Multidrug therapy against leprosy

Development and implementation over the past 25 years

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* * * * * * * * * *

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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
Director, TDR

Geneva, October 2003

References

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: “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.

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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

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 in 1972 (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


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 IMMELP 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
