THE TREATMENT OF LEPROSY

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From whatever standpoint leprosy is viewed, whether from that of the clinician or the epidemiologist, the objective must be to diagnose and treat the maximum number of leprosy patients, not only because the disease is curable but because treatment renders 'open' cases non-contagious long before cure is obtained. Now that it is becoming generally accepted that the way to leprosy eradication lies through case-finding and treatment, an increasing responsibility falls upon doctors working in the tropics to undertake the treatment of leprosy in hospital or rural clinic out-patients, for facilities in leprosy hospitals (leprosaria) are far too limited to deal with the numbers of patients involved, and, in any case, admission to leprosaria should not be indiscriminate but should be restricted to cases where special social or medical indications exist.⁵ At present there are about 211,900 leprosy in-patients throughout the world, but seven times as many are receiving out-patient treatment, and on the estimated world incidence of 10-12 million leprosy sufferers, there are at least seven undiagnosed and untreated patients for every one under treatment.⁵

It is apparent, therefore, that in countries where leprosy is highly endemic, doctors without previous special training are likely to be called upon to shoulder the responsibility of treating leprosy out-patients, making use of the services of a leprosy specialist when difficulties arise, and it is for doctors such as these that this paper has been written.

Chemotherapy. (1) Drugs which can be Recommended

(1) *The Sulphones.* The sulphone group of drugs hold pride of place in treatment and possess two important advantages over other anti-leprosy drugs: first, they are much cheaper, and, secondly, leprosy bacilli have not been known to develop sulphone resistance. Before describing the sulphones in common use, I would like to make some general remarks which apply to them all: (1) There is little to choose between them for effectiveness. (2) They have certain side-effects

in common (see below). (3) Dosage should be built up gradually, taking 4-5 months to reach the maximum, particularly in dimorphous (borderline) and lepromatous cases because of the tendency to develop reactional states which may damage important structures such as peripheral nerves, but there is good evidence that in tuberculoïd leprosy maximal doses can be given from the beginning.¹⁸ (4) Sulphones act bacteriostatically and the minimum effective dose for each compound is not known. Speaking generally, it is my belief that patients are given larger doses than they need, and the most important lesson in the treatment of leprosy is that it is better to give too little sulphone than too much. (5) Care must be taken not to increase the dose if there are signs of reaction (see below). (6) Some clinicians give their patients rest periods from sulphone, such as 'two weeks' rest every three months, but others have not observed any ill-effects from giving the drug continuously. (7) Regarding the length of treatment, the Inter-Regional Leprosy Conference at Tokyo in 1958 recommended that tuberculoïd and indeterminate cases should be treated for two years, or until all signs of activity have ceased for 18 months, whichever is longer; treatment of lepromatous and dimorphous cases should go on for at least two years after all signs of activity have ceased.⁵ An alternative scheme would be to carry out a lepromin test when the disease has become inactive, and I would recommend treating patients with a positive test for 18 months after this, and patients with a negative test for *as long as possible* on half the maximal dose. This should radically reduce the incidence of relapses of lepromatous leprosy years after apparent cure.

(a) *Dapsone.* The most widely used sulphone at the present time is dapsone (4 : 4'-diaminodiphenyl sulphone); it is also known as DDS, DADPS, or the 'parent sulphone'. The B.P. preparation is put up in tablets of 100 mg., but the I.C.I. product (tab. Avlosulfon) is put up in tablets of 50 mg. and 100 mg. The commencing dose is 25 mg. twice a week, increasing slowly over the next 4-5 months to 350 mg. twice a week; at this stage 100 mg. can be given daily if more

convenient, especially to out-patients who find it easier to remember to take treatment daily than at longer intervals. In either case the tablets are taken in a single dose. The maximal dosage of 700 mg./week will prove suitable for most adult patients in the tropics, but where heavier patients are being treated, or where it is desired to correlate dosage with body weight (as in children), the maximum dosage can be calculated as 14 mg./kg./week or 2 mg./kg./day.

Under certain conditions it may be preferable to treat on a fortnightly basis, and various long-acting preparations are being tried. One is a suspension of dapsone in arachis oil to which aluminium stearate has been added; another is a suspension in equal parts of chaulmoogra oil and ethyl esters of chaulmoogra.¹⁷ Such 'depot' preparations contain 1.2 g. of dapsone in 5 ml. of oil, and one injection of 5 ml. is given intramuscularly every fortnight. Oily injections are inclined to be painful, however, and may give rise to abscesses, and it is clear that the ideal preparation has yet to be found. In this respect it has recently been observed that 'Avlosulfon' Soluble (see below) injected fortnightly gives results on a par with those obtained from oral DDS given twice weekly or from long-acting oily preparations.⁸

(b) '*Avlosulfon*' Soluble. I.C.I. chemists have overcome the problem of dapsone's insolubility in water by preparing an aqueous solution of a disubstituted derivative of DDS which breaks down in the body to liberate half its weight of dapsone, i.e. 1 ml. of '*Avlosulfon*' Soluble = 200 mg. of dapsone. It is put up in rubber-capped bottles containing 50 ml. and dosage is 0.25 ml. intramuscularly twice weekly, increasing by 0.25 ml. every fortnight and remaining on the maximal dose of 2-3 ml. twice weekly.

