

# Treatment of Leprosy: science or politics?

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## Summary

**OBJECTIVE** To review the history of the treatment of leprosy and leprosy reactions after World War II.  
**METHODS** Treatments based on experience and clinical evidence are compared with those advised by the WHO in their quest to eliminate leprosy by the year 2000, later extended to 2005.  
**RESULTS** Leprosy is not eliminated. Analyses of data on reaction treatment suggest that the treatment regimens for leprosy reactions as advised by the WHO may lead to more impairment among leprosy patients than the 'old' established regimes.  
**CONCLUSION** WHO policies to eliminate leprosy may have jeopardized the proper treatment of leprosy for years to come.

**keywords** leprosy, leprosy reactions, treatment, public health, who

## Introduction

Over the centuries leprosy has remained a feared disease with severe social repercussions for the sufferers. Until the Second World War no effective treatment was available; health authorities had to resort to segregation so as to prevent the spread of the disease (Hansen 1897; Rogers & Muir 1940). This may have had some effect on the leprosy endemic in, for instance, Bergen, Norway, but in general it only increased suffering and stigmatization.

## Antimycobacterial therapy

In 1941, Faget in the USA was the first to use a dapsone derivative (Promin®) intravenously to treat leprosy. Prior to this, dapsone derivatives had been shown to be partially effective against *Mycobacterium avium* and *M. tuberculosis* infections. Cochrane used it intramuscularly in India in 1946, and in 1947 Lowe used the mother substance dapsone (DDS, diaminodiphenylsulphone) orally in Nigeria. From 1950 onwards this drug, which had been synthesized in 1908 by Fromm & Whittmann in Germany, became the mainstay of leprosy treatment (Naafs 1988).

For some time it was hoped that leprosy patients could be cured, the transmission interrupted and that leprosy could be eradicated. However, this was not the case. In fact, careful scrutinizing and interpretation of the curves and statistics of the new cases registered showed that there was no effect that could be contributed to the extensive use of dapsone treatment. In 1960 it became clear that relapses occurred even after regular and prolonged dapsone treatment (Bushby 1964). In the subsequent decade, dapsone resistance became a problem (Shepard *et al.* 1969).

In the meantime, a number of new drugs had become available, notably rifampicin and clofazimine (Lampren®). Rifampicin proved to be extremely effective, killing 99.9% of *M. leprae* with a single dose of 600 mg. But a leprosy patient may harbour as many as  $10^{12}$ – $10^{13}$  *M. leprae* and it was thought, therefore, that the treatment of these patients should be prolonged. Unfortunately, resistance to this effective drug developed quickly (Jacobson & Hastings 1976), whereas resistance to clofazimine has been rare (Warndorff-Van Diepen 1982; Naafs 1988).

Under the auspices of the international league of donor organizations in the field of leprosy (ILEP) and, later, WHO, experts designed a new drug regimen. This regimen, Multiple Drug Treatment (MDT), was introduced in 1982 (WHO 1982). For paucibacillary (PB) patients, the treatment consisted of the supervised administration of 600 mg of rifampicin once monthly and 100 mg of dapsone daily, unsupervised, for 6 months. For multibacillary (MB) patients, a supervised dose of 300 mg of clofazimine once monthly was added to the rifampicin and 50 mg of

\* Dr Naafs was awarded the Eijkman Medal on 1 October 2003 for his contribution to tropical dermatology, in particular for his unrelenting effort to improve treatment and control of leprosy based on clinical evidence and many years of experience. The Eijkman Medal, established in 1923 in honour of the discoverer of the causes of beriberi, is awarded every 2 years to scientists who made a major contribution to tropical medicine.

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clofazimine daily was added to the dapsone. This treatment was given for at least 24 months or until the bacteriological index (BI) was negative. PB patients were defined as Indeterminate (I), Tuberculoid (TT) and Borderline Tuberculoid (BT) leprosy patients with a BI of <2 at all sites, the others: Mid Borderline (BB), Borderline Lepromatous (BL) and Lepromatous Leprosy (LL), with a BI of 2 or more were defined as MB.

The definition of PB was later changed because a sizeable number of relapses among PB patients were seen. Bacteria could be detected in most of these patients. From that time onward a PB leprosy patient is defined as a patient without detectable *M. leprae* in smear or biopsy. All others are considered MB.

When a considerable number of patients demonstrated that it was impossible to comply with the Release From Treatment (RFT) requirements concerning the length of the treatment, the treatment duration was also changed: 6 monthly doses within 9 months for BP patients and 24 monthly doses within 36 months for MB patients (WHO 1985).

