Editorial

THE TREATMENT OF TUBERCULOSIS AND LEPROSY

The recently published ninth report of the WHO Expert Committee on Tuberculosis (1974) describes the very considerable advances that have been made during the past decade in the treatment of tuberculosis. It is timely therefore to consider some of the reasons why progress in the control of tuberculosis appears to be more rapid than that of leprosy, the nature of the areas where the most important advances in the treatment of tuberculosis are being made and their possible relevance to the treatment of leprosy.

Reasons for the relatively rapid advances in the treatment of tuberculosis

Many of the reasons for the more rapid advances that have been made in the treatment of tuberculosis are readily appreciated. A major factor has been the extensive screening of potential antituberculosis drugs *in vitro* and *in vivo* that has been carried out over the past 30 years in commercial as well as non-commercial laboratories. By contrast *Mycobacterium leprae* still cannot be cultivated *in vitro*, and the use of the mouse footpad model for screening potential antileprosy drugs *in vivo* is such a lengthy process that it has only been used by a small number of workers since its introduction 10 years ago, and apparently has not yet been commercially exploited.

Another major factor has been the numerous clinical trials that have been carried out during the past 20 years in Europe, North America and the Third World to establish the efficacy of alternative combinations of drugs in the treatment of pulmonary tuberculosis. Many of these have been meticulously controlled and in some of the trials the therapeutic responses of over a thousand patients have been assessed (East African/British Medical Research Council, 1974). These studies have been used to evaluate the influences of varying drug dosages and combinations, rhythms of drug admistration and durations of treatment on both therapeutic efficacy and toxicity (Fox, 1971*a*). By contrast far fewer controlled clinical trials have been mounted in the treatment of leprosy and most of them have been carried out on relatively small numbers of patients. Again, these differences are easy to understand.

The response to treatment of patients with bacteriologically confirmed pulmonary tuberculosis can readily be established. Thus patients are often considered to have responded favourably if tubercle bacilli can no longer be cultivated from their sputum during the last three months of a year of treatment. If treatment is then discontinued, normally only about 5% of such patients will subsequently relapse with active tuberculosis. Evidence can also be obtained by means of simple *in vitro* sensitivity tests as to whether patients failing to respond adequately to chemotherapy did so because of the inability of the drugs they took to kill a sufficient proportion of the initial population of drug-sensitive

bacilli, or whether it was on account of the drugs' failure to prevent the growth of drug-resistant mutants. The interpretation of the results of controlled clinical trials in tuberculosis has also been facilitated by the demonstration that the factor of overwhelming importance in determining the response of patients to treatment is simply the efficacy of the drugs they actually ingest during the treatment period (Fox, 1968; 1972).

By contrast it is still impossible to measure with precision the response of leprosy patients to treatment. Sufficient numbers of viable *Myco. leprae* for reliable bacteriological estimates of therapeutic response to be obtained are only present in lepromatous patients and it is only in such patients that the rate of elimination of viable leprosy bacilli is likely to be predominantly determined by the potency of chemotherapy. Treatment is also complicated by the occurence of *erythema nodosum leprosum* (Type 2 reactions) in lepromatous patients and reversal (Type 1) reactions in non-lepromatous patients.

Although the demonstration of a significant fall in the Morphological Index of a lepromatous patient indicates that the drug given has antileprosy activity, this method is normally only able to demonstrate whether during the period of treatment the population of viable *Myco. leprae* has been reduced to about 10% of its original number. Furthermore, because the process whereby dead leprosy bacilli become morphologically degenerate is relatively slow, this method inevitably grossly underestimates the rate of killing of *Myco. leprae* when a bactericidal drug is given. A subsequent rise in the Morphological Index despite continued treatment may suggest that the patient is relapsing on account of the appearance of drug-resistant *Myco. leprae*, but this can only be proved by subsequently demonstrating that inocula can multiply in the footpads of mice fed with doses of the drug that would normally prevent the growth of strains of *Myco. leprae* isolated from untreated patients.

