresh mice to repeat the tests. Unfortunately, these strains failed to multiply; perhaps the number of viable organisms was too small when the final harvests were done 14 months after the first inoculation.

Discussion

The number of patients examined for the present study represented about 30% of the total eligible population. In most instances fully documented data for treatment before 1977 were not available. However, DDS monotherapy was organized by the leprosy control programme established in 1962 and distributed free of charge to the patients. Since 1972, efforts began to be made to administer the drug under supervision and this was fully accomplished together with the introduction of the RMP-DADDS 2-phase regimen. Nevertheless, even before 1962 DDS was available to many patients when prescribed by private doctors or obtained at some public outpatient clinics for leprosy and venereal diseases scattered throughout the country or at the 2 leprosy hospitals then existing. Thus, the finding of a doubly resistant strain, 3 others showing resistance to DDS alone and another with inconclusive results for RMP but with DDS resistance, all from patients who received DDS monotherapy before the implementation of the RMP-DADDS 2-phase regimen, proves that drug resistance developed among the pre-1977 patients. The number of DDS resistant strains might have been greater, as is suggested by the observation that 114 (21·0%) of 541 patients treated for more than 6 years (diagnosed before 1971) still remained skin-smear positive in 1977 as compared to only 29 (6·6%) among 437 post-1977 patients, provided the 2-phase regimen did not speed up the clearance of dead bacilli and assuming that the proportion of those skin-smear positive among both pre- and post-1977 patients was of the same order. Therefore, it seems likely that a greater DDS resistant reservoir had developed but had mostly been sterilized by the RMP action. This presumption is further supported by the observation that the majority of those pre-1977 patients found positive when examined for the present study showed scanty granular or fragmented organisms in the Ziehl–Neelsen stained smears.

As concerns RMP resistance, it is remarkable that only a single strain exhibiting this condition was found. Since the relapsed patient harbouring this RMP-DDS resistant strain was diagnosed in 1966 and received DDS monotherapy, it is conceivable that his *M. leprae* were already DDS resistant when he started the RMP treatment in 1977. Otherwise, the reduced number of DDS susceptible organisms persisting after the 6-month RMP course would probably not have multiplied due to the subsequent DADDS therapy. Recently, Grosset *et al.*[4] reported on 22 RMP resistant *M. leprae* strains isolated from 39 multibacillary patients who relapsed among a group of 408 who were known to have been treated by some non-standard RMP regimen. It was also found that almost all of these RMP resistant strains were resistant to DDS as well. It is difficult to put forward an explanation for the striking difference concerning the frequency of RMP resistance noted between the strains from the Cuban patients and those reported by Grosset *et al.*[4] However, the results of an earlier study on primary DDS resistance conducted by the author[5] from 1982 through 1985 could help. In that study, only 3 of 46 untreated lepromatous patients were found to harbour resistant strains, all 3 showing low-grade resistance. Moreover, both the proportion of 0·0001% DDS treated mice showing multiplication and the number of organisms recovered were much less than in the control mice. Had the present criterion for multiplication been used at that time, then the number of primary DDS resistant strains would have been 2 instead of 3. Since primary DDS resistance is regarded as an epidemiological indicator of acquired DDS resistance it may be that the latter was relatively late in occurrence in Cuba due to the effort to achieve regular unsupervised and supervised treatment made since 1962 and 1972, respectively. If

this was so, then the DDS resistant *M. leprae* population in most patients in whom it emerged might not, by 1977, have reached the size required for the spontaneous emergence of RMP resistant mutants, which is thought to be not greater than 1 in 10^9 to 10^{10} viable organisms.[4]

The failure to find RMP resistant strains among the post-1977 patients might also be explained from the results of the above-mentioned primary DDS resistance study. RMP resistant mutants could have multiplied to some extent during the 6-month RMP course but being presumably susceptible to DDS their multiplication would be arrested by the subsequent DADDS treatment.

The fact that 4 patients actually relapsed clinically and/or bacteriologically with RMP susceptible *M. leprae*, 3 of them with proved DDS resistance (Patients 656, 684 and 736) and a 4th (Patient 905) with proved DDS resistance, though with inconclusive results for RMP, points to the risk of relapse after effective treatment is stopped because of the activity of the so-called *M. leprae* 'persisters' and to the need for a long period of surveillance before a multibacillary patient is released from control. The present results serve to add to the amount of previously existing evidence and knowledge which gave rise to the currently accepted views in favour of MDT as a means of avoiding the emergence of drug resistance in multibacillary leprosy.

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References

[1] Abreu D. *et al. Neuvo Programa de Control de Lepra.* Ministerio de Salud Pública. Cuba. 1977.
[2] Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. *J Exp Med*, 1960; **112:** 445–54.
[3] Shepard CC, McRae DH. A method for counting acid-fast bacteria. *Int J Lepr*, 1968; **36:** 78–82.
[4] Grosset JH, Guelpa-Lauras CC, Bobin P, Brucker G, Cartel JL, Constant-Desportes M, Flageul B, Frederic M, Guillaume JC, Millan J. Study of 39 documented relapses of multibacillary leprosy after treatment with rifampicin. *Int J Lepr*, 1989; **3:** 607–14.
[5] González AB, Hernández O, Suárez O, González-Abreu E, Rodríguez JE. Survey for primary dapsone resistance in Cuba. *Lepr Rev*, 1986; **57:** 341–6.

Enquête sur la résistance secondaire à la dapsone et la rifampicine à Cuba

A. B. Gonzalez, J. L. Maestre, Olenia Hernandez, Yolanda Columbié, N. Atrio, Maritza Martin, Ana M. Fernandez et J. Rodriguez

Résumé Un total de 1211 Cubains lépreux multibacillaires, traités pendant au moins 5 ans, ont été examinés cliniquement et bactériologiquement. Ils recevaient un traitement basé sur une monothérapie à deux phases, avec RMP en premier lieu, suivi de DADDS en un deuxième temps. A l'examen d'un frottis de peau, 50 patients ont été trouvés positifs, dont 9 présentaient un IB de 3+ ou plus à tous les sites. Quant à l'état clinique, les seuls cas présentant des signes cliniques de rechute ont été 5 des 7 patients anciens avec des IB de 4+ et 5+. Un sixième patient de ce groupe à IB élevé, qui était en bonne condition clinique à part une forte infiltration des lobes des deux oreilles, recevait un second traitement de RMP lorsqu'il a été soumis à un examen et une biopsie pour ce projet de recherche. Des biopsies et des tests de sensibilité à RMP et à DDS ont été pratiqués chez ces 9 patients. Les résultats ont montré que dans un cas *M. leprae* était résistant aux deux drogues; les germes isolés de deux autres patients étaient sensibles à RMP mais faiblement résistants à DDS. Ceux d'un autre patient étaient sensibles à RMP et complètement résistants à DDS. Dans 3 autres cas les bacilles ne se sont multipliés dans aucune des souris, mais une de ces souches provenait du patient en cours de son second traitement par RMP, donc cette souche pourrait aussi être sensible à RMP et résistante à DDS. Dans lex deux derniers cas, on a observé la multiplication seulement chez deux des témoins et chez une des souris traitées au DDS à 0,0001%; on ne pouvait donc pas conclure sur ces expériences; les AFB récupérés ont été inoculés à des souris neuves pour répéter les tests, mais ne se sont pas multipliés.

Estudio sobre la resistencia secundaria a la Dapsona y la Rifampicina en Cuba

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Resumen Un total de 1211 pacientes leprosos multibacilares cubanos que habían sido tratados por un mínimo de 5 años, fueron examinados clínica y bacteriológicamente. Fueron tratados de acuerdo con un régimen monoterápico bifásico primero con RMP y luego con DADDS. 50 pacientes fueron positivos al examen por frótis, 9 con un BI de 3+ o más en cualquier sitio. Respecto al estado clínico, los únicos casos con indicaciones clínicas de recaída fueron 5 de 7 pacientes de mucho tiempo con BI de 4+ y 5+. Un sexto paciente de este grupo de alto BI en buen estado clínico excepto por una infiltración intensa de los lóbulos de las orejas, recibía una segunda serie de RMP cuando se le examinó e hizo una biopsia para este estudio. Se realizaron pruebas de biopsia y susceptibilidad a RMP y DDS en 9 pacientes. Los resultados indicaron que en 1 caso, *Mycobacterium leprae* resistía ambas drogas; los organismos de 2 otros pacientes erán sensibles a la RMP, pero tenían resistencia inferior a DDS. Los de otro paciente eran sensibles a RMP y totalmente resistentes a DDS. En 3 otros casos, los bacilos no se reprodujeron en cualquiera de los ratones, pero 1 de esta cepas era del paciente en la segunda serie de RMP y, por lo tanto, es posible que esta cepa sea sensible a RMP y resistente a DDS. En los últimos 2 casos, se observó reproducción solamente en 2 de los controles y en 1 de los ratones tratados con 0,0001% de DDS. Por lo tanto, estos experimentos no fueron conclusivos y se inocularon ratones nuevos con el AFB que se recuperó para repetir las pruebas, pero no se reprodujo.

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Efficacy and safety of multidrug therapy in paucibacillary leprosy in Singapore

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Summary A total of 49 patients with paucibacillary leprosy (PB) who completed multidrug therapy (MDT) between 1985 and 1990 were analysed retrospectively for efficacy and complications; 20 (40·8%) patients had borderline–tuberculoid (BT), 13 (26·5%) had tuberculoid (TT), 1 (2·1%) had indeterminate (I) and 15 (30·0%) had pure neural (N) leprosy; 26 patients (76·5% of 34 non-neural leprosy) were skin biopsied for histological cure before MDT was stopped. Of these 26 patients, 19 had histological clearance at 6 months while the remaining 7 cleared beyond 1 year (18–36 months). The remaining 8 non-neural patients who refused rebiopsy had MDT for 6–8 months and the MDT was stopped when there was clinical clearance. Of the 15 neural (N) leprosy patients, 11 were given MDT for 6 months while the rest had 12–18 months of treatment; 1 patient with neural leprosy, who was treated for 6 months, relapsed with BT leprosy 18 months post-treatment.

There were few complications among the 49 patients—4 (8·2%) patients developed reaction to dapsone, 1 (2·0%) had the dapsone syndrome, 2 (4·1%) had haemolytic anaemia and 1 (2·0%) had dapsone hepatitis; 7 (14·3%) patients had type I reaction.

Introduction

Multidrug therapy (MDT) treatment, as recommended by WHO for paucibacillary (PB) leprosy,[1] has been in existence since 1982. Although efficacious there are now reports of relapses with this treatment.[2–5] In Singapore, leprosy patients are being treated in only a single government dermatology centre, the National Skin Centre, Singapore (formerly the Middle Road Hospital). We had 49 PB patients who completed MDT between June 1985 and May 1990. The aim of this paper is to evaluate the efficacy and safety of MDT among our PB leprosy patients.

* Correspondence

Materials and methods

A total of 49 PB patients (according to the Ridley–Jopling classification) who completed MDT between June 1985 and May 1990 were analysed retrospectively for efficacy and complications. MDT consisted of rifampicin (600 mg monthly, taken under supervision), and dapsone (100 mg daily). Our treatment regime differed from the standard WHO recommendations in that MDT was not arbitarily terminated at 6 months but continued with regular assessment until histological or clinical cure, or both, were achieved.

Only newly-diagnosed PB patients who completed MDT were included in the study. All non-neural PB leprosy patients had both clinical and histological diagnosis of leprosy, and 4 of our neural (N) leprosy patients had histological diagnosis while in the remaining 11 the diagnosis was made on clinical grounds. All patients were clinically assessed initially at 3 weeks for Lepromin Test reading and subsequently at monthly intervals. Baseline investigations included slit skin smears for acid-fast bacilli (AFB), lepromin test, Glucose 6-phosphatase deficiency (G6PD) screen, blood counts and liver function tests. At monthly follow-up visits the urine was checked for the presence of dapsone, and blood for haemoglobin and reticulocyte count. Liver function tests were done where indicated.

We considered *failed MDT* if the patients continued to develop new lesions, had a worsening of existing lesions, or developed new neurological deficits while on treatment. There should also have been an increase in histological activity. If the patients had some improvements while on MDT, they were not considered to be treatment failures. These patients were not considered to have late reversal reactions as they had no initial improvement while on treatment. Patients who *failed MDT* were treated with rifampicin 600 mg and clofazimine 300 mg under supervision monthly; and clofazimine 100 mg 3 times a week with ethoionamide 375 mg per day, unsupervised.

Clinical cure for neural patients with grade 2 or 3 deformities (WHO definition) was defined arbitrarily when patients had recovery of sensory but not motor deficits.

As far as possible, post-treatment biopsy of the same site as at diagnosis was done after 6 months' treatment. If histological activity persists at 6 months rebiopsies should be repeated every 6 months or before MDT was stopped. After MDT was stopped all patients were followed up at 6–12 monthly intervals for clinical relapse. Clinical relapse was defined as the emergence of new skin lesions with or without the increase in redness, thickness and diameter of existing skin lesions or new muscle paralysis. A histological diagnosis is needed to confirm clinical relapse. Patients are released from surveillance after being disease-free for 5 years.

Results

We had 20 (40·8%) patients with borderline–tuberculoid (BT), 13 (26·5%) with tuberculoid (TT), 1 (2·1%) with indeterminate (I) and 15 (30·6%) with neural (N) leprosy. There were 31 male patients and 18 female patients giving a male to female ratio of 1·7:1. The age of onset ranged from 19 to 87 years. There were 37 Chinese (75·5%), 8 Malays (16·3%) and 4 Indians (8·2%) in the study, which reflected the racial composition in Singapore.

In all, 38 (77·6%) patients had 6 months of MDT while the remaining 11 (24·5%) had

Table 1. Results of treatment

Treatment duration (months)	Type of cure	No. of patients BT	TT	I	N	Subtotal	Total (%)
6	Clinical cure	2	5	1	11*	19	38 (77·6)
	Clinical and histological cure	12	7	—	—	19	
12	Clinical cure	—	—	—	3	3	3 (6·1)
	Clinical and histological cure	—	—	—	—	0	
18	Clinical cure	—	—	—	1	1	3 (6·1)
	Clinical and histological cure	1	1†	—	—	2	
24	Clinical cure	—	—	—	—	0	3 (6·1)
	Clinical and histological cure	3†	—	—	—	3	
30	Clinical cure	—	—	—	—	0	2 (4·1)
	Clinical and histological cure	2‡	—	—	—	2	
Total		20	13	1	15	49	49 (100)

* Signifies that: 1 patient (biopsied proven, positive AFB) developed BT within 2 years; † 1 patient in each group had clinical and histological activity at 12 months— therapy change to rifampicin and clofazimine (failed MDT treatment); ‡ 1 patient had dapsone induced hepatitis within 6 months— clofazimine replaced dapsone; 1 patient had rifampicin and clofazimine (failed MDT treatment).

MDT from 12 to 30 months (Table 1). Of the 38 patients who had 6 months of treatment, 19 had a clinical and histological cure while the remaining 19 had clinical inactivity. Among the patients who received MDT for longer than 6 months, 4 were neural (N), 6 were BT and 1 was TT leprosy. Of these patients 3 were considered to have *failed MDT treatment* after 6 or 12 months and given rifampicin and clofazimine instead, 2 patients had BT and 1 patient had leprosy (Table 1).

