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EDITORIALS

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Rationale of the Multidrug Regimens Recommended by a World Health Organization Study Group on Chemotherapy of Leprosy for Control Programs[1]

This is a personal presentation of some of the most important factors influencing the treatment recommendations made by a World Health Organization Study Group on Chemotherapy of Leprosy for Control Programs[2]. Evidence is presented for the increasing prevalence of dapsone-resistant leprosy and a hypothetical model is described to account for the observed time pattern of this increase. The implications of widespread dapsone resistance for controlling leprosy by case finding and treatment are then discussed, and evidence from the treatment of pulmonary tuberculosis presented to support the conclusion that the problem of drug resistance in the treatment of leprosy could be contained by using multidrug regimens. Finally, the reasons for the choice of the regimens recommended for the treatment of multibacillary and paucibacillary patients are described and their anticipated efficacy in routine practice considered.

Increasing prevalence of dapsone resistance. The prevalence of dapsone-resistant strains of leprosy bacilli is increasing at an alarming rate[2, 3]. The most convincing data to document this conclusion have been obtained in a series of investigations carried out at the Research Unit in Sungei Buloh in Malaysia, over the past 20 years. Extremely well-supervised, high-dosage dapsone treatment (averaging more than 50 mg per day) was introduced there in the early 1950s, and the first cases of proven dapsone resistance were demonstrated in 1964[4]. Initially[5], the prevalence of dapsone resistance was estimated at only about 1 per 1000 but this rose 25-fold over the next decade[6] and is now about 100 per 1000.

[1] Based on paper presented at the Meeting on Action Plans for Leprosy Control, New Delhi, India, 23–25 August 1982.

[2] WHO Study Group. Chemotherapy of leprosy for control programs. Geneva: World Health Organization, Tech. Rep. Ser. 675, 1982.

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TABLE 1. *Hypothetical model for selection of dapsone-resistant* M. leprae *in a previously untreated lepromatous patient prescribed 100 mg dapsone daily.*

Dapsone sensitivity of *M. leprae*	Initial no. viable bacilli	Therapeutic margin	Treatment gap before bacterial multiplication is possible
Fully sensitive	10^{10}	500-fold	10 days
Low-grade resistance	10^{4}	50-fold	6 days
Medium-grade resistance	None	5-fold	3 days
High-grade resistance	None	None	None

Numerous studies indicate that dapsone resistance is now a worldwide problem. Dapsone-resistant strains of *Mycobacterium leprae* have already been isolated from patients in at least 25 countries[2], and it is apparent that wherever dapsone resistance has been sought among treated and relapsed patients with lepromatous or borderline leprosy, it has been found. In several countries, current dapsone-resistance prevalence rates among multibacillary patients are on the order of about 50 per 1000.

Hypothetical model to account for increasing prevalence of dapsone-resistant leprosy. The extraordinarily delayed appearance of dapsone resistance and its subsequent greatly increasing prevalence revealed by the studies carried out at Sungei Buloh can be explained by the long mean generation time of *M. leprae* (about 11 days[7, 8]), its extreme sensitivity to inhibition by dapsone, the pharmacokinetics of dapsone in man, and the assumption that resistance to dapsone in *M. leprae* occurs by a stepwise mutation from low-grade to medium-grade resistance and from medium-grade to high-grade resistance.

The assumption that mutation to dapsone resistance in *M. leprae* occurs in a stepwise fashion is in accord with the classical biochemical genetic studies undertaken by Hotchkiss and Evans on the mechanism of sulfonamide and dapsone resistance in pneumocci[9].

Peak serum and tissue concentrations of dapsone after dosage with 100 mg of the drug exceed its minimal inhibitory concentration against fully sensitive *M. leprae* (about 0.003 μg/ml[10, 11]) some 500-fold. Such a therapeutic margin is quite exceptional[12]. Furthermore, since dapsone is eliminated from the body with a half-life averaging about 27 hours, even a single 100 mg dose of the drug should maintain inhibitory levels of the drug for about ten days.