Determining the length of treatment required before inocula from lepromatous patients become non-infectious for mice is a much more informative method of monitoring response to treatment. This method can be used to compare the relative bactericidal activity of different antileprosy drugs and is capable of following the reduction in numbers of viable *Myco. leprae* to about 1% of their original total. Although this method is fundamentally analagous to that used so successfully to assess the response of tuberculosis patients to treatment, it is much less sensitive and suffers from several very serious limitations. Firstly, because the numbers of viable leprosy bacilli have to be reduced to far less than 1% of their original total before there can be any reasonable hope of a "cure", it is unable to determine whether or not an adequate therapeutic response has been obtained. Thus while daily treatment with dapsone (DDS) for three months (Shepard *et al.*, 1972), or with rifampicin for as little as a week (Rees *et al.*, 1970; Shepard *et al.*, 1974) results in inocula from skin biopsies becoming non-infectious for mice, viable bacilli can still be isolated from other sites in the body after as many as 10 years continuous treatment with dapsone (Waters *et al.*, 1974) or after two years treatment with rifampicin (Rees, 1975), and would almost certainly result in the patients relapsing if treatment were stopped. Other major limitations to the method include the expertise required, its cost, and the many months that must elapse before conclusive evidence can be obtained that inoculated animals have become infected. As a consequence the method has been employed by few workers. Clearly much more sensitive methods are required to be able to detect far smaller proportions of viable *Myco. leprae* among inocula containing large

numbers of dead bacilli, if a satisfactory bacteriological definition of therapeutic response is to be obtained.

Relevance of the chemotherapy of tuberculosis to the treatment of leprosy

In view of the much greater wealth of knowledge concerning the treatment of tuberculosis, it is important to consider which findings may be particularly relevant to future advances in the treatment of leprosy. I believe there may be three such areas; firstly, the use of combinations of drugs to prevent patients relapsing because of the appearance of drug-resistant strains, secondly the use of supervised intermittent treatment to try to overcome the failures of chemotherapy caused by patients not taking their medicaments, and thirdly the importance of bactericidal drugs.

(1) The prevention of drug resistance

As Rees (1973) has pointed out, the introduction of dapsone for the treatment of leprosy preceeded the introduction of effective drugs for the treatment of pulmonary tuberculosis and the studies that demonstrated the necessity of giving combined chemotherapy to prevent tuberculosis patients relapsing through the appearance of drug-resistant strains of *Myco. tuberculosis*. Since treatment with dapsone alone appeared not to result in leprosy patients relapsing it is understandable that dapsone monotherapy became and has remained the standard antileprosy treatment. However the demonstration by the mouse footpad technique that a significant proportion of lepromatous patients ultimately relapse on account of the appearance of dapsone-resistant strains of *Myco. leprae* after many years of dapsone monotherapy, and the possibility that this may be a problem of increasing importance (Meade *et al.*, 1973), has suggested to several workers that the lessons gained from the treatment of tuberculosis should be applied to the management of lepromatous patients, and that such patients ought initially to be treated with combined chemotherapy (Pattyn, 1972; Shepard, 1972; Rees, 1973; Ellard, 1974; 1975*a*; Pearson *et al.*, 1975). The rationale for such an approach is the likelihood that less than 1 in 10^6 of the viable *Myco. leprae* present at the start of treatment will be naturally resistant to a given drug and that less than 1 in 10^{12} resistant to two drugs. Since the pretreatment population of viable *Myco. leprae* harboured by even the most florid lepromatous patient is unlikely to exceed 10^{11}, giving two effective antileprosy drugs ought to prevent the growth of all leprosy bacilli.

Controlled studies are urgently needed to investigate which companion drug would be most suitable for administering with dapsone, and the length of time for which it should be given before treatment can be successfully continued with dapsone alone. The most effective companion drug would almost certainly be rifampicin, but its extremely high cost severely limits how much can be given. The possibility of preventing the emergence of dapsone resistance in lepromatous patients by giving high dosage dapsone supplemented by an initial week of 600 mg rifampicin daily is discussed elsewhere (Ellard, 1975*a*). Long-term treatment with dapsone plus clofazimine (B.663) would probably be unacceptable to many patients because of skin discolouration. Other companion drugs that might be considered are thiambutosine (1500 mg daily) or thiacetazone (150 mg daily), although the adverse side-effects encountered with thiacetazone are such that one could not recommend its long-term use in several areas of the world (Miller *et al.*, 1970).

