Lepr Rev (2012) **83,** 221–240

EDITORIAL

The chemotherapy of leprosy: An interpretive history

ROBERT H. GELBER* & JACQUES GROSSET**
**University of California San Francisco, California, USA*
***John Hopkins University, Baltimore, Maryland, USA*

Accepted for publication 14 July 2012

The Sulphone Monotherapy Era

The introduction of effective antimicrobial treatment for leprosy, first with the sulphones by Faget[1] in 1943, was the major scientific development of the twentieth century to actually alter disease course and provide patients reason to hope. Initially promin and solapsone, injectable sulphones, were utilised, but these injectables were soon abandoned for oral dapsone which had the additional advantages of providing superior plasma levels, being generally well-tolerated and exceptionally inexpensive (US $1/year for the standard adult dose of 100 mg daily). From that time to the general application of multidrug therapy, largely in the 1980 s, monotherapy with dapsone became the standard of care throughout the world. On this treatment new leprous lesions ceased appearing and further neuropathy generally was prevented. Early diagnosis and the institution of dapsone therapy were hugely successful where applied.

As early as the 1950 s it was observed that lepromatous leprosy patients treated for several years relapsed if treatment was stopped when they were still skin-smear positive at treatment cessation, and a policy was adopted of continuing dapsone therapy for 1 year after skin-smear negativity was attained.[2] Yet the outcome in these MB patients was disappointing, almost half becoming smear-positive and more than 25% showing signs of clinical relapse.[2] Furthermore, several clinical investigators noted that generally a duration of dapsone monotherapy for lepromatous leprosy of 5 of so years frequently resulted in disease relapse after the cessation of treatment.[3] Thus for lepromatous leprosy lifelong sulphone therapy was generally recommended. In much of the developing world where leprosy was endemic, then and even now, a medical infrastructure and the availability of a reliable and motivated drug delivery system, especially one that could be depended upon for the provision of lifelong therapy, were often either nonexistent or unreliable.

Correspondence to: Robert Gelber (Tel: 00-1-415-454-8765; e-mail: ikgelber@hotmail.com)

0305-7518/12/064053+20 $1.00

The Tropical Disease Research (TDR) and the Therapy of Leprosy (THELEP) Eras

In 1975 Shepard, Gelber, and Levy presented a position paper on leprosy chemotherapy to Sansaricq, the director of the leprosy branch of the World Health Organization, Geneva. That paper ushered in the First Scientific Working Group of the TDR (Tropical Disease Research Program) – THELEP (for Therapy of Leprosy). The paper identified two problems confronting successful treatment of leprosy patients, namely drug resistance and bacterial persistence. In 1975 dapsone monotherapy remained virtually the only treatment utilised to treat all forms of leprosy world-wide. At that time, despite the fact that rifampicin had already proved decidedly more active than dapsone both in mice and clinical trials it had not yet been incorporated into the therapy of leprosy.

Though secondary dapsone resistance, resulting in relapse in dapsone-treated patients was suspected clinically in the 1950 s, it was only confirmed in 1964[4] after the emergence of the mouse footpad technique in 1960.[5] The largest survey for secondary dapsone resistant relapse occurred in one of the largest leprosaria in the world, Sungi Buloh, Malaysia,[6] where 100 patients treated with sulphone monotherapy relapsed clinically (2·5% of MB patients) with strains of *M. leprae* which could be confirmed to be resistant to dapsone in the mouse footpad, mostly high level resistance, (0·01% dapsone in mouse chow). Such a low rate of resistance was quite surprising in lieu of the rather regular resistance obtained in pulmonary tuberculosis in adults treated with monotherapy. This is particularly true because dapsone is primarily bacteriostatic, lepromatous leprosy has the highest bacterial burden of all human bacterial diseases and is associated with *M. leprae*-specific cellular immune defect which is not generally the case in pulmonary tuberculosis. It is noteworthy that almost all patients in Malaysia[6] who relapsed with dapsone resistant-organisms began their treatment with dapsone twice weekly or the injectable sulphone, solapsone, which resulted in considerably lower plasma levels of dapsone, and all were lepromatous. Furthermore, in the Malaysian monotherapy cohort, lepromatous leprosy patients who were treated with solapsone relapsed with dapsone-resistant organisms at a considerably higher rate (8%) than those treated with dapsone.

Because patients treated at Sungi Buloh were hospitalised for the duration of their treatment in a well-organised programme, many other locales found considerably higher frequencies of dapsone resistant relapse. Ji[7] reviewed the relative risk of developing secondary dapsone resistance in several countries, and found in all locales surveyed that dapsone resistance was prevalent and mostly of high-level (0·01% in mouse chow-equivalent to 100 mg in man). In Costa Rica, it was found that 6·8% of lepromatous patients developed dapsone resistance when treated with sodium glucosulfone (promin), which like solapsone results in dapsone blood levels considerably lower than when patients are treated with full dosage dapsone.[8] In Ethiopia, Pearson[9] reported that fully 15% of lepromatous leprosy patients developed dapsone resistant relapse. When those Ethiopian strains were tested in the mouse footpad, unlike most other locales, the large majority were resistant to only 0·0001% dapsone in mouse chow and not higher levels. Likely, the problem of the high frequency of secondary dapsone resistance encountered in Ethiopia was a consequence of the practice there of initiating dapsone therapy at 10 mg weekly and gradually increasing it over the next 6 months to a maintenance level of 200 mg weekly, thereby selecting relatively low grade dapsone-resistant strains. In summary, the surprising findings of the prevalence of secondary dapsone-resistant relapse is not that it occurred, but only occurred at a low frequency, which

was especially low when given in the most ideal settings as in Malaysia, and did not occur in all patients.

Of even greater concern to the Scientific Working Group of the WHO which began its deliberations in 1977 was that secondary dapsone-resistant relapse cases seemed to be spreading their bacilli to previously untreated individuals, and primary dapsone resistance was beginning to be recognized. Of greatest concern to the scientific working group was that fully half of untreated lepromatous cases in Ethiopia were found to harbour *M. leprae* resistance but almost entirely to 0·0001% in mouse chow and not higher levels.[10] Again, this may have been ultimately a consequence of the selection of relatively low grade resistant *M. leprae* strains as a by-product of the low doses of sulphones employed in that locale. Furthermore, though it had been found earlier that wild strains of *M. leprae* were generally sensitive to between 0·00003% and 0·001% of dapsone in mouse chow, few strains required somewhat higher levels of dapsone for growth inhibition.[11] Recent genetic analysis which has demonstrated mutations of the fol 1b gene responsible for dapsone resistance to 0·01% dapsone and 0·001% dapsone, did not find mutations which produce resistance to 0·0001% dapsone and not higher levels.[12] Also, the vast majority of 'primary dapsone resistance' observed in several countries up to 1985 were only resistant to 0·0001% dapsone in mouse chow but not higher levels.[7] A recent report from Cebu in the Philippines using genomic analysis has found mutations in the fol 1b gene in untreated lepromatous leprosy patients to be quite rare and largely confined to a village adjacent to the leprosarium where a large proportion of the population were previously treated leprosy patients, some with monotherapy dapsone.[13] In the late 1970 s Jacobson[14] reported that in Carville, Louisiana, there were several untreated lepromatous leprosy patients harbouring *M. leprae* which was found resistant to 0·001% and even 0·01% dapsone; however, subsequently at that institution that experience could not be replicated, and primary dapsone resistance was not found again. We conducted the largest survey for primary dapsone resistance utilising the mouse footpad to evaluate drug sensitivity in *M. leprae* in all lepromatous leprosy patients encountered in San Francisco over several years. These patients were immigrants who had obtained their organism in quite a number of countries. We[15] found in those 101 patients that all of their *M. leprae* were susceptible to all three levels of dapsone except in one patient from the Philippines where the strain was resistant to 0·0001% dapsone in mouse chow but not higher levels, again this being in the range of susceptibility of some wild strains. In short, primary dapsone resistance in retrospect appears to be exceedingly rare and only largely to a level of dapsone which is seen in some wild strains and for which no relevant mutation has been established. In any event, 0·0001% in mouse chow produces plasma levels equivalent to what is obtained in man by 1 mg of dapsone and would prove clinically irrelevant to patients treated with the usual 100 mg daily dose generally employed.[16] In summary, the prospect that multidrug therapy for leprosy was required in 1982, owing to the significant problems of not only of secondary but primary dapsone resistance, now does not appear totally convincing. Though secondary dapsone-resistant relapse is rare if dapsone is maintained at full dosage as was done in Malaysia, which is generally not feasible, giving weight to the need for one or more other agents where regular treatment cannot be assured, while primary dapsone resistance appear to be largely nonexistent. As acquired dapsone resistance was of considerable concern, the only means to reliably prevent drug resistance in treated patients was to use drug combination therapy as in the treatment of tuberculosis.