Evidence for differing degrees of resistance of *M. leprae* to dapsone is well documented[13, 14]. Low-grade resistance mutants are usually defined as those capable of growth in mice fed 0.0001% dapsone in their diet but inhibited by 0.001%; medium-grade resistant mutants, as those only inhibited by 0.01% dapsone in the diet; and high-grade resistance, as those uninhibited by such a concentration. The model also assumes that the natural frequency of mutants

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[13] Rees, R. J. W. Drug resistance to *Mycobacterium leprae* particularly to DDS. Int. J. Lepr. **35** (1967) 625–638.

[14] Shepard, C. C., Levy, L. and Fasal, P. The sensitivity to dapsone (DDS) of *Mycobacterum leprae* from patients with and without previous treatment. Am. J. Trop. Med. Hyg. **18** (1969) 258–263.

of *M. leprae* with low levels of dapsone resistance (resistance ratios of about 10) might be on the order of 1 in 10^6, and that the naturally occurring resistant mutants with intermediate or high-grade resistance (resistance ratios of approximately 100 and 1000, respectively) are much rarer (fewer than 1 in 10^{10}). Such proportions are based on evidence concerning the frequencies of drug-resistant mutants encountered in *M. tuberculosis* to isoniazid, streptomycin and rifampin. The proportion of isoniazid- and streptomycin-resistant mutants with resistance ratios of about 4–8 is about 1 in 2×10^5 and 1 in 10^6, respectively; while those with higher resistance ratios are much rarer[15, 16]. Rifampin-resistant mutants are rarer (1 in 10^6–10^7) but in this case all the mutants are highly resistant, with resistance ratios of at least 8[17] and often as great as 128 (J. M. Dickinson, personal communication).

As shown in Table 1, it is assumed that prior to treatment a typical lepromatous patient might harbor approximately 10^{10} viable *M. leprae*[18]. Among such a population there might therefore be some 10^4 mutants with low-grade dapsone resistance but it is assumed that there would probably be none with higher degrees of resistance. Since treatment at Sungei Buloh was by and large very well supervised[6], treatment gaps of ten days or more would have been extremely rare, with the consequence that only exceptionally would fully sensitive bacilli be able to multiply between doses. However, substantial unsuspected irregularities in dapsone ingestion certainly must have occurred among at least a small number of the patients as evidenced by the finding that of the 2500 originally screened for *prima facie* evidence of dapsone resistance, five had relapsed with fully dapsone-sensitive *M. leprae*[5]. Treatment gaps of six days or more would have been more common, permitting mutants with low degrees of dapsone resistance to multiply for a few days. Little by little one assumes that the populations of such mutants gradually increased with each successive lapse in patient compliance. Eventually, in a few patients these populations of low-resistant mutants would grow to such a size (say, to 10^6 or more) that they would generate mutants with medium-grade dapsone resistance.

Medium-grade mutants would be able to grow when less extended lapses in compliance occurred (three days or more), and in their turn spawn a new generation of still more resistant mutants. Eventually mutants would arise that were fully resistant to the dapsone levels achieved when every dose was taken, and at this point the patient would relapse both clinically and bacteriologically. Hence the great delay before the first dapsone-resistant cases were suspected, followed by the increasingly rapid subsequent rise in their prevalence.

Such a model would also explain the much speedier emergence of dapsone resistance in Ethiopia[19], where considerably lower doses of dapsone were employed, and by evidence that irregular treatment is a major factor encouraging the emergence of drug resistance[13, 20].

