

## Editorial

### CHEMOTHERAPY OF LEPROSY FOR CONTROL PROGRAMMES:\* SCIENTIFIC BASIS AND PRACTICAL APPLICATION

When dapsone (DDS) was introduced as the first effective drug against leprosy in the 1940s, it was assumed that its mass administration to large numbers of leprosy patients would result not only in arrest or cure of the disease in individuals, but also in a steady decrease in the incidence of new cases. It was assumed that the latter would result from the reduction in the pool of infectious patients, so that the chain of transmission would be broken. Unfortunately, and notwithstanding WHO's backing for the introduction of mass DDS control programmes, it was apparent by the mid-1960s that global leprosy had not been controlled by DDS monotherapy. In fact, DDS treatment had only been given to some quarter of those estimated to have leprosy, and of those treated less than half took dapsone regularly. Moreover, although by then the efficacy of DDS for the treatment of leprosy was amply confirmed, experience showed that for lepromatous patients arrest or cure required many years of regular treatment and this was difficult if not impossible to ever achieve in an unsupervised control programme.

Thus by the mid-1960s there was already an air of pessimism and frustration among those directly or indirectly concerned with the treatment and control of leprosy in the field. This was heightened by the increasing frequency of relapses among patients with lepromatous leprosy while under treatment with DDS or among those apparently successfully treated and released from control. In contrast with the frustration and deficiencies facing the field side, in this same period, research programmes based on the mouse footpad infection<sup>1</sup> were being exploited and applied successfully for the first time to the study of DDS and other antileprosy drugs. These studies revealed two serious and complicating phenomena arising in patients with lepromatous leprosy receiving standard DDS monotherapy. Both related to relapses in these patients. Thus resistance to DDS *per se* was first proved by the mouse footpad infection in 1964.<sup>2</sup> By 1976, based on

\* This editorial is based on the recently published WHO Technical Report Series No. 675, 1982 of a Study Group Report on the Chemotherapy of Leprosy for Control Programmes, Geneva, October 1981

detailed and longitudinal studies on the evolution of DDS resistance in Malaysia<sup>3</sup> and Ethiopia<sup>4</sup> and the monitoring of strains of *Mycobacterium leprae* from relapses among DDS-treated lepromatous patients from other countries, it was clear that DDS resistance was a serious and universal phenomenon and was on the increase. Moreover, because of the very long time (5–20 years or more)<sup>3, 4</sup> taken for the emergence of DDS resistance, this will inevitably result in more patients relapsing with DDS resistance from the ever increasing worldwide pool of lepromatous patients receiving DDS monotherapy. The other complication related to the phenomenon of ‘bacterial persistence’. In 1974 it was reported that small numbers of viable and DDS-sensitive *M. leprae* may persist in the tissues of lepromatous patients (as revealed by footpad inoculation using T-cell deficient mice) treated with DDS for 10–12 years.<sup>5</sup> Thus the concurrent leprosy research programmes by defining the phenomena of DDS resistance and bacterial persistence provided for the first time a scientific explanation for the relapses reported in lepromatous patients receiving DDS monotherapy. In retrospect the emergence of drug resistance to monotherapy for leprosy exactly paralleled the inevitability observed many years earlier of drug resistance with monotherapy for tuberculosis, which could be prevented by giving two or more drugs together (combined therapy).

In 1976 the WHO Expert Committee on Leprosy, albeit somewhat belatedly, emphasized the need to prevent the serious and much feared development of DDS resistance, and, in view of this recommended that all active cases of multibacillary leprosy (LL, BL and BB), whether previously untreated or relapsed, should be treated with two effective drugs.<sup>6</sup> In 1977 ILEP (Heathrow Report) went much further in emphasizing the urgency of introducing multidrug regimens; without which the whole future of the treatment and control of leprosy by chemotherapy, including DDS, would be in jeopardy.<sup>7</sup> The Report recommended applicable regimens as well as outlining the operational requirements. Unfortunately, in spite of these clear warnings and recommendations, few countries subsequently introduced multidrug therapy in their leprosy control programmes. Therefore, by and large, DDS monotherapy continued to be standard treatment in control programmes, or where governments or donor agencies funded the purchase of rifampicin and/or clofazimine, these antileprosy drugs were used haphazardly in various multidrug regimens.