These regimens proved to be extremely effective; unexpectedly, relapses were very rare: 1.09% in PB patients and 0.74% in MB patients over a 9-year period. This was an overall relapse of <0.1% per year (Noordeen 1993; WHO 1994). The relapsed patients reacted favourably to a repeated course of treatment, and very little drug resistance was encountered. Health authorities also noticed that the regimens seemed to be extremely successful. The number of registered leprosy cases declined from 4–5 million in the mid-1980s to a little over 800 000 in 2000 (Visschedijk *et al.* 2000), a reduction of 85%. For the first time, both patients and health workers began to believe that leprosy might be cured. This resulted in an increased effort by the leprosy workers to detect and treat patients and those afflicted with leprosy came forward earlier, often before severe damage was done. 'Leprosy elimination by the year 2000' was proposed for the first time in 1986 (Lockwood 2002).

In 1991, the 44th World Health Assembly, encouraged by the efficacy of these treatment regimens, established the goal of eliminating the disease as a public health problem by the year 2000. The goal was defined as a prevalence (patients on treatment) of <1:10 000. This cut-off point was chosen because within the WHO it was thought that when this point was reached, the disease would 'die out'. Critics remarked that there was no evidence that this would occur (Lockwood 2002).

At the start of the elimination campaign, many leprosy programmes used the year prevalence to report the number of registered patients. Later, WHO advised that the method of determination should be changed into point

prevalence, resulting in a marked decline in the number of registered (especially PB) patients.

The 1990s saw a decrease in leprosy stigma, resulting in an improved and altered outlook for the patients. Public understanding had increased considerably and had benefited from WHO's goal of 'eliminating leprosy as a public health problem by the year 2000'. Unfortunately, this goal has led many to believe that leprosy has been or will be eradicated soon. Despite the fall in the number of registered patients, the incidence of the disease had changed very little, remaining constant at 500 000 to 600 000 cases worldwide until 1995 (Visschedijk *et al.* 2000). Thereafter a steady increase occurred; 719 330 cases were detected in 2000 (Lockwood 2002). History should have taught us that the eradication of a bacterial infectious disease such as leprosy is unlikely using chemotherapy alone (Jacobson & Krahenbuhl 1999). In his PhD thesis, Meima, using mathematical modelling of leprosy epidemiology, came to the same conclusion (Meima 2004).

Operationally, the number of patients under treatment in the leprosy programmes declined so markedly that the cost-effectiveness of the programmes became jeopardized. This and the belief of the authorities that leprosy was nearly eradicated led to a dismantling of leprosy services. Some were combined for practical purposes (drug delivery) with tuberculosis control; others were integrated into the general health services (Naafs 1998). This resulted in more workers involved in the diagnosis and treatment of leprosy. It expanded the possibility for treatment. But these workers, being less experienced and less trained, were unable to distinguish MB from PB leprosy on clinical grounds. In the meantime WHO had abandoned skin smears for practical reasons. It was decided that counting the number of lesions would be no less sensitive than counting the bacilli in a skin smear and much more practical. A PB patient was defined as a leprosy patient with five or fewer skin lesions, and an MB patient as a patient with more than five lesions (WHO 1998). Attempts at improving laboratory tests for the diagnosis of leprosy were to no avail. The experienced clinician remained the golden standard for the diagnosis of leprosy (Naafs B, 2002, unpublished data).

In 1998 the WHO Expert Committee on Leprosy convened 'to review the global situation and the technology available for eliminating leprosy, so as to identify the remaining obstacles for achieving the goal of eliminating leprosy as a public health problem and to recommend appropriate measures on technical and operational matters for the future'. On the basis of field trials and clinical studies, the expert committee concluded that a single dose of a combination of rifampicin, ofloxacin and minocycline (ROM) was an acceptable and cost-effective alternative

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regimen for the treatment of single-lesion PB leprosy and that the duration of the MDT regimen for MB leprosy might be shortened to 12 months (WHO 1998). It was even suggested that all leprosy patients should be treated for only 6 months (WHO 2002b). This resulted in such a storm of criticism, notably during the World Leprosy Congress in Salvador, Brazil, that WHO decided to run trials before implementing this policy.

The new recommendations certainly helped to achieve the goal set by the World Health Assembly. By shortening the treatment duration of MDT for MB patients from 24 to 12 months, the number of MB registrations halved, thus improving the statistics, especially in countries with a high percentage of MB patients such as Brazil and Indonesia. The ROM therapy for single-lesion leprosy improved the statistics in India, a country with relatively many single-lesion patients. The 6-month treatment for all would have 'eliminated leprosy in the year 2000' as planned. Nevertheless, despite the fact that the WHO was not able to shorten the treatment of MB patients to the intended 6 months, the prevalence of leprosy declined further as a result of changing treatment regimens and definitions. However, a question remains: were these recommendations also beneficial to the individual patient or to a leprosy control programme?

