Multidrug therapy against leprosy

Development and implementation over the past 25 years

World Health Organization
Geneva
2004

WHO Library Cataloguing-in-Publication Data

Multidrug therapy against leprosy : development and implementation over the past 25 years / [editor]: H. Sansarricq.

1.Leprosy - drug therapy 2.Leprostatic agents - therapeutic use 3.Drug therapy, Combination 4.Health plan implementation - trends 5.Program development 6.World Health Organization I.Sansarricq, Hubert.

ISBN 92 4 159176 5 (NLM classification: WC 335) WHO/CDS/CPE/CEE/2004.46

Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

Acknowledgements

The Editor wishes to thank the persons listed below for their special written contributions and for providing background data.

Dr H. Sansarricq, Editor

Contributors

Dr V.L. Gomes de Andrade (Brazil); Mrs S.S. Griño (Philippines); Drs Kyaw Lwin, Tin Myint, Mg Mg Gyi, Mya Thein, Tin Shwe, Kyaw Nyunt Sein (Myanmar); Professor M.F. Lechat (Belgium); Dr L. Levy (Israel); Dr S.K. Noordeen (India); Dr S.R. Pattyn (Belgium); Dr C.K. Rao (India); Dr L. Some and Dr A. Tiendrebeogo (Burkina Faso); Professor S.J. Yawalkar and Mrs P. Grewal (Switzerland); Dr Y. Yuasa (Japan).

WHO Secretariat

Dr D. Daumerie; Dr V. Pannikar.

* * * * * * * * * * *

The Leprosy Programme would like to pay special tribute to Dr Hubert Sansarricq.Using his broad knowledge of the Programme's work, he participated extensively in the preparation of the report, generously dedicating much of his time to this substantial undertaking.

Special thanks are also addressed to our English Editor, Mrs Sarah Balance.

Foreword

It is an honour and a pleasure to be invited to write the foreword of this report on the development and implementation of multidrug therapy (MDT) against leprosy. MDT has transformed leprosy from being a scourge of humankind into a curable disease. But unfortunately leprosy still remains a *neglected* disease. Despite scientific and technological developments, investment in neglected diseases – by the pharmaceutical industry, personnel-training agencies, governments, research institutes, etc. – is still far too small, while important gaps in knowledge still remain, preventing the full deployment of MDT and the development of additional and complementary interventions.

In spite of this, the global policy for control of leprosy has had a major impact since 1981, when the World Health Organization (WHO), supported by the WHO Expert Committee on Leprosy, officially recommended that endemic countries adopt MDT.

Within the recommendations on use of WHO MDT was an explicit proposal to reorganize the health services and a great incentive to decentralize leprosy control activities in the general health services. Together, these three actions would greatly benefit leprosy control: use of MDT would address primary and secondary resistance to drug monotherapy and prevent the emergence of resistant *Mycobacterium leprae*; the second and third actions would allow close monitoring of patient treatment, greater coverage of affected populations by control activities, and hence greater access of leprosy patients to medical care. The first results were so positive that, in 1991, the World Health Assembly approved resolution WHA44.9 – *Elimination of Leprosy as a Public Health Problem by the Year 2000* – elimination being defined as a prevalence rate of less than one patient per 10 000 population.

The contribution of research to the development of MDT and to the generation of future interventions cannot be underestimated; it is carefully described in this report and other publications (*1*). The first possibility for serious study of *M. leprae* – a microorganism that does not fulfil Koch's postulates and cannot be grown in vitro – arose with the techniques developed by Shepard and Rees in the 1960s. Since then, advances in the biomedical sciences have radically changed the situation: decoding of the *M. leprae* genome (*2*) and its comparison with that of *M. tuberculosis* (*3*) have allowed these two pathogens to be studied through genomics and proteomics applications, opening new ways to study disease transmission and pathogenesis, and allowing the development of new diagnostic and therapeutic approaches as well as the management of reversal reactions, powerful triggers of the physical disabilities that constitute such important elements of the disease that lead to patient isolation.

This report also demonstrates that many lessons have been learned and great progress has been achieved, both in research and in leprosy control. Although the year 2000 came and went without the originally planned target being met, the huge effort of implementing MDT has been rewarded: more than 12 million patients have been cured.

This is the best reward that the thousands of concerned health professionals, nongovernmental organizations, governments, and intergovernmental agencies such as WHO and PAHO could wish for.

It is now time to move forward. The lessons of history described in this report should guide us in the discussion and establishment of new goals, priorities, and targets that will shape the continuing battle against leprosy in this new millennium.

Carlos M. Morel *Geneva, October 2003*
Director, TDR

References

1. Milleron R, Fujisaki T, Reich M. *TDR's contribution to the development of multidrug therapy for leprosy: a report*. Geneva, World Health Organization, 1998 (document TDR/ER/RD/98.4).
2. Cole ST et al. Massive gene decay in the leprosy bacillus. *Nature*, 2001, 409:1007–1011.
3. Cole ST et al. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature*, 1998, 393:537–544.

Introduction

The saga of dapsone

M.F. Lechat

For centuries, the care of leprosy patients was mired in ignorance, prejudice, and denial. Universal fear led to "lepers" being isolated, couples separated, and children removed from their parents. While isolation may not have been entirely ineffective in reducing the transmission of the disease, it was often a tragedy for the patients, leaving them with no hope of cure or redemption, for no treatment existed at the time.

The only drug available was chaulmoogra oil, extracted from the nut of a tree native to India, where it had been used for centuries. Administered as an ointment, by injection or by mouth, chaulmoogra oil was, in the words of one leprologist, given "externally, internally and eternally" – but to no great avail, since it was largely ineffective.

For the majority of leprosy patients, isolation was shown to be pointless. There are now known to be two main clinical types of leprosy. In 1936, in Cebu, Philippines, Doull et al. (*1*) demonstrated that patients affected with one of these types – corresponding roughly to what would today be called paucibacillary leprosy – had a very low potential for transmitting the disease. Segregation of those patients was thus irrelevant.

In 1941, Guy Faget, the medical officer in charge at the U.S. National Leprosarium in Carville, Louisiana, took it upon himself to administer Promin® to a number of volunteers (*2*). Promin® is a drug of the sulfone group, which had been shown to confer some protection to guinea-pigs infected with human tuberculosis bacilli (*3*). Patients improved dramatically, and effective treatment of leprosy became a reality. Indeed, it was said that demonstration of the effectiveness of the sulfone constituted the most dramatic event in the history of leprosy since the discovery of the leprosy bacillus by Hansen, a Norwegian physician, in 1873 (*4*)

Faget, however, in his seminal report published in 1943, was cautious in his conclusions. He wrote: "As yet no case of leprosy has become arrested under its influence… It is hoped that further synthesis of sulfa compounds may produce a substance which will succeed in saving countless lives in this still dark field of medicine." How visionary this simple statement was to prove.

In a narrative written several years later, Stanley Stein, a Carville patient, gave a vivid description of this first experimental programme of sulfone treatment (*5*). Initial scepticism on the part of the volunteers, who were more ready to try remedies such as an elixir of herbs steeped in kerosene than to submit to cautious clinical trials, was followed by the enthusiasm of the patients who flocked to try the new drug. This account reflects both the despair of those who, until this time, had been abandoned to a therapeutic "vacuum", and their relief at being liberated from chaulmoogra oil. It is hard nowadays to imagine the life of leprosy patients before chemotherapy brought them deliverance from antiquated drugs.

It is interesting to note that sulfones, had been synthesized much earlier, at the beginning of the century (*6*), but for the next 30 years had remained, so to speak, on the shelf. Had a laboratory model been available for *Mycobacterium leprae*, it is a safe bet that sulfones would have been tested for their potential effectiveness against the organism. In the absence of such a model, millions of patients lived and died with Hansen's disease for a third of a century. This should serve as a reminder of the importance of research for the timely and appropriate application of technical developments.

Promin® and other similar derivatives were the first sulfones to be used, because 4,4´-diaminodiphenylsulfone (DDS, dapsone), the parent compound, was considered too toxic. It was not until 1947 that dapsone was administered in leprosy (*7*, *8*). Subsequently, it entirely replaced its derivatives. While dapsone should have been the first sulfone shown to possess activity against *M. leprae*, it was not advocated for the treatment of leprosy until its derivatives had been in use for about 10 years. The reason was insufficient pharmacological knowledge of sulfone metabolism – yet another example of the difficulties of applying new therapy when basic knowledge is wanting.

The availability of sulfones led the way to the ambulatory treatment of leprosy. By the early 1950s, the stage was set for a massive attack on the disease through chemotherapy. The task ahead was immense. The number of patients worldwide was variously estimated at 10–12 million and even 15 million (*9*); in some areas of Africa, prevalence was approaching 2% – that is, 1 person in 50 had the disease (Lechat, 1956, unpublished data).

Dapsone was particularly well suited to ambulatory treatment (*10*). It is given by mouth, which requires no equipment and makes on-the-spot administration easy. It is effective when taken weekly, which simplifies the treatment of a large number of patients and makes it achievable with relatively few staff. Moreover, the drug has a long shelf-life, which reduces the likelihood of logistic difficulties.

Thus began the saga of dapsone for the control of leprosy. All that was needed was a paramedical worker – travelling on a bicycle, on a motor scooter, by camel, by canoe, or on foot – to distribute tablets by the handful to patients gathered under a tree, along the road, or at a river-crossing.

The United Nations Children's Fund, UNICEF, was called upon to provide both antileprosy drugs and drugs to deal with side-effects, certain laboratory and clinical equipment, and – most importantly – transport (cars, motorcycles, bicycles) (*11*) Where no dispensaries existed or local conditions precluded the deployment of mobile teams, untrained laypersons were coopted to distribute tablets; in some cases, large quantities of tablets for self-medication were provided to patients who travelled for many days to receive their monthly or quarterly supply of dapsone.

This was a time of great enthusiasms and great expectations. Throughout the world, thousands of workers were engaged in intensive case-finding and early treatment. With enough enthusiasm, enough workers, and enough transport, it looked as if every patient would have access to the weekly dapsone dose of the drug over a number of years – and that, eventually, the disease would disappear.

Concern for an epidemiologically based objective in treating patients was expressed by the Panel on Leprosy Control on the occasion of the Eighth International Leprosy Congress in Rio de Janeiro in 1963:[1] "Regular and prolonged sulfone treatment, generally over several years, reduces infectiousness in the majority of cases. It follows, that if a considerable proportion of bacteriologically positive patients are treated, the disease will decline."

The rationale for this control strategy was quite sound. Since there is consensus that the disease is caused by *Mycobacterium leprae* and that patients with the disease constitute the sole reservoir for the microorganism, destruction of all *M. leprae* through treatment of all patients should put an end to transmission of the disease. Two conditions had to be met – early detection, and appropriate and regular treatment of patients. And the strategy worked. Patients were cured, or at least improved considerably, by the thousands. Moreover, the face of leprosy changed dramatically. Severely crippled patients and the florid, so-called leonine, faces that were a common sight 50 years earlier were no longer seen. However, the results of dapsone monotherapy during the first decade of its use have not been properly evaluated. While dapsone was probably responsible for the discharge from care of large numbers of patients, the drug has several drawbacks. It is slow-acting and takes several years to render lepromatous patients bacteriologically negative. As a consequence, compliance with treatment was poor.

Furthermore, dapsone was always considered to be toxic, particularly when administrated orally. Attempts made several years earlier to treat severe streptococcal infections in man, using daily doses of 1–2 g, had led to severe secondary effects (*12*) – hence the caution recommended in the treatment regimens for leprosy. According to the first report of the WHO Expert Committee on Leprosy (*13*), doses should not exceed 600 mg per week. The complications most feared included anaemia, severe psychosis, and an exfoliative dermatitis (*14*). Reactions such as erythema nodosum leprosum (ENL) were reportedly frequent and serious, especially at the beginning of treatment. To prevent these complications, it was recommended that the initial dosage should be low and increased very gradually, over several months. Chemotherapy had to be discontinued if a reaction occurred, and subsequently resumed following a still more conservative schedule.

During the first two decades of sulfone therapy, the tendency was therefore to use lower and lower doses, as is clear from successive reports of the WHO Expert Committee on Leprosy in 1952, 1959, and 1965 (*13*, *15*, *16*), as well as from the report of the Ninth International Leprosy Congress in London, 1968 (*17*). Poor compliance was deplored. However, at the WHO Inter-regional Leprosy Conference in Tokyo, 1958, assertions that patients defaulting at 25% of the treatment sessions showed no less improvement than those receiving full doses led to the target for effective treatment being set at 75% of the prescribed doses (*18*). Obviously, the design of regimens was then dominated by what could be termed the "principle of convenience". For leprosy drugs to be administered to large numbers of patients in remote locations by auxiliary workers with minimal training and only distant supervision, they had to be free of toxicity and undesirable reactions. This approach, under the cover of preventing side-effects, actually heralded a shift of focus in leprosy control from the individual patient to public health.

[1] *Eighth International Congress of Leprology: Final Reports of the Technical Panels Approved by the Plenary Session of September 20th 1963*. Rio de Janeiro, 1963, pp 23–46.

With the problem of dapsone toxicity apparently controlled, leprosy specialists were subsequently confronted with a new problem, that of the "persistently positive lepromatous case" (*14*). It was a common observation that, after several years of clinical and bacteriological improvement, patients – particularly those who had not taken dapsone regularly – were showing no further improvement. Among irregularly treated lepromatous cases in southern India, 40% remained bacteriologically positive even after 10 years of dapsone therapy (*19*).

Until this time, the likelihood of drug resistance in *M. leprae*, based on the model derived from studies of *M. tuberculosis*, had not been given serious consideration. Yet as early as 1959 Cochrane had written: "I am fully aware that many authorities do not admit of resistance developing in leprosy, but it is difficult to believe this … the *M. leprae* is hardly likely to be exceptional in this respect when the great majority of bacteria, sooner or later, show resistance to antibiotics and chemotherapeutic agents" (*14*).

What is most probably the third major event in the modern history of leprosy occurred in 1960, when Shepard demonstrated that *M. leprae* recovered from skin biopsy specimens could successfully be grown in the footpads of mice (*20*). This brilliant achievement – eagerly awaited since the identification of *M. leprae* almost one century earlier – opened the way to a new area of research in leprosy. From this point on, it became possible to test the sensitivity, or resistance, of *M. leprae* to existing drugs, and to screen new therapeutic compounds for activity against the organism. It was also possible to determine the minimal inhibitory concentration of supposedly effective drugs in the blood of mice. This development was soon followed by the report in 1964 of the first confirmed cases of dapsone-resistance in patients from Malaysia who had been treated under careful supervision with high-dosage dapsone for more than 10 years (*21*).

There are two types of microbial drug resistance: secondary, or acquired resistance, following inadequate chemotherapy, and primary resistance, resulting from infection with drug-resistant organisms originating from another patient who has relapsed with secondary resistance (*22*). Irregular drug intake, interruption of chemotherapy, very gradual increases in dose in the drug regimens, and low dosages are all factors that concur by a stepwise process (*17*) to select drug-resistant mutants. These mutants multiply and ultimately replace the initial population, giving rise to relapses and, in the long term, infecting new cases with primary resistant bacilli. The low and progressive doses prescribed at the start of treatment of the individual provided ideal conditions for the development of resistance. While relapse due to secondary resistance is a serious setback for the patient concerned, the development and spread of primary resistance, creating an "epidemic" of leprosy that is not amenable to usual therapy, could indeed pose a threat to the whole community. It could jeopardize and ultimately nullify the results of leprosy control acquired over the preceding decades. Primary dapsone resistance was documented for the first time in 1977 (*23*).

The emergence of drug resistance in *M. leprae* was slow in being widely recognized – possibly because clinicians were reluctant to question the effectiveness of an excellent medicine used with such success and convenience for more than 15 years.

In spite of the experimental confirmation of what until then, failing a laboratory model, had been only a theoretical possibility, and faced with these recent developments, the WHO Expert Committee on Leprosy, at its third meeting (*16*) in 1965, took an ambiguous position. Under the heading "Research" the Committee specifically suggested that mouse footpad

infection be used for screening new antileprosy drugs and detecting drug-resistant strains of *M. leprae*, yet the body of the report declared that "Fortunately, the question of drug resistance to DDS is not an important one. The possibility of development of drug resistance has been reported recently, but only in a negligible proportion of the cases under treatment." As at its previous meetings, the Committee unequivocally reiterated the recommendations for those regimens although they were suspected of generating drug resistance.

Meanwhile, footpad-proven secondary resistance was being reported from an increasing number of countries worldwide (Costa Rica, Ethiopia, India, Israel, Malaysia, the Philippines, and Upper Volta (now Burkina Faso)), with a frequency ranging from an estimated prevalence of about 2% in Israel and Malaysia to an incidence of as much as 3% per annum in Ethiopia (*24*).

To make matters worse, at the Ninth International Leprosy Congress in London in 1968, dapsone was reported as inhibiting the growth of *M. leprae* in the mouse model at extremely low concentrations. Some leprologists were quick to claim that the drug should be administrated at much lower doses – as low as one-hundredth of conventional doses – in order to prevent side-effects and adverse reactions. It is a paradox that the footpad system, which had allowed the demonstration of drug resistance, was also called upon to justify the very doses leading to the development of resistance. At the same Congress, however, the Workshop on Clinical Aspects and Therapy warned that use of such low doses necessitated constant vigilance for the possible emergence of resistant strains (*25*).

At its fourth meeting, in 1970, the Expert Committee (*26*) endorsed its previous recommendations regarding dapsone regimens, emphasizing again the importance of gradual dosage increments. The Committee stressed the advantages of very low doses but also mentioned the fear that these doses could lead to the emergence of drug resistance. It was therefore recommended that properly controlled trials be carried out to settle the question. The Committee also declared that the "search for better drugs continues to be one of the major objectives in leprosy research" and that "research of antileprosy drugs should be based on controlled clinical trials of sufficient duration".

These recommendations were repeated in the *A guide to leprosy control*, issued by WHO in 1970 (*11*). For good measure, the document formally reiterated the statement issued at the third meeting of the Expert Committee – that "fortunately, the question of drug resistance is not an important one". In the meantime, data were accumulating regarding new drugs. In 1962, Browne & Hogerzeil (*27*) had reported that clofazimine (B663, Lamprene®), a riminophenazine used in a small series of patients, produced results comparable to dapsone. The inhibitory activity of this compound against the growth of *M. leprae* in the mouse footpad was demonstrated in 1964 by Shepard & Chang (*28*).

By the time of the 1968 London Congress, it was known that clofazimine, though still waiting to be tested in controlled clinical trials, was active in patients with footpad-proven sulfone-resistant bacilli. A lower incidence of reaction (erythema nodosum leprosum) was observed than with dapsone, although a purple pigmentation of the skin was an unpleasant side-effect (*29*). No relapses were reported after four and a half years of treatment.

Rifampicin was originally tested in the mouse footpad for activity against *M. leprae* in 1967. It was shown to be equally active against both dapsone-sensitive and dapsone-resistant strains (*30*).

Initially, clofazimine and rifampicin were used as substitutes for the treatment of patients who were intolerant of or unresponsive to dapsone, relapsing, or subject to recurrent reactions. Monotherapy with any chemotherapeutic agent risks the development of drug resistance – and it would be considerably more hazardous to use the compounds separately and sequentially, for example to accommodate irregular drug supplies.

As early as 1965, following a suggestion by Cochrane in 1959 that drug resistance would explain the unchanged status of leprosy in some patients, Spickett (*31*) argued for the concurrent use of two or more drugs, even though the immediate clinical improvement might be no greater than that produced by any one of the drugs used alone. While many clinicians considered that combined use of drugs should enhance their therapeutic activity (a synergistic effect) or accelerate cure, this was in no way the purpose: as stressed by Rees, the paramount objective of combined therapy was to reduce the incidence of drug resistance resulting from monotherapy to insignificant proportions (*32*).

References

1. Doull JA et al. The incidence of leprosy in Cordova and Talisay. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1942, 10:107–131.
2. Faget GH et al. The Promin treatment of leprosy: a progress report. *Public Health Reports*, 1943, 58:1729–1741.
3. Feldman WH, Hinshaw HC, Moses HE. Effect of Promin on experimental tuberculosis. Preliminary report. *Proceedings of the Mayo Clinic*, 1942, 15:695.
4. Hansen GA. Undersøgelser angaaende spedalskhedens aarsager [Investigations concerning the etiology of leprosy]. *Norsk Magazin for Lægevidenskaben*, 1874, 4:1–88.
5. Stein ST, Blochman LG. *Alone no longer*. Carville, LA, The Star, 1963.
6. Fromm E, Whittmann J. Derivative des p-nitrothiophenols. *Berichte der Deutsche Chemischen Gesellschaft*, 1908, 41:2264.
7. Cochrane RG et al. Two-and-a-half years' experimented work on the sulphone group of drugs. *Leprosy Review*, 1949, 20:4–64.
8. Lowe J. Treatment of leprosy with diamino-diphenyl sulfone by mouth. *Lancet*, 1950, i: 145–150.
9. Lechat M.F. Milestones on the road to elimination. In: *Eliminating leprosy.* Geneva, World Health Organization, 1998 (document WHO/LEP/98.4, Fifteenth International Leprosy Congress, Beijing):7–9.
10. Lechat M.F. *The way toward eradication of Hansen's disease*. Tokyo, Sasakawa Memorial Health Foundation, 1980.
11. *A guide to leprosy control*. Geneva, World Health Organization, 1970 (reissued in 1973 as document 73/1).
12. Bushy SRM. Chemotherapy. In: Cochrane RG, Davey TF, eds. *Leprosy in theory and practice*, 2nd ed. Bristol, John Wright, 1964:344–370.
13. *WHO Expert Committee on Leprosy. First report*. Geneva, World Health Organization, 1953 (WHO Technical Report Series, No. 71).
14. Cochrane RG, ed. *Leprosy in theory and practice*. Bristol, John Wright, 1959:203–238.
15. *WHO Expert Committee on Leprosy. Second report*. Geneva, World Health Organization, 1960 (WHO Technical Report Series, No. 189).
16. *WHO Expert Committee on Leprosy. Third report*. Geneva, World Health Organization, 1966 (WHO Technical Report Series, No. 319).

17. Browne SG. Transactions of the Ninth International Leprosy Congress, London. Some highlights of the week's work. Chemotherapy of leprosy: experimental aspects. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1968, 36:566–567.
18. *WHO Inter-Regional Leprosy Conference, Tokyo*. Geneva, World Health Organization, 1959 (document WHO/Lep.Conf/21).
19. Vellut C. Follow-up study of over 10 years of lepromatous leprosy with reference to response to specific treatment and occurrence of relapses. *Leprosy in India*, 1969, 41:276–281.
20. Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into foot-pads of mice. *Journal of Experimental Medicine*, 1960, 112:445–454.
21. Pettit JHS, Rees RJW. Sulfone resistance in leprosy. An experimental and clinical study. *Lancet*, 1964, ii: 673–674.
22. Ji BH. Drug resistance in leprosy – a review. *Leprosy Review*, 1985, 56:265–278.
23. Pearson JMH., Haile GS, Rees RJW. Primary dapsone resistant leprosy. *Leprosy Review*, 1977, 48:129–132.
24. Sansarricq H. Leprosy in the world today. *Leprosy Review*, 1981, 52:15–31.
25. Browne SG. Transactions of the Ninth International Leprosy Congress, London. Some highlights of the week's work. Chemotherapy of leprosy: clinical aspects and therapy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1968, 36:567.
26. *WHO Expert Committee on Leprosy. Fourth report*. Geneva, World Health Organization, 1970 (WHO Technical Report Series, No. 459).
27. Browne SG, Hogerzeil LM. B663 in the treatment of leprosy: preliminary report of a pilot trial. *Leprosy Review*, 1962, 33:6–10.
28. Shepard CC, Chang YT. Activity of antituberculous drugs against *Mycobacterium leprae*. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1964, 32:260–271.
29. Ninth International Leprosy Congress, London, 1968. Symposium on B.663 in the treatment of leprosy and leprosy reactions. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1968, 36:560–561.
30. Rees RJ, Pearson JM, Waters MF. Experimental and clinical studies on rifampicin in treatment of leprosy. *British Medical Journal*, 1970, 1:89–92.
31. Spickett SS. Genetic mechanisms in leprosy, in: Cochrane RG, Davey TF, eds. *Leprosy in theory and practice*, 2nd ed. Bristol, John Wright, 1964,98–124.
32. Rees RJ. In: Discussion on the chemotherapy of leprosy today and tomorrow. Second International Colloquium, Borstel, 1974. *Leprosy Review*, 1975, 46:241–242.

Improved knowledge and new hopes

H. Sansarricq, S.R. Pattyn

While the impossibility of cultivating *M. leprae* in artificial media has doubtless been the main obstacle to progress in experimental leprosy, researchers trying to elucidate the relationship between the leprosy bacillus and its human host were for many decades hampered by the extremely complex clinical and histological aspects of the disease. These challenges were taken up in the late 1950s – and the striking progress that was to be made during the 1960s and early 1970s is the subject of this overview.

The mouse footpad model

In 1960, Shepard (*1*) described the measurable – though limited – multiplication of *M. leprae* in the hind footpads of normal mice, which revolutionized experimental leprosy by making possible a wide range of new investigations. A few years later, Rees proposed another useful model, the thymectomized/irradiated (T/900r) mouse (*2*). Both mouse models proved to be invaluable in several critical areas, described below.

Generation time of M. leprae

In the logarithmic phase of growth in the mouse footpad, the generation time of *M. leprae* was calculated to be 12–13 days (3) – much longer than for any other bacterium. Such a prolonged generation time is consistent with the long incubation period and chronicity of leprosy.

Identification of purported isolates of M. leprae and monitoring of their viability

Most mycobacteria do not grow in the mouse footpad; those that do, show growth curves and histological features that are appreciably different from those of *M. leprae* (*3*). Thus, the mouse footpad method could be used for identifying *M. leprae* isolates from patients' nasal discharges and for monitoring of the viability of the organism.

Correlation between morphological aspect and infectivity

It was possible to demonstrate that only uniformly staining bacilli, the percentage of which determines the "solid ratio" (Shepard) or the "morphological index" (Ridley), are viable, as measured by infectivity for mice (*4*).

Use of the mouse footpad model in experimental chemotherapy

It is certainly in experimental chemotherapy that the mouse footpad model – in most instances Shepard's normal mouse – has been most widely used and has provided the most significant results (*3*, *5*, *6*). Applications of the model include the screening of new drugs, with determination of minimal inhibitory concentration and type of activity (i.e. bactericidal or bacteriostatic) against *M. leprae*; monitoring of drug trials; and demonstration of drug-resistant *M. leprae*. Developments of the mouse footpad model relevant to the preparation and confirmation of effectiveness of the 1981 combined drug regimens are discussed in Chapter 2 under the heading "Scientific factors (1972–1981)".

Chemotherapy

Progress made during the 1960s and 1970s in the field of chemotherapy of leprosy are discussed in detail elsewhere in this report. Here we recall only the most important milestones reached during those years:

- In 1964, the first cases of dapsone-resistant leprosy were demonstrated by the mouse footpad method.
- During the 1960s, the efficacy of clofazimine as an antileprosy drug and its anti-inflammatory activity were reported.
- In 1970, the rapid bactericidal activity of rifampicin against *M. leprae* was demonstrated.
- Although it had been known since the earliest days of the chemotherapy of leprosy that multibacillary patients can relapse if they stop treatment, it was only in 1974 that the existence of persisting viable *M. leprae* was detected for the first time in lepromatous patients treated for 10–12 years with dapsone. Thus, the concept of "persisters" was established.

The Ridley–Jopling spectrum

The concept of the leprosy spectrum, with a five-group classification system, was proposed by Ridley & Jopling in the 1960s (*7*, *8*). It is based on correlated clinical and histological features, the latter being interpreted as indicative of cell-mediated responsiveness. At the two ends of the spectrum are two stable forms of the disease – the polar tuberculoid (TT) highly resistant form and the polar lepromatous (LL) low resistant form. Between these two lie the intermediate borderline (BT, BB, BL) forms, which can undergo some evolution towards either end of the spectrum.

The Ridley–Jopling spectrum and classification represented a landmark, and the classification became the mandatory reference system for any scientific investigation involving leprosy patients. It was thus of crucial importance in two essential areas of studies on such patients – drug trials (for correct selection of patients) and immunological investigations. With regard to the latter, it is noteworthy that the spectrum concept was developed before the importance of immunological determinants was revealed by experimental studies in mice and more definitive studies in leprosy patients (*9*).

Immunology

The histopathological and clinical features of the Ripley–Jopling classification provided unequivocal evidence that the relationship between *M. leprae* and its host was dependent on the degree of the cell-mediated immune response of the host to the organism (*10*). The initial step appears to be the antigenic stimulation of the T (thymus-dependent) lymphocytes, either directly by the pathogen or after processing of the pathogen by macrophages. This leads to lymphocytic proliferation and release of lymphokines, some of which are able to enhance the antimicrobial capacity of the macrophages. It is an important feature of the lepromatous form of leprosy that the macrophages are unable to digest the organisms that they have phagocytosed.

During the late 1960s and early 1970s, intensive investigations were carried out, using all available techniques, with the main objective of establishing immunological determinants in leprosy, in relation to the Ridley–Jopling spectrum. The progress made was reviewed at a WHO meeting held in New Delhi in 1972 (*11*, *12*). Here, we provide an overview of the investigations of the relationship between *M. leprae* and its human host before the establishment of IMMLEP – the Immunology of Leprosy programme.

In vivo studies

- The correlation between the level of response to the Mitsuda reaction in the various forms of the disease is one of the characteristics of the Ridley–Jopling classification. "Lepromin positivity has become accepted as a measure of host resistance in patients with leprosy … However, a positive lepromin reaction is not specific for leprosy" (*13*).
- Histological examination of lymph nodes in patients distributed over the whole disease spectrum showed that paracortical (thymus-dependent) areas were well developed in tuberculoid patients and extensively replaced by macrophages loaded with leprosy bacilli in lepromatous cases (*14*, *15*).
- No consistent relationship was found between the late lepromin reaction and reactions to purified protein derivative (PPD) and other antigens derived from cultivable mycobacteria in the various forms of leprosy (*13*, *16*).
- A high proportion of lepromatous patients failed to respond to two sensitizing agents (1-chloro-2,4-dinitrobenzene and 2-chloro-1,3,5-trinitrobenzene); healthy persons and tuberculoid patients did respond (*16*, *17*).
- Skin allograft rejection was delayed in patients with the lepromatous and, to a lesser degree, the tuberculoid form of the disease (*18*).

In vitro studies

- The lymphocyte transformation test (LTT) was established, using as antigen non-autoclaved *M. leprae* extracted from infected human tissues: TT patients responded quite strongly, whereas negative results were regularly obtained in LL patients (*19*, *20*). Patients in the BT group showed variable responsiveness and results in patients with untreated BL disease were usually negative (*21*). Although leukocytes from lepromatous patients did not transform in the presence of *M. leprae*, they responded to a varying degree to other mycobacterial antigens such as whole BCG and PPD (*21*). The level of reactivity appeared to be related to the status of treatment, i.e. reactivity was lower in untreated lepromatous patients than in patients who had received prolonged chemotherapy (*22*).
- Results of the leukocyte migration inhibition test (LMIT) also showed great variation, from strong responses to *M. leprae* in TT patients to a virtual absence of response in the LL group (*21*).

Humoral responses in leprosy

- The production of antibodies to antigens unrelated to *M. leprae*, such as typhoid/paratyphoid vaccines, appeared to be normal in patients with lepromatous and tuberculoid leprosy (*23*, *24*).
- Levels of circulating antibodies against a polysaccharide antigen common to *M .leprae* and other mycobacteria were high in a very large proportion of lepromatous patients and in a minority of tuberculoid patients (*12*).

Immunological complications in leprosy

- Some experimental evidence supporting a role for immune complexes in the pathogenesis of erythema nodosum leprosum (*25*, *26*).
- Evidence indicated that reversal reactions are due to a rapid increase of cell-mediated immune response to *M. leprae*, with a shift in histological classification – in both skin and lymph nodes – towards the tuberculoid end of the spectrum (*15*, *27*). These changes were associated with strong responses to *M. leprae* in vitro as measured by LTT and LMIT (*28*). In thymectomized/irradiated mice with lepromatous lesions, injections of syngeneic lymphoid cells resulted in changes in the lesions which resembled the reversal reaction in humans (*29*).

Vaccination

One of the main topics of discussion in the early 1970s was the possibility of using BCG as a tool for leprosy control, particularly in view of the shortcomings of dapsone-based treatment. Three BCG trials had been undertaken (*12*): in child contacts and relatives of known leprosy cases in Uganda; in persons of all ages in New Guinea; and in a population of children, mainly not exposed at home, in Burma (now Myanmar). Although conclusions were premature, the preliminary results collated in 1972 were strikingly different in the three trials: 80% protection was attributable to BCG in the Uganda trial, 46% in New Guinea, and 44.2% (restricted to the group aged 0–4 years at intake) in Burma.

The fact that numerous studies had demonstrated the effectiveness of BCG against experimental infection by *M. leprae* in mice featured prominently in the discussions (*30*).

Epidemiology

Existing knowledge of the epidemiology of leprosy had been reviewed by Newell (*31*) in 1966 at the request of WHO. Some important issues were investigated in subsequent years.

M. leprae portal of exit

It was shown that, in the early stage of the disease, lepromatous (BL, LL) cases excrete 10^6–10^9 leprosy bacilli daily in nasal mucus (*32*); that these organisms were indeed *M. leprae* was demonstrated by the mouse footpad method.

Survival of M. leprae outside the human body

The survival time of leprosy bacilli in nasal discharges kept under defined conditions for varying periods of time was also measured by the mouse footpad method (*33*).

Subclinical infection

It had long been observed that few of those exposed to heavy sources of infection in fact contract leprosy. Subclinical infection should therefore be common. Godal & Negassi (*34*) applied the LTT for the first time in investigating contacts and non-contacts of leprosy patients. They concluded that leprosy is more highly infectious than prevalence of the disease indicates, and that a subclinical infection commonly follows exposure to *M. leprae*. The relatively low response found in contacts of lepromatous patients suggests that, in these contacts, a “super exposure” to *M. leprae* can bring about a lowering in host resistance.

Establishment of global programmes for leprosy research

In the late 1960s and early 1970s, the means to prevent and cure tropical diseases (including leprosy) were unequal to the problem, yet less than 0.5% of the world's total medical research resources was devoted to tropical diseases. Moreover, a large proportion of these resources was spent in developed countries (*35*). As a consequence, the World Health Assembly of May 1974 adopted a resolution requesting WHO to initiate a coordinated effort for research in tropical diseases.

A few years earlier two meetings – in Geneva in 1970 (*36*) and in New Delhi in1972 (*11*, *12*) – had been convened by WHO on the joint initiative of the Immunology and Leprosy units. In November 1972, immediately following the second of these meetings, Howard Goodman, Chief, Immunology, and one of the authors, H. Sansarricq, then Chief, Leprosy, initiated joint activities aimed at coordinating and supporting investigations on the immunology of leprosy, on a global basis. In August 1973, Tore Godal, who had made important contributions particularly on cell-mediated immunity in leprosy, was appointed as a consultant by the Immunology unit, with the task of drafting a global plan for research on immunology of leprosy (*37*); financial support for this was requested from the Norwegian Agency for International Development (NORAD). The next logical step was the establishment of the Immunology of Leprosy programme (IMMLEP), which held its first meeting in November 1974 (*38*).

At the same time, Goodman had started to put in writing the ideas that served as a basis for discussion in a WHO Intra-Secretariat Planning Group set up in June 1974 for developing proposals for a Special Programme for Research and Training in Tropical Diseases (TDR).

The draft plan for IMMLEP was completed in mid-1974. At an informal meeting in August of the same year, at the suggestion of Professor Bergstrom from Norway, it was decided that IMMLEP should start immediately (with financial support pledge by NORAD) as a pilot activity for the research programme in tropical diseases then in preparation *(38)*.

Immunological investigations of leprosy had long been hampered by the unavailability of sufficient amounts of *M. leprae* and its antigens. In 1971, however, Kirchheimer & Storrs reported on the first successful experimental generalized leprosy in the nine-banded armadillo infected with *M. leprae* (*39*) – which would in principle provide a large supply of *M. leprae*. This success, plus the advent of new immunological methods, made it feasible to identify the development of a leprosy vaccine as a first objective for IMMLEP. Other objectives of the programme were the development of skin tests and further studies in immunopathology aimed at the development of immunotherapeutic measures.

At the request of the programme sponsors, detailed proposals for TDR were prepared during 1975 and 1976 and, in December 1976, the Special Programme was formally set in motion.

In 1976 the establishment of the programme for research on chemotherapy of leprosy (THELEP) – as a part of the normal growth of TDR – was to be an essential step towards the development of the 1981 Study Group regimens (see Chapters 2 and 6).

References

1. Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. *Journal of Experimental Medicine*, 1960, 112:445–454.
2. Rees RJW. Enhanced susceptibility of thymectomised and irradiated mice to infection with *Mycobacterium leprae*. *Nature*, 1966, 211:657–658.
3. Shepard CC. The first decade in experimental leprosy. *Bulletin of the World Health Organization*, 1971, 44:821–827.
4. Shepard CC, McRae DH. *Mycobacterium leprae* in mice: minimal infectious dose, relationship between staining quality and infectivity, and effect of cortisone. *Journal of Bacteriology*, 1965, 89:365–372.
5. Ellard GA. The chemotherapy of leprosy: Part 1. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1990, 58:704–716.
6. Ellard GA. The chemotherapy of leprosy: Part 2. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1991, 59:82–94.
7. Ridley DS, Jopling WH. A classification of leprosy for research purposes. *Leprosy Review*, 1962, 33:119–128.
8. Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five-group system. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1966, 34:255–273.
9. Rees RJW, Waters MFR. Recent trends in leprosy research. *British Medical Bulletin*, 1972, 28:16–21.
10. Turk JL. Cell-mediated immunological processes in leprosy. *Bulletin of the World Health Organization*, 1969, 41:779–792.
11. Immunological problems in leprosy research: 1. *Bulletin of the World Health Organization*, 1973, 48:345–354.
12. Rees RJW. The significance of the lepromin reaction in man. *Progress in Allergy*, 1964, 8:224–258.
13. Turk JL, Waters MFR. Immunological basis for depression of cellular immunity and the delayed allergic response in patients with lepromatous leprosy. *Lancet*, 1968, ii: 436–438.
14. Turk JL, Waters MFR. Immunological significance of changes in lymph nodes across the leprosy spectrum. *Clinical and Experimental Immunology*, 1971, 8:363–376.
15. Turk JL, Bryceson ADM. Immunological phenomena in leprosy and related diseases. *Advances in Immunology*, 1971, 13:209–266.
16. Bullock WE. Studies of immune mechanisms in leprosy. *New England Journal of Medicine*, 1968, 278:298–304.
17. Han SH, Weiser RS, Kau ST. Prolonged survival skin allografts in leprosy patients. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1971, 39:1–6.
18. Bullock WE, Fasal P. Studies of immune mechanisms in leprosy. *Journal of Immunology*, 1971, 106:888–899.
19. Godal T et al. Characterisation of the cellular immune defect in lepromatous leprosy: a specific lack of circulating Mycobacterium leprae-reactive lymphocytes. *Clinical and Experimental Immunology*, 1971, 9:821–831.
20. Myrvang B et al. Immune responsiveness to M. leprae and other mycobacterial antigens throughout the clinical and histopathological spectrum of leprosy. *Clinical and Experimental Immunology*, 1973, 14:541–553.
21. Godal T et al. Evidence that the mechanism of immunological tolerance (‘central failure’) is operative in the lack of host resistance in lepromatous leprosy. *Scandinavian Journal of Immunology*, 1972, 1:311–321.

22. Sheagren JN et al. Immunological reactivity in patients with leprosy. *Annals of Internal Medicine*, 1969, 70:295–302.
23. Jha P et al. Status of humoral immune responses in leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1971, 39:14–19.
24. Wemambu SCN et al. Erythema nodosum leprosum: a clinical manifestation of the Arthus phenomenon. *Lancet*, 1969, 2:933–935.
25. Moran CJ et al. Evidence for circulating immune complexes in lepromatous leprosy. *Lancet*, 1972, 2:572–573.
26. Ridley DS. Reactions in leprosy. *Leprosy Review*, 1969, 40:77–81.
27. Godal T et al. Mechanism of "reactions" in borderline tuberculoid (BT) leprosy. A preliminary report. *Acta Pathologica et Microbiologica Scandinavica*, 1973, 236(suppl.):45–53.
28. Rees RJW. Immunological aspects of experimental leprosy in the mouse. *Proceedings of the Royal Society of Medicine*, 1970, 63:1060–1062.
29. Shepard CC. Vaccination against infection with *M. leprae*. *American Journal of Epidemiology*, 1965, 81:150–163.
30. Newell KW. An epidemiologist's view of leprosy. *Bulletin of the World Health Organization*, 1966, 34:827–857.
31. Davey TF, Rees RJW. The nasal discharge in leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1973, 41:512.
32. Davey TF, Rees RJW. The nasal discharge in leprosy: clinical and bacteriological aspects. *Leprosy Review*, 1974, 45:121–134.
33. Godal T, Negassi K. Subclinical infection in leprosy. *British Medical Journal*, 1973, 3:557–559.
34. Stenson B, Sterky G. Background. In: Challenges in research on tropical diseases. *SAREC Report*, 1977.
35. Immunological problems in leprosy research. *Bulletin of the World Health Organization*, 1970, 43:879–890.
36. Sansarricq H, Torrigiani G, Walter J. The WHO programme for research on immunology of leprosy (IMMLEP). A: Background and management. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1976, 44:276–283.
37. Godal T. Two years with a Scientific Working Group. In: Challenges in research on tropical diseases. *SAREC Report*, 1977.
38. Kirchheimer WF, Storrs EE. Attempts to establish the armadillo (*Dasypus novemcintus* Linn.) as a model for the study of leprosy. I. Report of lepromatoid leprosy in an experimentally infected armadillo. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1971, 39:693–702.

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

V. Pannikar

Under the co-sponsorship of the United Nations Development Programme (UNDP), the World Bank, and WHO, the Special Programme for Research and Training in Tropical Diseases (TDR) was established as an international response to the urgent needs of developing countries in the tropics. The Programme involves the scientific community from several endemic countries and other experts from special agencies, collaborating in a global effort to develop and apply better methods to treat and prevent selected diseases endemic in the tropics and to build the capacity of affected countries to cope with them.

It took some 4 years, from 1974 to 1977, before all the organizational and functional elements of TDR were fully established. The role played by the first "pilot" component, the programme for research on immunology of leprosy (IMMLEP), is recalled where appropriate throughout this report.

A brief summary describing the main characteristics of TDR[1] corresponding to the period during which one of its researchers groups, the Steering Committee on Chemotherapy of Leprosy (THELEP) made important contributions to the development of the multidrug therapy for leprosy that was to be recommended by WHO in 1981. More recently, in 1994 and 2000, TDR was subjected to important re-organizational processes.

Objectives

The Special Programme has two interdependent objectives:
- to develop new and improved tools for the control of tropical diseases; and
- to strengthen the biomedical research capability of tropical countries.

Scientific and technical scope

The six diseases originally included in the Special Programme were:
- malaria
- schistosomiasis
- filariasis (including onchocerciasis)
- trypanosomiasis (including both African sleeping sickness and Chagas disease)
- leishmaniasis
- leprosy.

The research and development operations of TDR focus on improving and developing:
- drugs (chemotherapy and chemoprophylaxis)
- vaccines

[1] Based on a handbook for participants in TDR Scientific Working Groups.

– new approaches to the control of disease vectors
– simple, reliable, sensitive, and inexpensive diagnostic tests
– epidemiological and operational bases for the application of new and improved tools.

It was intended that TDR would support the development of new tools to the point of proven effectiveness and then makes them available to national health services for widespread application.

Scientific and technical organization

The main policy- and decision-making body of TDR is the Joint Coordinating Board (JCB), a permanent committee composed of representatives of the Programme's three co-sponsors and of other cooperating agencies/partners. This Committee is responsible for the overall effective functioning of the Special Programme.

A Scientific and Technical Advisory Committee (STAC) examines all major components of the Special Programme and makes recommendations on priorities and the allocation of available funds.

WHO is the executing agency for the Special Programme and provides personnel (TDR core group and disease control units) and other resources at headquarters and in the regions. The research activities are planned and carried out by multidisciplinary groups – the Scientific Working Groups – made up of scientists from various countries.

Scientific Working Groups and Steering Committees

Scientific Working Groups (SWGs) define the research objectives for a specific aspect of the Programme (e.g. chemotherapy of leprosy), devise a strategic plan to achieve them, carry out the research according to the plan, and review the plan and the research as the work progresses. The Steering Committee of an SWG, elected from within the SWG, manages and guides the Group's activities in working towards the objectives. Important characteristics of the SWGs may be summarized as follows:

- SWGs are open groups to which researchers are co-opted exclusively on the basis of their scientific merits.
- The funds allocated to research projects selected by the Steering Committees are sufficient to cover all or almost all of the related expenses (see below), thus making the projects viable.

Relationship between "classical" WHO and TDR structures

Before the establishment of TDR, there were WHO structures with responsibility for maintaining – and updating, when necessary – the technical policies related to the control of tropical diseases, including leprosy. These structures are still in existence and complement the disease control measures and aspects of their implementation. However, during the early years of TDR (about 1974–1977), a series of problems had to be resolved concerning the expected relationships between existing technical units and the planned TDR structures.

On the general principle that research on specific diseases had the primary aim of improving methods of controlling those diseases, the links that were forged were as follows:

- The chief of each technical unit concerned with a specific disease was designated as Secretary of the SWG dealing with research on that disease. For example, Chief, Leprosy unit, became Secretary of IMMLEP and THELEP.
- Secretaries of Steering Committees were recruited as TDR staff and located in the corresponding disease control unit.
- The chiefs of disease units reported to both the Director of their Division (Malaria and other Parasitic Diseases or Communicable Diseases) and to Director, TDR.

Financial aspects

The funds required for TDR operations, over and above the contributions from the Programme co-sponsors, come from "cooperating agencies", which include governments, intergovernmental organizations, and various foundations and associations.

Contributions for the period 1974–1984 (*1*) amounted to a total of US$ 158 672 200, of which the largest sums came from the USA (US$ 20 403 912), Sweden (US$ 17 962 970), UNDP (US$ 13 777 378), the World Bank (US$ 9 960 000), and WHO (US$ 9 984 000).

As an example of expenditure, the budgetary amounts allocated to THELEP (*2*) rose from US$ 185 000 in 1977 to US$ 400 000 in 1979, thereafter remaining more or less stable for several years.

References

1. *Tropical diseases research. TDR Seventh programme report, 1 January 1983 – 31 December 1984*. Geneva, World Health Organization, 1985.
2. *Draft report of the Scientific and Technical Review Committee to STAC on the leprosy component of the Special Programme, 2–4 April 1979.* Geneva, World Health Organization, 1979.

Chapter 1

Preparation of the Study Group on Chemotherapy of Leprosy

1.1 Scientific factors (1972–1981)

L. Levy

Modern chemotherapy of leprosy may be said to have begun with the trial of Promin® (glucosulfone) at Carville in the early 1940s (*1*). Over the next 20 years, a number of agents – including dapsone, thiambutosine, ethionamide, thiacetazone, and clofazimine – were employed as monotherapies in clinical trials that were supported only by clinical observation and interval measurements of the bacterial index. Until Shepard's development of the mouse footpad technique, first reported in 1960 (*2*, *3*), there had been no means existed for assaying the antimicrobial activity of a drug against *Mycobacterium leprae* outside the body of the leprosy patient. Moreover, the change in bacterial index proved to be a very insensitive measure of the patient's response to antimicrobial chemotherapy. The decrease was slow – approximately one order of magnitude (one "plus") per year – and it was impossible to distinguish more potent from less potent drugs by this method.

During the decade that followed Shepard's report of the multiplication of *M. leprae* in the hind footpad of the immunologically intact mouse (*2*, *3*), individual drugs were screened for antimicrobial activity against the organism, primarily in Shepard's laboratory (*4–8*), but also at the National Institute for Medical Research in London, England (*9*) and in San Francisco (*10–14*). Initially, each drug was screened at the highest concentration tolerated by the mice by the "continuous" method: drug administration began when the organisms were inoculated and continued for the duration of the experiment. If the organisms multiplied at the same rate and to the same maximum number in treated mice as in untreated controls, the drug was considered to be inactive. Active drugs were those that appeared to inhibit, either partially or totally, multiplication of the organisms in the treated mice.

With increasing experience of the action of antimicrobial drugs in *M. leprae*-infected mice, Shepard recognized that he could estimate the minimal inhibitory concentration of an effective drug by measuring its concentration in the blood of mice given the minimal effective dosage (*15*). Further, he could attempt to characterize the action of the drug by means of his "kinetic" method (*16–18*), which required that the drug be administered for a period of only 60–90 days, beginning once logarithmic multiplication of the organisms had been observed in the control mice. By observing the behaviour of the organisms in the treated mice after drug administration had been stopped, he could posit that the drug exerted only bacteriostatic effects if multiplication of the organisms appeared to resume immediately after cessation of treatment, or that it had bactericidal (or, more precisely, "bactericidal-type") activity if there was an apparent delay in the resumption of multiplication.

A second important contribution by Shepard was application of the mouse footpad technique to "short-term" clinical trials. A drug already shown to be effective in the *M. leprae*-infected mouse was administered, for periods ranging from a few days to a few months, to small numbers of previously untreated patients with multibacillary (MB) leprosy; skin lesions were biopsied at intervals during treatment, and the *M. leprae* were crudely separated from the tissues, counted, diluted, and inoculated into mice. In short-term clinical trials of individual antimicrobial drugs, carried out primarily in San Francisco (*19–23*), Cebu (Philippines) (*24*, *25*) and Sungei Buloh (Singapore) (*9*), the administration as monotherapy of dapsone, clofazimine, and rifampicin was shown to result in more rapid death of *M. leprae* than other drugs. Moreover, potency could be judged from the average rate at which a particular drug rendered the patients' *M. leprae* incapable of multiplication in mice.

Application of these techniques established that dapsone, administered at a dose of 100 mg daily, was capable of killing more than 99% of viable organisms within 100 days of treatment; clofazimine, administered at the same dosage, appeared to kill the patients' *M. leprae* at the same rate, but only after an initial delay of some 50 days (*19*). Rifampicin, administered in single doses of 600–1500 mg, killed more than 99% of the viable *M. leprae* within 3 or 4 days (*20*). Thus, by 1976, the bactericidal efficacy of these three antimicrobial agents had been established.

Two additional events of great importance had occurred in the meantime. Rees and his colleagues demonstrated (*26–29*), by inoculation of mice and administration of dapsone to a proportion of the mice, that dapsone-resistant *M. leprae* could emerge and cause relapse in patients who had been treated with high-dose dapsone for many years. By inoculating immunosuppressed mice with large numbers of organisms, Rees et al. also demonstrated the persistence of *M. leprae* in patients who had been treated with rifampicin, whose organisms were no longer capable of multiplying in immunologically intact mice (*30*). They had earlier demonstrated survival of drug-susceptible *M. leprae* in patients who had been treated with dapsone at high dosage for at least 10 years, remained under treatment, and been apparently cured (*31*).

The theoretical basis of the strategy for developing effective drug regimens was elucidated by the Committee on Experimental Chemotherapy, convened under Shepard's chairmanship in Bergen, Norway, on the occasion of the Tenth International Leprosy Congress. The Committee's report (*32*) emphasized the need to study in clinical trial only those drugs already shown to be effective against *M. leprae* in the mouse footpad system, with known pharmacokinetics and toxic potential. The Committee described both short-term and long-term trials of chemotherapy in MB patients, and also considered trials in patients with paucibacillary (PB) leprosy.

Of particular interest is the possibility suggested in the Committee's report of administering rifampicin intermittently. The rationale for this included the fact that rifampicin administered daily induces its own metabolism (*33*), a phenomenon that might not occur if the drug were administered intermittently. Intermittent schedules had been shown to be effective in the treatment of tuberculosis (*34–36*). However, the potentially serious toxicity of intermittently administered rifampicin, especially when given in doses larger than 600 mg at intervals longer than one week, was of great concern (*34*, *37*).

In an attempt to avoid toxicity while exploiting the bactericidal potency of rifampicin against *M. leprae*, Rees undertook a trial in the early 1970s in which the drug was administered in two consecutive daily doses of 600 mg each once monthly. An interim report (*38*) stated that no adverse reactions had occurred and no circulating rifampicin-dependent antibodies had been detected among 30 patients treated in this way for approximately 12 months.