The BT leprosy patients tend to achieve histological clearance at a later date—of the 20 patients 6 cleared after 18–30 months' treatment. Only 1 of the 13 TT leprosy patient required treatment after 6 months. This patient had activity at 12 months which cleared after he was given rifampicin and clofazimine for 6 months; 11 of the 15 neural patients had MDT for 6 months while the remaining 4 had 12–18 months of MDT. However, 1 neural patient with Grade 1 deformity (sural nerve biopsied proven and acid fast bacilli positive) who had 6 months of MDT, relapsed with BT leprosy 18 months later. He had had no previous skin lesions but now presented with new skin lesions. He was re-treated with rifampicin and clofazimine.

The complications of treatment are summarized in Table 2. Only 4 (8·2%) patients had drug reactions—1 (2·0%) had dapsone syndrome, 1 (2·0%) had dapsone hepatitis and 2 (4·1%) had haemolytic anaemia (both are G6PD positive); 7 (14·3%) patients, all of whom had BT leprosy, developed Type I reactions.

Table 2. Treatment complications

Complications	Type	No. of patients
Drug reactions	Dapsone syndrome	1 (2·0)
	Haemolytic anaemia	2 (4·1)
	Dapsone hepatitis	1 (2·0)
Type I reactions	Erythema/Oedema of existing lesions	5 (10·2)
	Nerve pain/tenderness	2 (4·1)
Total		11 (22·4)

Discussion

The efficacy of MDT has been generally accepted. Some authors[4,6] accepted it with some reservation mainly with regard to the duration of therapy. In Singapore, leprosy is being treated only in a single government centre and here clinical and histological assessment could be done before stopping therapy. We do not stop treatment abruptly at 6 months if there is evidence of clinical or histological activity.

After 6 months of MDT we had a cure rate of 77·6% (38 patients) while 22·4% (11 patients) had either clinical or histological activity. Other authors[2–4,7] also have had similar experiences with the persistence of disease at the end of 6 months of MDT, ranging from 6·5% to more than 30%. However, our cure rates improved when MDT was continued after 6 months, with cure rates of 83·7% at 12 months, 89·8% at 18 months, 95·9% at 24 months and 100% at 30 months (Table 1). Other field studies[2,3,7] continued with dapsone monotherapy or MDT after 6 months until clinical cure. They too, showed a further increase in cure rates ranging from 6·5% to 57% (Table 3), suggesting that 6 months of MDT might not be adequate.

Of the patients who required more than 6 months of treatment, 6 had BT, 1 had TT, 1 had indeterminate and 4 had neural leprosy. The 6 BT patients had treatment beyond 18 months, 2 of whom required *failed MDT treatment* and 1 had clofazimine instead of dapsone (as he had dapsone induced hepatitis). Repeated biopsies at 6-monthly intervals from these BT patients showed histological activity beyond 12 months. This suggested that some BT patients required a longer duration of treatment.

Table 3. Clinical cure rates compared with other studies

Study	No of patients	Cure rates at 6 months (%)	Additional cure rates at 12 months (%)
J. Lim *et al.* (1990)	49	77·6	+6·1*
Chopra *et al.* (1990)[2]	10,995	93·5	+6·5*
Katoch *et al.* (1989)[7]	88	66	+28†
Grugni *et al.* (1988)[14]	736	44	+25*

* Continued with WHO MDT.
† Continued with Dapsone monotherapy.

Revankar[8] found disease activity among 17% of his BT patients 3 years after MDT. He also suggested that BT leprosy should be treated longer. Studies[3,9,10] have also shown that BT leprosy patients have a higher rate of relapse compared to other groups. However, no relapse was observed among our BT patients, probably because of our extended treatment period.

In total, 11 of our 15 neural patients had only 6 months of MDT. These patients had recovery of sensory deficits. However, 1 of these patients developed BT within 2 years (sural nerve biopsy showed AFB). He was re-treated with rifampicin and clofazimine. Whether neural patients, especially those with positive AFB, should be treated beyond 6 months is still uncertain.

It could be argued that patients who still had clinical or histological activity at 6 months might continue to improve even if MDT was then stopped. As this is a retrospective study with no such control groups, there is no way of knowing this. However, it seemed unlikely as 10 of these patients had neural or BT leprosy. It had been suggested that both these groups of patients require longer periods of treatment to prevent relapse.[8] Besides, we and others,[2–4,7] had shown that disease activity persisted beyond 6 months of MDT.

Our relapse rate is low (2%) compared to others (Table 4). This might be due to the fact that treatment was individualized and extended where necessary. We followed up 34 patients (69·4%) for at least 2 years post-treatment.

MDT appeared safe as only 4 (8·2%) of our patients developed reactions to dapsone. No reaction to rifampicin or clofazimine was reported. The 2 patients who developed dapsone-induced haemolytic anaemia were G6PD positive and haemolysis was dose-related. No haemolysis recurred when dapsone was reduced to 50 mg daily. Hypersensitivity reaction to dapsone occurs in less than 0·5% of those taking the drugs, and usually begins 1–4 weeks after administration of the drug.[11]

The full dapsone syndrome was developed by 1 of our patients.[12] Another patient had hepatocellular damage after a latent period, which could be either a hepatoxic effect or even be a partial dapsone syndrome.[13] However, both recovered fully on stopping dapsone.

Table 4. Relapse rates compared with other studies

Study	No. of patients	Relapse	
		No. of patients	Rate
J. Lim *et al.* (1990)	49	1	(2)
Chopra *et al* (1990)[2]	10,995	21	(0·19)
Grugni *et al.* (1990)[3]	1,509	85	(5·63)
Pavithran (1988)[4]	25	3	(12)
Reddy *et al.* (1988)[5]	92	4	(8·4)
Katoch *et al.* (1989)[7]	70 (MDT)	9	(12·9)
	84 (modified MDT)	1	(1·2)
Rangarai *et al.* (1986)[9]	237	14	(5·9)
Van Brakel *et al.* (1989)[10]	555	16	(2·9)

Conclusion

We concluded from our data that short-term WHO MDT is effective and safe. We have a cure rate of 77·6% at 6 months of MDT, a low relapse rate of 2% and a complication rate of 8·2% (from dapsone). We agree with others[3,14] that the duration of MDT should be tailored to the individual. It should not be arbitrarily stopped at 6 months, and extended periods of treatment may be necessary, especially in some cases of BT leprosy.

References

[1] WHO Study Group. *Chemotherapy of leprosy for control programme.* Technical Report Series No. 657. WHO: Geneva, 1982.

[2] Chopra NK, Agarawal JS, Pandya PG. A study of relapse in paucibacillary leprosy in a multidrug therapy project, Baroda District, India. *Lepr Rev*, 1990; **61:** 157–62.

[3] Grugni A, Nadkarni NS, Kini MS, Mehta VR. Relapses in paucibacillary leprosy after MDT—a clinical study. *Int J Lepr Other Mycobact Dis*, 1990; **58:** 19–24.

[4] Pavithran K. Relapse of paucibacillary leprosy after a short-course of multidrug therapy. *Ind J Lepr*, 1988; **60:** 225–9.

[5] Reddy PK, Mohinuddin SK. Pattern of relapses in paucibacillary leprosy patients treated with MDT (WHO 1982). *Ind. J Lepr*, 1988; **60:** 581–8.

[6] Dharmendra Correspondence—Editorial Comment. *Ind J Lepr*, 1985; **57:** 227.

[7] Katoch K, Ramanathan U, Natrajan M, Bagga AK, Bhatia AS, Saxena RK, Ramu G. Relapses in paucibacillary leprosy patients after treatment with three short-term regimens containing Rifampicin. *Int J Lepr Other Mycobact Dis*, 1989; **57:** 458–64.

[8] Revankar CR, Karjivkar VG, Gurav VJ, Ganapati R. Clinical assessment of paucibacillary leprosy under multidrug therapy—three years follow up study. *Ind J Lepr*, 1989; **61:** 355–8.

[9] Rangaraj M, Rangaraj J. Experience with multidrug therapy in Sierra Leone. Clinical, operational and managerial analysis. *Lepr Rev*, Suppl 3, 1986; **57:** 77–91.

[10] Van Brakel W, Kist P, Nable S, O'Tovle S. Relapses after multidrug therapy for leprosy: a preliminary report of 22 cases in West Nepal. *Lepr Rev*, 1989; **60:** 45–50.

[11] Sherlock S. Prediction of hepatotoxicity due to therapeutic agents in man. *Medicine*, 1966; **45:** 453–8.

[12] Kromann NP, Vilhelmsen R, Stahl D. The Dapsone Syndrome. *Arch Dermatol*, 1982; **118:** 531–2.

[13] Johnson DA, Cattau EL, Kuritzky JN, Zimmerman HJ. Liver involvement in the sulfone syndrome. *Arch Intern Med*, 1986; **146:** 875–7.

[14] Grugni A, Nadkarni NJ. Kini MS. Multidrug therapy in paucibacillary leprosy—a five year experience. *Ind J Lepr*, 1988; **60:** 589–92.

Lepr Rev (1993) **64,** 136–142

Éfficacité et sureté de la thérapeutique multidrogue dans la lèpre paucibacillaire à Singapour

JOYCE TENG-EE LIM ET TULIP TAN

Résumé Quarante neuf patients atteints de lèpre paucibacillaire (PB), qui avaient suivi jusqu'à complétion un traitement multidrogue (MDT) entre 1985 et 1990 ont été examinés rétrospectivement pour rechercher l'efficacité et les complications. La lèpre était borderline tuberculoïde (BT) chez vingt patients, tuberculoïde (TT) chez treize patients (26,5%), indéterminée (I) chez un patient (2,1) tandis que quinze patients (30,0%) présentaient une lèpre névritique pure. Vingt-six patients (76,5% des 34 lèpres non névritiques) ont subi une biopsie cutanée pour rechercher la guérison histologique avant l'arrêt du traitement multidrogue. Sur ces vingt-six patients, dix-neuf ont obtenu la clearance histologique à 6 mois tandis que les autres 7 mettaient plus d'un an à l'atteindre (18 à 36 mois). Les huit derniers patients non névritiques qui ont refusé la seconde biopsie ont reçu MDT pendant 6 à 8 mois et le MDT a été arrêté à la clearance clinique. Sur les quinze patients atteints de lèpre névritiique (N), onze ont reçu MDT pendant 6 mois tandis que le reste avait 12 à 18 mois de traitement. Un patient atteint de lèpre névritique, traité pendant 6 mois, a rechuté avec une lèpre BT 18 mois après l'arrêt du traitement.

Il y a eu quelques complications chez les 49 patients. Quatre patients (8,2%) ont présenté une réaction à la dapsone, un (2,0%) a eu le syndrome dapsone, deux (4,1%) ont eu une anémie hémolytique et un (2,0%) a eu une hépatite dûe à la dapsone. Sept patients (14,3%) ont eu une réaction de type I.

Efficacia y seguridad de la terapia multidroga en la lepra paucibacilar, en Singapúr

JOYCE TENG-EE LIM Y TULIP TAN

Resumen Se analizaron retrospectivamente cuarenta y nueve pacientes sufriendo de lepra paucibacilar (PB) que habían completado terapia multidroga (MDT) durante los años 1985 a 1990, para eficacia y complicaciones. Veinte pacientes (40,8%) tenían Lepra Tuberculoide Dudosa (BT), trece (26,5%) Tuberculoide (TT), uno (2,1%) tenía Indeterminada (I) y 15 (30,0%) Neural pura (N). Veinte y seis pacientes (76,5% de los 34 con lepra no neural) fueron examinados por biopsia de la piel para una cura histológica antes de descontinuar el MDT. De estos veinte y seis pacientes, diez y nueve pasaron el examen histológico después de 6 meses, y los demás pasaron después de l año (18 a 36 meses). Los restantes 8 pacientes no neurales que rehusaron la biopsia recibieron MDT por 6 a 8 meses, descontinuando después de pasar el examen clínico. De los quince pacientes con lepra neural (N), 11 recibieron MDT por 6 meses, y los demás fueron tratados por 12 a 18 meses. Un paciente con lepra neural que fue tratado por 6 meses, tuvo una recaída de lepra BT 18 meses después del tratamiento.

Hubieron pocas complicaciones entre los cuarenta y nueve pacientes. Cuatro (8,2%) desarrollaron una reacción contra la dapsona, uno (2,0%) tuvo el síndrome de la dapsona, dos (4,1%) tuvieron anemia hemolítica y uno (2,0%) hepatitis debido a la dapsona. Siete (14,3%) de los pacientes tuvieron una reacción de Tipo 1.

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An epidemiological survey of deformities and disabilities among 14,257 cases of leprosy in 11 counties

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Summary This study was planned and conducted in Yang Zhou Prefecture, covering 11 counties that were formerly areas with a high prevalence of leprosy. Out of 14,257 leprosy patients, 8122 (56·97%) cases with deformities and disabilities were found. The disability rate is much higher in patients with MB leprosy (81·15%) than in PB leprosy (53·04%). The statistical data and the type of deformities and disabilities are presented. The influences of various host factors and disease factor which cause disability and deformity are discussed.

Introduction

Leprosy produces deformities and disabilities which can leave a permanent mark on the patients and result in stigma. Therefore, disability control is of great importance in a leprosy control programme, and our government is giving more attention to this than ever before. In order to find out the magnitude of the problem—the distribution of disabilities by sex, age and type of leprosy, the distribution of hand, foot and eye deformity according to type, the number of patients requiring reconstructive surgery and/or protective shoes—and to draw up the national rehabilitation project, an epidemiological study of disability was carried out in Yang Zhou. This prefecture has 11 counties with a population of more than 10 million.

Material and methods

The epidemiological survey of disability and deformity was carried out from March 1988 to the end of the year by a team of 55 paramedical workers and doctors in the field and 3 medical supervisors. All were fully trained before the study commenced. Patients with

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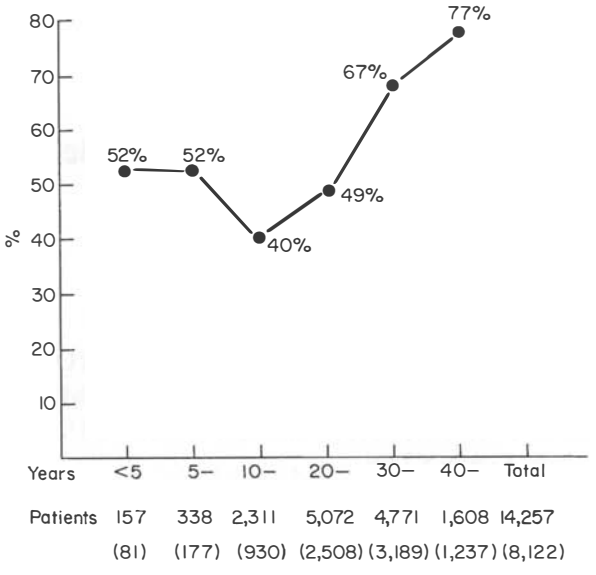

Figure 1. Duration of disease and disability.

deformities and disabilities were assessed according to the grading system recommended by the WHO Expert Committee (1970), with a little modification by us.

Out of 14,257 leprosy patients there were 10,356 males and 3901 females. The largest number of patients were PB (12,256 cases). Most patients had a long leprosy history of 20–29 years, followed by 30–39, 10–19, over 40 years, 5–9 years and less than 5 years in that order (Figure 1). A detailed history of each patient was taken, including the duration of the disease, the origin of complaints, the regularity of treatment, and the origin of deformities and disabilities. Detailed examinations were carried out, both local and systemic, including eyes, nose, face, sensory modalities, motor modalities, ulcers, hand and foot, etc. All the data were stored in a computer.