There is no evidence that ROM will cure single-lesion leprosy that is not self-healing (Lockwood 1997; Katoch 1998). Single-lesion leprosy is often indeterminate leprosy. It is described that indeterminate leprosy heals spontaneously in >80% of patients (Ekambaram & Sithambaram 1977; Browne 1984). This pleads for the case of not treating the patient but of taking an approach of 'wait and see'. However, an experienced leprosy worker has to be available for such an approach. As such a person, especially in integrated programmes, is unlikely to be available, many health workers will treat all the single-lesion patients. Critics warn that even though these patients are not visible in the statistics, they nevertheless are part of the leprosy endemic. But it is too early to tell whether the 20% of the patients who eventually would have developed classifiable leprosy would benefit from a single ROM treatment. Most likely, the treatment will only delay the onset of frank leprosy although it may cure some patients (Naafs 2000a). Quite a number of the single lesions persist, especially at the polar tuberculoid end of the spectrum (SK Noordeen, personal communication). A patient may question whether he or she is actually cured; which could discredit the programme.

There were no definite data establishing that 1-year treatment of MB would be sufficient to prevent relapses; in fact, there were indications that patients with a high number of bacilli (a BI of 4–6) might relapse (Waters 1998;

Girdhar *et al.* 2000). Moreover, it could be expected that the number of leprosy reactions in the year after RFT would increase, leading to more disability in the so-called 'cured' leprosy patients (Naafs 2000a). A study from north India confirmed this fear (Kumar *et al.* 2004).

In 2000 WHO's goal had been achieved in many countries, but not in those where most (85%) of leprosy patients live: India, Brazil, Nigeria, Myanmar, Madagascar and Indonesia. Critics noted that the number of new cases registered, the incidence, had not decreased but increased (Naafs 1998, 2000a; Visschedijk *et al.* 2000). WHO attributed this rise to the efforts made to treat all leprosy patients by raising public awareness and active case finding. However, like its critics, WHO was aware that it would not reach its goal in the year 2000. Therefore, it initiated the Global Alliance for the Elimination of Leprosy (GAEL), which involved, notably, the Novartis Foundation, the Sasakawa Memorial Foundation, the Nippon Foundation, the Danish organization Danida and, until it was expelled in 2002, ILEP. GEAL used 'the final push' as a campaign slogan, implying that the elimination goal would be achieved in 2005. In 2001, WHO claimed that leprosy had been eliminated 'at global level'. However, in the top 27 countries where leprosy is endemic, the incidence did not fall between 1985 and 1999 and in the six countries that account for 88% of the new cases, both number and incidence of new cases were rising (WHO 2000; Lockwood 2002).

In her opening speech during the Asian Leprosy Congress, Maria Neira (2000, unpublished data), at that time head of the Communicable Disease Programme of WHO, accused Indian leprosy workers of over-diagnosing leprosy so as to keep their jobs. A validation of the diagnosis of new leprosy patients in India led WHO to conclude that indeed there was a marked over-reporting of new leprosy cases, including incorrect diagnosis, re-registration and registration of non-existing patients. Overall, 27.9% of new cases belonged to these groups, ranging from 8.1% in Jharkand to 71.1% in New Delhi (WHO 2002b). PaHo, the American branch of the WHO, plans a similar validation in Brazil. Their 'gold standard' for the validation of the diagnosis of leprosy was: 'loss of sensation to ballpoint test in skin lesions or in areas supplied by peripheral nerves, from which the following should be palpated: both ulnar and both lateral popliteal nerves' (PAHO 2004).

However, the generally accepted criteria for the diagnosis of leprosy are loss of sensation in a skin lesion to *light touch*, an enlarged nerve among *all* palpable peripheral nerves and a positive *skin smear*. Two of the three criteria are needed for the diagnosis of leprosy. After comparing these two definitions, it can be expected that the same

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conclusion, a marked over-diagnosis of leprosy, will be drawn in Brazil as was done in India (Naafs 2005).

The most recent recommendations of the Technical Advisory Group (TAG) include strengthening data collection within the programmes as well as cleaning the registers of incorrectly registered patients so as to achieve the goal of less than one patient per 10 000 population. Moreover, the TAG stated that as this goal is nearly achieved, active case finding should not be encouraged (WHO 2002b). After or due to, but most likely due to, these recommendations and accusations the number of newly registered leprosy patients decreased for the first time.