During this same period, a regimen consisting of 1500 mg rifampicin administered once every three months was employed in a trial among patients with MB leprosy in Cebu, Philippines, under the sponsorship of the U.S. Leprosy Panel of the US–Japan Cooperative Medical Science Program and the Leonard Wood Memorial (Levy, personal communication). This very large dose was justified on the grounds that an even larger single dose of 1800 mg had been approved by the United States Food and Drug Administration for meningococcal prophylaxis. Approximately one-third of the patients exhibited signs of toxicity**,** although not of the type linked to the presence of rifampicin-dependent antibodies. These toxic manifestations were sometimes encountered after the first dose, did not always recur after subsequent doses, and did not occur when the dosage was divided over two consecutive days.

The experimental data were reviewed in the summer of 1975, during a workshop on the chemotherapy of leprosy sponsored by the U.S. Leprosy Panel, and held at the National Institutes of Health in Bethesda, MD (*39*), and the need to develop combined drug regimens for the treatment of MB leprosy was discussed. It was obvious that drug resistance could be prevented only by the use of combinations of bactericidal agents, each agent acting by a different mechanism, and it was hoped that any *M. leprae* persisting after treatment with a single drug would be killed by the other drugs in the combination.

The limited sensitivity of the mouse footpad system in immunologically intact mice was a practical difficulty: *M. leprae* fail to multiply in such mice if the inoculum is much larger than 10^4 organisms per footpad, and it is difficult to distinguish persistence of the inoculated organism in the footpad from true multiplication. The *M. leprae* persisting during treatment with rifampicin, demonstrated by Rees (*30*), constituted too small a proportion of the bacterial population to be detected by so small an inoculum. It was clear that rifampicin should be one of the components of any combined regimen because of its efficacy; however, rifampicin alone was so rapidly bactericidal that no additional effect of the other components of a combined regimen could be demonstrated by inoculating immunologically intact mice with a small number of *M. leprae*. The workshop concluded that clinical trials of combined drug regimens should be carried out in previously untreated patients with MB leprosy, and that immunosuppressed mice, inoculated with 10^5 *M. leprae* per footpad, should be used. Such trials became the first order of business of the Scientific Working Group on Chemotherapy of Leprosy, THELEP.

In addition to the clinical trials of combined drug regimens for MB leprosy, THELEP – which was established in April 1976 – set as its initial priorities surveys of primary dapsone resistance and the development of new drugs, primarily by screening analogues of existing drugs known to be active against *M. leprae* or *M. tuberculosis*. Subsequently, THELEP recognized the importance of research in additional areas, including clinical trials of chemotherapy in patients with PB leprosy, and "field trials" – trials involving many more patients than clinical trials, with the end-point being relapse after withdrawal of treatment rather than detection of persisting *M. leprae* – of potentially useful combined drug regimens

in previously untreated patients with either MB or PB leprosy. These activities and their contributions to the development of multidrug therapy (MDT) are discussed in Chapter 6 under the heading “THELEP”.

The author wishes to acknowledge the invaluable assistance provided by Dr Gordon A. Ellard and Professor Ji Baohong in the preparation of this section.

References

1. Faget GH et al. The Promin treatment of leprosy. A progress report. *Public Health Reports*, 1943, 58:1729–1741.
2. Shepard CC. Acid-fast bacilli in nasal excretions in leprosy, and results of inoculation of mice. *American Journal of Hygiene*, 1960, 71:147–157.
3. Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. *Journal of Experimental Medicine*, 1960, 112:445–454.
4. Shepard CC. Capreomycin: activity against experimental infection with *Mycobacterium leprae*. *Science*, 1964, 146:403–404.
5. Shepard CC. Activity of repository sulfones against *Mycobacterium leprae* in mice. *Proceedings of the Society for Experimental Biology and Medicine*, 1967, 124:430–433.
6. Shepard CC, Chang YT. Effect of several anti-leprosy drugs on multiplication of human leprosy bacilli in footpads of mice. *Proceedings of the Society for Experimental Biology and Medicine*, 1962, 109:636–638.
7. Shepard CC, Chang YT. Activity of antituberculosis drugs against *Mycobacterium leprae*. Studies with experimental infection of mouse footpads. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1964, 32:260–271.
8. Shepard CC, Levy L, Fasal P. Rapid bactericidal effect of rifampicin on *Mycobacterium leprae*. *American Journal of Tropical Medicine and Hygiene*, 1972, 21:446–449.
9. Rees RJW, Pearson JMH, Waters MFR. Experimental and clinical studies on rifampicin in treatment of leprosy. *British Medical Journal*, 1970, 1:89–92.
10. Jacobsen PL, Ng H, Levy L. The susceptibility of mycobacteria to hydnocarpic acid. *American Review of Respiratory Disease*, 1973, 107:1022–1029.
11. Levy L. The activity of chaulmoogra acids against *Mycobacterium leprae*. *American Review of Respiratory Disease*, 1975, 111:703–705.
12. Levy L, Merigan TC. Failure of an interferon inducer to inhibit multiplication of *Mycobacterium leprae*. *Proceedings of the Society for Experimental Biology and Medicine*, 1970, 134:87–89.
13. Levy L, Moon N. Inhibition of the multiplication of *Mycobacterium leprae* by methimazole. *American Review of Respiratory Disease*, 1972, 106:917–920.
14. Levy L, Ullmann N. Inhibition of multiplication of *Mycobacterium leprae* by several antithyroid drugs. *American Review of Respiratory Disease*, 1975, 111:651–655.
15. Shepard CC, McRae DH, Habas JA. Sensitivity of *Mycobacterium leprae* to low levels of 4,4'-diaminodiphenylsulfone. *Proceedings of the Society for Experimental Biology and Medicine*, 1966, 122:893–896.
16. Shepard CC. A kinetic method for the study of activity of drugs against *Mycobacterium leprae* in mice. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1967, 35:429–435.
17. Shepard CC. Further experience with the kinetic method for the study of drugs against *Mycobacterium leprae* in mice. Activities of DDS, DFD, ethionamide, capreomycin and PAM 1392. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1969, 37:389–397.

18. Shepard CC et al. Kinetic testing of drugs against *Mycobacterium leprae* in mice. Activity of cephaloridine, rifampin, streptovaricin, vadrine and viomycin. *American Journal of Tropical Medicine and Hygiene*, 1971, 20:616–620.
19. Levy L, Shepard CC, Fasal P. Clofazimine therapy of lepromatous leprosy caused by dapsone-resistant *Mycobacterium leprae*. *American Journal of Tropical Medicine and Hygiene*, 1972, 21:315–321.
20. Levy L, Shepard CC, Fasal P. The bactericidal effect of rifampicin on *M. leprae* in man: a) single doses of 600, 900 and 1200 mg; and b) daily doses of 300 mg. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1976, 44:183–187.
21. Shepard CC, Levy L, Fasal P. The death of *Mycobacterium leprae* during treatment with 4,4'-diaminodiphenylsulfone (DDS). *American Journal of Tropical Medicine and Hygiene*, 1968, 17:769–775.
22. Shepard CC, Levy L, Fasal P. The death rate of *Mycobacterium leprae* during treatment of lepromatous leprosy with acedapsone (DADDS). *American Journal of Tropical Medicine and Hygiene*, 1972, 21:440–445.
23. Shepard CC, Levy L, Fasal P. Further experience with the rapid bactericidal effect of rifampin on *Mycobacterium leprae*. *American Journal of Tropical Medicine and Hygiene*, 1974, 23:1120–1124.
24. Rifampin therapy of lepromatous leprosy. *American Journal of Tropical Medicine and Hygiene*, 1975, 24:475–484.
25. Spaced clofazimine therapy of lepromatous leprosy. *American Journal of Tropical Medicine and Hygiene*, 1976, 25:437–444.
26. Pearson JMH, Rees RJW, Waters MFR. Sulphone resistance in leprosy. A review of one hundred proven clinical cases. *Lancet*, 1975, ii: 69–72.
27. Pettit JHS, Rees RJW. Sulphone resistance in leprosy. An experimental and clinical study. *Lancet*, 1964, ii: 673–674.
28. Pettit JHS, Rees RJW, Ridley DS. Studies on sulfone resistance in leprosy. I: Detection of cases. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1966, 34:375–390.
29. Rees RJW. Drug resistance of *Mycobacterium leprae* particularly to DDS. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1967, 35:625–638.
30. Rees RJW et al. Long-term treatment of dapsone-resistant leprosy with rifampicin: clinical and bacteriological studies. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1976, 44:156–169.
31. Waters MFR et al. Ten years of dapsone in lepromatous leprosy: clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. *Leprosy Review*, 1974, 45:288–298.
32. Experimental chemotherapy in leprosy. *Bulletin of the World Health Organization*, 1976, 53:425–433.
33. Nitti V et al. Rifampicin blood serum levels and half-life during prolonged administration in tuberculous patients. *Chemotherapy*, 1972, 17:121–129.
34. Aquinas M et al. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *British Medical Journal*, 1972, 1:765–771.
35. Gyselen A, Verbist L. Has the intermittent therapy of pulmonary tuberculosis a future in industrialized countries? *Praxis der Pneumologie*, 1972, 26:269–282.
36. Verbist L et al. Intermittent therapy with rifampin once a week in advanced pulmonary tuberculosis. *Chest*, 1972, 61:555–563.

37. Poole G, Stradling P, Worlledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. *British Medical Journal*, 1971, 3:343–347.
38. Rees RJW. Rifampicin: the investigation of a bactericidal antileprosy drug. *Leprosy Review*, 1975, 46(Suppl.):S121–S124.
39. Gelber RH. US. -Japan Cooperative Medical Science Program Workshop on Leprosy Chemotherapy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1976, 44:369–373.

1.2 Increasing role of voluntary organizations

The Japan Shipbuilding Industry Foundation and the Sasakawa Memorial Health Foundation

Y. Yuasa

The late Mr Ryoichi Sasakawa, founder and first President of the Japan Shipbuilding Industry Foundation (JSIF), who as a result of his personal childhood experience was always deeply concerned about the global leprosy situation, began financially supporting the WHO global leprosy programme (WHO/LEP) in 1974. On the recommendation of his personal advisers, he approached WHO and subsequently made a contribution of US$ 30 000 towards five research activities under WHO/LEP.

At that time the global smallpox eradication programme was nearing its objective, but WHO lacked the necessary funds to complete the project. Early in 1975, Dr H. Mahler – then Director-General of WHO – made a personal appeal to all Member States of WHO for contributions to the Voluntary Fund for Health Promotion. Through the Japanese Ministry of Health, WHO – aware of his interest in leprosy – also wrote to Mr Sasakawa to request funding, stressing that, while the smallpox programme was the Organization's top priority, leprosy was also an abiding concern.

In response, Mr Sasakawa donated US$ 1 million from the JSIF fund in August 1975, to be shared equally between the smallpox and leprosy programmes; the smallpox contribution was unconditional, but the leprosy contribution was to be used in consultation with JSIF. Dr Mahler accepted the half million US dollars for leprosy with some hesitation: methods for leprosy control in use at the time required considerable improvement, which implied a long-term effort with no prospect of rapid and visible results – unlike the final stages of the smallpox eradication programme. No Memorandum of Understanding or any other formal agreement between WHO and JSIF was established in connection with that or any subsequent contribution. On a basis only of verbal commitment and mutual trust, contributions have continued for more than 28 years, without interruption and in steadily increasing amounts.

In 1974, Mr Sasakawa marked his 75th birthday by establishing a leprosy-related NGO in Tokyo – the Sasakawa Memorial Health Foundation – with full financial backing from JSIF. Thus, he was able to support global leprosy activities on two fronts, through WHO and through the Foundation, using JSIF as the funding source for both. It is perhaps noteworthy that the word "leprosy" does not appear in the name of the Foundation – a deliberate reflection of the basic concept of tackling leprosy within the context of general health problems.

As a specialized agency within the United Nations "family", WHO had ready access to the health authorities of leprosy-endemic countries that recognized the Organization's technical leadership. However, cooperation between governments and WHO required formal procedures that were often time-consuming. As an NGO, the Foundation enjoyed greater freedom and flexibility in its actions. Becoming a member of ILEP from the very beginning, the Foundation joined a global network of leprosy activities, which facilitated its entry to a number of leprosy-endemic countries, especially in east and south-east Asia.

In the latter half of the 1970s, JSIF's contributions to the WHO leprosy programme were used on an "ad hoc" basis to cover needs in relation to global coordinating activities as well as for the improvement of leprosy control services in a limited number of countries. The Medical Director of the Sasakawa Foundation acted as a de facto liaison officer for JSIF's annual contribution. Each year, he was invited to Geneva by WHO/LEP, where he discussed the possible utilization of the contribution, and assisted in the drafting of a letter of request for the following year, to be sent with a covering letter from the Director-General to Mr R. Sasakawa.

Professor M. Ishidate, known as the father of leprosy chemotherapy in Japan as a result of his pioneering work in the synthesis of Promin® in Japan during and immediately after the Second World War, was the first Chairman of the Foundation – a fact that strongly influenced its choice of activities. Two aspects of the Foundation's activities before 1982 were particularly relevant to subsequent events.

The Foundation supplied dapsone to countries such as Indonesia, Myanmar (then Burma), and the Philippines, which faced difficulties following the withdrawal of UNICEF which had supplied dapsone for a period of 10 years. Once WHO published its recommendations on MDT, the Foundation switched from supplying dapsone to supplying MDT.

A significant undertaking was the conduct of international trials of combined chemotherapy (i.e. multidrug therapy) on lepromatous leprosy involving workers and patients in the Philippines, the Republic of Korea, and Thailand, in response to the recommendation of the International Workshop on Chemotherapy of Leprosy, which took place in Manila in 1977 to address the disastrous spread of dapsone resistance. The Foundation organized both the workshop and the trials.

The International Federation of Anti-Leprosy Associations

H. Sansarricq

The European Federation of Anti-Leprosy Associations (ELEP), comprising 11 member associations, was founded in September 1966. In 1975, ELEP expanded to become the International Federation of Anti-Leprosy Associations (ILEP), admitting non-European members, notably the American Leprosy Mission and the Sasakawa Memorial Health Foundation (*1*). Current members of ILEP are listed in the appendix to this chapter.

ILEP is structured as a federation of nongovernmental agencies; each member retains full autonomy for its activities, while the secretariat headquarters in London plays a coordinating role. Members raise funds from private donors and other sources, which are spent in support of leprosy work – largely leprosy control, but also training, rehabilitation, research, etc.

During the early and mid-1970s, UNICEF, which had provided substantial support for vertical leprosy control programmes since the 1950s, revised its policy and began reducing its support for leprosy control activities in a number of countries. The national programmes in endemic countries were subsequently supported by ELEP/ILEP member associations.

This enhanced the importance of these associations, which became responsible for most of the technical support and expenses related to leprosy control in the vast majority of endemic countries.

From its inception in 1958, WHO/LEP fully acknowledged the crucial contribution made by voluntary organizations – essentially ELEP and later ILEP members and the Japan Shipbuilding Industry Foundation/Sasakawa Memorial Health Foundation – to leprosy activities.

At its third meeting, in the same year that ILEP was created, the WHO Expert Committee on Leprosy also recognized the important part played by voluntary organizations in leprosy control (*2*), but strongly recommended that the efforts of these organizations should conform to the plans developed by national health authorities. In 1976, the Expert Committee emphasized the crucial role of voluntary organizations (*3*), and its statement was reproduced in full in the 1980 edition of the WHO guide to leprosy control (*4*).

In December 1973, LEP invited the Medical Commission of ILEP for discussions in Geneva. For years, excellent cooperation characterized relations between the two agencies, as exemplified by the following:[1]

- Financial support from ILEP members to various projects was also supported by WHO. Examples include Myanmar (then Burma) – National Leprosy Control Programme, health systems analysis applied to leprosy, control, BCG project; the Republic of Korea – leprosy control; the Maldives – leprosy control.
- Jointly sponsored government / ILEP member / WHO seminars and workshops; ILEP invitations to WHO to the meetings of the ILEP Medical Commission.
- Meetings were organized by WHO/LEP with the objective of coordinating activities supported at country level by individual ILEP member associations and WHO/LEP.
- Increased contacts between ILEP members and WHO regional offices and governments of endemic countries that were also WHO Member States.
- Visits by individual ILEP member associations to the World Health Assembly and subsequent contacts with delegations from WHO Member States.

During the 1960s and 1970s, ILEP member associations supported a number of investigations of drugs that were to be included in the 1981 study group regimens.

In 1982 (i.e. just before the introduction of MDT), ILEP was composed of 25 national associations (in 20 developed countries) and was operating in 91 countries through 857 projects serving an estimated 1 120 000 patients (*5*).

[1] Walter J, Seal KS, Sansarricq H. *Goal-orientated WHO–Government–ILEP collaboration* (working paper for the meeting of ILEP Medical Commission, Madrid, June 1979).

References

1. Farine M. La Fédération internationale des associations contre la lèpre (ILEP) [The International Federation of Anti-Leprosy Associations (ILEP)]. *Acta Leprologica,* 1982, 86–87:243–251.
2. *WHO Expert Committee on Leprosy. Third report*. Geneva, World Health Organization, 1966 (WHO Technical Report Series, No. 319).
3. *WHO Expert Committee on Leprosy. Fifth report*. Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 607).
4. *A guide to leprosy control*. Geneva, World Health Organization, 1980.
5. Lechat MF. Control programmes in leprosy. In: Hastings RC, ed. *Leprosy*. New York, Churchill Livingstone, 1985.

Appendix

List of current ILEP Member Associations

AFRF	Association Française Raoul Follereau
AIFO	Amici di Raoul Follereau, Italy
ALES	Aide aux Lépreux Emmaüs-Suisse
ALM	American Leprosy Mission
DAHW	Deutsches Aussätzigen-Hilfswerk
DFB	Damien Foundation, Belgique
FL	Fondation Luxembourgeoise Raoul Follereau
FO	Fondation Père Damien, Belgique
LEPRA	British Leprosy Relief Association
NLR	Netherlands Leprosy Relief Association
OM	Comité international de l'Ordre de Malte
SF	Fontilles, Lucha contra la Lepra
SJ	Sasakawa Memorial Health Foundation
SLC	Le Secours aux Lépreux, Canada
TLMI	The Leprosy Mission International
TLRA	Taiwan Leprosy Relief Assocation

Chapter 2

The Study Group

H. Sansarricq

2.1 The problem

In 1979–1980, when the Study Group meeting was being planned, the problem of chemotherapy of leprosy, as seen from the WHO point of view, could be analysed as follows:

Effective and practicable MDT in sight?

In chemotherapy of leprosy, two major obstacles had been clearly identified:

- Secondary and primary resistance of *M. leprae* to dapsone
  The consequence of dapsone monotherapy was the development of:
  - secondary resistance of *M. leprae* (*1*) to the drug in lepromatous patients (by selection of pre-existing drug-resistant mutants), and
  - primary resistance in all forms of the disease (in individuals infected with resistant organisms) (*2*, *3*).

- Persistent *M. leprae* (*1*)
  Tiny numbers of *M. leprae* fully sensitive to antileprosy drugs had been isolated from lepromatous patients treated for many years with adequate doses of dapsone or for a few years with adequate doses of rifampicin. While the elimination of all persisters through chemotherapy had been supposed to be difficult or even problematic (*4*) in view of the absence of cell-mediated immunity against *M. leprae* in lepromatous patients, the results of two studies – one in Malaysia (*5*) and the other in Malta (*6*) – suggested that relapses due to persisting *M. leprae* and occurring in adequately treated lepromatous patients could be less frequent than might be feared.

Apart from the question of persisting *M. leprae* and its uncertainties, there remained the problem of recommending regimens for control programmes that could actually cope with the phenomenon of dapsone resistance. The recommendations made at the fifth meeting of the WHO Expert Committee (*1*), based on combinations of antileprosy drugs, had not been widely applied and thus had not provided an adequate response to the problem, at least from the operational point of view. This was a matter of increasing concern in WHO/LEP and THELEP.

Once primary resistance of *M. leprae* to dapsone had been demonstrated, surveys sponsored by THELEP and others proved beyond doubt that the epidemic of dapsone resistance was threatening to jeopardize the entire leprosy control effort (*7*). There was thus a clear and urgent need for combined drug regimens effective in curing patients and preventing drug resistance, and safe and practicable under field conditions.

For reasons explained earlier, the most difficult part of the problem concerned the design of regimens for multibacillary (LL and BL) patients. The whole chemotherapeutic armament available for such patients (*8*) was composed of just three drugs – the highly bactericidal rifampicin, plus dapsone and clofazimine, both weakly bactericidal. In addition, two interchangeable thioamides (ethionamide and protionamide) showed some potential, displaying a bactericidal activity intermediate between that of rifampicin and that of dapsone, but important questions remained about adequate dosages and toxicity.

As the only highly bactericidal drug on the list, rifampicin had to be the backbone of all theoretical MDT regimens: it was so effective against *M. leprae* that MDT regimens of finite duration for MB patients seemed feasible, even though there were lingering doubts about the results. A few years earlier, the general opinion – based mainly on experience in tuberculosis therapy (*9*) – had been that, to prevent severe toxic side-effects, the drug should be given in daily doses. However, daily treatment was prohibitively expensive and difficult to supervise, and these were the main reasons for the failure of the recommendations of the fifth meeting of the Expert Committee (*10*). A trial begun in 1973 (*11*) had shown that, at a dosage of 600 mg on two consecutive days every month, rifampicin was as effective as when given at a daily dose of 600 mg. This possibility of monthly administration made rifampicin treatment much cheaper and easier to supervise and might open the way to the required regimens (*11*, *12*; see Table 2.1).

In the field, identification of patients with dapsone-resistant *M. leprae* – either on clinical grounds or, particularly, by the mouse footpad method – was thought to be unlikely. The increasing frequency of secondary and primary resistance to dapsone meant that it was not feasible to propose regimens for MB patients containing only rifampicin and dapsone (*13*): a third drug was needed. In view of existing experience with use of clofazimine, and the unresolved questions relating to dosages and toxicity of the thioamides (*8*), THELEP chose clofazimine for their field trials on chemotherapy in lepromatous leprosy.

In March 1979, it was decided to undertake field trials of a regimen for lepromatous patients "which could be similar to regimens to be used in the future in control programmes", based on intermittent monthly administration of rifampicin (*14*). The protocol for these trials was prepared by THELEP (*15*) and sites were selected. Trials were to be launched in Karigiri and Polambakkam (southern India) in April and October 1982 respectively, i.e. after the Study Group Meeting (*16*). The regimen to be used in the trials is shown in Table 2.1.

The trials included only lepromatous patients previously treated with dapsone up to smear-negativity. They were to last 2 years, after which patients were to be observed for relapse during a 5-year period. THELEP considered it unethical to plan trials of limited duration on lepromatous patients who had not yet reached smear-negativity, because the time required for treatment with any drug or combination of drugs to kill all persisting *M. leprae* was unknown (*10*).

In designing MDT regimens for MB patients in general, and especially for untreated patients, it was thus very difficult to decide what duration of any regimen would reduce persisters to numbers consistent with a low frequency of relapse, resulting in interruption of *M. leprae* transmission in the community (i.e. control of the disease), or even with cure of patients. The problem could be resolved only by trials with varying duration of treatment and with several years of post-treatment observation.

Dapsone monotherapy was no more appropriate for PB patients, given the increasing frequency of primary resistance to dapsone. On the other hand, it was important to use the high bactericidal activity of rifampicin against *M. leprae* to cure PB cases – the vast majority of leprosy patients – as rapidly as possible. In view of the small number of organisms harboured by these patients, there was no risk of selecting drug-resistant mutants through chemotherapy, and monotherapy with rifampicin could, in principle, be used. However, it was important to consider the risk that, at field level, some borderline (MB) cases could be misclassified as PB patients – and in these cases rifampicin monotherapy *could* select resistant mutants.

Apart from the difficulties of designing MDT regimens, it was also obvious that the future implementation of such regimens would necessitate the complete reorganization of all elements of leprosy services (*10*, *17*). This would require substantial effort and additional resources, all sustained over a long period, yet the threat resulting from "the anarchic use of rifampicin" (Levy) meant that speed was essential – resistance to this drug had already been reported (*18*).

Table 2.1

MDT for MB patients – some successive regimens

References	Regimens
12	*Rifampicin*, 1200 mg once a month Dapsone, 50 mg daily
11 [a]	*Rifampicin*, 600 mg daily on 2 consecutive days every 4 weeks *Thiambutosine*, 1 g/week intramuscularly
THELEP Protocol for field trials (1979) [b]	*Rifampicin*, 600 mg daily on 2 consecutive days once a month *Clofazimine*, 600 mg daily on 2 consecutive days once a month *Acedapsone*, 225 mg bimonthly (injections) Dapsone, 100 mg daily
10	*Rifampicin*, 600 mg daily on 2 consecutive days in every 4 weeks (or monthly) (first dose supervised, second dose preferably supervised) *Clofazimine*, 600 mg daily on 2 consecutive days every 4 weeks (or monthly) (first dose supervised, second dose preferably supervised) *Dapsone*, 100 mg daily
22	*Rifampicin*, 600 mg one monthly, supervised *Clofazimine*, 300 mg once monthly, supervised, and 50 mg daily, self-administered *Dapsone*, 100 mg daily, self-administered

[a] Trial started in 1973.

[b] In: *Draft report of the planning meeting for a protocol for field trials of chemotherapy of lepromatous leprosy, Geneva, 15 October 1979.*

The anarchic use of rifampicin

By the mid-1970s, rifampicin had established its reputation as the most potent antileprosy drug and its use was expanding in many parts of the world. Voluntary agencies were increasingly receiving requests for the drug. While the need for rifampicin to be used in combination with another antileprosy drug was officially recognized, fear of toxic side-effects meant that it was always strongly recommended that it should never be used intermittently but only in *daily* and supervised dosages. The daily, supervised administration of rifampicin was advocated not only by the fifth meeting of the WHO Expert Committee on Leprosy (1) in 1976, but also by ILEP in the 1977 *Heathrow report* (*19*), by the 18th International Leprosy Congress in 1978 (*20*), and in WHO's *Guide to leprosy control* in 1980 (*21*).

The number of proposed combinations of rifampicin with other antileprosy drugs was somewhat confusing for those in charge of control programmes. Moreover, it was clear that regimens based on daily-supervised rifampicin were impracticable and too expensive.

The greatest concern was rifampicin being given as a single drug to lepromatous patients by fieldworkers either because they were unaware of the risk of rifampicin resistance or because the drug(s) to be combined with rifampicin had not been delivered in time. Faced with this pattern of rifampicin use, WHO – and many scientists and voluntary agencies – feared the emergence and spread of rifampicin resistance, which would compromise the potential of this potent antibiotic for improving leprosy control at a time when the development of new antibiotics highly active against *M. leprae* was not foreseen.

A strong demand for WHO recommendations

Both the reputation of rifampicin and its uncontrolled use grew with time. As a result, governments and voluntary organizations came increasingly to expect clear, applicable, and authoritative recommendations from WHO for MDT in leprosy. Recommendations for regimens that would be practicable under field conditions were needed, probably based on the monthly administration of rifampicin – commonly used by clinics – to allow reliable supervision of ingestion.

The urgent need of governments for recommendations from the Leprosy unit at WHO headquarters (Geneva) was underlined by the fact that two WHO regional meetings – in the South-East Asian region in 1980 and in the Western Pacific region in 1981 – discussed and made recommendations on various MDT regimens.
Recommendations from WHO were also eagerly awaited by NGOs, notably ILEP; this was demonstrated on a particular occasion in early 1981. At the time, the ILEP Medical Commission was planning a meeting at which it was intended to issue recommendations on combined chemotherapeutic regimens for field use. Following correspondence between members of the ILEP Medical Commission, the Chairman of the THELEP Steering Committee and Chief, LEP, the meeting organizers agreed to delay the issue of their recommendations until WHO had made its own.

To complicate matters further, MDT regimens involving rifampicin and Isoprodian® – a fixed combination of dapsone, protionamide, and isoniazid – had been promoted since the early 1970s by Freerksen and his colleagues (*6*). These regimens were based on experimental methods and interpretations whose value was not generally accepted, and their promotion risked causing further confusion for leprosy workers and health authorities in some countries.

The response from WHO

It was clear to WHO/LEP that putting an end to the anarchic use of rifampicin and responding to the general demand for guidance made it crucial to issue recommendations for MDT regimens *for immediate use*. At the same time, it was recognized that, whatever MDT regimens were selected, their implementation would require several years of preparation at all levels before any patient would start to benefit. Meanwhile, the anarchic use of rifampicin and the risk of resistance to rifampicin (and to both rifampicin and dapsone) would certainly continue to increase.

While this delay between the issue of recommendations and implementation was to some extent inevitable, WHO/LEP was also deeply concerned that, to comply with general ethical considerations, the relevant WHO authorities would advise that established WHO practices should be followed, i.e. the validity of the proposed MDT regimens should be demonstrated in clinical trials before the regimens could be recommended for field use. This would entail a further delay – of as much as 9 years – and risked further compromising the potential usefulness of rifampicin. The way in which this particular difficulty was dealt with is described in Chapter 6.

In 1981, in close collaboration with the THELEP Steering Committee and the Scientific Working Group, WHO/LEP organized a meeting of the Study Group on Chemotherapy of Leprosy for Control Programmes.

2.2 The meeting

Design of the meeting

It is useful to note here that, while WHO Expert Committee meetings deal with all aspects of a disease (or programme), Study Group meetings are concerned only with a specific or limited aspect of the disease/programme. To discuss chemotherapy of leprosy, it was thus appropriate to convene a Study Group meeting. In addition, no more than about 10 participants are generally invited to WHO Expert Committee meetings, a Study Group meeting can be much larger – and requires planning only a year in advance, as opposed to two years for an Expert Committee.

In view of the failure of the recommendations made by the fifth meeting of the WHO Expert Committee on Leprosy, WHO/LEP was anxious to maximize the chances of developing a set of recommendations on MDT for leprosy control that would be both effective and practicable – and hence readily acceptable by all concerned (patients, leprosy workers, scientists, and voluntary organizations).

Clearly, the scientific knowledge required for designing the type of regimen(s) needed, or at least adapting the regimen already designed for field trials in lepromatous leprosy, was to be found within the THELEP Scientific Working Group. It was also expected that recommendations seen as emanating from a group with the expertise and reputation of THELEP would be readily accepted by all users.

In view of the operational difficulties that had made it impossible to implement the recommendations of the fifth meeting of the Expert Committee, it was deemed crucial for the Study Group to include a significant number of experienced leprosy control workers. These participants would be able to explain to the researchers the operational constraints and practical problems to be expected at the various organizational levels of control programmes based on MDT. To ensure representation of a wide range of views in discussions, WHO/LEP considered that it was preferable to have a rather large number of participants. A total of 25 were invited, approximately half from the research side and half from the control side, of whom two were unable to attend the five-day meeting. The following details are given in the appendices to this section:

- the proposal for the Study Group meeting submitted by WHO/LEP (Appendix 1)
- meeting participants (Appendix 2)
- the provisional agenda (Appendix 3).

Progress in discussions

The Study Group meeting was held at WHO headquarters in Geneva. Professor M.F. Lechat chaired the meeting, Dr K. C. Das was Vice-Chairman, and Dr M. Christian the Rapporteur. As Chief of LEP, the author was responsible for organizing the meeting and acted as Secretary of the Study Group.

The meeting agenda (Appendix 3) included reports on leprosy control programmes in four countries of special significance, followed by information papers on the most important subjects for discussion. In addition, a working paper entitled *Points for discussion on chemotherapy in leprosy control programmes* (*10*) had been prepared by C. Vellut and M.F.R. Waters to summarize the information papers and to enlarge on the essential topic of MDT regimens that might be suitable for various categories of patients. Finally, two days of group discussions were planned, to deal with the points on which it was essential to reach conclusions.

The Vellut & Waters working paper was an excellent, detailed, and comprehensive document and an ideal basis for discussions. Its main points may be summarized as follows:

- Regimens for eight categories of MB patients were discussed. The regimen for "newly diagnosed, untreated multibacillary patients" is shown in Table 2.1. It was similar to the regimen for THELEP field trials, except that the regimen proposed by Vellut & Waters did not include injections of acedapsone: because this drug is only bacteriostatic, not bactericidal, it did not meet the requirements for inclusion in an MDT regimen of limited duration (*8*).

  Since the duration of combined chemotherapy necessary to kill all *M. leprae* persisters in MB patients (who have little, if any, cell-mediated immunity) was unknown, the working paper was very uncertain about the appropriate duration of the regimen. For discussion, it proposed 2 years, 5 years, or 2 years followed by dapsone monotherapy up to smear-negativity followed by a further 2 years of triple drug therapy, but other possibilities were not excluded.

  For all other categories of MB patients, the standard regimen – or a close alternative – was proposed; for patients refusing clofazimine, for example, the same regimen with clofazimine replaced by ethionamide was proposed.

For MB patients "under treatment with dapsone monotherapy with apparent success" but still smear-positive, the same standard regimen was proposed. It was suggested (subject to discussion) that the triple drug therapy be continued until the patient had become smear-negative and had remained negative for 2 years thereafter, "at the end of which time treatment should be stopped".

- For PB patients, it was suggested that a regimen of dapsone, 100 mg daily, with rifampicin – 600 mg on the first two days of treatment and 600 mg once every four weeks (supervised) thereafter – would be appropriate. However, the duration of treatment proposed for discussion was rather uncertain (6, 8, or 12 months).

The final section of the working paper, concerning the introduction of MDT into leprosy control programmes, drew attention to:

– the need for acceptance of MDT by all concerned, i.e. patients, health personnel, and administrators;
– the importance of health education;
– the need to train all categories of personnel in the new methods, including bacteriological examination;
– treatment activities, including post-MDT follow-up of PB and MB cases; and
– managerial and logistic aspects – drug procurement and delivery records, human and financial resources.

Discussions progressed smoothly in the formal setting of the meeting, but many important topics were also addressed in the more informal context at participants' hotels. Indeed, it was the author's impression that consensus on at least one essential point (possibly the standard regimen for MB patients) was reached during one of these "extramural" sessions.

The Study Group appeared pleased with the outcome of the meeting, feeling that they had gone as far as they could in reaching a proper balance between the relative simplicity of the proposed regimens and the likelihood of satisfactory efficacy.

The final report (*22*)

The final report ran to a total of 33 pages in the English version and dealt clearly and concisely with the following topics:

1. The various aspects of the overall problem – primary and secondary dapsone resistance, secondary resistance to other bactericidal antileprosy drugs, persistence of *M. leprae*, difficulties in implementing the therapy recommended in the fifth report of the WHO Expert Committee on Leprosy, and the present situation.

2. Drugs for multidrug regimens, with a clear demonstration of why only dapsone, rifampicin, clofazimine, and ethionamide/protionamide should be considered for inclusion in multidrug regimens.

3. Recommended chemotherapeutic regimens
   - Treatment of multibacillary leprosy:
     – at least 2 years' duration and, wherever possible, up to smear negativity
     – recommended standard regimen:

rifampicin	600 mg once monthly, supervised
dapsone	100 mg daily, self-administered
clofazimine	300 mg once monthly, supervised, and
	50 mg daily self-administered.

   - Treatment of paucibacillary leprosy:
     – recommended standard regimen:

rifampicin	600 mg once a month for 6 months
dapsone	100 mg daily for 6 months

4. Operational aspects – case detection, laboratory facilities, drug delivery, medical care, records and follow-up, health education, equipment and drugs, human and financial resources, planning and evaluation, and training.

5. Research needs.

The most important points made in the report were as follows (the first is a quotation from the report).

- "Further delays in implementing well-planned and well-executed programmes of combined chemotherapy could result in a catastrophic situation, with a further increase in the prevalence of dapsone resistance and the development of multidrug resistance."
- Clear-cut definitions of MB and PB leprosy in relation to the Madrid and Ridley–Jopling classifications. When the bacteriological status was available, PB leprosy included all patients with bacteriological index <2 according to the Ridley scale at any site.
- Precise composition of regimens recommended for MB and PB leprosy and a precise duration of the regimen for PB leprosy. For MB leprosy, it was recommended that "combined therapy be given for at least two years and be continued, wherever possible, up to smear negativity".
- Definition of priorities for introducing MDT for various categories of PB patients (who represented the largest number of leprosy cases).
- In the light of the changes to be introduced in most aspects of leprosy control activities for the implementation of MDT, a comprehensive list of the operational requirements corresponding to the newly recommended chemotherapy.

Clearly, the most essential feature of the report was the standard regimen recommended for MB patients. It can be seen from Table 2.1 that the Study Group had modified the standard regimen proposed for discussion in the Vellut & Waters working paper in two ways:

- Simplification – only one 600-mg dose of rifampicin monthly, instead of two (on consecutive days). The Group had probably judged this reduction in dosage acceptable in view of the existing evidence of the effect of a single 600-mg dose of rifampicin over several weeks.
- Adaptation of clofazimine dosage – to increase its killing effect on rifampicin-resistant *M. leprae* mutants, the monthly dose of clofazimine was supplemented by daily doses.

The last chapter of the report, on research needs, identified relevant areas where important knowledge was lacking – mainly in relation to optimal doses of clofazimine for monthly and daily administrations and to the activity of ethionamide/protionamide on *M. leprae*. On the whole, however, regimens recommended by the Study Group were based on existing knowledge supplemented by reasonable extrapolations, and thus had a good chance of responding to the requirements. The Study Group's most important conclusion with respect to research needs was that "A particularly useful study … would be an investigation into the effectiveness of the recommended regimens under varying operational conditions. Other needs will be met by the ongoing or planned research sponsored by THELEP."

In addition to scientific aspects of MDT regimens, the Study Group was much concerned with the problems posed by the considerable increase in the cost of leprosy services resulting from the introduction and implementation of MDT. Participants were aware that the cost of the reorganization of leprosy control services required in advance of the implementation of MDT would greatly exceed that of the drugs to be used. As a consequence, MDT coverage would have to be expanded in a phased manner, allowing the increase of expenditure to be progressive and, it was hoped, affordable. In LEP, it was thought that the global level of annual budgets of voluntary organizations (about US$ 50 million in total for ILEP member associations) would be sufficient to cover the additional financial input that MDT implementation would require.

In conformity with WHO regulations, the report of the Study Group on Chemotherapy of Leprosy for Control Programmes – then already printed and ready for distribution – was reviewed and endorsed by the WHO Executive Board on 17 May 1982 (*23*). This was its official "date of birth".

References

1. *WHO Expert Committee on Leprosy. Fifth report*. Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 607).
2. Pearson JMW, Haile GS, Rees RJW. Primary dapsone-resistant leprosy. *Leprosy Review*, 1977, 48:129–132.
3. Pearson JMW et al. Dapsone-resistant leprosy in Ethiopia. *Leprosy Review*, 1979, 50:183–199.
4. Rees RJW et al. Long-term treatment of dapsone-resistant leprosy with rifampicin: clinical and bacteriological studies. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1976, 44:159–169.
5. *Third annual report of the Special Programme for Research and Training in Tropical Diseases*. World Health Organization, 1979 (document TDR/AR (3) 79.7).
6. Freerksen E, Rosenfeld M. Leprosy eradication project of Malta. First published report after 5 years of running. *Chemotherapy*, 1977, 23:356–386.
7. *Report of the third meeting of the Scientific Working Group (SWG) on the Chemotherapy of leprosy (THELEP)*. Geneva, World Health Organization, 1980 (document TDR/THELEP-SWG/80.3).
8. Ellard GA. *Available drugs for the treatment of leprosy*. Geneva, World Health Organization, 1981 (document LEP/INF/81.3).
9. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *Journal of Antimicrobial Chemotherapy*, 1979, 3:115–132.
10. Vellut C, Waters MFR. *Points for discussion on chemotherapy in leprosy control programmes*. Geneva, World Health Organization (document LEP/SG/WP/81.1).

11. Laing ABG, Waters MFR, Rees RJW. Four-weekly ‘pulse’ therapy with rifampicin in sulfone-resistant lepromatous leprosy – interim report. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1979, 47:437.
12. Languillon J, Yawalkar SJ, McDougall AC. Therapeutic effects of adding rimactane (rifampicin) 450 mg daily or 1200 mg once monthly in a single dose to dapsone 50mg daily in patients with lepromatous leprosy. *International Journal of Leprosy and Other Mycobacterial Disease*, 1979, 47:37–43.
13. Levy L. *Design of chemotherapeutic regimens for the control of leprosy*. Geneva, World Health Organization (document LEP/INF/81.4).
14. *Report of the second meeting of the Scientific Working Group (SWG) on the chemotherapy of leprosy (THELEP)*. Geneva, World Health Organization (document TDR/THELEP-SWG (2) 79.3).
15. *Fourth annual report of the Special Programme for Research and Training in Tropical Diseases*. Geneva, World Health Organization, 1980 (document TDR/AR (4) 80.8).
16. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. *Tropical disease research: a global partnership. Eighth programme report: the first ten years, with highlights of the 1985–86 biennium*. Geneva, World Health Organization, 1989.
17. Christian M. *Operational aspects of chemotherapy of leprosy*. Geneva, World Health Organization (document LEP/INF/81.5).
18. Jacobson RR, Hastings RC. Rifampicin-resistant leprosy. *Lancet*, 1976, ii: 1304–1305.
19. *Heathrow report: how to combat dapsone-resistance*. London, International Federation of Anti-Leprosy Associations, 1977.
20. Report of the Workshop on epidemiology and control including field therapy of the 18th International Leprosy Congress, Mexico City, 13–18 November 1978. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1979, 47:304–306.
21. *A guide to leprosy control*. Geneva, World Health Organization, 1980.
22. *Chemotherapy of leprosy for control programmes. Report of a WHO Study Group*. Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 675).
23. *Seventieth session of the Executive Board, Geneva, 17–18 May 1982. Volume 1. Resolutions and decisions*. Geneva, World Health Organization, 1982 (document EB70/1982/REC/1).

Appendix 1

Study Group on Chemotherapy of Leprosy for Control Programmes

Geneva, 12–16 October 1981

1. Background and justification

1.1 The last meeting of the WHO Expert Committee on Leprosy (October 1976) made recommendations on chemotherapeutic regimens for leprosy and, in particular, lepromatous leprosy. Since then, there has been no significant application of the recommended use of multidrug regimens for lepromatous leprosy in large-scale control programmes.

1.2 The applicability of some of the regimens then recommended appears to need review,

1.3 More information on drugs and drug regimens has been accumulated since the last Expert Committee meeting. In particular, the possibility of using drugs like rifampicin and clofazimine intermittently has gained acceptance, and this could well be a solution to the main difficulties encountered in the application of the Expert Committee's previous recommendations.

1.4 There is a need to review therapy of paucibacillary leprosy and to consider "fixed duration" treatment.

1.5 There is a need to look into further research possibilities in terms of clinical trials and operational studies.

1.6 Recently, recommendations have been made in WHO regional meetings, i.e. SEARO Intercountry Consultative Meeting on Leprosy, 2–7 July 1980, and the WPRO Working Group on Drug Policy and Operational Research in the Leprosy Programme, Manila, 16–18 February 1981. These recommendations need review in order to establish proposals for a shortlist of the most effective and practicable regimens.

1.7 Also, the International Federation of Anti-Leprosy Associations has recently made its own recommendations. It appears necessary to review these proposals and maintain WHO technical leadership in this area.

2. Objectives of the meeting

2.1 To review the information on problems related to chemotherapy and on chemotherapeutic regimens for leprosy, which has accumulated since the fifth meeting of the WHO Expert Committee.

2.2 To recommend alternative multidrug regimens for dapsone-treated and new multibacillary cases in control programmes.

2.3 To recommend regimens for clinically suspected dapsone-resistant multibacillary cases in control programmes.

2.4 To recommend regimens for paucibacillary cases in control programmes.

2.5 To identify further research needed in clinical and operational aspects of chemotherapy of leprosy.

3. Participation

A great deal of scientific knowledge on drugs for leprosy and the rationale for designing drug regimens exists within the THELEP Scientific Working Group. This expertise is, of course, essential. On the other hand, those in charge of control programmes are well acquainted with the practical problems encountered in the field. In order to achieve the best possible interaction between both types of experts, it is proposed to have an equal number of participants from both sides.

Also, because epidemiological and socioeconomic conditions have implications in treatment delivery, a proper balance has to be kept between representatives from areas with different epidemiological and socioeconomic conditions. In total, it is planned to have about 25 participants plus secretariat (members).

4. Report

It is expected that the report of the Study Group will include recommendations of practical applicability in all leprosy control programmes, and therefore its publication in the Technical Report Series will be requested.

Appendix 2

Study Group on Chemotherapy of Leprosy for Control Programmes: List of participants

Members *

Dr R.B. Adiga, Chief, Leprosy Services Development Board, Ministry of Health, Pachali, Kathmandu, Nepal
Dr H.A. Ahmed, Director, Epidemiology Department, Ministry of Health, Khartoum, Sudan
Dr M. Christian, Chief, Epidemiology and Control, Schieffelin Leprosy Research and Training Centre, Karigiri, India (*Rapporteur*)
Dr K.C. Das, Assistant Director General of Health Services (Leprosy), Directorate General of Health Services, New Delhi, India (*Vice-Chairman*)
Dr K.V. Desikan, Director, Central Jalma Institute for Leprosy, Taj Gang, Agra, India
Dr Le Kinh Due, Clinic of Dermatology and Venereology, Bach Mai Hospital, Hanoi, Viet Nam
Dr G.A. Ellard, National Institute for Medical Research, London, England
Professor J.H. Grosset, Professor of Bacteriology, Faculté Pitié-Salpêtrière, Paris, France.
Dr R.R. Jacobson, Chief, Clinical Branch, National Hansen's Disease Center, Carville, LA, USA
Dr Lim Kuan Joo, National Leprosy Control Centre, Sungei Buloh, Selangor, Malaysia
Dr Kyaw Lwin, Deputy Director (Leprosy Control), Department of Health, Ministry of Health, Rangoon, Burma[1]
Professor M.F. Lechat, Head, Epidemiology Unit, School of Public Health, Catholic University of Louvain, Louvain, Belgium (*Chairman*)
Dr D.L. Leiker, Royal Tropical Institute, Amsterdam, Netherlands
Dr L. Levy, Department of Comparative Medicine, Hebrew University – Hadassah Medical School, Jerusalem, Israel
Dr Roushdy Mohareb, Director of Leprosy Control, Ministry of Health, Cairo, Egypt
Dr S.J. N'kinda, Senior Medical Officer-in-Charge, Tuberculosis/Leprosy Control, Ministry of Health, Dar es Salaam, United Republic of Tanzania
Dr D.V.A. Opromolla, Chief Medical Officer, Hospital Lauro de Souza Lima, Bauru, São Paulo, Brazil
Dr D.M. Owili, Director, Alupe Research Centre, Busia, Kenya
Professor S.R. Pattyn, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium
Dr J.K. Seydel, Department of Medicinal and Pharmaceutical Chemistry, Borstel Research Institute, Borstel, Federal Republic of Germany[2]
Dr Teera Ramasoota, Director, Leprosy Division, Bangkok, Thailand
Dr Claire Vellut, Honorary Consultant, Hemerijckx Government Leprosy Centre, Polambakkam, Tamil Nadu, India
Dr Ye Gan Yun, Deputy Director, Institute of Dermatology, Chinese Academy of Medical Sciences, Taizhou, Jiangsu Province, China
Dr Y. Yuasa, Medical Director, Sasakawa Memorial Health Foundation, Tokyo, Japan

Secretariat

Dr S.K. Noordeen, Medical Officer, Leprosy, WHO, Geneva, Switzerland
Dr H. Sansarricq, Chief Medical Officer, Leprosy, WHO, Geneva, Switzerland
Dr M.F.R. Waters, National Institute for Medical Research, London, England (*Consultant*)

* Unable to attend:
Dr M. Adhyatma, Director General for Communicable Diseases, Department of Health, Jakarta, Indonesia; Dr C.C. Shepard, Chief, Leprosy and Rickettsia Branch, Centers for Disease Control, Atlanta, GA, USA.

[1] Now Myanmar.
[1] Country name correct at the time of the Study Group meeting.

Appendix 3

Study Group on Chemotherapy of Leprosy for Control Programmes: Agenda

Monday 12 October 1981

09:30 Opening of the meeting
Scope and objectives of the meeting (Dr Sansarricq)

10:00 Review of country leprosy control programmes in relation to chemotherapy
Country reports:
- India (Dr Das)
- Burma[3] (Dr Kyaw Lwin)
- United Republic of Tanzania (Dr N'kinda)
- Brazil (Dr Opromolla)

General discussion and comments on other problems related to chemotherapy in leprosy control programmes in other countries

14:00 Information papers:
- Dapsone resistance (Dr Desikan)
- Microbial persistence in mycobacterial infections (Professor Grosset)
- Available drugs (Dr Ellard)
- Design of regimens (Dr Levy)

Tuesday 13 October 1981

09:00 Information papers (continued):
- Operational aspects (Dr Christian)

Working paper:
- Points for discussion on chemotherapy in leprosy control programmes (Dr Vellut and Dr Waters)

14:00 Group discussions:
- Group 1: Regimens for new and previously treated multibacillary cases
- Group 2: Regimens for resistant multibacillary cases
- Group 3: Regimens for paucibacillary cases

Wednesday 14 October 1981

09:00 Preparation of Group reports

14:00 Discussion on the first part of the final report of the meeting

Thursday 15 October 1981

09:00 Discussion of Group reports

14:00 Discussion of the strategy for implementation of regimens and research needs

Friday 16 October 1981

10:00 Discussion and adoption of the final report of the meeting

[3] Now Myanmar.

Chapter 3

Implementation of MDT

3.1 Successive steps

D. Daumerie

This section attempts to analyse the various aspects of the evolution of MDT implementation from 1982 to date.

Implementation of MDT started gradually, on a pilot basis, over the period 1982–1985; coverage during this time was less than 1%. Subsequently, MDT was implemented in many endemic countries, and the geographical coverage began to increase significantly, reaching almost 50% by the end of 1992 (see Table 3.1).

Table 3.1
MDT coverage from 1985 to 2000

End of year	Registered cases	New cases	Patients treated with MDT	Cumulative total cured with MDT	Geographical MDT coverage
1985	5 368 202	550 224	78 752	9 425	1%
1986	5 341 000	573 790	468 222	93 216	9%
1987	5 078 000	594 145	1 318 964	515 144	26%
1988	4 908 000	553 597	1 604,927	627 919	33%
1989	3 866 000	550 743	1 751903	853 706	45%
1990	3 737 000	571 792	2 080 998	1 204 821	56%
1991	3 087 788	584 412	1 295 640	2 870 944	42%
1992	2 291 581	653 354	1 117 508	4 238 118	49%
1993	1 671 497	590 933	911 802	5 658 989	55%
1994	1 291 848	560 646	984 005	6 687 189	76%
1995	926 259	529 376	842 438	7 988 404	91%
1996	888 340	566 604	862 998	8 416 321	97%
1997	804 396	693 462	803 021	9 095 409	100%
1998	820 205	804 449	820 205	9 974 000	100%
1999	753 263	738 284	753 263	10 759 213	100%
2000	611 000	655 000	611 000	>11 million	100%
2001	597 232	719 330	597 232	12 million	100%
2002	534 311	620 672	534 311	13 million	100%

However, the definition of MDT coverage was not standardized among countries, and the statistics from 1989 to 1994 should be analysed with caution. During this period India, for example, defined MDT coverage as the proportion of districts in which MDT was implemented; thus, even if only one health facility in a district began implementing MDT, the whole district was considered to be under MDT. Moreover, although the figures reported at that time implied that all registered patients in a district where MDT had been implemented were treated with MDT, this was not the case – most patients continued to get dapsone monotherapy. Information collected later showed that it was only after 1998 that all the patients in India were treated with MDT.

Main events, 1982 onwards

Four successive periods, or phases, can be identified in the implementation of MDT:

- 1982–1985 – Introduction of MDT on a global basis
- 1986–1990 – Expansion of MDT (into the "less difficult" areas)
- 1991–1999 – Elimination strategy
- 2000 onwards – a fourth period, planned to last 6 years, designated for the "Intensive elimination strategy" or the "Final push".

1982–1985: Introduction of MDT

During the 4 years 1982–1985, the use of MDT as recommended by the 1981 Study Group was very actively promoted by WHO and more precisely by headquarters leprosy unit (LEP) and the two Regional Offices for South-East Asia and the Western Pacific (see section 6.1).

The Study Group recommendations on MDT were promptly endorsed by JSIF and ILEP (except, in the latter case, in relation to Isoprodian®). From the very first, the active cooperation and financial contributions of these agencies were of critical importance for the implementation of MDT. Not unnaturally, the early "pilot" projects were undertaken in areas where conditions were relatively favourable.

Two meetings proved particularly important to the preparation for, and early steps in, MDT implementation. At a meeting on action plans for leprosy control (*1*), organized by LEP in New Delhi in August 1982, representatives from WHO headquarters and regional offices and from JSIF and ILEP were able to discuss in detail all the implications of MDT implementation. In October 1985, at a WHO consultation on implementation of MDT therapy for leprosy control (*2*), the same partners reviewed several MDT implementation projects and began to draw lessons from the experiences of these projects. At that time – 4 years after the Study Group meeting, and 3 years after the publication of its recommendations – global MDT coverage was about 1%.