Table 1. Disabilities by age

	Males			Females			Total		
Age	No. of cases	No. of disabled	% disabled	No. of cases	No. of disabled	% disabled	No. of cases	No. of disabled	% disabled
< 15	11	5	45·45	5	2	40·00	16	7	43·75
15–24	45	22	48·89	27	10	37·04	72	32	44·4
25–34	329	163	49·54	176	91	51·70	505	254	50·30
35–44	2086	1229	58·92	824	479	57·77	2910	1708	58·69
45–54	3654	2134	58·40	1137	627	55·15	4791	2761	57·63
55–64	2599	1551	59·68	951	473	49·74	3550	2024	57·01
65–	1621	918	56·63	772	405	52·46	2393	1323	55·29
Unknown	11	6	54·54	9	7	77·78	20	13	65·00
Total	10,356	6028	58·21	3901	2094	53·68	14,257	8122	56·97

Results

FREQUENCY OF DEFORMITIES AND DISABILITIES

Out of 14,257 cases of leprosy, 8122 cases (56·97%) were found with deformities or disabilities (Table 1). Males were more often disabled than females (58·21% for males, 53·68% for females—difference significant at $p < 0·0001$).

DISABILITIES AND AGE (Table 1)

The older the patient, the more frequent and serious were their disabilities. Males had more disabilities than females.

DISABILITIES IN RELATION TO THE TYPE OF LEPROSY

The details of disabilities and the type of leprosy are recorded in Table 2. The percentage of disabled cases varies with type, the highest being the LL group (89·12%). The disabled percentage among MB (81·15%) is higher than those among PB (53·04%) (difference significant at $p < 0·0001$). A total of 3734 cases out of 6501 disabled PB leprosy patients (57·44%) and 863 cases out of 1610 disabled MB patients (53·60%) became disabled before the commencement of antileprosy treatment while 1059 cases of PB leprosy and 434 cases of MB leprosy were deformed during or after treatment.

DURATION OF DISEASE AND DISABILITY

Figure 1 illustrates the number of disabled persons in relation to duration of disease. The disabled rate increased with the length of disease.

PROPORTION OF GRADES 1, 2 AND 3 DISABILITY

Table 3 shows the proportion of Grades 1, 2 and 3 disability among 8122 disabled cases—Grade 3 is the highest (62·04%).

Table 2. Disabilities by leprosy type

Type	No. of cases	No. of disabled	% disabled	% disabled before treatment	% disabled during treatment	Unknown
I	41	16	39·02	14 (87·5)	0	2
PB TT	8000	3,456	43·2	2069 (59·87)	417 (12·07)	970
BT	4215	3,029	73·43	1651 (54·51)	642 (21·20)	736
Total	12,256	6,501	53·04	3734 (57·44)	1,059 (16·29)	1,708
BB	167	114	68·26	62 (54·39)	22 (19·30)	30
MB BL	751	546	72·7	254 (46·52)	165 (30·22)	127
LL	1066	950	89·12	547 (57·58)	247 (26·00)	156
Total	1984	1,610	81·15	863 (53·60)	434 (26·96)	313
Unknown	17	11	64·71	5	0	6

Table 3. Proportion of Grades 1, 2 and 3

	PB	MB	Unknown	Total
Grade				
1	197 (3·03)	65 (4·04)	0	262 (3·23)
2	2272 (34·95)	305 (18·94)	5 (45·45)	2582 (31·79)
3	3695 (59·91)	1138 (70·68)	6 (54·55)	5039 (62·04)
Facial	137 (2·11)	102 (6·34)	0	239 (2·94)
Deformity Total	6501 (100·00)	1610 (100·00)	11 (100·00)	8122 (100·00)

The actual disabilities and deformities of hands, feet and eyes are recorded in Tables 4, 5, and 6.

Table 4. Actual disabilities and deformities of hands

	PB	MB	Unknown	Total	Bilateral
No. of cases	12,256 (%)	1984 (%)	17 (%)	14,257 (%)	
Anaesthesia	2679 (21·86)	971 (48·94)	6 (35·29)	3656 (25·64)	1668 (11·70)
Mobile claw hand	3715 (30·32)	1042 (52·52)	5 (29·41)	4762 (33·40)	1814 (11·70)
Thumb paralysis	1532 (12·5)	528 (26·61)	4 (23·53)	2064 (14·48)	882 (6·19)
Cracks and wounds	370 (3·02)	208 (10·48)		578 (4·05)	299 (2·1)
Slight absorption	975 (7·96)	323 (16·28)	1 (5·88)	1299 (9·11)	373 (2·62)
Contractures	1115 (9·10)	380 (19·15)	2 (11·76)	1497 (10·50)	495 (3·47)
Wrist drop	386 (3·15)	70 (3·53)	1 (5·88)	457 (3·21)	73 (0·51)
Stiff joints	2723 (22·22)	804 (40·52)	5 (29·41)	3532 (24·71)	1296 (9·09)
Severe absorption	1270 (10·36)	482 (24·29)	2 (11·76)	1754 (12·30)	685 (4·81)

Table 5. Actual disabilities and deformities of feet

	PB	MB	Unknown	Total	Bilateral
No. of cases	12,256 (%)	1984 (%)	17 (%)	14,257 (%)	
Anaesthesia	2223 (18·14)	1100 (55·44)	4 (23·53)	3327 (23·34)	1570 (11·01)
Foot drop	1911 (15·60)	321 (16·18)	5 (29·41)	2237 (15·69)	295 (2·07)
Cracks, injuries	283 (2·31)	127 (6·4)		410 (2·88)	116 (0·81)
Simple ulcers	404 (3·30)	204 (10·28)		608 (4·26)	93 (0·65)
Slight absorption	705 (5·75)	341 (17·19)		1046 (7·34)	391 (2·11)
Fixed equinovarus	211 (1·72)	143 (7·21)		354 (2·48)	86 (0·60)
Complicated ulcers	793 (6·4)	481 (24·24)		1274 (8·95)	303 (2·13)
Shortened foot	998 (8·14)	596 (30·04)		1594 (11·20)	500 (4·07)
Amputation				565 (3·96)	

Table 6. Actual disabilities of eyes

	PB	MB	Unknown	Total	Bilateral
No. of cases	12,256 (%)	1984 (%)	17 (%)	14,257 (%)	
Insensitive cornea	948 (7·73)	394 (19·86)	2 (11·77)	1344 (9·43)	700 (4·91)
Lagophthalmos	1500 (12·24)	609 (30·70)	5 (29·41)	2114 (14·13)	900 (6·31)
Eversion of lower lid	736 (6·01)	275 (13·86)	2 (11·76)	1013 (7·11)	409 (2·87)
Keratitis E	588 (4·80)	220 (11·09)		808 (5·67)	297 (2·08)
Iridocyclitis	195 (1·59)	136 (6·85)	1 (5·88)	332 (2·33)	150 (1·05)
Blurring vision	605 (4·95)	281 (14·16)	3 (17·65)	889 (6·24)	372 (2·61)
Marked impairment of vision	206 (1·68)	127 (6·40)		333 (2·34)	92 (0·65)
Blindness	210 (1·71)	154 (7·76)	1 (5·88)	365 (2·56)	113 (0·79)

Table 7. Facial deformities

	PB	MB	Unknown	Total
No. of cases	12,256 (%)	1984 (%)	17 (%)	14,257 (%)
Facial paralysis				
lateral	1289 (10·52)	290 (14·62)		1579 (11·10)
bilateral	284 (2·32)	176 (8·87)		460 (3·23)
Loss of eyebrow	97 (0·79)	1173 (59·12)		1270 (8·91)
Collapsed nose	20 (0·16)	156 (7·86)		176 (1·23)

The actual disabilities and deformities of hands, feet and eyes are recorded in Tables 4, 5 and 6.

Some deformities of the hands, feet and eyes may benefit from reconstructive or plastic surgery, such as a mobile claw had (33·40%), a foot drop (15·69%), median nerve paralysis of the thumb (14·48%), wrist drop (3·21%), lagophthalmos (14·83%), etc. Other disabilities may be reversed by health education of the patients in hand-, foot-, and eye-care, MCR shoes, protective gloves, and so on.

FACIAL DEFORMITIES

Table 7 shows various facial deformities which may be suitable for plastic surgery. A total of 744 out of 3488 patients with facial deformities had no deformities of the hands and feet.

Discussion

In this study the disability rate* (56·97%) in Yang Zhou Prefecture is rather high compared to other countries, such as Rao[1] 42·9%; Hasan[2] 44·3%; Koticha and Nair (1979)[9] 37·1%; Prasad[3] 20%; Chawdhary[4] 25·8% and Mishra[5] 21·2%. However, this is

* This totals 55% if Grade 1 is excluded.

lower than that observed by other researchers in China, such as Zheng Tisheng[6] 67·5%; Zhang Zhengwei[7] 73·13% and Song Fuyuan[8] 63·62%. Perhaps the assessments were made in different situations or the criteria of disability grading, definition and samples used for study were quite different. For example, the observations of Zheng Tisheng[6] were carried out in the community and some leprosariums, whereas the observations of Zhang Zhengwei[9] were made in a leprosy hospital containing many old patients with severe disabilities. Furthermore, their study concerned a series of defaulter patients. Therefore an exact comparison is impossible.

The disability rate rose in older age groups. In the age groups of 35–44, 45–54 and 55–64, the prevalence of disability and deformity was very high (58·69%, 57·63% and 57·01% respectively). This is similar to the results of Bravo,[9] Noodeen,[10] and Zheng Tisheng.[6]

In the present study, the disability rate in the male is higher than in the female. This agrees with the data of Kushwah,[11] Nilakanta Rao[12] and Bravo.[9]

In this study the lepromatous type of leprosy was more prone to develop deformities and disabilities than the borderline type. The difference of disability rate between PB and MB leprosy is significant ($p < 0{\cdot}0001$). These findings are similar to those reported by Noordeen[10] and Zheng Tisheng[6] and can be explained by the widespread and progressive nature of lepromatous leprosy. Other leprosy types are more localized and have a shorter evolution. A shorter duration means less spread of disease, and less involvement of the nerves. Therefore, early detection of the disease and neuritis, and adequate therapy and health education are very important for disability control in a leprosy control programme.

In this study, 57·4% of PB cases and 53·60% of MB cases had developed deformities and disabilities before the commencement of anti-leprosy treatment, which agrees with the observation made by Zheng Tisheng.[6] This is probably due to late detection and treatment of the disease, and neuritis.

We have observed that the disability rate increased with increased duration of disease. Similar observations have been made by Zheng Tisheng[6] and Noordeen[10] etc. We consider the duration of the disease to be a more important factor than the age of patients in causing deformities and disabilities.

There was little difference in the prevalence of anaesthesia of the hands and feet in both types of leprosy (PB, MB), (25·64% and 23·34%) but the prevalence of anaesthesia in patients with MB leprosy was more than double that of patients with PB leprosy in both hands (48·94%/21·86%) and feet (55·44%/18·14%). These observations agree with those made by Prasad[3] and Zheng Tisheng.[6] Of 8122 cases disabled in this study, 3656 cases had insensitive hands and 3327 cases had insensitive feet, needing protective gloves/shoes. Education in self-care of the hands and feet is necessary to prevent patients' hands and feet suffering further injury and wounds, etc.

The observation of various types of hand deformities, foot deformities and eye disabilities in this study is basically in agreement with the observations of Zheng Tisheng.[6] However, the amputation rate in this study is much higher than that observed by any other researcher. The reason is not known.

The incidence of facial deformities was very low and not comparable with those of the hands and feet, which corresponds to the observation made by Zheng Tisheng.[6]

In this study, 10–25 of 8122 disabled cases are suitable for consideration for possible reconstructive or plastic surgery. However, patients' attitudes during the survey demonstrate that the majority (58·54%) would refuse any surgical treatment. Education

of these patients is therefore essential for their rehabilitation. Analysis of disability and deformity in this study demonstrated that health education in the self-care of hands, feet and eyes, and protective shoes, etc. had a greater potential to reduce disability in leprosy than reconstructive and plastic surgery.

References

[1] Rao *et al. Int J Lepr*, 1970; **38:** 1–11.
[2] Hasan S. *Lepr India*, 1977; **49**(3): 393–9.
[3] Prasad S. *Lepr India*, 1981; **53**(4): 626.
[4] Chawdhary RC. *Lepr India*, 1981; **53:** 259–65.
[5] Mishra B *et al. Ind J Lepr*, 1988; **60**(2): 260–6.
[6] Zheng Tisheng *et al. China Lepr J*, 1988; **4**(4): 198–204.
[7] Zhang Zhengwei. *China Lepr J*, 1987; **3**(3): 160.
[8] Song Fuyuan *et al. China Lepr J*, 1989; **5**(3): 152.
[9] Bravo, *et al. Lepr Rev*, 1977; **48:** 247–60.
[10] Noordeen SK *et al. Int J Lepr*, 1966; **34:** 159–69.
[11] Kushwah SS *et al. Lepr India*, 1981; **53:** 240–8.
[12] Nilakanta Rao *et al. Lepr India*, 1980; **52:** 236–44.

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Une enquête épidémiologique des difformités et des infirmités dans 14.257 cas de lèpre dans 11 départements

ZHANG GUOCHENG, LI WENZHONG, YAN LIANGBIN, YAN ZHONGMIN, CHEN XIANGSHENG, ZHENG TISHENG ET YE GANYUN

Résumé Cette étude a été planifiée et exécutée à la Préfecture de Yang Zhou couvrant 11 départements qui étaient auparavant des régions où la lèpre était fréquente. Sur 14.257 patients lépreux, 8.122 cas (56,97%) de difformités et d'infirmités ont été observés. Le taux d'infirmités était bien plus élevé chez les lépreux MB (81,15%) que chez les lèpreux PB (53,04%). Les données statistiques et le type de difformités et infirmités sont présentés. L'influence des divers facteurs de l'hôte et le facteur maladie qui causent l'infirmité et la difformité sont discutés.

Un estudio epidemiológico de las deformidades y deshabilidades entre 14.257 casos de la lepra en 11 condados

ZHANG GUOCHENG, LI WENZHONG, YAN LIANGBIN, YANG ZHONGMIN, CHEN XIANGSHENG, ZHENG TISHENG Y YE GANYUN

Resumen Este estudio fue preparado y realizado en 11 condados en la Prefectura de Yang Zhou, anteriormente zonas en que había una prevalencia alta de la lepra. De 14.257 pacientes de la lepra, se encontraron 8.122 (56,97%) casos de deformidades y deshabilidades. El porcentaje de deshabilidades es mucho más en los pacientes con lepra multibacilar (81,15%) que en el paucibacilar (53,04%). Se presentan los datos estadísticos y los tipos de deformidad y deshabilidad. Se discuten los efectos de varios factores de huésped y de factor de enfermedad que causan deshabilidades y deformidades.

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Inventory of skin smear practices in 6 leprosy control programmes in Nigeria

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Summary A study of slit skin smear (SSS) examination practices in 6 Nigerian Leprosy Control Programmes was undertaken to assess the quality of smearing, staining and reading. Results indicated that the standard of SSS practices fall below the ideal. There is a great need for training as well as supervision and support of laboratory staff if this deplorable situation is to be improved.

Introduction

One of the cardinal signs for the diagnosis of leprosy is the demonstration of *Mycobacterium leprae* in slit skin smear (SSS). In some patients the demonstration of this causative organism provides the only proof of the diagnosis of leprosy. For differentiating between the 2 main classes of leprosy, i.e. paucibacillary and multibacillary, determining the treatment regimen, the assessment of SSS is often taken as the final arbiter. In many leprosy-endemic countries there is a severe shortage of laboratory staff skilled in the processing of SSS.

