Editorial

COMBINED THERAPY IN PRINCIPLE AND PRACTICE FOR THE CONTROL OF DAPSONE RESISTANCE

The widespread emergence of dapsone-resistant strains of *Mycobacterium leprae* in patients with lepromatous leprosy who had been treated with dapsone as monotherapy, is now fully accepted (WHO, 1977). This growing problem of acquired (secondary) dapsone resistance among the large pool of dapsone-treated lepromatous patients at risk, could be still more foreboding with the recent reports of new and previously untreated lepromatous patients presenting *de novo* with dapsone resistance (primary resistance) in known areas with secondary dapsone resistance (Pearson *et al.*, 1977; Jacobson, 1977). While it was anticipated that cases of primary dapsone resistance would be likely to occur eventually, once secondary resistance was proven, these reports substantiate our worst fears and establish that dapsone-resistant strains of *M. leprae* are infectious for man. Although the cases reported had lepromatous type leprosy all types will present with primary dapsone-resistant infections. In fact a proven case of primary dapsone resistance presenting as tuberculoid leprosy is reported by Waters and colleagues on page 127. Therefore alternative drugs are already required for treatment of the very substantial numbers of relapsed lepromatous patients with acquired dapsone resistance; if primary dapsone resistance should reach serious proportions, alternative drugs will also be required for tuberculoid as well as lepromatous patients and then the future use of dapsone would be uncertain. Any significant spread of primary dapsone resistance would be catastrophic for the control of leprosy, because there is no sure way of distinguishing in the field a dapsone-sensitive infection from a dapsone-resistant one, and therefore all new cases would require additional alternative drugs even if dapsone was given in combination. (While only the mouse footpad technique can identify a dapsone-resistant strain of *M. leprae*, the test takes at least 6 months, and can only be applied to bacilliferous patients. Hence the technique would not be universally applicable for identifying primary dapsone, since no tuberculoid patients could be tested and treatment of the lepromatous patients would have had to be initiated long before results were available from the mouse test.)

Now the existence of secondary
seriousness appreciated, it is clear from the discussions above that unless therapeutic regimens are rapidly introduced to diminish the emergence of secondary resistance and the chances of the spread of primary resistance, the whole future of the control and treatment of leprosy by chemotherapy, including dapsone, will be in jeopardy.

Therefore it is essential to introduce urgently other available anti-leprosy

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drugs and therapeutic regimens for the prevention of dapsone resistance before the problem becomes still more serious. There are two aspects of the problem, one is to prevent the emergence of dapsone resistance and the other is to treat dapsone resistance once established. For the prevention of drug resistance in general, combined therapy has proved to be highly successful, particularly in tuberculosis. For leprosy this would involve every new lepromatous patient being treated at onset with dapsone at full dosage with at least one companion drug. For the treatment of leprosy patients with established dapsone resistance alternative drugs would be required, as combined therapy for lepromatous patients and as monotherapy for tuberculoid leprosy.

For tackling these aspects of the problem, the essential requirement is for other currently available anti-leprosy drugs. Although the choice is small, it is important to select drugs with maximum potency and tolerance. The two papers by Colston and his colleagues in this number of *Leprosy Review* are highly relevant since they present a very detailed assessment of the anti-*M. leprae* and relevant pharmacological features of all the drugs available. Although most of the data is from their own studies, they have brought together data from the world liturature in presenting their final assessment of the best drugs to be selected for combined therapy.

Since *M. leprae* cannot be cultured *in vitro*, the mouse footpad model had to be adapted for assessing anti-leprosy drugs. In the last decade this model has played a major role in clarifying the bacteriological and pharmacological properties of anti-leprosy drugs and in rationalizing the chemotherapy of leprosy. Applying all the available and now highly sophisticated mouse models and pharmacological methods, Colston and colleagues have evaluated and compared the bacteriological and pharmacological activities of companion anti-leprosy drugs, or group of drugs, that are available for combined therapy. The drugs studied included two diphenyl thioureas-thiambutosine (Ciba, 1906) and thiocarlide (Isoxyl); thiacetazone (TBI); a long-acting sulphonamide—sulphamethoxypyridazine (Lederkyne, Medicel) and two thioamides—ethionamide and the propyl analogue, prothionamide. Each drug was tested against several strains of *M. leprae* and the minimum effective dose (MED) fed to mice that prevented bacterial multiplication in the footpad, was determined. The minimal inhibitory concentration (MIC) of each drug in the mouse was determined by estimating the serum concentration corresponding to the MED.These estimations involved the development of the very sensitive radiochemical and novel gas–liquid chromatographic procedures described in their current papers. Furthermore, the model was adapted to determine whether the drug was bacteriostatic or bactericidal against *M. leprae,* using the kinetic or proportional bactericidal tests. Finally, for each drug the ratio of its peak serum concentration in man, from an acceptable and non-toxic dose, to its MIC in the mouse was calculated, as was the duration in which the serum concentration exceeded the MIC.