1986–1990: Expansion of MDT into the "less difficult" areas

The profound changes that were needed in the structure and function of all leprosy control programmes before MDT implementation led to the recommendation that MDT be expanded in a phased manner, covering first the areas with more favourable conditions. Indeed, some countries started MDT only for selected MB patients while a number of others significantly modified the recommended regimen. In general, the areas covered during this period were the less difficult ones. Globally, geographical coverage with MDT increased steadily from 1% in 1985 to around 40% in 1990 – progress that may be considered quite satisfactory under the circumstances.

Understandably, there were no important change in policy during this period. At its sixth meeting, in November 1987, the WHO Expert Committee on Leprosy (*3*) endorsed the recommendations of the 1981 Study Group regarding the content and duration of MDT regimens and post-treatment surveillance. However, the Committee made a change to the definition of MB and PB cases provided by the Study Group: for the purpose of MDT, all smear-positive cases were henceforth to be included in the MB group. Consequently, good bacteriological services continued to be considered essential for correct MDT implementation.

In 1988, WHO published the second edition of *A guide to leprosy control* (*4*), incorporating all considerations relevant to MDT and its implementation as well as other aspects of leprosy control.

Strenuous efforts to strengthen cooperation between LEP and WHO's regional offices, as well as among WHO, governments, and voluntary agencies, were made. To this end, two further coordinating meetings on implementation of MDT were held, in November 1986 (*5*) and September 1988 (*6*) respectively. At the September meeting, it was pointed out that Africa was far behind other parts of the world in implementing MDT and a meeting was planned for 1989 to decide on the mechanisms by which African countries could catch up (*7*).

A number of international technical meetings were convened by WHO during this period to discuss methods of accelerating MDT implementation. Subjects of special importance were training in leprosy (*8*), MDT and primary health care (*9*, *10*), and assessment of the leprosy situation (*11*, *12*).

By the end of 1990, accumulated experience had advanced the thinking on MDT implementation. A consultation on technical and operational aspects of leprosy (*13*) held in Malé, Maldives, in June 1990 accepted that MDT could be started "even in areas with relatively limited health development and human resources", and concluded that it should be possible to start MDT "even before establishing reliable skin smear services" and that "programmes should consider wider application than hitherto considered of fixed-duration treatment of 24 months of MDT for MB patients".

1991–2000: Elimination of leprosy as a public health problem

In May 1991, the World Health Assembly adopted resolution WHA44.9 (see Appendix 1) on elimination of leprosy as a public health problem, committing the governments of endemic countries to reach the global target prevalence of less than one case per 10 000 population by the year 2000. The rationale of the elimination initiative included the following three points:

- the availability of highly effective treatment (MDT) to cure the disease;
- willingness to change the attitude of passively accepting leprosy as a perennial problem;
- in many endemic countries, the favourable epidemiological trend of a "naturally decreasing epidemic".

The adoption of the WHA resolution by all Member States was a crucial step, which unquestionably allowed the most effective use to be made of the MDT-based elimination strategy. It resulted in a period of intensive expansion of MDT during which geographical coverage increased from 42% in 1991 to 100% in 1997 (and subsequently). Implicit in the elimination strategy was the notion that, with leprosy prevalence reduced to less than one case per 10 000 population, and provided that all cases were detected and all patients cured as a

result of complete MDT coverage, prevalence would continue to decline and the disease would finally disappear (*14*). This vision, while clearly most appealing from the public health viewpoint, was strongly questioned by some renowned epidemiologists (*15*).

The elimination phase was essentially characterized by ever-greater efforts to tackle the wide range of problems related to the expansion of MDT coverage to areas or population groups that were increasingly remote or difficult to access. During this phase the Nippon Foundation's pledge of US$ 50 million, made at the first International Conference on Elimination of Leprosy held in Hanoi in July 1994 (*16*), for the procurement of MDT drugs over the succeeding five years was of critical importance.

Evolution in technical policy and introduction of new strategies

- At its meeting in November 1993, the WHO Study Group on Chemotherapy of Leprosy, (*17*) recommended two important simplifications related to MDT implementation:
  - The regimen for MB patients should be of a standard duration of 2 years.
  - Post-MDT annual surveillance of patients should be discontinued.

  The Group also suggested some flexibility concerning the use of bacteriological services and relaxed the requirement for supervision by health workers of monthly doses of rifampicin and clofazimine.

  In 1992 the gradual introduction of MDT "calendar" blister packs had begun, and WHO began global supply of these packs for fixed-duration MDT for MB and PB patients in 1995.

- *A guide to eliminating leprosy as a public health problem* (*18*) was published in 1995.

- At its meeting in May/June 1997, the WHO Expert Committee on Leprosy introduced some important changes (*19*):
  - For purposes of MDT, patients should be classified in three categories:
    - PB leprosy (single skin lesion)
    - PB leprosy (2–5 skin lesions)
    - MB leprosy (more than 5 skin lesions).
  - For MDT regimens, the Committee made the following recommendations:
    - PB leprosy, single skin lesion: a single 600-mg dose of rifampicin plus 400 mg ofloxacin and 100 mg minocycline (ROM) is an acceptable alternative regimen.
    - PB leprosy: no change.
    - MB leprosy: the duration of the current MDT regimen could be reduced to 12 months without significantly lowering its efficacy.

  More than one month's supply of MDT blister calendar packs could be given to the patient whenever necessary. To increase MDT coverage, two new strategies were recommended:
  - leprosy elimination campaigns (LECs) in pockets of high leprosy prevalence;
  - special action projects for the elimination of leprosy (SAPEL) to reach patients living in remote areas or under difficult conditions.

- Other important documents that provided updated guidelines for implementing the elimination strategy were published in 1994 (*20*) and 1995 (*18*).

- At the fourth meeting of the Leprosy Elimination Advisory Group (LEAG), held in Geneva in June 1998, WHO noted that "virtually every patient was receiving MDT" but that "some countries may need to continue and intensify activities beyond the year 2000 to reach their elimination targets" (*21*).

  In April 1999 a special meeting of the LEAG held with potential partners (*22*) acknowledged that about 12 countries would not reach the national elimination target by the end of the year 2000. The elimination strategy should therefore focus on these 12 countries, intensifying efforts of LECs. A consultative meeting on LECs held in July 1999 reviewed the results of campaigns carried out until that date and provided guidelines for improving their effectiveness (*23*).

- The Third International Conference on the Elimination of Leprosy (*24*), held in Abidjan in November 1999, reviewed the status quo (*25*):
  - The registered global prevalence of leprosy was around 1.4 per 10 000 inhabitants.
  - Almost all leprosy patients were treated with MDT.

  Clearly, the elimination process had made tremendous progress and the elimination strategy remained valid. However:
  - The number of new cases detected annually remained constant or was increasing.
  - Around 735 000 registered cases and 750 000 new cases – which represented 90% of the prevalence and detection worldwide – were found in the 12 most highly endemic countries. Just one year before the target date for elimination, the aggregate prevalence rate in these top endemic countries was still 4.5 per 10 000 inhabitants, more than 4 times the elimination level.

  In response to this situation, WHO and its partners launched the Global Alliance for the Elimination of Leprosy (GAEL). The general objective of GAEL was to reach the elimination target prevalence at country level by the end of 2005 by focusing its activities on the 12 top endemic countries; a strategic plan to that end was adopted (*26*). Financial contributions to GAEL were pledged, notably by The Nippon Foundation/Sasakawa Memorial Health Foundation, the Novartis Foundation for Sustainable Development, and ILEP. Shortly thereafter, however, ILEP withdrew its pledge. The GAEL action plan became known as "The Final Push" (towards elimination).

Advocacy at the highest level and coordination

The most significant efforts made to enhance the commitment and active participation of all partners – principally the major endemic countries themselves – were the three International Conferences on the Elimination of Leprosy. The first of these (*16*), held in Hanoi, Viet Nam, in July 1994, was organized by WHO at the initiative of its then Director-General, Dr Hiroshi Nakajima, and co-sponsored by the Sasakawa Memorial Health Foundation (SMHF). It was attended by more than 100 participants from a large number of countries (including the 28 with the highest leprosy prevalence at the time). Dr Nakajima announced the creation of a WHO Special Programme for the Elimination of Leprosy, estimating the cost of implementing the elimination plan over the coming 6 years as around US$ 420 million. Mr Yohei Sasakawa, President of The Nippon Foundation, pledged US$ 50 million over the next 5 years, which represented one-third of the estimated cost of drugs for MDT.

The second International Conference (*27*), held in New Delhi, India, in October 1996, was again organized at the instigation of the Director General of WHO and co-sponsored by the SMHF and the Government of India. The 150 participants, from 25 countries, included the health ministers of 14 endemic countries. Emphasis was again placed on the need to accelerate progress in increasing MDT coverage, and the importance of LECs and SAPEL programmes was agreed. It was recommended that the Leprosy Elimination Monitoring initiative (LEM) be implemented as soon as possible. LEM was designed by WHO as standard procedures for the collection and analysis of data required for a set of key indicators on leprosy and its elimination through independent monitors.

The third of the International Conferences (*24*), again organized by WHO and co-sponsored by SMHF, the Association Française Raoul Follereau, and the Government of Côte d'Ivoire, was held in Abidjan in November 1999. It was at this Conference that the need to extend the elimination plan for a further 6 years was acknowledged and GAEL was established. In 2000, ILEP established official relationships with WHO.

Programme intensification and monitoring

- *Action Programme for the Elimination of Leprosy*
  In December 1994, the WHO Leprosy unit was replaced by the Action Programme for the Elimination of Leprosy (but continued with the same acronym, LEP). The programme was made up of the following components:
  - Office of the Director for overall management
  - Country support and special action projects (CSP)
  - Monitoring and evaluation of elimination (MEE)
  - Capacity building and health systems research (CBH).

- *Advisory groups*
  Achieving the global elimination of leprosy as a public health problem necessitated the redefining of priorities and strategic plans. In this task, LEP was assisted from 1991 to 1994 by the WHO Working Group on Leprosy Control and from 1995 to 1999 by the Leprosy Elimination Advisory Group (LEAG). These two advisory groups included WHO regional advisers for leprosy, representatives from national and international NGOs (International Leprosy Union – ILU, International Federation of Anti-Leprosy Associations – ILEP, International Leprosy Association – ILA, The Nippon Foundation/Sasakawa Memorial Health Foundation – TNF/SMHF, etc.), other contributing agencies (e.g. World Bank), and individual experts. The LEAG had a larger number of members from the various organizations than the Working Group.

  The Working Group and the LEAG held annual meetings (*21, 28–34*) which were important opportunities for exchanges of views and information between NGOs, other contributing agencies, and WHO representatives from headquarters and regional offices. Regular items on the agenda of these meetings were a review of the current status of the elimination programme at global and regional level (and the most highly endemic countries since 1995), as well as statements from representatives of NGOs and other contributing agencies.

  There was full agreement between NGOs – especially ILEP – and WHO on the main final objective of leprosy control activities: in 1990, ILEP had adopted the objective of "MDT for all leprosy patients by the year 2000" which was essentially the same as

WHO's elimination target (*28*). However, voluntary agencies were unhappy with the definition of a leprosy case used and recommended by WHO, according to which patients "bacteriologically cured" but having residual disabilities were no longer "cases" of leprosy. They were also concerned that the general public would believe that, with the *elimination* of leprosy, the task had been completed and this would adversely affect fundraising activities.

At its first meeting, the Working Group recommended that WHO should establish a task force to promote health systems research (HSR). This task force held three meetings – in 1992 (*35*), 1993 (*36*), and 1994 (*37*) – and organized various workshops and training activities. Following a recommendation made at the fourth meeting of the Working Group (*31*), two further task forces – Monitoring and Evaluation of Elimination of Leprosy (MEE), and Capacity Building and Health Systems Research (CBH), replacing the original task force on HSR – were established, together with a Steering Committee on Special Action Projects. The activities of these task forces and of the Steering Committee were reviewed at LEAG meetings.

At the first meeting of the LEAG (*32*), WHO introduced the concept of the LEC, which has proved to be one of the most effective tools for detecting hidden cases. In October 1996, the second meeting of the MEE task force reported to the LEAG that analysis of data from 24 countries for the period 1985–1995 showed a dramatic fall in prevalence, although the number of newly detected cases had remained static (*33*).

In June 1998, at the fourth meeting of the LEAG, WHO indicated for the first time that "some countries may need to continue and intensify activities beyond the year 2000 to reach their elimination targets". As a consequence, the LEAG recommended that "a long-term comprehensive strategy for leprosy" be developed for presentation in 1999. This appeared as *The final push towards elimination of leprosy: strategic plan 2000–2005*, prepared by the WHO Leprosy Elimination Group (*26*).

2000 onwards: the Final Push

At the end of 2000, the global prevalence rate was just below one per 10 000 population, enabling WHO and its partners to announce in May 2001 that the overall target set 10 years earlier for the global elimination of leprosy as a public health problem had been reached.

The Strategic Plan

The preface to the Strategic Plan document (*26*) stated, "Today, we can be confident that elimination – the reduction in prevalence to less than one case per 10 000 population at national level – is within reach in all countries by the end of 2005." The Plan classified the endemic countries in three groups:

- *Group 1*: 12 countries that need special efforts to intensify the elimination strategy (Angola, Brazil, Central African Republic, Democratic Republic of the Congo, Guinea, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, and Niger).
- *Group 2*: 12 countries where the elimination strategy should be accelerated.
- *Group 3*: 26 countries where the elimination strategy should be sustained.

In countries of Group 1, "Epidemiological trends over the last 10 to 15 years show high and often increasing detection rates, and geographical coverage with MDT is not complete or has been completed only recently." In those countries, which represent the core of the problem, the specific activities to be intensively implemented, included:

- enabling all health facilities in endemic districts to diagnose and treat leprosy;
- promotion of case-finding by informing the public about the disease and encouraging individuals with suspicious skin lesions to come forward for treatment;
- changing the community image of leprosy through information, education and advocacy.

In other words, as in previous years, the essential conditions for the success of the elimination strategy in its Final Push, were the integration of MDT services into the general health services, and changing the negative image of leprosy and encouraging people to seek treatment.

The Strategic Plan insisted on the key importance to the integration process of capacity building at local level (i.e. concerning general health workers and community health volunteers). With reference to IEC activities, strategies for promoting community action needed to be developed and sectors other than health involved in the elimination plan. The key role of local community leaders in all aspects of the elimination process was identified, as was the need to improve communication and cooperation with the mass media. The Strategic Plan also mentioned the importance of activities related to drug supply and to surveillance and programme monitoring.

Subsequently, WHO established the Global Alliance for the Elimination of Leprosy (GAEL), responsible for advocacy and coordination at the highest level, and a Technical Advisory Group (TAG), concerned with the intensification and monitoring of the elimination programme.

Global Alliance for the Elimination of Leprosy

GAEL was established during the Third International Conference on Elimination of Leprosy, held in Abidjan, Côte d'Ivoire, on 15 November 1999 (*24*). The core members of GAEL then comprised governments of major leprosy-endemic countries, WHO (as secretariat), TNF, ILEP, Novartis, the Danish International Development Assistance (DANIDA), and the World Bank (*38*). The offices of Chair and Vice-chair of GAEL are held by Member State on a rotational basis.

The first meeting of GAEL, held in New Delhi in January 2001, was a kind of forum similar to the three International Conferences on the Elimination of Leprosy, which had taken place during the previous decade. The meeting issued the Delhi Declaration, essentially endorsing the Final Push strategy and recommending that "members of GAEL collaborate in a true spirit of partnership in order to eliminate leprosy as a public health problem from every country by the year 2005".

Brasília was the venue for the second meeting of GAEL, in January 2002, which was attended by high-level delegates of eight major leprosy-endemic countries, representatives from Novartis Pharma AG/Novartis Foundation for Sustainable Development, TNF/SMHF, TAG members, 20 members of the WHO Secretariat, and 84 State Leprosy Coordinators from Brazil; invited representatives from four other countries and from DANIDA and the World

Bank were unable to attend. Observers from 20 United Nations agencies and NGOs (including 14 ILEP member associations) had been invited, but only the Presidents of SMHF and of the American Leprosy Mission were present; this was a consequence of the withdrawal of ILEP from membership of GAEL (in December 2001).

WHO Technical Advisory Group on Elimination of Leprosy

The TAG is responsible for programme intensification and monitoring – much as the WHO Working Group and the LEAG had been responsible during the previous decade. Recommendations made by the TAG at its first meeting, held in May 2000, may be summarized as follows (*40*):

- The present *definition of elimination* should be retained. It was noted, however, that additional indicators would be needed.
- There was a need to improve *reporting systems*.
- "Special efforts will be made to raise awareness and enlist political commitment in order that *countries accept 'ownership' of their leprosy elimination programmes* at national and sub-national levels."
- "*National Task Forces* will be established where necessary in endemic countries. These will provide the medium to greatly enhanced collaboration between national leprosy elimination programmes, nongovernmental organizations, donor agencies, the scientific community and all other partners. At the same time, national task forces will play a leading role in ensuring that leprosy elimination programmes become integrated within the general health services."
- Information, education and communication (IEC): "Primary health care workers need to develop a system of … advocacy activities … to assist people to recognize the early signs of leprosy". "For those without easy access to health services, '*accompanied*' treatment needs to be encouraged."
- "*Operational research* will be the major research priority for the leprosy elimination programme."

The second meeting of the TAG (*41*), held in February 2001, recommended:

- expanding the use of LEM-like exercises;
- developing advice on all aspects of integration using current experiences from integration efforts for other disease-specific programmes.

A TAG subgroup on monitoring and evaluation concluded that the certification of leprosy elimination was not relevant and made a series of detailed recommendations on the use of LEM exercises to provide objective and independent information on progress towards leprosy elimination.

Another subgroup on field studies for strengthening implementation of the elimination strategy identified a number of field studies to be initiated by the Secretariat on: accompanied MDT, integration, relapses following 12 months of MDT and ROM, impact of IEC activities, SAPEL, leprosy in urban areas, use of Prednipacs (each pack containing one standard 12-week course of prednisolone for managing lepra-reactions), MDT regimens of shortened duration, rifampicin resistance, epidemiological models, and leprosy classification systems.

The third meeting of the TAG, in February 2002, made recommendations on various aspects of the elimination strategy; the following two were of special importance (*42*):

– large-scale implementation of accompanied MDT;
– implementation of a research study using 6-month MB MDT regimen as uniform MDT for all leprosy patients (PB and MB)

One of the conclusions of the TAG subgroup on monitoring and evaluation was that significant numbers of patients are kept on treatment registers even after completion of treatment and these patients should be removed from those registers. (*42*).

At its fourth meeting, in June 2002 (*43*), the TAG's main task was to agree on a draft protocol for studying a uniform MDT regimen for all leprosy patients (as indicated above). The protocol was finalized on 20 August 2002. The study is currently being undertaken in several areas/programmes with reasonably well organized leprosy elimination programmes capable of recruiting at least 500 new leprosy patients (250 MB and 250 PB) within 2 years. The patients will be followed for any occurrence of relapses up to seven years after completion of treatment. The final results will be available in 2010.

In view of the alarming increase in the number of new cases detected in some major endemic countries, notably India, this TAG meeting also included a special session on global case-detection trends over the previous 4 years. The trend was paradoxical: information coming from the majority of endemic countries clearly showed that, after repeated LECs, the detection trends showed a significant decline in new cases. It was agreed that these trends in some major endemic countries were mainly the result of a number of operational and administrative shortcomings.

These findings led Dr Neira, in her statement at the 16th International Leprosy Congress (Bahia, Brazil, August 2002), to say that "some countries will not reach the elimination target at the national level by the end of the year 2005".

One might therefore have accepted the view expressed by Professor Lechat when the time target for the elimination was postponed for the first time – that the year 2000 was only a milestone (*21*). The elimination target, and its time-bound nature, have contributed to increasing the crisis that has developed among the partners of the Global Alliance.

References

1. *Report of a meeting on action plans for leprosy control, New Delhi, 23–25 August 1982*. Geneva, World Health Organization, 1983 (document WHO/LEP/83.1).
2. Sansarricq H. *Preliminary review of some points for discussion on implementation of multidrug therapy*. Geneva, World Health Organization, 1985 (document LEP/cons./WP/85.1).
3. *WHO Expert Committee on Leprosy. Sixth report*. Geneva, World Health Organization, 1988 (WHO Technical Report Series, No. 768).
4. *Guide to leprosy control*, 2nd ed. Geneva, World Health Organization, 1988.
5. *Report of the Second Coordination Meeting on Implementation of Multidrug Therapy in Leprosy Control Programmes, Geneva, 4–5 November 1986*. Geneva, World Health Organization, 1987 (document WHO/LEP/87.2).

6. *Report of the Third Coordination Meeting on Implementation of Multidrug Therapy (MDT) in Leprosy Control Programmes, The Hague, 13 September 1988*. Geneva, World Health Organization, 1988 (document WHO/LEP/88.4).
7. *Report of the Interregional Conference on Leprosy Control in Africa, Brazzaville, 6–10 November 1989*. Geneva, World Health Organization, 1989 (document WHO/LEP/89.1).
8. *Training in leprosy*. Geneva, World Health Organization, 1986 (document WHO/LEP/86.2).
9. *Report of a Consultation on Implementation of Leprosy Control through Primary Health Care, Geneva, 16–18 June 1986*. Geneva, World Health Organization, 1986 (document WHO/CDS/LEP/86.3).
10. *Report of the Consultation on Leprosy Control within Urban Primary Health Care, Alexandria, 14–17 November 1988*. Geneva, World Health Organization, 1988 (document WHO/CDS/LEP/88.5).
11. Sundaresan TK. *Sample surveys in leprosy: an introductory manual*. Geneva, World Health Organization, 1986 (document WHO/LEP/86.1).
12. *Report of a Meeting on Methods for the Rapid Assessment of the Leprosy Situation, Geneva, 15–16 April 1988*. Geneva, World Health Organization, 1988 (document WHO/LEP/88.2).
13. *Report of the Consultation on Technical and Operational Aspects of Leprosy, Malé, Maldives, 11–15 June 1990*. Geneva, World Health Organization, 1990 (document WHO/CTD/LEP/90.3).
14. Noordeen SK. Elimination of leprosy as a public health problem. *Leprosy Review*, 1992, 63:1–4.
15. Fine PEM. Reflections on the elimination of leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1992, 60:71–80.
16. *Report of the International Conference on the Elimination of Leprosy as a Public Health Problem, Hanoi, Viet Nam, 4–7 July 1994*. Geneva, World Health Organization, 1994 (document WHO/CTD/LEP/94.5).
17. *Chemotherapy of leprosy. Report of a WHO Study Group*. Geneva, World Health Organization, 1994 (WHO Technical Report Series, No. 847).
18. *A guide to eliminating leprosy as a public health problem*. Geneva, World Health Organization, 1995 (document WHO/LEP/95.1).
19. *WHO Expert Committee on Leprosy. Seventh report*. Geneva, World Health Organization, 1998 (WHO Technical Report Series, No 874).
20. *Global strategy for the elimination of leprosy as a public health problem*. Geneva, World Health Organization, 1994 (document WHO/CTD/LEP/94.2).
21. *Action Programme for the Elimination of Leprosy. Report of the Fourth meeting of the Leprosy Elimination Advisory Group (LEAG), Geneva, 24 and 25 June 1998*. Geneva, World Health Organization, 1998 (document WHO/LEP/98.3).
22. *Report of a special meeting of the Leprosy Elimination Advisory Group (LEAG) with potential partners, Geneva, 12 and 13 April 1999*. Geneva, World Health Organization, 1999 (document WHO/LEP/99.1).
23. *Report of a consultative meeting on leprosy elimination campaigns, Geneva, 14 and 15 July 1999*. Geneva, World Health Organization, 1999 (document WHO/LEP/99.3).
24. *Elimination of leprosy in sight: Global Alliance created to achieve complete elimination by the end of 2005*. Geneva, World Health Organization, 1999 (press release WHO/70, 15 November 1999).
25. *Elimination of leprosy: status report 1999* (draft). Geneva, World Health Organization, 1999.

26. *The final push towards elimination of leprosy: strategic plan 2000–2005*. Geneva, World Health Organization, 2000 (document CDS/CPE/CEE/2000.1).
27. *Report of the Second International Conference on the Elimination of Leprosy as a Public Health Problem, New Delhi, India, 11–13 October 1996*. Geneva, World Health Organization, 1997 (document WHO/LEP/97.1).
28. *Report of the First Meeting of the WHO Working Group on Leprosy Control, Geneva, 1–3 July 1991*. Geneva, World Health Organization, 1991 (document WHO/CTD/LEP/91.4).
29. *Report of the Second Meeting of the WHO Working Group on Leprosy Control, Geneva, 7–9 July 1992*. Geneva, World Health Organization, 1992 (document CTD/LEP/92.5).
30. *Report of the Third Meeting of the WHO Working Group on Leprosy Control, Geneva, 14–16 July 1993*. Geneva, World Health Organization, 1993 (document WHO/CTD/LEP/93.5).
31. *Report of the Fourth Meeting of the Working Group on Leprosy Control (LWG), Hanoi, 8 July 1994*. Geneva, World Health Organization, 1994 (document WHO/CTD/LEP/94.4).
32. *Report of the First Meeting of the Leprosy Elimination Advisory Group (LEAG), Geneva, 12 and 13 July 1995*. Geneva, World Health Organization, 1995 (document WHO/LEP/95.2).
33. *Report of the Second Meeting of the Leprosy Elimination Advisory Group (LEAG), 14 October 1996, New Delhi, India*. Geneva, World Health Organization, 1997 (document WHO/LEP/97.2).
34. *Report of the Third Meeting of the Leprosy Elimination Advisory Group (LEAG), Geneva, 16 and 17 July 1997*. Geneva, World Health Organization, 1997 (document WHO/LEP/97.6).
35. *Report of the First Meeting of the Task Force on Health Systems Research (HSR) in Leprosy, Geneva, 18–19 June 1992*. Geneva, World Health Organization, 1992 (document CTD/LEP/92.4).
36. *Report of the Second Meeting of the Task Force on Health Systems Research (HSR) in Leprosy, Geneva, 12–13 July 1993*. Geneva, World Health Organization, 1993 (document CTD/LEP/93.4).
37. *Report of the Third Meeting of the Task Force on Health Systems Research (HSR) in Leprosy, Geneva, 24–25 May 1994*. Geneva, World Health Organization, 1994 (document CTD/LEP/94.3).
38. *First meeting of the Global Alliance for Elimination of Leprosy (GAEL), New Delhi, 30and 31 January 2001*. Geneva, World Health Organization, 2001 (document WHO/CDS/CPE/CEE/2001.27).
39. *Second meeting of the Global Alliance for Elimination of Leprosy (GAEL), Brasilia, 29–31 January 2002*. Geneva, World Health Organization, 2002 (document WHO/CDS/CPE/CEE/2002.31).
40. *Report on first meeting of the WHO Technical Advisory Group on Elimination of Leprosy, Geneva, 2 and 3 May 2000*. Geneva, World Health Organization, 2000 (document WHO/CDS/CPE/CEE/2000.4).
41. *Report on second meeting of the WHO Technical Advisory Group on Elimination of Leprosy, New Delhi, 1 February 2001*. Geneva, World Health Organization, 2001 (document WHO/CDS/CPE/CEE/2001.21).
42. *Report on third meeting of the WHO Technical Advisory Group on Elimination of Leprosy, Brasilia, 1 and 2 February 2002*. Geneva, World Health Organization, 2002 (document WHO/CDS/CPE/CEE/2002.29).

43. *Report on fourth meeting of the WHO Technical Advisory Group on Elimination of Leprosy, Geneva, 19 and 20 June 2002*. Geneva, World Health Organization, 2002 (document WHO/CDS/CPE/CEE/2002.32).
44. Let's work together – an appeal to ILEP and WHO. *Bulletin of the Leprosy Elimination Alliance*, 2002, 2:14–16.
45. Leprosy research at the new millennium. Proceedings of a workshop, 26–28 June 2000. Paris, France. *Leprosy Review*, 2000, 71(Suppl.):S1–S192.
46. Report of the International Leprosy Association Technical Forum. Paris, France, 22–28 February 2002. *International Journal of Leprosy and Other Mycobacterial Diseases*, 2002, 70(Suppl.):S1–S62.

3.2 Some important factors contributing to the implementation of WHO MDT

M.F. Lechat

Wide acceptance of MDT

Multidrug therapy has been at the core of the leprosy elimination strategy for the past 20 years. The worldwide implementation of MDT has been a considerable success, proving effective in curing the disease and rendering patients non-infectious after a treatment of relatively short duration, with very few subsequent relapses and no emergence of drug-resistant strains of *M. leprae*. Furthermore, the WHO prescription for standard regimens of MDT has resulted in the discharge of millions of patients; in statistical terms, this translates into prevalence rates approaching minimal levels.

In October 1981, when the Leprosy unit of WHO took the initiative of convening a Study Group on the Chemotherapy of Leprosy for Control Programmes (*1*), documented evidence of the efficacy of MDT in humans was scarce. Clinical field trials were not expected to provide data rapidly, since the end-point of the trials was the observation of relapses that could occur 5–7 years after completion of at least 2 years of treatment. The Study Group was confronted with a dilemma: while field data were lacking and unlikely to become available for several years, leprosy control was faced with the rapidly increasing prevalence of dapsone-resistant *M. leprae* strains which jeopardized more than 30 years of efforts to control the disease by dapsone monotherapy. After much debate, the Group opted for MDT – a momentous decision ultimately justified by the subsequent retreat of leprosy.

How did WHO manage to enforce – or, better, persuade – the leprosy world, from governments to NGOs, laboratory scientists to field workers (and not forgetting the patients themselves) to adopt and accept the standard MDT regimens recommended by the 1981 Study Group? How was success in marketing the new strategy of leprosy control achieved in the face of, inter alia, governments with other priorities, indifferent or ignorant health workers, sceptical scientists, old-fashioned clinicians entrenched in their traditional approaches, and nongovernmental organizations pursuing their own agendas? To the outside observer, the general acceptance of MDT over the past 20 years would seem to be the result of a number of factors – some part of a deliberate plan, other circumstantial. Not all factors were operative at the same time, nor did they necessarily intervene in a logical sequence.

Standardization and simplification of procedures

Notwithstanding the scientific backing for the MDT regimens provided at the fifth meeting of the WHO Expert Committee on Leprosy in 1976 (*2*) and by the THELEP Scientific Working Group in 1977 and 1979 (*3*), a major reason for the acceptance of MDT was that it was not presented as solely a pharmacological “recipe”. Its implementation was to be accompanied by modifications in diagnostic and treatment procedures – standardization of the drug regimens, classification of patients into two main clinical categories, and a fixed duration for the treatment. These measures did not develop all at once; they evolved gradually to form what could be called the WHO MDT package.

Standardization of treatment

The 1981 Study Group (*1*) recommended strictly standard MDT regimens, differing only with the clinical type of patient. Standardization of regimens was doubtless extremely important in accelerating acceptance of MDT: not only did it facilitate the procurement of drugs – it was also patient-friendly and convenient for field workers. In 1987, the availability of calendar blister packs was a crucial improvement in the drug delivery process.

Case definition and diagnosis

For years, the diagnostic criteria and clinical classification of leprosy were the object of heated debate. Eventually, the decision was made to adopt a case definition based on the clinical signs of the disease for detection purposes, and on the number of skin lesions for operational categorization with respect to the choice of MDT regimen. Thinking on the role of bacteriological examination changed gradually. The 1981 Study Group (*1*) still considered bacteriological examination to be "very important and highly relevant to leprosy control", yet in November 1987, at the sixth meeting of the WHO Expert Committee, its poor quality was recognized as "the weakest link in most control programmes" (*4*). At its seventh meeting, 10 years later, the Expert Committee (5) stated that, while skin smears "are useful", "since it is possible to classify leprosy without skin smear results, there is no need to establish skin smears services. Such services should not be a prerequisite for implementing MDT." This statement ratified a de facto situation: what had been tolerance became a prescript, and the simplification doubtless facilitated the life of the leprosy field worker and contributed to wide acceptance of MDT.

Duration of the treatment

Dapsone monotherapy, used since the 1940s, required more than 5 years of regular treatment to render most, but not all, lepromatous (multibacillary) patients eligible for discharge. By contrast, MDT was effective within a short time, possibly even weeks. The consequent recommendations were that the treatment of MB patients be continued for at least 2 years and, whenever possible, up to smear negativity (*1*, *4*). Treatment for PB patients was to be given for 6 months.

At its seventh meeting in 1997, the WHO Expert Committee (5) stated cautiously that "it is possible that the duration of the current MDT regimen for MB leprosy could be further shortened to 12 months without increasing the risk of developing rifampicin resistance". This was by and large interpreted as a recommendation to stop all treatments after 12 months.

In view of the threat of drug resistance, the recommendation for a standard multiple chemotherapy was well received and widely accepted by a large number of researchers, managers of leprosy control programmes, and NGOs. The Medical Commission of ILEP endorsed the WHO recommendations regarding standard MDT regimens (*6*) – an important consensus, since ILEP coordinates the activities of 22 NGOs that support leprosy control in more than 100 endemic countries. In some circles, however, the recommendations met with a degree of resistance or at least were accepted with reluctance. Some academics and private practitioners tended to favour more accurate diagnosis, more sophisticated MDT regimens, or treatment of longer duration, all of which had the disadvantage of making treatment generally

more costly (though not less effective). As the effectiveness of standard MDT became apparent, and large quantities of free drugs were supplied by or through WHO or NGOs, this resistance gradually evaporated.

The decision to enforce reduced duration of the treatment of MB patients (to 1 year) was criticized by a number of scientists and programme managers, who considered that the modification had been made on the basis of insufficient evidence and of an abusive interpretation of the Committee's statement. This controversial matter was never openly debated, either at subsequent congresses and meetings or on the Internet; no doubt, however, it helped to increase the coverage of MDT.

Epidemiological intelligence

The development of epidemiological intelligence contributed significantly to the success of MDT. Assessing the size of a problem is a prerequisite for health authorities at all levels to decide priorities, take appropriate decisions, monitor activities, and evaluate results.

In 1976 – in advance of the 1981 recommendations on MDT – and working through a university department affiliated to its network of collaborating centres, WHO fostered the collection and retrieval of relevant statistics in leprosy-endemic countries by sponsoring the development of a recording and reporting system for leprosy patients – OMSLEP. This system became operational in 1980. As stated at the time, " ... the information compiled should be as simple as possible, so that it can be collected at the periphery by multipurpose health workers with the minimum of specific training. This requires the identification and selection of the minimum information necessary to evaluate the progress of control activities." (*7*).

As early as 1982, computerization of the system was being mooted on the assumption that "mini" (later, personal) computers be used increasingly in the health services of endemic countries, making it possible to produce reliable and continuously updated information. A workshop was organized in Kuala Lumpur, in cooperation with SMHF, to familiarize leprosy workers from south-east Asia and western Pacific regions with the system (*8*). These activities raised awareness among health authorities and professionals of the importance of leprosy as a public health problem. Overall, the wide acceptance of MDT was one of the main factors that prepared the ground for the momentous World Health Assembly resolution WHA44.9 in May 1991, which declared WHO's commitment to global elimination and urged Member States to give it full political support.

Extremely low relapse rates after MDT treatment

The reappearance of acknowledged signs of active disease in a patient declared cured is not only a disastrous setback for the individual concerned, it is also the most dependable indication of unsuccessful chemotherapy. Relapse was common after dapsone monotherapy came into use (*10*): as early as 1950, Erickson noted that, of 33 lepromatous patients who had been treated with disubstituted derivatives of dapsone and had been bacteriologically negative for 12 months, 20 had relapsed within 6–60 months (*11*).

In 1954, Lowe (*12*) reported an 11% relapse rate among 148 lepromatous patients discharged as arrested after sulfone treatment. These relapses occurred early, usually within 1 year, and almost always within 2 years, of discharge. Rodriguez (*13*) observed relapses in 4.4% of 1125 cases who had been negative for periods ranging from 2 months to 10 years.

To minimize relapse, he advocated that sustained treatment of discharged cases be continued for a minimum period of 5 years. Most relapses were occurring in patients who considered themselves completely "cured" and had stopped taking their medicine – hence the growing consensus of opinion among leprologists that treatment should be continued for life to prevent relapse (*14*). The first aim of MDT being to prevent the emergence of drug-resistant strains of *M. leprae*, the absence of relapses is, so to speak, the litmus test of the effectiveness of chemotherapeutic regimens.

Assessing the frequency of relapses, however, is no easy task, since different definitions are used to describe the phenomenon; this makes comparison difficult. WHO defined a relapsed case as "a patient who successfully completes an adequate course of multidrug therapy, but who subsequently develops new signs and symptoms of the disease either during the surveillance period or thereafter" (*15*). Among the criteria for relapse are the following (*16*):

- new skin lesions;
- new activity in previously existing skin lesions;
- bacteriological index (BI) 2+ or more in two sets of skin smears;
- new loss of nerve function;
- histological evidence of relapse in skin or nerve biopsy;
- lepromatous activity in the eye(s).

Some have defined relapse simply as "the reappearance of *Mycobacterium leprae* in skin smears", while others (*10*) have referred to "the finding of a new skin lesion with high smear BI-containing solid-staining bacilli, and an histological appearance. Bacilli obtained from a new lesion will multiply in the footpad of mice."
Since relapses may occur in both PB and MB patients, specific definitions were put forward for each type of the disease. A proposed definition of relapse in a PB patient was "appearance of a new skin lesion or the increase in size of a pre-existing skin lesion, provided there was either strong clinical or definite histopathological evidence (or both) of leprosy in such a lesion" (17). The following seven criteria were proposed for defining relapse in PB leprosy (18): extension of the lesion, infiltration, erythema, occurrence of fresh lesions, pain and tenderness of nerve, new paralysis of muscles, and bacteriological positivity.

While relapse in MB cases is relatively easy to recognize clinically, it may be difficult to distinguish it from reversal reaction occurring some time after therapy is completed (*4*). In marked contrast to the frequency of relapses following dapsone monotherapy, relapse rates following MDT were considerably lower.

A number of reports on relapses in both PB and MB patients were published; these used different definitions and were based on a number **of** criteria such as clinical signs, morphological aspects of the bacilli, neural function, and combinations thereof. In spite of the wide variety of definitions, the rates provided in these reports, after revision and standardization by WHO, are minimal, ranging from 2.4 to 8 per 1000 person-years of observation for MB leprosy and from 6.5 to 30 per 1000 person-years for PB leprosy.

In order to assess more precisely the risks of relapse, field trials of MDT regimens were initiated in the early 1980s for MB leprosy in southern India and for PB patients in Indonesia and Malawi. These trials followed the protocols designed by the THELEP (Chemotherapy of Leprosy) Steering Committee, a component of the UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases (TDR). Most of the 2241 MB patients recruited in the trial and monitored for several years had had

prolonged dapsone monotherapy before starting on MDT. About 22% were skin smear positive for *M. leprae* at the time of starting the new treatment. Preliminary results indicated a relapse rate of 0.26 per 100 person-years. In the two PB trials, the relapse rate of follow up was 0.65 per 100 person-years after 4 years in Malawi and 0.12 per 100 person-years after 5 years in Indonesia (*10*).

A decade later, the Leprosy unit at WHO undertook a pilot survey by questionnaire of post-MDT relapses in 17 countries; this provided information on the follow-up of almost 100 000 MB and more than 150 000 PB cases, for a total of some 600 000 person-years of observation. Relapses were few and the relapse rates well below the acceptable level of 1 per 100 person-years, despite most respondents' using a very wide range of criteria to define relapse. (Experts agree that a theoretical relapse rate of 1 per 100 person-years is acceptable for any new regimen; relapses with MDT are far below this, at around 0.1 per 100 person-years or 1 per 1000 person-years.)

Since the information collected in the pilot survey was not considered sufficient for calculating the chances of relapse in individual patients, it was decided to identify programmes that maintain excellent information systems and so could provide information on cohorts of patients observed over a period of time. Twenty-eight such programmes participated, providing information on annual cohorts of patients who began treatment with MDT between 1982 and1990. The results of this study, covering more than 20 000 MB and 50 000 PB patients, revealed that the risk of relapse was very low: 0.77% for MB and 1.07% for PB, 9 years after stopping MDT. The risk was thus 10 times lower than for dapsone monotherapy. It was therefore postulated that the introduction of MDT had probably prevented close to half a million relapses during the 1980s (*10*).

Further results from these studies had considerable operational implications. For example, there was strong evidence that 50% of relapses in MB patients occur within the first 3 years of stopping MDT and 75% within 6 years. Among PB patients, 50% of relapses occur within 2 ½ years and 75% within 5 years. Moreover, there were indications that there is no increase over time in the annual risk of relapse in either MB or PB patients. In other words, if there is no relapse within the first 5–6 years, the individual patient's risk of relapsing is negligible. With such a low risk of relapse, and since the majority of relapses occur within a few years of stopping MDT, there seems to be no need for active, long-term, post-MDT follow-up of patients for the sole purpose of detecting relapses (*10*): patients can be declared "cured" after completion of treatment.

These findings no doubt contributed greatly to convincing all concerned partners, from national leprosy programme managers to NGOs, that MDT represented an enormous advance in the control of leprosy.

References

1. *Chemotherapy of leprosy for control programmes. Report of a WHO Study Group*. Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 675).
2. *WHO Expert Committee on Leprosy. Fifth report*. Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 607).
3. Dapsone-resistant leprosy – the THELEP approach. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1981, 49:421–422.
4. *WHO Expert Committee on Leprosy. Sixth report*. Geneva, World Health Organization, 1988 (WHO Technical Report Series, No. 768).

5. *WHO Expert Committee on Leprosy. Seventh report*. Geneva, World Health Organization, 1998 (WHO Technical Report Series, No. 874).
6. Reports, news and notes. ILEP: 26th working session, Bonn, December 1981. *Leprosy Review*, 1982, 53:142–143.
7. Lechat MF et al. *Recording and reporting system for leprosy patients*, 1st ed. (1981), 2nd ed. (1983), 3rd ed. (1987). Louvain-la-Neuve, Epidemiology Unit, Catholic University of Louvain.
8. *Proceedings of the Fourth International Workshop on Leprosy Control in Asia. Kuala Lumpur, Malaysia, 7–11 June 1982*. Tokyo, Sasakawa Memorial Health Foundation, 1983.
9. *Risk of relapse in leprosy*. Geneva, World Health Organization, 1994 (document WHO/CTD/LEP/94.1).
10. Erickson PT. Relapse following apparent arrest of leprosy by sulfone therapy. *Public Health Report*, 1950, 65: 1147.
11. Lowe J. Late results of sulphone treatment of leprosy in East Nigeria. *Leprosy Review*, 1954, 25:113–124.
12. Rodriguez JN. Relapses after sulfone therapy in leprosy of lepromatous type. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1959, 26:305–312.
13. Tolentino JG. The present status of leprosy therapy. In: *Report on the First Regional Seminar on Leprosy Control, Manila, 1965.* Manila, WHO Regional Office for the Western Pacific, 1967 (document 163/67)
14. *A guide to leprosy control*, 2nd ed. Geneva, World Health Organization, 1988.
15. Becx-Bleumink M. Relapses among leprosy patients treated with multidrug therapy: experience in the leprosy control programme of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Ethiopia; practical difficulties with diagnosing relapses; operational procedures and criteria for diagnosing relapses. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1992, 60:421–435.
16. Boerrigter G et al. Four-year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1991, 59:255–261.
17. Pandian TD et al. A study of relapse in non-lepromatous and intermediate groups of leprosy. *Indian Journal of Leprosy*, 1985, 57:149–158

3.3 Technical difficulties in the expansion of MDT

S.K. Noordeen

The widespread implementation and expansion of MDT following the recommendation of the 1981 WHO Study Group depended upon:

- technical experts accepting the scientific rationale and justification for and the recommendations on MDT as defined by the Study Group;
- programme managers and policy-makers of national leprosy programmes accepting the cost and other implications of MDT (at that time there was no assured funding for purchase of MDT drugs);
- donor agencies, including donor NGOs, accepting the financial and other implications, as they would be asked by national leprosy programmes to support the additional costs of MDT.

In order to meet the challenge of the growing failure of leprosy control, the three groups had to interact closely and work towards implementing MDT. The technical experts comprised:

- experts from THELEP and those who interacted closely with them;
- experts who were generally outside the THELEP group, who looked at treatment of leprosy mainly as a dermatological problem and as a result did not fully understand the antibacterial focus of chemotherapy of leprosy; for them, clinical response was the key indicator of successful treatment, and many did not believe that leprosy treatment could be stopped after a finite period, irrespective of the bactericidal activity of MDT drugs.

Of the three groups – technical experts, national policy-makers, donor agencies – who reacted to the recommendations on WHO MDT, it was the donor agencies that were relatively easy to deal with. They could see the great advantage in accelerating leprosy control and reducing the negative image of leprosy through MDT, even if it meant additional costs and human resources inputs. The lead role provided by agencies such as TNF and SMHF encouraged the acceptance of MDT by many others. After extensive internal discussions, ILEP agencies agreed to implement and support MDT, even though one member agency promoted drug combinations other than WHO MDT – Isoprodian® – within the ambit of what they could call MDT.

Most national programmes simply accepted what WHO and/or ILEP members recommended without necessarily going into the merits or implications of MDT. This was facilitated by the earlier participation of many national programme managers in the 1981 Study Group itself. In two countries, India and Brazil, with the preponderance of the world's leprosy burden problem, experts discussed at length the issue of implementing MDT. Improving chemotherapy for disease control was already on the agenda in India and preliminary field studies had begun as early as 1979, but serious discussion of MDT began just a few months before the 1981 meeting of the WHO Study Group. This was done through a Working Group on the Eradication of Leprosy, set up by the Government of India in July 1981 under the chairmanship of a renowned scientist, Dr M.S. Swaminathan.

The Working Group's discussions on MDT coincided with those of THELEP and with the 1981 WHO Study Group. Thus, by the time the Government's Working Group published its reports in February 1982, it was able to accept the recommendations of the WHO Study Group (whose report was also published in 1982), with a minor modification to the treatment

of MB leprosy. This modification involved incorporating an additional daily rifampicin dose for the initial 2 weeks of treatment, but was abandoned by the Indian programme in 1990. MDT was also the subject of intense discussion at meetings of the Indian Association of Leprologists (IAL); WHO MDT was discussed in a special seminar of IAL in March 1982, and adopted by the Association's general assembly in November 1983. IAL also introduced a minor modification to the WHO MDT regimen for MB patients, adding an optional 3 weeks of daily rifampicin at the start of treatment.

The situation in Brazil was far more difficult. The national programme was dominated by traditional leprologists who by and large regarded leprosy as a dermatological problem rather than a communicable disease problem. They were not willing simply to accept the recommendations of an external group – even WHO – unless and until they were themselves satisfied with the rationale for and results of WHO MDT. However, a few pilot studies on MDT were carried out and reported favourable results. Even so, it took more than 10 years for the Brazilian national leprosy programme to accept WHO MDT as standard treatment.

The most common problems faced with regard to WHO MDT, particularly in the field, were the following:

- inadequate understanding of the microbiological rationale of MDT and the effectiveness of rifampicin when given at monthly intervals;
- skin discoloration and icthyosis as a result of clofazimine;
- difficulties in classifying a proportion of patients mainly because of inadequate laboratory services;
- disappointment with the slow decrease of BI in MB patients after MDT;
- slow clinical response in a proportion of patients;
- lack of impact on disability status;
- difficulties in educating patients about what to expect from MDT and why treatment should be stopped after a finite period;
- inadequacy of the health infrastructure to cope with the implementation of MDT in certain areas;
- lack of assured availability of MDT drugs in the long term;
- confusion in the field resulting from the promotion of alternative MDT regimens, including Isoprodian®, by some agencies.

Most of these problems were resolved by better understanding of the potential of MDT, patient education, increased commitment at all levels, and – principally – experience, in terms of the observed effectiveness of MDT. The extraordinary clinical improvement seen by health workers and patients alike far exceeded their expectations and led to increased enthusiasm and commitment at every level for implementing MDT. MDT came to be seen as a therapeutic revolution and a breakthrough in the hitherto stagnant leprosy control situation.

Appendix 1
WHA44.9 Leprosy

The Forty-fourth World Health Assembly,

Having considered the report of the Director-General on leprosy;

Recalling resolution WHA40.35 and previous resolutions of the Health Assembly and the Executive Board on leprosy;

Noting with satisfaction the significant progress made during the past five years with multidrug therapy for leprosy control and with case-finding in the majority of Member States where leprosy is endemic – progress which has led to reductions in disease prevalence;

Recognizing the substantial and increasing support for leprosy control being provided by nongovernmental and other donor organizations;

Aware of the increasingly high priority accorded by several Member States to the elimination of leprosy as a public health problem;

Further aware of the opportunities to reduce disabilities due to leprosy through early case-detection, multidrug therapy and increased emphasis on managerial capabilities within leprosy control programmes and on disability prevention,

1. DECLARES WHO's commitment to continuing to promote the use of all control measures including multidrug therapy together with case-finding in order to attain the global elimination of leprosy as a public health problem by the year 2000;

2. URGES Member States in which leprosy is endemic:

(1) to further increase or maintain their political commitment and give high priority to leprosy control so that the global elimination of leprosy as a public health problem is achieved by the year 2000;

(2) to strengthen managerial capabilities within leprosy programmes, particularly at the intermediate level, and to improve training in leprosy for health workers at all levels, including medical students and student nurses;

(3) to ensure that coverage of multidrug therapy is maintained at the highest level possible and that patients comply with treatment;

(4) to strengthen case-finding activities through various approaches, including health education, community participation and training of health workers;

(5) to integrate leprosy control within general health services and provide appropriate social and economic rehabilitation measures as soon as possible in accordance with local realities;

(6) to improve national information systems in order to facilitate monitoring and evaluation of the elimination of leprosy;

(7) to coordinate the technical and financial resources made available for leprosy control by international and nongovernmental organizations so that they are utilized in the best way;

3. REQUESTS the Director-General:

(1) to strengthen technical support to Member States for the implementation of multidrug therapy together with case-finding so as to achieve the global elimination of leprosy as a public health problem by the year 2000;

(2) to continue to mobilize and coordinate scientific, technical and additional financial resources for implementing multidrug therapy together with case-finding, disability prevention and social and economic rehabilitation;

(3) to continue to strengthen national capabilities for leprosy control through support for training activities;

(4) to continue to support research for the development of improved drugs, diagnostic tools and vaccines through the Special Programme for Research and Training in Tropical Diseases;

(5) to promote further coordination with Member States and nongovernmental organizations in order to achieve the global elimination of leprosy as a public health problem by the year 2000;

(6) to keep the Executive Board and the Health Assembly informed of the progress made.

Chapter 4

The role of countries

This section is composed of reports on MDT implementation in five countries selected with the intention of showing the types of constraints encountered and the results achieved in different contexts.

4.1 Implementation of WHO MDT in Brazil

V. Andrade

Serious reservations about the introduction of WHO MDT

The recommendation of the WHO Study Group to introduce MDT for the treatment of leprosy met with considerable resistance in Brazil. The National Department for Dermatological Disease (DNDS) advanced a number of arguments against the adoption of WHO MDT by Brazil (*1*) including:

- significant risk of side-effects;
- efficacy not proven;
- lack of evidence to confirm:
  - speedier attainment of smear-negative results,
  - reduction of disease incidence, not achieved by dapsone monotherapy
  - reduced resistance to dapsone,
  - reduction of relapse caused by bacterial persistence;
- stigmatizing changes in skin pigmentation caused by clofazimine;
- costs and availability.

In 1983, the Ministry of Health set up an advisory committee of experts on alternative treatments in order to evaluate and coordinate the introduction of the new treatment for leprosy (*2*). The committee's first task was to review existing proposals for local treatments in Brazil (Amazonas, Amapá, and Rio de Janeiro) by interviewing the officials responsible for the studies, which had been under way since 1982 (*2*).

At a meeting held later in the same year, with financial support and technical assistance from WHO and the Pan American Health Organization (PAHO), Brazil confirmed its decision not to introduce WHO MDT before a detailed analysis of the results from the ongoing studies was available. Information about two additional projects with alternative treatments for leprosy, one in Pará and the other in the Federal District (*3*), was also provided at the meeting.

In June 1984, the committee defined its operational strategy, designated an expert for each alternative treatment study, and drew up a schedule for a site visit. The committee's key recommendations were as follows:

- Clinical trials with proper controls should be carried out by national centres to verify the efficacy of the WHO MDT regimens.
- These studies should compare WHO MDT with new drugs or with drugs already shown to be effective but not fully tested.

