THIOSEMICARBAZONE IN THE TREATMENT OF THE REACTIONAL AND BORDERLINE FORMS OF LEPROSY

H. W. WHEATE, M.B., B.S., D.T.M. & H.

Makete Leprosarium, Tanganyika.

The first report of the use of thiosemicarbazone (TBI 698) in leprosy was a note of 6 months' treatment of one lepromatous case. (Hohenner, 1949.) This was followed by a preliminary communication by Vegas et al. (1950), working in Venezuela, on the treatment of 42 lepromatous cases for periods of 3 to 6 months. The therapeutic effect was marked and a notable feature was the tolerance exhibited to doses as high as 900 mgms, daily. Two papers by Lowe (1953, 1954), one covering 2½ years' and the other 38 months' experience in Nigeria, give a painstaking analysis of the relative advantages and disadvantages of this drug as compared with sulphone (DDS). He found a greater toxicity (agranulocytosis, severe anaemia, allergic dermatitis, drug fever and hepatitis occurred variously in 16 out of 273 patients), and that the need for closer medical supervision and the apparent development of drug resistance during the second year of treatment make it unsuitable for large scale use, especially in out-patient centres. Further disadvantages are the daily dosage regimen and the greater cost. Its value, as shewn by Lowe and now generally agreed by the majority of workers, is that it is a most useful alternative to sulphone in lepromatous cases in which, because of repeated reactions, sulphone therapy has to be interrupted or stopped altogether, and in cases which develop sulphone toxicity (follicular and exfoliative dermatitis being commonest manifestations of this).

Thiosemicarbazone in the Neuritis of Leprosy

In tuberculoid leprosy, Lowe (1953, 1954) found that, while on the whole the subsidence tended to be slower than with sulphone, his impression was that it had more often been accompanied by a return of pigment and of sensation to the affected area of skin. The subsidence of nerve thickening was also, perhaps, more marked. He reported one case of severe tuberculoid reaction and one of severe neuritis (tuberculoid), both occurring in the course of sulphone therapy, in which there was no clear indication that the response was any better than would have been given in continued sulphone therapy—it is in this respect that my own experience differs.

In borderline leprosy, Lowe found a good clinical and bacteriological response, but relapse occurred in one case—contrary to what is usual in sulphone therapy and possibly due to the development of drug resistance.

The only report specifically concerned with the beneficial effect of thiosemicarbazone in the painful neuritis of leprosy is by Farinas (1951). His series of cases comprised 4 lepromatous, 2 tuberculoid and 1 indeterminate. He concluded, however, that this finding may have been due to a non-specific effect and that the drug might be equally efficacious in other forms of neuritis, a view which has not, as far as I know, been confirmed.

The Dangers of Sulphone in Atypical Forms of Leprosy

Garrett (1956), writing of his experiences of 5 years' mass treatment with DDS in Nigeria says:—

“ In the borderline and atypical tuberculoid leprosy, particularly if the lesions are much raised and situated on the hands, feet or face, severe reactions with paralysis often occur early in treatment. This is particularly true if the dosage is rapidly raised.”

It has long been known that East Africans appear to tolerate sulphone less readily than Nigerians and it is not therefore surprising that in my experience such reactions occur, not merely when the dosage is rapidly raised but *even after only one or two twice weekly doses of 100 mgms. DDS.*

DDS is being used on an increasingly wide scale in out-patient treatment centres, but there exists a minority group of leprosy cases for whom even the most cautious routine dosage regimen is likely to be disastrous. Prompt diagnosis, which is not beyond the ability of African subordinate medical staff given training in it, will avert the tragedy of permanent crippling. Having laid particular emphasis on this matter at this leprosarium, we have collected a considerable number of such cases, sent in by Mission and Native Authority out-patient treatment centres.

The Diagnosis of the Atypical Forms of Leprosy in which Sulphone is Dangerous.

1. *Those recognisable before sulphone therapy has commenced.*
 - (a) Cases presenting with lesions of the “major” tuberculoid type but with these differences—that there is a flat, hypopigmented zone, extending beyond the most raised portion of the patch and frequently involving:—
 - (i) The palms of the hands and soles of the feet
 - (ii) The mucosae of lip, nostril or conjunctiva.

The ulnar and peroneal nerves may be enlarged and tender and early palsy of the small muscles of the hand may be evident. In some cases these neural signs may be absent.