It was against this background that WHO determined to convene a Study Group in Geneva in 1981 to review the information since their 1976 Expert Committee Report on the problems related to chemotherapy of leprosy in the field, and above all to propose the most appropriate and universally applicable multidrug regimens to overcome these problems.<sup>8</sup> As was to be expected a further 5 years of DDS monotherapy had resulted in a spiralling increase in the prevalence of DDS resistance of 2–7% in surveys of lepromatous patients from China, Burundi, India, Israel and Mali, and with the isolation of DDS-resistant strains of *M. leprae* from such patients from more than 25 countries, it was

undoubtedly now a very serious world-wide problem.<sup>8</sup> Even more serious was the Study Group's report that since 1976, previously untreated lepromatous patients were presenting *ab initio* with DDS-resistant strains of *M. leprae*, indicating for the first time the spread of DDS-resistant leprosy (primary resistance) among the population at large. Already a devastatingly high incidence of 50% primary DDS resistance in untreated lepromatous patients had been reported from Ethiopia.<sup>9</sup> Similar patients with primary DDS resistance had been reported also from India, Malaysia, Mali, Philippines and USA.<sup>8</sup> Secondary resistance to rifampicin had also been reported.<sup>9</sup> The rapidly increasing prevalence throughout the world of multibacillary patients with mouse footpad proven secondary or primary DDS resistance convinced the Work Group that it was imperative to introduce as rapidly as possible multidrug regimens suitable for control programmes on a world-wide basis, for *both* multi- and paucibacillary patients. The reason for now having to use multidrug regimens for patients with paucibacillary leprosy (and therefore for all types of leprosy) is that primary DDS resistance is just as likely to occur in tuberculoid as in lepromatous patients. In fact, primary DDS resistance in new tuberculoid patients may well be occurring more commonly than in new lepromatous patients, because the incubation period is shorter for tuberculoid than for lepromatous leprosy.

In reviewing how best to deal with this crisis situation, the Study Group considered that the classical strategy of leprosy control based on early detection and effective chemotherapy (secondary prevention) was likely to remain unchanged for many years; since although ideally primary prevention (i.e. an antileprosy vaccine) might be more effective, no such vaccine was immediately available. Therefore the Study Group confined their review to the most efficacious and *immediately* available antileprosy drugs with proven activity against *M. leprae* in the mouse footpad infection, other than DDS, as potential candidates for multidrug regimens. Only three drugs met these criteria (rifampicin, clofazimine, ethionamide/prothionamide)<sup>10</sup> as well as their proven potency and acceptability in leprosy patients. Rifampicin was by far the most potent of the three drugs and from its very rapid bactericidal activity on *M. leprae*,<sup>11</sup> clinical trials have shown that once-monthly doses of 600 mg were as effective as daily, without resulting in any of the known serious toxic manifestations associated with rifampicin given once weekly. Clofazimine, although a bacteriostatic drug, because of its 'depot' property, was fully potent in man at a dose of 100 mg thrice weekly rather than daily, although its potency declined even with larger doses on a monthly basis. Although clofazimine has no toxicity in man over a wide range of doses, it unfortunately causes red-blue pigmentation of the skin/lesions at therapeutic doses to a degree that is unacceptable to most lighter-skinned patients. Ethionamide/prothionamide (both thioamides) are bactericidal, potent drugs against *M. leprae*, but because of their short half-lives and slower rate of killing *M. leprae* than rifampicin, they have to be administered daily. Moreover, both drugs (prothionamide less than ethionamide), at 500 mg daily, can cause

**Table 1.** WHO Study Group's recommended combined antileprosy regimens

<i>For multibacillary leprosy</i>		
(Duration, 2 years)*	Rifampicin	600 mg once-monthly, <i>supervised</i>
	Dapsone	100 mg daily, self-administered
	Clofazimine	300 mg once-monthly, <i>supervised</i> , and 50 mg daily, self-administered
	(Ethionamide/ prothionamide)‡	250–375 mg daily, self-administered
<i>For paucibacillary leprosy</i>		
(Duration, 6 months)†	Rifampicin	600 mg once-monthly, <i>supervised</i>
	Dapsone	100 mg daily, self-administered

\* Minimum of 2 years; wherever possible, to smear negativity; then stop chemotherapy.