The other concern of the scientific working group in 1977 was the problem of persisting *M. leprae* ('persisters') despite significant durations of antimicrobial therapy. In Malaysia,

seven of 12 lepromatous patients treated with 10–12 years of dapsone were found to harbour viable dapsone-sensitive persisters, in at least one of the following four sites: skin, peripheral nerve, skeletal muscle, or dartos muscle.[17] Soon thereafter we[18] found that even 5 years of rifampicin did not eliminate these persisters in 20 out of 32 patients when the same four tissues were evaluated for *M. leprae* viability in the mouse footpad.

Of course the issue for the treatment of leprosy patients is the propensity that these persisters pose for clinical relapse. The fact that 'persisters' may result in clinical relapse was not a new phenomenon and was recognized, as was noted previously, as early as the 1950 s. By 1977, most experienced clinicians had seen lepromatous patients treated with single or multiple agents for years who relapsed after therapy had been interrupted, but little information was available concerning the magnitude of that risk. Evidence that bacterial persistence might be a problem in the treatment of lepromatous leprosy, also, came from a study of the Karimui of Papua New Guinea in which five of 28 lepromatous patients were found to have solid-staining bacilli (indicative of live bacilli) in their skin smears despite regular treatment with acedapsone for 3–5 years and expected blood sulphone levels.[19] Furthermore, in what was at that time a controversial therapeutic leap, the director of the leprosarium at Sugai Buloh, Bhojwani, discontinued dapsone monotherapy in 362 polar lepromatous and borderline lepromatous patients who had been treated for 18·5 to 22 years and were for several consecutive years skin smear negative. In these patients it was found that 25 patients (8·6%) relapsed over the next 8–9 years, beginning in the first year and at a steady rate of 1% annually.[20]

The aforementioned studies present evidence that following sulphone monotherapy persisters have the propensity to result in relapse disease. Perhaps multidrug therapy, including rifampicin, would reduce that risk. In a trial in Malta rifampicin, dapsone, prothionamide, and isoniazid therapy for a total of 18–24 months prior to discontinuation was claimed to result in no clinical relapse over a 4-year follow-up.[21] Unfortunately, the type of leprosy treated in Malta was largely unknown, and most patients had received monotherapy dapsone for many years previously.

The goals of the scientific working group of the WHO in its many deliberations and funding focused on chemotherapy in animal models and clinical trials which were almost exclusively devoted to better evaluate the four available effective antimicrobials, dapsone, rifampicin, ethionamide/prothionamide and clofazimine, alone and in combination. Thus, in 1977 and for the next several years thereafter, the WHO sponsored several studies to enlarge our knowledge of chemotherapeutic agents for the treatment of leprosy. The largest of these was a multidrug therapy trial in lepromatous leprosy patients who were treated for 2 years with five separate regimens and was conducted in but 39 patients.[22] This study monitored the presence of *M. leprae* viability in mice from skin biopsies obtained at 3, 12 and 24 months after the initiation of therapy. Regimens consisted of a variety of combinations which always included some rifampicin, but at various doses and frequencies of administration, together with one or more other agents — dapsone 100 mg, clofazimine 100 mg, and prothionamide 500 mg each administered daily. Owing to the small number of patients in each treatment arm, conclusions were hard to reach, but each regimen resulted in 'persisters,' approximately 9% of the time irrespective of regimen or duration of therapy. It is noteworthy in the introduction to the publication of those findings that it was stated: "At that time because it appeared likely that relapse-rates would be unacceptably high, as a consequence of the ubiquity of persisters, it was considered unethical to conduct clinical trials in which chemotherapy of patient with lepromatous leprosy was deliberately used and relapse-rates

subsequently measured. Therefore, the Planning Committee could not undertake to measure the risk to patients presented by the persisting *M. leprae*."

In another important study sponsored by THELEP in that era[23] we compared the *M. leprae* viability obtained from treated patients of 5×10^3 *M. leprae* injected into normal mouse footpads and of on average 10^6 *M. leprae* inoculated in the footpads of the immune-suppressed neonatally thymectomized Lewis rat (NTLR). Groups of seven to eight patients each were treated with either an initial dose of rifampicin 1500 mg and daily dapsone for 1 month or weekly rifampicin 900 mg and daily dapsone again for a 1-month duration. From the previous experience with the rapid kill of *M. leprae* in lepromatous patients treated with rifampicin, it is not surprising that in these studies biopsies taken in the first few days, 1 week, 2 weeks and 4 weeks later rather regularly did not grow in normal mice [two of 54 biopsies (4%)]. From these same biopsies 30 of 58 (52%) grew in NTLR. These findings established that the NTLR is a more sensitive model for the detection of persisters. In these studies no statistically significant difference in viability between the two rifampicin schedules was noted. While the rifampicin 1500 mg dose had not been utilised to any significant extent and hence could not be considered a candidate dose in the treatment of leprosy, the unique opportunity to establish herein if daily rifampicin was superior to intermittent was discouraged, perhaps owing to the fact that daily rifampicin would prove prohibitively costly for most locales where leprosy was endemic. Anyway the unique opportunity to evaluate whether daily rifampicin therapy was or was not superior to intermittent rifampicin was lost. This issue to this day still remains unresolved. Unfortunately after this work the NTLR model to monitor clinical trials was abandoned.

Several overwhelming issues were self-evident from the beginning of THELEP's Scientific Work Group:

(1) In particular, in much of the developing world, where leprosy was endemic the medical infrastructure that would insure life-long drug supply was not everywhere available. Thus the success of leprosy control programs necessitated treatment control regimens of a limited and finite duration.

(2) Though rifampicin had been found highly bactericidal for *M. leprae* in mice and leprosy patients as early as in 1970[24] and consistently so in other clinical trials,[25,26] it had been used sparingly in patients largely owing to its cost of $1/day. However, rifampicin was felt absolutely necessary to any new treatment regimen. Owing to concerns with sulphone resistance and the success of multidrug therapy in tuberculosis, rifampicin's inclusion in a multidrug regimen was considered required in the future treatment of leprosy. However, daily administration of rifampicin would prove prohibitively expensive in most leprosy endemic locales.

(3) Because of the perception that owing to the prevalence of dapsone resistance, combined therapy with only rifampicin and dapsone could result in rifampicin monotherapy and thus not be relied upon. Hence a third agent, would be required in addition to dapsone and rifampicin, for any new regimen to treat MB leprosy in order to overcome the risk of rifampicin monotherapy in case of dapsone resistance, that could lead to selecting rifampicin resistant *M. leprae*. Since clofazimine and ethionamide/prothionamide were the only effective agents available at the time, one of them by necessity would be required in any recommended regimen for multibacillary (MB) leprosy. Owing to ethionamide's hepatotoxicity, likely emphasised by the concomitant use of rifampicin, as well as its frequent GI intolerance, clofazimine became the agent of choice — though

in its first recommendation, but not later ones, the WHO allowed the substitution of ethionamide/prothionamide as an alternative, especially for lighter-skinned individuals where skin discolouration would be cosmetically objectionable.

(4) The WHO had no obvious remedy for the risk posed by persisters and held the hope that their risk to result in relapse would prove minimal.

Some, including Gelber, objected early on to 2-year MDT for MB leprosy, fundamentally on the basis that how can worldwide treatment recommendations be made without prior supportive clinical trials monitored by relapse rates. However, the previously described arguments for MDT were felt by the majority of the Scientific Working Group sufficiently compelling to advocate its implementation. It is important to note that the WHO MDT regimen was always entitled 'Chemotherapy of Leprosy for Control Programmes.'[27] This implied that it was not to be considered to be a recommendation where alternative and even superior regimens could be implemented, and even lifelong therapy were economically feasible. At no point during multiple meetings of THELEP during the late 1970 s and early 1980 s was the prospect of chemotherapy as a tool to eliminate leprosy ever entertained.