**Leprosy reactions**

Although the treatments proved to be very effective, a few problems were encountered (Waters 1993). Similar to the complications occurring during dapsone monotherapy, nerve-damaging reactions remained a problem. Reversal Reaction (RR), a delayed-type hypersensitivity reaction (Type IV Gell and Coombs) directed against *M. leprae* antigenic determinants, and the less understood Erythema Nodosum Leprosum (ENL)-type reaction, probably immune complex-mediated (Type III Gell and Coombs), continued to occur during treatment (Prabhavolkar & Ansari 1997), although the number of ENL-type reactions in MB patients under treatment had markedly diminished thanks to the suppressive effect of the clofazimine used in MDT (Post *et al.* 1994).

A new alarming phenomenon was encountered. Many patients developed reactions after RFT, when they were considered cured. A RR after RFT, which was not observed during dapsone monotherapy because of the length of treatment, is often indiscernible from a relapse (Waters 1993). It is called 'late reversal reaction' and may be triggered by the discontinuation of dapsone, which has a suppressive effect on RRs (Naafs *et al.* 1986). Late RR occurs in 5–10% of PB and MB patients (Post *et al.* 1994; Kumar *et al.* 2004).

The frequency and the severity of ENL-type reactions also increased in MB patients after RFT (Post *et al.* 1994), probably because of the discontinuation of clofazimine. Recently Kumar *et al.* (2004) confirmed that ENL reactions occurred mostly during the second and third year after starting MDT – when patients were off MDT. Obviously leprosy is not merely a bacteriological disease but an immunological one as well, which often seems to be forgotten.

The seventh WHO expert committee on leprosy stated in June 1997 (WHO 1998) that 'the crucial elements in the management of leprosy reactions and thereby the prevention of disabilities are early diagnosis of reactions together

with prompt and adequate treatment'. The committee also stated: 'most reactions and neuritis can be treated successfully under field conditions by a standard 12-week course of prednisolone'. The former statement on the importance of early diagnosis cannot be overestimated. However, the latter statement, that most reactions and neuritis can be successfully treated in 12 weeks, is most likely incorrect.

Nerve damaging reactions are the cell-mediated Type I leprosy reaction (RR) and the Type II leprosy reaction (ENL), which seems to be immune-complex driven. Very little is known about the duration of these reactions. It is assumed that a Type I reaction lasts for many months (Naafs *et al.* 1979; Li 2000) while a Type II reaction usually lasts 2–4 weeks (De Souza Araujo 1929; Naafs 1996).

During the 15th World Leprosy Congress in Beijing in 1998 it became apparent that no evidence-based treatment schedules were available for these reactions (Lockwood & Scollard 1998). At that time evidence-based meant 'double-blind, placebo controlled studies'. However, this understanding has changed during the past few years, giving more credit to careful monitoring of individual patients and retrospective studies.

**Type I leprosy reaction (Reversal Reaction)**

Although WHO stated in 'The Final Push Strategy to Eliminate Leprosy as a Public Health Problem: Questions and Answers' that most leprosy reactions can be controlled by non-steroidal drugs (WHO 2002b), steroid treatment (prednisolone) is still considered the treatment of choice for RR (Naafs 1996, 2003a), and the starting dose of 30–40 mg is beyond debate. However, the duration of treatment is not.

In 1950, Chaussinand (1950), in his textbook 'La Lèpre', commented that a 4–7 day course of injections with cortisol or adrenocorticotrophic hormone (ACTH) had been used successfully but the reactions usually re-appeared once the treatment was stopped. Treatment with steroids was also a matter of discussion during the sixth World Leprosy Congress in Madrid (1953). It was considered effective but 'rebounds' were feared.

Cochrane cited Cap Oliver in his textbook on leprosy: 'Acute forms of neuritis associated with dimorphous or tuberculoid reactions are best treated with corticosteroid drugs, prednisolone, 20–40 mg daily depending on the severity, and a gradual decrease of the dose corresponding to the stage of clinical resolution. Treatment given for 1 week to 1 month, or occasionally longer, is usually sufficient to deal with the pain' (Cochrane 1964). This treatment schedule, based solely on clinical observation,

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was used by most leprologists, as they were afraid to use steroids for prolonged periods.

In 1968, Goodwin (1968) published the Voluntary Muscle Test (VMT), which was adapted for leprosy patients. Since then, it became possible to objectively assess motor nerve function during treatment. Not long thereafter, Pearson introduced Weddell's graded bristle test to assess sensory nerve function (Pearson & Weddell 1971).