In Nigeria, with about 156,000 registered leprosy cases,[1] leprosy is still an important public health problem and in view of the relevance of reliable SSS for the confirmation of diagnosis and classification,[2] decisions on the duration of treatment and the diagnosis of multibacillary relapse,[3] a study on the SSS examination practices in 6 leprosy control projects in Nigeria was undertaken to determine:

(a) the quality of smearing;
(b) the quality of reagents used for staining, appropriateness of the staining procedure and the accuracy of the staining;
(c) the accuracy of the microscopic reading, and
(d) other factors relevant to the improvement of the quality of SSS results (e.g. laboratory facilities, quality of control and job satisfaction for laboratory staff).

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Methods

At least 1 leprosy project from each of Nigeria's 4 primary Health Care zones (i.e. Zone A—Ogun and Bendel States; Zone B—Imo State; Zone C—Kaduna and Zone D—Gongola and Bauchi States) was chosen for the study.

In all, 3 approaches were used to assess the laboratory services for leprosy control operating in the centres participating in the study:

1 A brief questionnaire about SSS practices in each project, facilities available, quality control activities and constraints to efficient laboratory output, training and job satisfaction.
2 A sample of SSS from the laboratory unit of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) was offered to serve as a set for test reading of the Bacteriological Indices (BI) by the laboratory technicians of these Nigerian programmes.
3 A request that a sample of slides from each of the centres, together with their BI readings, be sent to ALERT for quality control, comment and advice.

The quality control presented here is based largely on the criteria proposed by de Rijk *et al.*[4]

A copy of the filled-in quality control form, as received from ALERT, together with comments, on the form as well as on the questionnaire, was sent to each of the participating technicians and programme managers so as to enable them to identify their strong and weak areas.

Results

The study revealed that as at August 1990 only about 50% of the leprosy hospitals in Nigeria have the facilities and manpower for regular SSS examination. This information was obtained through personal communication with the programme managers of the Nigerian leprosy referral centres.

QUESTIONNAIRE

In most of the leprosy control projects studied, each laboratory technician prepares and examines an average of 3–7 slides per working day. There is no defined protocol on whom to smear, and when.

All but 2 of the 11 laboratory workers who answered the questionnaire earn less than ₦500.00 monthly; they are not given any incentives, be it cash or kind, and feel that their contributions to the leprosy control services are not appreciated. Only 3 of the 11 respondents were taught the technique of SSS while in the medical laboratory school, and of those, 2 felt their exposure was too inadequate to be of any practical benefit. All the laboratories have at least 1 functioning microscope each and 4 of the six projects experience significant periodic shortages in laboratory reagents, water and electricity; 3 of the projects undertake, albeit irregularly, some form of quality control with laboratories in Amsterdam and Germany; 8 of the 11 respondents admit to being unhappy with their jobs. The main reasons advanced were:

Table 1. Quality of smearing

Project code	No. of smears sent by individual leprosy projects	No. of smears judged as being of good quality	Percentage of well-smeared slides
01	24	0	0
02	10	2	20
03	24	4	17
04	24	4	17
05	14	2	14
06	24	2	8
07	20	2	10
Total	140	16	12 (average)

(a) lack of 'recognition';
(b) slow career advancement;
(c) inadequacy of overseas training, compared to that obtained by leprosy control supervisors and doctors.

QUALITY OF SMEARING

Only 12% of SSS sent by the projects for assessment of smear quality were adjudged as being of good quality by the ALERT laboratory staff (Table 1). Reasons for the poor smear quality include too much blood in the smears and too little smear material on the slide.

QUALITY OF STAINING

Only 1% of slides sent by the projects for assessment of quality were considered to be properly stained (Table 2). It follows that poorly smeared slides are likely to be of poorly stained quality, but other reasons for poor staining included excessive granules on the stained smears (probably due to improperly filtered reagents) and overdecolourization during staining procedures.

Table 2. Quality of staining

Project code	No. of smears sent by individual leprosy projects	No. of smears judged as being of good quality	Percentage of well-stained slides
01	24	0	0
02	10	0	0
03	24	0	0
04	24	0	0
05	14	0	0
06	24	2	8
07	20	0	0
Total	140	2	1 (average)

Table 3. BI readings (I)

Project code	No. of smears sent to ALERT	No. of smear readings showing good correlation (−1, 0, +1)	Percentage of smears showing good correlation
01	24	0	0
02	10	3	3
03	24	18	75
04	24	17	71
05	14	14	100
06	24	11	46
07	20	19	95
Total	140	82	59 (average)

ACCURACY OF BI READINGS

In assessing the accuracy of BI readings, a difference of ± 1 was considered to be of little significance, and therefore acceptable. Thus a good correlation was assessed as the sum of the number of readings with differences -1, 0, $+1$ taken as a percentage of the total number of smears assessed.

Using this criterion, only 59% of all the smears sent by individual projects to ALERT for assessment were found to show good correlation (Table 3). Similarly, using the above criterion, only 52% of the readings done in the Nigerian institutions on slides sent from ALERT showed good correlation (Table 4). This is much lower than the 80% correlation proposed by de Rijk *et al.* or the 95% correlation that is achieved by ALERT laboratory staff.[5]

Table 4. BI readings (II)

Project code	ALERT No. smears examined for BI	No. of smear readings showing good correlation (−1, 0, +1)	Percentage of smears showing good correlation
01	24	0	0
02	22	13	59
03	20	12	60
04	20	15	75
05	24	19	79
06	22	20	91
07	20	0	0
Total	152	79	52 (average)

Discussion

Bacteriological examination is very important and highly relevant to leprosy control, but the standards of SSS examination practices, especially in leprosy-endemic countries like Nigeria, is probably the weakest link in most leprosy control programmes.[6,7]

From the results, it is obvious that a lot needs to be done if the existing situation *vis-à-vis* SSS practices in these projects is to be improved, and 2 approaches are recommended:

i. training;
ii. supervision and support for laboratory technicians.

i. *Training*

The National Tuberculosis and Leprosy control programme should, as a matter of policy, ensure that each States' leprosy referral hospital has a good laboratory and trained manpower.

The training of general laboratory technicians needs to be reviewed to include the taking, smearing and reading of smears. Because the treatment of leprosy has always operated as a 'special service' most schools of laboratory technology lack the access to patients needed for this training. While in the long term, the integration of leprosy into Primary Health Care is expected to correct this anomaly, a desirable short-term measure would be to arrange for trainee laboratory technicians and assistants to come and work for some weeks in laboratories involved in leprosy work.

Laboratory workers currently working in these leprosy hospitals would definitely benefit from refresher courses on the smearing, staining and reading of SSS. The laboratory department of ALERT has already indicated a willingness to (re)train these workers, either in Nigeria or at ALERT, in Ethiopia.

ii. *Supervision and support*

A system of quality control is desirable. In view of the low quality of SSS smear practices currently existing, it may be wise, in the short term, to organize periodic quality controls with reference laboratories in ALERT, Germany and the Netherlands, while aiming for the development of the laboratory service in at least 1 leprosy project in each Primary Health Care zone to that of a reference laboratory for the zone.

It is noteworthy that the feedback obtained so far from the participants reveals a high degree of stimulation and enthusiasm, and such positive feedbacks have been reported by other workers.[8,9]

It is hoped that experiences gained in quality control should stimulate further training and correct other factors that hinder the attainment of high quality SSS practices.

It is important that clear and uniform guidelines be given on:

1 whom to smear and when;
2 the technique of staining smears;
3 the technique of smearing and fixation.[10]

In view of the limited resources available for SSS practices, it may be necessary to give up the routine laboratory examination of PB patients so that more time can be spent on

bacteriological examination of MB cases where it is actually needed to monitor response to chemotherapy.[11] Also, the morale of some of our technicians who, especially during periods of MDT implementation, are burdened with the examination of large numbers of negative smears, will be raised.

It is basic to management that managers should 'lead from the front', appreciating the skills and responsibilities of their staff, and they should care for and value their staff and understand their problems. Unfortunately, most leprosy programme managers have little or no experience in skin smear practices. They are therefore unable to adequately encourage, aid or advise their laboratory staff.[10] The fact that this study reveals the frustration and demotivation of the laboratory staff shows that it would be wise for senior managers, whether medical or non-medical, to have laboratory and personnel management included in their training.

These factors require urgent attention if the existing unsatisfactory state of SSS practices operating in these Nigerian leprosy projects is to improve.

Acknowledgements

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References

[1] WHO Bulletin. Vol. 70, 1992.
[2] Jopling WH. *Handbook of Leprosy*, 3rd edn, London: Heineman, 1984, pp. 42.
[3] WHO/CTD/LEP/91.3 MDT Questions and Answers. Q 31.
[4] de Rijk AJ, Nilson T, Chonde M. Quality control of skin smear practices in leprosy programmes, preliminary experiences with inter-observer comparison in routine services. *Lepr Rev*, 1985; **56:** 177–91.
[5] de Rijk AJ (1990) personal communication.
[6] Georgiev GD, McDougall AC. The bacteriological examination of slit skin smear in leprosy control programmes using multidrug therapy: a plea for radical changes in current operational methodology. *Ind J Lepr*, 1987; **59:** 373–85.
[7] WHO Expert Committee on Leprosy. *Sixth Report*. Technical Report Series No. 768. WHO: Geneva, 1988, pp. 16–17.
[8] Vettam L, Pritze S. Reliability of skin smear results: experience with quality control of skin smears in different routine services in leprosy control programmes. *Lepr Rev*, 1989; **60:** 187–79.
[9] Vettam L, Pritze S. Experiences with repeated quality controls of skin smears in different routine services in leprosy control programmaes (letter). *Lepr Rev*, 1990; **61:** 394–6.
[10] ILEP Medical Bulletin: *Improving skin smears and reading of the Bacteriological Index in MDT leprosy control programmes*. Issue No. 3, December 1990.
[11] Rao PS *et al*. Is bacteriological examination by skin smear necessary in all paucibacillary leprosy patients in mass control programmes? *Lepr Rev*, 1991; **62:** 303–9.

Lepr Rev (1993) **64,** 150–156

Inventaire de l'exécution des frottis de peau dans six programmes de contrôle de la peste au Nigéria

NIYI AWOFESO

Résumé Une étude de l'exécution de examens de frottis de peau fendue (SSS) dans 6 programmes nigériens de contrôle de la peste a été menée dans le but de juger la façon dont le frottis, la coloration et la lecture étaient exécutés. Les résultats ont indiqué que les techniques standards de SSS laissaient beaucoup à désirer. Il y a un besoin urgent de formation autant que de supervision et de soutien du personnel de laboratoire pour améliorer cette situation déplorable.

Inventorio de los métodos de frotis dérmico ("SSS") en seis programas para el control de la lepra en Nigeria

NIYI AWOFESO

Resumen Se realizó un estudio de los métodos de frotis dérmico (SSS) en 6 programas para el control de la lepra en Nigeria para evaluar la calidad de los métodos de frotis, coloración y lectura. Los resultados indican que la calidad de los métodos SSS usados son mucho menos que perfectos. Hay una gran necesidad para la capacitación además de supervisión y soporte del personal si se pretende mejorar esta situación deplorable.

Lepr Rev (1993) **64,** 157–163

Borderline–tuberculoid relapse in lepromatous leprosy

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Accepted for publication 13 November 1992

Summary We report details of 2 patients who had been treated for a long time by dapsone monotherapy and who had remained smear negative for over 10 years, but were found to have relapsed with borderline–tuberculoid (BT) leprosy.

Introduction

Relapses in lepromatous leprosy (LL) following treatment are not uncommon. Long after smear negativity has been achieved with DDS monotherapy, patients are known to relapse.[1–6] Almost all of these relapses have been of lepromatous or borderline lepromatous type with skin smear positivity and continued lepromin negativity.

However, in the past, a few patients on relapse or reactivation presented with a tuberculoid picture, and this was usually because of late reversal reaction secondary to continued treatment.[7] In retrospect, it is now considered that these patients were more probably of BL rather than of lepromatous type.

In contrast to the above, reports of Jonquieres[8] and Waters & Ridley[9,10] concern the appearance of BT relapses in long-treated LL patients. A similar observation of BT relapse in 2 old lepromatous patients, treated for long periods with dapsone montherapy and who had remained skin smear negative for a number of years, was made by us and is reported.

PATIENT 1

This Indian female was diagnosed as a case of leprosy 28 years ago. To begin with she had impaired sensation on the right lower limb. She had no patch or any other problem 5 years later, following her first child's birth, she had painful eruptions, appearing rapidly over the buttocks and face. This was associated with fever, joint pains and severe pain in the limbs. She was diagnosed as a case of leprosy and put on DDS together with antireaction drugs. She improved in the ensuing 3–4 weeks. Subsequently, she was continued on 25 mg DDS doses, which she took irregularly. During her next ENL

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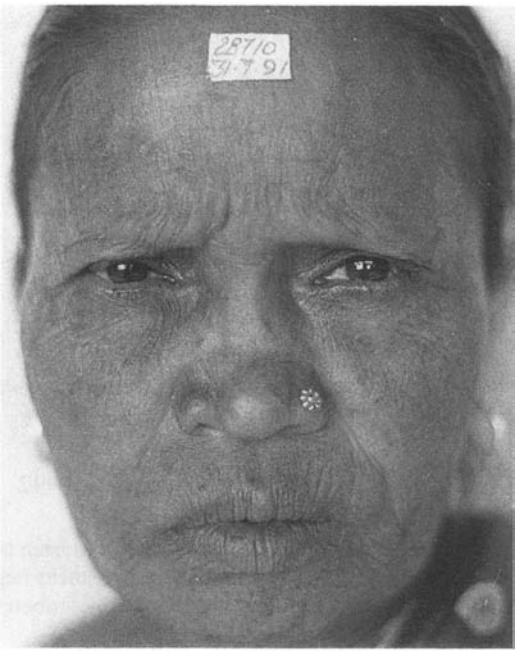

Figure 1.

episode, which was 3 years later, she had severe pain, down the left elbow initially and later in the right hand. This resulted in clawing of the hands. She was treated with steroids but without improvement. She was continued on increasing doses of DDS, which she took irregularly for the next 18 years (regularity around 70%). All her symptoms subsided except the deformities.