Thus in 1982 the WHO[27] recommended that for adults with paucibacillary (PB) leprosy ($BI < 2$) treatment of 6 months duration with rifampicin (600 mg) supervised monthly plus dapsone (100 mg) unsupervised daily.

The recommended standard regimen for adults with multibacillary (MB) leprosy ($BI \geq 2$) for 2 years or up until smear negativity was:

Rifampicin:	600 mg once a month, supervised;
Dapsone:	100 mg daily, self-administered;
Clofazimine:	300 mg once a month, supervised, and
	50 mg daily, self-administered.

The recommendations in 1982 of WHO MDT were after some delay strongly endorsed both by national public health policies and established nongovernmental organisations. Furthermore, WHO MDT was enthusiastically supported by leprosy treatment programmes and implemented worldwide almost without exception. Though difficult to substantiate critically, it was repeatedly maintained and likely true that with the introduction of WHO MDT leprosy programmes and governments were energised and mobilised, programmes revitalised, and morale among patients and healthcare workers improved. Surely the promise that an often incurable disease had been replaced with what was thought to be a reliably curable one provided profound motivation to both leprosy providers and patients. However, because leprosy disabilities, which are primarily consequent to neuropathic processes, generally were obtained prior to the initiation of chemotherapy, there was little hope that MDT would have much impact here. Naysayers to WHO MDT on whatever basis were considered pessimistic heretics. Little or no problems with implementation of this treatment strategy was publicly acknowledged, including side effects/ toxicities, while compliance and completion of therapy were never conceived problems. Furthermore, large-scale clinical trials assessing outcome and in fact relapse potential were not recommended and sponsored by the WHO.

Outcomes of WHO MDT

Ultimately, the measure of the success or failure of WHO MDT for individual patients rests squarely on whether treatment results in cure or relapse. To complicate this matter further relapse in treated patients may be a consequence of persisters or reinfection with a new strain of *M. leprae*. Though currently advances in strain differentiation in *M. leprae* are now available which could answer this question, fixation and embedding tissues in paraffin does not allow by current methods the performance of strain differentiation from that source, and hence the distinction between relapse and reinfection has not yet been possible. Also, there is no generally recognized definition of what comprises a relapse either for PB or MB patients. For patients near the tuberculoid pole (mostly PB) there are rarely demonstrable organisms, and hence relapse hinges on clinical grounds alone with the complication that actual relapsed leprosy and late Type 1 reactions are often difficult to distinguish from one another. Published studies of MB relapse do not utilise uniform criteria for what actually constitutes a relapse. Criteria for relapse focused on one to a few of the following observations: new or growing lesions, an increase in bacteriologic index (BI) at any site (generally 2+ or more) and growth of *M. leprae* in the mouse footpad. Studies on the frequency of relapse in MB patients are difficult to compare as some require but one of these three outcomes, some two, and some all three. Also, the rates at which relapse occurred in different studies are affected by the actual duration of patient follow-up. Unfortunately, in most locales skin smears are no longer performed and footpad facilities largely unavailable. Though in some studies relapsed lesions regularly contain *M. leprae* which multiplies in mice, persisters without demonstrable relapse may confound that issue.

PB leprosy often heals spontaneously, some reporting 70% of the time. Nonetheless, WHO MDT for PB leprosy of 6-month duration has generally been reported to perform well.[28–31] This is not surprising as both dapsone resistance in the monotherapy era and relapse from persisters were almost entirely confined to BL/LL (MB) leprosy. Of particular interest is that in the Philippines 66 PB patients, mostly BT, who were treated with WHO MDT and followed-up for a mean of 11·3 years thereafter resulted in two late relapses at 8 and 12 years after treatment ceased. It is noteworthy in that study 6 months of monthly rifampicin (600 mg), ofloxacin (400 mg) and minocycline (100 mg) (ROM) performed equally well. Those 58 patients followed-up for a mean period of 12·8 years resulted in only one relapse, 3 years after treatment was discontinued. On the basis of a multi-centric double-dash-blind field trial in India in single lesion PB leprosy single dose ROM proved marginally superior to standard MDT PB therapy[32] and was recommended by the WHO in 2002 as an alternative to 6-month PB treatment for single lesion PB leprosy.[33]

In the largest MB cohort followed regularly after the completion of 2-year MDT and for the longest time, relapse frequencies which were found not to be low were three times higher when patients were followed by seasoned leprologists rather than well-trained healthcare workers.[34,35] In that cohort relapse was defined as the development of new leprous lesions and an increase of BI of 2+ or more. Lesions from all relapse patients contained viable *M. leprae* which grew in the mouse footpad. Of the 23 relapses all were found sensitive to rifampicin and clofazimine therein, and only one resistant to high-level dapsone. In that study the first relapse occurred 6 years after the completion of therapy, eight relapsed between 6 and 9 years after therapy was discontinued, while 15 relapses occurred 10 or more years after, the final one noted a full 16 years after MDT was discontinued. It is noteworthy that all patients but one who relapsed had an initial average bacterial index of $\geq 2{\cdot}7$ (4 or more skin sites) and all

but two became smear negative prior to relapse. In the Philippines of MB patients with a BI of at least 2·7 who were followed up for 12 for more years by seasoned leprologists, 21% relapsed. The BI from relapse lesions was generally not merely marginally elevated, but in the vast majority $4-5+$.

Also, in patients treated with 2-year WHO MDT, the Marchoux Study Group[36] (Mali) reported after a mean follow-up of just 5 years that both clinical and bacteriologicial relapse occurred in 20% (7/35) of MB patients, and 39% (7/18) with a pre-treatment BI $\geq 4+$. Furthermore, in Agra, India, after 2-year WHO-MDT and a mean follow-up of 4 years, bacteriological, but not clinical, relapse was detected in 7% (20/260) of MB patients and 17% (18/107) in those with a pre-treatment BI $\geq 4+$.[37] It is noteworthy that in previously conducted clinical trials for pulmonary tuberculosis designed to established effective short-course regimens, relapse rates greater than 5% were considered unacceptable.[38–40] Furthermore, Shetty[41] recently presented findings of 62 referrals cases of relapsed leprosy in Mumbai, mostly treated with WHO-MDT and some who were PB. Thus there is considerable evidence that, particularly MB patients, are at risk for relapse, and in some studies at an unacceptably high level.

Though after 18 years of dapsone monotherapy and when treatment is discontinued, relapses begin to occur in the first year and occur at 1% per year for the succeeding 9 years,[20] there was considerable evidence, as long ago as 1989,[42] that when rifampicin is part of the regimen for MB leprosy relapses, as were found in the Philippines,[34,35] begin considerably later. In 1989, Grosset *et al.*[42] reported 39 patients treated with rifampicin, generally as monotherapy for presumptive dapsone-resistance and found that relapse was obtained on average 8 years after the initiation of therapy, 22 rifampicin-resistant and 17 rifampicin-sensitive. A similar experience was reported by Pattyn[43] after a 6-week intensive quadruple regimen (rifampicin, ofloxacin, dapsone, and minocycline), wherein relapses were first detected at 6 years with a doubling in years 8 and 9. The Marchoux Study Group[36] found that MB relapse after 2-year WHO MDT occurred at a mean of $6 \pm 1{\cdot}5$ years after the completion of therapy, while in Agra, India, where relapses were defined on bacteriologic grounds about 30% of the time without concomitant clinical manifestations, the average time to relapse was four years.[37] It is noteworthy that the Marchoux Study Group[44] first reported that when follow-up after the completion of therapy averaged only 3·5 years, the relapse rate was low, 2·9% which prompted Ji to feel that 2-year WHO MDT might reasonably be reduced to 1 year. However, he[45] reversed that view when noting in the aforementioned longer follow-up period that relapse occurred in fully 20% of MB patients and 40% in those with a BI >4.[36] Also in Agra, relapses were significantly higher in those MB patients followed up greater than 4 years than in those followed up for a lesser duration.[37] Finally, in Karigiri, India, the two relapses detected in MB patients were found 14 and 15 years after the completion of 2-year MB therapy.[46]

In 1982[27] and again in 1988[47] the WHO recommended that MB patients be followed-up for 5 years after the completion of therapy. In fact at the International Congress of Leprosy in Florida in 1993, the Expert Committee on Chemotherapy chaired by Waters noted a significant number of relapses between 5 and 10 years after therapy was discontinued, particularly those found in Africa, and recommended follow-up of MB leprosy for an increased duration, 10 years.[48] It is noteworthy that in 1994, but a year later, the WHO, with the confidence that MDT for MB leprosy was regularly successful, recommended no follow-up for MB patients after the completion of treatment.[49] It is important to realize that a fall in BI in MB patients, generally one unit/year, occurs at a rate that is unrelated to the

potency of anti-leprosy therapy, and that for MB patients neither the rate of fall of BI nor attaining smear-negativity can be useful in predicting success or failure of a regimen, i.e. relapse. Only actual relapse rates which require very long follow-up, as much as fifteen years, can reliably serve that purpose.