- The projects already under way (in Manaus, Macapá, Federal District, and Curupaiti hospital in Rio de Janeiro) should be continued with the following revisions:
  - use of ethionamide or protionamide as alternative drugs;
  - classification of cases as MB or PB without using the Mitsuda reaction;
  - longer duration of treatment;
  - ascertaining the acceptance by patients of skin discoloration caused by clofazimine.
- An agency should be established by Ministry of Health/DNDS to coordinate the recommended measures.
- Nationwide introduction of the regimens recommended by WHO was unacceptable, because of the risk of poor results (similar to those achieved when thioacetazone treatment for tuberculosis was introduced in Brazil).
- There should be no direct links between local or state services and international organizations without the approval of the Government of Brazil.

The main features of these studies were:

- Because of their overall objectives, they did not systematically comply with the criteria laid down by the committee of experts.
- With one exception, they were financed from abroad, and provided with human and financial resources, including local coordinators.
- A total of only 531 MB and PB patients (male and female, children and adults) were included in the studies.

Treatment regimens tested

The studies with WHO MDT did not adhere to the WHO guidelines – the treatment was not supervised, and clofazimine was administered only to patients with primary dapsone resistance. Lepromatous, borderline, and indeterminate patients were examined twice yearly, when they received their drugs for self-administration, and tuberculoid patients once a year (*4*, *5*). The DNDS treatment regimens for adults (over 15 years of age) were as follows *(6)*:

- **Regimen I** – indication, lepromatous or borderline patients never treated before
  Phase 1: Daily for 3 months – rifampicin 600 mg + dapsone 100 mg
  Phase 2: Daily from 3 months and for up to 5 years after the disease became inactive – dapsone 100 mg
- **Regimen II** – indication, tuberculoid and indeterminate patients never treated before
  Daily for 18 months after the disease became inactive – dapsone 100 mg

It was estimated that 32% of new cases and 20% of former lepromatous and borderline cases would require thalidomide to manage likely ENL reactions and that 11% of new cases would develop type 2 reactions requiring prednisolone.

DNDS set up an advisory committee on alternative treatment to monitor the ongoing studies and provide technical coordination.

Factors that convinced the experts to adopt the WHO MDT regimen

At the end of 1984, Brazil had 217 317 registered active cases of leprosy (prevalence of 16.3 per 10 000 inhabitants); 53% of registered patients had abandoned treatment. The average duration of treatment of patients was over 11 years. Almost 40% (85 557) of registered cases had been detected in the previous 5 years (1980–1985). Prevalence varied widely between states, from 0.2 to 129 per 10 000 population; similarly, case detection rates varied from 2 to 82.3 per 100 000.

An evaluation carried out in 1985 highlighted serious operational problems that needed to be addressed, including the lack of standardized laboratory diagnostic procedures, and deficiencies in the knowledge of personnel, as well as staff shortages as a consequence of the low priority assigned to leprosy by the health service. Other problems included a significant dissatisfaction among health professionals, the large number of patients following non-standard treatment regimens (i.e. not strictly recommended by either WHO or DNDS) and the low confidence of patients in the treatment regimens.

The evaluation recommended that the Government of Brazil undertake an immediate restructuring of leprosy services, based on new guidelines (*6*), in order to control the disease effectively. This decision was supported by broad discussions with specialists from Brazil's four macro-regions.

Brazil believed that WHO-recommended MDT alone would have no impact on the leprosy situation in Brazil. However, the new treatment regimens would serve as an entry point for the reorganization of all levels of the health services and improve the population's access to treatment (*7*, *8*). Moreover, the debate about MDT focused attention on the quality of care, notably case holding. The introduction of MDT was considered as an opportunity for the introduction of other changes in the leprosy programme that would significantly increase the coverage and intensity of control measures (*9*).

The lack of standardization of, and confidence in, the treatment regimens followed at the time was closely related to shortcomings in the strategy adopted to implement them (*7*). The DNDS was determined not to make the same mistake twice, with potentially graver consequences. Recognizing the value of the new regimens proposed by WHO, DNDS proposed to introduce MDT in a number of pilot units, with the primary objective of evaluating the operational feasibility of the regimens in Brazil's health services (*9*).

Adoption of MDT would succeed only if the regimen were introduced gradually, with meticulous planning that included retraining of personnel and development of strategies for integrating the necessary actions into the routine activities of the health services. Continuous monitoring and evaluation of all stages of the project were also essential. A longitudinal supervisory study of leprosy patients was therefore proposed to identify the parameters that would permit evaluation of the feasibility of the WHO-recommended treatment regimens for Brazil's health services (*10*, *11*). Throughout all phases of the five-year project, supervision and assistance in the pilot areas were integral elements of the systematic evaluation (*11*).

In January 1986, after the National Scientific Committee, PAHO, WHO, and the American Leprosy Missions (ALM) had approved the guidelines for gradual introduction of MDT, the protocol for MDT WHO in Brazil was developed. It drew heavily on experience at the Curupaiti State Hospital (Rio de Janeiro), the Alfredo da Mata Centre for Tropical Dermatology and Venereal Disease (Manaus-AM), and in the Federal District. The protocol

was introduced, in "pilot demonstration areas", in 1987. It included a proposal for extensive and specific staff training in order to implement the project, with funding from ALM, and the development and dissemination of the tools (bibliography, forms, agreements, etc.) necessary for the project to become operational (*10*, *11*).

In parallel with the gradual introduction of WHO MDT, DNDS implemented the following measures to reorganize the leprosy programme:

- analysing leprosy trends to identify priority areas;
- promoting increased coverage by the programme;
- training health workers;
- decentralizing administration and control;
- integrating the programme into basic health services;
- organizing the information system;
- carrying out health education activities through a campaign in the mass media;
- establishing formal exchanges between the government and international agencies (PAHO/WHO and NGOs).

Within 6 months of the start of the project, more than 65 health units in 21 states, covering 4% of the total number of cases in Brazil, had introduced the WHO MDT regimen under the coordination of DNDS. Implementation of the new treatment regimens proved easy: 94% of patients complied with treatment and only 0.1% of patients refused clofazimine on the grounds of skin discoloration (*12*).

Findings from the first national evaluation of WHO MDT, in March 1988, were as follows (*13*, *14*):

- The introduction of WHO MDT promoted the decentralization of basic health services – more than 88 new health facilities adopted the MDT regimen.
- More than 2500 health professionals were trained in five reference centres under DNDS monitoring **.**
- Treatment compliance was high and clofazimine well accepted.
- The gradual introduction of WHO MDT, in conjunction with the reorganization of health services, was well suited to Brazil's health services.
- The supervised monthly administration had many advantages:
  - individual patient education;
  - early and appropriate treatment of adverse reactions;
  - prevention and treatment of disabilities;
  - systematic supervision of self-administered drugs;
  - ensuring that rifampicin remained a highly effective drug.

Following the evaluation, the key recommendations were:

- The general guidelines for the extension of MDT should be the same as those that had proved feasible for its introduction.
- The health services should assign priority to leprosy control programmes and gradually encourage them to rely on funds from NGOs.
- Full patient compliance should be sought and guaranteed.

From the operational standpoint, however, the need for monthly supervised **administration** of the WHO MDT regimen limited the extension of the coverage to basic health facilities. A detailed analysis was needed to identify obstacles that might prevent WHO MDT being extended to as many patients as possible – a major factor in leprosy control (*13*).

The 1988 evaluation also revealed that the number of cases detected annually had been steadily increasing since 1978 (*14*). Of the 18 326 cases detected in 1988 (detection rate 13.8/100 000), 45% were lepromatous and borderline; 1659 patients were aged under 15 years (under-15 detection rate 3.34/10 000). Although this increase did not reflect increased transmission, it was noteworthy in view of the low coverage of leprosy services.

Table 4.1 shows the changes in the epidemiological pattern and MDT coverage over seven years (1985–1991) with decentralization and an extensive training programme involving an average of 5600 health professionals each year (MS, 1989, 1990 and 1992b) (*15–17*):

- Adoption of MDT for new cases rose from 6% in 1986 to 55% in 1991.
- The proportion of patients discharged from the register after being cured rose from 24.3% in 1987 to 59% in 1991.
- WHO MDT coverage increased from 4% in 1986 to 29% in 1991.
- The estimated time for which patients remained registered as clinically active fell from 12.2 years in 1987 to 8.3 years in 1991.
- Between 1987 and 1991, prevalence increased by 9.2%; over the same period, the new case detection rate increased by 29%.

Table 4.1
Changes in epidemiological pattern and operational capacity of the programme over the seven years (1985–1991) of gradual introduction of WHO MDT in Brazil[a]

Year	No. of new cases	New cases beginning WHO MDT (%)	No. of registered cases	Time on register (years)	Defaulters (%)	Cured (%)	% patients on register receiving MDT
1985	19 265	–	223 973	11.62	60.00	–	–
1986	18 400	6.20	234 006	12.71	62.11	–	4.00
1987	19 685	36.00	239 328	12.15	37.04	24.30	6.00
1988	26 578	24.00	256 976	9.66	41.39	43.80	8.00
1989	27 837	29.00	266 578	9.57	25.00	31.30	11.00
1990	28 482	41.20	278 104	9.76	23.41	37.20	15.00
1991	30 094	55.44	250 066	8.30	46.64	59.00	29.00

[a] Data from National Programme Coordinating Office reports/Ministry of Health.

In 1991, DNDS adopted WHO MDT as the sole treatment for leprosy patients in Brazil based on its efficacy, acceptance by patients and relative ease of use in health facilities (*18*).

Adjustment of the norms and guidelines of the leprosy control programme to implement WHO MDT

The introduction of WHO MDT in 1986 in pilot areas of Brazil necessitated many changes to technical norms and also provided an opportunity for a much-needed reorganization of the leprosy services (*12*, *19*). DNDS prepared a manual with the new technical norms and procedures for the diagnosis and treatment of leprosy. In addition, a manual was developed to guide the implementation of WHO MDT, as part of the national plan, and national reference centres were established (*20*, *21*).

Changing the classification of the disease

Operational classification of leprosy depended largely on the results of the Mitsuda test. Indeterminate Mitsuda-negative cases were considered to be MB. Brazil also made extensive use of smear examinations to classify patients as MB or PB by detection of acid-fast bacilli.

After 1994, tuberculoid and indeterminate cases were classified as PB, regardless of Mitsuda results, and lepromatous and borderline cases were considered as MB; this facilitated expansion of the treatment (*22*). Although the DNDS recommended Madrid classification (*22*), some states introduced elements of the Ridley–Jopling classification (*23*) into their training programmes, thus changing the proportion of the MB forms.

Changing the criteria for ending treatment

The average duration of treatment in Brazil was about 11 years. Lepromatous and borderline patients remained under treatment for more than 10 years after becoming clinically inactive and under observation for an undetermined period. Indeterminate cases (Mitsuda-negative) were prescribed 5 years' treatment after becoming clinically inactive. Treatment of tuberculoid and indeterminate (Mitsuda-positive) cases was continued for 18 months after clinical inactivity; cases were not kept under observation after treatment. The difficulties of declaring patients cured were accentuated during this phase, when the proportion discharged as cured was lowest and leprosy prevalence consequently rose.

With the introduction of WHO MDT, the average duration of treatment decreased, although patients were discharged from treatment only after a completely negative smear examination: some patients received more than 48 doses of WHO MDT.

In 1992, fixed-duration treatment was adopted and smear examination was no longer a requirement for declaring patients cured (*22*, *24*, *25*). Patients were considered cured after 6 doses of treatment for PB taken within 9 months and 24 doses of treatment for MB taken within 36 months (*22*, *26*).

Brazil officially reduced the duration of MDT for MB cases from 24 to 12 months in the year 2000 and adopted rifampicin–ofloxacin–minocycline (ROM) for single-lesion PB cases at centres authorized by the Ministry of Health (*26*).

Changes in the epidemiological situation, impact, side-effects, relapses, and cure

A pilot study had already shown that there were fewer reactions with WHO MDT *(27)*. However, the significance of this reduction in MB patients treated with the WHO MDT regimen was confirmed only in a study comparing it with the regimen previously administered in Brazil *(28)*. The statistically significant difference between groups of patients in terms of reactions, both during and after the end of treatment, confirmed the effectiveness of including clofazimine in the WHO MDT regimen to prevent reactions and reduce their severity, principally with regard to ENL *(29)*.

In the same study, there was no significant difference between groups in terms of distribution by clinical form, sex, age, degree of disability, or average bacteriological index. Two cases of relapse (2.87%) were recorded in patients using daily rifampicin (600 mg) + dapsone (100 mg) for 3 months, followed by dapsone (100 mg) for 21 months; no relapses occurred among patients using the WHO MDT regimen *(28)*.

Even with monthly visits to administer supervised doses, which ensures better personal contact between health services staff and patients, it was recommended that prednisolone be used in the field to treat reactions and recent nerve damage. When treatment is administered by physicians, however, there is an alarming trend, particularly in Brazil, towards more frequent use of steroids – even in cases for which they are not required. Moreover, some patients are aware of the anti-inflammatory effect of prednisolone and demand the drug, or purchase it themselves, to control their symptoms – thus creating further problems (*30*).

The frequency of adverse reactions to the WHO MDT drugs was very low. When such reactions did occur, the standard regimen was simply adjusted, making it possible for the treatment to continue (*27, 31 – 34*).

The impact of MDT

With the adoption of simplified diagnosis and case management, fixed-duration treatment, increased coverage of MDT services, and reorganization of Brazil's health information system, the epidemiological profile of leprosy in Brazil has changed dramatically. Over the past 40 years, the number of newly detected cases had increased each year (*35*). Until the 1990s, Brazil experienced a simultaneous increase in prevalence and detection rates (Figure 4.1). When the DNDS treatment regimen was the norm (1977–1987), prevalence increased by 25% and detection by 65%; during the period of WHO MDT (1991–2001), prevalence rates fell (by 75%) for the first time and the increase in the rate of detection was under 3% (Table 4.2).

Figure 4.1
Leprosy: rates of prevalence and detection Brazil, 1977–2001

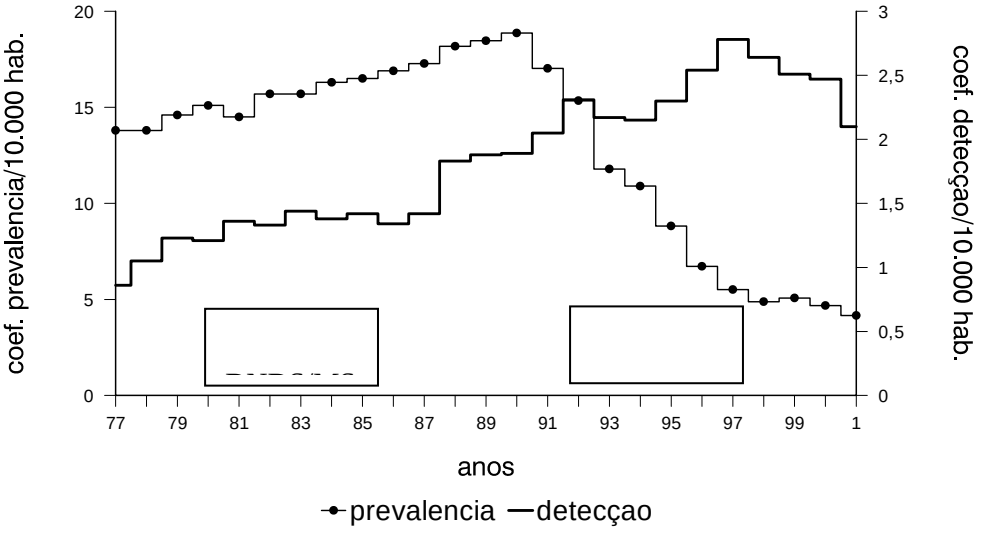


Table 4.2
Leprosy detection and prevalence in Brazil 1977–1987 and 1991–2001

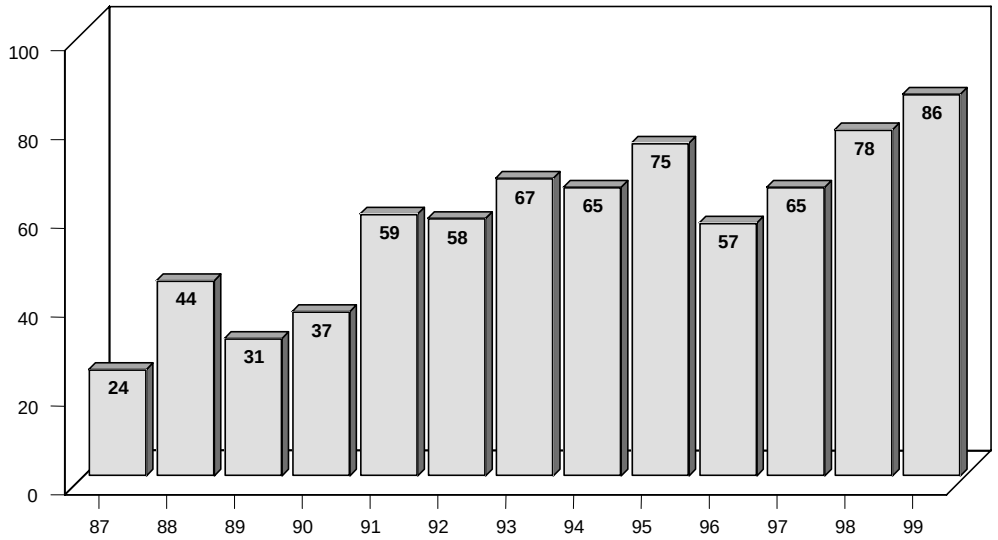
Indicator	Pre-MDT 1977–1987			MDT 1991–2001		
	1977	1987	% variation in period	1991	2001	% variation in period
Prevalence rate (per 10 000 population)	13.8	17.3	25.22	17.0	4.1	–75.57
Detection rate (per 10 000 population)	0.86	1.4	62.79	2.0	2.1	2.44

Between 1995 and 1997, there was an increase in the number of new cases in all the 26 states and the Federal District; between 1998 and 2001, an increase occurred in only 14 administrative entities.

The rate of new cases presenting with deformities has dropped to 7% during the past 5 years. In absolute numbers, during the period after adoption of MDT (1991–2001) 20 000 patients with at least one physical disability have begun treatment in Brazil's health services.

With the adoption of WHO MDT, and as a result of the introduction of new norms for declaring patients clinically cured – an issue that was previously controversial among scientists and ignored or even discredited among the public *(36)* – the proportion of cured patients removed from the register of active cases increased, from 24.3% in 1987 to 86% in 1999 (Figure 4.2).

Figure 4.2
Proportion of patients cured of leprosy, Brazil 1987–1999



Source: ATDS/MS

The significant increase in the number of new MB cases detected after the introduction of MDT resulted more from overestimation of MB on account of the excess number of borderline forms than from genuine high endemicity *(35, 37, 38).*

As WHO recommends early diagnosis and treatment of all patients with MDT, efforts also need to focus on improving patients' access to treatment. A study based on the analysis of data from 5 years after the introduction of MDT indicated that the number of patients that remained to be detected could exceed 52% of the number of known cases (*39*). This suggests that leprosy will not be eliminated from Brazil until MDT coverage is expanded and a concerted effort made to detect new cases. As long ago as the 1950s, there was evidence that dapsone could prevent indeterminate Mitsuda-negative cases from becoming future sources of transmission and thus that the detection and treatment of patients at that stage could eliminate the disease. However, little was achieved in that respect because of the limited coverage of the programme (*30*).

The increase in detection rates of new leprosy cases in Brazil during the past 10 years is largely the result of improvements in the coverage of MDT services and in the capacity of health services to detect and treat new cases. In addition, as the data-collection system is undergoing transition, analysis of the data from earlier periods may reveal misleading trends.

The current leprosy situation in Brazil indicates that MDT has been significantly more effective in curing and controlling the disease than either dapsone monotherapy or the DNDS regimen.

Lessons learned

The adoption and gradual introduction of WHO MDT:

- enabled the Ministry of Health to develop a method to directly supervise Brazil's states, which has been backed up by training for more than 180 000 specialists in the past 10 years;
- fostered the development of partnerships, with financial support from international agencies such as PAHO and WHO plus NGOs such as ALM, Fondation Follereau, German Leprosy Relief Association, Amici di Lepra, Damien Foundation, and the Sasakawa Memorial Health Foundation, which have supported both national efforts and individual local projects;
- made a significant contribution to improving the organization of leprosy control programmes;
- extended coverage of public health services for patients.

In addition:

- patient acceptance of monthly doses of rifampicin and clofazimine is good;
- reactions to the WHO MDT regimen are far less frequent than reactions to the earlier regimen;
- to date, the referral centres in Brazil have detected no significant drug resistance;
- the risk of relapse is apparently lower than with the DNDS regimen;
- the number of severe disabilities is gradually declining;
- the significant number of cases cured each year and acceptance of treatment by patients has resulted in a more positive attitude on the part of the community towards leprosy patients.

References

1. *Controle da hanseníase em serviços básicos de saúd. 4. Congresso Brasileiro de Hansenologiae, Porto Alegre [Leprosy control in basic health services. 4th Brazilian Conference on Leprosy, Porto Alegre]*. Brasilia, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1982.
2. *Relatório da reunião técnica sobre alternativas terapêuticas em hanseníase [Report of the technical meeting on alternative treatments for leprosy]*. Brasilia, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1983.
3. Gonçalves A, Gonçalves N. A poliquimioterapia na hanseníase, com especial referência ao Brasil [Multidrug therapy of leprosy, with special reference to Brazil]. *Brasil-Médico*, 1986, 23:5–10.
4. Ministério da Saúde/Secretaria Nacional de Saúde/Divisão Nacional de Dermatologia Sanitária. Instruções para a execução das normas de controle da hanseníase, baixadas pela Portaria Ministerial N^{o} 165/Bsb, de 14 de maio de 1976 [Instructions for implementation of leprosy control norms, laid down by Ministerial Decree No. 165/Bsb of 14 May 1976]. *Boletim da Divisão Nacional de Dermatologia Sanitária*, 1976, 36:7–12.
5. *Memória da reunião nacional de avaliação do programa de controle da hanseníase no Brasil [Minutes of the national evaluation meeting on the Brazilian leprosy control programme]*. Brasilia, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1985.
6. *Guia para o controle da hanseníase*, 2^{a} ed. [*Guide for the control of leprosy*, 2nd ed.]. Brasília, Centro de Documentação do Ministério da Saúde, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, 1984.

7. *Relatório de consultoria sobre avaliação do programa de controle de hanseníase no Brasil [Report of a consultation on evaluation of the Brazilian leprosy control programme]*. Brasília, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1985.
8. Zuniga M. *O papel do tratamento quimioterápico nos programas de controle da doença de Hansen – informe de assessoria [Paper on chemotherapy in leprosy control programmes – assessment information]*. Brasília, Divisão Nacional de Dermatologia Sanitária, 1988.
9. *Proposta para implantação de esquemas multidrogas OMS [Proposal for the implementation of the WHO multidrug regimen]*. Brasília, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1985.
10. *Diretrizes do programa da hanseníase, 1986–1990 [Management of the leprosy control programme, 1986–1990]*. Brasilia, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1986.
11. *Manual de normas e procedimentos para implantação de esquemas multidrogas OMS [Manual of norms and procedures for the implementation of WHO multidrug regimens]*. Brasília, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1986.
12. *Hansen's disease: gradual setting up of multidrug therapy in Brazil*. Brasília, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1987.
13. *Situação da hanseníase no Brasil: oficina de trabalho sobre quimioterapia da hanseníase nas Américas [The leprosy situation in Brazil: workshop on chemotherapy of leprosy in the Americas]*. Brasília, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1988.
14. *Relatório da 1ª reunião de avaliação da utilização da poliquimioterapia para tratamento de pacientes de hanseníase no Brasil [Report of the first evaluation meeting on the use of multidrug therapy for the treatment of leprosy patients in Brazil]*. Brasília, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1988.
15. *Situação da implantação gradual da PQT em hanseníase no Brasil [Status of the gradual implementation of MDT for leprosy in Brazil]*. Brasília, Secretaria Nacional de Programas Especiais de Saúde, Divisão Nacional de Dermatologia Sanitária, Ministério da Saúde, 1989.
16. *Relatório quadrienal 1986–1989 [Four-year report, 1986–1989]*. Brasília, Fundação Nacional de Saúde, Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1990.
17. *Elimination of leprosy: review of progress made, Brazil 1986–1992. Evolution of the indicators*. Brasília, Fundação Nacional de Saúde, Centro Nacional de Epidemiologia, Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1992.
18. *Relatório do grupo técnico: instruções normativas, regulamentação referente a Portaria Ministerial Nº 862/GM de 07/08/92 [Technical group report: normative instructions, with reference to Ministerial Decree No. 862/GM of 07/08/92]*. Brasília, Fundação Nacional de Saúde, Centro Nacional de Epidemiologia/Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1992.
19. Nogueira W et al. Perspectivas de eliminação da hanseníase [Perspectives on the elimination of leprosy]. *Hansenologia Internationalis*, 1995, 20:19–28.
20. *Relatório da avaliação nacional do programa de controle da hanseníase [Report on the national evaluation of the leprosy control programme]*. Brasília, Fundação Nacional de Saúde, Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1991.

21. *Relatório final da avaliação independente do programa nacional de controle e eliminação da hanseníase [Final report on the independent evaluation of the national leprosy control and elimination programme]*. Brasília, Fundação Nacional de Saúde, Centro Nacional de Epidemiologia, Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1992.
22. *Portaria Ministerial Nº 133 de 01/09/94 [Ministerial Decree No. 133 of 01/09/94]*. Conselho Nacional de Saúde, 1994 (Diário Oficial, ano CXXXII Nº 177).
23. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1966, 34:255–273.
24. *Ata da reunião do Comitê Assessor da Dermatologia Sanitária [Minutes of the meeting of the Assessment Committee of the National Coordination for Dermatological Disease]*. Brasília, Fundação Nacional de Saúde, Centro Nacional de Epidemiologia, Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1993.
25. *Relatório da Reunião do Comitê Técnico Assessor da Coordenação Nacional de Dermatologia Sanitária [Report of the meeting of the technical committee for assessment of the National Coordination for Dermatological Disease]*. Brasília, Fundação Nacional de Saúde, Centro Nacional de Epidemiologia, Coordenação Nacional de Dermatologia Sanitária, Ministério da Saúde, 1994.
26. Departamento de Imprensa Nacional, Diário Oficial da União, Ministério da Saúde Nº 1073/GM de 28 de Setembro de 2000.
27. Andrade VLG et al. Feasibility of multidrug therapy (MDT) in Hansen's disease in urban population – Curupaiti State Hospital, Rio de Janeiro, Brazil. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1987, 55:435–440.
28. Gallo ME, Alvim MF, Nery JA. Estudo comparativo com dois esquemas poliquimioterápicos (duração fixa) em hanseníase multibacilar – seguimento de 50.32 ± 19.62 e 39.70 ± 19.47 meses [Comparative study of two multidrug regimens (fixed duration) in multibacillary leprosy – followed up for 50.32 ± 19.62 e 39.70 ± 19.47 months]. *Hansenologia Internationalis*, 1997, 22:5–14.
29. Beck-Bleuminck M. Operational aspects of multidrug therapy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1983, 57:540–551.
30. Opromolla DVA. A hanseníase após a cura [Leprosy after cure]. *Hansenologia Internationalis*, 1998, 23:1–4.
31. Biot MPN. *Multidrogaterapia hansênica – resultado no acompanhamento de 480 pacientes no município de São Gonçalo, após 7 anos (Dissertação) [Multidrug therapy of leprosy – results of accompanied treatment of 480 patients in São Gonçalo, after 7 years (Dissertation)]*. Rio de Janeiro, Universidade Federal Fluminense, 1993.
32. Brasil MT et al. Results of a surveillance system for adverse effects in leprosy's WHO/MDT. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1996, 64:97–104.
33. Cunha MGS. *lntercorrências medicamentosas em pacientes submetidos a PQT e que resultam em suspensão do medicamento [Drug interactions resulting in cessation of treatment, in patients given MDT]*. Personal communication, 1992.
34. Gallo MEN, Garcia CC, Nery JAC. Intercorrências pelas drogas utilizadas nos esquemas poliquimioterápicos em hanseníase [Interactions between the drugs used in multidrug treatment of leprosy]. *Hansenologia Internationalis*, 1995, 20:5–8.
35. Andrade VLG. *Evolução da hanseniase no Brasil e perspectiva para a sua eliminação como um problema de saúde publica (Tese) [Evolution of leprosy in Brazil and perspectives on its elimination as a public health problem (Thesis)]*. Rio de Janeiro, Escola Nacional de Saúde Pública/FIOCRUZ, 1996.

36. Oliveira MLWR.. *Cura da hanseniase: estudo de recidivas (Tese) [Cure of leprosy: study of relapse (Thesis)]*. Rio De Janeiro, Universidade Federal do Rio de Janeiro, 1996.
37. Martelli CMT et al. Changes in leprosy clinical pattern after multidrug therapy implementation. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1995, 63:95–97.
38. Soares LS et al. The impact of multidrug therapy on the epidemiological pattern of leprosy in Juiz de Fora, Brazil. *Cadernos de Saúde Pública*, 2000,16:343–350.
39. Pereira GFM. *Características da hanseníase no Brasil: situação e tendência no período 1985 a 1996 (Tese) [Characteristics of leprosy in Brazil: status and trends from 1985 to 1996 (Thesis)]*. São Paulo, Universidade Federal de São Paulo, Escola Paulista de Medicina, Departamento de Medicina Preventiva, 1999.

4.2 Implementation of MDT in Burkina Faso

A. Tiendrebeogo, L. Some

Burkina Faso is a west African country lying within the sweep of the Niger River. In 2000, the population numbered 12 000 000 – up from 7 752 000 in 1980. Burkina Faso attained the leprosy elimination threshold of less than one case per 10 000 inhabitants in 1994, largely as a result of the introduction of a control programme based on MDT as recommended by WHO. The path to this goal was not without difficulties, however, given the country's meagre resources and the scale of the endemic: in 1965, there were 140 000 cases of leprosy and prevalence in some villages exceeded 5%, i.e. 500 cases per 10 000 inhabitants (*1*). In 1966, Sansarricq et al**.** showed that the number of cases declined gradually from the south to the north of the country (see Figure 4.3). Nonetheless, the introduction of MDT regimens was made easier by the existence of treatment circuits dating from the time of dapsone monotherapy.

Burkina Faso is a former French colony, previously known as Upper Volta; it formed part of French West Africa where, in 1957, the Médecin-Général, Pierre Richet, head of the Service des Grandes Endémies, launched the mass leprosy control campaign using dapsone monotherapy (*2*, *3*). The health services in each country of French West Africa were subdivided into sectors for the major endemic diseases (leprosy, onchocerciasis, yaws, and trypanosomiasis). Each sector had mobile teams that conducted annual surveys in villages to detect cases of these diseases. Leprosy diagnosis was the responsibility of specialized nurses and leprosy controllers trained at the Marchoux Institute in Bamako, Mali. Once detected, leprosy cases were treated with dapsone monotherapy; dapsone tablets were distributed to patients in villages by travelling health workers who made their rounds by bicycle.

During its annual survey, the mobile team performed clinical examinations of the leprosy patients under treatment. It took decisions to end treatment; patients were declared as "under observation without treatment" (UOWT) or "clear" and were required to attend the annual visits to their village by the mobile team. After a period of 2–5 years, patients were declared "dispensed from control" – the word "cured" was not used. Some leprosy patients remained under treatment for the rest of their lives.

Introduction of MDT: 1981–1988

The WHO Study Group recommended the adoption of MDT for leprosy in 1981, and Burkina Faso introduced the new regimens in 1983, through a pilot project in Houet province, a region in the south-west of the country that included the villages of Bobo Dioulasso, Banfora, and Orodara (*4*). The treatment regimen adopted for MB patients initially included ethionamide, but the drug was later withdrawn because of side-effects, particularly digestive effects. Thereafter, treatment continued with the drugs now used in WHO MDT – rifampicin, clofazimine, and dapsone for MB cases, and rifampicin and dapsone for PB cases. The duration of treatment was 24 months for MB and 6 months for PB cases.

This pilot project confirmed the efficacy of the proposed regimens. Between 1983 and 1986, more than 1000 patients were treated. A 1997 survey by the Marchoux Institute found 255 patients who had been treated with the regimen and confirmed that the relapse rate was less than 1 case per 1000 patients per year after more than 10 years of follow-up (*5*).

In view of the success of this pilot project, the national health authorities proposed to introduce MDT in all the provinces of Burkina Faso. Introduction was preceded by a period of transition (1986–1988) during which the provincial directors of health were informed about the new regimens and the procedures needed to prepare for the introduction of MDT. Leprosy registers were brought up to date by the leprosy nurses. During this period, community information/education on leprosy consisted mainly of World Leprosy Days, which were organized at both national and provincial levels. In addition, the leprosy teams continued with their control rounds to villages, visiting patients under treatment or under observation without treatment and taking the opportunity to examine patients' contacts and to identify new cases of leprosy. The transitional phase before introduction of MDT made it possible:

– to replace the earlier "lepromatous, borderline, tuberculoid, and indeterminate" classification with the new classification (PB and MB) proposed in WHO's *Guide to leprosy control* (*6*) and based on skin-smear examination;
– to reduce the number of patients included in leprosy registers by excluding the large number who had been cured by dapsone monotherapy but retained on the registers because of complications (reactions and deformities) (see Figures 4.3, 4.4 and 4.6 and Table 4.3).

During the preparatory phase, the Association Française Raoul Follereau (AFRF) provided vehicles and motorbikes to the leprosy teams in the different provinces; the number of teams increased from 25 to 30 between 1983 and 1984. AFRF also subsidized training for leprosy specialists and controllers at the Marchoux Institute in Bamako to ensure that there was a nurse trained in clinical and skin-smear diagnosis of leprosy in each province in the country.

Efforts were also made during this preparatory phase to decentralize state services. The subdivision of the country into 25, and then 30, administrative districts in 1983–1984 made it possible to provide better nationwide health coverage. Each Provincial Health Directorate (PHD) had at least one physician and a pharmacist, plus a specialized health worker or leprosy controller who was to become the leprosy supervisory nurse (LSN) for the MDT programme. The government authorities stressed the importance of good management of public funds, and each PHD was made responsible for managing the resources provided by AFRF for leprosy control activities. World Leprosy Day was celebrated in one of the provinces by the national authorities in the presence of the Head of State, and provided an opportunity to present the province and to invite partner countries to become involved in development activities there.

A number of problems arose as a result of the shortage of transport in the new provinces. On many occasions, the vehicle provided by AFRF specifically for leprosy, with assigned funds for fuel and maintenance, was the only serviceable vehicle available to the PHD – or indeed in the whole province. Use of the vehicle by the PHD, or by provincial authorities for purposes unconnected with health, prompted complaints by the LSN. At times, AFRF funds were used to finance all health activities, giving rise to conflicts with the AFRF representative, whose half-yearly release of funds was conditional on documentary proof of compliance with the expenditure forecasts and budgetary items defined in the International Federation of Anti-Leprosy Associations (ILEP) request for funding. Despite these difficulties, however, it proved possible to organize a control programme in every province. By the end of 1988, the provinces were in a position to adopt the new leprosy treatment regimens recommended by WHO and tested with success in Houet province (see Figure 4.4).

Extension of MDT coverage: 1989–1993

The first step in the extension of MDT coverage to all the provinces was the appointment, in 1989, of a coordinator for the national leprosy and tuberculosis control programme (*7*). Two training sessions on leprosy programme management were organized for the PHDs and LSNs from the provinces: the first, in 1990, covered 17 provinces, including those involved in the pilot project, and the second, in 1991, the remaining 13 provinces. New programme management tools, including the treatment register and the drug-stock card, were proposed and adopted by all provinces.

After the training sessions, each province drew up a provincial leprosy control plan based on MDT, and organized training on MDT implementation for the head nurses of health centres and travelling health workers. Laboratory technicians from health centres were also trained to carry out skin smears to detect the leprosy bacillus. This "cascade" training strategy was encouraged by WHO, and funding from AFRF made it possible to cover the whole country quickly (*8)*. Dapsone monotherapy was rapidly replaced by MDT regimens – by the end of 1992, all leprosy cases registered in Burkina Faso were receiving WHO MDT (*9*).

During this period, leprosy case detection was essentially passive; cases were identified at health centres and the diagnosis confirmed by the specialized nurses and leprosy controllers. The opportunity was always taken to identify new patients in the villages visited in the course of control rounds; however, the rounds were no longer carried out regularly, and in any case focused on distributing MDT to patients already registered. Two treatment strategies were followed by each health centre. Patients living less than 5 km from a village with a health facility were treated locally; otherwise, the nurse or itinerant health worker travelled by motorcycle to deliver the drugs to patients. In addition, the monthly administration of rifampicin was carefully supervised by health workers responsible for distribution and strict compliance was expected of patients. If treatment was interrupted for two consecutive months, the treatment had to be started again from scratch.

One of the most tedious aspects of the early part of the programme was the long nights spent in medical centres, filling packets with monthly courses of leprosy drugs. Fortunately, this period lasted only until the remaining stocks of bulk dapsone and clofazimine were used up. Bulk drugs were soon replaced by MDT blister packs from the Novartis (formerly Ciba-Geigy) laboratories, making MDT delivery to patients much easier.

In three years (1990–1992), all 30 provinces of Burkina Faso introduced MDT blister packs, and by the end of 1992, MDT was available from every health and welfare centre (HWC). The existence of complete coverage was confirmed by a joint country/AFRF/OCCGE (Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies)/WHO evaluation survey carried out in May 1993 (*10*). The MDT treatment regimens were much shorter and more effective than dapsone monotherapy; as a result, patient compliance with treatment improved and the number of patients declined rapidly during the period.

One of the first provinces to achieve the elimination threshold (less than 1 case per 10 000 population) distinguished itself by presenting the MDT regimens on World Leprosy Day. Addressing the crowd that gathered for the ceremony, the provincial Director of Health invited the provincial authorities to give the first MDT packs to patients. After the ceremony, a rumour went round the province that the High Commissioner (the senior authority in the

province) had brought a new and highly efficient remedy for leprosy. This prompted numerous leprosy patients to go voluntarily to health centres in the province for screening; thanks to MDT, they were cured.

Leprosy elimination: 1994–2000

Achievement of the elimination threshold in one province in 1991 encouraged the other provinces and stimulated healthy competition. Each PHD redoubled its efforts to improve patient compliance with treatment and to reduce the number of patients registered. Inspection rounds by the specialized nurses ceased and were replaced by supervisory visits to HWCs, which served to consolidate and improve the performance of the nurses. For purposes of monitoring, the patient treatment register was produced in duplicate – the original was kept by the health worker responsible for treatment at the HWC and the duplicate by the leprosy supervisory nurse at the provincial level. At the suggestion of one of the provincial directors of health, a monthly report form on leprosy treatment was filled out by the heads of health posts, which made it possible to keep the duplicate treatment register up to date. The most widely used monitoring indicators for assessing the quality of services were regularity (rule: two-thirds of rifampicin doses taken under supervision during a given period of treatment) and compliance (completion of 6 doses of MDT for PB leprosy in a maximum of 9 months or of 24 doses of MDT for MB leprosy in a maximum of 36 months).

These efforts enabled Burkina Faso as a whole to reach the elimination threshold by the end of 1994 – an achievement that was proclaimed when World Leprosy Day was celebrated in 1995. Perversely, however, this achievement led to setbacks that jeopardized the programme's progress in the provinces.

One setback was a waning of interest in leprosy activities at the national level. As a result, the position of national leprosy programme coordinator was held by three physicians in the space of five years and also remained vacant for long periods. Finally, in February 2000, the leprosy and tuberculosis programmes were separated, and the first leprosy programme coordinator resumed his post in 2001.

The second – and no less significant – setback was a cut in funds for the leprosy programme. There has been no AFRF representative in Burkina Faso since 1993, and the Association has considerably reduced its financial and material support for the provinces. The programme's vehicles and motorcycles were not replaced, funds for maintenance and fuel shrank to negligible levels, and the supervisory visits had to be abandoned. Training/retraining of staff ended in 1995 and a significant number of supervisory nurse positions (vacant because of retirement, reassignment, or death) remained unfilled. As a result, more than half of the provinces, which now number 45, were without a provincial health worker to supervise and monitor of leprosy control activities (*11*).

As a final setback, the only information on leprosy provided to the public was that delivered by the celebration of World Leprosy Day, and active case detection came to an end when the leprosy control rounds were discontinued. Although the number of new cases detected was very low and prevalence considerably reduced, many leprosy cases remained hidden in villages. In 1997, a survey in Bazèga province by the national programme team detected three times as many leprosy cases as in previous years, revealing the huge gap between estimated and recorded prevalence. The number of new cases detected annually in the country as a whole, which had been less than 800 in the previous two years, rose to 900 in 1997.

These setbacks shifted the focus away from information and case-detection activities to MDT treatment of registered cases. Consequently, the recorded level of prevalence remained below the elimination threshold. In 1997, a survey by a team from the Marchoux Institute showed estimated prevalence to be 2–3 times higher than the levels recorded in the 10 provinces visited (*12*). Monitoring of leprosy elimination during the same survey showed up the following problems:

- MDT (drugs and information material) was no longer available in all the health and welfare centres (HWC).
- Capacity for leprosy diagnosis at the HWC was essentially non-existent.
- Fewer than 50% of the nurses at the HWC had been given any training in leprosy case management.
- Activities to prevent or treat disabilities caused by leprosy were non-existent or undertaken only by the few services still handling patients with deformities or reactions.

Analysis of the distribution of leprosy cases in 2000 (see Figure 4.5) shows that the provinces with the highest endemicity are grouped in the northern third of the country, where the operational difficulties that have to be dealt with in implementing MDT are compounded by demographic factors (low population density, remoteness of health facilities, and nomadic populations). In contrast with the epidemiological situation described by Sansarricq et al. in 1966 and published in 1968, there is a gradual decline in the number of cases from the north to the south of the country.

On the basis of this situation analysis, the national leprosy programme coordinator drafted a plan of action to revitalize the programme's activities. Unfortunately, the plan's implementation has so far been delayed by the frequent changes of national coordinator and the lack of funds from the programme's partner NGO. Now that the first coordinator of Burkina Faso's leprosy programme has returned to the position, it is hoped that steps will be taken to enable the country to consolidate its achievement of the elimination threshold nationwide through the effective elimination of leprosy in all 45 provinces. The fine example of MDT Burkina Faso will be upheld only by a genuine effort to revive the Programme's activities by means of:

- reorganization of the diagnosis and treatment network;
- training/retraining of staff responsible for diagnosis and treatment in the HWCs;
- assignment of funds to the provinces for the supervision of HWC staff by the provincial or district teams;
- organization of information campaigns and ad-hoc measures in provinces where the disease is still endemic.

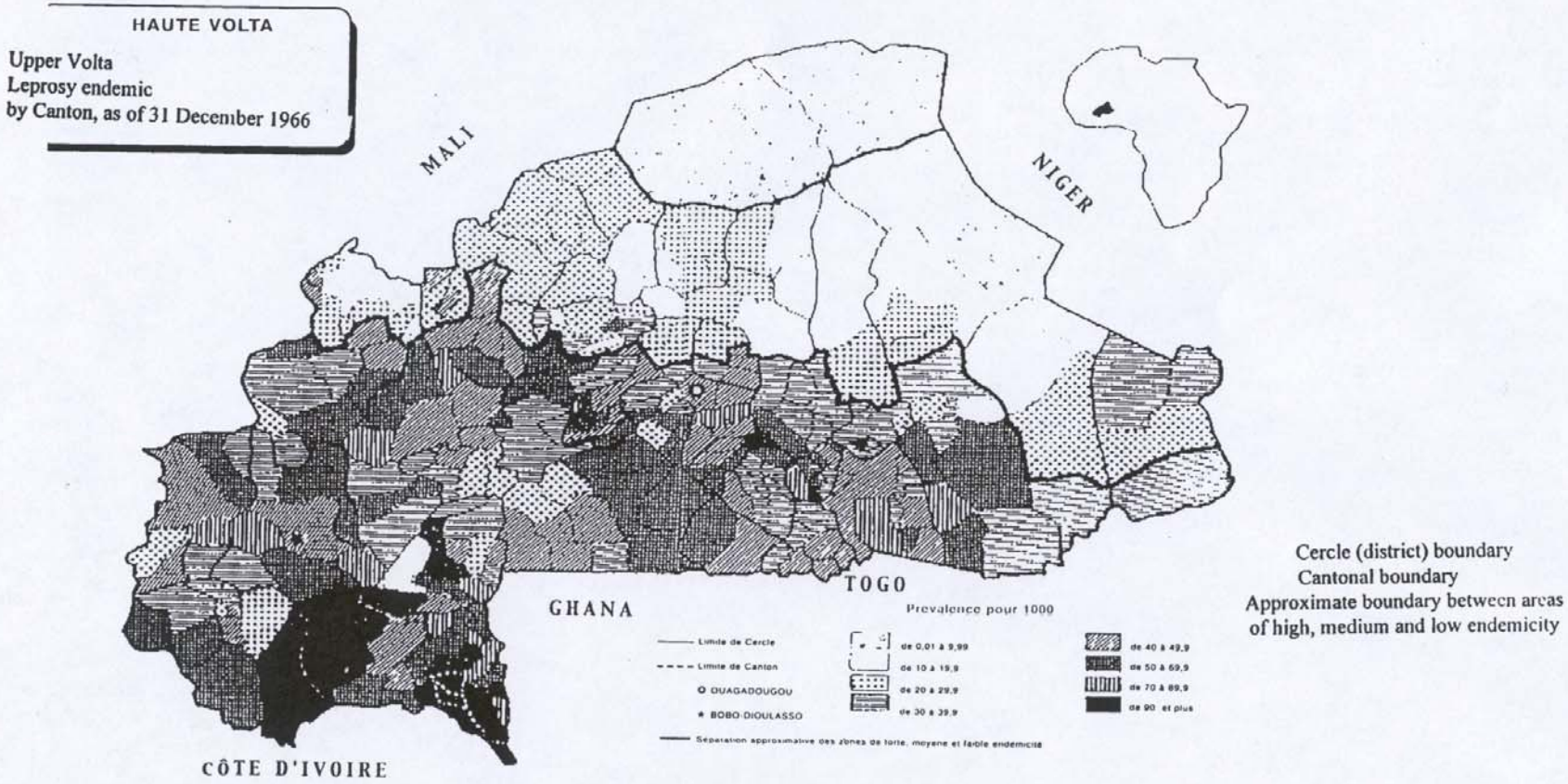
References

1. Sansarricq H, Hélies H, Lagardère B. Caractères épidémiologiques de la lèpre en Haute-Volta [Epidemiological features of leprosy in Upper Volta]. *Médecine Tropicale,* 1968, 28:327–344.
2. Laviron P. *Les médicaments antilépreux. Le traitement de la lèpre dans une campagne de masse [Antileprosy drugs. Leprosy treatment in a mass campaign]*. Léopoldville, Bureau Permanent Interafricain de la Tsetse et de la Trypanosomiase, 1957 (B.P.I.T.T. Publication, No. 8/0).
3. Laviron P Les campagnes de masse et leurs difficultés dans la lutte antilépreuse en Afrique noire [Mass campaigns and their difficulties in leprosy control in Africa south of

Sahara]. *Annales de la Société Belge de Médicine Tropicale*, 1964, 44:105-113.
4. Daumerie D. *Le projet de PCT pilote dans la province du Houet au Burkina Faso [MDT Pilot Project in the Province of Houet in Burkina Faso]*. Rapport de mission, 1986, archives de l'Institut Marchoux, Bamako, Mali.
5. Sow OS, Tiendrebeogo A. *Enquête sur les rechutes lépreuses chez les sujets traités par la PCT pilote dans la province du Houet au Burkina Faso [Survey on leprosy relapses following treatment during the MDT Pilot Project in the Province of Houet in Burkina Faso]*. Rapport de mission, 1997, archives de l'Institut Marchoux, Bamako, Mali.
6. *A guide to leprosy control*, 2nd ed. Geneva, World Health Organization, 1988.
7. *Programme national de lutte contre la lèpre [National leprosy control programme]*. Ouagadougou, Ministry of Health, 1989.
8. Tiendrebeogo A et al. La formation du personnel par l'Institut Marchoux de Bamako de 1979 à 1995 [Staff training in the Marchoux Institute of Bamako from 1979 to 1995]. *Acta Leprologica*, 1996, 10:37–44.

9. Tiendrebeogo A, Blanc L, Sylla PM. La polychimiothérapie antilépreuse dans les Etats Membres de l'OCCGE: une décennie de mise en oeuvre (1983–1993). Coordonnateurs nationaux des programmes lèpre des huit Etats de l'OCCGE [Multidrug therapy for leprosy in OCCGE Member States: a decade of implementation (1983–1993). Coordinators for national leprosy programmes from eight states in OCCGE]. *Acta Leprologica*, 1995, 9:139–148.
10. *Rapport de l'évaluation conjointe du programme lèpre du Burkina Faso en mai 1993 [Report of a joint assessment of the leprosy programme in Burkina Faso, May 1993]*. Ouagadougou, Ministry of Health, 1993.
11. Tiendrebeogo A, Touré I, Zerbo P-J. A survey of leprosy impairments and disabilities among patients treated by MDT in Burkina Faso. *International Journal of Leprosy*, 1996, 1:15–25.
12. Tiendrebeogo A et al. Evaluation de l'élimination de la lèpre au Burkina Faso [Assessment of leprosy elimination in Burkina Faso]. *Acta Leprologica*, 1998, 11:7–16.

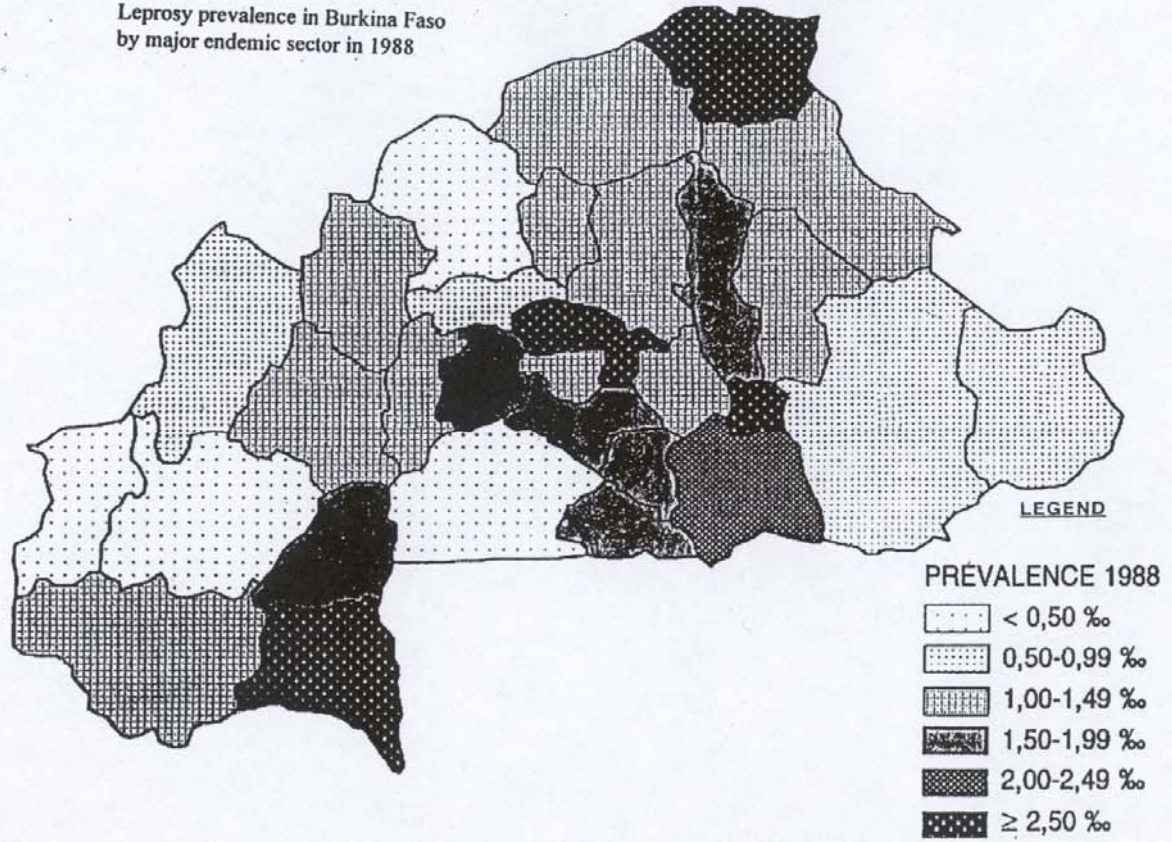
Figure 4.3
Leprosy situation in Burkina Faso in 1966 when dapsone monotherapy was in use



Cercle (district) boundary
Cantonal boundary
Approximate boundary between areas of high, medium and low endemicity

The number of cases registered was probably close to the actual number of cases and had not yet been significantly reduced by the mass campaign using dapsone
(After Sansarricq H. et al. (71)

Figure 4.4
Leprosy situation in Burkina Faso in 1988, before MDT was extended to all provinces



As a rule, prevalence rates have declined significantly in comparison with 1966, as a result of the leprosy control programmes using first dapsone and then MDT
(After Declercq et al. Atlas Mondial de la lèpre
Ecole de Santé publique, Université Catholique de Louvain, Brussels.