She was seen in this hospital for the first time in 1987. She had shrivelling all over the face, ears and other parts of the body and no obvious infiltration/induration or active skin lesions on any part of her body (Figure 1). Her nerves were mildly thick, soft but not tender. She was considered as a clinically regressed patient of lepromatous leprosy, with residual signs including supraorbital and ciliary madarosis, a depressed tip of the nose, looked old for her age, and had a bilateral partially fixed ulnar claw. Her skin smears, *repeated on 3 occasions*, from 4 different sites each time, were uniformly negative. Because she had taken prolonged DDS treatment and was available for regular follow-up, she was not put on any further anti-leprosy treatment. Since that time she had been regularly examined once every 3 months and her skin smears were taken every year. These had indicated no problems. In February 1991, she had herpes zoster of the right lower back (T11) with neuralgia. Since she presented very early and had neuralgia, she was given a short course of steroids. After 3 weeks, she noticed 3 asymptomatic, raised, mildly oedematous, red, moderate sized lesions, one each on the left flank, right side abdomen and left shoulder. The left shoulder lesion was arcuate (Figure 2) whereas the other two were oval, 10 cm and 4–5 cm in diameter, respectively. The surface was dry and scaly with slightly sloping edges and impaired sensations. There was no local nerve thickening. She

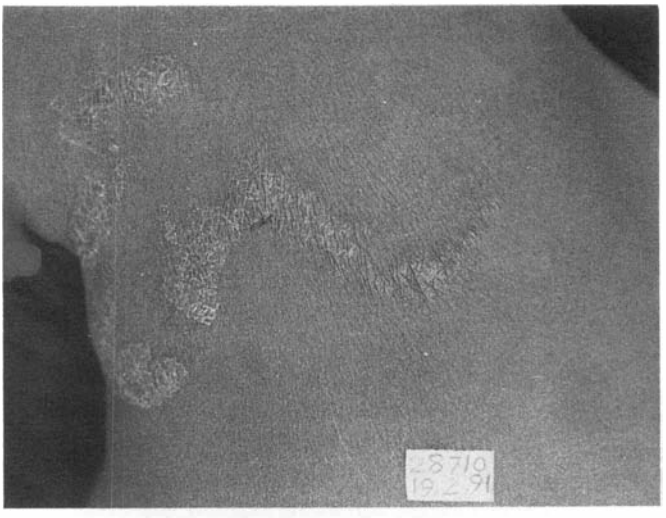

Figure 2.

was diagnosed as BT relapse (in treated LL). Her skin smears, from both ear lobes and 2 lesions, were found negative on 3 occasions. Her lepromin response, to Dharmendra antigen, was also negative. The biopsy from back lesions showed a typical BT picture with some oedema suggesting reaction. No AFB were seen in tissue sections. Biopsy suspension was also negative for AFB and therefore mouse foot pad inoculation, to confirm viability and drug sensitivity, was not attempted.

PATIENT 2

A Nepali man had an ulcer on the back of his left foot about 35 years ago, and shortly afterwards he developed a patch on his right buttock; 2–3 years later the patient had stuffiness of the nose and on blowing it had frequent blood stained nasal discharge. For this, he was prescribed some treatment, which he took for 9–10 months, and the symptoms disappeared.

About 6–7 years later, the patient had facial swelling and the blood stained nasal discharge reappeared. With this he was diagnosed to have leprosy. His skin smears were 3+ from each of the 4 sites (Dharmendra grading). He was put on DDS which he continued to take regularly. In 1969, when he first came to this hospital, he had in addition to the widespread infiltration, loss of eyebrows, depressed nose, nasal ulcers, symmetrical nerve thickening and impairment of superficial sensations over distal parts of his limbs. He had ENL eruptions, together with bilateral chronic uveitis (with firm posterior synechiae) and bone pains. He was treated accordingly and his DDS dose was gradually increased to 100 mg a day, which he continued to take regularly. His skin smears became negative in 1977. He continued on DDS for another 10 years i.e., till 1986, without any reactivation (Figure 3). He did, however, become blind.

He had no problems until 1991 (5 years without drugs). During this time he had been clinically examined at least once every 3 months and his skin smears were examined

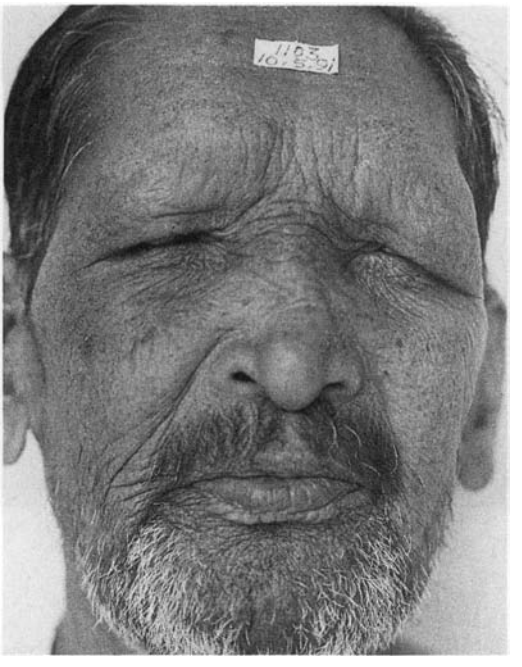

Figure 3.

yearly. In May 1991 he noticed 2 raised, red, asymptomatic lesions of approximately 10 and 4·5 cm diameter on the right pectoral region and mid back. Both the lesions had indistinct borders, dry surface and showed some sensory impairment (Figure 4). He was diagnosed as BT relapse on lepromatous background. His skin smears from both ears and both fresh lesions were found negative. A lepromin test, using Dharmendra antigen, showed negative early response. Biopsy of the chest lesion showed active BT with epithelioid cells, giant cells and a thick cuff of lymphocytes together with damage to nerve fibres. Biopsy showed no bacilli even in nerves. Biopsy suspension was also negative for AFB.

Discussion

Even with the absence of earlier skin biopsies, from the details of the patients and their appearance (Figures 1 and 3), it is evident that both of them were lepromatous as they have the evidence of generalized shrivelling/atrophy (more marked on the face with the hanging of the ear lobes), ciliary and supra orbital madarosis, depressed nasal tip and history of frequent ENL with bone pains in the past, etc. The male patient also had bilateral uveitis and uniform skin smear positivity. A long duration of 8 years for bacillary clearance further supports such a contention. However, they do not seem to have had polar lepromatous disease, as the female patient had bilateral ulnar median palsy and the male patient had passed through a phase of possibly indeterminate leprosy, since he at one

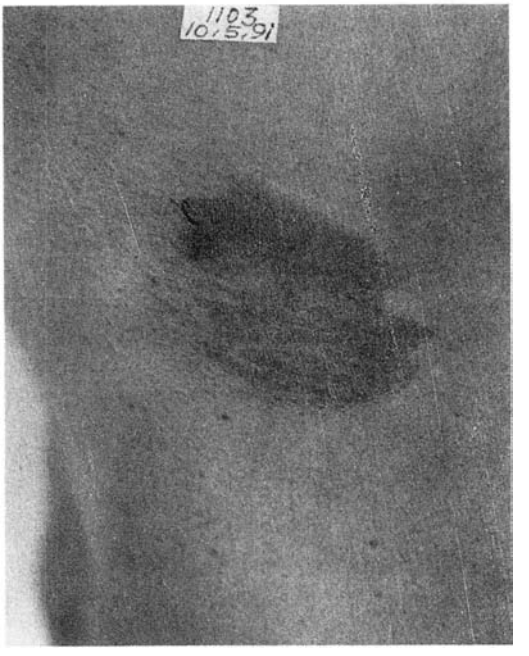

Figure 4.

time had a hypopigmented macule on the right buttock. The patients had remained clinically inactive and bacteriologically negative *for at least* 5 and 15 years, respectively. The relapse in the first case was preceded by the appearance of herpes zoster associated with neuralgia (for which short course steroids were given) but in the male patient no precipitating factor was available, which could have caused or was indicative of immune suppression.

Most of the earlier reported relapses among long-treated patients have been of the lepromatous type.[5,6] Their frequency has been about 1 per 100 patient years of observation in conditions where drug intake was ensured.[6] The relapses have more often been secondary to the emergence of dapsone resistance.[11,12] Even the bacilli obtained from relapsed long-treated patients, reported by Waters & Ridley,[10] who had histologically BT relapse, were found to be fully resistant of dapsone in 3 patients with a suspicion of resistance in the rest. Thus, there is a strong possibility that the relapses in our patients were also on account of dapsone resistance, as the patients had received only DDS in the past and that, too, in comparatively smaller doses and not very regularly. However, dapsone resistance could not be proved or shown in our patients as even the biopsy homogenates from both the patients did not contain any countable bacilli, possibly because the relapses were detected very early. This was in line with the observation of not finding any bacilli, on repeated skin smear examinations and in the biopsies of both the regressed and the active lesion sites in these relapsed patients.

As indicated above, although relapses in DDS treated and long-smear negative patients are not uncommon, relapses with a clinical picture akin to tuberculoid pole have

not occurred frequently. Following a mention of such an occurrence in the literature,[13,14] Jonquieres *et al.*[18] and Waters & Ridley[9,10] have given details of such patients observed by them. In contrast to the above-reported patients, only 1 of the 2 patients observed by us had evidence of a reaction, both clinically and histologically. Further, the lesions in this patient were fairly rapid in evolution. It is possible that the symptoms of reaction in the patient were less pronounced on account of the viral infection (which could also be a manifestation of temporary immune-suppression) or secondary to steroid administration. No such precipitating factor(s) was observed in the male patient.

Another unusual finding has been the negative early (Fernandez) reaction to Dharmendra antigen, despite the relapses being of a BT type clinically, bacteriologically and histologically. The negative lepromin response could possibly be because of a rather shorter duration of treatment and a shorter length of time since smear negativity. Lepromin tests using both Dharmendra and Mitsuda antigens were repeated after 1 year follow-up. Although an 8 mm early reaction was noticed with Dharmendra antigen, the Mitsuda response was negative. This indicates that an adequate time had not yet passed for the clearance of some of mycobacterial products (antigens) which have been shown to produce generalized immunosuppression through stimulation of suppressor T cells.[15–17] It will, therefore, be worth while repeating the lepromin test periodically hereafter in these patients.

In view of the reports of relapses in long-smear negative patients treated with dapsone monotherapy years ago, it has been felt desirable and has also been recommended by some national agencies that a short course of combined chemotherapy similar to multibacillary patients should be given to cured smear + ve patients treated earlier with dapsone monotherapy. However, the duration of chemotherapy required to be given to these patients is not clear and needs to be researched.

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References

[1] Erikson PT. Relapse following apparent arrest of leprosy by sulphone therapy. *Int J Lepr*, 1951; **19:** 63–74.
[2] Rodriquez JN. Relapses after sulfone therapy in leprosy of lepromatous type. *Int J Lepr*, 1958; **26:** 305–12.
[3] Price RB. Relapses of leprosy in American Samoa. *Amer J Trop Med Hyg*, 1959; **8:** 358–63.
[4] Quagliatto R, Bechelli MM, Marques RM. Bacterial negativity and reactivation (relapse) of lepromatous patients under sulfone treatment. *Int J Lepr*, 1970; **38:** 250–63.
[5] Pearson JMH, Rees RJW, Waters MFR. Sulphone resistance in leprosy. A review of one hundred proven clinical cases. *Lancet*, 1975; **2:** 69–72.
[6] Waters MFR, Rees RJW, Laing ABG, Fah KK, Meade TW, Parikshak N, North WRS. The rate of relapse in lepromatous leprosy following completion of twenty years of supervised therapy. *Lepr Rev*, 1986; **57:** 101–9.
[7] Fernandez JMM, Carboni EA, Mercan RA, Sereal A. Transformation of 2 borderline lepromatous cases to tuberculoid with healing. *Int J Lepr*, 1962; **30:** 254–65.
[8] Jonquieres EDL, Melamed AJ, Manzi RO. Tuberculoid relapse in a healed lepromatous (L3) case. *Int J Lepr*, 1963; **31:** 1–8.
[9] Waters MFR, Ridley DS. Tuberculoid relapse in lepromatous leprosy. *Int J Lepr*, 1979; **47:** 350.
[10] Waters MFR, Ridley DS. Tuberculoid relapse in lepromatous leprosy. *Lepr Rev*, 1990; **61:** 353–65.

[11] Pearson JMH, Ross WF, Rees RJW. DDS resistance in Ethiopia—A progress report. *Int J Lepr*, 1976; **44:** 140–2.
[12] Pearson JMH, Haile GS, Barnetson RStC. Dapsone resistant leprosy in Ethiopia. *Lepr Rev*, 1979; **50:** 183–99.
[13] Davey TF. In discussions. *Transections VII International Congress of Leprology, Tokyo, 1958*. Tokyo: Tofu Kyokai, 1959; 241.
[14] Brown SG. Relapses in leprosy: Uzuakoli Settlement 1958–1964. *Int J Lepr*, 1965; **33:** 273–9.
[15] Smelt AHM, Rees RJW, Lien LF. Failure to induce delayed-type hypersensitivity to *Mycobacterium leprae* in long treated lepromatous patients. *Clin exp Imm*, 1981; **44:** 507–11.
[16] Liew FY. Regulation of delayed-type hypersensitivity. 1. T suppressor cells for delayed type hypersensitivity to sheep erythrocytes in mice. *Eur J Immunol*, 1977; **7:** 714.
[17] Loblay RH, Pritchard-Briscoe H, Basten A. Suppressor T-cell memory. *Nature*, 1978; **272:** 620.

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Rechute borderline–tuberculoïde dans la lèpre lépromateuse

B. K. Girdhar, A. Girdhar, S. L. Chauhan, G. N. Malaviya, S. Husain et A. Mukherjee

Résumé Chez deux patients sous monothérapie à long term à la dapsone, dont les frottis étaient restés négatifs pendant plus de 10 ans, on a observé une rechute de lèpre borderline–tuberculoïde (BT). Les détails de ces patients sont rapportés.

Recaída tuberculoide–dudosa en casos de lepra lepromatosa

B. K. Girdhar, A. Girdhar, S. L. Chauhan, G. N. Malaviya, S. Husain y A. Mukherjee

Resumen Se encontró que dos pacientes sometidos a la monoterapia de dapsona a largo plazo, que habían permanecido frótis negativos por más de diez años, tuvieron recaída de lepra tuberculoide–dudosa (BT). Se presentan detalles sobre los pacientes.

Lepr Rev (1993) **64,** 164–165

Obituary

WILLIAM ROBERT EDGAR
1942–92

The sudden death of Bill Edgar just after his 50th birthday saddened and shocked The Leprosy Mission International and a wide section of the international leprosy community. At the time of his death Bill was General Director of TLMI, and had been newly inducted as President of the International Federation of Anti-Leprosy Associations (ILEP).

An Australian, Bill was born into leprosy work. His father was deeply involved in TLM affairs, becoming the Mission's National Secretary.

Bill read economics and politics at Monash University, Melbourne, receiving a Bachelor's degree in 1964. This was followed by a Masters in Business Administration in 1971. He entered business, travelling widely, and was appointed Managing Director of MICA and Insulating Supplies Company. During these years he maintained his interest in leprosy as a member of the TLM Australia Council.

In 1977, following his participation in a TLM conference in Singapore, Bill accepted a challenge to relinquish his business career for a full-time appointment as Secretary for Australia. This involved him in promotional and fund raising activities in which his dynamism soon became evident.

In 1980 he was offered appointment as Communications Director for The Leprosy Mission International, based in London, a position he and his family readily accepted, even though it meant transfer to the UK.

In 1987 he was appointed General Director, the senior executive position in the Mission. Bill brought many talents to the role. He was a skilled and active manager whose gifts of analysis were matched by an ability to work out practical applications. Bill got results. He also understood the difference between the possible and the desirable.

As headboy and cricket captain at school (he never lost his enthusiasm for sports), through university lectureships in management, throughout his business career and subsequent work with TLMI, Bill led from the front.

At times his management showed a superficial toughness, but underneath this there lay both a deep compassion for people, particularly for those suffering the results of neglected leprosy, and a strong commitment to do whatever was possible to help. His primary concern was for the individual and his needs, although he had a wide understanding of leprosy work and its objectives, and the need for positive management.

During his 5 years as General Director of TLMI the international team of key workers was transformed. Under his vigorous leadership the Mission expanded its already extensive work in India, and added significant new commitments in Africa and South-East Asia.

In all he did he was lovingly and actively supported by his wife Mary, and their 2 daughters Narelle and Delise.