Between 1968 and 1974 researchers at the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Addis Ababa used two different regimens for treating RRs (Naafs *et al.* 1979). One regimen required a 45–60 mg dose of prednisolone daily, tapered off over 1 month to 5 mg daily, and then continued this daily dose for another month. The other regimen started with 15 mg and tapered off to 5 mg daily during the course of 1 month and continued at the same daily dose for another month. This regimen was repeated once or twice when patients' RR showed increased activity. Patients were monitored carefully using the VMT. Retrospective analyses comparing the two regimens did not reveal any difference in the outcome of treatment (Naafs 2003a).

Pearson was one of the first to adjust treatment to an objective change in nerve function parameters and he consequently gradually lengthened the treatment period. With the introduction of EMG equipment at ALERT in 1974 by Baar, motor nerve conduction velocity (MNCV) could be used in combination with VMT and sensory testing as parameters of nerve involvement (Naafs *et al.* 1976; Naafs & Dagne 1977).

Since 1974, patients at ALERT with an RR were started on 30–40 mg of prednisolone once daily; after a month this was reduced over a 2 to 3-month period to 20–25 mg. Thereafter, the prednisolone dose was reduced by 5 mg every month (Naafs *et al.* 1979). The dose was increased to the previous dose when nerve function parameters deteriorated, or when improvement came to a halt after dose reduction. A dose of 15–20 mg ( $\pm 0.30$ – $0.35$  mg/kg) was the critical dose of prednisolone to control an RR after the initial period. The total duration of treatment was 4–9 months for BT patients, 4–14 months for BB patients and 6–20 months for BL patients (Naafs *et al.* 1979). The duration of this treatment is in accordance with recently reported data on the length of RR by Li (2000).

The ALERT prednisolone treatment used before 1974 was compared with the prednisolone treatment used after 1974 using the VMT as parameter. Patients were followed for 3 years. It was obvious that when the steroids were given for 6 months or more this was far superior to the treatment of 3 months or less, as was done prior to 1974.

Clearly the process of nerve damage in most patients was not arrested by a short period of prednisolone treatment.

When prednisolone treatment was longer, very few patients deteriorated once treatment was initiated and none did after 3 months of treatment (Naafs *et al.* 1979, 2003a).

Obviously, in the field, individually tailored anti-reaction treatment was not feasible. Therefore, fixed and semi-fixed schedules were recommended and implemented (Naafs 1981; Touw-Langendijk *et al.* 1984; Kiran *et al.* 1985). The results, in general, were good, although no long-term follow-up was performed at that time.

WHO advised a shorter treatment regimen (WHO 1998), in which the prednisolone dose stayed above the crucial dose of 15–20 mg during the first 2–3 months only; the WHO supplied blister packs for this treatment. The results at the end of the treatment appeared to be good (Bernink & Voskens 1997). However, there was no proper follow-up of the patients during the post-treatment period.

Based on the paper by Naafs *et al.* (1979) and the data supplied by Li (2000), it seemed unlikely that such a short period of treatment could be effective in the long run. Therefore, patients who had been treated with the WHO-advised regimen and had been followed-up with VMT were reassessed 3–8 months after the treatment with prednisolone terminated (Otters & Gieteling 1995; Naafs 1996, 2003a).

It was shown that the VMT deficit improved markedly in nearly all patients during prednisolone treatment. During the follow-up it emerged that the VMT deteriorated in more than half of the patients after treatment to values not much different from pre-treatment values. The average result in VMT deficit before and 6 months after treatment was about the same (Naafs 2003a).

This small study showed clearly that at least half of the patients that had suffered from a Type I leprosy reaction would have benefited from prolonged prednisolone treatment.

There are more data available to support this statement. Nicholls (2000, unpublished data) remarked in a workshop on nerve damage at the Asian Leprosy Congress in Agra, India, that recurrent Type I reactions were frequent. Most participants of that session concurred, but I did not. I had treated (patient-tailored) and carefully monitored, over a period of at least 3 years between 1974 and 2003, an estimated 400 patients with Type I leprosy reaction using VMT and graded sensory testing; moreover, electrophysiological parameters had been measured in approximately 200 of these patients. Less than 2% who followed the recommended treatment had a recurrent reaction (Naafs 2003a). However, the prednisolone treatment often exceeded the 6-month duration, whereas the duration of treatment courses the other participants of the workshop referred to (a.o. WHO blister packs) were much shorter.