There is certainly contradictory data demonstrating that relapse rates following 2-year WHO-MDT for MB leprosy is low. However, these studies are wanting on several grounds, particularly, that data was either based on questionnaires, a short duration of follow-up, or a low percentage of patients with a high bacterial burden.

A study from Karigiri, India,[46] in smear positive MB patients followed up for 16·4 ± 1·8 years showed a low relapse rate (two of 84; 2%) in MB patients, but that study admittedly had features that would prejudice towards that outcome: only 12% of those patients had an initial BI $\geq 3+$; approximately half of the MB patients put on therapy could not be followed-up; those patients not amenable to follow-up had a significantly greater percentage of borderline lepromatous (BL) and LL patients, and a higher initial BI; additionally many of these patients had received prior dapsone monotherapy, and more than half of the patients received more that 2 years of MDT, being treated until smear negativity. Nonetheless, in that study, 20% of patients with a BI $\geq 3+$ relapsed.

Gebre *et al.*[50] found no relapses in 256 MB patients treated with 2-year MDT followed up by experienced healthcare workers, not seasoned leprologists. Unfortunately, follow-up was short-lived – only 38% of patients completing 5-year surveillance, 97 total cases and 20 cases with a BI of $>4+$.

Finally, there is only one significant published study on relapse in MB patients treated with 1-year MDT.[51] In that study it was reported that only one relapse occurred in 300 MB patients. Unfortunately, the mean follow-up was only 6·4 years, a period when in the same locale (Cebu) following 2-year MDT, MB relapse had just begun.[34,35] Even more unfortunately, that study was discontinued at that time without further follow-up planned.

Changes in MDT MB Therapy Duration and Classification of MB/PB Leprosy

In 1998,[52] not based on data from clinical trials but mainly for operational convenience the WHO leprosy unit recommended to reduce MB therapy to 1-year. At that time 2-year WHO MDT for MB leprosy appeared generally successful and significant numbers of relapses after completion of 2-year MDT for MB leprosy were few; however, since MB relapse occurs generally after many years, it was not yet evident. In 2002, the further diminution of treatment duration for MB leprosy to 6 months,[53] also, was not preceded by any published relapse data on 1-year MDT.

In 1982[27] the designation of MB and PB patients was somewhat arbitrary, at first a BI $\geq 2+$, and later (1988)[47] any skin smear site being positive. By 1995 MB classification required >5 skin lesions,[54] in order to obviate the need for skin smears and biopsies, important tools in identifying those patients most at risk for treatment failure. Though lesion counting surely makes it easier for leprosy classification by healthcare workers and thereby can contribute to leprosy elimination, its very definition of anesthetic skin lesions or nerve enlargement precluded the most severe MB patients, those previously classified as BL or LL, as having leprosy at all.

Furthermore, particularly in locales where patients often presented with a high bacterial burden, lesion counting resulted in a considerable number of patients who previously would

have been classified by skin smears as MB considered PB with the result that they became under treated.[55] In the Philippines[55] we found that 57% of patients classified as PB by lesion counting were smear positive, 31% with a BI $\geq 2+$ at one or more sites and 36% were histopathologically BL or LL. Also, lesion counting not uncommonly resulted in patients who would have previously been classified as PB, classified as MB, resulting in over treatment.[56]

Integration into the General Health Services

The WHO encouraged the integration of leprosy into general health services.[57] Surely this is of some definite advantage in terms of political correctness and theoretical accessibility to additional resources for diagnosis and treatment. The WHO claimed: "The clinical signs of early leprosy are easily visible and the cardinal diagnosis sign, i.e., loss of sensation in the affected skin, is unique to the disease. All health workers can be educated in simple procedures for diagnosis and prescribing the appropriate MDT blister pack."[57] On the other hand, contrary to this view, leprosy is not infrequently confused with other dermatologic diseases and the diagnosis not uncommonly uncertain, even to seasoned leprologists. A diagnosis of leprosy is even more problematic in the current era when skin biopsies and smears have been abandoned. Furthermore in many endemic locales, general healthcare services are quite limited and primarily provide care for acute medical problems – the maintenance of therapy for more chronic illnesses, not only leprosy, but such problems as diabetes, hypertension, AIDS, and tuberculosis are wanting. Integration has also diminished leprosy expertise which was the cornerstone of the strength of vertical programmes. Rao *et al.*[58] made note that in Tamil Nadu prior to integration practically all patients were followed up to ensure that completion of therapy was obtained, while since integration completion was not monitored and appeared to decrease. Successful integration of leprosy into general health services requires intensive education of a large number of providers. Surely it is likely that the skills and expertise obtained in these locales, let alone the dedication necessary to a successful leprosy treatment and control programme had the potential to suffer.

A consequence of integration is that the knowledge and experience of dedicated leprologists has waned, and because the general health services have a lesser awareness of leprosy, early diagnosis and implementation of treatment surely had the likelihood to diminish. Integration thus might well have assisted the perceived success that MDT had in diminishing the prevalence and even incidence of leprosy. But was that success not more a downgrading of leprosy services with less case-finding and less treatment completion, thus better statistics in favour of leprosy elimination, rather than what it is claimed to have accomplished? In the literature there is little dialogue suggesting these consequences.

Uniform MDT (U-MDT)

In 2002, the third meeting of the WHO Technical Advisory Group on Elimination of Leprosy (TAG)[53] identified key challenges to ensure integration and sustainability of leprosy services which were identified "to further simplify and shorten the current multidrug regimens" and to "abolish classification for treatment purposes." These were meant to ease the application of treatment under field conditions.

The first, U-MDT,[53] was a diminution of the MB leprosy regimen to be applied to all forms of leprosy with a duration of 6 months (U-MDT). A first important lesson which this policy ignored is that leprosy presents as a continuous spectrum which includes clinical, bacteriologic, histopathologic and immunologic manifestations.[59] A second lesson is that on both sulphone monotherapy and MDT, only skin smear-positive cases tended to relapse if therapy was discontinued and in the sulphone monotherapy era only leprosy patients with high bacterial burdens were predisposed to dapsone-resistant relapse.[2,3,20,32–36] For PB patients U-MDT required the addition of clofazimine to the previous 6-month PB regimen, which had already proved reliable; thereby adding another agent, clofazimine, which did not appear needed together with its unfavourable skin discolouration. Also, since introducing lesion counting > 5 for MB and $\leq$ for PB, the percentage of PB patients when smear positivity was utilised for classification increased substantially. Thus, uniform MDT resulted in over treatment for a larger (50–60%) fraction of leprosy patients.[60] At the time when uniform MDT was recommended, already worrisome frequencies of relapse in MB patients who had been treated with 2-year MDT had been found, while as yet no studies on MB relapse following 1-year MDT, let alone 6-month MDT, with a long duration of follow-up had been published. Thus to yet further reduce MDT duration in MB patients was not scientifically sound and, in fact, unconscionable. In short, U-MDT had the distinct propensity to under treat MB leprosy and over treat PB leprosy. Based on theoretical grounds, it is a typical example of wishful thinking.

It is noteworthy, that though intolerance resulting in side effects / toxicities of each of the components of MDT has been well documented, recommendations for alternative antimicrobials when these occur have not been addressed by the WHO. Also, for cases that relapse after MDT, the WHO recommends to repeat the failed course which is counterintuitive and not supported by data.