Bill was greatly strengthened by his Christian faith. He was not a 'pious' or exhibitionist Christian but his beliefs, attitudes and actions were motivated by his lifetime commitment.

He faced his sudden serious illness, which accelerated after a relatively short period of feeling unwell, with the same strength he brought to his life and work, looking openly and honestly at the prospect of his death with great courage and assurance.

He leaves The Leprosy Mission International, ILEP and the international community of leprosy, both patients and workers, the poorer by his absence. He is deeply missed by his family, to whom our loving sympathy goes, but we rejoice at a life lived warmly, creatively and positively.

A. D. ASKEW

Lepr Rev (1993) **64,** 166–173

Letters to the Editor

DIVORCE AMONG SAUDI FEMALE LEPROTIC PATIENTS: AN EXPERIENCE AT IBN SINA HOSPITAL

Sir,

As divorce is becoming a social and family threat to leprotic women elsewhere, we would like to share our experience on this important subject here at the Ibn Sina Hospital, Hadda, Makkah, Kingdom of Saudi Arabia.

Social problems in leprosy are common and complex in character. Poverty plays an important role in the development of these problems. Unfortunately, leprosy is common among poor countries in general. In such places drugs are inadequately available, lack of health education and a stigma is attached to the disease leading to social rejection of the patients. Moreover, the life span of the leprotic patients is nearly normal enabling them to live longer within the community as they develop severe complications throughout life. This phenomenon adheres to the people's mind, and a malconcept about leprosy becomes the rule. It is a fact that in the management of leprosy the difficulty lies not only in eradicating the mycobacteria but also the backlog of terminal complications such as irreversible deformities and disabilities.

In Saudi Arabia leprosy is not an alarming national health problem. During the last 8 years 1276 cases were diagnosed and treated at Ibn Sina Hospital, comprising Saudis, Yemenis and other nationals, especially from the expatriate communities (Table 1). The previous treatment we used was Dapsone alone. However, from 1982 this hospital adopted Multi-Drug Therapy (MDT) as recommended by the WHO. Generally all cases responded satisfactorily and some had excellent results.

The role of the social workers is to help to educate the patients about their illness, participate in solving their social problems and problems in their job, help them acquire financial assistance from the Social Welfare Office, convince the patients to undergo regular hospital-OPD follow-up, education of the patients and their families about the use, importance and efficacy of MDT and help the leprologist to keep the patient admitted for as long as necessary or help discharge the patient to join normal life.

Divorce is a serious social and family problem affecting leprosy patients, especially women. Presence of deformities, lack of adequate information about the disease and family hesitation to receive back the patient are all contributing factors. However, our experience showed that a long period of hospitalization is the single, most important factor leading to divorce, notably among female patients. Furthermore, as per Islamic rules of the country, the hospital discharges female patients only to their immediate relatives or guardians.

In Ibn Sina Hospital leprotic women divorced by their husbands comparatively constituted a very low percentage. Our study concentrated on admitted married Saudi women aged between 17 and 50 years old with leprosy mainly as the cause for divorce. Non-Saudi women were not included as they were difficult to follow-up because most of them returned to their respective country. Likewise, Saudi women over 50 years old were not included as there was no single case of divorce in their group (Tables 2–5).

Our study showed that during the last 8 years total divorce was 14·4%. The age group of 40–45

Table 1. The total number of patients interned at Ibn Sina Hospital during the 8-year period (1404H–1411H)

	Saudi nationals		Non-Saudi nationals	
Year	Female	Male	Female	Male
1404H	19	53	18	93
1405H	12	67	12	86
1406H	30	96	15	121
1407H	20	75	18	90
1408H	19	50	29	72
1409H	13	15	11	30
1410H	15	42	6	56
1411H	21	47	6	19
Total*	149	445	115	567

* Grand total: one thousand two hundred and seventy-six (1276).

Table 2. The total number of divorce cases among female Saudi leprotic patients during the 8-year period (1404H–1411H)

Year	Total number of female Saudi patients (17–50 years old)	Number of divorce due mainly to leprosy	Percentage
1404H	18	4	22·2
1405H	14	3	21·4
1406H	26	3	11·5
1407H	19	2	10·5
1408H	19	2	10·5
1409H	13	2	15·3
1410H	13	2	15·3
1411H	17	2	11·8
Total	139	20	14·9

* The average rate of divorce was 14·9%.

has the highest rate of divorce comprising 35% of the whole group. We believe that this could be even less had we decreased the length of hospitalization. These patients (139) represent the accumulated number of married leprotic women from the previous years. They were taken from 149 total number of Saudi leprotic female cases admitted during the 8-year period (1984–1992). The time of divorce does not correspond to the year of admission. On the other hand during the same period we successfully convinced 10 female patients to marry 10 male patients inside the hospital; and 4 more female patients married a leprosy-free man, while seven male patients married a leprosy-free woman.

Table 3. The total number of divorce cases among Saudi female leprotic patients aged 17–50 years during the 8-year period

No. of patients	Length of hospitalization (years)	Percentage
4	4·5	20·0
3	4·0	15·0
3	3·5	15·0
2	3·0	10·0
2	2·5	10·0
2	2·0	10·0
2	1·0	10·0
2	0·5	10·0
Total 20	Average 2·9	Total 100

* There were 139 patients aged between 17 and 50 years, all married; 10 patients were eliminated from a total of 149 patients, because they were single or more than 50 years old.

* The average length of hospitalization among the divorced women was 2·9 years.

Table 4. The total number of undivorced Saudi female patients during the 8-year period (1404H–1411H)

No. of patients	Length of hospitalization (years)	Percentage
14	2·5	5·8
11	2·0	8·6
23	1·5	9·4
17	1·0	10·8
17	0·83	13·0
11	0·66	13·7
11	0·5	19·4
15	0·25	19·4
Total 119	Average 1·0	Total 100

* The average length of hospitalization period was 1·0 year.

Table 5. The length of hospitalization for all patients interned at Ibn Sina Hospital during the 8-year period (1404–1411H)

No. of patients	Length of hospitalization (years)	Percentage
12	4·5	7·40
13	4·0	8·80
15	3·5	10·10
19	3·0	12·80
19	2·5	12·80
20	2·0	13·50
21	1·0	14·20
31	0·5	20·20
Total 149	Average 2·25	Total 100

* The average length of hospitalization period was 2·25 years.

Cooperation between the social workers and the medical staff in order to shorten the period of hospitalization is a policy. We admit patients on the following basis: initial admission, those with reaction (ENL, Upgrade), patients with other medical problems, those with deformities and disabilities for reconstructive surgical management, orthopaedic and physiotherapeutic management. Whenever possible an effort is always tried to treat the patient on an OPD basis only. The hospital has developed special procedures to treat reaction in order to prevent deformities, with the cooperation of the Rehabilitation Center for providing suitable prosthesis. A Physiotherapy Department with optimal equipment has also been set up. Altogether these provisions have decreased the incidence of deformities and disabilities. In the health educational aspect the hospital has printed and distributed booklets, featured programmes on national radio, including interviews, and several articles have also been published in national newspapers regarding the usefulness, necessity and efficacy of anti-leprotic treatment (MDT), ways on how to deal with leprosy patients, and we tried an all-out effort to reverse the bad concept and stigma of this particular human affliction.

The different factors that help us shorten the length of the hospitalization period

1 Encourage out-patient treatment and management.
2 Health education (example; that he/she can be rendered less infectious after few days of MDT).
3 Follow-up all cases treated on OPD basis (e.g. contact those patients who delay their next hospital-OPD visit either by telephone or by mail).
4 Extensive treatment of reaction to prevent the occurrence of irreversible deformities.
5 Admit the patient for a short duration only during reaction or if surgical operation is required.
6 Encourage the spouse, relatives or guardians to visit the patient in the hospital, and perhaps allow a stay at home for a short period while during admission.

Conclusion

The role of the social worker is very important in leprosy hospitals. The percentage of divorce due to the disease itself may fall by shortening the length of hospital admission time. Furthermore, treatment is best done on an OPD basis in the absence of threatening complications. Health education, unscrupulous treatment of reactions (e.g. ENL, Upgrade), management of deformities and disabilities by physiotherapy, reconstructive surgery, and orthopaedic procedures are all important factors in the total care of leprosy patients.

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& FAIZAH AHMAD

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Kingdom of Saudi Arabia

TUBERCULOID RELAPSE IN LEPROMATOUS LEPROSY

Sir,

Waters & Ridley[1] recently reported 6 patients who had been lepromatous and who, after many years of chemotherapy and bacteriological negativity, were found on relapse to have upgraded to borderline-tuberculoid (BT) leprosy. In a related article,[2] they reported the development of weakly positive lepromin reactions in some lepromatous patients treated for more than 22 years; a control group of BL patients remained lepromin negative, when less than 20 years of treatment had been given.

We have recently seen tuberculoid relapses in 2 previously lepromatous patients, from western Uganda, 7 and 12 years after initial diagnosis. They had had multiple-drug regimens and had never shown signs of reaction. Condensed histories of both cases are given below.

Case 1

A.M., female, aged 20, presented in 1979 with a 2-year history of multiple skin lesions. No nerves were enlarged and she had no disability. Smears showed a BI of 4 at all sites and an MI of 20%. She was classified clinically as BL, but no biopsy was done. She was treated for 10 years with dapsone and clofazimine, and also had rifampicin (1500 mg) as an annual dose in 6 of the 10 years. Follow-up smears were negative after 1983 and treatment was stopped in 1989. Attendance has been good throughout and she remained without any disability.

After stopping treatment for 10 months she presented with about 20 new lesions, suggestive of borderline-tuberculoid leprosy. Skin smears of the lesions were negative and the biopsy was reported as follows:

> The biopsy shows a borderline-tuberculoid leprosy with dermal nerve disruption; no acid-fast bacilli were seen in multiple sections.

Several family members and neighbours have had leprosy, so a reinfection is a possibility. There is no clinical sign of a reaction and otherwise she remains well. MDT (WHO—2-year regimen) is in progress. A recent HIV test was negative.

Case 2

E.N., male, aged 29, presented in 1984 with a 1-year history of ill-defined macular skin lesions; he had some infiltration of the ear-lobes and his skin smear had an average BI of 2·8 (highest 5) and an MI of 2%. One patch was well-defined with marked loss of sensation, suggesting that he was down-grading from BT to BL or LLs. He had no disability and no biopsy was done.

He was treated with dapsone and clofazimine for 5 years, and also had 6 doses of rifampicin (1500 mg) at 12-monthly intervals. Smears were negative after 1985; his attendance was good and he had no disability.

After stopping treatment for 13 months he presented with about 25 new lesions, typical of borderline-tuberculoid leprosy. The smear was negative and a biopsy was reported as follows:

> 'The histology shows a borderline-tuberculoid leprosy with no evident acid-fast bacilli.'

He has had no sign of a reaction and is currently making good progress on MDT (WHO—2-year regimen). There is no disability and he is HIV negative.

Discussion

Both cases were clinically BL when first treated, supported by the fact that the smears became negative quickly. It is unclear what the new lesions are due to, but DDS-resistance is not a factor, because 3 drugs were used from the beginning; HIV infection, widespread in the area, is also excluded in these cases.

Bacterial relapse due to persisters or reinfection, and delayed hypersensitivity reaction are all possibilities, none being excluded by the biopsy. Waters & Ridley[1] comment that BT lesions could represent a late reversal reaction, not necessarily a relapse, in a BL patient who had taken 12 years of DDS. On the other hand, neither of our cases had any clinical features of a reversal reaction, that is, the lesions were uninflamed and there was no pain or neurological deficit.

In one of our cases there was evidence of recent down-grading on initial presentation and it is perhaps not surprising that silent (or symptomatic) up-grading occurs quite rapidly in this situation. However, it remains the case that both these patients have moved from being near-lepromatous to being tuberculoid, without an overt reaction, in approximately half the time found by Waters & Ridley.

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References

[1] Waters MFR, Ridley DS. Tuberculoid relapse in lepromatous leprosy. *Lepr Rev*, 1990; **61:** 353–65.

[2] Waters MFR, Ridley DS., Lucas SB. Positive Mitsuda lepromin reactions in long-term treated lepromatous leprosy. *Lepr Rev*, 1990; **61:** 347–52.

DISAPPOINTING EXPERIENCES WITH BLISTER–CALENDAR PACKS

Sir,

In the provincial leprosy control programmes of south and south-east Sulawesi, Indonesia, blister–calendar packs (MB-Combi and PB-Combi, produced by Ciba Geigy) have been used since 1990 for selected patients. Only patients in remote areas, where it is difficult or impossible to attend monthly clinics, are provided with blister–calendar packs for unsupervised MDT for a maximum of 3 months.

For these patients blister calendar packs have logistical and operational advantages over loose drugs, but our experiences with the MB-Combi packs have been disappointing.

Our patients often find it extremely difficult to remove the clofazimine capsules from the pack. In our experience clofazimine tends to stick to the plastic, which causes the capsules to rupture, even when gently trying to remove them. The 100 mg capsules are usually more difficult to remove than the 50 mg capsules. If patients without disabilities face problems, it can be imagined what difficulties are encountered by patients with a loss of sensation or other disabilities of the fingers.

It should be remarked that the climate in south, as well as in south-east Sulawesi, is warm and humid. However, with loose clofazimine in containers of 1000 capsules, we face few problems. For patients not eligible for blister–calendar packs we use small personal containers where the somewhat sticky clofazimine is mixed with DDS, which provides a powdery white coating to the clofazimine.

We would like to know if there are other control programmes facing similar problems with blister–calendar packs.

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P. LEVER

COMMENT: NASAL MYIASIS IN LEPROSY

Sir,

With reference to the paper on Nasal Myiasis[1] and the Letter to the Editor[2] on the same topic, I would like to report my experience, confirming that even today it is not an uncommmon problem. Between 1982 and 1991, while working at a leprosy hospital in western Maharashtra, I saw several cases each year of nasal infestation in leprosy patients. The majority were 'cured' BL or LL cases with atrophic mucosae, but some still had active disease. Most of our cases had slept outdoors but they were not all beggars. They walked unaided into the hospital, so they were not 'almost moribund', unable to flick the flies from their faces,[2] nor 'in chronic debilitated condition'.[1] Hence, I feel that, rather than their poor general physical condition, it was specific disability due to leprosy that predisposed them to nasal myiasis: first the loss of the sneezing reflex and second their inability to clean the nose properly on account of severe hand deformity.

Most of our patients presented with the complaint of bleeding from the nose and on examination they had a persistent sero-sanguineous discharge from the nostrils, with or without perinasal/periorbital oedema. Some complained of feeling the maggots moving in the nose and sinuses. All were acutely distressed, embarrassed, anorexic and unwell. They had often sought help elsewhere (Primary Health Centre or Civil Hospital) before coming to us.

Treatment such as described by Hussain *et al.*[1] was applied but we preferred Ether to turpentine as it is less nauseating to the patient, yet equally effective. Great importance must be paid to nursing care of such patients: besides skilful nasal lavage, and sympathy, the patient needs to be propped up in bed, to reduce facial oedema, and attention should be paid to fluid balance and oral hygiene.

Apart from fistulae to the skin, complications we saw included excessive bleeding and dysphagia. A lady with nasal infestation vomited about 1 litre of swallowed blood; 2 male patients had total dysphagia, even spitting out their saliva, and required intravenous infusions for 24–48 hours, both were found to have 'quinsy' due to infestation of the tonsils as well as the nose. Occasionally bronchitis followed infestation, presumably as a result of inhaling infected secretions, or debris.