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Before the introduction of WHO/MDT, recurrent RR was seen only in patients who developed dapsone resistance (Naafs 2003a). Some patients on dapsone monotherapy developed a recurrent reaction after the introduction of MDT, indicating that they probably were resistant to dapsone. RR frequently recurred in patients who had prematurely stopped their prednisolone treatment; this is similar to the present-day situation, where WHO advises the patients to stop treatment after only 3–4 months thereof (WHO–Novartis blister packs). After the introduction of MDT, recurrent RR was occasionally seen in MB patients released from anti-leprosy treatment (Post *et al.* 1994; Naafs 2003a, probably because of the disappearance of the protective effect of dapsone (Barnetson *et al.* 1976; Naafs *et al.* 1986). Similar reactions have also been seen recently in patients infected with HIV who received highly active anti-retroviral treatment (HAART) (Opromolla *et al.* 2000; Lawn *et al.* 2003; Bianconcini Trindade *et al.* 2005; Collen *et al.* 2005). HAART treatment leads to a restoration of the CMI among which the CMI against *M. leprae* antigenic determinants and this may give rise to a Type I leprosy reaction as a reconstitution syndrome (Lawn *et al.* 2003).

Thacker *et al.* (1996) studied leprosy patients electrophysiologically during and after reactions. The patients were treated with prednisolone over a 6-week period. The authors observed significant improvement during treatment, but noted deterioration after prednisolone was stopped. Li (2000), reporting on the duration of an RR, found that only 39.6% subsided in <3 months and 62.1% within 6 months. In 22.2% of the BL patients RR lasted at least 7–12 months. These findings confirm the data of Naafs *et al.* (1979) who found that BT patients needed 4–9 months of anti-reaction treatment, BB patients 4–14 and BL patients 6–20 months.

Other evidence supporting prolonged treatment with prednisolone comes from Little *et al.* (2001). Using immunohistochemistry, they observed continued Th1 cytokine activity for up to 180 days after the start of prednisolone. Based on this and on recent data from Nepal and Ethiopia, reported during the congress in Salvador, Bahia, Brazil, Lockwood remarked that it might be necessary to prolong the treatment of RR. Thus it seems likely that the anti-reaction treatment advocated and provided by WHO is insufficient (Naafs 2003a).

Public health-oriented leprologists recommend that patients should be instructed concerning the signs and symptoms of reactions and as to when they should return for (re)assessment and treatment. This has become a general WHO policy. However, the study of Otters and Gieteling (1995) showed that hardly any of the patients

who had deteriorated after discontinuation of the prednisolone treatment would have reported back voluntarily. The reasons were that they had not noticed any pain, that the deterioration had been very gradual (silent nerve damage) and that it did not bear resemblance to the ‘disease’ for which they had been treated in the past. As far as they were concerned, they had no cause to return to the doctor. The 3-month prednisolone treatment may, therefore, not only be insufficient, it could even be counterproductive (Naafs 2003a)! Silent nerve damage is a major problem (Croft *et al.* 2000); it is difficult to detect and to treat. However, a number of clinicians reported at the World Leprosy Congress in Salvador that nerve function might improve after prolonged treatment with steroids. Richardus *et al.* (2003) published a double-blind study of long-standing nerve damage (6–12 months) treated with a standard 16-week prednisolone course compared with placebo. They found no additional improvement in nerve function in the treated group. However, there was some indications of less deterioration in this group (Richardus *et al.* 2003). It is likely that their treatment period was too short, as they noticed leprosy reactions and new nerve damage to occur in one-third of the study group.

**Erythema nodosum Leprosum Type II leprosy reaction and thalidomide**

Erythema nodosum leprosum is a common and serious condition occurring in lepromatous MB patients (Lockwood & Bryceson 2003). ENL was described before effective anti-leprosy treatment was introduced. Prior to the Second World War it occurred in 80% or more of all lepromatous patients (DVA Opromolla, personal communication). After the introduction of dapsone the incidence went down markedly, but it still occurred in more than half of the patients (Cochrane 1964).

Erythema nodosum leprosum lesions may recur episodically or become chronic; the lesions may become more extensive involving different organs and may even persist over many years. ENL is a systemic illness with fever, weight loss and pain, as well as a cause of damage to nerves, skin, eyes, testes, etc. Lockwood and Bryceson quote Levy saying, ‘that ENL produces greater disability than the underlying LL and was the commonest reason for admission in hospital’ (Lockwood & Bryceson 2003). Chronic recurrent ENL especially has become a major problem as these patients are treated with long periods of prednisolone and become steroid dependent (Schreuder & Naafs 2003).