Accompanied MDT (A-MDT)

Also, in 2002, the third meeting of the WHO Technical Advisory Group on Elimination of Leprosy (TAG) advocated A-MDT.[53] This allowed that the full medication supply required for the treatment of both forms of leprosy be provided to the patient upon diagnosis with the proviso that someone close to the patient will assist them in completing the therapeutic course. Previously WHO recommended treatment for leprosy was patterned on the tuberculosis experience, wherein directly observed therapy (DOT) was found to be the cornerstone of successful treatment. Certainly for many chronic diseases, including diabetes and hypertension compliance with prescribed therapy has been found shoddy, and compliance is necessary to prevent complications. Earlier in the monotherapy dapsone era, Ellard[61] found by evaluating dapsone/creatinine ratios in the urine that in dapsone-treated patients attending clinics, patients on the average only were found to ingest half the dapsone prescribed and a quarter of all patients self-administered their medication very irregularly. The monthly supervised administration of clofazimine and particularly rifampicin were from the beginning of WHO MDT therapy for leprosy considered vital to its success. To reverse this policy and allow entirely unsupervised treatment and without further clinical monitoring certainly would decrease the workload of the health services but just as certainly be a formula for treatment failure. The fact that compliance to the partially supervised WHO MDT regimen was also a considerable problem was documented by the published experience of

Weiand *et al.*[62] In a highly respected and well organised research and clinical programme devoted to leprosy in southern India, he found, either by questionnaire or spot tests for dapsone, that 48% of outpatients were noncompliant, while another one-third of patients did not appear for DOT. Though there is admittedly little information on compliance to leprosy chemotherapy, there is next to nothing of what comprises the successful completion of MDT. In the treatment of active pulmonary tuberculosis successful completion of therapy is considered to have occurred if completion of a standard 6-month regimen is attained after 9 months. In tuberculosis chemotherapy both inadequate compliance and completion of therapy have been demonstrated repeatedly to be the major cause of treatment failure in tuberculosis, as well as the emergence of drug resistance. Though the WHO had recommended that the 6-month regimen for PB leprosy be completed in 9 months and the one year MDT regimen be completed in 18 months, worldwide these standards have largely not been applied and implemented in leprosy control programmes. In a WHO publication (2000) "The Final Push Towards the Elimination of Leprosy" the WHO claimed: "10 million cases had been cured."[57] Without a standard for completion of therapy, it is not clear how that claim can be justified. Especially since follow-up in patients after the completion of MDT had been abandoned by the WHO as policy in 1994[49] and relapse in MB leprosy does not begin for several years, the claims made by the WHO of cure appear to have no basis. It appears that now the initiation of MDT seems to be the criteria for both cure and completion. Issues of compliance, what comprises completion, and how cure is substantiated appear absent.

The Elimination Campaign

At the 44th World Health Assembly in 1991 it was proclaimed that by the year 2000 and as a consequence of multidrug treatment, leprosy would be eliminated as a public health problem, defined as less than one case per 10,000 population. It is generally acknowledged that the elimination campaign was never endorsed by WHO leprosy expert committees or its Geneva leaders. Furthermore, though for some infectious diseases, primarily viral ones such as influenza A, when the prevalence of infectious cases falls below a certain number, transmission ceases, while for leprosy there is no information about what that number might be. Thus the elimination goal of less than one case in a population of 10,000, in fact had no clear credentials. Though by the time of the announcement of the elimination campaign several others TDR programmes devoted to infectious diseases primarily found in the developing world were initiated, none of these had in 1981 developed a 'product,' that being provided for leprosy by MDT. So where did the elimination campaign come from? It is our and others speculation that following the successful smallpox eradication scheme, the WHO was politically motivated to seek another victory. Smallpox elimination was made possible because of the confluence of several critical factors:

(1) A highly and very early effective vaccine which had the advantage of being lyophilized such that it could be reconstituted and administered in locales without refrigeration.
(2) Smallpox was not associated with environmental sources, nonhuman animal carriers, or asymptomatic human carriage.

None of these several prerequisites necessary to successful smallpox control can be claimed for leprosy. Furthermore, though some consider it an old argument, elimination of no bacterial disease had historically ever been accomplished, let alone by chemotherapy.

Pressures to reach elimination goals at national levels have been enormous, and it is entirely unclear if the success claimed for elimination has in fact occurred or the claim injudicious. The WHO claimed that by 2004 elimination had occurred in 122 previously endemic countries, leaving only nine countries which have not met the elimination goals (Brazil, Republic of the Congo, Madagascar, Nepal, Tanzania, Angola, Liberia, Mozambique, and Central African Republic).[63] However, the WHO itself readily admitted that the number of cases of leprosy confirmed in its statistics may well be flawed: "In a significant number of endemic countries, it is still virtually impossible to get a clear picture of what the situation is, what has been achieved, and what remains to be done."[57]

Elimination had been claimed in India by 2004, the country where previously had the highest number of leprosy patients. It was projected in India that the new detection rate fell by 75% between 2000 and 2006, from 559,938 to 139,252.[64] Since the minimal incubation period of leprosy is 5–7 years, most cases detected in India in 2006 were already incubating the disease in 2000. Thus the dramatic fall in the incidence of leprosy claimed to have occurred between 2000 and 2006 was epidemiologically unreasonable and, in fact, resulted from changes in definitions of leprosy cases, in leprosy-detection practices, in integration of leprosy services in general health services and/or manufactured by interpretation of data. Those means employed have been well-documented:

(1) Single lesion leprosy which accounts for one-third of leprosy cases in India became no longer leprosy at all.
(2) A case of leprosy was no longer counted if diagnosed by the treating physician but required verification by programme managers at the state and district levels — those individuals under pressure to produce improved statistics.
(3) Active case finding which was extensively performed in India previously was discouraged. Owing to the stigma of leprosy, self-reporting often does not occur.
(4) Once a case was confirmed, whether MB or PB, and was given treatment (actually has been given a complete pack of drugs) it was no longer considered a case.

Thus elimination in India appears to have been accomplished by 'sleight of hand.' Similar incentives to meet elimination goals clearly occurred elsewhere. Where there is no accountability, political pressures and national pride surely can contribute to successful elimination claims.

The actual accomplishments of the WHO MDT treatment regimens for the elimination campaign were, and remain, clearly controversial. The promise that WHO MDT could cure leprosy in a finite period and eliminate it as a public health problem surely encouraged the important provision of generally available free medication, first by the Sasakawa Foundation and later by Novartis. This was no small accomplishment. But, it is hard to substantiate elimination of leprosy; where it has been claimed to have been achieved may be unlikely or sustainable as commitment to an eliminated disease may well deteriorate.

Elimination targets where they were claimed to have occurred are, to a great extent, a redefinition of what comprised a leprosy case. While prior to the elimination campaign the prevalence of leprosy was the accepted yardstick to be counted as a 'case,' a 'case' thereafter consisted of only those patients who had not completed MDT. As the course for the treatment

of MB patients mandated by the WHO became progressively shortened the number of cases of leprosy fell accordingly. The reduction of MB therapy in 1998 from 2 years to 1 year effectively diminished the number of MB cases by one-half. When the treatment course was further reduced in 2002 to 6 months again the number of MB 'cases' fell by another one-half. Where A-MDT was fully implemented and upon diagnosis a complete therapeutic course of MDT was provided, by WHO criteria there would consequently be no leprosy cases at all.

Antimicrobials to Treat Leprosy and Animal Models for Leprosy Chemotherapy Evaluation

It appears to us that the most compelling finding derived from several clinical trials of individual effective antimicrobial agents active against *M. leprae* derives from the actual period of time required to render undetectable viable *M. leprae* from skin biopsies of lepromatous patients when the usual 5,000 bacilli are inoculated into mice. For dapsone,[65] clofazimine,[65] ethionamide/prothionamide[65,66] (prothionamide being superior to ethionamide[66]) this result took between 3 and 6 months; for ofloxacin,[67,68] minocycline[68–71] and clarithromycin[71,72] a few weeks to a few months were required, while for rifampicin[24–26] and moxifloxacin,[73,74] viable bacilli were lost in a single day to a few weeks.