Nasal infestation is largely preventable by adequate hygiene (e.g. daily salt water douching of the nose), but we can surely expect to see it occasionally for many years to come, since there is still a cohort of patients, who, although released from treatment, have residual damage which predisposes them to this condition. Such patients need to be taught nose care (as do newly diagnosed MB cases) and need help from a friend or relative if a hand deformity prevents adequate self care.

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References

[1] Hussain S. *et al.* Nasal myiasis in leprosy. *Lepr Rev*, 1991; **62:** 389–4.
[2] Ramanujam K. Comment. *Lepr Rev*, 1992; **63:** 295.

REPLY: TREATMENT OF SMEAR NEGATIVE MB PATIENTS WHO HAD RECEIVED PREVIOUS DAPSONE MONOTHERAPY

Sir,

With reference to a Letter to the Editor on the above topic (*Lepr Rev*, 1992; **63:** 185) I would draw your kind attention to the following:

Are the 'Smear negative MB patients' about whom we are talking really patients at all? Reference was made (*Lepr Rev*, 1991; **62:** 339–40) only to those individuals who for over a decade (quite often much longer) have shown no clinical, bacteriological or histopathological evidence of the disease. I see no scientific soundness in even calling them patients, notwithstanding the Cartel *et al.* (*Lepr Rev*, 1991; **62:** 186–92) reference and the Fiji experience reporting high relapse rates. It is those relapsing who pose a significant challenge to the progress made in leprosy control.

Also, even if statistics do finally point to higher relapse rates, i.e. in the range of 22–28% referred to above, how does that still justify multiple drug therapy in the remaining 70% of healthy individuals? It must be kept in mind that any drug whatsoever is potentially toxic and therefore must be avoided in all unwarranted situations. I would therefore suggest that even if for epidemiological reasons MDT were to be given in old monotherapy treated MB cases it must be done so only with the informed consent of the patient.

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Lepr Rev (1993) **64,** 174–175

Book Reviews

An Epidemiological Review of Pune Urban Leprosy Investigation Centre.

This book reviews 17 years of the operation of the Pune Urban Leprosy Investigation Centre Project, launched in 1974 by the Poona District Leprosy Committee, aiming at 'wiping out the problem of leprosy in urban Pune'. The book first describes the background and objectives of the project, which intends to deliver an integrated 'package' of services, including early detection and treatment of cases, prevention of dehabilitation and health education programmes to an urban population, with priority on schools and slum areas. It then describes the project itself, the population and geographical characteristics, and the type of treatment delivered to patients.

The review of data collected during the 17 years of programme operation is divided into 2 parts: pre-MDT period (1974–83) and post-MDT period (1984–91).

For the first period, estimates of prevalence and incidence rates are calculated for each year. Case-detection rates are calculated since inception of the programme, with a breakdown by area (schools, slums), age (children/adults), type of detection (survey, vountary reporting, contact) and type of leprosy (lepromatous/non-lepromatous). The number and percentage of cases with disability amongst registered cases are given for each year per age and leprosy type.

The post-MDT period is characterized by the adoption of MDT regimens given to *all* leprosy patients, stopping active case-finding surveys (in slums and schools) and a change in follow-up procedures. The number of cases are broken down for each year by age, sex, leprosy type (MB/PB) and mode of detection. The disability rates are calculated among new cases by age and leprosy type. Information is also given on the number of cases on MDT, number of cases released from treatment, number of relapses and number lost to follow-up.

The rest of the book describes mainly specific activities such as health education (type, content, beneficiaries), rehabilitation, training activities and a cooperative rehabilitation model. Finally, lessons learnt from these 17 years of operation are outlined, giving rise to future projects.

Numerous data have thus been collected over a period in this programme, covering various fields. Assembled here, they are interesting as they allow comparison over a period and give indications on trends, which is important and useful when assessing a control programme. For the pre-MDT period, the authors are aware of the limits and constraints of the data they present (especially concerning population data) and mention the difficulty of drawing definite conclusions out of them. It could have been interesting though to examine and compare pre- and post-MDT data. Also, a map of the area would have been useful to understand the facts and results of this project.

As a whole, with this comprehensive review of data for the last 17 years, this document gives extensive and valuable information on a longstanding urban leprosy control programme, which is very useful to assess trends in leprosy control over the years as well as to analyse the impact of treatment and rehabilitation of leprosy in an urban community.

J. M. Mehta, M. P. Dandare and D. G. Jogaikar

Poona District Leprosy Committee, 1992.

***Pioneering Steps in Leprosy Control*, by Bombay Leprosy Project, 1976–1991. (Booklet, 10 pp, 2 Figures.)**

The comprehensive leprosy control work of this project during the past 15 years is reviewed. The field studies on the prevalence of leprosy in metropolitan slum areas, among patients in the wards of general hospitals and in self-settled leprosy colonies were the first of their kind and serve as important models for similar situations.

Studies related to treatment, especially on MDT, have greatly influenced the strategy adopted in India at the national level.

The involvement of local medical colleges and general hospitals in leprosy control has been actively encouraged and this has led, on the one hand, to improved teaching of leprosy to medical students and, on the other, to the acceptance of leprosy patients at skin and STD clinics. Both these measures have constituted important steps towards the integration of leprosy control into the general health services.

The care and prevention of deformity has been an important aspect of the work and field studies on the use of prefabricated splints for the hand and epoxy resin 'grip-aids' have yielded valuable results. Municipal, government and private hospitals have been enlisted to provide facilities for reconstructive surgery for leprosy patients and an integrated rehabilitation training programme has been established.

***Bombay Leprosy Project—'As Others See'*. (Booklet, 28 pp.)**

This is a companion booklet to the above and is a collection of impressions recorded by visitors to the project and compiled by the Director, Dr R. Ganapati. It is noteworthy that this project has attracted visitors not only from India but also from other parts of the world and it is to be hoped that both these small publications will encourage many more workers, especially those dealing with the control of leprosy in an urban setting, to see for themselves what can be done and the practical methods of doing it. This review would be incomplete without noting the very fine tribute paid to the leprosy voluntary agencies which have given financial support and encouragement to the project and its staff.

H. W. Wheate

***Proceedings of the National Workshop on Foot Care in Leprosy*, Bombay, 7–8 April 1990.**

This Workshop was organized by the Bombay Leprosy Project and sponsored by the Danish International Development Agency. Its objective, set out at the outset, was to reduce and prevent disability due to foot problems. The opening papers emphasized that the care of the insensitive foot needs to be constant and continuous and can therefore be carried out only by the patients themselves, who must be given the appropriate instructions. A total of 11 short papers, all relevant and of high quality, were presented and discussed. A review of the biomechanics of the normal foot is clear and concise. Neuritis and its medical and surgical management are discussed and good results of posterior tibial nerve decompression are presented. The deformities of the foot other than plantar ulceration and their management are described. That protective footwear should be both effective and acceptable is exemplified by the report of a new type of mass (factory) produced plastic sandal. The rehabilitation measures to achieve maximum restoration of function are well covered. There are brief papers on disability prevention through community participation and on disability and stigma. A short report on the effectiveness of simple orthoses made of thermoplastic material is of practical interest and the final papers deal with the surgical management of plantar ulcers and a field approach to foot care, the latter naturally oriented to the conditions of rural India. The programme concludes with a number of practical recommendations on both strategy and research.

This booklet should be studied by all who are treating leprosy out-patients whether in hospital or in the field.

H. W. Wheate

Lepr Rev (1993) **64,** 176–178

Teaching Materials and Services

Schieffelin Leprosy Research and Training Courses, Karigiri, 1993

Schedule of Courses for 1993

Course	Qualifications	Duration	Commencing date
Medical Officer			
(a) Condensed course in leprosy	Doctors and senior medical personnel	1 week	Apr. 5–10 Nov. 1–6
(b) Medical students' course	Undergraduates	1 week	*October/ November
(c) Medical officers' course	Medical personnel engaged in Leprosy work	6 weeks	Jan. 18–Feb. 27 Jul. 5–Aug. 14
(d) Special course for ophthalmology teachers		3 days	*(Proposed)
(e) Ophthalmic aspect in leprosy	Qualified medical personnel (included in 6 week course)	4 days	Mar. 1–6
Other Categories			
(a) Non-medical supervisors' course	Qualified paramedical workers with a minimum of 3 years' experience	2 months	Mar. 8–May 8
(b) Orientation course in leprosy	For paramedical personnel (nurses, physios, O.T. and administrators)	1 month	Apr. 5–30 Nov. 1–27
(c) Paramedical workers' course	+2 passed graduates preferred (with science subjects)	4 months	Aug. 16–Dec. 18
(d) Physiotherapy technicians' course	+2 passed or P.U.C. (with science subjects)	9 months	Jun. 2
(e) Laboratory technicians' course	+2 passed science graduates preferred	12 months	Jun. 12
(f) Prosthetic technicians' course	+2 passed or P.U.C. (with science subjects)	18 months	Jan. 4 Jul. 7
(g) Shoe-makers' course	V standard with knowledge of English preferred	6 months	Jan. 4 Jul. 7
(h) Smear technicians' course	+2 passed (with science subjects)	3 months	Jan. 4 Jun. 7 Sept. 13
In-Service Training			
(a) Advanced course in leprosy control	Selected, experienced medical supervisors	12 months	By arrangement
(b) Medical record keepers	+2 passed with proficiency in typing and good English	2 months	By arrangement
(c) Inservice training in med., surgery, pathology, lab. technology & epid. and lep. control	For qualified medical personnel	3 months	By arrangement

Note: * for latest information, please contact the Training Officer. Refresher courses for all categories by special arrangement.

English fluency is essential. The courses are recognized by the WHO and the Indian Government (all paramedical and technical courses are fully recognized by the Indian Government). Some accommodation is available.

For further details contact: Training Officer, SLRTC, SLR Sanatorium PO, Karigiri 632 106, Tamil Nadu, India. Tel: (0416) 21522. Grams: 'Lepsearch' Vellore-7.

NB. For courses that have already taken place it is possible that they may run again in 1994.

AHRTAG and ICH—primary health care resources and training

AHRTAG (Appropriate Health Resources and Technologies Action Group) has been working since 1977 to support staff working in primary health care programmes in developing countries. AHRTAG:

has a primary health care resources and information centre open to visitors by appointment,
provides an international enquiry service for health and rehabilitation workers,
provides an audiovisual service consisting of a photographic, video and slide library,
publishes a wide range of practical newsletters, manuals, resource lists and training directories on health issues,
collaborates with primary health care organizations on developing resource centre and publications activities,
supports the development of international health information networks,
organizes courses and workshops for health workers

For more information please contact AHRTAG, 1 London Bridge Street, London SE1 9SG, UK. Tel: 44 71 378 1403; Fax: 44 71 403 6003 E-mail: GEO2: AHRTAG.

ICH (International Child Health Unit) belongs to the University of Uppsala, Sweden. It is committed to the promotion of health in developing countries by:

- training doctors, nurses and rehabilitation personnel for work in developing countries,
- carrying out research on child health and development and on nutritional deficiencies that may lead to various dysfunctions and disabilities,
- advising national and international organizations in development co-operation on projects for and with disabled people,
- providing library and information services, among these the one on disability and rehabilitation in collaboration with AHRTAG.

SIDA, the Swedish International Development Authority, which supports health and rehabilitation projects in African and Asian countries, is the main funding agency of ICH.

For more information please contact ICH, University Hospital, S-751 85 Uppsala, Sweden. Tel: 46 18 66 59 96, Fax: 46 18 50 80 13

ECHO: Joint Mission Hospital Equipment Board Ltd, UK

For over 12 years, ECHO has been providing a comprehensive medical supply service to mission, charity and government hospitals, rural health care units and medical relief and emergency programmes outside the UK. As a Christian charity, ECHO provides these services world-wide on a non-profit basis regardless of race, caste or creed. The *Pharmaceutical Price List* shows all items normally held as stock in the warehouse. Most other drugs and vaccines (including veterinary items) are also available and prices can be given on request for specific items. ECHO does not supply second-hand or surplus drugs or any drugs whose use is banned in the UK. Further enquiries: ECHO International Health Services Ltd, Ullswater Crescent, Coulsdon, Surrey CR5 2HR, England. Telephone 081-660-2220; fax 081-668-0751.

Centre for World Development Education (CWDE) Worldaware Education Catalogue

This exciting collection of materials for development education has just been revised. The resources listed include teaching packs, books, leaflets, maps, posters, slides and filmstrips, videos, classroom games, and computer software. All are designed to enhance young people's awareness and understanding of world development issues and of sustainable development. CWDE is an independent educational agency that promotes education about world development issues and the interdependence of developed and developing countries. The orientation of some materials towards students in industrialized countries, particularly Britain where CWDE is based, does not undermine their relevance to learning situations in other parts of the world.

Further information on CWDE and copies of the *Worldaware Education Catalogue* may be obtained from:

Centre for World Development, 1 Catton Street, London WC1R 4AB, United Kingdom.

School of Medical Education, New South Wales, Australia

The School conducts postgraduate academic programmes at Masters and Doctoral levels and also arranges special programmes and short courses to meet specific needs.

Degree courses available:

Master of Health Personnel Education (by coursework or research); Master of Clinical Education; Graduate Diploma of Clinical Education; Master of Public Health (by coursework or research); Doctor of Philosophy.

The School also undertakes research and development activities focused on educational development, management development and health promotion.

The School is unique in its strong orientation to international health development. The staff and graduate students represent a wide range of health-related disciplines from many different cultures. Through its affiliation with WHO and other international organizations the School participates in field activities in developing countries.

Mission

The School of Medical Education/WHO Regional Training Centre aims to contribute to the promotion of national and international health through the development of the health professions. Its main goals are:

- to improve capabilities in teaching and educational planning;
- to design educational programmes directed to national health priorities;
- to conduct research focused on the development and application of health professions' education and management;
- to improve capabilities and systems for workforce planning;
- to improve the management of human resources in health;
- to improve capabilities in planning, management and evaluation of health services;
- to cultivate institutional leadership and responsiveness to changing requirements of health systems;
- to promote staff development and in-service training of the health professions;
- to develop community-based education programmes and health promotion.

School of Medical Education, WHO Regional Training Centre, University of New South Wales, PO Box 1, Kensington NSW 2033 Australia, Phone (02)697 2500 Fax (02) 663 4946

Lepr Rev (1993) **64,** 179–184

News and Notes

Auto-destruct syringes

The following information is extracted from No. 13 (1992) of *Essential Drugs Monitor*:

An auto-destruct syringe is a disposable syringe that after 1 use cannot be re-used. This new technology has recently been introduced into many EPI programmes. As 5 of the 6 vaccines used in the EPI are administered by injection it was considered a priority that injections given for vaccination be of the highest safety standards. The injections given with the EPI syringe are simple as the dose is a standard volume. Auto-destruct syringes for the injection of other essential drugs are not currently manufactured but could be made available.

Auto-destruct syringes provide good protection against cross-infection to the patient but new risks will be introduced if there are any stock shortages. If health workers use all the auto-destruct syringes and still need to give injections they will be unable to do so. Some health workers may stop giving injections. Others may seek out the few conventional disposable syringes remaining and reuse them repeatedly. The EPI recommends that each health centre using auto-destruct syringes should have an emergency contingency supply of sterilizable syringes and sterilizer as a back-up in the event of stock shortages.