Figure 4.5
Leprosy situation in the provinces in Burkina Faso at the end of 2000

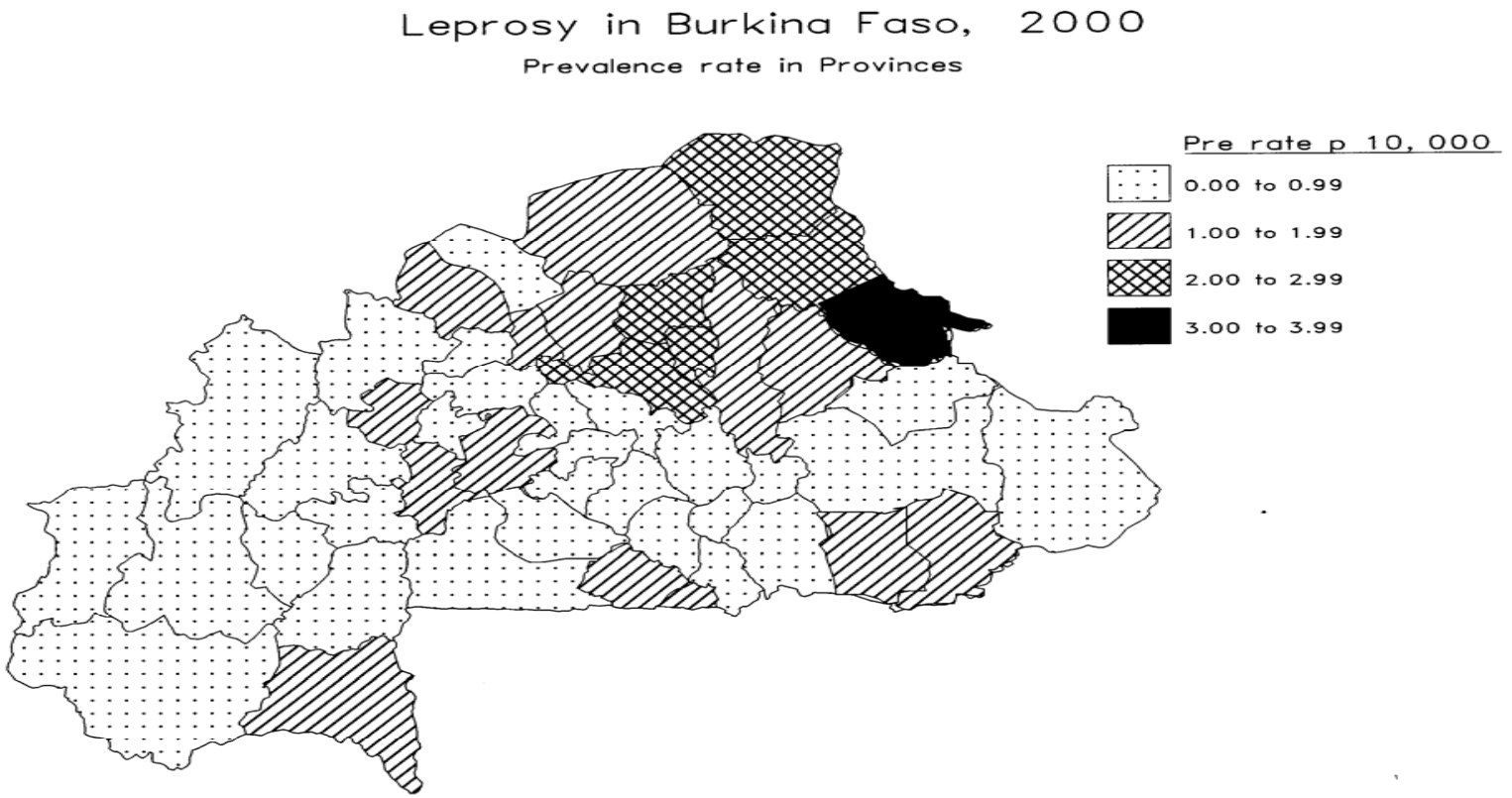
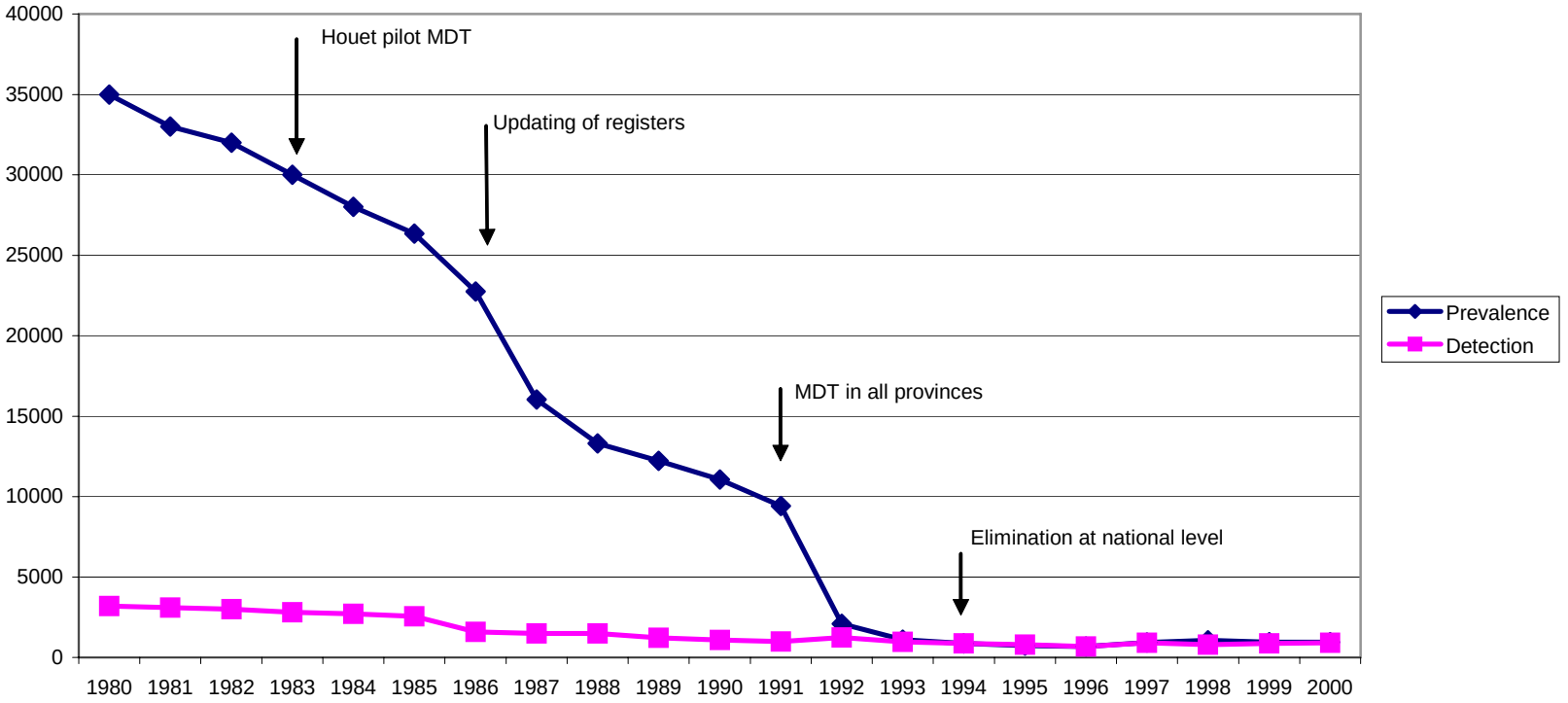


Table 4.3
Data on the leprosy endemic and leprosy control in Burkina Faso, 1980–2000

Year	Population (thousands)	Prevalence		Detection		% New cases			Ratio prevalence:detection	% under MDT
		n	Rate/10 000 pop.	*n*	Rate/100 000 pop.	Deform.	MB	Children		
1980	7 752	35 000	45.14	3 200	41.27				10.94	0
1981	7 928	33 000	41.62	3 100	39.10				10.64	0
1982	8 104	32 000	39.49	3 000	37.02				10.66	0
1983	8 280	30 000	36.23	2 800	33.82				10.71	3
1984	8 456	28 000	33.11	2 700	31.93				10.37	5
1985	8 632	26 335	30.51	2 558	29.63				10.30	2
1986	8 808	22 746	25.82	1 581	17.95		10		14.39	0
1987	8 988	16 040	17.85	1 491	16.59		9		10.76	0
1988	9 171	13 312	14.52	1 487	16.21		10		8.95	0
1989	9 358	12 220	13.06	1 218	13.02		12		10.03	5
1990	9 549	11 062	11.58	1 079	11.30		11		10.25	41
1991	9 744	9 429	9.68	990	10.16		18		9.52	90
1992	9 943	2 092	2.10	1 230	12.37		14		1.70	100
1993	10 146	1 094	1.08	967	9.53		20		0.88	100
1994	10 353	879	0.85	875	8.45	10	23		1.00	100
1995	10 564	726	0.69	801	7.58	7	32		0.91	100
1996	10 780	682	0.63	668	6.20	3	42		1.02	100
1997	11 000	925	0.84	900	8.18	5	49		1.03	100
1998	11 350	1 062	0.94	791	6.97	4	55		1.34	100
1999	11 725	940	0.80	879	7.50	7	60		1.07	100
2000	12 000	942	0.79	913	7.61	7	58		1.03	100

Figure 4.6
Evolution of leprosy prevalence and detection in Burkina Faso between 1980 and 2000



4.3 Implementation of WHO MDT in India 1982–2001

C.K. Rao

Progress

One of the most significant features of MDT in India is the priority it was accorded by, and the attention it received from, influential political leaders and decision-makers. Addressing the World Health Assembly in 1981, Mrs Indira Gandhi, the late Prime Minister of India, called for a global effort to eliminate the scourge of leprosy. Shortly thereafter, a commitment was made at the highest level to eradicate leprosy in India by the year 2000.

The basic WHO strategy for reducing the prevalence of leprosy by detecting cases and curing them with MDT has worked well; MDT proved to be a safe, acceptable, and effective tool that made leprosy a curable disease. By 1991, all 201 highly endemic districts were using MDT, of which 66 (mainly in Bihar, Uttar Pradesh, Madhya Pradesh, and West Bengal) lacked a full leprosy infrastructure. At that time, no efforts were made to get additional support from general health staff in these districts. .

Before the introduction of MDT, the estimated number of leprosy cases in India was 3.9 million; this fell to 3.4 million in 1986 and, by the end of September 2001, to 384 000. The prevalence rate has declined from 57 cases/10 000 population in 1983 to the current level of 3.7 cases/10 000. The decline was very rapid during the 3–5 years following MDT introduction but slowed considerably thereafter. Time-limited treatment with MDT of a large number of registered cases from the era of dapsone monotherapy (i.e. before MDT), and subsequent discharge, explained the initial steep decline in prevalence.

The number of new cases detected each year rose steadily with the extension of MDT to more areas, reaching more than 650 000 during the early 1990s, but has fallen to about 500 000 during the past 3–4 years. The increase in case detection during the period 1998–2000 was the result of two nationwide Modified Leprosy Elimination Campaigns (MLEC), which detected more than 450 000 new cases.

The number of new cases detected annually showed an increasing trend over the years because the continual expansion of MDT coverage to previously uncovered areas, leading to increased detection of new cases, and as a result of active search campaigns. Targets for case detection, assigned to states and districts, have contributed significantly to over-diagnosis of new cases, including reregistration of some old cases as “new”. As mentioned, the campaigns have also led to over-diagnosis of cases and this has contributed to the stability of case detection.

The rapid reduction in leprosy prevalence has encouraged India in its work towards the goal of eliminating leprosy as a public health problem by reducing the national prevalence rate to less than 1 case/10 000 by the year 2000. National plans for achievement of this goal were implemented in 1993. Individual states also implemented plans for bringing all districts of moderate and low endemicity under MDT by 1995. All of the country’s 563 districts have now been brought under MDT. However, despite efforts to improve the accessibility of MDT in all areas and for all population groups, the existence of areas/groups not covered by MDT cannot be excluded.

More than 10 million cases of leprosy were cured with MDT between 1982 and 2001. The reduction of state prevalence rates during this period is directly related to pre-MDT prevalence and to MDT coverage and duration. Of the 35 states, 13 have already achieved the goal of less than 1 case/10 000 population; nine states have fewer than 3 cases/10 000 and are expected to reach the goal soon. Special efforts are needed in eight states where the prevalence rate remains between 3 and 5 cases/10 000, particularly Andhra Pradesh, Maharashtra, Tamil Nadu, and Uttar Pradesh, which contribute most to the substantial prevalence. In the remaining five states – Bihar, Chattisgarh, Jharkhand, Orissa, and Madhya Pradesh – prevalence rate currently exceeds 5 cases/10 000. Orissa, with its strong leadership and commitment, should be able to reach the goal, but far more intensive efforts and substantial outside support will be needed if Bihar, Jharkhand, and Chattisgarh are to achieve the goal before the revised target date of 2005.

The visible deformity (grade-2) proportion among new cases in the country has declined from over 13% before 1982 to the current level of 2%. However, deformity rates are higher in some of the low-endemicity states because of an influx of old cases from elsewhere that are detected as new cases.

The effectiveness and popularity of MDT have made it possible to extend leprosy programme services and appropriate IEC (information, education, communication) activities, designed to raise community awareness of leprosy, to all areas of the country irrespective of the level of leprosy prevalence. Moreover, the fact that leprosy can be cured with MDT facilitated the repeal, in 1984, of the inhuman and unjust Leper Act of 1898, allowing leprosy patients to be brought into the mainstream of the society. The establishment of new colonies to house those with leprosy was discontinued in 1982; the number of colonies and, more importantly, the number of patients confined in them have dwindled over the years. Patient interviews by monitors/evaluators have shown that increasing numbers of patients – more than 98% in highly endemic rural areas – live with their families.

Several new partners and many long-term partners, especially international nongovernmental and bilateral organizations, have provided or increased their support for the extension of MDT to more areas.

The advent of MDT has enabled the leprosy programme to be restructured as a public health programme. Certain changes based on feasibility and cost-effectiveness have been made in the implementation of strategies. Leprosy programme managers' posts at national and state levels has become attractive and competitive – facilitating the selection of the best candidates with a background in public health. However, field-level activities had remained the preserve of vertical, specialized leprosy staff since the introduction of leprosy control in 1955, and this situation continued even after MDT was introduced. Special privileges and cash incentives were provided to attract competent leprosy field staff and professionals, in view of the demand for timely delivery of MDT drugs near the patients' homes. This system of incentives has delayed by nearly a decade the integration of leprosy programmes into the general health service in an effort to improve the accessibility of MDT services. The reluctance of vertical staff to allow transfer of programme tasks and the unwillingness of general health staff to accept these additional tasks without the privileges/incentives available to leprosy staff hindered the successful implementation of integration plans in 1989 and again in 1994.

As a result of bold decisions taken recently, and in consultation with WHO, at the highest political, administrative, and technical levels, the integration of leprosy control into general health services will be achieved soon. Nevertheless, further strengthening is needed in a number of states to accelerate this process.

Developments

Genesis

The availability of MDT as an effective tool to cure leprosy has enabled the Government of India to accord the highest priority to control of this disease and to allocate substantial funding to the programme. A working committee of eminent scientists, established in 1981, drew up recommendations for the rapid expansion of MDT to all affected areas. The leprosy control programme was renamed the leprosy eradication programme and aimed to treat all leprosy cases with MDT by the year 2000 in order to minimize transmission of the disease. Three very highly endemic districts (prevalence rate 100 cases/10 000) with a population of about 2 million each were brought under MDT in 1983 after careful preparation. The preparation involved ensuring full vertical leprosy infrastructure, detection of 80% of the estimated cases, updating of case records, training of all the staff, the availability of sufficient MDT drugs, and adequate funding.

Extension of MDT

Extension of MDT was based on the district as the implementation unit. By 1989, 45 out of 201 highly endemic (prevalence more than 50 cases/10 000) districts were covered by MDT, and by 1992 all such districts were covered. From 1985, MDT was also supplied to all states on demand for supervised administration to leprosy patients in districts not covered by MDT. Between 1991 and 1995, coverage was extended to the remaining districts, of moderate and low endemicity, so that, by the end of 1995, all 563 districts were under MDT.

Diagnosis and classification

WHO criteria for diagnosis and classification of leprosy cases have been adopted. At the time of introduction of MDT in a district, all cases, especially MB cases previously under dapsone treatment, were considered to be active cases.

Since the introduction of MDT, diagnosis has been based on clinical examination of suspected cases. However, between 1982 and 1995, skin-smear examination was also carried out in all MB cases at the time of diagnosis and at the end of treatment with MDT, but ceased to be mandatory for diagnosis between 1996 and 1998. From the beginning of 1999, skin-smear testing has not been required for diagnosis.

Until 1995, leprosy cases with more than 10 lesions (counting number of skin and nerve lesions involved) were classified as MB. In addition, all cases where skin-smear testing gave positive results were classified as MB, irrespective of the number of skin and nerve lesions. Since 1996, the WHO criterion of six or more skin lesions has been used for MB classification. Single skin lesion (SSL) cases were recorded separately from PB cases from 1998 onwards in view of their increasing proportion among new cases and of the availability of a single-dose regimen for their treatment.

Treatment regimens and duration

The MDT drugs and dosages recommended by WHO were modified as follows.

- The duration of treatment for MB cases differed from that recommended by WHO. At the time of MDT introduction in a district, all prevalent MB cases were given 14 daily supervised doses of three drugs before the WHO-recommended regimen. This additional treatment was based on the recommendation of the Indian leprologists' committee. It was considered that some of the prevalent MB cases previously on dapsone monotherapy would need longer initial treatment. New cases detected subsequently were given the remaining number of supervised daily doses. For example, cases detected on the eighth day of 14 daily doses were given the remaining seven daily supervised doses, and cases detected on the twelfth day received only two daily supervised doses before the start of the WHO-recommended regimen. MDT drugs for 27 days of self-medication were delivered after the monthly supervised drugs for a minimum of 24 times or until skin-smear negativity. From 1994 onwards, MB cases were treated for 24 months and from 1998 only for 12 months in accordance with the WHO recommendation.
- PB cases received only 6 months of the WHO-recommended regimen from the introduction of MDT in 1982.
- In 2000, accompanied MDT was introduced as a new and flexible approach for leprosy cases who for various reasons are unable to attend the monthly clinics and are at risk of not completing treatment. Such patients are given the remaining monthly blister calendar packs (BCPs) to allow them to complete the full course. This innovation was recommended by WHO to reduce treatment defaulters and promote MDT completion.

Annual follow-up of cured cases

Annual clinical and bacteriological follow-up of all MB cases was undertaken for 5 years after completion of MDT treatment. Cured PB cases were followed clinically once a year for two years. Since 1996 there has been no follow-up of cured cases, either MB or PB.

MDT drugs

Central to the successful cure of leprosy cases is the availability of adequate quantities of good-quality drugs. Loose MDT drugs were delivered to patients between 1982 and 1994. Drugs came from a variety of sources: some were purchased by the programme, and some were supplied by participating NGOs. They were delivered to patients, according to disease classification, at the place and time of first diagnosis and subsequently every 28 days for the prescribed duration of treatment by leprosy staff at drug distribution points near patients' homes. Each mobile team in a district planned monthly circuits to deliver drugs to all patients – a system that continued until 2000. The number of mobile teams in a district varied with the area, the population, and the number of leprosy cases.

The availability since 1995 of MDT drugs free of charge in BCPs has greatly simplified drug delivery and ensured good quality, better storage, and improved compliance with self-administered daily doses.

There were very few instances of shortages of MDT drugs before 1997, and possibly none since.

Delivery of MDT services

Vertical leprosy staff delivered leprosy services, including MDT, until 1998–1999. Plans to involve general health staff in supporting mobile leprosy treatment units, of which two were established in each of the 79 districts of moderate endemicity and one in every low-endemicity district during 1992–1993, did not come to fruition for want of advocacy and of commitment and motivation among both general health staff and decision-makers. Despite the simplification of diagnosis, classification, treatment regimens, drug delivery, and reporting, leprosy programme activities could not be successfully integrated into general health services: there was opposition from leprosy staff and reluctance among general health staff to assume the responsibilities. Concerted efforts since that time, and advocacy meetings with decision-makers at the highest level since 2000, have facilitated the active participation of general health staff; health centres in particular are taking over important tasks related to MDT services from leprosy staff. The involvement of general health staff in MLEC in 1998 has done much to facilitate the integration of the leprosy programme into general health services. This integration needs to be strengthened and sustained.

All 563 districts are expected to have fully integrated leprosy programme by the end of 2003.

Capacity-building of staff

A large body of vertical leprosy staff was created between 1982 and 1991, especially in the highly endemic districts, as a prerequisite for MDT. The increasing demand for training the new staff in leprosy necessitated the establishment of new training centres and the strengthening of existing centres; eventually, there were 49 such centres, 10 of them run by NGOs. To make the courses relevant, practical, and task-oriented, course content for certain categories of health worker has been simplified and course duration shortened. After the integration of leprosy services into general health services, the leprosy course was further simplified and shortened for general health staff.

With declining demand for training of vertical leprosy staff, some of the training centres ceased functioning or were closed down altogether from 1992 onwards.

Operational guidelines were developed and distributed to all implementing units from 1985 and were updated from time to time to ensure uniformity in planning and implementation and to provide reference material.

Information, education, and communication

Before the advent of MDT, leprosy was shrouded in mystery and fear. The vision and concern of Mahatma Gandhi and of other luminaries who followed him and championed the fight against the diseases, heralded an era in which leprosy became everyone’s concern. Nevertheless, the notion of leprosy being curable disease came only with the availability of MDT.

Community health education on leprosy, an important component of leprosy control even before MDT, was greatly strengthened between 1982 and 2001 by the advances in communication technology. Starting with traditional tools – word of mouth, posters, print media, and so forth – IEC activities have been strengthened and extended, and sustained by increases in budget allocations. The interest, expertise, and resources of several NGOs and bilateral agencies have also played a significant role. Several independent evaluations of the programmes assessed the level of community awareness and allowed appropriate messages to

be developed for identified target groups. The modified leprosy elimination campaign, implemented in 1998–1999, has greatly contributed to increasing community awareness nationwide by involving electronic media – television and radio – in addition to traditional channels to spread messages about leprosy.

The BBC World Service Trust undertook a well conceived project for 16 months in 1999–2000, interacting with the government-owned television and radio network to relay appropriate messages/programmes that reached more than half the country's population. Since then, television and radio have continued to disseminate similar material.

Disability prevention and correction

The national cumulative number of leprosy cases cured by MDT has now exceeded 10 million, and the number of disabilities prevented in leprosy patients is estimated to be over 1.5 million: MDT is the biggest contributory factor in the prevention of disability. Some NGOs introduced special activities in a few districts to prevent worsening of deformities through distribution of "physical aids" such as protective footwear and gloves to leprosy patients with deformities but the impact of such measures is unknown. The World Bank, in its financial support to the programme, has earmarked funds for surgical correction of leprosy-related deformities.

Modified leprosy elimination campaigns

The leprosy elimination campaign (LEC) approach conceived by WHO in 1995 to detect hidden leprosy cases in relatively small communities was successfully adapted in India in 1997. Subsequently, a successful modified LEC (MLEC) was launched nationwide during 1998. This involved almost a million general health staff and community volunteers being trained as search workers and then using house visits to detect suspected leprosy cases (which would be confirmed later). To promote self-reporting of leprosy cases, a large-scale community leprosy awareness campaign involving electronic and print media was launched before the 6 days of house visits. More than 450 000 new leprosy cases were detected by the MLEC; most of these were from Bihar, Orissa, and Uttar Pradesh states where the programme had not previously been very effective in detecting new cases. In 12% of new cases there was only a single skin lesion.

MLEC was successfully repeated in 1999–2000 in the highly endemic states of Bihar, Uttar Pradesh, Orissa, Madhya Pradesh, and West Bengal and again in late 2001 in highly endemic districts of these states. While the number of new cases detected was less than half the number detected in the earlier MLEC, over-diagnosis of new cases increased.

Preceded by wide publicity and advocacy by political and community leaders at all levels, MLEC proved a useful tool for detection of new cases and subsequent initiation of MDT.

Incentives to staff, states, and districts

Providing MDT services to the needy was considered to be a demanding and arduous task, since the drugs need to be delivered to the patients on time, every month, near their homes by the vertical leprosy staff. A system of monthly cash incentives to vertical leprosy staff, on a scale linked to staff grade/status, was therefore started after the introduction of MDT and continued until 31 March 2000. Ending this scheme, however, was deemed to be a prerequisite for securing the willing participation of general health centres in leprosy programme tasks. Currently no category of staff involved in leprosy programme is paid incentives of any kind.

A national scheme of awards to the best performing state or district has recently been introduced to create the healthy competition that leads to improved performance.

District Leprosy Society

It was observed that the MDT activities were interrupted on occasion because the substantial additional funds provided to the districts brought under MDT and sent through the state government did not reach the districts in time or were sometimes either used for purposes other than MDT/leprosy in the districts or used elsewhere. To overcome these problems, a registered District Leprosy Society was created for each district, with the District Magistrate as its chairperson and the District Leprosy Officer as secretary. MDT funds were sent to the Society directly by the national government, together with guidelines on their use. Subsequent review showed that this system functioned very satisfactorily. Each of the 563 districts in the country now has a District Leprosy Society to manage – and account for – additional MDT funds. The success of this scheme has prompted other national health programmes (for example, AIDS, tuberculosis, blindness prevention) to create their own district societies.

In order to facilitate the decentralization of the programme to the states, similar societies were created at the state level during 2000–2001, with the State Health Secretary as chairperson and State Leprosy officer as secretary, to manage, operate and account for the additional funds needed for MDT activities. The Government of India transfers these funds to the State Leprosy Societies, which, in turn, distribute to the District Societies as needed. This decentralization has made the states fully responsible for proper use of funds and their timely distribution to the districts.

Independent evaluation of the programme

The introduction of MDT, greater priority for the programme, and higher fund allocation necessitated a system of periodic independent evaluation of the programme. Between 10 and 12 teams – each with three members, of whom one is a WHO expert – were put together for each independent evaluation. So far, there have been eight independent evaluations of the programme, carried out jointly with WHO; the first was carried out in 1986. The objectives of each evaluation, lasting 10–12 days, were to validate the reported data, assess the competence of staff and the level of community awareness, and identify problems and suggest remedial measures. In the last independent evaluation in March/April 2000, the World Bank was a partner with the Government of India and WHO.

These exercises proved to be useful and cost-effective means of reviewing progress and also, from time to time, of motivating leaders at all levels, strengthening and sustaining their commitment to leprosy elimination.

International and bilateral agencies

Several international organizations apart from WHO were partners at different times between 1982 and 2001. UNDP and UNICEF have supported MDT activities in selected highly endemic districts, and the World Bank supported the programme with a “soft” loan up to the end of 2003.

WHO has continued to be a natural partner since the leprosy control programme started in 1955. Introduction of MDT, subsequent expansion to cover the whole country, and the goal of elimination of leprosy were all based on the technical advice of WHO. Over the years, WHO

has not only acted as a catalyst, identifying partners willing to support the programme, but has also enhanced its own resource support: the MDT drugs required for the programme were supplied in BCPs free of charge from 1995 and this will continue until the goal is achieved.

The Swedish International Development Agency (SIDA), Norwegian Agency for Development (NORAD), Danish International Development Agency (DANIDA), and United States Agency for International Development (USAID) have supported the extension of MDT to selected districts for some time, and DANIDA has supported the strengthening of various MDT activities in four states over the past 6 years.

Nongovernmental organizations

Nongovernmental organizations (NGOs) have long played a pioneering role in leprosy control in India, and since the introduction of MDT their number has increased to about 285 – mostly national organizations. A number of international NGOs – including The Leprosy Mission International (TLMI), the Damien Foundation India Trust (DFIT), the German and British Leprosy Relief Associations (GLRA and LEPRA), the Associazione Italiana Amici di Raoul Follereau (AIFO), Swiss Emmaus, and, more recently, Netherlands Leprosy Relief (NLR) and American Leprosy Missions (ALM) – have played a considerable role in extending MDT to more areas, supporting staff training, promoting community awareness, providing rehabilitation and disability correction, and strengthening and monitoring of the programmes. Some of them have also funded the activities of national NGOs. Since 1984, the Government of India has also supported the national NGOs, reviewing their contributions and providing cash assistance. The resources, commitment, and expertise of a large network of NGOs, working with the programme as partners, have helped to augment leprosy elimination efforts.

In recognition of the contributions made by these organizations, the programme has organized annual meetings with representatives of participating NGOs since 1985 to allow them to share their progress, plans, and problems, to promote coordination among themselves and with the government, and to ensure the implementation of all activities in accordance with the national guidelines.

Monitoring and supervision

District consultant leprologists

In 1982 the programme found it necessary to provide technical support and guidance to the districts brought under MDT. This was achieved by identifying consultant leprologists and assigning one to each district for about 5 days a month on a part-time basis. Duties included validation of diagnosis, classification, treatment regularity, and management of problem patients. Salary and travel costs were borne by the organization supporting additional MDT costs for the assigned district – in most districts, this was the Government of India. After 1990, it became impossible to provide consultant leprologists to all 201 districts that had been brought under MDT; it was no longer easy to find either the required number of experienced and willing consultant leprologists or the funds required to hire them. However, since 1998, NGOs and WHO have created full-time zonal/district support teams to assist and guide high-prevalence districts in highly endemic states.

National Leprosy Eradication Programme consultants/leprosy coordinators

During the early years of MDT, states faced administrative, operational, and financial problems in extending MDT to more areas. The national programme headquarters did not have sufficient human resources to monitor the progress through field visits or to provide timely assistance to the states. At the request of the programme, WHO has assisted since 1985 with the services of 13 full-time national public health experts as NLEP consultants to cover all states. Each was assigned one or more states on the basis of leprosy prevalence and of such factors as size, population, geographical contiguity etc. WHO supported the salaries and other costs until 2000. WHO replaced these positions in 2001 with state/zonal leprosy coordinators, assigned to problem states/zones to monitor, guide, and support leprosy elimination efforts.

Sample survey-cum-assessment units

In 1986, the programme created 22 sample survey-cum-assessment units (SSAUs) in highly endemic states to validate the reported data; more were established later. However, SSAUs were not able to achieve the intended objectives. The less experienced and less committed staff of SSAUs could not win the confidence of their colleagues in the districts and at higher levels. District data were often found to be more accurate than data generated by SSAUs. Moreover, the mobile nature of SSAU duties meant that experienced staff were often reluctant to take up positions in these units. The net effect is that SSAUs have gradually become non-functional, and a number of them have been abolished.

Information system

A very comprehensive and elaborate card for patients under MDT was started in 1982. It was later abridged, retaining only the core data for use by general health staff. The report format has been similarly simplified over the years to enable the health centre to report on progress to the district, but it is possible that not all the reporting units use the same reporting format.

National Leprosy Eradication Commission

The Chairman and Secretary of the National Leprosy Eradication Commission were the union Health Minister and union Health Secretary. Several union ministers of related departments – Planning, Finance, Information and Broadcasting, Education, Social Welfare – and a number of Chief Ministers of states, by rotation, were the members. The Government has established the Commission to translate the recommendations of the working group formed in 1981 and to review and formulate the policies of the leprosy programme. The Commission functioned between 1984 and 1989; it was able to minimize delays in decision-making for rapid expansion of MDT and provided significant support to the programme.

National Leprosy Eradication Board

With the Health Secretary as Chairman and the Deputy Director-General (Leprosy) as Secretary, the National Leprosy Eradication Board was created in 1984 to implement the policies of the Commission, minimizing bureaucracy, providing an opportunity to review progress, and taking decisions at its twice-yearly meetings to strengthen the programme. Members of the Board were Union Secretaries from related departments – Planning, Finance, Education, Social Welfare, Information and Broadcasting, etc. All the decisions taken at meetings of the Board implied acceptance by all the concerned departments. Huge financial resources needed for the programme and support from other departments became available within a few months of decisions taken by the Board. Like the Commission, the Board functioned between 1984 and 1989.

Office of the Prime Minister and Planning Commission

From 1984 to 1991 the leprosy programme was reviewed through annual reports by both the Prime Minister's office and the Planning Commission (which allocates funds to all programmes). The programme was adjudged to be one of the best of the health programmes, thanks to the effectiveness of MDT and its implementation, and these favourable reviews gave rise to extensive support and funds from interested parties; several NGOs and bilateral agencies became partners and supported the programmes as a result of these positive reviews.

Conclusion

Clearly, MDT is the "jewel in the crown" of the Indian leprosy programme and, over a period of some 20 years, emerged the winner in the battle against the disease. Cutting-edge technology and financial support to the Government of India and its leprosy programme have been provided by WHO; in turn, WHO has learned lessons from its Indian experiences. In fact, WHO, the various international and national NGOs, and the Government of India have gained much by sharing their knowledge, experiences, and resources in the course of the inexorable march towards the goal of leprosy elimination – and the Indian leprosy programme has derived enormous benefits from this synergism, allowing it to fight effectively and relentlessly against this once dreaded disease. It is to be hoped that the programme will continue to receive this much-needed support from all its partners until the goal is achieved.

Experiences and anecdotes

1. Considerable time and skill were needed to convince the father of a child with PB leprosy that 6 months' MDT treatment would cure the condition. Familiar only with the very protracted treatment with dapsone, the father nursed the misconception that the doctor treating the child was unhappy or angry with the child and/or that the government was short of funds. *(Dr V. Ekambaram)*

2. Only long interaction with a PB patient under MDT convinced him that 6 months' treatment was sufficient to achieve cure (although skin patches did not disappear). The patient thought that the doctor wanted to divert the drugs meant for treating him beyond 6 months in order to treat his relative a for longer period. The patient was finally convinced of the effectiveness of MDT treatment when the skin patches disappeared some months after the end of his 6-month treatment. *(Dr V. Ekambaram)*

3. One MB patient who had received dapsone treatment for nearly 5 years before MDT was surprised to find the treatment duration reduced to 24 months and eventually to 12 months, after which an MB patient could be declared cured. He joked with programme staff that the day was coming when it would suffice just to show the patient the MDT drugs before declaring him cured. *(Dr V. Ekambaram)*

4. Default in completing 14 daily supervised MDT drugs before WHO recommended regimen was, surprisingly, very rare. New innovations associated with MDT drug delivery, such as timely delivery of drugs near patients' houses, supervised drug intake, and pre-clinic monthly contacts at patients' homes to remind them of or educate them about regular drug collections, convinced patients that the new drugs were as effective in curing the disease as they had been told. *(Dr K.V. Desikan)*

5. In one district, MDT was restricted to MB patients only in 1982, but was extended to all leprosy patients from 1983. *(Dr K.V. Desikan)*

6. Some community leaders/NGO representatives were of the opinion that statistics were overshadowing human considerations when they observed the high priority being given to MDT delivery compared with the minimal attention being paid to the care of leprosy-disabled patients. *(Dr K.V. Desikan)*

7. The highest priority was accorded to leprosy programme following a special meeting in 1981 between the late Prime Minister Indira Gandhi and several leprologists, at which she expressed her wish for plans to be developed for eradicating leprosy from India by the year 2000. *(Dr Claire Vellut)*

8. During the initial period of MDT introduction in a district, 21 daily, supervised MDT drugs were given to lepromatous leprosy patients after hospitalization. Subsequently, MDT drugs for 14 daily supervised doses were delivered to or near the homes of MB leprosy patients. Later still, only the WHO recommended regimens were followed. *(Dr Claire Vellut)*

9. Several new initiatives associated with MDT – such as delivery of drugs near patients' homes by teams led by a medical officer, and monthly contacts before and during MDT delivery – convinced patients and the general public that something new, progressive, and effective was available to cure leprosy patients. The new regimen was acceptable and popular, and it reduced the social stigma attached to leprosy. *(Dr Claire Vellut)*

10. Daily movements of vehicles, from 06:00 to 17:00, delivering MDT drugs to leprosy patients in villages created considerable awareness of the leprosy programme in the community and among the local administrators. District magistrates made repeated public declarations that the leprosy programme was the only programme working in the villages; they offered significant support to the programme. *(Dr D. Anandraj)*

11. Leprosy workers used their bicycles to carry disabled active leprosy patients receiving MDT to and from drug distribution points to ensure monthly, supervised MDT drugs. These strict precautions, not even trusting leprosy workers to deliver monthly supervised MDT, seem surprising now, when "accompanied MDT" is accepted as a flexible and standard means of delivering MDT. (*Dr D. Anandraj*)

12. A number of female leprosy patients with reversible claw hand had been abandoned by their husbands but were accepted back after MDT and physiotherapy had corrected the problem. A tailor who also had reversible claw hand was able to continue his work after correction with MDT and physiotherapy. Through patients such as these, and their relatives, MDT grew in popularity. *(Dr D. Anandraj)*

13. A team representing SIDA visited a particular district to support MDT implementation. After a meeting with villagers, the team wanted to see some of the local leprosy patients – several who were sitting with other villagers came forward. The team members were surprised to find the leprosy patients mixing freely with the other villagers, and realized that the social stigma attached to leprosy patients was much less than they had imagined. *(Dr B. Kameswara Rao)*

14. The commitment of leprosy staff to regular delivery of MDT drugs and leprosy patients to compliance with treatment regimens was generally very high during the early years of MDT. Even in conditions of heavy and continuous rain, supervisors often found that staff and patients attended drug distribution points punctually. *(Dr B. Kameswara Rao)*

15. The commitment of staff, patients, and community alike, and the high priority given to the programme by decision-makers, made it particularly pleasurable to be associated with the leprosy programme. *(Dr B. Kameswara Rao)*

16. Red coloration of urine following MDT was mistaken for blood in the urine as a side-effect of the treatment and provoked the leprosy patient concerned into assaulting a medical officer. Considerable time and effort on the part of supervisors was needed to convince the patient that the red colour was not blood in the urine but only a harmless side-effect of rifampicin, one of the three constituent drugs of MDT. *(Dr T.P. Patro)*

17. During supervised intake of MDT at a drug distribution point, one patient was given the three drugs but later spit out the dapsone tablet when the team members were not watching. A supervisor who observed this questioned the patient as to why he spat out the dapsone but swallowed the rifampicin and clofazimine; the patient said that he had had problems whenever he took dapsone in the past (before MDT). Once the supervisor had explained about the safety of dapsone when taken with the other two drugs, the patient agreed to try taking all the drugs. He subsequently completed the full treatment course without any problem. *(Dr T.P. Patro)*

18. A lecturer in a college and a prosperous farmer from a village manhandled a leprosy worker who told them in public (without preparing them) that they had leprosy and should take MDT. However they completed the treatment after the supervisor contacted them at their home and explained that with the availability of MDT, the disease is fully curable and leprosy is milder and less infectious than many other diseases. They later became big promoters of leprosy programme activity, especially MDT. (*Dr T.P. Patro*)

19. A specialist from a medical college discouraged a patient with MB leprosy from taking the drugs provided by the programme, telling him they were cheap and of inferior quality. The specialist then prescribed the same drugs that the patient had purchased for some time. During defaulter retrieval, the patient was finally convinced that the drugs provided by the programme were the same as those he was purchasing on prescription and that he was spending his money unnecessarily. He completed the full course with the drugs provided by the programme. *(Dr T.P. Patro)*

20. A mother of a newborn baby had MB leprosy with ENL reaction and was banished from the house by her husband once he learned of her disease. Her condition improved dramatically with MDT and other drugs; the husband was subsequently persuaded by senior programme staff that she was fully cured of the disease and took his wife and baby back. *(Dr T.P. Patro)*

21. The extent of community awareness of leprosy can be judged from changes in attitude over a period of nearly two decades. In the early days, MDT drugs were distributed outside the village to avoid the anger of the community; later they were distributed to leprosy patients within the village and now they are distributed at the health centres. *(Dr T.P. Patro)*

22. The regimen of 14 daily supervised doses, followed in the early years of MDT, had to be abandoned in one particular unit in a district, because the unit was short-staffed. The patients were given the WHO-recommended regimen only until smear-negativity. Senior officials took a poor view of this and much explanation was needed to justify what had been done. However, the difficulty should be viewed in the light of the present 12-month regimen for cure. *(Dr T. Prabhakar Rao)*

23. In the absence of guidelines on continuing treatment during pregnancy, there was considerable anxiety among an expert group at a leprosy research and training centre when an MB patient under MDT became pregnant. A bold decision was taken to continue the treatment but to monitor the patient continuously for adverse outcome. There was great relief when a healthy baby was born and the mother suffered no untoward reaction. After the birth, the patient continued to take MDT until she reached smear-negativity. *(Dr P. Vijaya Kumaran)*

24. A leprosy worker who delivered MDT drugs to a close relative of the patient, when the patient was away from home, was reprimanded and faced disciplinary action. At that time, no one had thought of "accompanied MDT". *(Dr P. Vijaya Kumaran)*

25. One MB leprosy patient had to be given a special allowance as well as his MDT drugs to meet the increased appetite he claimed to have developed during treatment and thus to ensure that he completed the full course. *(Dr P. Vijaya Kumaran)*

26. An elderly MB patient treated with MDT for 5 years questioned the need for 5 years of treatment to achieve cure when he had recently observed some of his family members being told that they were cured after 12 months of MDT. *(Dr P. Vijaya Kumaran)*

27. The drugs needed for MDT were purchased mainly by the Government until WHO started to supply them. During 1986, a private firm submitted a quotation for supplying clofazimine at very low cost to the procuring agency (outside the health ministry) for the programme. It was learned unofficially that the product supplied by this firm was of substandard quality but that the mandatory quality test report, required before the order was placed, had been falsified. An alternative, and cheaper, source of good-quality clofazimine was essential if the risk of jeopardizing the programme was to be avoided. An urgent request for clofazimine was therefore made to WHO's Regional Office for South-East Asia; after consultation with WHO in Geneva, it was agreed within 10 days that clofazimine worth US$ 500 000 would be supplied free of charge. The original purchase order for clofazimine from the local firm was then cancelled. The speed of WHO's response and the willingness to absorb a substantial and unplanned expense were greatly appreciated by senior government decision-makers in the government and convinced them of the high priority accorded by WHO to the Indian leprosy programme. It was also a salutary lesson for private firms of the importance of supplying a product of assured quality in response to a purchase order from the procuring agency. Thereafter, the procuring agency ensured that purchase orders were placed only with firms manufacturing clofazimine of standard quality. *(Dr C.K. Rao)*

28. The first MLEC in India in 1998 detected some 450 000 new leprosy cases in the country. Of these, 150 000 were in the state of Bihar; this state was not only the largest contributor to numbers of cases but also had the largest new case-detection rate. This undermined the credibility of earlier reports, from several levels of supervisors and from many external evaluators, of satisfactory case-detection efforts in Bihar. *(Dr C.K. Rao)*

Contributors

Dr D. Anandraj, Consultant Leprologist for several districts, 1985–1992.
Dr K.V. Desikan, Consultant Leprologist for several districts, 1982–1990.
Dr V. Ekambaram, Consultant Leprologist for several districts, between 1982 and 1992.
Dr P. Vijaya Kumaran, Faculty of Schieffelin Leprosy Training and Research Centre – Schieffelin, Karigiri, 1982–1990.
Dr T.P. Patro, District Leprosy Officer, Garnjain, Orissa, 1984-1990.
Dr B. Kameswara Rao, Consultant, National Leprosy Elimination Programme, 1985–1994.
Dr C.K. Rao, Deputy Director-General of Health Services (Leprosy), Nirman Bhawan, New Delhi, 1984-1988.
Dr T. Prabhakar Rao, District Leprosy Officer and later Special Officer (Leprosy), Andhra Pradesh, 1985–1992.
Dr Claire Vellut, Consultant Leprologist for several districts, 1982–1990.

4.4 Implementation of WHO MDT in Myanmar

Kyaw Lwin, Tin Myint, Mg Mg Gyi, Mya Thein, Tin Shwe, Kyaw Nyunt Sein

History of leprosy

Leprosy has been well known to be endemic in Myanmar for many centuries. However, the earliest scientific record relating to the magnitude of the national leprosy problem in Myanmar comes from a report by the Leprosy Commission of India (1890–1891) – Myanmar at that time was included under India during the British rule (*1*). In 1891, the Commission estimated the prevalence to be 8.6 per 10 000 population for the country as a whole and 14.4 per 10 000 for central Myanmar. The 1932 census of Myanmar reported 11 127 leprosy cases (prevalence 7.6 per 10 000 population, which was probably an underestimate based on obvious and easily recognized signs of the disease. In 1935 Dr Santra reported a prevalence of 250 per 10 000 population in the Mandalay area, and in a 1951 report, Dr Dharmendra (a WHO consultant to Myanmar) estimated that there were 100 000 cases in the country and a prevalence of 50 per 10 000 population (*2)*. Dharmendra's estimate was subsequently revised upwards by Dr Lampe (also a WHO consultant to Myanmar, from 1953 to 1955) to 100 per 10 000 population (about 200 000 cases).

Based on the findings of a survey conducted in 1963–1964 by a WHO Leprosy Advisory Team, the estimate was again revised upwards, with prevalence being reported as 250 per 10 000 population for the whole country (about 590 000 cases).[1] In some areas of central Myanmar the estimate was as high as 400 per 10 000. During the survey, the prevalence reported by the leprosy control project teams in Shwebo and Myingyan districts was 322 and 443 per 10 000 population respectively. In 1973, the national authorities conducted a parallel survey – the National Leprosy Programme Prevalence and Assessment Survey – and reported an estimated prevalence of 242 per 10 000 population.

Leprosy control in Myanmar

In 1952, in consultation with WHO, the Government of Myanmar launched an intensive programme for leprosy control under Health Department Plan No. 9. This plan was based on early case-finding and on providing home-based treatment with dapsone to all patients in the country. At that time, there were very few primary health centres at township level serving the rural population and most of the services were centred on hospitals and dispensaries. To address the problem of leprosy from a public health point of view and to achieve the necessary coverage within a relatively short period of time, special leprosy control projects were established in each district (comprising 5–8 townships, depending on the population) to cover the whole country. Case-finding activities included mass (village), school, contact, and special group surveys. In addition to the technical support from WHO, UNICEF provided the necessary supplies and equipment, including a free supply of dapsone, to the national programme.[2]

The Central Unit of the Disease Control Programme in the Department of Health was responsible for the planning and implementation of leprosy control activities in the whole country, and for training, monitoring, and assessment; it was headed by the Deputy Director for

[1] Cap JA et al. *Report of a survey in Burma, January to June 1963*. MOH/PA/11364, dated 4 June 1964.
[2] Government of Union of Burma, WHO, UNICEF. Plan of Operation on Leprosy Control Programme, Burma, signed in 1957, and consecutive addenda.

Leprosy Control. In addition to the special leprosy control project teams, leprosy hospitals in Yangon and Mandalay served as specialized institutions for referral services, training, reconstructive surgery, rehabilitation, and research activities.

As part of the Disease Control Programme, the Government established Regional Leprosy Control Teams in the 14 States and Divisions, under the authority of the State and Division Health Departments. In areas where the disease burden was high, one regional leprosy officer was stationed at the State and Division level; at district level there were several leprosy control project teams, covering several townships according to the endemicity. Each team consisted of a medical officer, between one and three leprosy inspectors, 20–30 junior leprosy workers, and a laboratory technician.

All relevant information and experience acquired from 1952 to 1973 with regard to epidemiology, control strategy, organization, and management were reviewed. On this basis, future strategies were developed and implemented by the leprosy control programme. The most important operational milestones during the period 1970–1977 were as follows:

- The increase in the number of mid-level management personnel, such as regional leprosy officers and leprosy specialists for Bago, Ayeyarwady,and Yangon Divisions, and support staff for these officers.
- The first-ever systematic national health planning process, with the cooperation of WHO and UNICEF, to formulate the Peoples' Health Plan (1977–1981).
- Research activities to strengthen leprosy control measures:
  - dapsone-resistance prevalence survey in Myingyan Township
  - rifampicin trial in Singu Township
  - continuation of BCG trial follow-up studies in Singu area.
- Revision of criteria for determining inactivity of the disease in leprosy patients after a sufficient period of regular treatment with dapsone. Patients who were inactive were released from control and discharged from the treatment register. This was carried out in a timely manner with the intention of reducing the heavy load of registered leprosy patients.
- Introduction of the concept of integrating leprosy control activities into basic health services (BHS) by conducting pilot studies in Yangon, Mandalay, and Magway Divisions and Mon State from 1970.

During the period 1973–1977, the leprosy control programme registered the highest number of cases in the country (262 171 cases), with a prevalence of 86.2 per 10 000 population (*3*).

In 1978, based on the primary health care concept promoted by WHO and under its First People's Health Plan, the Ministry of Health integrated vertical disease control programmes – such as malaria, tuberculosis, leprosy, and trachoma – within the BHS. The first phase of the plan covered 147 townships, and leprosy control activities were carried out under the Primary Health Care and Basic Health Services Programme of the Department of Health. By the end of the Second People's Health Plan in 1986, integration was completed in all the remaining townships of the country. More than half of the (mainly paramedical) staff in the leprosy control programme, who numbered over 900, were retrained as multipurpose health workers and transferred to the primary health care service of the township health department. The remaining leprosy staff were assigned as technical support staff to the various divisional, district, and township health departments.

Situation during the early 1980s

The leprosy situation during the early part of the 1980s can be summarized as follows:

- A large number of leprosy cases were detected and brought under regular treatment. It was estimated that 89% of lepromatous cases in the country had already been detected and registered for treatment.
- Case-finding activities continued to progress well in all project areas based on routine referrals, self-notifications, contact examination, examination of schoolchildren, and planned mass surveys.
- At the end of December 1980, a total of 262 081 leprosy cases had been registered for treatment, of which 231 469 cases were actually receiving treatment. The treatment regularity rate (patients getting dapsone tablets every month during the year) was 87.6%. During 1980, 2120 cases were treated in leprosy hospitals, homes, and colonies.
- Among those undergoing treatment, 23.1% had lepromatous leprosy and 5.9% were children.
- A total of 4069 non-lepromatous cases were released from control during 1980.
- The annual incidence throughout the early 1980s remained at 1–3 per 1000 population.
- The lepromatous rate was constant at 3 per 1000 population. After more than 6 years of treatment with dapsone monotherapy, 18% of lepromatous cases had negative skin smears compared with 50% of borderline cases.
- Among patients with lepromatous leprosy who had been under treatment with dapsone monotherapy for more than 10 years, a significant proportion remained bacteriologically positive. The dapsone resistance survey in Myingyan Township in 1980–1983 showed that 38.6 % of patients were dapsone-resistant. The annual incidence of dapsone resistance was 3.4 % per year.
- As a result of a timely case detection and early treatment, especially among children, 72% of tuberculoid cases and 96% of the indeterminate cases were free from deformities.
- The number of children under 15 years of age among the treated cases fell markedly, from 26% in 1957 to 5.9 % in 1980. The impact of sustained leprosy control efforts was especially evident among schoolchildren, most of whom were under 15 years of age. During 1962–1963, 9375 new cases (26 per 1000) were detected among 350 798 schoolchildren screened. In 1980, however, only 345 new cases (0.71 per 1000) were detected among the 480 282 school children examined, which clearly demonstrated the effect of mass treatment in protecting children from leprosy.

Challenges faced

Dapsone resistance

A dapsone resistance survey was carried out in Myingyan District in 1980 and 1983. In 1980, there were 779 lepromatous patients who had been treated with dapsone monotherapy for more than 5 years (90% of them for more than 10 years); 38.6% of them were found to be dapsone-resistant.[1] The annual incidence of dapsone resistance in 1981 and 1982 was 40 and 45 per 1000 lepromatous patients respectively; the average annual incidence of dapsone resistance was 3.4%. At that time, it was thought likely that dapsone resistance had developed some 10 years earlier: certainly, a 1973 assessment report recorded that solid-staining bacilli were found in the skin smears of 24–27% of the lepromatous and borderline cases examined in the survey.

[1] Lwin K et al. *Survey of prevalence of dapsone-resistant leprosy in Myingyan District, Upper Burma, 1980–1983, and a preliminary report submitted to THELEP SC meeting in Rangoon, 16–12 November 1981* (unpublished report).

High disease burden

The burden of disease in the country was still huge at the time of integration, with more than 250 000 cases under treatment and more than 10 000 new cases being detected annually. Additional information on the incidence of the disease was obtained from the WHO BCG trial in Singu Township in Mandalay Division. Throughout this trial, which ran from 1964 to 1975, the incidence of leprosy remained constant at about 5 per 1000 population per year. The trial showed that dapsone monotherapy was ineffective in controlling transmission of the disease. Moreover, some 10% of lepromatous patients included in the trial were found to be dapsone-resistant; dapsone resistance was subsequently confirmed by animal inoculation tests.