† Six months, then stop chemotherapy; if treatment is interrupted, re-start regimen to complete full 6 month course.

‡ Alternative drug when clofazimine is totally unacceptable.

unacceptable gastric symptoms in some patients. None of these three drugs develop cross-resistance with DDS or cross-resistance with themselves.

On the basis of all this currently available and carefully assessed experimental and clinical data on the only three potent antileprosy drugs for dealing effectively with the problems of DDS resistance, the Study Group recommended two multidrug regimens (Table 1). The great merit and applicability of these regimens for treatment in the field is that they will provide effective therapy for patients with pauci- or multibacillary leprosy irrespective of their past history of DDS (previously treated or untreated) or whether currently definite or potential cases of secondary or primary DDS resistance respectively. The need for two regimens, for pauci- or multibacillary patients respectively is essential as the regimen for the paucibacillary patients has only to cope with the possibility of primary DDS resistance with very small numbers of resistant organisms, whereas the regimen for multibacillary patients will have to cope with large potentially DDS-resistant bacterial populations, requiring two additional drugs to prevent the emergence of resistance to either one.

The absolutely vital component to both these regimens is dependent upon the potency of rifampicin and therefore to ensure its ingestion by the patient, every monthly dose *must be supervised*. Supervised administration of rifampicin entirely by the leprosy control staff, rather than by patient self-administration, will also help to prevent this expensive and highly sought-after drug getting into the black market. Daily self-administered DDS is included in both regimens. The regimen for multibacillary patients includes a third drug to prevent the emergence

of rifampicin resistance in those patients who may already be fully DDS resistant. In such patients the administration of rifampicin would equate to monotherapy. The choice for the third drug rests between clofazimine and prothionamide. From the data available, clofazimine is undoubtedly the drug of preference and to ensure maximum potency clofazimine is self-administered at a daily dose of 50 mg with a monthly supervised dose of 300 mg, at the same time the patient attends for the monthly supervised dose of rifampicin. Although there will undoubtedly be lighter-skinned patients who refuse to take clofazimine, every effort should be made to persuade the patient to continue in spite of the pigmentation. Since there is little experience on the degree of pigmentation resulting from the recommended WHO regimen for clofazimine it is important that this should be investigated as soon as possible. Prothionamide should only be included as the third drug for patients who from experience find clofazimine totally unacceptable. For although prothionamide is a bactericidal drug, it has to be administered daily because of its short half-life, thus relying entirely on the compliance of the patient for self-administration. Rifampicin alone would undoubtedly be fully effective for paucibacillary patients (based strictly on I, TT and BT cases), but the Study Group decided to include DDS to provide uniformity for the two regimens, as well as providing DDS as a second drug to help prevent the emergence of rifampicin resistance in more bacilliferous patients that might have been wrongly classified.

The objective of the Study Group was to come up with the most effective regimens for overcoming the very serious problem of DDS resistance that was threatening the whole future for the treatment and control of leprosy by chemotherapy. Therefore the regimens had also to be practical and applicable to control programmes. The recommended regimens admirably achieve these prerequisites, at the same time providing the most potent antileprosy therapy currently available. By taking advantage of the efficacy of pulsed rifampicin therapy, the administration of all doses of this valuable drug will be supervised. Another, and certainly the most appealing, feature of the recommendations to those responsible for maintaining efficient control programmes is the shortening of regimens to 6 months for paucibacillary patients and to a minimum of 2 years for multibacillary patients. Although these shorter courses may not be long enough for all patients, the inclusion of rifampicin will undoubtedly provide effective long-lasting therapy. Where the services can afford, it would certainly be preferable to continue the regimen for multibacillary patients to skin negativity and follow up these patients after stopping treatment. The great asset of both regimens is that they will stop the emergence of drug resistance and therefore any patients that relapse after stopping treatment will immediately respond on restarting with the same regimen.