Controlled clinical trials in tuberculosis have also shown that if only a single drug (isoniazid) is used, its efficacy is improved if higher doses are given, due to the ability of such doses to suppress the multiplication of mutants with low degrees of resistance (Selkon *et al.*, 1964). Retrospective evidence from Malaya has also demonstrated that the incidence of dapsone resistance among lepromatous patients who were initially treated with sulphetrone is significantly higher than among those who were originally treated with dapsone (Mead *et al.*, 1973). Since the dapsone blood levels achieved by giving sulphetrone were considerably lower than when dapsone was given (Gelber *et al.*, 1974), there is therefore a strong case for treating lepromatous patients from the start with the highest doses of dapsone that are well tolerated (50-100 mg daily), whether or not a companion drug is also given (Pattyn, 1972; Rees, 1973; Waters and Helmy, 1974; Ellard, 1975*a*).

No case has been demonstrated of non-lepromatous patients relapsing through the appearance of drug-resistant bacilli, presumably because of the much smaller populations of *Myco. leprae* present pre-treatment and the greater immunological competence of the host. For these reasons monotherapy with dapsone remains the treatment of choice for non-lepromatous patients. Little additional therapeutic benefit would be expected by giving such patients high doses of dapsone. Indeed, in view of the widespread belief that the incidence of neuritis associated with reversal reactions in non-lepromatous patients is directly related to the dosage of dapsone employed, the accepted practice of treating such patients with more modest doses of dapsone (e.g. 25 mg/day) ought probably to be continued. Hopefully direct evidence concerning whether or not the incidence of such reactions is related to the dose of dapsone given will be obtained from a controlled study at present being carried out in Ethiopia (Personnal communication, R. St. Barnetson & J. M. H. Pearson). Further investigations in this area are to be encouraged since if it were true that the triggering of reversal reactions were directly related to the ability of treatment to prevent the multiplication of *Myco. leprae* it would be impossible to envisage a situation in which the risk of reaction could be minimized without the concomitant loss of all therapeutic benefits from treatment.

(2) Supervised intermittent chemotherapy

As Fox (1968*a*, 1972) has pointed out, the greatest threat to the success of even excellent regimens in the treatment of pulmonary tuberculosis is the difficulty of obtaining the long-term cooperation of the patient in the self-administration of oral medicaments for many months. The possibility of overcoming this problem by giving patients their drugs intermittently under full supervision was therefore investigated (Tuberculosis Chemotherapy Centre, Madras, 1963). A series of experimental studies were also undertaken at the Medical Research Council's Unit for Studies of Tuberculosis in London and at the Pasteur Institute in Paris to establish which antituberculosis drugs might be the most suitable for this purpose. These studies showed that drugs that were effective when given intermittently in the treatment of experimental tuberculosis in the mouse or guinea pig were those which were either capable of inducing prolonged bacteriostasis *in vitro* or possessed marked bactericidal activity. During the past 12 years a series of controlled clinical trials have demonstrated that twice-weekly supervised treatment can not only be highly therapeutically effective, but can also carry significant benefits in terms of lower toxicity and

cost (Fox, 1971*b*; WHO Expert Committee on Tuberculosis, 1974;; Ellard, 1975*b*). These clinical trials have also demonstrated the value of experimental studies in predicting the drugs that were most likely to be effective when given intermittently.

Inevitably the problem of leprosy out-patients failing to take the supplies of dapsone tablets that they have been given for self-administration is also of considerable importance. Thus Pettit and Rees (1964) showed that 4 out of 7 patients who had apparently failed to respond to sulphone treatment of over 13 years duration, promptly improved when their chemotherapy was fully supervised. More recently a study from Malawi has demonstrated that patients attending out-patients clinics had taken only about a half of their prescribed dapsone doses in the days immediately preceeding the clinic and that approximately 30% of the patients were grossly irregular in their drug taking (Ellard *et al.*, 1974). Similar findings have been reported from Ethiopia (Low and Pearson, 1974). Clearly, as Davey (1974) has pertinently commented, dapsone is not being taken by the numbers of patients intended, nor in the dosage expected, and although dapsone may be made freely available on the widest possible scale it does not follow that patients are going to take it in a way calculated to lead to the control of leprosy in the forseeable future. The irregular taking of dapsone may also be a major contributory factor to the development of dapsone resistance (Shepard *et al.*, 1969).

