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The Diagnosis and Management of Dapsone-resistant Leprosy

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Based on experience gained with some 120 proven dapsone-resistant patients, the clinical and bacteriological diagnosis of secondary sulphone resistance is described, and the differential diagnosis discussed. The various findings in the clinical trial and experimental proof of sulphone resistance are interpreted according to the pharmacokinetics of dapsone resistance in lepromatous (LL and BL) leprosy. The results of treatment of dapsone-resistant patients with clofazimine (for over 13 years) and with rifampicin (for up to 8.5 years) are compared and contrasted, and the scientific basis for future alternative regimens is briefly discussed.

Introduction

Although the sulphones were first introduced in 1941 (Faget *et al.*, 1943), *prima facie* evidence of sulphone resistance was not reported until 1953 by Wolcott and Ross, and the first clinical and experimental proof was obtained by Pettit and Rees in 1964. Twelve years ago, sulphone resistance was thought to be relatively rare (Pettit, Rees and Ridley, 1965); today, it is met with steadily increasing frequency. Experimentally-proven cases have been reported from the majority of laboratories which use the mouse foot-pad technique. Many other centres have also reported *prima facie* or clinically proven resistance, confirming that dapsone resistance has become a world-wide phenomenon.

Sulphone resistance is of the greatest importance; to the medical services because all alternative drugs are more costly and are usually more toxic than dapsone (DDS); to the patient, because relapse will result in a further period of ill health and perhaps in additional tissue damage; and to contacts, because primary sulphone resistance may only slowly be recognized during an initial period on dapsone therapy in which important clinical deterioration can occur. Therefore it is essential for the diagnosis to be suspected early, to be confirmed clinically and/or experimentally, and for correct alternative treatment to be instituted quickly. The following account of the diagnosis, differential diagnosis and treatment of dapsone-resistant leprosy is based on experience gained with some 120 proven cases seen at the National Leprosy Control Centre, Sungei Buloh between 1961 and 1977.

Diagnosis

Sulphone resistance should be suspected in every lepromatous or borderline-lepromatous (LL and BL on the Ridley-Jopling, 5-point spectrum) patient who

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relapses. Relapse here means the renewed multiplication of leprosy bacilli resulting in the appearance of new lesions, in a patient who had been responding normally to chemotherapy, and whose disease was becoming or had become quiescent or even arrested. Relapse may be due either to the emergence of drug-resistant *Myobacterium leprae,* or to the multiplication, when chemotherapy is stopped, of those small numbers of viable, drug-sensitive *M. leprae* which persist for many years despite adequate sulphone therapy (Waters *et al.,* 1974). The occurence of a relapse in a patient still receiving dapsone is *prima facie* evidence of drug resistance. On the other hand, relapse occurring in a patient who (either on the advice of his doctor or of his own accord) has ceased to take dapsone for at least several months, is usually due to the multiplication of "persisters", but is occasionally due to the emergence of dapsone-resistant mutants. Irregular treatment predisposes to sulphone resistance (Jacobson, 1973), as also does low-dose treatment (Meade *et al.,* 1973), and especially, initial very low dose followed by low-dose dapsone maintenance therapy (Pearson *et al.,* 1976). Patients treated in the past in this way require particularly careful long-term follow-up.

Evidence of relapse due to sulphone resistance has been detected between 3 and 24 years after the start of dapsone treatment, with an average of 15.8 years in Malaysia (Pearson *et al.,* 1975), where dapsone was widely used in full dosage, and of 6-7 years in Ethiopia (Pearson *et al.,* 1976), where low-dose treatment was long in vogue. Sulphone resistance is thought to develop in a step-wise fashion.

The Malaysian patients found to be suffering from secondary dapsone resistance have either been LL or BL (87 and 13 respectively in the first 100 diagnosed); none has been BB. The great majority of patients have had a distinctive clinical appearance. On a background of old resolving lepromatous leprosy, were new active asymmetrical relapse papules and plaques. The ears were frequently lax and wrinkled, and smears from the lobes were either negative for acid-fast bacilli, or else had a low bacterial index (BI) with a morphological index (MI) of 0. On the other hand, the relapse papules were clinically active, some having the appearance of histoid lesions (histologically, 25 of 100 were graded histoid, expansile or hyperactive by Ridley). Such lesions had a high BI, usually 5+ on Ridley's logarithmic scale, with a raised MI. A few patients delayed reporting until their bodies and ears were covered by large numbers of relapse papules, and therefore their lesions appeared nearly symmetrical. But only one of the first 100 dapsone-resistant patients seen at Sungei Buloh was clinically indistinguishable from previously untreated lepromatous disease, with widespread symmetrical infiltration and a small number of near-symmetrical papules. Therefore the combination of history, clinical appearance and smear results gave the diagnosis in almost every case.

