

Letters to the Editor

Dapsone Dosage and Drug Resistance

Dr Browne's recent contribution in the Field Workers' Forum (*Leprosy Review* Vol. 45, 276) on the subject of drug resistance in leprosy gives practical and helpful advice concerning the dangers of dapsone resistance. The dilemma is clearly outlined that one needs to consider lower dosage for tuberculoid patients because of the danger of nerve damage, but at the same time be sure that adequate dapsone is given to suppress bacterial growth in patients with lepromatous leprosy. Obviously the type of leprosy must be correctly determined, and this basic ability is essential in every worker who aspires to treat leprosy patients.

Problems arose in the past because we erred in treating tuberculoid leprosy too enthusiastically, and lepromatous leprosy too conservatively, on the assumption that because it was the serious form of the disease greater caution was necessary. In fact it has been proved that low dose dapsone therapy suffices in patients with tuberculoid leprosy to assist the immune process and control the multiplication of bacilli, but in lepromatous leprosy the battle depends on the effectiveness of the drug, since host immunity is too low to control the infection alone. Now that this has been clarified, can we not develop a treatment schedule that will apply to all situations?

In such a schedule three variables need to be taken into consideration:

- (a) The body weight of the patient.
- (b) The type of leprosy.
- (c) Complications arising in the course of treatment.

At a recent Leprosy Conference of the English speaking countries in West Africa, a committee was asked to work on a dapsone dosage scheme which we would agree would be the best, and yet simple, so that it would be practical for out-patient programmes and for paramedical staff to supervise. This committee included Drs Ross, Wheate, Odoghe, Beniccio, Pfaltzgraff and Professor Schaller. Treatment *on a daily basis* was strongly recommended, and the following routine schedule was agreed upon.

1. Dapsone treatment to be given daily, using 25 and 50 mg tablets only.
2. For all types of case:

Adults Initial dose 25 mg daily
 After three months 50 mg daily
 After six months in BL/LL cases only, 100 mg daily.

Children Under the age of five years, the diagnosis to be confirmed by an experienced person, preferably M.D. and a maintenance dose of 2 mg/kg/day given.
 Age 5-12 years; a standard daily dose of 25 mg, both for initial treatment and maintenance, in all types of leprosy.

This proposed scheme offers three advantages:

1. It makes allowance for the problem of neuritis in tuberculoid leprosy, and yet provides an adequate dose for the control of lepromatous disease.
2. The scheme is simple to follow, and can easily be remembered by auxiliary staff.
3. It allows for an average dose of 2 mg/kg daily in lepromatous patients, in whom this dose is essential.

At this stage in the development of adequate dosages to treat leprosy in control programmes, it seems to me imperative to develop a treatment regime that can be universally accepted. Could not the above suggestions serve as a starting point for discussion on this subject?

If such a scheme as this is to be used more extensively, it will be important for UNICEF to supply tablets of 25 and 50 mg dapsone as routine, distinctively coloured. The 100 mg tablet could become redundant.

Since it is only the complications of leprosy that lead to disability, it is sometimes more important to control the complications than to treat the disease. Whenever there is danger of the development of permanent disability, whether as the result of neuritis or iritis, the patient should at once be placed under experienced and expert medical care.

To refer back again to Dr Browne's notes; I question the validity of a maintenance dose of half the therapeutic dose for lepromatous patients after arrest. May this not give a level of dapsone concentration in the blood below that necessary to provide bacteriostasis?

Finally, how long must a patient with dapsone resistant bacilli be treated with clofazamine before treatment can be stopped or resumed with dapsone? We have tried to start dapsone again at a level of 600 mg per week after two years treatment with clofazamine, but after four years on dapsone it is evident that a dapsone resistant clone of bacilli has again appeared. A report of the experiences of others in this regard will be welcome.

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Further contributions on this subject will be welcomed.

Ed.

COMMENT BY DR GORDON ELLARD

Dr Davey has invited me to respond to Dr Pfaltzgraff's letter concerning dapsone dosage and drug resistance. The most important point I would like to make is concerning the last paragraph of the letter in which Dr Pfaltzgraff asks how long a patient with dapsone-resistant bacilli must be treated with clofazimine before treatment can either be stopped or else resumed with dapsone. My response would be that if a lepromatous patient relapses with bacilli that have been shown by the foot-pad technique to be fully resistant to dapsone (i.e. they multiply in mice fed 0.01% dapsone in the diet) and the only other antileprosy drug available is clofazimine, then treatment with clofazimine should be continued until it is believed the patient has been cured.