Undoubtedly these regimens will be more costly (see Table 2), but will have to be accepted in the present 'crisis' situation which will only worsen if multidrug regimens are not introduced. Moreover, the additional cost of these drugs is only

**Table 2.** Cost per patient for combined antileprosy regimens recommended by WHO Study Group (January 1983 prices)

Drug	Multibacillary case who accepts clofazimine (per year)		Multibacillary case who rejects clofazimine (per year)		Paucibacillary case (per 6 months)	
	No.	Cost (\$)	No.	Cost (\$)	No.	Cost (\$)
Rifampicin						
300 mg capsules	24	3.60	24	3.60	12	1.80
Clofazimine						
100 mg capsules	36	2.70	—	—	—	—
Clofazimine						
50 mg capsules	365	13.69	—	—	—	—
Dapsone						
100 mg tablets	365	0.95	365	0.95	182	0.47
Prothionamide						
250 mg tablets	—	—	365	20.08	—	—
Surface shipment		4.35		5.09		0.50
Total cost per patient		\$25.29		\$29.72		\$2.77

Costs are based on the prices quoted by WHO Leprosy Division of Communicable Diseases, Geneva, when the drugs are bought in large quantities. The price for 50 mg capsules of clofazimine was not available and the estimate is based on half the 100 mg capsule price. The cost per patient includes a 20% allowance for the cost of surface shipment of the drugs to a project.

a small fraction of the additional costs to the control service who at present have increasing numbers of relapsed lepromatous patients who are maintained for many years on treatment. More importantly, the introduction of these new regimens will have to be preceded by extensive replanning of the treatment service and retraining of the treatment staff. The patients' cooperation will also be paramount and therefore time must be given for explaining the new treatment regimens, toxic drug symptoms to be reported and, above all, assurance that the shorter course of treatment is effective. This particularly applies to the paucibacillary patients, who may welcome not having to take tablets for several years but may still have one or more visible skin lesions when treatment is stopped after only 6 months.

R J W REES

*Clinical Research Centre  
 Division of Communicable Diseases  
 Watford Road, Harrow  
 Middlesex HA1 3UJ*

## References

- <sup>1</sup> Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into foot pads of mice. *J exp Med*, 1960; **112**: 445.
- <sup>2</sup> Pettit JHS, Rees RJW. Sulphone resistance in leprosy. An experimental and clinical study. *Lancet*, 1964; **ii**: 673.
- <sup>3</sup> Pearson JMH, Rees RJW, Waters MFR. Sulphone resistance in leprosy. A review of one hundred proven clinical cases. *Lancet*, 1975; **ii**: 69.
- <sup>4</sup> Pearson JMH, Haile GS, Barnetson RStC, Rees RJW. Dapsone-resistant leprosy in Ethiopia. *Lepr Rev*, 1979; **50**: 183.
- <sup>5</sup> Waters MFR, Rees RJW, McDougall AC, Weddell AGM. Ten years of dapsone in lepromatous leprosy: clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. *Lepr Rev*, 1974; **45**: 288.
- <sup>6</sup> WHO Expert Committee on Leprosy. *Fifth Report*. Technical Report Series No. 607, 1976.
- <sup>7</sup> ILEP. *Heathrow Meeting Report*, No. 1, 1977. Colchester: LEPRAs.
- <sup>8</sup> WHO Study Group. *Chemotherapy of Leprosy for Control Programmes*. Technical Report Series No. 675, 1982.
- <sup>9</sup> Jacobson RR, Hastings RC. Rifampicin-resistant leprosy. *Lancet*, 1976; **ii**: 304.
- <sup>10</sup> Colston MJ, Ellard GA, Gammon PT. Drugs for combined therapy: experimental studies on the antileprosy activity of ethionamide and prothionamide, and a general review. *Lepr Rev*, 1978; **49**: 115.
- <sup>11</sup> Shepard CC, Levy L, Fasal P. Further experience with rapid bactericidal effect of rifampicin on *Mycobacterium leprae*. *Amer J Trop Med Hyg*, 1974; **23**: 1120.

There will be two further editorials in 1983 on 'The Organisation and Management of Chemotherapy in the Field' and 'The Toxic Effects of Antileprosy Drugs in Common Use', both relating to the 1982 WHO Study Group Report on the Chemotherapy of Leprosy for Control Programmes.