Shift in donor interest

In the early 1980s, UNICEF – which had been the major provider of drugs (dapsone) and other supplies and equipment to the leprosy control programme – shifted its focus and began to gradually phase out its support for leprosy control. The national programme then had to explore other possibilities and establish new networks with other interested donors to obtain the necessary drugs for the programme.

Finding alternative regimens (1981–1986)

A study of rifampicin treatment was carried out from 1976 to 1984 in the same area – Singu Township – that had been the focus of a BCG trial running. The study involved all bacteriologically positive lepromatous, borderline-lepromatous, and borderline patients, who were given 600 mg of rifampicin daily for 30 days in addition to the usual daily dose of 100 mg of dapsone. A further single dose of 1500 mg of rifampicin was given annually in subsequent years until the skin smears were negative or skin lesions became inactive. Patients who showed signs suggestive of dapsone resistance were given 100 mg of clofazimine daily in addition to the other two drugs.

Cases registered in the Shwebo and Wetlet Townships (also former sites of BCG trials) were designated as controls and were given standard dapsone monotherapy.[1] Two years after the administration of rifampicin (daily for 30 days), all cases showed clinical improvement and the bacteriological index had fallen satisfactorily. Nasal smears were, almost without exception, negative for acid-fast bacilli, and solid-staining bacilli were very seldom seen. In 12 out of 271 patients there was evidence of reactivation during the fifth year, which was controlled in all cases by a further 1500-mg annual dose of rifampicin at the time of full annual assessment. The objective of rendering lepromatous patients non-infectious therefore appears to have been achieved. The annual incidence of leprosy among the study population declined from 49 per 10 000 population in 1976–1977 to 9 per 10 000 population in 1983–1984.

The results of the studies of dapsone resistance and rifampicin treatment encouraged the national programme to add rifampicin to dapsone in its regimen for treating lepromatous cases, which was used from 1982 to 1986 in highly endemic areas – the Divisions of Yangon, Bago, Ayeyarwady, Magway, Mandalay, and Sagaing (Shwebo, Sagaing, and Monywa project areas only). During the preparatory phase (1982–1983), all registered cases were screened and assessed both clinically and bacteriologically. From 1983 to 1985 all lepromatous cases were given 1200 mg rifampicin once a month for 6 consecutive months in addition to daily dapsone.

[1] Lwin K et al. *Rifampicin trial in Upper Burma*. WHO, SEARO Research Grant, 1976–1984 (unpublished report).

This was followed by an annual dose of 1500 mg rifampicin while dapsone treatment continued; the recommendation at that time was lifelong treatment of lepromatous cases with dapsone monotherapy.

In the second year of this initiative, 32 071 lepromatous cases (55% of those registered) were given rifampicin once a month for 6 months. In the third year, an additional 33 676 cases were treated with rifampicin, and all cases treated during the second year were given their annual rifampicin dose. These activities were undertaken by the existing staff of the leprosy control programme. In addition, the specialized staff also treated dapsone-resistant cases, managed leprosy reactions and other complications, carried out clinical and bacteriological assessments, and conducted training and research activities. Altogether, 67 747 lepromatous cases were brought under treatment. At the same time, all non-lepromatous cases were treated with dapsone monotherapy in the BHS.

In Myanmar's other States and Divisions – which at that time were categorized as low-endemic areas – the BHS continued to provide dapsone monotherapy to both lepromatous and non-lepromatous cases as part of the integrated disease control programme. Rifampicin was not given to patients in these areas because of the low endemicity, lack of drugs, and shortage of human resources needed to deliver the services. As well as treating patients, BHS staff also carried out case-finding, clinical assessments, and health education activities under the supervision of township medical officers. The low-endemic areas included: Chin, Kachin, Kayah, Kayin, Rakhine, Shan, and Mon States, and Tanintharyi Division.

Inactive non-lepromatous cases in the six highly endemic regions were screened by the BHS and then reviewed by the medical officers or leprosy inspectors. Cases that met the criteria were released from control. At the end of 1987, 61 587 cases treated with dapsone monotherapy were released from control and discharged from the treatment register.

During the maintenance phase (1985–1986), patients who were given rifampicin underwent annual clinical and bacteriological assessment. The number of registered cases at the end of 1987 was 204 282, and the registered prevalence rate 53.4 per 10 000 population.

Introduction of WHO MDT, 1988

During 1986 and 1987, Myanmar introduced WHO MDT (*4*) on a small scale in some selected areas of the country. In 1988, with the support of drugs received from WHO, MDT was introduced, in a phased manner, in the six hyperendemic divisions (Ayeyarwady, Bago, Magway, Mandalay, Sagaing, and Yangon), covering about 85% of the country's registered cases of leprosy. To simplify the operational aspects of delivering MDT drugs in the field, fixed-duration treatment was adopted and MB cases were given 24 monthly doses of MDT. After completion of the recommended fixed course of treatment, both PB and MB cases were discharged, regardless of skin-smear status. In these hyperendemic areas, delivery of MDT drugs at village level, as well as case-holding, was made the responsibility of the specialized staff of the leprosy control programme.

By the end of 1990 (Appendices 1 and 2), 167 townships were covered with MDT. The outcome of this treatment was reflected in the dramatic reduction of registered prevalence from 53.4 per 10 000 population (204 282 registered cases) in 1987 to 27.6 per 10 000 population (112 129 registered cases) in 1990. This reduction was the result both of curing 52 566 cases (cumulative figure) with WHO MDT and of "cleaning" the registers as part of the review

process before introduction of the new regimen. Reviewing the progress made, the leprosy control programme realized that further expansion of coverage in the targeted townships, at least in the short term, was impossible using only the existing staff of the leprosy control programme. The nature of home-based treatment and the need to supervise the monthly dose of MDT required the staff to visit each village every month, which made it impossible for them to cover new areas in the townships. However, the following favourable conditions encouraged the leprosy control programme to hand over to the BHS the task of delivering MDT drugs to patients:

- The existing coverage of the basic health infrastructure was adequate and strong except in a few townships in the border areas of the country.
- MDT was simple to administer, had few side-effects, and was effective; operationally, it was easy for the BHS to handle this task as part of their routine activities.
- The disease was declining and township health departments were able to manage the leprosy problem as part of their routine work without becoming over-burdened.

In 1991, the task of delivering MDT was handed over to the BHS and the following measures were undertaken to ensure full collaboration from all the agencies involved:

- Essential administrative steps for the handing over of MDT activities were taken at central, state, and divisional levels.
- Orientation and capacity-building activities were carried out for staff of the leprosy control programme and the BHS.
- Clear and simple mechanisms for monitoring and supervision were established.
- Referral centres for management of complications and other problem cases were also established.
- Support and technical assistance provided by the leprosy control programme to the BHS was strengthened.

With these measures in place, township medical officers were made programme managers for leprosy control in their respective townships. The staff of the BHS, such as health assistants, female health visitors, and public health supervisors grade 1, were made responsible for field supervision, while midwives and public health supervisors grade 2 were designated as implementers and given responsibility for case-finding and for treatment with MDT.

Staff of the leprosy control programme were reassigned as technical advisers, supervisors, and coordinators with responsibility for training, verification of diagnosis in difficult cases, management of leprosy reactions and other complications, and preparation of reports for the BHS.

Expansion of MDT coverage, 1995–1996

The 1991 World Health Assembly resolution WHA 44.9 to eliminate leprosy as a public health problem by the year 2000 gave substantial impetus to leprosy elimination efforts in Myanmar. With the pledge of sufficient supplies of MDT drugs from WHO in 1994, the national programme was able to extend MDT coverage to all 320 townships in the country and to make MDT drugs available in all health facilities (township hospitals, station hospitals, rural health centres and sub-centres) in the country. The BHS staff provided domiciliary treatment to all registered cases within their jurisdiction. By 1996, all 18 758 cases registered for treatment in the country were given MDT in 320 townships.

As a result of expansion of MDT coverage, leprosy prevalence declined further from 6.11 per 10 000 population (24 082 cases) in 1994 to 2.5 per 10 000 population (11 906 cases) by the end of 1998, and the cumulative number of cases cured with MDT throughout the country reached 183 731 (*5*).

Achievements due to integrated MDT services

Integrated MDT services made possible the following achievements:

- There was a marked reduction in registered prevalence from 59.3 per 10 000 population in 1986 to 2.5 per 10 000 in 1998 (Figure 4.7).
- Significant increases in MDT coverage were achieved in terms of both patients and geographical area. In 1988, only 19.3% of the registered patients were on MDT; by 1996, all registered cases were on MDT (i.e. there was 100% coverage). At the geographical level, only 15% of the country was covered with MDT in 1988 – by 1996 coverage was 100%.
- Detection of new cases became more effective as more health workers were involved in case-finding activities. An average of 8000 to 10 000 new cases were detected annually from 1986 to 1997. The proportion of children among the new cases declined from 17.9% in 1986 (pre-MDT period) to 9.5% in 1997. The proportion of new cases with grade 2 disability fell from 27.6% in 1986 to 10.9% in 1996 (Appendix 2).
- The capacity for diagnosis and treatment among BHS staff was improved, and the health centres and sub-centres were able to provide leprosy services at the peripheral level. The integrated approach proved to be sustainable and highly effective.
- IEC activities were intensified with the involvement of BHS and voluntary health workers.
- A community-based rehabilitation programme for leprosy patients was initiated in selected townships, with the active involvement of the community.
- A coordinated system for supervision and monitoring was established. Key information on leprosy was included in the routine BHS reporting system.
- The leprosy control programme was able to participate in WHO multi-centre studies of new drug combinations (using ofloxacin and minocycline in addition to rifampicin) and health systems research.

Conclusion

The introduction of WHO MDT during 1988 in Myanmar dramatically changed the picture of leprosy. Leprosy patients could now look forward to effective treatment. The community too, with the expansion of MDT services, realized that the disease can be cured within a relatively short time – and this was one of the main reasons for the lessening of the stigma associated with leprosy. Information materials for the public could now be presented in a positive way without creating fear. Patients could be told that they were cured after finishing the recommended course of treatment. Equally significant is the fact that MDT also restored the credibility of the leprosy programme and renewed the enthusiasm of leprosy workers. The public health approach to dealing with leprosy lives on in Myanmar thanks to MDT.

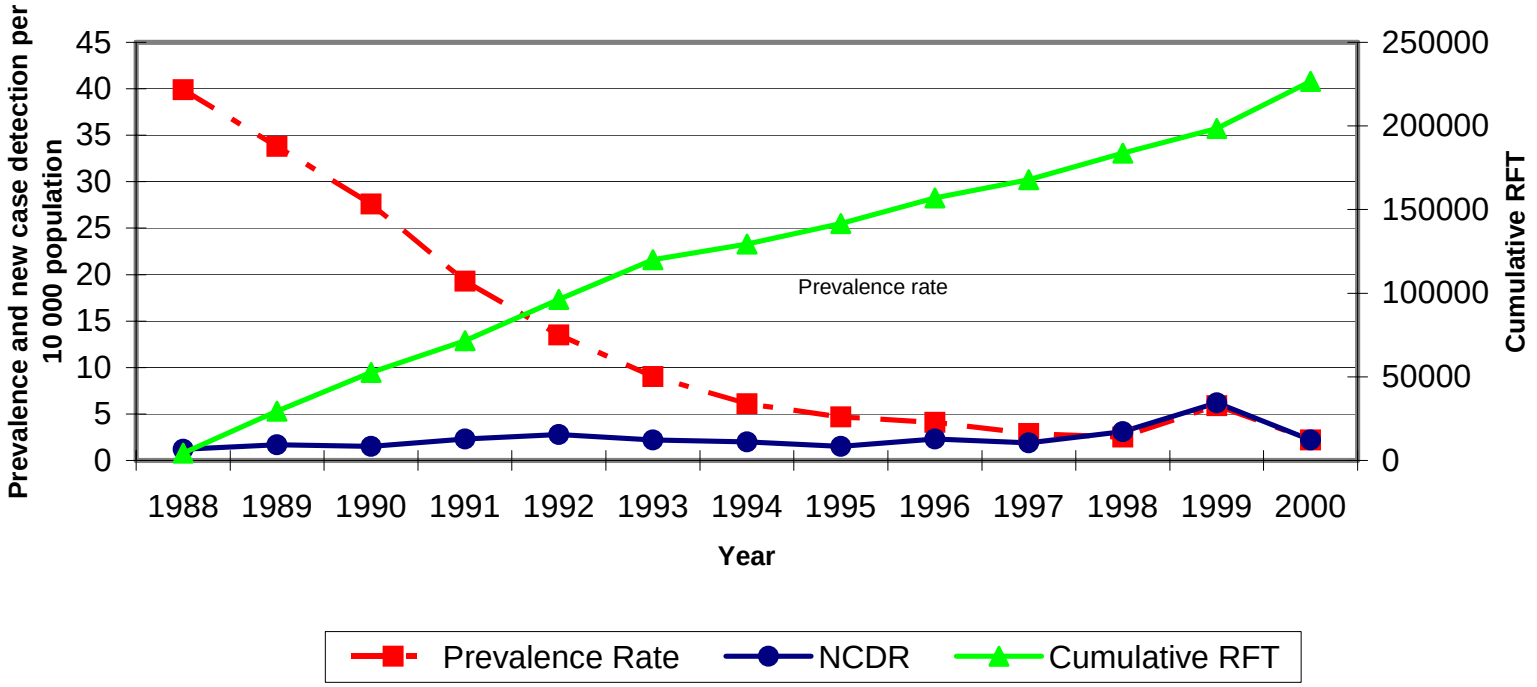
References

1. *Report of the Leprosy Commission in India 1890–91*. Calcutta, Superintendent of Government Printing, 1893.
2. Dhamandra. *Leprosy control in Burma*. Rangoon, Government Printing Press, 1953.
3. Myint T, Htoon M. Leprosy in Myanmar, epidemiological and operational changes, 1958–92. *Leprosy Review*, 1996, 67:18–27.

4. WHO *Chemotherapy of leprosy for control programmes: report of a WHO Study Group*. Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 675).
5. Lwin K, Sein KN. Leprosy elimination programme in Myanmar. In: *The conquest of scourges in Myanmar*. Yangon, Myanmar Academy of Medical Science, 2002:121–268.

Figure 4.7

Graph showing the trend of registered leprosy prevalence rate/10 000 population, new case detection rate/10 000 population, and cumulative RFT, 1988 to 2000



Appendix 1

Leprosy prevalence rates in Myanmar States and Divisions, 1984–2000

Sr. No.	State or Division	Year																
		1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
1	Ayeyarwady	66.5	56.1	54.7	53.7	38.7	34.4	29.1	25.2	11.0	4.4	3.2	3.0	2.9	2.2	3.1	7.8	1.9
2	Bago	81.5	80.4	74.7	76.4	49.0	36.6	26.9	16.4	9.7	6.2	3.7	4.6	5.4	6.7	5.1	8.9	2.6
3	Chin	18.5	14.9	15.1	15.4	26.1	14.4	14.1	13.6	16.3	11.9	10.1	9.4	3.2	4.4	2.7	2.7	1.4
4	Kachin	7.0	5.8	5.5	5.3	4.9	4.7	4.6	4.1	4.0	3.8	3.7	3.2	2.4	1.4	0.3	2.6	0.1
5	Kayah	22.2	17.0	16.5	16.7	14.9	14.4	14.0	13.8	13.6	12.4	11.2	11.0	5.4	4.4	2.6	2.1	2.2
6	Kayin	21.7	21.9	22.0	23.3	21.6	21.4	21.3	21.0	20.2	18.0	9.4	5.6	4.3	2.8	2.0	4.9	2.0
7	Magway	107.8	106.5	99.9	98.2	76.1	68.5	61.6	37.4	23.4	12.5	8.6	6.3	5.2	3.2	5.2	9.5	3.4
8	Mandalay	130.9	130.9	107.4	83.2	56.8	47.6	32.9	15.3	11.8	4.2	3.4	3.6	3.4	3.0	2.7	7.2	3.5
9	Mon	42.2	44.2	42.5	42.7	40.1	37.6	37.4	24.2	24.2	22.4	10.7	8.7	7.5	2.6	1.5	3.8	1.3
10	Rakhine	6.2	5.9	5.9	5.3	4.3	4.3	4.8	4.9	4.8	4.7	4.5	3.5	2.4	0.6	0.3	2.4	0.6
11	Sagaing	278.9	93.0	88.6	90.3	46.6	38.9	27.2	21.6	16.6	11.0	6.2	5.0	4.4	2.8	3.7	6.3	2.9
12	Shan	20.6	18.1	20.4	21.2	19.8	19.2	18.5	18.3	17.4	18.4	7.6	8.7	6.0	2.5	2.2	2.7	1.3
13	Tanintharyi	25.1	23.8	23.7	25.1	22.9	22.5	22.4	21.8	20.9	14.6	11.5	5.8	3.8	1.1	0.8	3.3	1.0
14	Yangon	54.2	51.9	39.6	43.5	33.1	22.7	18.0	11.2	6.1	3.4	2.6	2.1	1.0	1.8	1.6	4.0	2.0
Union		*66.7*	*65.4*	*59.3*	*53.4*	*39.9*	*33.8*	*27.6*	*19.3*	*13.5*	*9.03*	*5.5*	*4.7*	*4.1*	*2.9*	*2.5*	*5.9*	*2.2*

Appendix 2

Leprosy situation in Myanmar, 1985–2000

End of year	Prevalence	New case detection	Prevalence/ detection ratio (I)	New case detection						Cured with MDT
				Children		Disabled		MB		
				No.	%	No.	%	No.	%	
1985	240 474 (65.4)	6 600 (17.9)	36.44	908	13.76	1 822	27.6	2 383	36.11	—
1986	222 209 (59.3)	6 191 (16.5)	35.89	1 102	17.80	1 703	27.5	1 929	31.16	—
1987	204 282 (53.4)	5 725 (15.0)	35.68	421	13.39	1 466	25.6	1 966	34.34	—
1988	155 857 (39.9)	4 472 (11.7)	34.85	517	11.56	1 046	23.4	1 599	35.73	4 400
1989	134 487 (33.8)	6 496 (16.7)	20.70	716	11.02	1 176	18.1	2 459	37.85	25 143
1990	112 129 (27.6)	6 204 (15.3)	18.07	688	11.09	1 005	16.2	2 431	39.18	23 023
1991	79 973 (19.3)	9 632 (23.2)	8.30	1 126	11.69	1 350	14.1	4 259	44.22	19 103
1992	57 275 (13.5)	11 814 (28.0)	4.85	1 271	10.76	1 559	13.2	5 421	45.72	24 638
1993	38 945 (9.0)	9 669 (22.4)	4.03	1 374	14.21	977	10.1	4 502	46.56	23 750
1994	24 082 (5.5)	8 665 (19.7)	2.78	1 124	11.63	780	9.0	4 186	48.31	9 375
1995	21 071 (4.7)	6 577 (14.7)	3.20	934	14.20	612	9.3	3 460	52.60	12 229
1996	18 758 (4.1)	10 136 (22.5)	1.85	1 125	11.10	1 105	10.9	5 607	55.32	15 301
1997	13 581 (2.9)	9 086 (19.3)	1.49	863	9.50	1 009	11.1	5 015	55.20	10 987
1998	11 906 (2.5)	14 357 (30.7)	0.83	1 328	9.25	1 917	13.3	7 394	51.50	15 782
1999	28 481 (5.9)	29 765 (61.8)	0.96	2 335	7.84	3 519	11.82	15 459	51.94	14 798
2000	11 006 (2.2)	10 262 (20.52)	1.11	959	9.35	783	7.3	5 643	54.99	28 056
Total										*226 585*

4.5 Implementation of WHO MDT in the Philippines, 1981–2000

S.S. Griño

When regular health services resumed after the Second World War, the National Leprosy Control Programme in the Philippines used only dapsone monotherapy. However, following establishment of a good relationship between the Bureau of Disease Control, the Philippine Leprosy Mission, and the Sasakawa Memorial Health Foundation, MDT was introduced as the principal approach to leprosy control.

The pilot study

In 1981, Dr Yuasa broached the possibility of using the new MDT approach to leprosy control in the Philippines. It was decided by an ad hoc steering committee that the effort would start with a pilot study to test the feasibility of integrating leprosy services with MDT as the main approach into the general health service. The study was to last for two years, after which the leprosy services would submit the results to the Department of Health for approval of nationwide implementation of this approach. Agreed criteria for selection of the pilot study sites were:

- high prevalence
- a health service that functioned well, with good records available
- accessibility of all areas
- agreement by the health services to implement the pilot study and to sustain activities once satisfactory results were obtained.

Ilocos Norte and Cebu were selected on the basis of these criteria. Logistics for the project were guaranteed by the Sasakawa Foundation through WHO. The Philippine Leprosy Mission promised to provide logistics for emergency and unforeseen activities deemed necessary to expedite the process.

The steering committee selected a technical working group, chaired by the Director of the Bureau of Health Services. This working group met regularly to develop a training manual and a manual of procedures that would be the basis of implementation by the health workers of the two provinces. The head of the leprosy services was to have overall responsibility for the whole enterprise.

Logically, the projects started with the training of health workers who would be involved. Teams were created to undertake the training and worked with the local health workers, monitoring progress regularly. These teams stayed in the two provinces, working with staff of the provincial health office, the city health office, and the skin clinic. In Cebu, the medical officers of the leprosarium were also involved in the training and implementation. Once the health force was trained, the teams carried out the regular monitoring, based on schedules agreed by the main implementers.

Social preparation of the communities involved paralleled the training of health workers – as the staff of health units were trained, schedules for implementation were established. The roles and responsibilities of each sector were defined. Health workers were informed of evaluation and monitoring procedures at the end of training. The training team then went to another town to begin the process again.

At the start, loose drugs were dispensed, but blister packs were introduced as soon as they became available and the details of distribution and monitoring for compliance were worked out. Although early attempts at blister-packing the drugs were unsuccessful, Ciba-Geigy quickly developed the user-friendly blister packs that have made the work of the health units much easier and significantly increased acceptance by patients.

Within a year of implementation, the pilot study staff had collected enough data to prove that the integration of leprosy care and management was not only acceptable, but also easily manageable by health workers delivering general health services.

Findings/implications

Strengths

The strengths of the project, which made implementation easier and sustained enthusiasm for its continuation, are outlined below.

- The logistics of the project were guaranteed and sustained for the entire duration – a factor that probably contributed most to the project's success and to the commitment of the health workers and patients.
- The cooperation and commitment of the local authorities and the community were ensured before the project got under way.
- Networking and communication among the government health service, international funding agencies, and NGOs did much to maintain the quality of services, ensuring logistic support and resources that could be readily accessed and thus avoiding delays and frustrations in the local health units.
- The regular presence of the task force and oversight by the steering committee in monitoring progress, solving problems and encouraging proved to be the mainstay of continued motivation among both patients and health workers to comply with the requirements of the programme.
- The interest and support of local health authorities made possible the adoption of a monitoring tool that proved to be an excellent means of evaluating compliance and the completion of the MDT regimen. Each unit kept a record of visits, number of blister packs received, notes regarding status of regimen, etc. Workers in rural health units particularly appreciated the simple and quick method of calculating the expected time of the next visit taught to them by the provincial health officer of Ilocos Norte.
- The blister pack was probably the key to compliance, from the point of view of the patient. Individual patients suggested other aids to compliance, such as hanging the blister pack near the water jar, or on the wall where they could see it before going to bed or on waking up. When patients were unable to make the trip to the clinic, a follow-up service to their homes was provided. Many absentees were remotivated to take their drugs regularly because of this show of interest in their welfare.
- Patients who had made good progress with their treatment were recruited to help in motivating other patients to come for treatment or to comply with treatment requirements.
- The guaranteed accessibility/availability of leprosy expertise to field units ensured that problem cases could be rapidly referred to competent health personnel.

Barriers

Barriers that may delay or complicate implementation can be overcome in the following ways.

- Individuals expected to work regularly for the project should be recruited from areas with easy access to the central office and should be appointed permanently to the project until its completion.
- Training of health workers should not start until training and procedural manuals have been printed and are in place. Manuals for training and procedures should be available and each unit should have a copy for easy reference. Monitoring teams' schedules should be respected. Drinking-water and glasses must be available.,
- Compliance with treatment by all patients should be carefully checked.

Recommendations

Many recommendations derived from the findings/implications of the pilot study. However, some have evolved from frustrating experience and are emphasized here.

- A clean, paper copy of every report should be readily available in a number of strategic locations – both locally (in provincial, city, and rural health offices) and centrally (in the files of the national leprosy control programme). Heads of offices should not be allowed to "own" records and keep them for themselves. Turnover of officials should not be completed unless all files are endorsed and handed over to the proper authority.
- Feedback from monitoring/evaluation visits by authorized teams or individuals should be provided to the units concerned at the end of the visit; copies of written reports should be mailed back after these are received at the central office. If possible, follow-up visits to these units should be made shortly after each monitoring/evaluation visit to discuss strengths and to provide technical and/or material support in any areas where shortcomings have been revealed.
- The national leprosy control programme should ensure that procedural manuals and reference material on the management of leprosy as a disease and the leprosy control programme are available in every unit at all times. Information on new developments in the control programme should be sent to each unit, especially the referral centres. Two years after the start of the pilot study, many rural health units had lost their copies, resulting in errors by the health workers.
- Forms and other essential supplies should be made available in every unit before existing stocks are depleted.

National leprosy control programme

The year 1986 marked the completion of one year of MDT implementation, and the steering committee for the MDT pilot study had already planned a meeting of the major foreign and local donors to the pilot project for February of that year. The intention was to apprise the donors of the status of the programme with regard to its goals and objectives. The foreign donors had made firm plans to attend, and the technical working group of the national leprosy control programme persuaded the recently appointed Health Secretary, Dr Alfredo Bengson, to meet the donors. He spent an entire morning at the meeting, where the programme managers described the background to the project and reported on its progress and on the benefits accruing to the Department of Health's general public health programme.

The Health Secretary was sufficiently impressed to direct Dr Jesus Abella, Director of Communicable Disease Control and chairman of the technical working group, to immediately

convene a group to plan and organize integration of the programme into Department of Health activities nationwide. He believed that the data collected in one year of implementation in the pilot provinces was enough to warrant the nationwide expansion of the programme, provided that logistic needs could be met. The donors pledged continued support to both the pilot project and the integration of MDT into general health services. An administrative order was subsequently issued and several committees, composed of leprosy workers from both the Department of Health and the NGO partners in the pilot study project, were convened, as described in the following paragraphs.

- A National Leprosy Advisory Board was organized with representatives from WHO, the American Leprosy Missions, the Sasakawa Memorial Health Foundation, and the Canadian Leprosy Association, plus the Director of the Foundation for Assistance to Hansenites, the Director of the Philippine Leprosy Mission, a representative from the Sovereign Military Order of Malta, and another from the Soriano Foundation. The leprosy services staff were to implement the expanded programme. The Sasakawa Foundation guaranteed free drugs for the programme, and WHO guaranteed sustained technical advice and training for programme managers and key implementers as well as for any special projects arising from the needs of the programme. The National Leprosy Advisory Board was to provide technical and administrative guidelines for the programme, while agencies of the Department of Health were responsible for operational aspects. A 5-year budget proposal (1987–1991), presented by the steering committee at the first meeting of the Board, was approved in principle, pending confirmation from the International Federation of Anti-Leprosy Associations (ILEP).

  Note: In 1987, the National Board, through the ILEP Coordinator for the Philippines, John Sams, then President of the American Leprosy Missions, received US$ 200 000, which covered approximately 2 years' operation according to the budget proposal submitted: this ensured an early start for the programme and gave impetus to the scheduled activities. Other implementing bodies were instituted such as the national training and monitoring task force at the central, provincial, and local levels. A national leprosy coordinator was appointed, with regional, provincial city, and municipal counterparts. Orientation courses on the content and mechanics of the programme were conducted for each level in accordance with schedules.

- The technical working group established for the pilot study was directed to plan, organize, and implement the integration of services nationwide. It created a national training and monitoring task force composed of leprosy consultants from different regions, health educators, and leprologists from two sanitaria. The task force formed teams that would travel to different regions and provinces to train all health workers up to rural health unit (RHU) level, help set up the programme, and monitor the progress in each unit. The technical working group then undertook:
  - development of a training manual for general health workers based on the manual of procedures for the pilot projects;
  - development of a manual of procedures based on the existing infrastructure and lines of authority of the Department of Health;
  - development and production of clinic and reporting forms for use by the MDT programme;
  - setting schedules for orientation of officials from different regions;
  - orientation by regions.

- The plan was to conduct training in one area, so that MDT implementation could then be undertaken by the trainees themselves and any problems corrected before the process was repeated in another area. The plan and schedules were usually followed, although a degree of flexibility was essential to deal with unforeseen problems. As planned, the early years were spent in different regions conducting activities from training health workers to stabilizing the integration of MDT into rural health services. A total of about 15 000 workers were trained by 1989, by which time the programme was functioning countrywide. The period of implementation proved the feasibility and acceptability of integrating leprosy services into the Department of Health programme.
- Drugs and supplies were stockpiled in the regional offices, and funds were allocated and disbursed as scheduled; monitoring of continuing implementation in the pilot provinces was maintained.

Note: During 1987–1990, health ministries of neighbouring countries (Indonesia, Myanmar, Nepal, Republic of Korea, Sri Lanka, Thailand) and even from some of the Pacific island nations (Kiribati, Federated States of Micronesia, Palau, Papua New Guinea) sent groups of leprosy workers to learn from the Philippine experience of MDT implementation. The technical working group worked with many of these health workers, helping them to create training and procedural manuals suited to their needs.

MDT implementation accelerated from 1987 and peaked in 1991 (see Appendix 2). However, reorganization of the Department of Health as a consequence of the devolution of services to the local government units began to erode the hard-won gains of the programme. While adequate funds and drugs remained available to the programme, increased turnover and relocation left staff confused about their roles. This is probably a very important reason for the decline in the implementation of MDT treatment. Equally, it is possible that this decline may have been due to the decrease in inpatients, completion of treatment among existing cases, and reduced interest in the programme as a consequence of unsettled working conditions among the various levels of health workers. However, lack of resources made it impossible to test this hypothesis.

From 1986 to 1992, WHO supported activities to evaluate the programme externally, and reports submitted by the programme managers in the field were validated. For the most part, the reports were encouraging and confirmed the impression that the programme was generally successful and merited continuation.

During the years of implementation, WHO policy and strategy for MDT implementation underwent a number of changes which were communicated by the Department of Health to all field units by means of department circulars. Managers of the national leprosy control programme visited health workers to ensure that the changes were understood and that new instructions for patient management were being followed. The major changes were as follows:

- Initially, patients who failed to collect their blister packs for two months would have to repeat the whole regimen again. However, by 1992, the conditions under which the patients had to restart the whole regimen were radically revised. More patients were encouraged simply to continue treatment even after some absence, and this resulted in the drug consumption declining concomitantly as there was no need to restart treatment in a significant number of patients.

- The regimen initially called for MB patients to take 24 blister packs within 36 months; this was reduced to 12 blister packs within 18 months for MB patients and 6 blister packs within 9 months for PB patients. It took some time for this change to take place: most health workers believed that the earlier regimen worked and would not jeopardize their patients' welfare with "new ideas". The patients themselves, especially those who started with monotherapy, refused to conform and insisted on continuing treatment.
- Leprosy elimination campaigns (LECs) were launched in high-prevalence areas in 1995 (see Appendix 1); the health services and cooperating agencies mobilized resources to find all the patients in each targeted area. Implementation adhered closely to the concept and suggested steps developed by expert committees from WHO. Again, the first LECs took place in the pilot provinces of Ilocos Norte and Cebu, and other areas were identified subsequently. In some instances, "mini-LEC" activities were undertaken in small towns with high prevalence.
- Despite these efforts, some areas that were inaccessible to health services because of geographical conditions or for security reasons remained untouched by the programme. Special action projects for the elimination of leprosy were also launched in 1995, at more or less the same time as the LECs, for three such provinces – Abra in the north, and Sulu and Tawitawi in the south. Again, the suggested steps for implementing these special projects were in line with WHO recommendations. The projects were implemented by the Executive Director of the Philippine Leprosy Mission and the national coordinator in cooperation and collaboration with local officials and NGOs in the areas.

From 1991, the organizational structure of the Department of Health underwent several changes that affected budget, leadership, procedures, and staff turnover. The lack of reports – or, at best, delays in reporting and doubts about the validity of reported date – bore testament to the effects of these changes on the implementation process. Technically, the programme continues on as well as the situation and available human resources permit. It is hoped that this generation of leprosy service people, whenever they are assigned, will remain for a substantial period and be committed to sustaining the programme; otherwise, as feared by many leprologists and epidemiologists, there will certainly be a resurgence of the disease.

Strengths – factors that contributed to success

The principal contributions to success came from the following factors:

- Logistics for the programme being secured at the start of the programme.
- Competent health workers, highly motivated and dedicated, with constant access to expertise from partner organizations.
- A knowledgeable, competent, and committed National Coordinator.
- Regular supervisory visits to field units to follow up on the initial training and ensure regular submission of reports.
- Accessibility and availability of referral centres or, in places lacking such facilities, visits by leprologists or workers with the necessary expertise to help health workers to deal with problem cases.
- Commitment and cooperation on the part of local government officials and local health workers.
- Widespread social preparation of each community, securing the cooperation of barangay health workers who have access to individual homes and are trusted by the community.

- The constant presence of members of the technical working group and/or the national training and monitoring task force, helping with the activities that started the programme in each area.

Conclusion

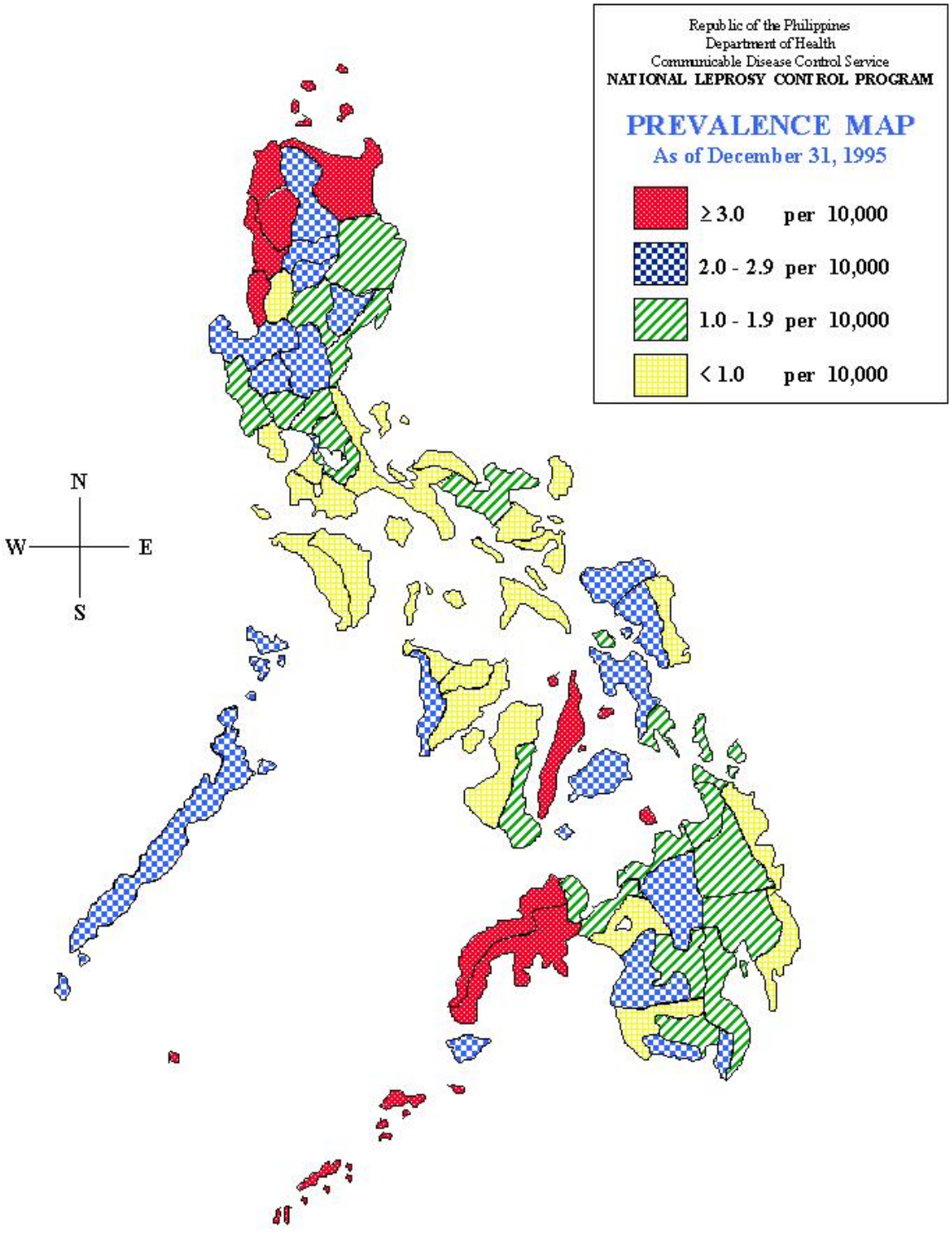
Findings from the MDT pilot study and recommendations emerging from the report were incorporated as far as possible into implementation of the national leprosy control MDT programme. Most of the recommendations were useful in the national expansion – and would be applicable to any national programme if the needed resources are available. The writer urges that the strengths of the Philippine programme be adopted and/or adapted by programmes elsewhere and that the pitfalls identified be avoided.

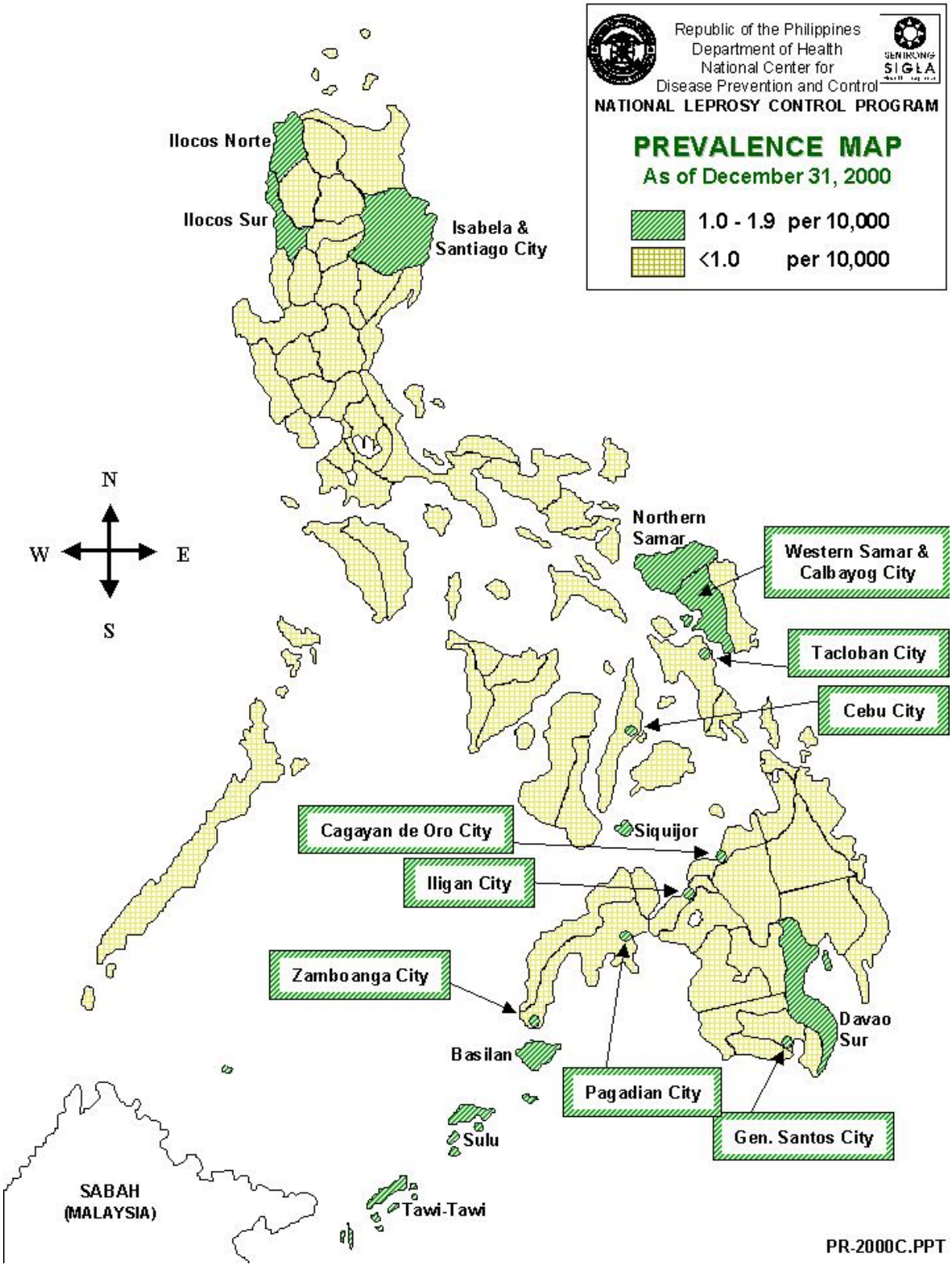
Information sources

Annual Reports of Communicable Disease Control, 1981–2000.
Annual Reports of the Philippine Leprosy Mission, Inc., 1981–2000.
Minutes of Technical Working Group of the National Leprosy Control Programme.
– Manuals of Procedures of: Pilot Study for provinces of Ilocos Norte and Cebu
– MOP 1987 –1991-1996 revisions.

Appendix 1

Maps of leprosy prevalence in the Philippines




Republic of the Philippines
Department of Health
National Center for
Disease Prevention and Control
NATIONAL LEPROSY CONTROL PROGRAM
PREVALENCE MAP
As of December 31, 2000
1.0 - 1.9 per 10,000
<1.0 per 10,000
Ilocos Norte
Ilocos Sur
Isabela & Santiago City
N
W
E
S
Northern Samar
Western Samar & Calbayog City
Tacloban City
Cebu City
Cagayan de Oro City
Siquijor
Iligan City
Zamboanga City
Davao Sur
Basilan
Pagadian City
Gen. Santos City
Sulu
SABAH (MALAYSIA)
Tawi-Tawi
PR-2000C.PPT

Appendix 2

Summary report on MDT implementation, 1987–2000

Year	Registered cases at start of year	New cases detected during the year	Cases removed from register		Cases on MDT	Completed treatment	Cases still on MDT at year end	Registered cases at year end	% of cases on MDT
			Died, lost, etc.	Register adjustment					
1987	38 104		51	847	4 588	1 925	2 612	35 281	7.4
1988	35 281	2 442	0	0	12 597	751	14 458	36 972	39.1
1989	36 972	4 163	2 033	3 479	8 301	3 676	17 060	31 947	53.4
1990	31 947	5 725	3 126	8 131	9 588	6 135	17 377	20 280	85.7
1991	20 280	7 169	2 100	0	9 506	8 002	16 781	17 347	96.7
1992	17 347	5 896	2 587	0	5 896	5 339	14 751	15 317	96.3
1993	15 317	4 697	2 204	2 436	4 697	4 245	16 001	16 001	100
1994	16 001	4 450	667	304	4 450	3 602	16 486	16 486	100
1995	16 486	2 685	no data	no data	2 685	2 826	14 679	14 679	100
1996	14 679	4 051	no data	no data	4 051	4 020	8 760	8 760	100
1997	8 760	4 942	no data	no data	12 916	3 549	8 749	8 749	100
1998	8 749	3 572	no data	no data	12 352	4 309	7 276	7 276	100
1999	7 276	3 692	no data	no data	10 515	5 005	4 807	4 807	100
2000	5 024	3 578	no data	no data	8 032	3 248	4 277	4 277	100

Chapter 5

The role of international agencies and nongovernmental organizations

5.1 The Nippon Foundation (formerly Japan Shipbuilding Industry Foundation) and the Sasakawa Memorial Health Foundation

Y. Yuasa

WHO's regular budget for leprosy was only about US$ 300 000 in 1975 and has remained at more or less the same level since then. However, the contribution of the Japan Shipbuilding Industry Foundation (JSIF) increased to US$ 2 million in 1976, of which two-thirds went to leprosy. By 1980, the total contribution of JSIF, now called The Nippon Foundation (TNF), had reached almost US$ 4 million. TNF also announced an additional contribution of US$ 50 million for the purchase of MDT drugs, for free global distribution through WHO, to meet the needs of leprosy-endemic countries from 1995 to 1999. The announcement was made in July 1994, on the occasion of the First International Conference on Leprosy Elimination, held in Hanoi, Viet Nam, under the joint sponsorship of WHO and TNF/SMHF. The main focus of that meeting, prompted by the forty-fourth World Health Assembly in May 1991, was "how to accelerate the global elimination of leprosy", and the announcement by Mr Yohei Sasakawa, son and successor of Mr Ryoichi Sasakawa, of the additional US$ 50 million contribution from TNF was intended to support the intended acceleration. At the inauguration of the Global Alliance for the Elimination of Leprosy (GAEL) in Abidjan, Côte d'Ivoire, in November 1999, again under the joint sponsorship of WHO and TNF/SMHF, Mr Y. Sasakawa announced that TNF would make a further contribution of US$ 24 million over the period up to 2005, taking the total contribution of TNF to WHO nearly US$ 150 million – a testimony to remarkable collaboration.

Collaboration between WHO/LEP and SMHF intensified in 1982 with publication of *Chemotherapy of leprosy for control programmes* (WHO Technical Report Series, No. 675), the report of the 1981 WHO Study Group on MDT. At this time, the financial support from SMHF to leprosy-endemic countries became concentrated on implementation of MDT in these countries.

A few years earlier, when WHO had established THELEP under TDR, the involvement of some key members of the THELEP group in a chemotherapy trial co-sponsored by SMHF was most beneficial. These trials were on a quite modest scale, and a limited number of drug combinations were used. However, an important contribution made by the trial was the annual standardization workshop, held at the Leonard Wood Memorial (LWM) laboratory in Cebu, Philippines, for doctors and laboratory technicians from the three countries directly involved in the trials but also with participants from other countries, including Indonesia, Myanmar, Nepal, and Viet Nam, with which SMHF had working relationships. When the WHO recommendation on MDT was published in 1982, these countries already had some knowledge of MDT, and some field workers had first-hand experience of MDT implementation, although the actual regimens recommended were

different. The involvement of these countries in the chemotherapy trial was one of the principal reasons that they were able to implement MDT with relative ease compared with many leprosy-endemic countries in other parts of the world. Equally significant for these countries was the undertaking by SMHF to supply MDT drugs rather than dapsone.

From the outset, the policy of SMHF was to supply MDT for MB patients for 2 years only; any extension of treatment beyond 2 years, mostly until smear negativity, would have to rely on drugs from other sources. Interestingly, however, the Minister of Health of Indonesia, Dr Adhyatma (the former head of a leprosy service), requested permission from SMHF to use MB MDT for one year only; his reasoning was that the quantity of drugs being supplied would mean many MB cases having to go without MDT altogether. This permission was not given but, with hindsight, agreement to this suggestion would have seen Indonesia become – by some years – the first country with a national policy to use a 12-month MB regimen, which is now standard throughout the world.

This supply of MDT drugs, to as many as 20 countries at times, continued until 1995, when the extra contribution of US$ 50 million from TNF was able to provide the required amount of MDT globally.

An important contribution to the implementation of MDT was the use of blister calendar packs. In 1984, a pilot study of MDT involving 2500 patients was undertaken in the provinces of Ilocos Norte and Cebu in the Philippines, with support from SMHF, WHO and others. In order to facilitate the delivery of MDT drugs and to avoid rifampicin being diverted to purposes other than leprosy treatment, the Government of the Philippines and WHO requested Ciba-Geigy to develop a presentation of MDT drugs in blister calendar packs. Following the success of the trial, albeit with a limited number of patients, the Government of the Philippines decided to use these packs for the entire national leprosy programme – and for the national tuberculosis programme as well.

SMHF/TNF and WHO/LEP, initially under Dr H. Sansarricq and later under Dr S.K. Noordeen, were able to work very closely towards common objectives. Formal annual visits by the Medical Director of SMHF – for consultation on TNF's annual contribution – continued but, since there were many other opportunities during a year to discuss issues of mutual concern, including the use of TNF funds, the period of formal consultation was eventually cut to just one day.

Dr H. Nakajima, first as Regional Director of the WHO Regional Office for the Western Pacific (WPRO) and later as Director-General of WHO, gave wholehearted support to the MDT programme; his understanding and cooperation were valuable in the collaboration between TNF/SMHF and WHO/LEP. The two bodies jointly organized the first International Conference on the Elimination of Leprosy (Hanoi, Viet Nam, 1994), and had similar involvement in the second and third International Conferences (in New Delhi, India, 1996, and Abidjan, Côte d'Ivoire, 1999). Coordination of their activities was particularly apparent in certain countries, including the Federated States of Micronesia and Papua New Guinea.

Without the TNF contribution, which covered a major portion of WHO's leprosy budget for 25 years from 1975, it is likely that global leprosy situation would be quite different from what it is now. It is particularly doubtful that WHO/LEP would have been able,

in 1991, to make the bold proposal of globally eliminating leprosy as a public health problem; even if it had done so, fewer of the world's leprosy-endemic countries would have reached the elimination target by the end of 2000 without the additional US$ 50 million for the free supply of MDT.

After 1982, SMHF channelled the major portion of its financial support to leprosy-endemic countries for purposes such as training, monitoring, transport facilities, equipment, etc. to support the implementation of MDT. It may be worth pointing out that SMHF, despite being an NGO and a member of ILEP, decided from the outset to support the leprosy control programmes of the national health authorities, rather than conduct its own projects or support projects by other NGOs. This approach was based on the belief that the national health authority is ultimately responsible for the health of a country's citizens, and that support from outside, whatever its extent and however long-lasting, could never meet the needs of the entire population permanently. Thus, SMHF tried always to strengthen national capacity so that, on withdrawal of that support, the national programme was better off than it had been. In the 1980s, a provisional time-limit was set for this support – usually 3 or 5 years. After 1991, SMHF's support was extended, lasting until the elimination target was achieved by the national health authorities; this meant that many of the countries of east and south-east Asia, such as China, Indonesia, Philippines, Republic of Korea, and Thailand, where leprosy control efforts have been successful, have gradually ceased to need that support. Now, the greatest proportion of SMHF support goes to three Asian countries – India, Myanmar, and Nepal – that have yet to achieve their national leprosy elimination goal. Elsewhere, some support is extended to three other countries (Brazil, Madagascar, and Mozambique) that also have yet to achieve the goal, as well as to a handful of others that have only recently achieved it. A limited amount of SMHF support also goes to non-elimination activities, such as the prevention of disabilities or empowerment of people affected by leprosy and education of communities about leprosy, in the belief that the ultimate goal, a world without leprosy, can be achieved only with the full participation of ordinary citizens and not by the efforts of health and medical professionals alone.

5.2 The International Federation of Anti-Leprosy Associations

H. Sansarricq

Most of the information given in this section regarding ILEP support for MDT implementation is based on statements of ILEP representatives at various meetings organized by WHO; figures on MDT thus include WHO MDT and a number of other combined drug regimens.

1981–1990: continuing good ILEP/WHO cooperation, with a few clouds

As mentioned in Chapter 2, the late 1970s saw a widespread demand – from voluntary organizations as well as from other quarters – for recommendations from WHO on MDT for leprosy. Chapter 2 also recalls that, in mid-1981, ILEP agreed not to issue recommendations before WHO had done so.

As early as 10 December 1981 (the WHO Study Group having met in mid-October), the ILEP Medical Commission endorsed the WHO MDT regimens and recommended that ILEP members follow the WHO recommendations in the projects that met the required standard. At its General Assembly in June 1982, the Federation approved a resolution to ensure the widest possible application of WHO MDT in the field (*1*, *2*). However, at the coordinating meeting of February 1984 (*1*), it was made clear that "the adoption by ILEP of

the new drug therapy as proposed by WHO does not mean that each member association is obliged to apply that regimen alone in its leprosy work". As a consequence, ILEP reports to WHO sponsored meetings never made a distinction between WHO MDT and other combined drug regimens, notably the rifampicin/Isoprodian® combination, use of which was supported in several projects by the German Leprosy Relief Association.

By the end of 1983, the ILEP reporting system was updated, in collaboration with WHO, in order to include relevant information on MDT regimens and patient statistics (i.e. numbers of registered patients, numbers of patients receiving or having completed MDT or under post-MDT surveillance, etc.). In 1983, ILEP published a booklet on the introduction of WHO MDT (*4*), prepared by its Medical Commission, which gave priority to assisting with implementation of MDT; a revised edition was published the following year.