Differential Diagnosis

Although the clinical appearances of relapse are so distinctive, several dapsone-resistant patients have been referred to the Leprosy Research Unit as suffering from Erythema Nodosum Leprosum (ENL). ENL papules are usually tender, are purple in colour, may be associated with systemic upset and fever, and change in appearance within 48-72 h; smears taken from them have a variable BI, but the MI is almost always O. Any difficulty in distinguishing between relapse

papules and ENL can be resolved by watching the lesions over 2-3 days, as the former will remain unchanged whereas the latter will show typical progression in this time.

Proof of Resistance

Scientific proof is essential, for once a patient has developed sulphone resistance, it is never possible to revert to dapsone therapy. We have isolated *M. leprae* from 2 resistant patients 5 years and $7\frac{1}{2}$ years respectively after changing treatment to clofazimine. Both strains remained fully sensitive to clofazimine, and both were still dapsone resistant (Rees and Waters, unpublished data).

Proof is by drug-sensitivity testing in the mouse foot-pad infection, and by clinical trial of dapsone, preferably 400 mg twice weekly (in a full-sized adult) given by injection, or else 100 mg daily by mouth with frequent urine tests for dapsone to confirm that the drug is being ingested. These experimental and clinical methods have been well described in the past (Pettit and Rees, 1964; Pettit, Rees and Ridley, 1966) although a few points need stressing.

Excellent correlation has been obtained between the 2 methods of proof, in keeping with the known pharmacokinetics of drug resistance. The latter in general arises from the presence of a few specific resistant mutants in the microbial population. Although not yet studied for *M. leprae,* such mutants have been extensively studied in *M. tuberculosis* where the mutation rate is 10^{-6}-10^{-7} for low, and 10^{-8}-10^{-9} for high resistance. Therefore, out of every thousand million (10^9) tubercle bacilli, one would expect to find perhaps 500 naturally occurring, slightly resistant mutant bacilli, 50 moderately resistant bacilli and one highly resistant mutant against any drug which produces step-wise, as opposed to single-step, resistance. The situation is probably similar for *M. leprae* (Ellard, 1975; Pearson *et al.*, 1975). Untreated LL patients may be infected with 10^9-10^{11} viable *M. leprae.* Because of the exquisite sensitivity of *M. leprae* to dapsone, one would anticipate regular high dosage dapsone therapy to be reasonably successful. Only a proportion of patients might be assumed to possess small numbers of such highly resistant mutants as could survive the blood and tissue levels achieved with doses of the order of 100 mg dapsone daily (although the majority might possess low resistant mutants), and because of the prolonged generation time of *M. leprae* (12-13 days), clinical signs of resistance would take many years to develop. Such is the case. On the other hand, initial low dose therapy would help to "breed out" resistant mutants, and might allow low resistant mutants to multiply sufficiently to produce small numbers of highly resistant mutants even when the latter were initially not present. The situation would be even worse with irregular therapy, or very low dosage maintenance therapy.

Now consider the situation in a patient who has relapsed. Should the patient have been receiving—and taking—dapsone regularly, in full dosage, then the relapse will be due to highly resistant mutants. On the other hand, should the patient have been on low dosage dapsone, then the majority of viable *M. leprae* in his relapse lesions are likely to be only slightly or moderately resistant. But small numbers of highly resistant mutants may well also be present. These points have important applications in the proof of resistance.

EXPERIMENTAL PROOF

The fresh tissue source of the *M. leprae* for mouse foot-pad inoculation, should be obtained by skin biopsy of an active relapse lesion, with a high BI and raised MI. It is advisable to take the biopsy before commencing the full dosage regular dapsone treatment of the clinical test of resistance. This is because, if the patient has been on low dose and/or irregular treatment, the great majority of bacilli in the relapse lesions may be only low or moderately resistant mutants; most of these bacilli will die within about 3 months of starting full dosage dapsone, and at this stage the number of highly resistant mutants may as yet be too few (i.e. less than one in 10,000 living and dead bacilli) to be detected in the mouse foot-pad. The experiment would therefore be a failure, with no evidence of multiplication in either the control or the dapsone-fed mice.