Combination antimicrobial therapy for leprosy has the potential, not only to prevent the emergence of drug resistance, but enhance the killing of *M. leprae*. There are some but not many studies in mice with combinations of two or more agents that alone have proved active against *M. leprae*.[75–77] These consistently show that additive/synergistic activity results, and antagonism is not found.[75–77] Because for such studies in normal mice the size of the inoculum is limited, for these purposes the neonatally thymectomized Lewis rat which allows for a 10,000-fold greater inoculum and is immune-suppressed is superior. In that model combination chemotherapy was only evaluated in one study, finding that as in mice additive/synergistic and not antagonistic activity resulted.[77] It is noteworthy in that model, which has now been abandoned, more than half the time after rifampicin alone or dapsone and rifampicin viable *M. leprae* remained, while viable *M. leprae* were only found in 10% of NTLR treated with rifampicin and ofloxacin and in none treated with rifampicin and ethionamide, or rifampicin and minocycline.[77]

It appears inconsistent that viable *M. leprae* cannot be detected in mice after a few months of dapsone or even a few days of rifampicin, but are regularly found after some years of dapsone therapy. This is most likely a methodological paradox. In the mouse footpad infection 5×10^3 organisms are inoculated and if more than 5 viables[78] are present in the initial inoculum, these grow yielding 10^6 *M. leprae* by 6 months. It is estimated that an untreated lepromatous leprosy patient may harbour up to 10^{12} organisms in his body of which $10^{10} - 10^{11}$ are viable. If initial antimicrobial therapy reduces the viables by 99·9% to 10^7 to 10^8 organisms, an inoculum of 5,000 organisms would contain no viable bacilli. However, as dead organisms are preferentially cleared, the proportion of viable organisms increases so that detection of *M. leprae* by mouse footpad inoculation again becomes possible.

The discovery of Shepard[5] in 1960 that *M. leprae* reliably and reproducibly multiplies in the mouse footpad ushered in the modern era of research in leprosy chemotherapy and became the cornerstone of leprosy research itself for the next few decades. Unfortunately, the technique is tedious and fraught with the potential for methodological errors, particularly because of the propensity of *M. leprae* to clump, and requires great care and technical

precision. Historically, and only once in the laboratories of Shepard and Levy, was the same *M. leprae* inoculum found to reproduce and multiply in an equivalent manner. The mouse footpad assay allowed for the evaluation of *M. leprae* viability both in mice infected with *M. leprae* and subsequently treated with antimicrobials, as well as in tissues of patients on antimicrobial treatment. The mouse footpad assay, also, provided a means to determine the presence of drug susceptibility or resistance, distinguish between bacteriostatic and bactericidal activity and quantitate bactericidal potential of individual antimicrobial agents and regimens.

The mouse footpad procedure was adopted and utilised extensively for antimicrobial research in but a few places and, even with some adjustment in technique generally in order to reduce labour requirements, results were generally reasonably similar in different laboratories both when mice were treated directly and when viability of tissues taken from patients on various antimicrobials were compared. Though mouse footpad studies of antimicrobials were performed sporadically in several laboratories, in the main these were conducted in but a few – those of Shepard, Rees/Colston, Levy, Pattyn, Grosset/Ji and Gelber in San Francisco as well with Walsh in the Philippines. With the advent of WHO MDT and its wide and generally enthusiastic reception world-wide, further studies in chemotherapy received little encouragement and funding. When the cure of all forms of leprosy was believed to be in-hand, enthusiasm for continued evaluation of individual agents and particularly regimens, even those containing components proved superior to dapsone and clofazimine, waned. Worldwide most footpad laboratories, particularly those experienced with antimicrobial studies closed, arguably leaving none now active and experienced in evaluating antimicrobials in *M. leprae*-infected mice and in treated patients.

The most compelling issue resulting from the loss of mouse footpad capacity is that chemotherapeutic developments remain important. Though MDT has been found generally effective, as we have delineated earlier, and Ji[45] has emphasised there is clearly a subset of MB patients, particularly those at the lepromatous pole of the spectrum and those with a high bacterial burden who are at substantial risk for relapse. Those we believe might benefit from a new generation of more bactericidal MDT composed of two other agents which have proved more active and bactericidal both in *M. leprae* infected mice and in MB patients and superior to two of the three individual components of MDT, namely dapsone and clofazimine, both of which are bacteriostatic.[65] To replace dapsone and clofazimine candidate agents include the fluoroquinolones, particularly moxifloxacin which has been established in mice and MB patients to be the only agent similarly bactericidal as is rifampicin, minocycline and clarithromycin. This prospect holds promise for the subset of leprosy patients prone to fail current MDT as the short course of chemotherapy of tuberculosis was found to require two or more bactericidal agents, while current MDT for leprosy has only one, rifampicin.[24–26]

The enormous problem posed by multidrug-resistant tuberculosis has spurred an emphasis on the discovery and development of other agents to treat tuberculosis. As a by-product such discoveries may prove advantageous for the future chemotherapy of leprosy as well. A particularly promising agent being developed for the treatment of tuberculosis, PA824, has proved ineffective in *M. leprae*-infected mice, as a consequence of the loss in *M. leprae* of genes present in *M. tuberculosis* which convert the parent agent to its active moiety.[79] Of considerable promise, for the future chemotherapy of leprosy is R207910 (TMC 207, Bedaquiline). R207910 is a representative of an entirely new class of antimicrobials, the diarylquinolines which is uniquely active against mycobacteria.[80] In murine tuberculosis, it alone is more bactericidal than the three drugs generally used to treat active pulmonary

tuberculosis (isoniazid, rifampicin, and pyrazinamide)[80] and have been effective in treating tuberculosis especially in those with multidrug-resistant disease.[81] In *M. leprae*-infected mice treated during logarithmic multiplication[82] and dormancy,[83] bedaquiline has been found bactericidal and even in distinctly low dosage and when administered intermittently – as infrequently as once monthly. As a result of these promising findings in *M. leprae*-infected mice, a clinical trial of bedaquiline in leprosy patients is poised to commence. Furthermore, there are certain newly developed antimicrobials (OPC-6728, LL3858, PNU100480 and SQ106) effective against *M. tuberculosis in vitro* and in infected mice which are now in clinical trials in tuberculosis.[84] Each of these antimicrobials boast new mechanisms of actions, no cross-resistance with existing drugs and activity against drug-resistant *M. tuberculosis*. Unfortunately, because of the waning of mouse footpad facilities, none of these have to date been studied for their potential to treat *M. leprae* in mice, let alone in leprosy patients.

In Conclusion (where are we and where are we going)

So where are we in fact today? WHO MDT has proved generally successful in treating PB leprosy and most MB patients, as well. Relapses in MB patients appear largely confined to BL and LL patients with high bacterial burden and those relapses in that subset of patients occur often late – in the Philippines beginning at 6 years and more commonly in greater than 10 years than 6–9 years after the discontinuation of treatment. Thus as Ji[45] summarised and together we[35] agreed there is an identifiable subset of MB patients who clearly might benefit from more robust therapy. Though that subset of patients can often be identified by seasoned leprologists on clinical grounds alone, the reinstitution of skin smears and biopsies would help considerably toward that end. Options for that subset of patients include:

(1) WHO MB MDT treatment followed by dapsone lifelong. Gelber[85] treated 125 BL/LL dapsone-sensitive patients with a similar regimen, dapsone 100 mg daily and rifampicin 100 mg daily for an average of 5 years and dapsone indefinitely thereafter. In that cohort followed up for a total average of 9·7 years and an average of 4·1 years after smear negativity, none developed new skin lesions nor became smear positive.

(2) A new generation of MDT might prove superior. In addition to a rifamycin, potential components include several fluoroquinolones, minocycline and clarithromycin. Amongst these alternatives, moxifloxacin is particularly attractive, being found in mice and clinical trial to be profoundly bactericidal and in this respect equivalent to rifampicin. Also, in mice rifapentine[83] was found superior to rifampicin and, also, owing to its considerably longer half-life might prove more advantageous than rifampicin for a new generation of MDT. At present, we would project that the new generation MDT would best be rifapentine, moxifloxacin and minocycline.

In summary, our work is not over. It is encouraging that relapse leprosy does not appear to be associated to any extent with neurologic sequelae, unless further treatment is considerably delayed. It is not entirely clear that the subset of MB patients who relapse would truly benefit from the more bactericidal finite regimen proposed above as those who relapse may be those who maintain a lifelong anergy to *M. leprae*.[86] On the other hand, treatment of pulmonary

tuberculosis with sufficiently bactericidal multidrug therapy in anergic AIDS patients has generally proved successful.

From the time of the original MDT recommendations, modifications to MDT designed to provide ease, simplification and a reduction in the operational requirements for leprosy chemotherapy have evolved. These include the redefinition of what comprises a leprosy case and methods for leprosy classification, shortened duration of MB treatment, integration, U-MDT and A-MDT. All these modifications have been implemented to ease control of leprosy in the field but also, to some extent, if not predominately, promote elimination. Though the hazards in each of these strategies have been detailed previously, we must be reminded that our primary responsibility is to treat leprosy patients early and effectively and not to attain bureaucratic elimination goals.