The efficacy of intermittent dapsone treatment is demonstrated by its ability when given once every week or fortnight to prevent the multiplication of *Myco. leprae* in the mouse footpad (Shepard, 1967*a*; Rees, 1967; Rees, cited Shepard, 1967*b*; Pattyn and Saerens, 1974), and the results obtained when lepromatous patients were treated in a controlled clinical trial with 50 mg dapsone twice-weekly (Pearson and Pettit, 1969). These findings suggest to the writer that the mass treatment of leprosy should be based on the daily self-administration of dapsone by out-patients *supplemented* by *fully supervised* intermittent dapsone administration. Thus lepromatous patients could be given 300 mg dapsone doses of dapsone to swallow under supervision at each visit to their out-patient clinic as well as a supply of 50 mg dapsone tablets for daily self-administration. Lower doses of dapsone (e.g. 25 mg) would be given to non-lepromatous patients for daily self-administration, together with larger supervised doses of dapsone *if* it could be shown by means of controlled studies that such doses did not significantly increase the risk of precipitating reversal reactions.

A major problem in the therapy of tuberculosis is that of patients ceasing to attend for treatment altogether. Such default probably reduces the total success of antituberculosis chemotherapy more than any other single factor (Fox, 1968*b*). The default of leprosy patients from treatment is also inevitably one of the most important factors hindering attempts at leprosy control in many parts of the world (Davey, 1974). Measures have been described for speeding up the visiting of defaulting tuberculosis patients (Fox, 1968*b*; WHO Expert Committee on Tuberculosis, 1974) that are equally applicable to leprosy patients. In this respect it is vital that clinics should be held as frequently as practicable. In many urban areas it should be possible to organize weekly clinics, while the use of mobile clinics in Malawi has demonstrated the feasability of organizing fortnightly clinics within reach of patients in rural areas. The practice of giving patients more than a month's supply of dapsone for self-administration should be strongly discouraged.

A further development that could greatly aid efforts to achieve and sustain effective levels of dapsone in leprosy patients stems from the demonstration by Shepard and his colleagues that continuously inhibitory dapsone levels can be maintained in patients by giving intramuscular injections of 225 mg acedapsone (DADDS), a slow-release form of dapsone, once every three months (Glazko *et al.*, 1968; Shepard *et al.*, 1968; Ozawa *et al.*, 1971; Russell *et al.*, 1973). The potentialities of using acedapsone in situations where medical resources are extremely scarce has been demonstrated in New Guinea by Russell *et al.* (1971). Several other workers have commented on the benefits that might be gained from the more widespread use of this remarkable drug, which is without parallel in the field of antituberculosis chemotherapy (Pattyn, 1972; Rees, 1973; Ellard, 1974; Pattyn and Saerens, 1974; Ellard, 1975*a*). Since acedapsone is well tolerated by all types of leprosy patients (Russell *et al.*, 1971; 1973), its use as an *additional supplement* for treating both lepromatous and non-lepromatous patients with oral dapsone regimens ought seriously to be considered.

(3) The importance of bactericidal drugs

Perhaps the most important recent advance in the chemotherapy of pulmonary tuberculosis has been the demonstration that certain regimens are capable of curing patients in as little as six months (Fox and Mitchison, 1975). Prior to this development treatment regimens have usually been of at least 12-24 months duration. A vital component of these "short-course" regimens appears to be the inclusion of at least two bactericidal drugs. Hopes that the introduction of the powerful bactericidal drug rifampicin might drastically reduce the length of treatment required to cure lepromatous patients have been dashed by the recent demonstration that viable *Myco. leprae* could still be recovered from certain selected sites after at least two years daily rifampicin treatment (Rees, 1975). It is tempting therefore to speculate about the possibility of curing lepromatous leprosy in a significantly shorter time if a second bactericidal drug could be discovered that could be used in combination with rifampicin and high dosage dapsone (Ellard, 1975*a*). Perhaps the most important characteristic required of such a second bactericidal drug would be the ability to kill the semi-dormant bacilli that appear insensitive to rifampicin's bactericidal action (Allen *et al.*, 1975, Fox and Mitchison, 1975, Rees, 1975).

However it must be admitted that speculation by itself is highly dangerous. All the major advances in the chemotherapy of tuberculosis resulted from extensive experimental studies and numerous controlled clinical trials. Similar advances in the treatment of leprosy can only be expected to result from much more extensive experimental investigations and the mounting of numerous large-scale controlled clinical trials. It is therefore of paramount importance than many more controlled clinical trials should be initiated, and that they should compare the efficacy of different alternative regimens in the treatment of many more patients and over a much greater period of time than has been the practice in the past.

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G. A. Ellard