From these extensive and comparative studies on the 6 companion drugs, only the two thioamides—ethionamide and prothionamide—are bactericidal and also have the highest peak serum/MIC ratios. The other companion drugs are only bacteriostatic, and with the exception of thiacetazone have poor peak serum/MIC ratios.

Using the same principles for determining the therapeutic activities of these 6 anti-leprosy drugs, Colston and colleagues review data for dapsone and the diacetetyl derivative, acedapsone (DADDS), clofazimine (B663) and rifampicin. By these criteria rifampicin, dapsone and clofazimine were bactericidal drugs, the former being the most powerful bactericidal anti-leprosy drug so far studied and in this respect clofazimine falling between the two. Regarding peak serum/MIC ratios, these were high for rifampicin and dapsone and in the case of dapsone significantly higher and more sustained than for any other anti-leprosy drug. Acedapsone giving by injection is dependent for its activity on the slow release of dapsone, and in the dose used sustains serum levels of dapsone approximately 15-fold above the MIC for some 200 days. The other criteria for assessing the anti-leprosy activities of drugs cannot be applied for clofazimine, because it is accumulated in the tissues.

From these basic principles on which the activities of anti-leprosy drugs can be defined using the mouse models, it remains to determine their practical application to the problems of the control and treatment of dapsone resistance.

In practice one of the principle criteria—that drugs with a low peak serum/MIC ratio have no value, excludes the use of thiambutosine (which also is no longer manufactured), isoxyl and any of the long-acting sulphonamides. Therefore, the two former drugs must never be used as companion drugs in combined therapy, and the long-acting sulphonamides must never be used as alternatives to dapsone. This leaves for consideration two sulphones, dapsone and acedapsone, rifampicin, clofazamine, thiacetazone and two thioamides, ethionamide and prothionamide. From the practical side however, there are other criteria, including drug toxicity and acceptability, likely cross-resistance between drugs and cost/effectiveness. By all these criteria dapsone is the first drug of choice and therefore it is *essential* that it retains this position. To prevent the emergence of dapsone resistance, all new lepromatous patients must be initiated on combined therapy i.e. dapsone and a companion drug. Because of the practical difficulties of ensuring unsupervised daily dapsone therapy, it is strongly recommended that dapsone intake should be boosted by also giving intramuscular injections of acedapsone every 3 months. The choice of the companion drugs rest between rifampicin, clofazimine, thiatezone and ethionamide/prothionamide. On the basis of cross-resistance, all are acceptable, since none of these companion drugs would show cross-resistance with dapsone. On the basis of drug toxicity and patient acceptability, the following criteria must be considered: (1) Thiacetazone toxicity appears to be regionally distributed, and in general is intolerable in countries east of India. (2) The intensity of skin pigmentation resulting from clofazimine therapy is intolerable for all paler skinned patients. (3) Of the two thioamides, prothionamide causes less gastric intolerance than ethionamide, and since this intolerance appears to be directly dose dependent, the new data of Colston and his colleagues indicating that a daily dose of 250 mg would still be bactericidal, strongly favours the use of prothionamide. Finally the cost of these companion drugs must be considered; on the basis of a standard daily dose the costs would be: rifampicin 95p, thiacetazone 1p, clofazimine 5.5p and prothionamide 13p.

For the treatment of lepromatous patients who have developed dapsone resistance, their subsequent therapy must depend entirely on "companion" drugs and also as combined therapy, to prevent the emergence of resistance to these drugs. The choice of drugs must take into account the criteria referred to above, but also the potential cross-resistance between the companion drugs. Unfortunately this does limit the number of companion drugs available for dual therapy because of cross-resistance between thiacetazone, ethionamide and prothionamide (Rees and Waters, unpublished data, 1978). Therefore, while these three drugs cannot be given together, they can be used in dual therapy with rifampicin or clofazimine, with no risk of cross-resistance. Of the three drugs, the choice would be between prothionamide as the least toxic and bactericidal, and thiacetazone as being only a bacteriostatic, but a very cheap, drug. Although the very high cost of rifampicin would rule its use out for most countries, its very high bactericidal activity must be considered. This exceptional activity should enable rifampicin to be administered for a much shorter time in combination. Where funds are limited the following extremes are suggested: a single initial 3-fold the standard dose, or initial courses using the standard dose for 1, 2, 3 or 4 weeks, all in combination with another drug. Thus, while the principles for treating and controlling dapsone resistance are reasonably well worked out, it is clear that to put these into practice each country will have to very carefully consider which approach would be feasible and financially possible. It is also clear that whichever one is chosen, it must go in parallel with a greatly upgraded leprosy control service, which can only be achieved by extensive retraining of all personnel at all levels (guidelines on these requirements are set out in the "*Heathrow Report*", copies of which can be obtained from LEPRA).

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