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”.

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References


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. 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).

References
### Appendix

**List of current ILEP Member Associations**

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<tr>
<th>Acronym</th>
<th>Full Name</th>
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<td>Aide aux Lépreux Emmaüs-Suisse</td>
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<td>American Leprosy Mission</td>
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<td>Deutsches Aussätzigen-Hilfswerk</td>
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<td>Damien Foundation, Belgique</td>
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<td>Fondation Luxembourgeoise Raoul Follereau</td>
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<tr>
<td>FO</td>
<td>Fondation Père Damien, Belgique</td>
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<tr>
<td>LEPRA</td>
<td>British Leprosy Relief Association</td>
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<td>Netherlands Leprosy Relief Association</td>
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<tr>
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<td>SF</td>
<td>Fontilles, Lucha contra la Lepra</td>
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