Leprosy can generally be cured by MDT and is less often an incurable disease that needs lifelong chemotherapy. Yet after MDT completion there is a substantial subset of MB patients with a high bacterial burden at risk for relapse. Thus, leprosy chemotherapy development remains a considerable concern, while leprosy now may well now be more neglected than previously. The substantial extent of what the 'elimination' campaign has accomplished remains controversial. What is clear is that though in the 1960 s both tuberculosis and malaria were declared controlled, now both are acknowledged to be major causes of mortality in the developing world. What is also clear is that worldwide the number of leprosy clinicians and researchers has diminished greatly, and fundamental tools used to properly evaluate leprosy patients, such as skin smears, skin histopathology and mouse footpad facilities, and leprosy control such as case finding, supervised drug administration and follow-up are almost nonexistent. Thus the stage for leprosy to reemerge is surely set. Our best wish is to be wrong.

Acknowledgements

Both authors have no conflict of interest which pertain to this manuscript.

References

[1] Faget GH, Pogge RC, Johansen FA *et al.* The promin treatment of leprosy: a progress report. *Publ Hlth Rept*, 1943; **58**: 1729.
[2] Erickson PT. Relapse following apparent arrest of leprosy by sulfone therapy. *Publ Hlth Rept*, 1950; **65**: 1147–1157.
[3] Price RB. Relapse of leprosy in American Samoa. *Am J Trop Med Hyg*, 1959; **8**: 358–363.
[4] Pettit JH, Rees RJ. Sulphone resistance in leprosy. An experimental and clinical study. *Lancet*, 1964; **2**: 673–674.
[5] Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into foot-pads of mice. *J Exp Med*, 1960; **112**: 445–454.
[6] Meade TW, Pearson JMH, Rees RJW *et al.* The epidemiology of sulphone-resistant leprosy. *Int J Lepr*, 1973; **41**: 684.
[7] Ji BH. Drug resistance in leprosy – a review. *Lepr Rev*, 1985; **56**: 265–278.
[8] Peters JH, Shepard CC, Gordon GR *et al.* The incidence of DDS resistance in lepromatous patients in Costa Rica: their metabolic disposition of DDS. *Int J Lepr Other Mycobact Dis*, 1976; **44**: 143–151.
[9] Pearson JM, Haile GS, Barnetson RS, Rees RJ. Dapsone-resistant leprosy in Ethiopia. *Lepr Rev*, 1979; **50**: 183–199.
[10] Pearson JM, Haile GS, Rees RJ. Primary dapsone-resistant leprosy. *Lepr Rev*, 1977; **48**: 129–132.
[11] Shepard CC, Rees RJ, Levy L *et al.* Susceptibility of strains of *Mycobacterium leprae* isolated prior to 1977 from patients with previously untreated lepromatous leprosy. *Int J Lepr Other Mycobact Dis*, 1986; **54**: 11–15.

[12] Kai M, Matsuoka M, Nakata N *et al.* Diaminodiphenylsulfone resistance of *Mycobacterium leprae* due to mutations in the dihydropteroate synthase gene. *FEMS Microbiol Lett*, 1999; **177**: 231–235.
[13] Li W, Sakamuri RM, Lyons DE *et al.* Transmission of dapsone-resistant leprosy detected by molecular epidemiological approaches. *Antimicrob Agents Chemother*, 2011; **55**: 5384–5387.
[14] Jacobson RR. Final report of the WHO regional working group on drug policy and operational research in the leprosy programme. Manila, Philippines, 1981; 10.
[15] Gelber RH, Rea TH, Murray LP *et al.* Primary dapsone-resistant Hansen's disease in California. Experience with over 100 *Mycobacterium leprae* isolates. *Arch Dermatol*, 1990; **126**: 1584–1586.
[16] Gelber RH. The chemotherapy of leprosy: lessons learned, some forgotten, current status and future prospects. *Malay J Derm*, 2005; **18**: 10–17.
[17] Waters MF, Rees RJ, McDougall AC *et al.* Ten years of dapsone in lepromatous leprosy: clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. *Lepr Rev*, 1974; **45**: 288–298.
[18] Waters MF, Rees RJ, Pearson JM *et al.* Rifampicin for lepromatous leprosy: nine years' experience. *Br Med J*, 1978; **1**: 133–136.
[19] Russell DA, Worth RM, Scott GC *et al.* Experience with acedapsone (DADDS) in the therapeutic trial in New Guinea and the chemoprophylactic trial in Micronesia. *Int J Lepr Other Mycobact Dis*, 1976; **44**: 170–176.
[20] Waters MF, Rees RJ, Laing AB *et al.* The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy. *Lepr Rev*, 1986; **57**: 101–109.
[21] Freerksen E, Rosenfeld M. Leprosy eradication project of Malta. *Chemotherapy*, 1977; **23**: 356–386.
[22] Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP). Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Persisting *Mycobacterium leprae* among THELEP trial patients in Bamako and Chingleput. *Lepr Rev*, 1987; **58**: 325–337.
[23] Gelber RH, Humphres RC, Fieldsteel AH. Superiority of the neonatally thymectomized Lewis rat (NTLR) to monitor a clinical trial in lepromatous leprosy of the two regimens of rifampin and dapsone. *Int J Lepr Other Mycobact Dis*, 1986; **54**: 273–283.
[24] Rees RJ, Pearson JM, Waters MF. Experimental and clinical studies on rifampicin in treatment of leprosy. *Br Med J*, 1970; **1**: 89–92.
[25] Shepard CC, Levy L, Fasal P. Rapid bactericidal effect of rifampin on *Mycobacterium leprae*. *Am J Trop Med Hyg*, 1972; **21**: 446–449.
[26] Shepard CC, Levy L, Fasal P. Further experience with the rapid bactericidal effect of rifampin on *Mycobacterium leprae*. *Am J Trop Med Hyg*, 1974; **23**: 1120–1124.
[27] WHO Study Group: Chemotherapy of leprosy for control programmes. WHO Tech Rep Ser, 1982; **675**: 1–33.
[28] WHO Expert Committee on Leprosy. World Health Organ Tech Rep Ser, 1988; **768**: 1–51.
[29] Katoch K, Ramu G, Ramanathan U, Desikan KV. Comparison of three regimens containing rifampin for treatment of paucibacillary leprosy patients. *Int J Lepr Other Mycobact Dis*, 1987; **55**: 1–8.
[30] Böerrigter G, Pönnighaus JM, Fine PE. Preliminary appraisal of a WHO-recommended multiple drug regimen in paucibacillary leprosy patients in Malawi. *Int J Lepr Other Mycobact Dis*, 1988; **56**: 408–417.
[31] Balagon MF, Cellona RV, Abalos RM *et al.* The efficacy of a four-week, ofloxacin-containing regimen compared with standard WHO-MDT in PB leprosy. *Lepr Rev*, 2010; **81**: 27–33.
[32] Efficacy of single dose multidrug therapy for treatment of single lesion paucibacillary leprosy. Si lesion multi centered trial group. *Indian J Lepr*, 1997; **69**: 121–129.
[33] WHO. Final push strategy to elimination of leprosy as a public health problem. Questions and answers. Document, 2nd edition. WHO, 2003.
[34] Cellona RV, Balagon MF, dela Cruz EC *et al.* Long-term efficacy of 2 year WHO multiple drug therapy (MDT) in multibacillary (MB) leprosy patients. *Int J Lepr Other Mycobact Dis*, 2003; **71**: 308–319.
[35] Gelber RH, Balagon VF, Cellona RV. The relapse rate in MB leprosy patients treated with 2-years of WHO-MDT is not low. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 493–500.
[36] Jamet P, Ji B. Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. Marchoux Chemotherapy Study Group. *Int J Lepr Other Mycobact Dis*, 1995; **63**: 195–201.
[37] Girdhar BK, Girdhar A, Kumar A. Relapses in multibacillary leprosy patients: effect of length of therapy. *Lepr Rev*, 2000; **71**: 144–153.
[38] Hong Kong Chest Service and British Medical Research Council Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis. First report. *Am Rev Respir Dis*, 1978; **118**: 219–228.
[39] East African/British Medical Research Council. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Third report. *Lancet*, 1974; **2**: 237–240.
[40] Blumberg HM, Burman WJ, Chaisson RE *et al.* American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med*, 2003; **167**: 603–662.
[41] Shetty VP, Wakade AV, Ghate SD *et al.* Clinical, bacteriological and histopathological study of 62 referral relapse cases between Jan 2004 and Dec 2009 at the Foundation for Medical Research, Mumbai. *Lepr Rev*, 2011; **82**: 235–243.