- (b) "Reactional" and borderline cases, in which there are grossly raised, succulent, plaque-like lesions, painful when pinched between finger and thumb. Some of the smaller lesions may resemble shotty, lepromatous nodules, extending deep into the cutis. The appearance of the ears is especially deceptive in its similarity to leproma, as is the tendency of the lesions to be symmetrical—whereas in typical tuberculoid leprosy the patches are asymmetrical. As in (a) above, some have enlarged tender nerves, others do not.

Both these groups have positive skin smears, the latter (b) frequently up to 4 plus. The majority have a positive lepromin, though some of the borderline cases give a negative or doubtful reaction. Some—indeed the majority of the borderline cases—tolerate sulphone well and respond dramatically if treated with care, but the policy advocated is that all such cases should be admitted to a leprosarium, not only because of the dangers of crippling deformities but also because of their infectivity, as evidenced by their positive skin smears.

2. *Those recognisable after the commencement of sulphone therapy.*

- (a) Cases, similar to Group 1(a) with minimal atypical signs missed at the initial examination, but "blowing up" after only a few weeks' treatment with a tuberculoid reaction and acute neuritis.
- (b) Cases of the indeterminate type, with pale, flat macules and variable alterations of sensation in the patches, which undergo a metamorphosis to the major tuberculoid type during sulphone therapy. Some, particularly children, develop paralyses remarkably rapidly and it is a good practice to admit all children with flat, cafe-au-lait coloured macules to a leprosarium, where the facilities for close observation reduce the dangers of sulphone.
- (c) A small minority of clinically lepromatous cases develop an unusual type of lepra reaction in the early stages of sulphone therapy, with oedema and subsequent desquamation of the infiltrated skin and acute neuritis, with incipient paralyses rapidly ensuing.

Case Histories

(1) Female, aet. 25 years: referred by Native Authority Clinic, which she first attended in January, 1956, at which time

she was given 100 mgm. of DDS. She failed to attend the clinic again because unable to walk the distance in the rainy season. She was admitted to Makete Leprosarium on 13th February, 1956 in a state of tuberculoid reaction involving the palms of the hands and mucosae; there was oedema of eyelids, and also enlargement of the left facial, both ulnar, and both peroneal nerves. She was given thiosemicarbazone and made good progress, apart from occasional ulcers of feet. About a year later, on 25th February, 1957, all lesions had resolved, and there was a slight degree of bilateral mobile claw hand, and shortening of the right thumb due to sepsis, and the nerve trunks were all normal clinically. She was considered fit to commence DDS in place of thiosemicarbazone.

(2) Male, aet. 32 years, was admitted on 12th September, 1955, with succulent borderline lesions, some peeling, particularly on the face and ears, shotty lesions on the arms, and the peroneal nerves slightly enlarged and tender. He was put on thiosemicarbazone and by 23rd December, 1955 the lesions were resolving and partially repigmented, and the peroneal nerves were clinically normal. On 9th March, 1956 he was changed to DDS and on 12th February, 1957 there were only a few residual hypopigmented lesions and the lepromin reaction was doubtful positive.

(3) Male, aet. 25 years, was admitted on 20th July, 1956 with extensive grossly infiltrated lesions, especially on face and ears, at that time thought to be lepromatous. The left ulnar nerve was enlarged and tender. He was given the routine twice weekly dosage of DDS, reaching 400 mgm. twice weekly in November. On 3rd December he developed severe reaction, with oedema of face, hands and feet, and there was no improvement on stopping the DDS. On 24th January, 1957 the skin smears were positive, averaging 2 plus. On 7th February of the same year he was considered to be of borderline type clinically, and had developed bilateral simian hand, with right drop foot. Both ulnar nerves and both peroneal nerves were enlarged and tender, the right peroneal more than the left. He was then on 25 mgm. of thiosemicarbazone daily. By 18th February there was slight improvement, and he was on 50 mgm. daily. By 27th February the lepromin reaction was 1 plus, the lesions showed some subsidence, and he was able to walk without discomfort.

(4) Female, aet. 27 years; referred by U.M.C.A. Hospital at Manda, where she began treatment in July, 1955 with twice weekly DDS, at that time having scattered tuberculoid macules. By October she was getting 200 mgm. of DDS twice weekly, the

macules were not anaesthetic, but there was anaesthesia of fingers and enlargement of the right ulnar nerve. A tuberculoid reaction developed in February, 1956 and she was admitted to Makete. At that time she had gross oedema of the right hand, with several enlarged cutaneous nerves in the right forearm and hand. The skin smears were positive, averaging 2.4. She was put on thiosemicarbazone. In August the operation of stripping the right ulnar nerve was carried out by Mr. W. A. A. Hodges, at which time the condition of the nerve was not acute. By February, 1957 the reaction had subsided completely, and DDS was begun. There was mobile right claw hand, and the patient reports an improvement in the palsy since before the operation. Massage and exercises were instituted since the oedema subsided.