The introduction of auto-destruct syringes into a programme normally using standard disposable syringes does not represent a change in policy. It is merely an additional step to reinforce the inherent safety of disposable syringes after use.

In summary all 3 methods have economic and/or safety advantages and disadvantages:

The reuse of syringes and needles after sterilization is usually culturally acceptable, the risk of not having sterile syringes and needles available when needed is greatly reduced, and the cost is the most advantageous at about US$0.02 per injection. However, if steam sterilizers are not available in the health centre, problems may arise through inadequate disinfection practice. Fuel supply can also represent a problem in some areas—particularly rural parts of the country without access to electrical supply.

Standard disposable syringes provide a very high degree of assurance of sterility when first used but are subject to abuse. They are moderately expensive at about US$0.05 per injection.

Auto-destruct syringes also provide the same high degree of assurance of sterility but are safer since they cannot be reused. However, this is the most expensive method of all, costing about US$0.13 per injection, which will be beyond the means of many health services. It should only be considered when disposable syringes are required but there is no assurance that standard disposable syringes will not be reused.

The Essential Drugs Monitor is produced and distributed by the WHO Action Programme on Essential Drugs and Vaccines and is published in English, French and Spanish. Since the Action Programme was launched in 1981, more than 100 countries have either drawn up essential drugs lists or started projects in support of primary healthy care, providing reliable essential drugs and vaccines which:

meet people's common health needs;
have significant therapeutic value;
are acceptably safe;
offer satisfactory value for money.

All correspondence should be addressed to:
The Editor, *Essential Drugs Monitor*, World Health Organization, CH-1211 Geneva 27, Switzerland.

HealthNet and SatelLife, Cambridge, Massachusetts, USA

The following information is extracted from *International Development Research Centre Reports* (IDRC), Vol. 20, No. 3, October 1992 under the title 'Help from above':

'HealthNet is an innovative use of satellite technology that will transmit medical information and enable physicians to communicate with their colleagues throughout the world'.

HealthNet was begun by SatelLife, an international, non-profit organization based in Cambridge, Massachusetts that aims to address health information and communication needs in the developing world. SatelLife chose to use low-earth orbit satellite technology to accomplish its goals.

IDRC is collaborating with SatelLife on the HealthNet project. This is a natural partnership; IDRC has been promoting the use of this technology since the early 1980s because of its interest in exploring the potential use of satellites to improve communication to and from the developing world.

Built by Surrey Satellite Technology Ltd. at the University of Surrey in the UK, the HealthNet satellite is designed to transmit information to and receive messages from ground stations based at medical institutions in Africa and other regions of the world.

Africa, with its severe communication problems, stands to benefit most from HealthNet's technology. Expensive and unreliable telephone systems, non-existent transmission lines, and costly medical literature make it hard for African physicians to keep abreast of recent medical developments and communicate with other health professionals.

Examples of communication difficulties abound. There are more telephones in Manhattan than on the entire continent of Africa.

Africa also suffers from a dearth of medical information. Financial constraints have forced medical libraries to cut their journal subscriptions; in some cases, the most recent acquisitions date back to the 1970s. In Uganda, where AIDS is a major health concern, current information on the virus is scarce. The first journal article on AIDS was published in 1981 and Makerere University, once considered the jewel of African medical institutions, has not been able to pay for a periodical since 1980.

The satellite that can transcend national boundaries is no bigger than a beach ball. It revolves around the earth in a 800-km orbit 14 times each day, sending out a continuous signal that is picked up by a modified amateur (HAM) radio attached to a personal computer. Once the signal is recognized, a message transfer takes place between the satellite and the ground station. When in range of a ground station, the satellite can transmit about 30 pages a minute.

In Africa, ground stations have been licenced in Congo, Ghana, Kenya, Mozambique, Tanzania, Uganda and Zambia. They are operating in all these countries, with the exception of Ghana where a station is in the process of being established. In total, 15 African countries are expected to participate in the project being funded by IDRC.'

For further enquiries write to: Dr Charles Clements, Executive Director, SatelLife, 126 Rogers Street, Cambridge, Massachusetts, 02142, USA.

Current global situation on the HIV/AIDS pandemic: WHO

The following summary has recently been received from the Global Programme on AIDS, WHO, Geneva:

'The World Health Organization (WHO) currently estimates that a cumulative total of 10–12 million adults and 1 million children worldwide have been infected with the human immunodefi-

ciency virus (HIV) since the beginning of the epidemic. The total of 11–13 million infected men, women and children includes approximately 1 million persons who were newly infected with HIV during the first 6 months of 1992.

The regional distribution of cumulative adult HIV infections is as follows: sub-Saharan Africa has over 7 million infections; North America and Latin America, including the Caribbean, have over 2 million; South and South-East Asia have over 1 million; Europe, including the countries comprising the former Soviet Union, has over 500,000; North Africa and the Middle East have about 75,000; Australasia has over 30,000; and East Asia and the Pacific have approximately 25,000.

Of the 1 million persons newly infected since January 1992, about one-half live in sub-Saharan Africa, about one-quarter live in Asia and the Pacific (the vast majority in South and South-East Asia), and a little more than a tenth live in Latin America and the Caribbean. It is estimated that nearly one-half of new adult infections have occurred among women.

As of 1 July 1992, a cumulative global total of over 500,000 adult AIDS cases have been reported from 168 countries; however, WHO estimates that when underdiagnosis, under-reporting, and delays in reporting are taken into account, the actual number of adult AIDS cases may be closer to 1·7 million. It is estimated that over half of all adult AIDS cases thus far have occurred in sub-Saharan Africa. Of the 1.7 million adults having developed AIDS since the start of the epidemic, the vast majority have most likely died.'

Preliminary recommendations on the use of surgery for the treatment of leprosy neuritis: ILEP

The above article appeared in the *Medical Bulletin* No. 4, which is published by the International Federation of Anti-Leprosy Associations (ILEP), 234 Blythe Road, London W14 0HJ. The following, which is taken from this article, appeared under a subheading entitled, 'Caution concerning the use of surgery for the treatment of leprosy neuritis':

1 The place of direct nerve surgery in prevention of deformities

Deformities and disabilities are the consequence of leprosy neuritis, thus the best prevention of deformities is:

- First, the early detection and treatment of as many patients as possible,
- Then, the early detection and appropriate treatment of reactions which involve the nerves.

The therapy of leprosy now uses well-tried MDT regimens and new drugs for treatment of both uncomplicated disease and leprosy reactions. Unfortunately, chemotherapy is not always used early enough, is not always well conducted, well tolerated or well followed.

In addition, anti-inflammatory treatment, even with corticosteroids (or thalidomide in ENL neuritis), cannot always relieve inflammation of nerves nor the mechanical compressions which occur in a thickened sheath, especially where the inflamed hypertrophied nerve passes through an unyielding osteo-fibrous tunnel and this also contributes to the destruction of nerve bundles.

Thus, *when medical treatment alone is not sufficient to relieve nerve damage*, it is clear that mechanical compression could be relieved by opening the tunnel and incision of the thickened sheath.

This nerve surgery has a long history and has been claimed to give good results when performed before the damage becomes irreversible.

However many therapists still have doubts about the efficiency of nerve decompression. They think it is not possible to determine whether nerve surgery will give better results than medical treatment alone.

There are 3 main explanations for their doubts:

- Even if for more than 30 years, good results of nerve surgery in leprosy have been reported by many authors, these authors have not had the same data and methods of evaluation. In particular, the duration or the type of neuritis and the duration of follow-up have hardly been specified. Furthermore, all surgeons have not had the same facilities and not all have used the same indications for surgery. Many of them have practised full-time in the hospitals of main cities, in institutes, or in research centres and some of them have practised in the field, in provincial or district hospitals.
- Sometimes, quite sincere therapists, who have asked surgeons for nerve decompression, have thought the immediate result of surgical decompression was a failure because they do not know that recovery is not immediate. Usually recovery duration may take some months or even 1 year for the ulnar nerve.
- Many authors have reported good results with medical treatment alone and they consider that the need for both external and internal nerve surgical decompression has been very much reduced. Nevertheless, it may be observed:

  —that medical treatment alone may have drawbacks
  —that in some published cases (but how many are unpublished?) of corticosteroid treatment, sometimes prolonged for more than 1 or even 2 years, there was no recovery. If nerve surgery is then subsequently performed, it has no utility.

In some of those cases, in which pain is finally relieved, it could be said that medical treatment alone has finally brought an improvement. However, decreased pain is not necessarily an indication of improvement of the nerve because pain may decrease as nerve function decreases.

In these cases, earlier surgical nerve decompression might have given recovery and therefore shortened the corticosteroid treatment duration of neuritis.

Indeed, some *good* results of MDT in a country where experienced surgeons are available have recently been reported *with no record of disability over grade 1.* What will be the evolution of these grade 1 disabilities in 3 or 5 years?

2 Research study on the place of surgical nerve decompression

Over 2 years ago, it was proposed to the ILEP Medical Commission to undertake a complementary investigation on *direct nerve surgery.* This proposal which was originally put forward during the ILA Hague Congress in September 1988 was accepted.

This multicentred and comparative study has to be undertaken with:

- statistically significant trials despite the large number of variables
- a necessarily long follow-up

And the objectives are:

- to compare surgical decompression with treatment of neuritis by medical treatment alone
- to confirm whether nerve surgical decompression is effective (when medical treatment is not sufficient to improve nerve damage)

So far, not one of these results has been supported by a convincing controlled study. However, at the time when the ILEP Medical Commission Therapy Discipline is developing a research study on *Reversal Reaction Treatment in Borderline (BT–BL) Leprosy*, this seems a good opportunity for a study on *The Place of Nerve Surgery for Better Treatment of Reaction Neuritis.* It could be conducted by the ILEP Rehabilitation Discipline in liaison with the Therapy Discipline research study.

Co-ordination of these trials will make the comparative study easier, broader, quicker and an assessment of the results by both surgeons and therapists more objective and less debatable.

3 Recommendations on indications and techniques now agreed for nerve surgery

Until the results of a multi-centre trial on the value of surgical decompression are reported, only basic recommendations are possible.

The recommendations listed below were agreed by a working group of the Rehabilitation Discipline of the ILEP Medical Commission which met between 5 and 6 July 1990 in London:

Recommendations

- In a certain number of cases *in addition to medical treatment*, surgery may be required for the prevention/recovery of nerve damage
- Surgery *without medical treatment is not recommended*
- The technique of surgery *should not be undertaken by untrained medical personnel*
- The following surgical techniques are *not recommended*:
  - Nerve decapsulation
  - Complete fascicular neurolysis
- The following conditions are *not acceptable*:
  - Surgery done by therapists who are not surgeons
  - Surgery without strict asepsis
- Neither surgical nor medical treatment should be undertaken without standardised pre- and post-treatment VMT and ST assessments of nerve function.

[The original text was prepared by Professor P. Bourrel.]

Further progress in leprosy control: Orissa, India

The Directorate of Medical Education and Training of the State Government, in association with the Damien Institute and the Health Education Unit of the Gandhi Memorial Leprosy Foundation (GMLF), recently organized a further series of meetings and orientation courses in Orissa in order to increase the coverage of multiple drug therapy (MDT), using the 'modified' system (see *Leprosy Review*, **63,** number 3, September 1992, page 288)—2-day courses were held in the districts of Kalahandi and Keonjhar, attended by a total of about 100 doctors from primary health care centres, with emphasis on the operational changes needed in order to detect, diagnose and allocate cases to pauci- or multibacillary regimens, using modified MDT through the primary health care system. A meeting was also held in Cuttack Medical College, attended by professors and heads of departments, many of whom have contributed through the years to the training of medical students in leprosy, and who have recently participated in meetings concerned with the revision of a GMLF publication: *Intensification of teaching of leprosy to medical students*, due to appear in early 1993.

Orissa, a high-endemic area of India, is now making excellent progress in leprosy control. A high percentage of the known, registered cases are either taking, or have completed MDT and the 2 districts mentioned above started implementation in January 1993. Only 2 districts then remain and these should start MDT later in 1993. There is excellent and continuing co-operation between the above Directorate, the Directorate of Health Services, the Government Training Centre at Aska, the Health Education Unit of GMLF at Jatni (not far from Bhubaneswar), the Damien Institute, DANLEP (DANIDA assistance to the National Leprosy Eradication Programme) and other non-government organizations. Teaching, training and orientation courses for leprosy in Orissa, together with health education, are all in advance of what is currently available for other public health problems of comparable importance. Teaching and learning materials, including the translation of several items into Oriya, are available and have been distributed. Finally it is encouraging to report that statistical information from the districts, coming to the Leprosy Cell of the Directorate of Health Services in Bhubaneswar, is both up-to-date and accurate, and more than adequate as a baseline for monitoring the progress of leprosy control in Orissa, hopefully towards an elimination level. [*Source*: A. Colin McDougall, Oxford, UK.]

Personal protection against malaria

The Guardian newspaper has recently drawn attention, yet again, to the problem of effective protection against malaria. Fears have been expressed by experts in this field that existing drugs for chemoprophylaxis may become ineffective within 5 years, due to the increasing incidence of drug-resistant strains. Specialists now stress that most of the cases being diagnosed every year in the UK could be avoided:

- Keep arms and legs covered after sunset.
- Sleep in screened accommodation or mosquito nets. (*The Lancet* recently reported that the use of insectide-treated bed-nets in Gambia had reduced malaria deaths among young children by up to 30%.)
- Use insect repellants and knockdown sprays.
- Seek medical help immediately if you develop a fever or feel ill on returning home.

Under the heading of 'Prophylaxis against malaria for travellers from the United Kingdom', the subject was reviewed in detail (Malaria Reference Laboratory and Ross Institute) in the *British Medical Journal*, 28 October 1989, pages 1087–89. A recorded information service on malaria prophylaxis, for all areas of the world, is run by the London School of Hygiene and Tropical Medicine on 071 636 8636. A wide range of products to protect against stinging and biting insects is available from Masta, Medical Advisory Service for Travellers Abroad Ltd, Keppel Street, London WC1E 7HT, UK, including impregnated mosquito nets for children (cots) and adults.

Errata—Weber *et al.*

The following corrections are for the paper by Weber, Van Soest, Neff, Chiang and Pfau entitled 'Results of surgical procedures for the correction of foot-drop and of lagophthalmus due to leprosy'. The paper was published in Volume **63**, pages 255–262:

p. 255, Summary, line 4, after lagophthalmus insert 'with the transposition of the temporalis muscle or for footdrop'.

p. 259, line 3, for '15–300°' read '15–30°'.

The figure captions should read as follows:

Figure 1. Tibialis posterior transposition. Ability to lift the foot above the neutral position (n = 25).

Figure 2. Temporalis transposition. Remaining gap when the eyes are intended to close (n = 33).

Figure 3. Social situation, the means of living are provided by: (men, n = 31; women, n = 8).

Addendum—Letter to the Editor, Sugita *et al.*

The authors would like to add N. Ishii to the list of authors for the Letter to the Editor entitled 'Rapid healing of a chronic wound surrounded by hyperkeratosis in a leprosy patient after hydrocolloid occlusive dressing' published in Volume **63**, pages 379–382.

Leprosy Courses, Fontilles, Spain, Autumn 1993

Sanatorio de Fontilles are running 2 courses which are to be held in Fontilles, Alicante, Spain: (1) for auxiliary staff between 18 and 30 October 1992; and (2) for paramedical workers between 15 and 20 November 1992.

For further details write to: Dr J Terencio de las Aguas, Sanatorio San Fco, de Borja, 03791 Fontilles, Alicante, Spain.