(c) *Solapsone* (*Sulphetrone*, *Burroughs Wellcome*). Solapsone is a disubstituted derivative of DDS which, taken orally, is hydrolyzed in the stomach to DDS. When given by intramuscular injection, however, it does not break down to DDS and its anti-leprosy activity is due to semi-solapsone. This is a monosubstituted derivative of DDS and is derived partly from semi-solapsone present in commercial solapsone and partly from chemical breakdown in the body.⁴ It is put up as a 50% aqueous solution, each millilitre containing 0.5 g. solapsone, and the dosage is 0.5 ml. intramuscularly twice a week, increasing by 0.5 ml. every fortnight to a maximum of 3 ml. (1.5 g. solapsone) twice a week and continuing at this level.

Toxic Effects of Sulphone

These are rare in the dosage outlined above, and the one most frequently encountered is haemolytic anaemia. Attention has been drawn

to the presence of Heinz bodies in the blood as an indication of impending haemolysis.²² One single case of agranulocytosis has been recorded.¹⁹ Other toxic effects include methaemoglobinaemia, hepatitis and dermatitis. Psychosis is usually listed as a toxic effect, but caution must be observed in accepting this as there are many possible factors accounting for the high incidence of psychosis in in-patients in leproseries, chief of which are the emotional stresses and strains associated with segregation. It has not been shown that out-patients taking sulphone are prone to psychosis, and it is significant that patients who recover from a psychotic illness are often able to resume sulphone therapy.

A recent report from the Belgian Congo describes black or dark brown macules developing during dapsone therapy and gradually disappearing on withdrawal of the drug.³

(2) *Thiambutosine*. This is the Approved Name for the diphenyl thiourea compound marketed under the name Ciba 1906 and previously called DPT, thiocarbanile or S.U.1906. Like sulphone, its action in leprosy is bacteriostatic. In the early stages of treatment it gives results which are better than those from sulphone and without any toxic effects,¹⁰ but there is a likelihood of drug resistance developing after about three years and, for this reason, sulphone should be added by the end of the second year of treatment and Ciba 1906 can be withdrawn by the end of the third year. Theoretically there is a risk of a thiouracil-like effect on the thyroid gland, but in practice this has not proved important. *Dosage*: 500 mg. (one tablet) daily for two weeks, increasing the daily dose by 500 mg. at fortnightly intervals to a maximum of 2-3 g. daily (4-6 tablets). For children the maximum daily dose can be calculated as 40 mg./kg. of body-weight. Maximal absorption occurs after a single dose of 1.5 g.,¹² therefore any daily dosage larger than this must be divided. One of the chief advantages of Ciba 1906 is that it is less likely than dapsone to precipitate reactions, and it is particularly useful in dimorphous leprosy complicated by neuritis.

Chemotherapy. (2) Potentially Useful Drugs Undergoing Trials

(1) *Ditophal*. This is the Approved Name of diethyl dithiolisophthalate, a compound manufactured by I.C.I. under the name Etisul (previously called Etip). It is put up as a cream for inunction and its anti-leprosy action is due to the release of ethyl mercaptan in the body after absorption through the skin. Unlike standard anti-leprosy drugs, ethyl mercaptan appears to act bactericidally, and there is rapid improvement at first.⁹ Davey has found that bacilli become

resistant to Etisul by the fourth month of treatment, and considers that it is best used in combination with DDS or Ciba 1906 for about three months and then stopped.¹⁰ Treatment should then be continued on standard lines.

(2) *Vadrine* (S. 131). This oxdiazolone compound, manufactured by Geistlich in Switzerland, has been shown to be effective,¹⁵ but drug resistance tends to develop after about a year. It is now being tried in combination with dapsone, and results are encouraging.

(3) *Cycloserine*. The literature on this antibiotic is in French, and the first report appeared in 1957.¹ Although it appears to be effective in leprosy, expense and side effects will probably preclude its general use.

(4) *Methimazole*. This compound, 1-methyl-2-mercaptoimidazole, introduced in 1949 for the treatment of thyrotoxicosis,²³ has an antithyroid activity much greater than that of thiouracil. There are indications that it is a very potent anti-leprosy drug, and its use in leprosy is being studied in Central America.