Consequences of the increasing prevalence of acquired dapsone-resistant leprosy. The relapse of a previously treated multibacillary patient with dapsone-resistant leprosy is a disastrous setback for the individual concerned. It also poses a threat to the whole community. Thus evidence of primary dapsone resistance among previously untreated patients demonstrates that relapsed patients with acquired resistance can infect their contacts with dapsone-resistant strains of *M. leprae*[3]. For this reason, primary dapsone-resistant leprosy can be expected to be found on an increasing scale

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among both tuberculoid and lepromatous patients. Continued reliance on dapsone monotherapy for the treatment of leprosy will, therefore, inevitably further enlarge the reservoir of dapsone-resistant *M. leprae* until, as in Ethiopia, it threatens the practical possibility of controlling leprosy by chemotherapy alone[19].

Necessity for introducing multidrug treatment. Fortunately, experience in the treatment of tuberculosis shows that the problem of drug resistance can be overcome by giving a combination of at least two fully potent drugs. Both drugs kill or prevent the multiplication of drug-sensitive organisms, and each drug prevents the growth of mutants that are resistant to the other drug. Furthermore, since the chances of finding bacilli that are naturally resistant to both drugs is extremely slight, perhaps 1 in 10^{12}, even among the huge mycobacterial populations found in patients with smear-positive pulmonary tuberculosis or lepromatous leprosy such bacilli are most unlikely to be encountered.

The success of tuberculosis treatment using combinations of drugs. Such an approach has been used in the treatment of pulmonary tuberculosis since the early 1950s, as soon as the original, controlled clinical trials demonstrated that if monotherapy was employed many patients rapidly relapsed with drug-resistant strains of *M. tuberculosis*[21–23]. Since that time, the use of combined therapy has largely controlled the problem of drug resistance and the prevalence of primary resistant strains has not risen to alarming proportions throughout the world.

Evidence for this conclusion is set out in Table 2 which summarizes the results of a series of investigations using the same carefully standardized methods of drug sensitivity testing[24] that enable comparable es-

TABLE 2. *Prevalence of strains of* M. tuberculosis *with primary resistance to isoniazid and streptomycin.*

Country	Date	Prevalence (%)	Footnote no.
England and Wales	1957	2.7	25
	1963	2.4	26
	1979	1.6	27
Scotland	1968	4	28
Singapore	1971	6	29
	1975	3	30
	1979	9	31
Kenya	1964	11	32
	1974	10	33
Tanzania	1970	9	34

[21] Medical Research Council Investigation. Streptomycin in treatment of pulmonary tuberculosis. Br. Med. J. **2** (1948) 769–872.

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[29] Singapore Tuberculosis Services/Brompton Hospital/British Medical Research Council Investigation. A controlled clinical trial of the role of thiacetazone-containing regimens in the treatment of pulmonary tuberculosis in Singapore. Tubercle **52** (1971) 88–116.

[30] Singapore Tuberculosis Service/British Medical Research Council. Controlled trial of intermittent regimens of rifampicin plus isoniazid for pulmonary tuberculosis in Singapore. Lancet **2** (1975) 1105–1109.

[31] Singapore Tuberculosis Service/British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Am. Rev. Respir. Dis. **119** (1979) 579–585.

[32] East African/British Medical Research Council Kenya Tuberculosis Survey. Tuberculosis in Kenya: A follow-up of a national sampling survey of drug resistance and other factors. Tubercle **49** (1968) 136–169.

[33] Second East African/British Medical Research Council Kenya Tuberculosis Survey. Tuberculosis in Kenya: A second national sampling survey of drug resistance and other factors, and a comparison with the prevalence data from the first national sampling survey. Tubercle **59** (1978) 155–177.

timates of the prevalence of primary resistance to isoniazid and streptomycin to be calculated for several countries over a number of years. In England and Wales, the prevalence of primary resistance to these two drugs, which was only 2.7% in 1957, has declined to still lower levels over the last two decades. Low levels of primary resistance have also been found in Scotland and Singapore, demonstrating the efficiency of their health care systems in delivering effective multidrug treatment to their patients. The prevalence of primary resistance in Kenya and Tanzania was considerably higher, reflecting poorer treatment services and the use of less potent combined regimens. Nevertheless, there is convincing evidence from both of these countries that the prevalence of primary resistance did not increase during the first decade following the introduction of combined treatment.