In the early 1980s ILEP-supported control projects covered some 1.2 million patients (*5*). In 1983, the Damien Foundation from Belgium, an ILEP member, created a Drug Fund for MDT, with an initial endowment of US$ 400 000; a number of other ILEP members provided additional grants. Also in 1983, most of the ILEP-supported projects with sufficient infrastructure (more than 150 projects out of 700) started "implementing MDT, in one way or another, covering an average of 10% of their patients" (*2*).

There was a steady increase in the use of MDT (WHO MDT and other combinations) in ILEP-supported leprosy control projects in the latter half of the 1980s; numbers of patients on MDT as reported by ILEP at the third coordinating meeting on implementation of multidrug therapy, September 1988 (*6*), were:

1984: 100 000
1985: 145 000
1986: 188 000
1987: 250 000

By the end of December 1988 a total of 768 706 patients were on chemotherapy in ILEP-supported projects, of whom 270 616 (35.20%) were receiving MDT (WHO-recommended MDT in most cases). Regionally, the proportion of patients on chemotherapy who were receiving MDT was nearly 42% in Asia, 32% in the Americas, and 27% in Africa. In 1988, ILEP members were supporting 814 field projects in some 92 countries, in addition to 136 other projects, with a total annual expenditure of about US$ 60 million (*7*).

1991–2000: growing difficulties in ILEP/WHO cooperation

In May 1991, the World Health Assembly adopted resolution WHA44.9, Elimination of Leprosy as a Public Health Problem. The objective of MDT for all leprosy patients by the year 2000 had already been adopted by ILEP in June 1990 (*8*). This objective had apparently the same practical meaning as the elimination target of WHO – with one important difference. ILEP did not accept the WHO definition of a case of leprosy as recommended by the WHO Expert Committee on Leprosy at its sixth meeting in 1987 (*9*), according to which all leprosy patients who had completed MDT were considered to be cured and were excluded from the prevalence. For ILEP, patients who had been treated with MDT but who presented deformities or permanent nerve damage continued to be cases of leprosy and therefore contributed to prevalence. This position had implications for the use of prevalence to monitor the elimination of leprosy as a public health problem and for fundraising activities.

At the second meeting of the WHO Working Group on Leprosy Control in July 1992, ILEP expressed concern over the slowing down of MDT coverage in recent years in their projects, which seemed to be facing some difficult areas (*10*). Concern was also voiced about "the limited progress made in developing a true collaboration between ILEP and WHO" and "the attitude of some ILEP member associations, which are reluctant to make national partners in the projects carried out in the country".

At the third meeting of the Working Group in July 1993 (*11*), ILEP made the following statement: "At the end of 1991, a total of 1.34 million patients were under treatment, surveillance or care by ILEP-supported projects; 636 000 people were registered for chemotherapy, 60% of whom were receiving MDT" (of unspecified nature). Expenditure by member associations in 1992 amounted to US$ 77 million, spent in 103 countries with 63% going to support of control work, 7% to research, 10% to training and 7% to rehabilitation. Further, "ILEP members were concerned about the potential negative impact on donors of loose use of the term 'elimination'. They considered that publicity should put the targets clearly in context and stress the continuing tasks set by the unchanged level of newly detected cases, areas where it would be difficult to implement MDT, and patients with disability".

At the first meeting of the Leprosy Elimination Advisory Group (LEAG) in July 1995 (*12*), ILEP reported that, at 31 December 1993, a total of 589 934 leprosy patients (35% of the global total of registered patients) were under chemotherapy in ILEP-supported projects. ILEP's interim target and first priority was to provide MDT by the end of 1995 for all patients in all ILEP-supported projects (other than those adopted during that current year). Other priorities included prevention of disabilities and rehabilitation. In 1996 (*13*), within ILEP-funded projects:

- A total of 402 072 patients were on MDT registers (46.8% of the world total).
- The total number of new cases was 246 829 (44.1% of the total worldwide).
- Support for socioeconomic rehabilitation was strengthening (217 projects in 34 countries).
- Support to combined leprosy/tuberculosis programmes was growing: 180 976 tuberculosis patients were being treated in 62 ILEP projects.
- Research expenditure totalled 5.62% of expenditure by all ILEP member associations, with efforts being made to increase this proportion.

At the third LEAG meeting in July 1997 (*14*), ILEP reported that the budget of the Federation in 1997 was about US$ 65 million, that support to leprosy and tuberculosis programmes amounted to US$ 6.8 million, and that support for socioeconomic rehabilitation accounted for 28% of projects. ILEP initiatives then included:

- joint ILEP/WHO efforts to reach undetected cases;
- guidelines on the sustainability of elimination activities;
- advice on socioeconomic rehabilitation;
- provision of essential learning materials to a wide range of health staff;
- integration of non-leprosy NGOs in leprosy control activities;
- advice on research priorities.

Meeting participants reported that some ILEP members were diverting their attention to diseases other than leprosy, but ILEP's president considered that combining leprosy and tuberculosis work was cost-effective.

Immediately after the third LEAG meeting, there was a joint ILEP/WHO workshop on reaching unknown patients (hidden prevalence) (*15*) – a non-controversial issue but a problem of central importance. In the course of this workshop, ILEP reported that the Federation and its partners were currently financing more than 40 special initiatives aimed at discovering undetected patients in 15 countries, using a variety of approaches. Among the recommendations to emerge from the workshop were the strengthening of the primary health care system and use of leprosy elimination campaigns (LECs) and special action projects for the elimination of leprosy (SAPELs). As indicated in section 3.1, 1997 – the year when this workshop was held – was the first year in which 100% geographical coverage with MDT was achieved worldwide.

At the fourth LEAG meeting in June 1998 (*13*), ILEP pointed out that the overall forecast annual budget of the Federation for 1998 stood at around US$ 65 million (for the third year running) and that, during the decade 1986–1996, the total expenditure of ILEP member associations in support of leprosy elimination was just under US$ 700 million. A second ILEP/WHO workshop followed immediately after the LEAG meeting. The topic was special initiatives for reaching undetected cases, and the workshop made a number of recommendations, essentially on means of improving coordination between partners (*15*).

The following box and Figure 5.1 summarize recent information on ILEP-supported projects.

ILEP global indicators end 2001[a]

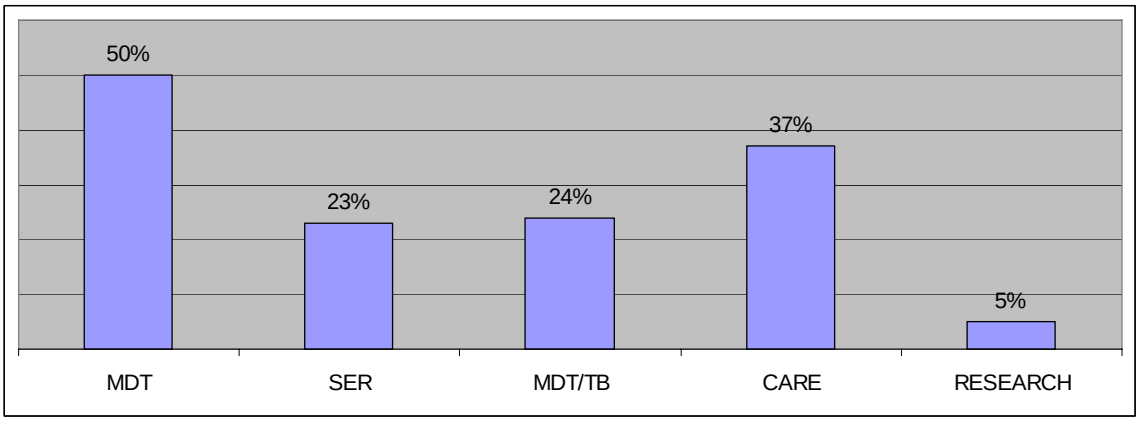
Reports have been received from 637 projects in 75 countries – 631 projects that submitted ILEP B questionnaires, 5 WHO national or state programmes, and for 1 project for which data came from previous years.

➢ **Total combined population of ILEP-supported projects***	2 196 787 454
➢ **Total number of patients registered for treatment at year end**	434 575
➢ **Total number of newly detected cases during 2001**	439 376
% MB among all new cases	42%
➢ **Total number of children among the newly detected cases**	60 737
% children among all new cases	14%
➢ N**ew cases with disability assessment at detection**	345 416
% new cases with disability assessment on all new cases	79%
➢ **New cases with disability 2 among all those assessed**	19 786
% of all new cases assessed	6%
% of all new cases	5%
➢ **MDT completion**	
PB patients having completed MDT as prescribed	182 696
Completion rate PB	84%
MB patients having completed MDT as prescribed	108 151
Completion rate MB	71%

[a] Total ILEP coverage is obtained by adding together the coverage of the individual projects.
Source: *ILEP annual report 2001–2002*.

Figure 5.1
Number of ILEP-supported projects by type of activities[a]

Note: Different types of projects overlap, and the same project may belong to several categories.



MDT:	All projects with a MDT component	637
SER:	Socioeconomic rehabilitation component	329
MDT/TB:	All projects with TB component	149
CARE:	All projects with a care component	490
RESEARCH:	All research and scientific support projects	63

[a] Source: *ILEP Annual Report 2001–2002.*

Clearly, collaboration between ILEP and WHO during the early part of the elimination strategy (1991–2000) was affected by differences of opinion, especially in relation to various aspects of the same strategy. Nevertheless, ILEP member associations have continued to support leprosy in endemic countries and to attend GAEL meetings.

References

1. Van Den Wijngaert P. *The role and objectives of ILEP. Report of a meeting on action plans for leprosy control, New Delhi, 23–25 August 1982*. Geneva, World Health Organization, 1983 (document WHO/LEP/83.1).
2. *Report of a Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control Programmes, New Delhi, 24 February 1984*. Geneva, World Health Organization, 1984 (document WHO/LEP/84.1).
3. *Report of the second Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control Programmes, Geneva, 4–5 November 1986*. Geneva, World Health Organization, 1987 (document WHO/CDS/LEP/87.2).
4. *The introduction of multidrug therapy for leprosy*. London, International Federation of Anti-Leprosy Associations, 1983, revised 1984.
5. *Thirty-sixth World Health Assembly, Geneva, 2–16 May, 1983. Volume 3. Summary records of committees* (document WHA 36/1983/REC.3).
6. *Report of the third Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control Programmes, The Hague, 13 September 1988*. Geneva, World Health Organization, 1988 (document WHO/CDS/LEP/88.4).
7. Martineau-Needham D, Lacey S. Leprosy control activities of the International Federation of Anti-Leprosy Associations. *World Health Statistics Quarterly*, 1991, 44(1).

8. *Report of the first Meeting of the WHO Working Group on Leprosy Control, Geneva, 1–3 July 1991*. Geneva, World Health Organization (document WHO/CTD/LEP/91.4).
9. *WHO Expert Committee on Leprosy. Sixth report*. Geneva, World Health Organization, 1988 (WHO Technical Report Series, No. 768).
10. *Report of the second Meeting of the WHO Working Group on Leprosy Control, Geneva, 7–9 July 1992*. Geneva, World Health Organization, 1992 (document WHO/CTD/LEP/92.5).
11. *Report of the third Meeting of the WHO Working Group on Leprosy Control, Geneva, 14–16 July 1993*. Geneva, World Health Organization, 1993 (document WHO/CTD/LEP/93.5).
12. *Report of the first meeting of the Leprosy Elimination Advisory Group (LEAG), Geneva, 12 and 13 July 1995*. Geneva, World Health Organization, 1995 (document WHO/LEP/95.2).
13. *Report of the fourth meeting of the Leprosy Elimination Advisory Group, Geneva, 24 and 25 June 1998*. Geneva, World Health Organization, 1998 (document WHO/LEP/98.3).
14. *Report of the third meeting of the Leprosy Elimination Advisory Group, Geneva, 16 and 17 July 1997*. Geneva, World Health Organization, 1997 (document WHO/LEP/97.6).
15. *Action Programme for the Elimination of Leprosy: status report 1998*. Geneva, World Health Organization, 1998 (document WHO/LEP/98.2).

5.3 Novartis

S.J. Yawalkar, P. Grewal

Drug development

In the past 15 years, more than 12 million patients with leprosy have been successfully treated with MDT in accordance with WHO's 1982 recommendations. Three drugs make up the recommended MDT – clofazimine (Lamprene®), rifampicin (Rimactane®), and dapsone. Two of these three drugs originated in the research laboratories of Novartis (created by the merger of Ciba-Geigy and Sandoz).

Lamprene

The active ingredient in Lamprene – clofazimine (B 663, G 30320) – is a substituted iminophenazine bright red dye. It was synthesized in 1954 by Vincent Barry et al. (*1*) at Trinity College in Dublin, Ireland, within the framework of a research agreement between Geigy and the Irish Medical Research Council. Clofazimine was originally developed for tuberculosis, against which it proved effective in the test-tube and in mice but ineffective in patients. Further development of the compound was almost abandoned. However, at the end of 1959, Chang (*2*) reported that clofazimine inhibited *M. leprae* in a murine leprosy model. In August 1960 at a meeting between Vincent Barry, Robert Cochrane and Wolfgang Vischer (Geigy) in London, Cochrane suggested asking Stanley Browne – who was in Uzuakoli, Nigeria, at the time – whether he would be willing to carry out a clinical trial. Browne agreed immediately, collected the drug in November 1960 and, working with Hogerzeil, started the clinical trials. Feedback from the trials was positive, and the scientists at Geigy increased their efforts to produce an acceptable formulation that would solve the problem of poor absorption.

Browne and Hogerzeil in Nigeria provided the first confirmation of the efficacy of clofazimine in lepromatous leprosy patients in 1962 (*3*), and Browne visited Geigy the same year for a discussion of their results. Clofazimine was judged very favourably from a therapeutic point of view, as patients seemed to feel much better after taking the drug and the morphological index decreased. However, Browne was of the opinion that its action was no quicker than that of dapsone. Clofazimine would be more expensive than dapsone and, since the reappearance of normally stained *M. leprae* had suggested the emergence of clofazimine-resistant bacilli, it was concluded that further development of the drug was not worthwhile. Since both handling and production were also proving problematic (the compound stained everything intensely red), a decision was taken to discontinue the development of clofazimine.

Nevertheless, Browne continued to treat more patients with clofazimine, using formulated material that remained in stock. In 1965 he reported that he had observed an anti-inflammatory action of clofazimine in erythema nodosum leprosum (ENL) reactions (*4*) and urged the scientists at Geigy to conduct further clinical trials. This observation, together with the first reports of dapsone resistance, highlighted the need for further development and bulk production of clofazimine, as well as for intensive testing of the product. Trials were organized in a number of countries and the results were presented at the Ninth International Leprosy Congress in London in 1968. In 1969, Geigy launched clofazimine under the trade name Lamprene®.

Clofazimine is the only antileprosy drug that displays anti-inflammatory action and is effective in the prevention and treatment of ENL reactions in leprosy patients. Its overall antileprosy effect is about the same as that of dapsone; it is principally bacteriostatic and only weakly bactericidal. Unlike rifampicin, clofazimine has no effect on dapsone excretion by leprosy patients (*5*).

To date there has been no confirmed case of clofazimine resistance.

Rimactane

While the development work on clofazimine continued at Geigy, scientists from the pharmaceutical company Ciba in Basel were also engaged in the search for new products against infectious diseases such as tuberculosis. They were collaborating closely with researchers from Lepetit in Milan who had isolated rifamycin from the bacterium *Streptomyces mediterranei* and found it to have an antibiotic effect.

As is often the case, chance played an important role in this discovery. The fermentation product rifamycin B has only a slight inhibitory effect and would therefore probably never have been picked up in a screening process. Fortunately, however, rifamycin B is relatively unstable and degrades very rapidly to rifamycin S, which is highly biologically active and produced striking results in the studies carried out at that time. On the basis of these studies, rifampicin – a semi-synthetic derivative of rifamycin S – was developed and introduced by Ciba in 1968, under the trade name Rimactane®, for the treatment of various bacterial infections.

Rifampicin acts by inhibiting bacterial RNA synthesis. It is the most potent bactericidal antileprosy drug available today: a single dose as low as 600 mg will kill most leprosy bacilli within a few days.

The first results of treatment of leprosy patients with rifampicin were published in 1970 by Rees (*6*). The commonly recommended dosage of rifampicin was 450-600mg daily. As regimens with daily rifampicin are very expensive, only a small percentage of patients could benefit from this treatment. Moreover, daily rifampicin without supervision led to patients taking the drug irregularly and the first reports of rifampicin-resistant leprosy emerged.

Clinical trials to establish the efficacy of once-monthly usage of rifampicin

Although dapsone, clofazimine and rifampicin were available to combat leprosy, none of them was ideal when used alone: resistance developed against dapsone, clofazimine caused skin discoloration at high doses, and rifampicin was too expensive to be accessible to most of patients in developing countries. For Shantaram Yawalkar, an Indian dermatologist and leprologist working in the medical department of Ciba-Geigy in 1974, the solution lay in administering the readily available dapsone once a day, together with rifampicin – the most highly bactericidal but much more expensive antileprosy drug – once a month. Since treatment of leprosy, even with a highly potent drug like rifampicin, can be futile if patient compliance cannot be assured, Yawalkar decided to administer it once a month only, under paramedical or medical supervision, to ensure regular treatment and follow-up.

An international, multi-centre, single-blind, controlled trial was therefore planned by Yawalkar to compare the therapeutic effects of dapsone in combination with rifampicin – 450 mg daily or 1200 mg once monthly under supervision – in patients with lepromatous leprosy. Languillon agreed to carry out the trial in Dakar, Senegal. The results revealed the high efficacy, good tolerability, and practicability of the once-monthly 1200-mg rifampicin schedule (*7*). The results were presented by Yawalkar at the International Leprosy Congress in Mexico City in 1978. Later, Opromolla and Ghosh repeated the trial in Bauru, Brazil, and at the Institute of Tropical Medicine in Calcutta, India, respectively (*8, 9*).

The bacteriological and histopathological investigations were carried out by A.C. McDougall in Oxford, and the data for all three centres presented by Yawalkar at the World Dermatology Congress in Tokyo in 1982. Interestingly, when Yawalkar submitted his paper to *The Lancet* for publication, it was returned with a request for an explanation as to why that journal should publish it. Yawalkar explained that publication of the findings in *The Lancet* would enhance acceptance of once-monthly rifampicin by the scientific community and would have significant public health impact if the regimens were to be adopted. *The Lancet* subsequently accepted the article without change and published it as the leading article in May 1982 (*10*).

WHO-recommended MDT regimens, also published in 1982, were the first to include once-monthly supervised administration of 600 mg rifampicin and 300 mg clofazimine in addition to 100 mg dapsone and 50 mg clofazimine once daily for at least 2 years for patients with multibacillary leprosy (BB, BL, LL) (*11*).

Contribution to implementation of WHO MDT

Involvement of the Novartis Foundation for Sustainable Development

Involvement of the Novartis Foundation for Sustainable development in leprosy field programmes was a natural extension of the Novartis tradition in leprosy drug development. Although MDT had been recommended as the standard treatment for leprosy by WHO in 1982, four years later fewer than 10% of registered patients were on treatment with MDT. This situation prompted the decision, in 1986, to directly support field programmes, to help improve understanding and overcome the obstacles to improving access to MDT treatment.

The Foundation set up an independent Scientific Advisory Committee of five members who selected and guided the programmes, which have always been developed and implemented in close collaboration with the local health authorities – from the outset, the Foundation has operated independently of the business interests of the company.

Key areas of the Foundation's work

Introducing MDT

The early programmes, such as those in the Democratic Republic of the Congo, Indonesia, and Sierra Leone, concentrated on meeting the prerequisites for the successful introduction of MDT. Introducing MDT necessitated a major change in the way leprosy control programmes were run, as the once monthly antibiotic dose had to be provided under supervision. A complete reorganization of leprosy control services was needed, including the establishment of laboratory facilities to diagnose and classify leprosy.

Social marketing – tackling the hidden disease burden

In 1988, like other countries, Sri Lanka had a large pool of "hidden cases" – people suffering from leprosy but not on treatment. It was clear that detecting and treating these hidden cases required an entirely new approach, which relied on people coming forward for treatment on their own initiative. In close collaboration with the Ministry of Health, the Novartis Foundation developed a social marketing approach to generate and meet "demand" for leprosy services. This involved large-scale advertising campaigns, developed by a leading local advertising agency, to improve the awareness of leprosy and dispel the fear surrounding the disease. To complement the campaign in the mass media, a wide cross-section of local leaders spread the message of the freely available treatment and the importance of seeking early cure (*14*). This initiative, together with the extension of the network of leprosy clinics, led to a sharp increase in the total number of patients, in particular those self-reporting. As a result, the disease had reached the elimination prevalence target at the national level within just eight years, by 1996.

After this success, a scaled-down version of the campaign was adopted by the Mexican authorities. Initially, the Foundation supported extensive public information campaigns, as well as training programmes to improve the diagnostic and treatment skills of health care workers in the 10 endemic states. Once leprosy had reached the elimination prevalence target at the national level, efforts focused on the four remaining endemic states.

Changing the image of leprosy

Public information campaigns designed to change traditionally negative perceptions of leprosy remain an important part of the Foundation's work. At the global level, the Foundation collaborates with WHO in the production of information and communication material. At the country level, it has been supporting Brazilian efforts to project a "positive" image for leprosy, aided in this by the advocacy of various celebrities, including the popular singers Ney Matogrosso and Targino. The Foundation also helped to extend the free telephone hot-line service, Telehansens, to the national level, thereby providing easy access to information about leprosy.

The Foundation is assisting the Ministry of Health in Madagascar in a campaign to conquer people's fear of leprosy and encourage patients to come forward for treatment. This campaign was developed in partnership with WHO and Tam Tam, a leading local advertising agency. The Foundation takes great pains to ensure that such campaigns are not launched before the local health services are in a position to deal with new cases seeking treatment.

Bringing treatment closer to patients

Extending the network of leprosy services to bring them closer to communities is the most crucial element in the elimination effort. Integrating leprosy services into the general health services offers the most effective way of doing this, and the Foundation has worked with local health ministries on the often difficult detail of achieving this.

In 2000, the Novartis Foundation helped the Sri Lankan Ministry of Health to develop the blueprint for integration and support its implementation. Leprosy is now part of the job description of every medical officer in the country and is treated within the general health services at all health facilities (*15*). In Brazil, together with the Ministry of Health,

CONASEMS (Association of Municipal Health Secretaries) and WHO, the Foundation supported efforts to decentralize leprosy services. The initiative was started in the north-east, and the programme has gained momentum among health authorities throughout the country.

These efforts are a natural complement to the Foundation's work to change the image of the disease and encourage people to come forward for diagnosis and treatment. The Foundation's first involvement in this sphere dates back to 1988, with its support to the International Nepal Fellowship in assisting the Nepalese Ministry of Health with integration. Mobile clinics were set up to help local health centres in the transitional phase of integration and provide on-the-job training to their staff. Subsequently, it helped to establish the Butwal referral clinic, which addressed the pressing needs, especially for disability care, in the south-west of the country.

From 1990 to 1996 in Turkey, mobile teams travelled by air and road to bring MDT treatment closer to patients; until that time, treatment facilities had been confined to the outpatient departments of the leprosy hospitals. The programme succeeded in reaching and treating 94% of all registered cases in the country, many of whom had previously been given only dapsone. In addition, the mobile teams were able to screen people in high-risk communities for signs of leprosy.

Comprehensive care

In 1989, the Foundation set up the Comprehensive Leprosy Care Programme (CLCP) in India, the aim of which is to provide comprehensive care services (MDT treatment and disability care) to patients. Emphasis is placed on simplifying disability care and bringing these services closer to patients through the network of government health care staff. Empowerment of patients is the guiding philosophy of the programme. Patients are helped in techniques of self-care, particularly in protecting insensitive hands and feet and caring for ulcers, using the self-care kit plus attractive microcellular rubber, or MCR, footwear designed and provided by CLCP. CLCP also pioneered the use in field programmes of simple, prefabricated hand and foot splints that help to correct disabilities and/or prevent their progression (*16*). Specialized services, such as reconstructive surgery, are provided where necessary. Patients with advanced, inoperable hand deformities are given made-to-measure grip aids. Those who need it also receive income-generation assistance. CLCP has a record of successful collaboration with state health ministries (Gujarat, Goa, and Maharashtra) and has pioneered the provision of disability care services at the village level. It has standardized data collection (including computer software) in order to assess the scale of the disability load in a community for purposes of planning and implementation. It has provided a model for integrated disability care in other countries, such as Sri Lanka.

The Global Alliance for the Elimination of Leprosy

Novartis and the Novartis Foundation joined GAEL at its creation in November 1999 in the final push to eliminate leprosy. The specific contribution of Novartis to GAEL is MDT donation and country-level support.

The MDT donation – providing free treatment to all patients worldwide through WHO

From 1995 to 1999, WHO provided high-quality MDT free of charge to patients around the world, financed through the drug fund provided by The Nippon Foundation. There were two sources for the MDT drugs, one of which was Novartis. In 1998 WHO dropped the other supplier on the grounds of inadequate drug quality and procured the MDT drugs exclusively from Novartis. Novartis therefore restarted manufacture of Lamprene® in India since existing stocks were being rapidly depleted.

As the drug fund was due to expire in 2000, concerns about maintaining the quality of MDT beyond that date loomed large, as WHO would have had to relinquish its role of quality control. In view of the long-standing involvement of Novartis in leprosy, informal discussions took place between WHO and Novartis/Novartis Foundation, culminating in the signing of a Memorandum of Understanding (MoU) on 12 August 1999. According to this agreement, Novartis is committed to:

– providing sufficient quantities of high-quality MDT, in blister packs, free of charge to WHO for six years (2000–2005) to treat and cure all leprosy patients worldwide;
– maintaining buffer stocks to respond to fluctuations in demand for MDT and to emergency requests from endemic countries;
– providing WHO with the necessary funds for the shipment of MDT and independent quality control; these funds are calculated at 9% of the value of the MDT to be shipped (based on 1999 MDT prices).

Novartis will also consider extending the donation beyond the expiry of the MoU. WHO and Novartis meet annually to discuss issues related to the donation, including logistics and orders for the following year.

MDT supplied

Close to 100% of the global supply of MDT is provided by WHO/Novartis. Working through the network provided by the United Nations system has proved to be an effective method of ensuring wide distribution of drugs to communities in need, together with the necessary technical support and monitoring at the country level. In the first 3 years of the donation, more than 24 million blister packs were distributed in line with official requests to WHO from more than 85 national governments. Buffer stocks of MDT are held in Denmark and by WHO in Geneva as an emergency supply.

The value of MDT provided in 2000–2003 amounts to about US$ 26 million. An additional sum of US$ 2.3 million was provided in cash to WHO Geneva to cover the costs of shipment and independent quality control.

Packaging: blister packs, patients packs, and field packs

The use of MDT blister packs was first proposed in 1983 by McDougall (*12*). A first model of the blister pack was manufactured in collaboration between Ciba-Geigy Manila and Ciba-Geigy Basel following a request from the Government of the Philippines (*13*). In 1987, Novartis introduced the first commercially available MDT blister pack, containing a 4 weeks treatment with each day's treatment clearly marked. These packs are now standard and they make a vital contribution in helping patients to comply with treatment regimens. They protect the drugs from moisture and insects, have greatly simplified dispensing, and have also eliminated the chances of shortages or expiry of an individual drug.

In 2002, WHO and Novartis developed and launched a new line of packaging – patient packs. Made of heavy-duty cardboard, these packs serve as further protection for the drugs, particularly in transit or when stored in health centres and homes. As standard units, they also simplify logistics and inventory control. The smaller patient pack makes it easier to manage the smaller quantities of drugs needed by some health centres, especially with the integration of leprosy into general health services. The packs are colour-coded for the four patient categories: MB child and adult, PB child and adult.

References

1. Barry VC et al. Rimino-compounds with antituberculosis activity. *Nature*, 1957, 179: 1013.
2. Chang YT. Chemotherapy of murine leprosy. IV: The effects of amithiozone (TB1/698), *p*-aminosalicylic acid (PAS), B283 (a phenazine pigment), five antibiotics and three diphenylthiourea compounds on murine leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1955, 23:167–180.
3. Browne SG, Hogerzeil LM. "B 663" in the treatment of leprosy., *Leprosy Review*, 1962. 33:6–10.
4. Browne SG. "B 663" possible anti-inflammatory action in lepromatous leprosy. *Leprosy. Review*, 1965, 36:9–11.
5. Yawalkar SJ. *Lamprene in leprosy*, 4th revised ed. Basle, Ciba-Geigy, 1993 (the first revision of this booklet in 1978 was prompted by WHO).
6. Rees RJW, Pearson JMM, Waters MFR. Experimental and clinical studies on rifampicin in treatment of leprosy. *British Medical Journal*, 1970, 1(688):89–92.
7. Languillon J, Yawalkar SJ, McDougall AC. Therapeutic effects of adding Rimactane (rifampicin) 450 milligrams daily or 1200 milligrams once monthly in a single dose to dapsone 50 milligrams daily in patients with lepromatous leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1979, 47:37–43.
8. Ghosh S et al. Controlled comparison of therapeutic effects of DDS in combination with daily or once-monthly rifampicin in patients with lepromatous leprosy. *International Journal of Dermatology*, 1981, 26:1–6.
9. Opromolla DVA et al. A controlled trial to compare the therapeutic effects of dapsone in comparison with daily or once-monthly rifampicin in patients with lepromatous leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1981, 49:393–397.
10. Yawalkar SJ et al. Once-monthly rifampicin plus daily dapsone in initial treatment of lepromatous leprosy. *Lancet*, 1982, i:1199–1202.
11. *Chemotherapy of leprosy. Report of a WHO Study Group*. Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 675).
12. McDougall AC. Letter to the editor. *International Journal of Leprosy and Other Mycobacterial* Diseases, 1983, 51:592–594.
13. Final report on the pilot study for MDT implementation in Ilocos Norte and Cebu, 1984–1988.
14. *Leprosy: learning from success*. Geneva, World Health Organization, 2001 (document WHO/CDS/CPE/CEE/2001.20.
15. Katuriaratchi ND, Settinayaka S, Grewal P. Processes and challenges: how the Sri Lankan health system managed the integration of leprosy services. *Leprosy Review*, 2002, 3:177–185.
16. Yawalkar SJ. *Leprosy for medical practitioners and paramedical workers*, 7th ed. Basle, Novartis Foundation for Sustainable Development, 2002.

Chapter 6

The role of WHO including TDR

6.1 The WHO Leprosy unit

Overview

S.K. Noordeen

The World Health Organization was chiefly responsible for developing and promoting – and to an extent implementing – MDT. The WHO Leprosy unit played a key role in promoting acceptance of the recommendations of the 1981 Study Group by WHO regional structures, Member States, NGOs, donor agencies, and technical persons responsible for leprosy control. The Organization's promotional efforts were carried out through global, regional, and national meetings and discussions. The support provided by WHO to countries through extrabudgetary funding, mainly from The Nippon Foundation, facilitated the process of implementing treatment with MDT greatly; significant support (including technical guidelines, training, logistics, and limited procurement of MDT drugs) was also provided to countries directly by international NGOs and other funding agencies. As long as countries had sufficient political commitment and reasonable health infrastructure, it was not difficult to mobilize funds for MDT drugs and related leprosy control activities. Implementation of MDT was also discussed in very positive terms at many of the scientific meetings held outside WHO, such as the International Leprosy Congresses. Member associations of ILEP were also able to increase MDT coverage in the projects they supported.

In terms of developments in different WHO regions, the situation in the Eastern Mediterranean and in the Western Pacific, where the leprosy problem was relatively limited and support from NGOs and donor agencies quite strong, were relatively favourable. The African region also received good support from NGOs, and in several African countries there was a downward trend in leprosy prevalence. In the region of the Americas, the problem was one of acceptance of MDT and its widespread application: until the early 1990s, implementation of MDT was somewhat limited in major countries such as Brazil.

The South-East Asia region had three-quarters of the global leprosy burden, with very high prevalence in many countries. Despite the relatively early introduction of MDT and significant reductions in prevalence, residual prevalence remained quite high.

Overall, it was possible by the end of the 1980s to implement MDT in all areas with good health development, political commitment, and donor support – yet more than half of all patients were still not receiving MDT. It therefore became necessary to vigorously promote political commitment to leprosy as well as to make the necessary resources available; this was made possible through adoption of the World Health Assembly resolution on elimination of leprosy in 1991 and the pledge of US$ 50 million for 5 years' support to purchase MDT drugs

made by the Nippon Foundation at the first International Conference on Leprosy Elimination (Hanoi, 1994). As a result of these two developments, without which it would have stagnated at around 50%, MDT coverage increased rapidly, reaching almost 100% by 1997 (see section 3.1).

From the technical point of view, WHO facilitated wider implementation of MDT through simplification of technical requirements and managerial capacity-building. The simplification of technical requirement included:

- classifying leprosy as MB and PB on clinical grounds without necessarily depending upon laboratory services as recommended by the WHO Study Group on Leprosy Chemotherapy in 1993;
- fixing the duration of MDT at 24 months in 1993 and reducing it to 12 months in 1997 on the basis of recommendations made by the seventh meeting of the WHO Expert Committee on Leprosy;
- introducing a single dose ROM treatment for single skin lesion leprosy, again on the recommendation of the seventh meeting of the Expert Committee;
- abandoning the requirement for active surveillance of patients after completion of treatment.

WHO also placed a major emphasis on training programme managers in leprosy control. Management workshops were organized in a number of countries in which managers were trained to plan, implement and evaluate leprosy control and elimination.

Detailed account

H. Sansarricq

The decade that prepared the ground for the 1981 Study Group Meeting

A series of important steps, many interrelated and some initiated directly by the WHO Leprosy unit, were taken over the 10-year period from 1972 that led up to the 1981 meeting of the WHO Study Group. Their importance, recalled below, can be better understood in the context of the situation in the late 1960s, which is briefly summarized.

Difficulties with dapsone resistance (late 1960s)

Although secondary resistance of *M. leprae* to dapsone was first demonstrated in 1964 (*1*), the WHO Expert Committee on Leprosy had concluded at its third meeting in 1966 that "the question of drug resistance to DDS is not an important one" (*2*). Indeed, dapsone resistance was not discussed as a specific topic at the fourth meeting of the Expert Committee in June 1970 (*3*). It was mentioned indirectly only twice, in relation to: (a) the fear that low doses of dapsone would favour the development of resistance, and (b) the possibility of demonstrating resistance by Shepard's mouse footpad method.

In the late 1960s, LEP did not feel that dapsone resistance was a serious problem, possibly because of the long duration of dapsone monotherapy necessary before drug resistance could be observed and the low frequency of the phenomenon at that time. It is also likely that, for strategic reasons, LEP was unwilling to recognize the importance of dapsone resistance as long as there was no alternative to the dapsone monotherapy regimen.

In the area of research, however, LEP seemed more progressive. In June 1970, a WHO informal consultation on immunological problems in leprosy research, organized jointly by LEP and IMM (Immunology unit), was held in Geneva. The final report of the meeting (*4*) gave a good account of immunological aspects of leprosy at that time, yet LEP still had reservations in respect of some important advances in the understanding of leprosy, particularly the significance of the Ridley–Jopling classification – an essential tool for immunological research in leprosy.

Change in the perception of research problems in LEP

The meeting of investigators on immunological problems in leprosy research (*5*), held in New Delhi in 1972 and jointly organized by Dr Goodman, Chief, IMM, and Dr Bechelli, Chief, LEP, proved to be a turning point. During that meeting, the author – participating as the new head of LEP – had the opportunity to demonstrate clearly that the Leprosy unit was now receptive to advances in leprosy research and willing to take advantage of these for improving leprosy control methods, cooperating fully with the scientific community.

New developments

- Establishment of IMMLEP and TDR
  After the New Delhi meeting, Howard Goodman and the author were wholly convinced that they should work together to promote research on the immunology of leprosy. With this aim, IMM (rather than LEP, which still lacked the resources) recruited Tore Godal on a one-year consultancy (1973–1974) to draft the outline of a research plan. The first meeting of the IMMLEP project group was convened subsequently (4–8 November 1974) (*6*).

  At that time, there was general recognition of the need to actively develop research in the area of tropical diseases (see Introduction), and this was reflected, for example, in resolution WHA27.52, adopted on 23 May 1974 at the Twenty-seventh World Health Assembly (*7*). Although it was *parasitic* tropical diseases that were cited, the fact that the IMMLEP group was already set up allowed WHO to respond to the resolution by promptly establishing in November 1974 an overall plan for a programme for research and training in tropical diseases (*8*) – later to become the UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases, TDR. Since this plan started with the IMMLEP model, leprosy was included in the list of TDR diseases from the outset, in addition to the five strictly parasitic diseases. Table 6.1 outlines the process that resulted in the establishment of IMMLEP and TDR during the years 1973–1976 and indicates the involvement of LEP in these steps as appropriate. It may be noted that certain components of TDR (e.g. THELEP) started work before the overall TDR machinery was set in motion.

  The launching by WHO of an important and innovative research programme, involving scientists of world repute and with adequate financial resources permitting for effective support of the selected projects, soon gave real strength and visibility to the leprosy programme, which would grow and develop with time – first through IMMLEP and subsequently through THELEP.

- Donations by Mr Sasakawa
  Following the establishment of IMMLEP and TDR, there was an important development in the form of a donation by Mr Ryochi Sasakawa – a grant of US$ 502 000 which was transferred to the WHO budget for leprosy in 1975. Previously, WHO was frequently able

to offer only advice and recommendations to leprosy-endemic countries, whose governments would then have to seek funding for the implementation of that advice. With this grant and other extrabudgetary funding that became available, WHO was able not only to provide the appropriate advice but also to support financially its implementation. As a consequence, government authorities and WHO officials at all levels – country representatives, regional advisers, and headquarters leprosy staff - grew increasingly confident and enthusiastic about the feasibility of controlling leprosy at the global level. With the support provided directly by other voluntary agencies, it was now possible adequately to cover the needs of practically all leprosy control projects.

Over the years, the support to leprosy control activities contributed to a general improvement in and reorganisations of a number of national programmes and thus to the sustainability of their activities. Its important long-term impact was in preparing the ground for the implementation of future MDT activities. However, WHO was not yet in a position to respond effectively to the current leprosy problem as control methods based on dapsone monotherapy alone had not yet been improved.

- Establishment of THELEP

  The purpose of TDR was to stimulate, coordinate, and support investigations of all aspects of six selected tropical diseases. Apart from immunology, chemotherapy merited immediate consideration – which is why a Scientific Working Group (SWG) on Chemotherapy was set up for each of the six diseases. The first step in establishing the THELEP SWG was a meeting of a few selected leprosy researchers in Geneva, 28–30 April 1976 (*9*), at which the following objectives of the THELEP programme were identified:
  - field studies on dapsone resistance (mainly dapsone resistance surveys);
  - laboratory studies aiming at improving methods in chemotherapeutic investigations;
  - clinical drug trials;
  - development of new antileprosy drugs.

- The fifth meeting of the WHO Expert Committee on Leprosy (*10*)

  With regard to the efforts of LEP to acknowledge the most recent advances in leprosy research and stimulate further research on improving control methods, the establishment of IMMLEP and THELEP provided an invaluable opportunity. While participating in the TDR specialized research activities, LEP continued to be responsible for the definition and adaptation of WHO technical policy for leprosy control, principally through meetings of WHO Study Groups and the WHO Expert Committee on Leprosy. Taking account of the advances made during the previous decade in the understanding of leprosy – including those that had not been acknowledged by the fourth meeting of the Expert Committee in 1970 – LEP considered it timely to convene a fifth meeting of the Expert Committee in October 1976.

  The Committee acknowledged the existence of secondary dapsone resistance and of microbial persistence. The possibility of primary dapsone resistance was also recognized, although it had not yet been reported. At that time, “clinical experience of combined therapy with rifampicin and clofazimine in combination with dapsone was too limited to allow of decisions on optimum regimens for different forms of leprosy. Furthermore, there was fear of toxicity and other complications” (*11*).

To prevent the emergence of secondary sulfone resistance, the Committee considered that "initial combined therapy should be given to newly diagnosed lepromatous and borderline cases". For initial combined therapy it was proposed to add to dapsone in full dosage:

- *either* clofazimine, 100 mg daily or three times a week during the first 4–6 months of treatment, followed by dapsone alone;
- *or* rifampicin, 300–600 mg daily for a minimum of 2 weeks, followed by dapsone alone.

In dapsone-resistant cases, suggested treatment was 600 mg of rifampicin daily with 100 mg of clofazimine daily for 2–3 months, followed by clofazimine indefinitely. In a footnote, daily treatment with rifampicin was "strongly advocated … because of the known toxic effect of rifampicin when the drug is taken intermittently".

The basic recommendations on combined regimens were based on sound scientific knowledge, but clinical experience was too limited to permit a decision on optimal regimens for different forms of the disease. The most significant difficulty was that "intermittent therapy could not be recommended at this stage" (*12*). In the few attempts that were made to implement these recommendations (only in India), the organization of supervised daily delivery sessions for rifampicin and clofazimine met insuperable difficulties. Thus, although the fifth meeting of the Expert Committee showed that the importance of dapsone resistance was now fully appreciated in WHO, its recommendations – while based on the available scientific knowledge – had virtually no impact on the leprosy problem.

The 1981 Study Group meeting

LEP recognized that the recommendations included in the report of the fifth meeting of the Expert Committee, published in 1977, did not respond to the needs of control programmes but fervently hoped that THELEP would find an appropriate solution. In 1979, there was particular hope that the MDT regimen of the THELEP protocol for field trials (*13, 14*) in lepromatous leprosy would meet LEP expectations for MB patients. However, it was soon realized that the need to carry out the protocol *before* recommendations for field use could be derived from the results would cause a long delay – and a rational alternative to the anarchic use of rifampicin was urgently needed. Thus, although it was decided to convene the Study Group on chemotherapy of leprosy for control programmes in 1981, recommendations were made for *immediate* field use of regimens proposed by the study group. The roles of THELEP and LEP in the development of the Study Group regimens are summarized in Table 6.2.

The role of THELEP

It is clear that the regimen recommended by the 1981 Study Group for MB patients – the most important conceptually – was not very different from that designed by THELEP in 1979 for its field trials (*14*). Clearly, the Study Group's recommendation for MB patients was essentially the result of discussions that had been taking place since March 1979 within the THELEP SWG and Steering Committee. The changes incorporated during the Study Group sessions were also, to the best of the author's recollection, the result of discussions between THELEP experts within the Study Group. The regimen for PB patients, proposed for discussion in the working paper by Vellut & Waters (*12*) and recommended by the Study Group, was also the result of previous THELEP discussions. Thus, the development of the 1981 Study Group regimens was essentially a product of THELEP work and discussions.

The role of LEP

The WHO meetings of experts – Expert Committees and Study Groups – generally recommended for implementation only therapeutic schemes that had already been shown to be effective and safe in controlled trials of acceptable methodology. Leprosy, however, posed greater problems in this regard than other microbial diseases since demonstrating the efficacy of any MDT regimen for MB patients required the observation of relapses in patients over several years following the completion of chemotherapy. The course of MDT administration itself had been fixed at 2 years in the THELEP protocol for MB MDT. It was clear that a different approach would have to be used if recommendations for immediate implementation were to be issued.

During the preparatory phase of the Study Group meeting, LEP could have tried to convince its senior management that the risks inherent in the growing anarchic use of rifampicin justified WHO's designing MDT regimens which, *in all likelihood*, would be effective and safe and recommending them for immediate implementation. However, it was thought that such an approach would be refused, probably on the basis that experience with the monthly administration of rifampicin was too limited. It was also feared that any similar attempt by THELEP would have been judged to be outside its terms of reference, which were for research rather than control procedures.

Thus, convinced that the experimental THELEP regimen for MB patients, designed in 1979, was likely to respond to the needs, LEP decided to convene the 1981 Study Group in an effort to:

- obtain from THELEP researchers proposals for MDT regimens for MB and PB patients that were the most likely to be effective, safe, and practicable;
- have these regimens recommended for immediate implementation by a group of THELEP and leprosy control experts;
- have these recommendations for immediate implementation approved by WHO decision-makers and governing bodies (i.e. the Executive Board).

It seemed that the best way to have the expected recommendation approved by the WHO decision-making level for immediate implementation was to mention this requirement clearly but with great discretion. This is the reason for that essential point being deliberately omitted from the proposal for a Study Group meeting submitted to the decision-making level, and mentioned only briefly in both the working paper by Vellut & Waters (*12*) and the final report of the Study Group meeting (*11*).

Promoting the Study Group recommendations (1981–1985)

Once the Study Group recommendations were formulated, it became a top priority for LEP that they be implemented as accurately and as widely as possible – and the author was witness to just how actively and enthusiastically this new and complex goal was pursued. Clearly, the greater complexity of the new treatment procedures meant that the total workload – and the associated costs – would increase substantially. To make the implementation of MDT possible in any control programme, important changes had to be made in almost all control procedures then in use (*11*, *12*). In addition, a complete reorganization of leprosy services was absolutely essential before MDT could be introduced, and this required that a detailed plan of

operations for MDT implementation be prepared and important additional human and financial resources secured. It was therefore expected that leprosy control coverage based on MDT would have to be effected in a phased manner in every endemic country.

The principal role of LEP in the tremendous task that lay ahead was to promote the new strategy and to assist endemic countries with implementation by providing increased technical cooperation, mobilization and coordination of all necessary additional inputs, and continuous assessment.

In 1985, four years after the Study Group meeting, 78 752 patients were reported as being treated with MDT, corresponding to a 1% geographical coverage with MDT at global level (*15*). This figure, while modest, was the first indication of a tangible achievement in MDT implementation – and the first signal that MDT coverage might increase in subsequent years. The most significant of the successive steps that marked progress from the recommendations to the start of the implementation are outlined in the following paragraphs.

Significant steps in the introduction of MDT

At the 14th General Assembly of ILEP, held in Amsterdam in June 1982, members fully endorsed the recommendations of the ILEP Medical Commission that WHO's new policy be applied in the treatment of leprosy, and adopted a resolution to ensure implementation in the field of the new approach (*16*). Nevertheless, the German Leprosy Relief Association continued to support the use of MDT based on rifampicin and Isoprodian® in a number of projects. In the early 1980s, ILEP provided annual contributions to LEP that ranged from US$ 400 000 to US$ 800 000, and ILEP member associations were supporting projects that reportedly covered a total of about 1.2 million leprosy patients (*17*). In 1983, the Damien Foundation of Belgium, an ILEP member association, established a drug fund for MDT with an initial endowment of US$ 400 000, and a number of other ILEP associations provided additional grants to the fund.

The Japan Shipbuilding Industry Foundation (JSIF) accepted the new WHO recommendations on MDT immediately and without reservation. As a consequence, US$ 600 000 of the annual JSIF grant for 1982 was available for WHO-supported activities related to the preliminary steps in MDT implementation at all levels (*17*). In the subsequent years, the JSIF contributions were increased and could be used as necessary for MDT-related activities.

In August 1982, a WHO meeting on action plans for leprosy control (*18*) was organized in New Delhi and attended by all WHO Regional Advisers for leprosy and representatives from international, bilateral, and voluntary agencies. The meeting made recommendations on most aspects of MDT implementation: priorities for introduction of MDT; optimal strategy for case-detection and case-holding; integrated services and primary health care; reorganization of leprosy control services; outline plan of operations at country level; mechanisms for strengthening cooperation between governments, contributing agencies, and WHO to mobilize financial resources.

In September 1982 and September 1983, respectively, the WHO Regional Committees of the South-East Asia and Western Pacific regions endorsed the implementation of WHO-recommended MDT regimens (*16*). Meetings to prepare plans of action for MDT implementation in regional leprosy programmes were held in the WHO South Pacific

subregion (*19*) (June/July 1982), the Eastern Mediterranean (*20*) (Mogadishu, October/November 1982), and South-East Asia regions (*21*) (New Delhi, December 1983) and in Manila (October 1984) for both the Western Pacific and South-East Asia (*22*).

Meeting in November 1983, the WHO Study Group on epidemiology of leprosy in relation to control discussed important technical issues not covered by the 1981 Study Group on chemotherapy and made precise recommendations on practical aspects of monitoring the implementation of MDT (*23*):

- a set of working definitions that included:
  - definition of adequate treatment, i.e. the maximum period over which the total prescribed treatment could be completed, for both MB and PB cases;
  - definition of surveillance after completion of treatment (then considered as important);
- precise sets of epidemiological and operational indicators in leprosy control, including those for monitoring MDT.

By 1984, some governments, including those of Ethiopia and India, had held national meetings, and in some cases formed national committees, and adopted WHO MDT and initiated its introduction (*16*). At the same time, joint efforts between governments, contributing agencies, and WHO were being made to introduce MDT in other projects, countries, and geographical areas (Caribbean countries, Fiji, and India) (16).

In 1983, with a revision in 1984, the member associations of ILEP issued a booklet entitled *The introduction of multidrug therapy for leprosy*, which referred exclusively to the 1981 WHO recommendations for MDT and gave priority to the provision of technical and financial assistance to their projects for the effective introduction and use of MDT (*24*).

A WHO consultation on implementation of MDT for leprosy control (*25*), held in Geneva in October 1985, was important for a number of reasons:

- "…virtually all endemic countries either had commenced or were in the process of commencing the implementation of MDT in leprosy control programmes".
- There was evidence of good acceptability and excellent tolerance of the WHO MDT regimens.
- There was also some evidence that the regimens were capable of preventing and overcoming dapsone resistance.

In preparation for the meeting, LEP had obtained detailed reports on experience of MDT implementation in 27 projects in 22 countries (including three THELEP field trials: MDT for MB leprosy in Karigiri and Polambakkam, MDT for PB leprosy in Malawi, and two projects using the combination of rifampicin and Isoprodian®). These reports were carefully analysed; a working paper summarized the field experience and identified a number of points for discussion from which it was possible to draw lessons and make recommendations for future action (*26*).

WHO efforts

Since MDT was a methodology newly recommended by WHO and relatively complex to implement, it was obviously part of WHO's role to advocate its implementation among all concerned and to provide technical assistance. Moreover, the implementation of this new methodology required the mobilization of important additional technical and financial assistance from a number of partners, and WHO had therefore also to play an important coordinating role. These three elements – advocacy, technical assistance, and coordination –

characterized all WHO efforts in promoting MDT during the first few years, as summarized in Table 6.3. The activities with which LEP was most concerned during the years immediately after the Study Group meeting were:

– technical meetings, especially those sponsored by WHO at global and regional levels, at which the rationale of MDT regimens and problems related to their implementation were discussed and possible solutions identified; and
– negotiations with representatives of contributing agencies, essentially JSIF and ILEP and some ILEP member associations.

➢ WHO technical meetings

Technical meetings were the most important means used by WHO for promoting MDT and providing technical assistance to endemic countries, at both global and regional levels, in order to prepare the introduction of MDT. In due course they were also used to monitor the progress of early activities related to MDT. The meetings were organized at the initiative of either a regional office or headquarter (LEP), although both levels cooperated closely in planning and organization. Care was being taken to invite all current or potential partners to meetings in efforts to secure the cooperation – including financial contributions – from all those who were or might be interested. A list of these meetings is given in Table 6.4.

Table 6.4 shows that WHO headquarters (LEP) and the Regional Offices for South-East Asia and Western Pacific were particularly active in stimulating MDT implementation. The Regional Office for the Eastern Mediterranean, in an area where leprosy was less prevalent, organized a meeting in 1982 to discuss activities in preparation of MDT implementation (*20*). The Pan American Health Organization/WHO Regional Office for the Americas, covering another area where leprosy was less prevalent, organized a sub-regional workshop for five Andean countries and national workshops in three other countries in 1982 (*16*). Training courses on MDT were organized in the leprosy institutes of Caracas (Venezuela) and Bauru (Brazil), and the recommendations of the 1981 WHO Study Group were presented at several other meetings on general public health problems.

By 1984, the Regional Office for Africa had supported national workshops and training courses on MDT in six countries (*16*). WHO MDT was also discussed on other occasions, for example at the Conference of OCEAC *(Organisation pour la lutte contre les endémies en Afrique centrale)* in April 1982. Generally, however, despite the high prevalence of leprosy in many African countries, the Regional office for Africa, did not take an active stance with regard to MDT implementation: a general meeting for that purpose was organized for the Sub-Region 1 of the African region for the first time in December 1986, in Abidjan (*27*).

➢ Discussions with contributing agencies

Since it was obvious that the global acceptance of MDT regimens, the changes in strategy, and the greater associated costs would require special increased efforts from all contributing agencies (ILEP, JSIF, etc.), LEP was particularly aware during these years of all likely opportunities for discussions and negotiations with these partners. Not only were they invited to WHO meetings (see Table 6.4), but LEP was also keen to attend their meetings whenever possible and to facilitate contacts and discussions between contributing agencies and governments representatives, especially during World Health Assemblies.