The reason for advocating this approach is that dapsone resistance appears to be a stable characteristic of dapsone-resistant *Myco. leprae*. Thus dapsone-resistant strains of *Myco. leprae* can be successfully passaged for many years in untreated mice (Shepard *et al.*, 1969). As a consequence one must expect that a patient with fully dapsone-resistant *Myco. leprae* will always remain unresponsive to dapsone treatment.

Unfortunately, the length of treatment required to cure lepromatous patients with clofazimine has still to be established. It is almost certainly many years since the initial rates of fall in the numbers of viable *Myco. leprae* when such patients are treated with dapsone or clofazimine are similar (Pettit and Rees, 1966; Pettit *et al.*, 1967; Levy *et al.*, 1972) and it is clear that considerably more than 10 years of dapsone treatment must be given before hopes of curing all patients can be entertained (Waters *et al.*, 1974).

The results described by Dr Pfaltzgraff, when a patient with dapsone-resistant leprosy was treated for two years with clofazimine and then switched to dapsone, are therefore readily understood. Clearly significant numbers of viable dapsone-resistant *Myco. leprae* still remained after two years clofazimine treatment, which were then able to multiply again when treatment was changed to dapsone until four years later they resulted in the patient relapsing bacteriologically.

Although clofazimine-resistant strains of *Myco. leprae* have yet to be isolated, the possibility that long-term treatment with clofazimine alone may result in lepromatous patients eventually relapsing with drug-resistant *Myco. leprae* must still be seriously considered. For reasons discussed more fully in the Editorial of this issue, I would therefore recommend that every effort should be made to treat patients with dapsone-resistant leprosy with combinations of two other antileprosy drugs. In Sungei Buloh such patients are treated with combinations of clofazimine, rifampicin or thiambutosine (Helmy *et al.*, 1973). The potential value of even as little as a week of rifampicin treatment in reducing the likelihood of lepromatous patients relapsing with drug-resistant strains of *Myco. leprae* has been discussed elsewhere (Ellard, 1975). Thereafter thiambutosine or thiacetazone might be used as long-term companion drugs.

In most countries resources are simply not available for establishing by the mouse foot-pad technique whether or not patients are infected with dapsone-resistant *Myco. leprae*, and even when the method can be carried out it would normally take the best part of a year for the results to become available. In such a situation I would recommend that lepromatous patients, who have been treated with dapsone for over five years and who are clearly relapsing clinically and bacteriologically despite fully supervised dapsone treatment (Pettit *et al.*, 1969), should continue treatment with high dosage dapsone (100 mg per day) and that this treatment should be supplemented with clofazimine and another companion drug for as long as seems reasonably possible. In this way patients whose bacilli are partially sensitive to dapsone (Pearson *et al.*, 1968; Shepard *et al.*, 1966) would benefit from the therapeutic activity of all three drugs and relapse due to the appearance of drug-resistant strains of *Myco. leprae* would be extremely unlikely.

Finally, I should like to make two further points concerning Dr Pfaltzgraff's letter. Firstly, I would suggest that the chances of lepromatous patients eventually relapsing with dapsone-resistant leprosy would be significantly reduced (and without any concomitant increase in the incidence of *erythema nodosum leprosum*) if treatment was begun immediately with 100 mg dapsone daily,

instead of after six months daily treatment with 25-50 mg dapsone as in the proposed dosage schedule. Secondly, I would emphasize that doses of as little as 1 mg dapsone a day are effective in preventing the multiplication of *fully sensitive* strains of *Myc. leprae*. The rationale for giving the highest doses of dapsone that are well tolerated, is the hope that in this way the growth can be prevented of the small numbers of naturally dapsone-resistant *Myc. leprae* that are presumed to be present in the enormous populations harboured by lepromatous patients prior to treatment.

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The Broach Biopsy Technique in Infective Granulomatous Diseases

It is sometimes difficult to obtain full patient co-operation in taking pathological specimens in leprosy using Wade's scraped incision technique. This applies especially to children who are often terrified at the sight of a doctor and a scalpel. A simple technique is available which largely avoids these problems and at the same time provides a reliable pathological specimen. An endodontic broach is used by dentists to remove the nerve from the apical canal (Fig. 1). It consists of a disposable fine tempered steel needle with a screw thread or barbs on one end.

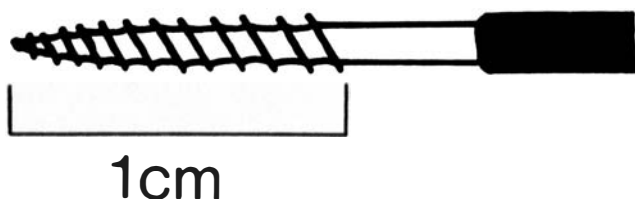


Fig. 1. Endodontic broach. (X 5.)