Implications for treatment of multibacillary leprosy patients. The problem of lepromatous patients relapsing through the selection of drug-resistant *M. leprae* should therefore be overcome by using a combined treatment of at least two fully potent drugs. A combination of dapsone plus one other potent drug ought to provide effective treatment for patients infected with fully drug-sensitive *M. leprae,* while those infected with fully dapsone-resistant organisms should be treated with a combination of two other drugs. However, in view of the increasing prevalence of both acquired (secondary) and primary resistance and the virtual impossibility of diagnosing dapsone resistance under field conditions, every multibacillary patient must be considered to be potentially suffering from dapsone-resistant leprosy. Hence the WHO Study Group recommendation that all multibacillary patients should be treated with a combination of dapsone plus two other potent drugs. Then, whatever the level of their dapsone resistance, every patient would be prescribed fully effective chemotherapy[3].

Choice of appropriate antileprosy drugs. The most important factors affecting the choice of drugs for use in combined regimens are their antibacterial potency and patient acceptability. Considerations of cost should be of secondary importance since, however expensive the drugs may be, their cost is never more than a tiny fraction of that required to finance the treatment service to identify the patients and regularly deliver chemotherapy to them until they can be released from control. To set up an efficient treatment service that delivers unsatisfactory chemotherapy can never make sense.

An effective antileprosy drug may be defined as one that is able to completely prevent the multiplication of drug-sensitive *M. leprae.* If a drug has only bacteriostatic activity so that as soon as tissue levels have fallen below its minimal inhibitory concentration against *M. leprae* the bacilli are able to resume multiplication, the regularity with which it is ingested by patients will be critical. However, numerous studies have shown that the drug compliance of leprosy patients is often very poor[35].

When drugs have significant bactericidal or bacteriopausal activity and are capable of either killing the bacilli or preventing regrowth for a significant period of time after the drug has been eliminated from the body, it is not essential to maintain continuously inhibitory levels in the body. Patient compliance then becomes much less important and the possibility arises of devising effective regimens based on supervised intermittent dosage. Examples of antileprosy drugs with increasing degrees of experimentally determined bacteriopausal and bactericidal activity are clofazimine, dapsone, ethionamide/prothionamide and rifampin, in that order[9, 36–41].

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[34] East African/British Medical Research Council Tanzania Tuberculosis Survey. Tuberculosis in Tanzania: A national sampling survey of drug resistance and other factors. Tubercle **56** (1975) 269–294.

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The relative potency of individual components for the combined treatment of multibacillary patients can be assessed by determining the time required for the drugs, when given as monotherapy, to result in the killing of at least 99–99.9% of the viable leprosy bacilli, the point at which inocula are no longer infectious for mice. Any drug treatment that achieves such a loss of infectivity in the average patient within 4–6 months may be regarded as efficacious. The enormous potency of rifampin is demonstrated by the fact that such bacterial killing is achieved within four days after giving just a single 600 mg dose of the drug[38].

Clofazimine given at a dose of 100 mg thrice weekly is also highly effective[42]. However when it was given at a dose of 600 mg on two consecutive days every month there was evidence that its efficacy was impaired[43]. It was therefore concluded that once-monthly treatment with clofazimine would probably be inadequate and that supervised monthly doses of 300 mg clofazimine should be given supplemented by 50 mg doses for daily self-administration.

The efficacy of ethionamide and prothionamide has not been properly evaluated, although promising results were previously obtained among small numbers of patients in San Francisco and Sungei Buloh. However, investigations of their antileprosy activity when given at daily dosages of 250 mg or 500 mg have recently been started in Cebu, The Philippines, with the support of THELEP.