It is customary to include groups of mice fed on 3 different concentrations of dapsone in their diet, namely 0.01%, 0.001% and 0.0001%. These produce serum levels of dapsone of the same order as those obtained in man with 100 mg, 10 mg and 1 mg dapsone daily, respectively. Until very recently, all strains of *M. leprae* obtained from previously untreated cases of leprosy were sensitive to 0.0001% dapsone (Ellard *et al.*, 1971; Levy and Peters, 1976). Patients infected with strains of *M. leprae* resistant to 0.0001% but sensitive to higher concentrations of dapsone, would be expected to respond to full dosage dapsone, taken regularly. However, such patients may also harbour small numbers of highly resistant mutants. Patients whose bacilli are found to be resistant to 0.001% are most likely also to harbour some mutants resistant to 0.01% dapsone in the mouse diet.

CLINICAL PROOF

Clinical proof is both important and practical. The majority of leprosy control schemes and leprosaria do not have access to the mouse foot-pad test, and must rely entirely on the clinical testing of resistance. However, it is desirable, wherever possible, for a proportion (say one in 10) of patients with *prima facie* evidence of dapsone resistance, to be subjected to experimental as well as clinical proof, to substantiate and support the clinical findings. A clinical trial is also of value in convincing a patient that dapsone is no longer of value in his case, and that he must change treatment.

It is essential that the clinical test of resistance should be carried out formally and scientifically, so that there can be no doubt subsequently of the validity of the result. It has been our practice to assess all patients referred with *prima facie* evidence of resistance by full clinical examination, by smears from both ear lobes and at least 4 other skin sites (usually taken from active, relapse lesions) for the BI and MI, and by skin histology, before commencing trial treatment. The latter has been dapsone 400 mg twice weekly by injection in full-sized adults, and 300 mg twice weekly in small adults, given either by the leprosarium or, by arrangement, by district hospitals or rural health centres. Very rarely, for example when a patient has been travelling in connection with his work, we have been forced to rely on the patient himself taking dapsone 100 mg daily by mouth. In such circumstances, it is essential to test the urine regularly to confirm the presence of sulphone.

Throughout the period of the trial, patients have been seen regularly. Smears have been taken at $1\frac{1}{2}$, 3, $4\frac{1}{2}$ and 6 months, and thereafter usually every 3 or 6 months. Clinical and histological assessments have been performed at 6 months,

1 year and thereafter annually (or earlier, should a patient be found to be relapsing).

The response to full dosage parenteral dapsone has varied from patient to patient. Some patients, especially those who were receiving full dosage dapsone regularly at the time of their relapse or referral, have shown no improvement. The lesions have remained active in appearance, sometimes new papules have continued to appear, and the MI has not fallen, so that proof of resistance has taken only 3-4½ months to complete. Such patients are assumed to harbour many highly resistant mutants. Other patients, especially those previously receiving lower dose dapsone, have shown an initial response to parenteral dapsone. The relapse papules have become less active for a time, and those which were ulcerated or scabbed have healed, and the smear MI has fallen towards or to zero, but within a few months the lesions have become active again, new lesions have once more started to appear, and the MI has started to climb. Such patients presumably had a mixed population of high and moderately resistant leprosy bacilli. Still other patients have shown a full response to treatment, with the MI falling to zero within 3-4½ months, and with the papules flattening at a rate comparable to that seen in previously untreated lepromatous leprosy. But after many months or years of clinical improvement with the MI remaining at zero throughout, further new lesions have begun to appear, with a high BI and MI. Such patients are considered to have had relatively few highly resistant mutants of *M. leprae* (at the 0.01% dapsone level) at the time of the first relapse, the majority of bacilli being resistant only at the 0.001 or 0.0001% level. The latter bacilli were killed by the high dosage dapsone therapy, resulting in the initial clinical improvement, but eventually the highly resistant mutants multiplied enough to cause the late relapse. This situation is similar to the "temporary sputum conversion" seen in some patients suffering from drug-resistant pulmonary tuberculosis.