[42] Grosset JH, Guelpa-Lauras CC, Bobin P. Study of 39 documented relapses of multibacillary leprosy after treatment with rifampin. *Int J Lepr Other Mycobact Dis*, 1989; **57**: 607–614.
[43] Pattyn S, Grillone S. Relapse rates and a 10-year follow-up of a 6-week quadruple drug regimen for multibacillary leprosy. *Lepr Rev*, 2002; **73**: 245–247.
[44] Marchoux Chemotherapy Study Group. Relapses in multibacillary leprosy patients after stopping treatment with rifampin-containing combined regimens. *Int J Lepr Other Mycobact Dis*, 1992; **60**: 525–535.
[45] Baohong J. Does there exist a subgroup of MB patients at greater risk of relapse after MDT? *Lepr Rev*, 2001; **72**: 3–7.
[46] Norman G, Joseph G, Richard J. Relapses in multibacillary patients treated with multi-drug therapy until smear negativity: findings after twenty years. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 1–7.
[47] WHO Expert Committee on Leprosy. WHO Tech Rep Ser, 1988; **768**: 1–51.
[48] Chemotherapy Workshop: 14th International Leprosy Congress. *Int J Lepr*, 1993; **61**: 729–730.
[49] WHO Study Group. Chemotherapy of Leprosy — Report of WHO study group. WHO Tech Rep Ser, 1994; 847.
[50] Gebre S, Saunderson P, Byass P. Relapses after fixed duration multiple drug therapy: the AMFES cohort. *Lepr Rev*, 2000; **71**: 325–331.
[51] Maghanoy A, Mallari I, Balagon M *et al.* Relapse study in smear positive multibacillary (MB) leprosy after 1 year WHO-multi-drug therapy (MDT) in Cebu, Philippines. *Lepr Rev*, 2011; **82**: 65–69.
[52] WHO Expert Committee on Leprosy. Seventh Report. WHO Tech Rep Ser. WHO, 1998; 874.
[53] WHO. Report on third meeting of the WHO Technical Advisory Group on Elimination of Leprosy, 2002; WHO/CDS/CPE/CEE: 2002–29.
[54] WHO. Guide to eliminate leprosy as a public health problem. WHO, 1995.
[55] Pardillo FE, Fajardo TT, Abalos RM *et al.* Methods for the classification of leprosy for treatment purposes. *Clin Infect Dis*, 2007; **44**: 1096–1099.
[56] Oskam L. Diagnosis and classification of leprosy. *Lepr Rev*, 2002; **73**: S17–S26.
[57] WHO. The final push towards elimination of leprosy. Strategic Plan 2000–2005. WHO, 2000; WHO/CDS/CPE/CEE/2000:1–13.
[58] Rao PS, Gift N, Rao GS *et al.* Elimination of leprosy: the integration of leprosy related activities into the general health services of Tamil Nadu. *Lepr Rev*, 2002; **73**: 123–129.
[59] Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis*, 1966; **34**: 255–273.
[60] Ji B, Saunderson P. Uniform MDT (U-MDT) regimen for all leprosy patients-another example of wishful thinking. *Lepr Rev*, 2003; **74**: 2–6.
[61] Ellard GA. The chemotherapy of leprosy. Part 2. *Int J Lepr Other Mycobact Dis*, 1991; **59**: 82–94.
[62] Weiand D, Smith WC, Muzaffarullah S. Qualitative assessment of medication adherence at an urban leprosy outpatient clinic in Hyderabad, India. *Lepr Rev*, 2011; **82**: 70–73.
[63] WHO. Global strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities. Plan Period: 2006–2010. WHO, 2005.
[64] Prasad PV, Kaviarasan PK. Leprosy therapy, past and present: can we hope to eliminate it? *Indian J Dermatol*, 2010; **55**: 316–324.
[65] Shepard CC. A brief review of experiences with short-term clinical trials monitored by mouse-foot-pad-inoculation. *Lepr Rev*, 1981; **52**: 299–308.
[66] Fajardo TT, Guinto RS, Cellona RV *et al.* A clinical trial of ethionamide and prothionamide for treatment of lepromatous leprosy. *Am J Trop Med Hyg*, 2006; **74**: 457–461.
[67] Grosset JH, Ji BH, Guelpa-Lauras CC *et al.* Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. *Int J Lepr Other Mycobact Dis*, 1990; **58**: 281–295.
[68] Fajardo TT, Jr, Villahermosa LG, Cruz EC *et al.* A clinical trial of pefloxacin and ofloxacin in lepromatous leprosy. *Lepr Rev*, 2004; **75**: 389–397.
[69] Gelber RH, Fukuda K, Byrd S *et al.* A clinical trial of minocycline in lepromatous leprosy. *BMJ*, 1992; **304**: 91–92.
[70] Fajardo TT, Jr, Villahermosa LG, dela Cruz EC *et al.* Minocycline in lepromatous leprosy. *Int J Lepr Other Mycobact Dis*, 1995; **63**: 8–17.
[71] Ji B, Jamet P, Perani EG *et al.* Powerful bactericidal activities of clarithromycin and minocycline against *Mycobacterium leprae* in lepromatous leprosy. *J Infect Dis*, 1993; **168**: 188–190.
[72] Chan GP, Garcia-Ignacio BY, Chavez VE *et al.* Clinical trial of clarithromycin for lepromatous leprosy. *Antimicrob Agents Chemother*, 1994; **38**: 515–517.
[73] Pardillo FE, Burgos J, Fajardo TT *et al.* Powerful bactericidal activity of moxifloxacin in human leprosy. *Antimicrob Agents Chemother*, 2008; **52**: 3113–3117.
[74] Pardillo FE, Burgos J, Fajardo TT *et al.* Rapid killing of *M. leprae* by moxifloxacin in two patients with lepromatous leprosy. *Lepr Rev*, 2009; **80**: 205–209.
[75] Shepard CC. Combinations of drugs against *Mycobacterium leprae* studied in mice. *Int J Lepr Other Mycobact Dis*, 1972; **40**: 33–39.

[76] Gelber RH, Siu P, Tsang M *et al.* Activity of combinations of dapsone, rifampin, minocycline, clarithromycin, and sparfloxacin against *M. leprae*-infected mice. *Int J Lepr Other Mycobact Dis*, 1995; **63**: 259–264.
[77] Gelber RH. Chemotherapy of lepromatous leprosy: recent developments and prospects for the future. *Eur J Clin Microbiol Infect Dis*, 1994; **13**: 942–952.
[78] Welch TM, Gelber RH, Murray LP *et al.* Viability of *Mycobacterium leprae* after multiplication in mice. *Infect Immun*, 1980; **30**: 325–328.
[79] Manjunatha UH, Lahiri R, Randhawa B *et al. Mycobacterium leprae* is naturally resistant to PA-824. *Antimicrob Agents Chemother*, 2006; **50**: 3350–3354.
[80] Andries K, Verhasselt P, Guillemont J *et al.* A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. *Science*, 2005; **307**: 223–227.
[81] Diacon AH, Pym A, Grobusch M *et al.* The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med*, 2009; **360**: 2397–2405.
[82] Gelber R, Andries K, Paredes RM *et al.* The diarylquinoline R207910 is bactericidal against *Mycobacterium leprae* in mice at low dose and administered intermittently. *Antimicrob Agents Chemother*, 2009; **53**: 3989–3991.
[83] Ji B, Chauffour A, Andries K *et al.* Bactericidal activities of R207910 and other newer antimicrobial agents against *Mycobacterium leprae* in mice. *Antimicrob Agents Chemother*, 2006; **50**: 1558–1560.
[84] Mitnick CD, McGee B, Peloquin CA. Tuberculosis pharmacotherapy: strategies to optimize patient care. *Expert Opin Pharmacother*, 2009; **10**: 381–401.
[85] Gelber RH. Our experience with another multidrug therapy regimen for leprosy. *Int J Lepr Other Mycobact Dis*, 1998; **66**: 9a–10a.
[86] Cree IA, Smith WC, Rees RJ *et al.* The influence of antimycobacterial chemotherapy on delayed hypersensitivity skin-test reactions in leprosy patients. *Lepr Rev*, 1988; **59**: 145–151.