The treatment of ENL is less straightforward than that of RR. As in RR, the antigenic load should be reduced

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(Naafs 1996). Many therapies have been considered effective, but as ENL is an episodic self-limiting disease, many drugs have been wrongly judged to be of therapeutic value (Naafs 1996).

From their introduction after WWII steroids became the drugs of choice for the treatment of ENL although obvious benefit was also noted for aspirin, other NSAIDs, anti-malarials and antimonies, but only for mild ENL (Naafs 1996). With the introduction of thalidomide by Sheskin and Sagher, a second highly effective drug became available (Sheskin & Sagher 1968). Clofazimine (Lampren®), a normal constituent of MDT has been shown to suppress ENL. Since the introduction of the WHO-advised MDT, which includes clofazimine, the prevalence of ENL in patients under treatment appears to have dropped (Post *et al.* 1994).

For severe cases of ENL presenting with orchitis, iridocyclitis with glaucoma, or neuritis with deterioration of nerve function, corticosteroids or thalidomide are still considered the main treatments (Naafs 1996, 2000b; Opromolla 2000). A high initial dose is often required. However, at the high dose that is necessary, side effects are numerous, especially in patients with chronic or recurrent ENL (Schreuder & Naafs 2003). It has been theorized that, as ENL is episodic, pulse therapy with high dose of steroids should be given and tapered off quickly within 2 or 3 weeks. If, during the gradual reduction of the drug, the ENL flares up, the dose should be doubled and tapered off quickly again. Maintenance therapy with steroids should be avoided as this may lead to steroid dependence and side effects (Schreuder & Naafs 2003). Thalidomide appears to be the drug of choice for maintenance therapy. It is extremely effective but it has a number of side effects, which usually do not warrant discontinuation of the drug. Teratogenicity is well known and limits its uses. Neuro-pathy may occur more frequently than is reported. When it occurs, it is usually masked by the neuropathy of leprosy. In other conditions it is known to occur in 20–30% of the recipients (Naafs 2003b).

The action of thalidomide is still unclear. Recent publications suggest that it may be very effective in lowering tumour necrosis factor (TNF- $\alpha$ ). However, it is doubtful that this is the way it works (Naafs 2000b; Tadesse & Shannon 2005). Because of the teratogenic effect of thalidomide researchers have been looking for alternatives. Cyclosporine A has been shown by some to be effective in severe ENL and may be a substitute for thalidomide in affluent societies. Although thalidomide is more effective, it frequently cannot be used because of restrictive political legislation. However, during field trials, cyclosporine A was of little benefit in preventing ENL, indicating that it may be less effective in suppressing the

Th-2 type CD4 cells than the Th-1 type CD4 cells involved in the RR (Naafs 2000b).

A strong anti-ENL effect has recently been claimed for pentoxifylline when it is administered in high dosages (Sampaio *et al.* 1998). Other researchers, however, were not that impressed (Naafs 1996; Opromolla 2000). It was tried because some investigators thought that TNF- $\alpha$  is of major importance in ENL and pentoxifylline is known to effectively suppress its production (Sampaio *et al.* 1998). However, TNF- $\alpha$  is also present in RR and here neither thalidomide nor pentoxifylline is of much help in curtailing this condition (Naafs 2000b).

In 2003, Pannikar, the medical officer of communicable diseases (Leprosy group) of WHO, published a paper on ENL and thalidomide and later advised the European Union not to register thalidomide. He focused on the teratogenicity of thalidomide and stated, 'there is no place for thalidomide'. According to him, prednisolone is more effective than thalidomide. Disregarding all other research, he stated that the action of thalidomide in ENL is mainly because of its antipyretic action. According to Pannikar, who, it is assumed, is presenting the view of the WHO, 'today ENL reaction is a rare complication, limited to a small proportion of MB patients. Most of the ENL reactions are mild in nature and do not require any specific treatment except with some analgesics or antipyretics. In those suffering ENL-associated neuritis, the drug of choice is prednisolone. For chronic recurrent reactions the drug of choice is clofazimine' (Pannikar 2003).

Data from Brazil show that 50% of the patients diagnosed were MB and that 30% of these developed ENL (Pereira 2003), confirming data from other countries such as Nepal (Van Brakel & Khawas 1994), China (Li *et al.* 1990), Thailand (Schreuder 1998) and north India (Kumar *et al.* 2004). Thus ENL is certainly not a rare condition.