In the Sungei Buloh series of 100 dapsone-resistant patients, of 74 patients whose leprosy bacilli were fully resistant to 0.01% dapsone in the mouse diet, the duration of the clinical trial before proof of resistance was obtained ranged from 3 months to 5 years and 4 months. Of 8 patients, whose bacilli were found to be resistant to 0.001%, but sensitive to 0.01% dapsone in the mouse diet, the clinical proof of resistance in 6 took from 7 months to 5 years, 10 months, to complete; one patient has not yet undergone further relapse (after initial improvement) after 4 years of trial, and the eighth who was previously grossly irregular, taking only 100-200 mg dapsone a month at the time of his relapse, has improved steadily since October, 1969, when he was started on dapsone, 300 mg twice weekly by injection. It is probable that this last patient had very few highly resistant mutants at the time of his initial relapse, but his long-term prognosis remains most uncertain.

In both groups of patients, in general the very prolonged clinical trials occurred among BL or BL/LI patients, who had been very irregular with their treatment up to the time of relapse, and whose relapse lesions were few in number.

Treatment

Drug-resistant patients pose a therapeutic problem, as they (together with lepromatous patients who develop sulphone allergy), require long-term, effective anti-leprosy treatment. However, the earlier "second-line" anti-leprosy drugs, thiacetazone, thiambutosine and streptomycin, were considered inadequate, as

drug resistance was known to develop over the course of a few years in the majority of cases.

From 1963-1968 our treatment of choice was clofazimine (B663, Lamprene). From 1968-1970 it was rifampicin (rifampin, Rifadin, Rimactane), and subsequently rifampicin in combination with thiambutosine, as the majority of our light-skinned patients refused clofazimine when there was a satisfactory alternative drug.

To date, 23 proven sulphone-resistant patients have received clofazimine as monotherapy, and 19 LL patients have completed $1\frac{1}{2}$-13 years' continuous treatment. Of the latter, 18 were Chinese, one Indian, and 18 were males. Initial dosage was not less than 100 mg clofazimine daily, 6 days a week, although many patients received 300 mg daily. Once a good clinical response had been achieved, dosage was slowly reduced, but never below 100 mg twice weekly; during episodes of ENL the dose was often temporarily raised again.

From 1968 to the end of 1976, a total of 88 proven sulphone-resistant patients commenced treatment with rifampicin, including 75 Chinese, 9 Malays, 3 Indians and one Gurkha; 72 were males and 16 were females. The first 4 patients received rifampicin 600 mg daily as monotherapy; subsequently all patients, except 5 suffering from coincidental thiambutosine resistance, received combined therapy with thiambutosine, either parenterally (1 g weekly) or by mouth (1 g b.d.). Our standard dose of rifampicin has remained 600 mg daily; only 3 patients have been given the drug weekly, either 900 mg (2 patients) or 600 mg (one patient); and about 10 others are receiving 600 mg daily on 2 consecutive days every 4 weeks in a double-blind trial of intermittent therapy organized by Dr A. B. G. Laing. Fifteen of the 88 patients received initial treatment for 4-12 weeks with lower dose daily rifampicin in a pharmacological study but we would not now recommend this practice as we consider initial full-dose intensive therapy of great importance.

All patients received regular clinical, histological and bacteriological (BI and MI) assessments. Independent clinical assessors and Leprosy Research Unit (LRU) staff made clinical assessments at 0, 6 and 12 months, then yearly to 5 years, and subsequently either yearly or every $2\frac{1}{2}$ years. At the same times, 2 skin biopsies were sent to the Hospital for Tropical Diseases, London, for independent histological assessment for the Logarithmic Biopsy Index (LIB). Smears from both ears and at least 4 initially active skin sites were taken frequently over the first 6 months, thereafter every 3 months to 2 years, and then every 6 months. The smears were coded and read blind by a single observer. Any toxic effects, or episodes of ENL were carefully recorded

An analysis of the clofazimine patients and of 52 LL rifampicin-treated patients (omitting those who received initial very low dosage) was presented in 1973 (Helmy *et al.*). Three years' further experience has confirmed the earlier findings.

The development of dapsone resistance did not alter the rate of response, as measured by the rate of fall in the MI, to either drug. All the patients treated with rifampicin showed the dramatic rapid fall in the MI which we have previously reported (Rees *et al.,* 1970), and which we consider indicative of rapid bactericidal activity. No late rise in the MI has been observed save in the one clofazimine-treated patient who relapsed at $7\frac{1}{2}$ years through failure to continue on therapy.