Complications of Leprosy and their Management

Reactional States. A proportion of patients undergo reactional states (reactions) during treatment, and, to understand how to treat them, it is necessary to clarify this very confused subject.¹⁶ From the clinical standpoint there are two basic types of reaction. The first ('Type 1') occurs in any form of leprosy and is characterised by swelling and redness of existing leprosy lesions, with or without neuritis. The second ('Type 2') is quite distinct as it occurs only in lepromatous leprosy and existing leprosy lesions remain unchanged. It is known as *erythema nodosum leprosum* because of the crops of erythematous nodes and patches which may appear on the skin; other manifestations are fever, neuritis, arthralgia, bone pains, orchitis, irido-cyclitis, anaemia and mental depression.

There is no specific treatment for 'Type 1' reaction. If skin smears at the onset of the reaction contain an increased number of bacilli it would be reasonable to continue anti-leprosy treatment, but the drug could be stopped if bacilli were fewer or absent. In either case, the drug should be stopped immediately if muscle paralysis is threatened and, if possible, the patient should be admitted to hospital. Muscle weakness or paralysis requires suitable splinting and physiotherapy, and an injection can be given into the affected motor nerve: just above the elbow for the ulnar nerve, in the carpal tunnel for the median nerve, and at the neck of the fibula for the common peroneal nerve. A useful formula

for the injection is hyalase 1500 units dissolved in 1 ml. of 2% procaine solution and mixed with 1 ml. of hydrocortisone suspension containing 25 mg./ml., and a size 14 needle is ideal. This type of injection can be repeated if nerve function shows signs of improving; if improvement does not occur, systemic steroid therapy can be tried but its value has not been established.

'Type 2' reaction is much more responsive to treatment. Although no special treatment is required, apart from reducing the dose of the anti-leprosy drug, if the reaction is mild, further steps will be necessary if there is fever and systemic disturbance. In this event the drug must be stopped and the effect of antimony can be tried. This is conveniently given in the form of a daily intramuscular injection of 2 ml. of Stibophen, but antimony can be discontinued after a week if no improvement occurs and an oral antimalarial such as chloroquine can be tried. Steroid therapy¹⁴ can be instituted if these measures fail, and the effect is dramatic, but steroids should not be used without adequate reason or without knowledge of their side effects. Two tablets of cortisone (50 mg.) are given eight hourly on the first day, reducing by 12.5 mg. of 25 mg. each day so long as the reaction is being controlled; in this way a short course of 5-10 days may suffice, and the anti-leprosy drug can be resumed cautiously. Cortisone's tendency to cause electrolyte disturbance is countered by reducing salt intake and by taking potassium by mouth in the form of Mist. Pot. Cit. (B.P.C.) 1 fl. oz. daily. If a short course does not control the reaction it may be necessary to continue steroid at the lowest effective level, but in such case it would be desirable to change to one of cortisone's analogues such as prednisone or dexamethasone as these cause minimal electrolyte disturbance. If prednisone is selected it would be preferable to give it in an enteric-coated form to reduce the risk of gastric disturbance.²⁵ Relative dosages can be calculated on the basis that prednisone is five times more powerful than cortisone and dexamethasone is thirty times more potent. Anti-leprosy treatment is given concurrently.

If irido-cyclitis is the principal manifestation of a 'Type 2' reaction, systemic steroid may be avoided by instilling 1% cortisone eye-drops hourly by day; an ointment containing 1-2% can be applied at night. Atropine drops must be instilled twice daily to keep the pupil dilated. Similarly, if peripheral nerves are bearing the brunt of the reaction, intraneural injections can be given with very good effect in place of systemic steroids.

Paralysed Muscles. Paralysis of recent origin

calls for splinting on the orthopaedic principle that a paralyzed muscle must be supported, and this is combined with physiotherapy.²⁴ Surgical treatment is required for permanent paralysis; this may take the form of a fascial graft to correct facial palsy, a tendon graft to correct claw hand, or a tendon transfer for foot-drop. This important subject has been developed in a number of recent papers.^{2, 7, 11, 13}

Anaesthetic Hands or Feet. The danger lies in damage to skin and bone resulting from repeated (and avoidable) trauma, and the doctor has the important task of advising how damage can be prevented; it may mean a change of occupation, the wearing of gloves at work or when cooking, using a cigarette holder when smoking, or being supplied with suitable footwear.²⁰ Once a trophic ulcer of the foot has developed it must be healed by rest in bed or by a below-knee walking plaster retained for 4-6 weeks; after this it will be necessary to supply suitable footwear and to advise travelling by bicycle rather than on foot.

Burns and other hand injuries should be splinted until healed, otherwise the patient, feeling no pain, will continue to use the injured member. It is important, too, that the patient should learn to inspect his hands and feet daily so that splinters and minor injuries can receive early treatment. Neglected trophic ulcers lead to osteomyelitis and eventual amputation of digits.

Facial Disfigurement. Plastic surgery can play a very important part in the rehabilitation of the

leprosy patient, especially in the provision of eyebrows and in the correcting of facial disfigurement caused by saddle-nose, ectropion, pendulous ear-lobes, and by excessive folds of skin.

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