A large problem is that a considerable number of patients with ENL reactions become steroid dependent (Schreuder & Naafs 2003). An important reason for this could be, according to the authors, that the WHO-advised standard treatment for reactions, a.o. the blister pack (Prednipack) is the same for Type I and for Type II leprosy reactions. The advised 3 to 4-month period is too long for a Type II reaction. ENL, being episodic, lasts <1 month in most patients (De Souza Araújo 1929). And at the start the doses are too low. ENL should be treated for a short period with a high dose of steroids 1–2 mg/kg (Naafs 1996; Schreuder & Naafs 2003). Garbino at the Instituto Lauro de Souza Lima recently confirmed this (Garbino, unpublished data).

Lockwood and Bryceson (2003) state with me (Naafs 2003b) that Pannikar (2003) does not cite scientific research but non-peer reviewed book chapters and a WHO

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strategy document to underline his point that prednisolone is better than thalidomide. Moreira *et al.* (1998), comparing pentoxifylline, thalidomide and prednisolone in the treatment of ENL, demonstrated that thalidomide gave the fastest and most effective clinical response. Although thalidomide has important side effects, it should not be forgotten that corticosteroids have distressing and disabling side effects too, including dependency, especially in patients suffering from ENL (Lockwood & Bryceson 2003).

In 2003, when Pannikar advised clofazimine for chronic ENL, it often was not available for the patients in need, because clofazimine was available in MDT blister packs only and could not be prescribed in the WHO/Novartis sponsored leprosy programmes (Schreuder & Naafs 2003), as all blister packs had to be accounted for. However, recently clofazimine became available for the treatment of Type II leprosy reactions.

**Conclusion**

## WHO

- eliminates leprosy by changing definitions and treatment duration, which has led to the belief that leprosy has indeed been eliminated and this jeopardizes adequate leprosy control and treatment;
- simplifies diagnosis and treatment and puts more emphasis on data collection and drug delivery, which has resulted in reduced awareness and knowledge concerning clinical leprosy within the leprosy programmes;
- minimizes the necessity of prescribing steroids for leprosy reactions, stating that non-steroidal drugs can be given, a policy that ignores all published evidence;
- advocates uniform treatment for different leprosy reactions (a.o. Prednipack), resulting in too short treatment of Type I leprosy reactions, and too long treatment of Type II reactions (ENL), with doses that are usually too low;
- denies the seriousness and extent of ENL reactions and actively discourages the use of an effective drug, thalidomide, resulting in steroid dependency and permanent damage.

Thus WHO advice has led to treatments that do little good to patients and may even harm them.

**WHO, Quo Vadis?**

WHO's most recent report gives cause for hope: elimination is not the main emphasis anymore (WHO 2005).

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**Traitement de la lèpre: Science ou politique?**

**OBJECTIF** Réviser l'histoire du traitement de la lèpre et des réactions lépreuses après la 2<sup>e</sup> guerre mondiale.

**MÉTHODE** Les traitements basés sur l'expérience et les évidences cliniques ont été comparés à ceux recommandés par l'OMS dans le but d'éliminer la lèpre d'ici l'an 2000 et qui plus tard a été reporté à l'an 2005.

**RÉSULTATS** La lèpre n'est pas éliminée. Les analyses des données sur les réactions du traitement suggèrent que les réactions liées aux régimes de traitement recommandés par l'OMS peuvent mener à plus de réactions adverses parmi les patients lépreux comparés aux « anciens » régimes établis.

**CONCLUSION** Les recommandations de l'OMS pour l'élimination de la lèpre peuvent avoir compromis le traitement adéquat de la lèpre pour les années à venir.

**mots clés** lèpre, réactions lépreuses, traitement, santé publique, OMS

B. Naafs **Treatment of Leprosy: science or politics?****Tratamiento de la lepra: ¿Ciencia o política?**

**OBJETIVO** Revisar la historia del tratamiento de la lepra y las reacciones leprosas después de la segunda guerra mundial.

**MÉTODO** Se compararon los tratamientos basados en experiencia y evidencia clínica con aquellos recomendados por la OMS en su intento de eliminar la lepra antes del año 2000, período extendido posteriormente al 2005.

**RESULTADOS** La lepra no ha sido eliminada. El análisis de los datos sobre el tratamiento de reacciones sugiere que los regímenes de tratamiento para las reacciones leprosas recomendadas por la OMS pueden conllevar a una mayor discapacidad entre los pacientes leprosos que aquellos antiguamente establecidos.

**CONCLUSIONES** Las políticas de la OMS para eliminar la lepra pueden haber puesto en peligro el tratamiento adecuado de la lepra en los años venideros.

**palabras clave** lepra, reacciones leprosas, tratamiento, salud pública, OMS