The rapid kill of leprosy bacilli by rifampicin was reflected in the clinical

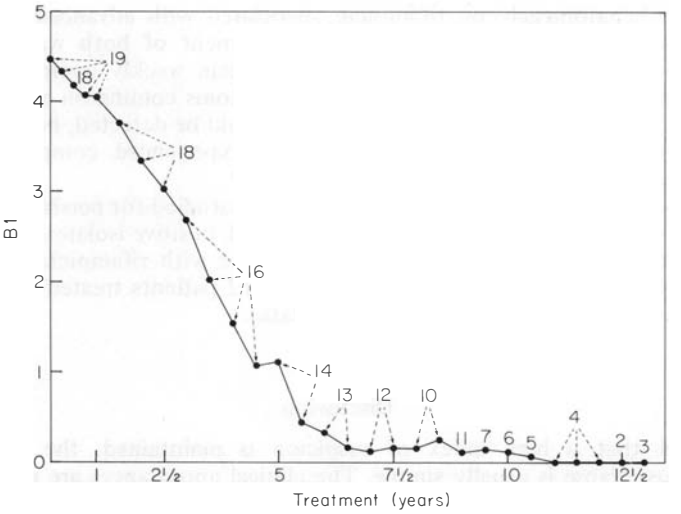

Fig. 1. Fall in bacteriological index (BI) in 19 dapsone resistant lepromatous patients treated with clofazimine. Number of patients given for each point.

assessment results. Over the first 4 months the inflammation and oedema of any very active relapse papules and plaques present tended to subside remarkably rapidly on rifampicin. Up to the end of the second year, higher scores for clinical improvement were given to these patients than to those receiving clofazimine. However, as clofazimine made clinical lesions easier to see, this could have biased the clinical assessor slightly against the latter drug.

Surprisingly, no difference could be detected in the rate of fall in the LIB in the 2 treatment groups. Mathematically, the major factor in the estimation of the LIB is the bacterial index. Figure 1 gives the rate of fall in BI in the clofazimine treated group of 19 LL patients. This shows no significant difference from that obtained with rifampicin (see Fig. 1, Rees *et al.,* 1976). We presume that neither drug affects the rate of removal of dead leprosy bacilli by the body.

An up-to-date analysis of ENL has not yet been carried out. However, in 1973 no very early and severe onset of ENL was detected in patients treated with rifampicin. At that time, 17 of the 28 patients (61%) on rifampicin included in the BI assessment (Fig. 1, Rees *et al.,* 1976) were suffering from ENL at 1 year, an incidence similar to that seen at Sungei Buloh in previously untreated patients receiving dapsone. This compares with only 7 of 21 patients (33%) in the clofazimine group, a figure reflecting the anti-inflammatory activity of clofazimine.

Although 5 patients (4 of the 23 in the clofazimine and one of the 88 in the rifampicin series) have died from intercurrent disease, drug toxic effects have been rare. A few patients on clofazimine complained of mild abdominal pain and diarrhoea while receiving 300 mg daily, and one developed mild eczema; all the light-skinned patients developed the typical and unpopular discolouration. One patient on rifampicin developed mild jaundice associated with occult cirrhosis, and a second whose liver was palpable at the initial assessment developed

progressive hepatomegaly on rifampicin, associated with advanced fatty change and increase of portal fibrous tissue; the treatment of both was changed to clofazimine. The one patient on 600 mg rifampicin weekly complained after 3 years of treatment of fever and abdominal symptoms coming on about 2 h after each dose; no rifampicin dependent antibodies could be detected, but on changing her dosage to rifampicin 600 mg daily, she experienced complete relief of symptoms.

Patients from both treatment groups have been studied for persistence of viable *M. leprae.* As already reported (Rees *et al.,* 1976), positive isolates were obtained from 20 of 28 patients treated from 0.5-5 years with rifampicin. In addition, positive isolates have been obtained from 9 of 12 patients treated 2-6 years with clofazimine (Rees and Waters, unpublished data).

Discussion

Provided that a high index of suspicion is maintained, the diagnosis of lepromatous relapse is usually simple. The clinical appearances are nearly always diagnostic, and we have found that reliable smear results, especially of the MI, provided very helpful additional evidence.

The main differential diagnosis lies between those patients who have relapsed while receiving dapsone therapy, i.e. who have *prima facie* evidence of sulphone resistance, and those who have relapsed through failure to continue on treatment. In the latter circumstance, relapse is assumed to be due to the multiplication of the small numbers of viable dapsone-sensitive *M. leprae* which persisted despite adequate chemotherapy. In some countries and cultures patients will state with considerable accuracy whether or not they had ceased to take dapsone. But recent studies of self-medication treatment schemes have revealed a disturbingly high proportion of patients who fail to take dapsone, or who take it in much less than the prescribed dosage (Ellard *et al.,* 1974; Low and Pearson, 1974; Huikeshoven *et al.,* 1976), despite attending clinics regularly.