(5) Male, aet. 27 years. Referred by Native Authority Leprosy Clinic as a major tuberculoid treated by 100 mgm. of DDS for 1 month only, when reaction developed. Admitted to Makete 14th March, 1956, he had right ulnar and both peroneals enlarged and tender and skin smears positive, averaging 1.2. On 21st August the left peroneal was still enlarged and tender, and was stripped. On 25th August the right ulnar was stripped and transplanted. There was slight wasting of the right interossei. Both operations were by Mr. W. A. A. Hodges. By 20th February, 1957 the skin lesions had resolved, equal power existed in both feet, and there was no increase in palsy of right hand. DDS was begun.

(6) Female, aet. 19 years. Referred by U.M.C.A. Hospital, Manda. In January, 1956 had been lepromatous, macular on trunk, infiltrative on nose and left ear, and was given 100 mgm. of DDS twice weekly. She lapsed from attendance in March, while having 300 mgm. of DDS twice weekly, and reported again in April, having had a reaction at home. She was admitted to Makete on 22nd May, with atypical leproma, and desquamation from the macules on the trunk and diffuse infiltration of extensor surfaces of the limbs. She had small nodules on the ears, thinned eyebrows, infiltration of forehead and nose, and ulceration of the nose. The right ulnar nerve was much enlarged, left also enlarged, both tender. There was early mobile right claw hand. The peroneal nerves were enlarged and tender. Skin smears were 4 plus. Thiosemicarbazone was begun and massage to right hand. By 22nd February, 1957 there was excellent resolution, the claw hand completely recovered, nerve trunks all normal, without tenderness. The skin smears were now positive, averaging 0.6. DDS was begun.

Summary of Treatment

1. The dosage of thiosemicarbazone given is:—50 mgm. daily on 6 days per week for 2 weeks, then 100 mgm. for 2 weeks, and then 150 mgm. daily. On this regime no toxic manifestations have occurred.
2. When the reaction has subsided, as evidenced by the flattening of the raised, succulent lesions and the disappearance of nerve tenderness, TB₁ is stopped and DDS given. This stage is usually reached after 6 months to one year.
3. The treatment of incipient palsies is of great importance. The surgical removal of the nerve sheath, with transplantation in the case of the ulnar nerve, is of value in the acute phase, but mainly as a means of relieving pain. Evidence that it actually prevents the development of paralysis is equivocal, though it is certain that no case with early palsy becomes worse after operation.
4. Simple massage and exercises to keep the fingers mobile are essential. A useful adjunct to these measures is a Bunnell knuckle-duster splint.
5. Concomitant infections, intestinal parasites, etc. are treated as a matter of course. The patient is kept under careful observation both as regards his general health and his response to specific therapy.

Summary

A brief resume of previous work on the use of thiosemicarbazone in leprosy is given and the evidence that it has an effect superior to that of sulphone in the neuritis of leprosy particularly noted. Attention is drawn to the dangers of sulphone therapy in cases of atypical tuberculoid and borderline leprosy, the diagnostic features of which are described. The value of thiosemicarbazone, given under close medical supervision in a leprosarium, in such cases is emphasised and illustrated by some case histories. A summary of the regimen of treatment, including a brief note on the place of surgery and simple physiotherapy is given.

My thanks are due to Mr. W. A. A. Hodges, District Medical Officer, Mbeya, who has operated on a number of these cases, to Dr. Hay of the U.M.C.A., who has referred cases of this type for admission to this leprosarium and to the Hon. the Director of Medical Services, Tanganyika, for permission to publish.

REFERENCES

- FARINAS, P. (1951). *Bol. Soc. Cubana de Dermat. y Sifil.* 8, 164.
 GARRETT, A. S. (1956). *Lep. Rev.* 27, 54.
 HOHENNER, K. (1949). *Med. Klin.* 44, 1378.
 LOWE, J. (1953). *Leprosy in India*, 25, 188.
 LOWE, J. (1954). *Lep. Rev.* 25, 186.
 VEGAS, M. et al (1950). *Int. J. of Leprosy*, 18, 451.