The needle is inserted into the centre of a granulomatous lesion, given a half-turn then pulled out, at the same time pressing on the skin near the puncture point to prevent "tenting" of the skin. A smear is made on a glass slide in a very small drop of saline and then stained with a modified Ziehl-Neelsen technique for *Mycobacterium leprae*.

Good specimens were obtained in two patients with lepromatous leprosy. In the second patient smears were made from the same nodules at three different sites using both the scraped incision and the broach biopsy techniques. All smears were positive with slightly more material being obtained with the standard technique (Figs 2 and 3).

The broach biopsy was first suggested by Gremliza (1956) for the diagnosis of cutaneous leishmaniasis. Further trials in an area where leishmaniasis is endemic fully confirmed the value of the technique for use in field work and screening clinics in this condition (Griffiths and Dutz, 1975).

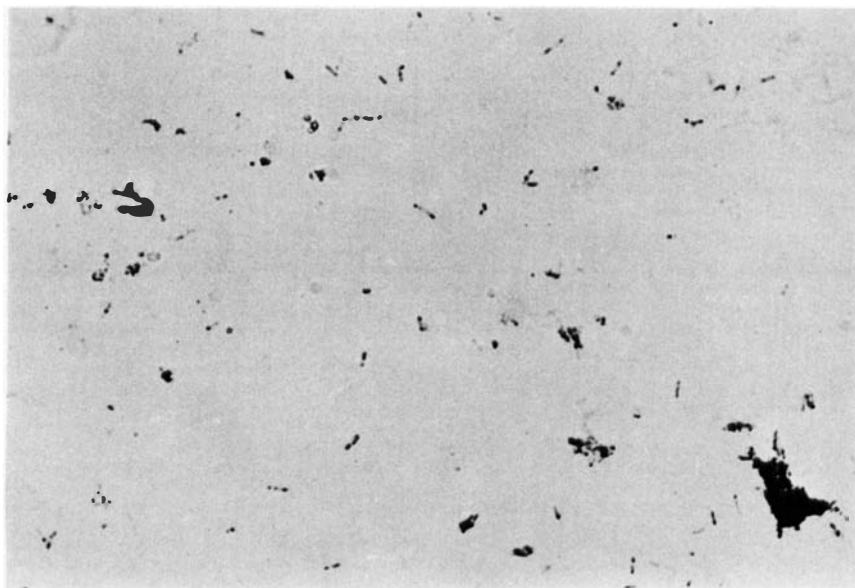


Fig. 2. Ziehl-Neelsen stain of tissue smear using broach. (X oil immersion.)

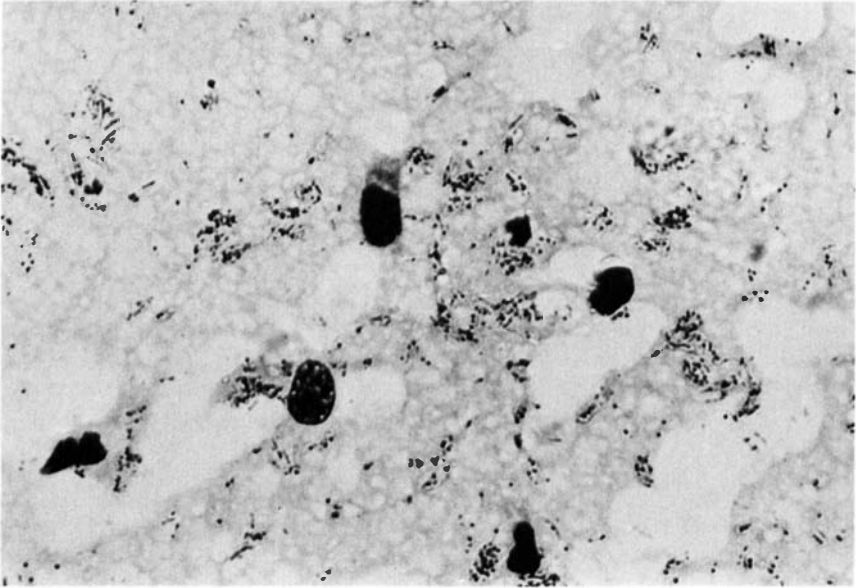


Fig. 3. Ziehl-Neelsen stain of tissue smear using scraped skin incision. (X oil immersion.)

The rapidity, simplicity and the cheapness of the broach biopsy method may make it a useful addition to the techniques available to leprologists.

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