- Discussions at regional office and country levels
  Discussions and negotiations between representatives of governments, contributing agencies, regional advisers for communicable diseases/leprosy, and WHO representatives were also taking place at regional office and country level.
  Certainly, many decisions from governments on MDT implementation were influenced by the assistance provided to governments by regional offices and WHO representatives, of which there are few records. One of the outcomes of this type of negotiation was the recruitment of WHO consultants to assist governments in the preparation of the national plans for MDT implementation.

THELEP

The Study Group regimens had been recommended without previous evaluation in controlled trials. Trials for concomitant evaluation were therefore essential, and THELEP members of the Study Group assumed that responsibility during the meeting. Trials of the regimens were subsequently undertaken as reported in section 6.2. THELEP also took an active part in the advocacy of the 1981 Study Group regimens, publishing a number of reports on the results of these trial as well as papers on their justification, such as that by Ellard (*28*) in 1984. Some THELEP leaders participated in a number of technical meetings on the MDT regimens recommended by the Study Group, notably the sixth meeting of the WHO Expert Committee on Leprosy (*29*) which endorsed the regimens.

Table 6.1
Preparatory steps in WHO of IMMLEP, TDR and THELEP

Date	Steps with significant LEP involvement	Other steps
30 November – 5 December 1972	Meeting on immunology of leprosy, New Delhi	
August 1973 – 1974	T. Godal drafting a plan for IMMLEP	
May 1974		Resolution WHA27.52 on research in tropical diseases
June 1974	A WHO Intra-Secretariat Planning Group established for developing proposals for the Special Programme for Research and Training in Tropical Diseases (TDR)	
August 1974	IMMLEP proposed as pilot activity for the planned TDR	
November 1974	4–8 November: First meeting of IMMLEP Project Group 12–15 November: Planning Group meeting on TDR	
1975–1976	Detailed proposals for TDR developed	
28–30 April 1976	Planning meeting for the THELEP Task Force	
December 1976		TDR set in motion

Table 6.2

WHO Study Group, 1981: Chemotherapy of leprosy for control programmes. Summary of roles of THELEP and LEP, including preparation of the meeting and implementation of MDT

1. Role of THELEP

- 1976–1980:
  - To organize dapsone resistance surveys unequivocally demonstrating the need for MDT regimens
  - To establish the rationale for the composition of MDT regimens for MB (and PB) patients based on monthly doses of rifampicin
- 1979 onwards:
  - To organize trials of MDT regimens for MB patients
- 1980–1981:
  - To take an essential part in the preparation and discussions of the 1981 WHO Study Group on chemotherapy of leprosy for control programmes
- 1981 onwards:
  - To organize the field trials required to validate the 1981 study group regimens for MB and PB patients
  - To participate in advocacy for these regimens
  - To participate in meetings where these regimens were endorsed (notably the sixth meeting of the WHO Expert Committee on Leprosy)

2. Role of LEP

- By organizing the 1981 WHO Study Group meeting, in close collaboration with THELEP:
  - To prompt the finalization of MDT regimens for MB and PB patients applicable in the field
  - To ensure that these regimens would be recommended for immediate use
- Actively to promote the introduction and implementation of MDT regimens, in cooperation with all partners (see Table 6.3).

Table 6.3

Introduction and implementation of 1981 WHO Study Group MDT regimens for leprosy: summary of the roles of LEP and WHO network

Advocacy and/or technical cooperation predominant

- WHO technical meetings on MDT and leprosy control at:
  - global,
  - regional/sub-regional, and
  - inter-country levels.
- WHO support to courses, workshops, etc., at various levels
- Participation in technical meetings organized by other agencies (International Leprosy Congress, Sasakawa Memorial Health Foundation, International Federation of Anti-Leprosy Associations, International Union Against Tuberculosis, etc.)
- Visits by LEP officers and regional advisers for leprosy to: countries, institutions, contributing agencies, etc.
- Special importance of WHO country representatives: advocacy, technical cooperation and coordination
- WHO consultants

Coordination role predominant

- Discussions at the World Health Assembly
- Discussions with contributing agencies (Sasakawa Memorial Health Foundation, ILEP and member associations, UNICEF, etc.).

Table 6.4
WHO meetings relating to MDT introduction and implementation, 1982–1986

Date and place	Title of meeting	Organizer	Attendance (in addition to organizer)	Main subjects
1–5 March 1982 Manila	Scientific Group on Tuberculosis and Leprosy Research	WPRO	8 countries in Western Pacific region, WHO/HQ (LEP/TB)	Research First national meeting at which the Study Group MDT was discussed
28 June – 2 July 1982 Suva, Fiji	Seminar on Drug Policy for Leprosy Programmes in the South Pacific	WPRO	16 countries in the subregion NZLTB LEP	Conditions for making MDT implementation feasible
23–25 August 1982 New Delhi	Meeting on Action Plans for Leprosy Control	LEP	Regional advisers for leprosy SMHF ILEP/5 member organizations ILA	Detailed analysis of leprosy situation in all WHO regions In-depth review of conditions for MDT implementation
30 October – 5 November 1982 Mogadishu	Second Meeting on Strategy for Leprosy Control	EMRO/SMHF	8 countries in Eastern Mediterranean region SMHF ILEP UNICEF	Review of activities to be undertaken in conjunction with MDT implementation
20–23 December 1983 New Delhi	Inter-Country Meeting on Multidrug Therapy in Leprosy Control in the South-East Asia Region	SEARO	8 countries in South-East Asia region LEP 3 VAs from Europe UNICEF	Country profiles for leprosy action plans for implementation of MDT Indicators for leprosy control based on MDT
24 February 1984 New Delhi	Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control	SEARO (further to meeting in August 1982)	LEP All regional advisers for leprosy ILEP/10 member organizations	Plans for MDT implementation exist in most countries. MDT implemented in a number of pilot projects. Statements by VAs Monitoring of MDT implementation could be based on the set of essential indicators prepared by the 1983 Study Group on Epidemiology of Leprosy in Relation to Control, which is close to ILEP revised Form B
25–29 October 1984 Manila	Interregional Meeting on Multidrug Therapy Regimens for Leprosy Control	SMHF/LEP/ WPRO/ SEARO	22 countries in South-East Asia and Western Pacific regions 8 VAs	Country reports Statements by VAs Planning for MDT

Date and place	Title of meeting	Organizer	Attendance (in addition to organizer)	Main subjects
16–19 October 1985 Geneva	Consultation on Implementation of Multidrug Therapy for Leprosy Control	LEP	Experts and leprosy programme managers (in personal capacity)	All endemic countries had started or were in the process of starting to implement MDT Analysis of problems based on detailed reports of 27 projects on MDT implementation
16–18 June 1986 Geneva	Consultation on Implementation of Leprosy Control through Primary Health Care	LEP (SDS, HSH)	Programme managers from countries (in personal capacity)	Integration of leprosy control based on MDT into the primary health care system
4–5 November 1986 Geneva	Second Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control	LEP	All regional advisers for leprosy except from the European region VAs	Cooperation with international, bilateral, and voluntary organizations in the implementation of MDT
2–5 December 1986 Abidjan	Meeting on Leprosy Control in the Countries of Subregion 1	AFRO	11 countries in the subregion 3 leprosy institutes OCCGE OCEAC FFF	Review of national leprosy programmes Problems related to MDT implementation

References

1. Pettit JHS, Rees RW. Sulphone resistance in leprosy. An experimental and clinical study. *Lancet*, 1964, 2:673–674.
2. *WHO Expert Committee on Leprosy. Third report*. Geneva, World Health Organization, 1966 (WHO Technical Report Series, No. 319).
3. *WHO Expert Committee on Leprosy. Fourth report*. Geneva, World Health Organization, 1970 (WHO Technical Report Series, No. 459).
4. Immunological problems in leprosy research. *Bulletin of the World Health Organization*, 1970, 43:879–890.
5. Immunological problems in leprosy research. *Bulletin of the World Health Organization*, 1973, 48(3):345–354 and 48(4):483–494.
6. Report of the first meeting of IMMLEP project group (4–8 November 1974). Geneva, World Health Organization, 1974 (document IMM/74.3).
7. *Intensification of research on tropical parasitic diseases*. Twenty-seventh World Health Assembly, Geneva, 7–236 May 1974, Resolution WHA27.52.
8. *Recommendations and report of the planning group on the Special Programme for Research and Training in Tropical Diseases, Geneva, 12–15 November 1974*. Geneva, World Health Organization, 1974 (document TDR/75.1).
9. *Report of the planning meeting for THELEP task force, Geneva, 28–30 April 1976*. Geneva, World Health Organization, 1976 (document TDR/THELEP/76.1).
10. *WHO Expert Committee on Leprosy. Fifth report*. Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 607).
11. *Chemotherapy of leprosy for control programmes. Report of a WHO Study Group*. Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 675).
12. Vellut C, Waters MFR. *Points for discussion on chemotherapy of leprosy control programmes*. Geneva, World Health Organization, 1981 (document LEP/SG/WP/81.1).
13. *Report of the fifth meeting of the Steering Committee of the Scientific Working Group on chemotherapy of leprosy, Geneva, 30–31 March 1979*. Geneva, World Health Organization, 1979 (document TDR/THELEP-SC (5)/79.3).
14. *Minutes of the seventh meeting of the Steering Committee of the Chemotherapy of Leprosy (THELEP) Scientific Working Group, Geneva, 24–25 April 1980*. Geneva, World Health Organization (restricted document). Annex: General protocol for field trials of chemotherapy of multibacillary leprosy.
15. *Report of the third coordinating meeting on implementation of multidrug therapy (MDT) in leprosy control programmes, The Hague, 13 September 1988*. Geneva, World Health Organization, 1988 (document WHO/CDS/LEP/88.4).
16. *Report of a coordinating meeting on implementation of multidrug therapy in leprosy control, New Delhi, 24 February 1984*. Geneva, World Health Organization, 1984 (document WHO/LEP/84.1).
17. *Thirty-sixth World Health Assembly, Geneva, 2–16 May 1983. Volume 3. Summary records of committees*. Geneva, World Health Organization, 1983 (document WHA36/1983/REC.3).
18. *Report of a meeting on action plans for leprosy control, New Delhi, 23–25 August 1982*. Geneva, World Health Organization, 1983 (document WHO/LEP/83.1).

19. *Report on a seminar on drug policy for leprosy programmes in the South Pacific, Suva, Fiji, 28 June – 2 July 1982*. Manila, WHO Regional Office for the Western Pacific, 1982 (document CHD/ICP/BVM/005).
20. *Report on the second meeting on strategy of leprosy control, Mogadishu, Somalia, 30 October – 5 November 1982*. Alexandria, WHO Regional Office for the Eastern Mediterranean, 1983 (document EM/LEP/33).
21. *Report on an inter-country meeting on multidrug therapy in leprosy control, New Delhi, 20–23 December 1983*. New Delhi, WHO Regional Office for South-East Asia, 1984 (restricted document SEA/LEP/93).
22. *Report on an interregional workshop on multidrug therapy regimens for leprosy control, Manila, Philippines, 25–29 October 1984*. Manila, WHO Regional Office for the Western Pacific, 1985 (document CHD/ICP/LEP/001-E).
23. *Epidemiology of leprosy in relation to control. Report of a WHO Study Group*. Geneva, World health Organization, 1985 (WHO Technical Report Series, No. 716).
24. *The introduction of multidrug therapy for leprosy*. London, International Federation of Anti-Leprosy Associations, 1983 (revised 1984).
25. *Report of a consultation on implementation of multidrug therapy for leprosy control, Geneva, 16–19 October 1985*. Geneva, World Health Organization, 1985 (document WHO/LEP/85.1).
26. Sansarricq H. *Preliminary review of some points for discussion on implementation of multidrug therapy*. Geneva, World Health Organization (document LEP/Cons./WP/85.1).
27. *Report on a meeting on leprosy control in the countries of sub-region 1, Abidjan, 2–5 December 1986*. Brazzaville, WHO Regional Office for Africa, 1986 (document AFR/LEP/47).
28. Ellard GA. Rationale of the multidrug regimens recommended by a World Health Organization study group on chemotherapy of leprosy for control programmes. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1984, 52:395–401.
29. WHO Expert Committee on Leprosy, Sixth meeting, 1987. WHO Technical Report Series, 768, 1988

6.2 THELEP

L. Levy

The author wishes to acknowledge the invaluable assistance provided by Dr Gordon A. Ellard and Professor Ji Baohong in the preparation of this section.

The Programme for Research on the Chemotherapy of Leprosy, THELEP, began in April 1976 with the meeting of the THELEP Planning Committee (*1*), which commissioned the preparation of a standard protocol for controlled clinical trials of combined chemotherapy among previously untreated MB patients (*2*). The primary focus of the trials was to be the detection of persisting *M. leprae* by the inoculation of thymectomized, irradiated mice with approximately 10^5 organisms per hind footpad. At the first meeting of the THELEP Scientific Working Group (SWG), in April 1977, a draft standard protocol was reviewed, amended, and adopted, experimental combined-drug regimens were designed, and applications were approved from the Institut Marchoux, Bamako, Mali, and the Central Leprosy Teaching and Research Institute, Chingleput, South India, to conduct trials of the regimens, and from the National Institute for Medical Research (NIMR), London, England, to inoculate mice with *M. leprae* recovered from biopsy specimens to be obtained at intervals from the patients recruited into the trials in Bamako and Chingleput and shipped to the London laboratory. In addition to the attempt to detect persisting *M. leprae*, the pretreatment susceptibility to dapsone of the patients' organisms was to be measured by inoculation of intact mice at St George's Hospital Medical School, London. The results of these trials are reviewed below under "THELEP controlled clinical trials".

Surveys of dapsone resistance

Even after Pettit & Rees (*3*) first demonstrated, in 1964, relapse caused by the emergence of dapsone-resistant *M. leprae*, the importance of this phenomenon was not immediately appreciated. Investigators who had been working in the area of the chemotherapy of leprosy were fully conversant with the evidence that drug-resistant strains of *M. tuberculosis* were certain to emerge among tuberculosis patients treated for even brief periods of monotherapy with any of the available bactericidal agents. However, relapse caused by the emergence of dapsone-resistant *M. leprae* at first appeared to be extremely rare, perhaps because of the enormous therapeutic ratio – approximately 500:1 (*4*). Only much later did it become apparent that secondary resistance to dapsone had become a widespread phenomenon (*5*), and instances of primary resistance were detected (*6*).

THELEP supplied the protocol for, and supported surveys of, primary dapsone resistance in Addis Ababa (*6*), which yielded a prevalence of 67 per 100 patients at risk, and Cebu (*7*), which yielded a prevalence of only 3–6 per 100. In addition, approximately 37% of the patients recruited into the THELEP trials of combined chemotherapy in Bamako and Chingleput were found to harbour *M. leprae* with primary dapsone resistance (*8*, *9*). The alarmingly high prevalence of primary dapsone resistance in Addis Ababa, Bamako, and Chingleput suggested that patients who relapsed during dapsone monotherapy infected their

contacts with dapsone-resistant *M. leprae*. This situation appeared to represent a serious threat to efforts to control leprosy, and led directly to the convening of the WHO Study Group.

Information regarding antileprosy drugs

From its inception, THELEP set as one of its priorities studies of drugs known or expected to exert antimicrobial activity against *M. leprae*. Among the studies subsequently supported by THELEP were the screening of compounds for antimicrobial activity and clinical trials of promising new drugs and drug combinations.

Drug screening

With support from THELEP, a large number of compounds were screened for activity against *M. leprae*. The studies employed both *M. leprae* and batteries of cultivable mycobacterial species, and tested representatives of many classes of compounds, including analogues of cycloserine, dapsone and rifampicin, as well as series of thiosemicarbazones, thioamides, cephalosporins, macrolides, and inhibitors of dihydrofolate reductase (*10*).

Clinical trials

THELEP controlled clinical trials

In Bamako and Chingleput, 215 patients were recruited into the two THELEP controlled clinical trials, and 769 biopsy specimens were shipped to London for inoculation of mice. The results of these trials, reported in a series of publications (*8*, *9*, *11–16*), may be summarized as follows:

- More than one-third of the patients were found to harbour dapsone-resistant *M. leprae* in the biopsy specimens obtained before treatment with the experimental regimens began.
- Persisting *M. leprae* were detected in approximately 9% of all biopsy specimens.

Detection of the persisters appeared to be a random event, in that these organisms were detected with approximately the same frequency in specimens obtained after 3, 12 and 24 months, regardless of the treatment regimen. In addition, the frequency with which persisting organisms were detected in more than one specimen from the same patient was no greater than that predicted by chance.

- Long-term “field” trials at Karigiri and Polambakkam
  At the first meeting of the THELEP SWG in April 1977, it was decided that THELEP could not ethically discontinue treatment once patients had completed two years of therapy with the experimental combined-drug regimens: it was feared that a significant proportion would relapse once treatment was withdrawn. Two years later, however, at its second meeting, the THELEP SWG learned of work in Sungei Buloh (*17*) and Malta (*18*), which suggested that the risk of relapse after withdrawal was very small among patients who had been correctly treated with the new regimens; in Malta, no clinical evidence of relapse had been observed among 116 patients with MB leprosy, although 10 patients were found to have positive skin-smears at the time of review. These results encouraged the SWG to conduct “field trials” in Polambakkam and Karigiri, both in South India, in

which large numbers (approximately 400 per regimen) of bacteriologically negative MB patients, previously treated by dapsone monotherapy, were given a combined-drug regimen for two years after achievement of skin-negativity, after which treatment was withdrawn and the patients were observed for evidence of relapse.

The treatment consisted of a total of 1200 mg/month rifampicin given in two consecutive daily doses of 600 mg; a total of 1200 mg/month clofazimine, also given in two consecutive daily doses of 600 mg; 225 mg acedapsone (diacetyl dapsone) intramuscularly every two months; and dapsone 100 mg daily. It later served as a model for the MDT regimen recommended for MB leprosy by the WHO Study Group.

Trials of WHO MDT regimens

- MB leprosy
  Immediately following the 1981 meeting of the WHO Study Group, THELEP added a second regimen – that recommended by the Study Group for treatment of MB leprosy, the WHO MDT regimen – to the "THELEP regimen" used in the Karigiri and Polambakkam trials described above. Newly recruited patients in Polambakkam and Gudyattham Taluk, south India, were randomly assigned to treatment with either the THELEP or the WHO MDT regimen. Almost no relapses occurred among the more than 2200 patients treated by either regimen (*19–22*).

- PB leprosy
  THELEP sponsored two field trials of chemotherapy among patients with PB leprosy – one in Indonesia and the other in Malawi. Only the results of the Malawi trial were published (*23*, *24*).

Participation in the 1981 Study Group and in subsequent technical meetings related to chemotherapy of leprosy

The Study Group included approximately equal numbers of laboratory and field workers; all of the former group were members of the THELEP SWG. The field workers, in particular, welcomed the Study Group's conclusion that rifampicin should be administered intermittently, since they were concerned about the cost of this expensive drug and the operational difficulty of supervising each dose. Intermittent administration of rifampicin would permit "stretching" the potentially limited supply of the drug and facilitate the supervision of each dose.

References

1. *Report of the Planning Meeting for THELEP Task Force*. Geneva, World Health Organization, 1976 (document TDR/THELEP/76.1).
2. *Standard protocol for chemotherapy trials in lepromatous leprosy*. Geneva, World Health Organization, 1977 (document TDR/SWG-THELEP (1)/77.3), Annex 1.

3. Pettit JHS, Rees RJW. Sulphone resistance in leprosy: an experimental and clinical study. *Lancet*, 1964, ii: 673–674.
4. Ellard GA. Rationale of the multidrug regimens recommended by a World Health Organization Study Group on Chemotherapy of Leprosy for Control Programmes. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1984, 52:395–401.
5. Pearson JMH. The problem of dapsone-resistant leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1981, 49:417–420.
6. Pearson JMH, Haile GS, Rees RJW. Primary dapsone-resistant leprosy. *Leprosy Review*, 1977, 48:129–132.
7. Guinto RS et al. Primary dapsone-resistant leprosy in Cebu, Philippines. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1980, 49:231–241.
8. Primary resistance to dapsone among untreated lepromatous patients in Bamako and Chingleput. *Leprosy Review*, 1983, 54:177–183.
9. Primary dapsone-resistance in Bamako and Chingleput – final report. *Leprosy Review*, 1987, 58:209–218.
10. Shepard CC, Van Landingham RM, Walker LL. Recent studies of antileprosy drugs. *Leprosy Review*, 1983, 54:23S–30S**.**
11. THELEP controlled clinical trials in lepromatous leprosy. *Leprosy Review*, 1983, 54:167–176.
12. Characteristics of patients in the THELEP trials of chemotherapy of leprosy in Bamako and Chingleput. *Leprosy Review*, 1987, 58:7–16.
13. Persisting *Mycobacterium leprae* among THELEP trial patients in Bamako and Chingleput. *Leprosy Review*, 1987, 58:325–337.
14. The THELEP controlled clinical drug trials. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1987, 55:864–871.
15. Characteristics of the multiplication of dapsone-resistant strains of Mycobacterium leprae in mice. *Leprosy Review*, 1988, 59:5–10.
16. Response to treatment by multidrug regimens in the THELEP controlled clinical drug trials. *Leprosy Review*, 1996, 67:260–279.
17. Waters MFR et al. The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy. *Leprosy Review*, 1986, 57:101–109.
18. Jopling WH et al. A follow-up investigation of the Malta-project. *Leprosy Review*, 1984, 55:247–253.
19. Vijaykumaran P, Manimozhi N, Jesudasan K. Incidence of late lepra reaction among multibacillary leprosy patients after MDT. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1995, 63:18–22.
20. Vijaykumaran P, Jesudasan K, Manimozhi N. Fixed-duration therapy (FDT) in multibacillary leprosy: efficacy and complications. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1996, 64:123–127.
21. Jesudasan K et al. Effectiveness of MDT in multibacillary therapy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1996, 64:128–132.
22. Jesudasan K et al. Absence of relapse within 4 years among 34 multibacillary patients with high BIs treated for 2 years with MDT. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1996, 64:133–135.

23. Boerrigter G, Ponnighaus JM, Fine PEM. Preliminary appraisal of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1988, 56:408–417.
24. Boerrigter G et al. Four year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1991, 59:255–261.

6.3 Evolution in WHO, including TDR/THELEP, from 1991 to 2000

Intensive elimination strategy

S.K. Noordeen

The start of the 1990s saw some evidence of stagnation in MDT implementation. The smaller and better-organized leprosy programmes and those that were better-funded were able to introduce MDT early and achieve results. In some of the larger countries, however, MDT coverage was only partial and progress was slow for various reasons including insufficient political commitment and inadequate funding for MDT drugs. Some did not fully appreciate the unique opportunity provided by MDT to bring about the end of leprosy as a public health problem.

It was under these circumstances that the Executive Board of WHO took up the issue of leprosy control in January 1991. A draft resolution for the subsequent World Health Assembly, introduced by the Board member from Nigeria, clearly recognized the potential of MDT to conquer leprosy and declared WHO's commitment to eliminating the disease as a public health problem by 2000, defining elimination as reducing the prevalence to below one case per 10 000 population. The draft resolution also recognized the substantial progress made in leprosy control, the increasing support from NGOs and other donors, and the growing priority for leprosy control in many countries. It urged Member States to increase political commitment and coordinate all available resources to extend MDT coverage and case-finding, to strengthen training and information systems, and to integrate leprosy control into general health services. The resolution requested the Director-General of WHO to strengthen technical support to Member States, to mobilize additional resources and promote coordination with NGOs, and to strengthen national capabilities and leprosy research.

The Board overwhelmingly supported the draft resolution. In May 1991, when the draft resolution was discussed at the World Health Assembly, it was sponsored by several countries, including China, India, the Netherlands, Nigeria, and USA, and was adopted unanimously.

Following the adoption of the resolution, a number of countries were able to strengthen their commitment and increase the priority accorded to leprosy elimination. International NGOs also increased their support for national leprosy programmes, although ILEP had some reservations – later to prove unfounded – about the impact on fundraising of the message on leprosy elimination. The leprosy research community was also concerned about the diminishing financial support for research, attributing it to funding agencies regarding leprosy as a disappearing problem as a result of the promotion of elimination.

In spite of these developments, many national programmes and major donors such as The Nippon Foundation saw an excellent opportunity to push ahead towards the goal set by the World Health Assembly and were keen to mobilize the necessary additional resources, including those required for MDT drugs. To accelerate this positive trend, WHO took another major step and brought together major leprosy-endemic countries, NGOs, and donor agencies through the First International Conference on Elimination of Leprosy held in Hanoi

in July 1994. This Conference not only helped in further consolidating political commitment but also provided the opportunity for The Nippon Foundation to announce that it would donate US$ 50 million to WHO for five years for the purchase of MDT drugs. This enabled WHO to meet the drug requirements of all the countries in need: since 1995, no registered patient has had to forego treatment for want of drugs. This "drug security" played a key role in increasing MDT coverage to almost 100% of registered cases within a couple of years following the Hanoi Conference.

The political commitment of the most endemic countries was further strengthened through the Second International Conference on Elimination of Leprosy, held in New Delhi in October 1996. By that time, the leprosy elimination strategy has been universally accepted by everyone including the international NGOs. When the Third International Conference took place in Abidjan in September 1999, the overall situation was quite promising in most of the countries, although it was clear that some – including larger countries such as Brazil and India – needed more time to reach their goal at the national level.

At about this time too, the continued supply of MDT drugs – beyond the year 2000 – was also assured through the generous undertaking by Novartis to meet drug needs for the next five years. This was most reassuring to the countries, which would otherwise have faced serious problems in this regard.

Other developments that facilitated progress towards leprosy elimination included the simplification of technical requirements, which was made possible by the recommendations of the 1994 WHO Study Group on chemotherapy of leprosy and the seventh meeting of the WHO Expert Committee on Leprosy in 1998.

WHO played a key role in coordinating the various agencies interested in leprosy, particularly in relation to national leprosy programmes. Conferences on elimination of leprosy in 1994, 1996, and 1999 greatly facilitated the coordination efforts and made it possible to formalize them through a mechanism of the Global Alliance for Elimination of Leprosy. The Global Alliance was set up in 1999 and has so far met in 2001 in New Delhi and again in Brasília in 2002.

Changes in research focus

L. Levy

The author wishes to acknowledge the invaluable assistance provided by Dr Gordon A. Ellard and Professor Ji Baohong in the preparation of this section.

New compounds highly bactericidal for Mycobacterium leprae

Identification of compounds

In work supported by THELEP, a number of new compounds with bactericidal activity against *M. leprae* were identified by Grosset and Ji. These compounds include the fluoroquinolones pefloxacin (*1*), ofloxacin (*2, 3*), sparfloxacin (*4, 5*), moxifloxacin (*6*), the macrolide clarithromycin (*7, 8*), the tetracycline minocycline (*8, 9*), and the rifamycin

rifapentine (*6*, *10–13*). Studies revealed that clarithromycin, minocycline, ofloxacin, and sparfloxacin exert a similar degree of bactericidal activity against *M. leprae*, and, although they are less potent than rifampicin, they are significantly more active than either dapsone or clofazimine alone. Moxifloxacin is the first and, thus far, the only non-rifamycin to display a degree of activity virtually identical to that of rifampicin in mice; it is far more bactericidal than ofloxacin, clarithromycin, and minocycline. Rifapentine is more powerfully bactericidal against *M. leprae* than either rifampicin or the rifampicin–ofloxacin–minocycline (ROM) combination.

These results clearly demonstrated that screening existing compounds is the most cost-effective approach to drug development in leprosy. They also indicated that it is most productive to screen compounds that display powerful activity against a wide spectrum of Gram-positive micro-organisms in general or cultivable mycobacteria in particular, or that exhibit more favourable pharmacokinetic properties than those of the member of the class currently used to treat leprosy (*6*).

Short-term trials in MB leprosy

Short-term trials require the recruitment of only 6–10 untreated MB patients per regimen. Treatment is administered either as a single dose or for no longer than a few months; skin lesion biopsies are taken at intervals during treatment, and the *M. leprae* recovered from the biopsy specimens are inoculated into mice. After treatment with the experimental drug or regimen has been completed, patients are treated with MDT as if they had not previously been treated.

Immediately after the active new drugs had been identified by screening in *M. leprae*-infected mice, short-term clinical trials of pefloxacin (*14*), ofloxacin (*14–16*), clarithromycin (*17*, *18*), minocycline (*17*, *19*), and sparfloxacin (*20*) were launched; in most trials, the therapeutic effects of the treatment were monitored by mouse footpad inoculation. Treatment with any of these compounds alone had considerable bactericidal activity against *M. leprae*. For example, 99.99% of viable *M. leprae* were killed by 22 daily doses of 800 mg pefloxacin or 400 mg ofloxacin (*29*), and >99% killing was observed after 28 days of daily administration of 100 mg minocycline, 500 mg clarithromycin (*17*), or 200 mg sparfloxacin (*20*). The bactericidal activity of single doses of the combinations clarithromycin–minocycline (*18*) or ofloxacin–minocycline (*15*) against *M. leprae* was equivalent to that of four weeks of daily treatment with the dapsone–clofazimine combination; however, the gastrointestinal side-effects associated with large doses of clarithromycin were not well tolerated by patients.

Encouraged by these results, the ROM combination was tested in a clinical trial; a single dose of this combination displayed considerable bactericidal activity against *M. leprae* (*15*). More recently, following the observations that moxifloxacin exerts a very powerful bactericidal effect on *M. leprae* (virtually identical to that of rifampicin), that rifapentine is far more bactericidal than rifampicin, and that a single dose of the combination rifapentine–moxifloxacin–minocycline (PMM) killed 99.9% of viable *M. leprae*, it appeared likely that PMM would be more efficient than ROM as a fully supervised, monthly-administered multidrug regimen for leprosy (*6*). A clinical trial is being conducted to compare PMM with

ROM and the moxifloxacin–minocycline combination with ofloxacin–minocycline, in terms of both therapeutic effects and side-effects. The results of this trial will become available shortly.

The ofloxacin multicentre trial (21)

In 1991 and 1992, THELEP (now known as THEMYC) launched a large-scale multi-centre field trial, the main objectives of which are to evaluate the efficacy, acceptability, and feasibility of ofloxacin-containing combined regimens in a randomized, double-blind, controlled clinical trial in both MB and PB leprosy patients. One of trial regimens is a combination of rifampicin *plus* ofloxacin daily for 4 weeks for both MB and PB leprosy. The other two regimens, both for MB leprosy, are the WHO-recommended MDT for 1 year, with or without daily ofloxacin supplementation during the first 4 weeks. The control regimen is the standard 24-month WHO-recommended MDT regimen.

The current trial has six arms: four for MB, and two for PB leprosy. For MB leprosy, the four arms are:

– WHO MDT for 2 years
– WHO MDT for 1 year
– WHO MDT for 1 year supplemented by daily ofloxacin for the first 4 weeks;
– ofloxacin plus rifampicin daily for 4 weeks.

For PB leprosy, the two arms are:

– WHO MDT for 6 months;
– ofloxacin plus rifampicin daily for 4 weeks.

Fifteen centres from eight endemic countries are participating in the trial. The intake of nearly 4000 patients was completed in June 1994, and treatment was completed in December 1996. Follow-up will continue until December 2003, and final results are expected to be available by mid-2004.

Participation in technical meetings after 1981

After 1981, technical meetings on new antileprosy drugs and their use in combinations included the meeting of a second WHO Study Group, convened in Geneva in November 1993 (TRS 847) in which Dr Jacobson and the author participated, and the seventh meeting of the WHO Expert Committee on Leprosy, convened in Geneva in May 1997, in which Drs Grosset and Ji participated. Finally, the WHO Technical Advisory Group, which included several former members of THELEP/THEMYC, has met on three occasions – in Geneva in May 2000, in New Delhi in February 2001, and in Brasília in February 2002.

References

1. Guelpa-Lauras CC et al. Activities of pefloxacin and ciprofloxacin against *Mycobacterium leprae* in the mouse. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1987, 55:70–77.
2. Grosset JH et al. Activity of ofloxacin against *Mycobacterium leprae* in the mouse. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1988, 56**:**259–264.
3. Pattyn SR. Activity of ofloxacin and pefloxacin against *Mycobacterium leprae* in mice (Letter to the editor). *Antimicrobial Agents and Chemotherapy*, 1987, 31:671–672.
4. Franzblau SG, White KE. Comparative in vitro activities of 20 fluoroquinolones against *Mycobacterium leprae*. *Antimicrobial Agents and Chemotherapy*, 1990, 34:229–231.
5. Traore I et al. Determination of the minimal effective dosages of ofloxacin and sparfloxacin against *M. leprae* in the mouse footpad system. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1996, 64:142–145.
6. Consigny S et al. Bactericidal activities of HMR 3647, moxifloxacin, and rifapentine against *Mycobacterium leprae* in mice. *Antimicrobial Agents and Chemotherapy*, 2000, 44:2919–2921.
7. Franzblau SG, Hastings RC. In vitro and in vivo activities of macrolides against *Mycobacterium leprae*. *Antimicrobial Agents and Chemotherapy*, 1988, 32:1758–1762.
8. Ji B, Perani EG, Grosset JH. Effectiveness of clarithromycin and minocycline alone and in combination against experimental *Mycobacterium leprae* infection in mice. *Antimicrobial Agents and Chemotherapy*, 1991, 35:579–581.
9. Gelber RH. Activity of minocycline in *Mycobacterium leprae*-infected mice. *Journal of Infectious Diseases*, 1987, 156:236–239.
10. Pattyn SR, Saerens E. Activity of three new rifamycin derivatives on the experimental infection by Mycobacterium leprae. *Annales de la Société Belge de Médecine Tropicale*, 1977, 57:169–173.
11. Pattyn SR. A comparison of the bactericidal activity of a series of rifampicins against *Mycobacterium leprae*. *Arzneimittel-Forschung*, 1982, 32:15–17.
12. Hastings RC, Jacobson RR. Activity of ansamycin against *Mycobacterium leprae* in mice. *Lancet*, 1983, ii: 1079–1080.
13. Ji B et al. Antimycobacterial activities of two newer ansamycins, R-76-1 and DL 473. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1986, 54:563–577.
14. Grosset JH et al. Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. *International Journal of Leprosy and Other Mycobacterial Diseases*, 1990, 58**:**281–295.
15. Ji B et al. Bactericidal activity of a single-dose combination of ofloxacin plus minocycline, with or without rifampin, against *Mycobacterium leprae* in mice and in lepromatous patients. *Antimicrobial Agents and Chemotherapy*, 1998, 42**:**1115–1120.
16. Ji B et al. Clinical trial of ofloxacin alone and in combination with dapsone plus clofazimine for treatment of lepromatous leprosy. *Antimicrobial Agents and Chemotherapy*, 1994, 38:662–667.
17. Ji B et al. Powerful bactericidal activities of clarithromycin and minocycline against *Mycobacterium leprae* in lepromatous leprosy. *Journal of Infectious Diseases*, 1993, 168:188–190.

18. Ji B et al. Bactericidal activity of single dose of clarithromycin plus minocycline, with or without ofloxacin, against *Mycobacterium leprae* in patients. *Antimicrobial Agents and Chemotherapy*, 1996, 40:2137–2141.
19. Gelber RH et al. A clinical trial of minocycline in lepromatous leprosy. *British Medical Journal*, 1992, 304:91–92.
20. Chan GP et al. A clinical trial of sparfloxacin for lepromatous leprosy. *Antimicrobial Agents and Chemotherapy*, 1994, 38:61–65.
21. Daumerie D. Current World Health Organization-sponsored studies in the chemotherapy of leprosy. *Leprosy Review*, 2000, 71:88–90.

Chapter 7

Lessons to be learned

H. Sansarricq

7.1 MDT development

Overview

The process that led ultimately to the design of the 1981 Study Group regimens can be viewed as the history – spanning some 40 years - of the modern chemotherapy of leprosy.

Original concepts

The concepts of bacterial resistance to drugs and its prevention, which served as a basis for the Study Group regimens, had been established in the late 1940s and the 1950s from experience with the chemotherapy of tuberculosis.

Two milestones

The first milestone to mark progress in leprosy chemotherapy was the introduction of dapsone in the early 1950s. Considered at the time to be a "miracle drug", dapsone was used in monotherapy worldwide for about three decades. During the 1960s, however, evidence was steadily accumulating that *M. leprae* resistance to dapsone – an inevitable consequence of the drug's use as monotherapy – could jeopardize all efforts to control leprosy based on dapsone alone. Nonetheless, it was many years before the importance of this phenomenon was generally accepted.

The second milestone was the introduction of the MDT regimens recommended by the 1981 WHO Study Group.

Experimental advances

For many years, the impossibility of cultivating *M. leprae* in artificial media was an insuperable problem for experimental chemotherapy. However, the mouse footpad model, proposed by Shepard in 1960, which largely overcame the difficulties, was to revolutionize this field of study. Later, the thymectomized–irradiated mouse model, proposed by Rees in 1966, which made possible the detection of *M. leprae* persisters, was used to monitor progress in field trials of the Study Group regimens for MB patients. Other important advances with implications for experimental chemotherapy – though concerned essentially with the relationship between *M. leprae* and its host – came from the Ridley–Jopling spectrum and classification.

Thus, through the meticulous and sustained efforts of numerous scientists and leprosy workers, clinicians and laboratory researchers, complex experimental methods were developed that overcame the considerable difficulties inherent in working with leprosy and its causative organism. In 1981 it finally became possible to design effective and practicable MDT regimens for leprosy control, using the few drugs then available, including rifampicin, which is strongly bactericidal against *M. leprae*.

MDT drugs

Much has already been said, in sections 1.1 and 5.3, about development of the drugs included in the Study Group regimens. Two of the three drugs included in the standard WHO MDT regimens – rifampicin and clofazimine – were developed by Ciba-Geigy (now Novartis, after merger with Sandoz). Of particular importance in relation to the effectiveness of MDT regimens for leprosy is the strong bactericidal activity of rifampicin against *M. leprae*. While the 1981 Study Group regimens were being implemented, a number of new compounds with similar activity against *M. leprae* were identified, meaning that alternative MDT regimens could be developed if necessary (which has already been done with the ROM combination for single-lesion leprosy patients).

THELEP

In 1976, early in the development of the WHO/UNDP/World Bank Special Programme for Research and Training in tropical diseases (TDR), the Scientific Working Group on Chemotherapy of Leprosy – THELEP – was established. THELEP provided a unique opportunity for the leading scientists engaged in research on the chemotherapy of leprosy – most of those responsible for the progress made since the early 1960s – to cooperate, exchange experiences, discuss their findings, and achieve important TDR funding for their work. There can be little doubt that progress in research was facilitated and considerably accelerated by this means.

The first task of THELEP was to organize and sponsor surveys that confirmed the gravity of the problem posed by *M. leprae* resistance to dapsone (see section 6.2).

Moving closer to the Study Group regimens

A failure

Addressing the problem of *M. leprae* resistance to dapsone, the WHO Expert Committee on Leprosy, at its fifth meeting in 1977, recommended the use of combined drug regimens in which rifampicin was to be used in daily doses, because of the fear, prevalent at the time, of toxic side-effects resulting from intermittent doses (see section 6.1, under “New developments”). However, these regimens – and similar regimens recommended by others in the late 1970s – proved impracticable in the field.

An increasing concern

In the later 1970s, as discussed in section 2.1, the anarchic use of rifampicin in leprosy field programmes was causing growing concern about the risk of *M. leprae* developing resistance to this most potent drug at a time when there was no alternative.

The latest steps and the 1981 study group

As explained in section 6.2 (under "Long-term "field" trials at Karigiri and Polambakkam"), in 1979 THELEP designed an experimental regimen – for field trials in MB patients – that was potentially usable for leprosy control. This regimen was based on supervised doses of rifampicin given monthly on two consecutive days. The results of these trials were expected to be available a minimum of 7 years after admission of the first patient, which took place in 1982.

Prompted by the urgent need to end the anarchic use of rifampicin (which implied taking action before the results of the THELEP field trials became available), and in close cooperation with THELEP, LEP convened a WHO Study Group on Chemotherapy of Leprosy for Control Programmes in 1981 (see section 2.1). This Study Group recommended immediate implementation of standard multidrug regimens for MB and PB patients, based on supervised monthly doses of rifampicin and of finite duration.

The respective roles of THELEP and LEP are explained in section 6.1. THELEP was responsible for the development of the MDT regimens for MB and PB patients that were recommended by the 1981 WHO Study Group. LEP took responsibility for catalysing the timely finalization of these regimens, for facilitating their recommendation for immediate implementation, and for securing their official endorsement by WHO. Subsequently, THELEP was responsible for the experimental validation of the Study Group regimens through field trials and publication of the results.

Conclusion

The development and recommendation of the 1981 WHO Study Group regimens provided an excellent example of genuine – and thus productive – cooperation between two WHO programmes dealing with research on chemotherapy of leprosy and technical policy for leprosy control. The regimens were developed and finalized with significant urgency, using the few antileprosy drugs then available (with rifampicin as a crucial component) and based partly on reasonable extrapolations to existing knowledge (see section 2.2).

The fact that these regimens were subsequently to prove not only highly effective but also robust was undoubtedly the result of the high quality of the experimental work on which they were based, complemented by the penetrating intuition of the researchers.

7.2 1982–1990: the first years of MDT implementation

MDT coverage

As described in section 6.1, the introduction of MDT was the top priority for LEP from the time of the Study Group meeting, and the programme spared no effort in putting MDT into practice with the full participation of all concerned. In just a few years, from 1982 to 1985, it was consequently possible to demonstrate, in a number of projects all over the world, that leprosy control based on MDT was entirely feasible, despite certain operational constraints that could not always be resolved.

During the next five years (1986–1990), geographical MDT coverage increased to more than 50% globally (see section 3.1). While this was fairly satisfactory, it is important to recognize that the numbers of cases reported to have been cured by MDT over that period included some patients under long-term dapsone monotherapy.

Although the geographical coverage increased fairly rapidly in the countries of south-east Asia and in western Pacific regions, most African countries and Brazil were rather slow in applying MDT. It is also clear that the countries/areas covered by MDT during these early years of implementation were those where operational conditions were the easiest. Later, in the early 1990s, there was some evidence of "stagnation" in MDT implementation (see under section 6.3), which gave rise to the initiative of resolution WHA 44.9.

Technical aspects

During the 1980s, almost no technical change was made to MDT policy, with the exception of 1987, when the WHO Expert Committee recommended that, for the purposes of MDT, all smear-positive cases should be included in the MB group.

This same decade saw increasing evidence of the robustness of the Study Group MDT regimens.

The reasons for success

The MDT regimens recommended by the 1981 WHO Study Group were in general readily accepted by all concerned patients, communities, health personnel, government authorities, NGOs and other supporting agencies. The reasons for this wide acceptance were that:

- The regimens responded to a felt need.
- Their effectiveness, safety, practicability, and acceptability were rapidly apparent and, in the course of time, convincingly demonstrated.
- In response to the need for complete reorganization of leprosy services required for MDT implementation, all inputs and supports, whether political, technical, or financial, were made available simultaneously – by governments, WHO, international and national NGOs, funding agencies, etc.

Critical factors in the implementation of MDT included the efforts made by the governments concerned in committing themselves to the new technology, and the tremendous work undertaken by national leprosy and health services, and their personnel at all levels, to effect the technical and administrative changes required by the new methods. Of particular importance were the retraining of all staff in the use of the new methods of treatment, and the information and education given to communities on the various practical aspects of MDT.

Conclusion

That all required elements for the successful implementation of MDT (good, practicable technology responding to a felt need, wide acceptability, strong political commitment, adequate technical back-up, and generous financial support) could be made available concomitantly and conveniently.

7.3 1991–2000: elimination strategy

Resolution WHA44.9 and plan for elimination of leprosy as a public health problem

It appears that the concept of eliminating leprosy as a public health problem – that is, identifying and treating with MDT *all* leprosy patients, until prevalence is reduced to a very low level – was first proposed, with a slightly different content, in the WHO Regional Office for the Western Pacific. Noteworthy, too, is that the elimination initiative was recommended by the WHO Executive Board and the World Health Assembly without a WHO Expert Committee meeting, Study Group, or other preparatory step. It may have been felt that a technical meeting was likely to express some reservations about the elimination concept, whereas a WHA resolution proposing a relatively simple objective could be readily adopted and would also have a greater impact on governments and other interested parties.

The elimination strategy included exactly the same technical components as the MDT-based leprosy control strategy, from which it differed in only in two respects – a time limit (the year 2000), and a target (prevalence below 1/10 000 inhabitants). It was rightly expected that these two conditions would ensure both intense commitment and dynamic action on the part of all partners.

Implementation of the elimination strategy

Overview

The period from 1991 to 2000 was marked by comprehensive, intense, and dynamic efforts to solve the problems related to the expansion of MDT coverage to increasingly difficult-to-reach geographical areas or population groups.

In the first years following the adoption of resolution WHA44.9, the response at country level was less positive than had been hoped. In 1994, however, The Nippon Foundation's promise of US$ 50 million for the purchase of drugs, in addition to technical and operational improvements, notably the leprosy elimination campaigns (LECs), resulted in a marked increase in the extent and efficiency of field activities, with the geographical MDT coverage ultimately reaching 100% in 1997. Sadly, bad news followed shortly afterwards. By 1998, it had become clear that some countries would have to continue their elimination activities beyond 2000.

With the publication of the WHA resolution and the elimination plan, a number of questions and criticisms had been raised by some WHO partners and leprosy experts. During implementation of the elimination strategy, WHO introduced a number of changes and simplifications in technical and operational procedures, with the objective of facilitating and accelerating the elimination plan. These modifications gave rise to further questions and criticisms, notably from ILEP. Over the years, despite the elimination strategy resulting in the cure of millions of leprosy patients, it appears that WHO did not respond in a wholly appropriate manner to such issues, and growing dissent led in the late 1990s to the crisis that has been summarized in section 3.1.

Main elements in the implementation of the elimination strategy

Strong political and financial commitment

It is probably safe to say that resolution WHA44.9 was most welcome in WHO: it responded to the wishes of the Director-General, Dr Nakajima who, as Director of the Regional Office for the Western Pacific, had proposed a similar concept in the late 1980s. Dr Nakajima was also able to secure from The Nippon Foundation – to which he had close ties – important additional financing that, together with other grants, provided the needed impetus to the elimination plan. This close cooperation between WHO and The Nippon Foundation was given prominence, particularly on the occasion of the first and second International Conferences on Leprosy Elimination. By the time of the third International Conference, however, the elimination effort was experiencing some difficulties.

Member associations of ILEP – with the exception of the German Leprosy Relief Association, which was supporting the use of the rifampicin/Isoprodian® combination – were in favour of WHO MDT, although they were most insistent on a number of prerequisites for its implementation, particularly in the early years. They had two principal reservations about the elimination plan:

- the definition of "a case" of leprosy recommended by the WHO Expert Committee on Leprosy at its sixth meeting in November 1987, and its implications (see section 5.2);
- fear that an over-optimistic interpretation of the elimination concept would have a negative effect on their fundraising activities.

Nonetheless, they made a most important contribution to the elimination strategy, described in section 5.2.

Simplifications in technology and additional strategies

As discussed in section 3.1, a number of simplifications were introduced in the technical procedures used in the elimination strategy, particularly in many aspects of MDT (regimens, rules for classification of patients, use of skin smears, post-MDT surveillance, etc). These procedural simplifications were made with the ultimate aim of getting more patients treated with MDT. In some instances, the prescribed changes in policy merely reflected simplifications in working methods that had been put into practice by field staff lacking certain skills; a typical example concerned skin smears examinations, which were regarded as extremely important during the 1980s but as unnecessary by the late 1990s.

In an effort to identify "hidden" prevalence, two new strategies were launched in 1995 – the LECs and the Special Action Projects for the Elimination of Leprosy (SAPELs). The LECs proved to be a highly effective tool for the identification of hidden cases provided that new patients were identified by staff of general health services.

Two general strategies that had rightly been considered of crucial importance from the start of MDT implementation received increasing attention during the elimination period. One was the integration of MDT services into general health services; the other was information, education, and communication (IEC) activities aimed at changing attitudes towards leprosy at community level. Even today, further improvement in these two strategies is needed in many countries – probably because this kind of change requires long-term actions, including significant political and administrative efforts, but the period of the elimination strategy has been relatively short.

Programme intensification and monitoring given special attention (see section 3.1)

The WHO global level was substantially reinforced in December 1994 and two successive advisory groups comprising representatives of all parties concerned were monitoring the progress of the elimination plan at all levels (particularly at country level) and proposing solutions for the current operational problems. These advisory groups were assisted by three or four task forces. However, information on operations in some countries, particularly large countries such as Brazil and India, did not always reach WHO by the required deadline.

Position in 2000

More than 12 million leprosy patients were cured as a result of the implementation of MDT-based leprosy control (1982–1990) followed by the elimination strategy (1991–2000). By the end of 2000, however, the overall prevalence for the 12 top endemic countries was still 4.1 per 10 000 inhabitants, and in 1999 it had already been decided to push back the elimination target date to 2005. In addition, 600 000 to 700 000 new cases were still being identified annually worldwide. The following conclusions can be drawn:

- Given the stagnation in MDT implementation in the late 1980s and early 1990s, the elimination strategy was absolutely necessary to reinforce MDT-based leprosy control if the approach was to achieve maximal efficiency.
- The number of patients cured has been increasing over the years and remains a strong *a posteriori* justification for the elimination strategy.
- The fact that the overall prevalence in the 12 most highly endemic countries was still 4.1 per 10 000 inhabitants and up to 700 000 new cases were still being identified annually worldwide was a matter of great concern and one that continues to merit investigation. The paradoxical trend in case detection observed in recent years in some countries, notably India, is particularly deserving of urgent and comprehensive investigation.

7.4 2000 onwards: the final push

While the main elements of the 2000–2005 strategic plan for the final push towards elimination of leprosy remained unchanged, i.e. integration of MDT services into the general health services, and full IEC for communities, new proposals were made for the strengthening or reinforcement of these approaches (see section 3.1). Given that all elements had been already included in the strategy for elimination since 1991 (and to some extent since the late 1980s), it has to be concluded that the progress made in relation to integration and IEC has so far not met the expectations, probably for the reasons explained above.

A recent recommendation from the WHO Technical Advisory Group (TAG) (now responsible for programme intensification and monitoring) is that efforts should be made to persuade national governments to accept "ownership" of their elimination programmes at national and sub-national levels. The lack of this sense of ownership of leprosy activities on the part of some governments may be the result of these activities having been run too exclusively by foreign agencies, with insufficient participation by national authorities. It goes without saying that such situations should be improved.

In 2001, a TAG subgroup recommended that a number of subjects – integration, relapses following 12 months' MDT in MB patients, ROM, impact of IEC, SAPELs, etc. – be investigated in studies initiated by WHO. From this, it can be inferred that there is some continuing difficulty in evaluating the impact of most of the procedures included in the elimination strategy. It remains urgent to carry out the recommended investigations, especially to reveal the impact of the various simplifications and changes effected during the previous decade.

In 2002, TAG extended the list of procedural simplifications, adding the extended use of accompanied MDT, and a field study on the use of 6 months' MB MDT regimen for all leprosy patients.

It can be estimated that up to now more than 14 million leprosy cases have been cured. Among the 12 countries that have not reached the elimination target some – notably Brazil and India – are at risk of missing even the 2005 target, largely, it would seem, because integration of leprosy services into general health services continues to be inadequate. If the target date is pushed back yet again, increasing doubts about the feasibility of the elimination plan are likely to arise.

7.5 Current concerns

The elimination strategy is clearly a significant success at national level in most leprosy-endemic countries. However, the time required to reach the elimination prevalence target in some of the most highly endemic countries, notably Brazil and India, and at the sub-national level – where the core of the problem lies – in many countries, remains uncertain.

While the elimination strategy has progressed satisfactorily in many countries, at the global level, since 1998–1999, a crisis has developed between WHO and two of its partners in GAEL – ILEP and TNF – and, more recently, ILA. As reported recently in a so-called independent evaluation, it appears that these three agencies are questioning WHO's leadership not only in implementation of the elimination strategy but also in technical guidance to governments and in research promotion. One of the main contributory factors is quite possibly the critical dependence of leprosy activities on JSIF/SMHF and, to a lesser extent, ILEP as a consequence of the generous support provided by these agencies over the past 25 years or so. In addition, ILEP makes the point that changes and simplifications in the elimination strategy were introduced by WHO without majority agreement from the Organization's partners.

Encouragement and financial support for research related to leprosy were steadily reduced, notably in TDR, probably because the elimination strategy was seen as *the* solution to the leprosy problem. This resulting decline in research is most regrettable, particularly in view of the current uncertainties on the future of the elimination plan. Research in leprosy needs to be stimulated, and it is especially important that the new perspectives provided by the recent sequencing of the *M. leprae* genome should not be missed.

Over the past 25 years or so, the tremendous developments in the WHO leprosy programme – IMMLEP, THELEP, MDT, and the elimination strategy – meant that effective treatment could be made available to all patients everywhere. The Organization's partners made, and continue to make, outstanding contributions, and WHO continues to have a critical role.