Proof of dapsone resistance is essential. Even though it takes 6-12 months to complete, drug sensitivity testing using the mouse foot-pad infection is very reliable and gives a helpful indication of the degree of dapsone resistance which has developed; moreover, if resistance to other drugs is suspected, they can be included in the test system using additional groups of mice. Provided that a satisfactory bacterial suspension has been obtained for foot-pad inoculation, the patient is able to change treatment immediately should this be indicated on medical and/or social grounds. However, the foot-pad test is available in only a small number of laboratories; the setting up of regional or national centres would appear highly desirable.

Clinical trial of dapsone resistance is also very reliable, provided that dapsone is given regularly by injection; if the drug is given by mouth, frequent urine testing for dapsone is essential. Clinical trial can be made available nearly everywhere, but it requires very regular supervision and medication of each patient for a period extending perhaps as long as 5 years, a discipline which may not always be acceptable. The trial is completed, and treatment changed, once there is evidence of either failure to respond to, or of further relapse after initial improvement on, full-dosage dapsone therapy.

The most satisfactory drug regimen(s), balancing efficacy, acceptability and

cost, for the treatment of dapsone-resistant leprosy remains uncertain, and further clinical studies are required. Although in the middle term we have found both clofazimine (over 13 years) and rifampicin (over $8\frac{1}{2}$ years) to be very satisfactory, it would appear from experience with dapsone that 20 years may be required for the full evaluation of an effective anti-leprosy drug. No case of secondary clofazimine resistance has so far been encountered, although Jacobson and Hastings (1976) have now reported the first patient suffering from rifampicin resistance. By analogy with the treatment of tuberculosis, we have strongly advocated (Pearson *et al.,* 1975; Waters, 1976) that patients suffering from dapsone resistance should be treated with combined therapy. This is because the risk of a naturally occurring mutant being present resistant to 2 as compared with only one drug is reduced from about 10^{-6} to 10^{-12} (from one in a million to one in a million million bacilli). Nevertheless, long-term treatment remains essential as it is still quite uncertain what effect, if any, combined therapy has on "persisters".

Once sulphone resistance has developed, there remain 3 proven bactericidal-type drugs (Committee on Experimental Chemotherapy, 1976) available, namely rifampicin, clofazimine and ethionamide. Of the "second-line drugs", thiambutosine and thiacetazone probably act by the same mechanism as, and give cross-resistance with, ethionamide (Colston and Hilson, personal communication), but their peak blood levels are but 3 and 4 times respectively the minimum inhibitory concentration, and they are only bacteriostatic (Colston and Hilson, 1976). Furthermore, thiambutosine is no longer being manufactured (Ciba-Geigy, personal communication). Streptomycin is bacteriostatic, has to be given by injection, and rapidly produces drug resistance in lepromatous leprosy (Hastings *et al.,* 1970).

It would appear, therefore, that dapsone-resistant patients should receive an initial intensive course of chemotherapy with at least 2 of the 3 drugs, rifampicin, clofazimine and ethionamide (or prothionamide). If the skin discolouration due to clofazimine is unacceptable, then rifampicin and ethionamide should be given; and Jacobson (personal communication) has used this combination on a long-term maintenance basis since 1973. If ethionamide cannot be afforded, then thiacetazone could be substituted provided that the limitations of this drug, and its high incidence of toxic effects in some races are appreciated. The use of thiacetazone as long-term maintenance monotherapy would appear inadvisable. Many patients will, however, accept clofazimine and we have recently started 7 patients (including 2 with coincidental thiambutosine resistance) on a combination of rifampicin 600 mg daily and clofazimine. The intention is to give at least 3 months of combined therapy, and then to continue with maintenance clofazimine, although we would not now advocate a minimum dosage below 100 mg 3 times a week.

The position of a lepromatous patient who develops sulphone resistance is uncertain. The most effective alternative drugs are all much more expensive and most are more toxic than dapsone. It is essential to prevent his developing further varieties of drug resistance. Formal long-term (open-ended) clinical trials of alternative regimens are essential. But such regimens must be selected on scientific merit as well as on the basis of cost and acceptability. For if leprosy is to be controlled throughout the world, it is essential for effective regimens to be selected and used now, even though it will take another 20 years for their efficacy to be proved.

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