To be of widespread applicability, it is essential that regimens recommended for worldwide use are excellently tolerated. The experience at Sungei Buloh, where over 200 patients have been treated for at least two years with daily dapsone plus two consecutive daily doses of rifampin each month (R. J. W. Rees, personal communication), testifies to the likely acceptability of once-monthly rifampin treatment. Considerable experience with clofazimine indicates that daily treatment, averaging 100 mg or less, is likely to be well tolerated by dark-skinned patients. However the acceptability of ethionamide and prothionamide may be expected to be much less satisfactory, primarily on account of gastrointestinal intolerance[44, 45].

Recommended treatment for multibacillary patients. The regimen proposed by the WHO Study Group for the treatment of lepromatous and borderline patients[2] consists of supervised once-monthly doses of 600 mg rifampin and 300 mg clofazimine together with daily doses of 100 mg dapsone plus 50 mg clofazimine for self-administration. This regimen should be given for at least two years and, wherever possible, to smear negativity. It may be supplemented by the addition of monthly supervised doses of 500 mg ethionamide or prothionamide, but studies are required to assess the potential contribution of such an addition to its efficacy. Every effort should be made to persuade patients to agree to treatment with clofazimine, despite the coloration of the skin lesions it causes, in view of the considerable uncertainties concerning the acceptability and efficacy of the only other alternative drugs, ethionamide or prothionamide.

Anticipated efficacy. Providing the drug components of the recommended regimen are both delivered by the treatment services and ingested by the patients, there should be no failures caused by the emergence of

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ment of *M. leprae* infections in mice. Int. J. Lepr. **44** (1976) 135–139.

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drug-resistant *M. leprae*. Furthermore, such a treatment regimen is applicable to all multibacillary patients, whatever their past history. In addition, there are reasonable grounds for concluding that such a regimen should result in acceptable relapse rates (less than 1% per annum) after treatment has been discontinued. Most importantly, one can expect that, as in the case of the short-course chemotherapy of tuberculosis[46, 47], any patients who relapse after stopping treatment should do so with drug-sensitive organisms with the consequence that it is possible to successfully retreat them with an additional course of the same regimen. The greatly shortened duration of therapy eventually will reduce considerably the number of patients under treatment. However, since the monthly supervised doses of rifampin are an absolutely vital component of the regimen, it will necessarily place much greater responsibility for the ultimate success or failure of leprosy control on the staff of the treatment services than was the case in the past.

The efficacy and acceptability of the recommended regimen is currently being studied in THELEP-supported field trials involving about 1000 multibacillary patients in Karigiri and Polambakkam, South India.

Recommended treatment of paucibacillary patients. Because the maximum bacterial load in paucibacillary patients is only about 10^6, the problem of drug-resistant mutants arising as a result of treatment is insignificant, and it is only necessary to administer a single effective antileprosy drug. However, treatment with dapsone alone can no longer be considered adequate because of the increasing proportion of new paucibacillary patients who are likely to be infected with dapsone-resistant strains of *M. leprae*. Furthermore, it is impossible to ascertain which paucibacillary patients may be infected with dapsone-resistant leprosy. The WHO Study Group therefore proposed that paucibacillary patients should be treated for six months with self-administered 100 mg dapsone daily supplemented by once-monthly supervised doses of 600 mg rifampin. Such a regimen should be fully effective whether or not patients have been infected with dapsone-resistant *M. leprae*. Furthermore, the addition of rifampin would also provide an additional margin of therapeutic security to forestall the possible emergence of drug resistance among any borderline patients who, under field conditions, might inadvertently be misclassified as paucibacillary cases. The fact that among lepromatous patients a similar degree of bacterial killing could be achieved by single doses of rifampin as with some three months' daily dapsone[36–38] treatment encouraged the belief that the proposed regimen should greatly reduce the length of treatment required to cure paucibacillary patients.

—Gordon A. Ellard, Ph.D.

National Institute for Medical Research
The Ridgeway, Mill Hill
London NW7 1AA, England

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