TREATMENT OF LEPROSY WITH THIOSEMICARBAZONE AND DDS; A COMPARATIVE SERIES AMONG AUSTRALIAN ABORIGINES

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The introduction of the complex sulfone derivatives marked a considerable advance in the treatment of leprosy, but it also meant a period of some confusion while the various kinds of derivatives were on trial. The period of trial has, in the main, ended by the acceptance of the majority of the parent substance, DDS, as the drug of choice. It is noted, however, that at the BELRA conference on sulfone therapy (1) there was support for sulphetrone given parenterally, particularly in mass treatment. Cochrane (2) supports this treatment. But whatever sulfone is preferred, sufficient experience has now been gained to enable one to say that the complete answer to invasion by Hansen's bacillus has not been found. Hence a number of trials with an unrelated substance, thiosemicarbazone (TB-1), have now been carried out.

Following the introduction of this substance for the treatment of leprosy by Hohener (3), a further account of successful treatment by Ryrie (4) induced us to undertake a trial among the patients at the leprosarium in Darwin, in the Northern Territory of Australia. The trial period was one year, commencing in November 1950 and ending in November 1951.

NATURE OF THE TRIAL

For the trial there were chosen 10 patients whose progress on previous forms of treatment had been unsatisfactory, and 28 newly admitted patients without previous treatment. The treated group had received sulphetrone for the previous two years, with a maintenance dose of 3 gm. daily by mouth. Prior to that there had been a short period of treatment with diasone, and before that with chaulmoogra. These patients were put onto the thiosemicarbazone. Of the 28 new patients, 14 were treated with DDS and 14 with thiosemicarbazone, one drug or the other being ordered alternately as the patients were admitted. No selection of cases was made. Of the total 38 patients, 31 were full-blooded aborigines; the remaining 7 were half-castes, that is, European-Aboriginal or Chinese-Aboriginal hybrids.

During the trial period the patients were examined regularly and alterations in the lesions and the findings in bacteriological smears were noted. Notes were also made of their general health and weight. Weekly

hemoglobin estimations were made on all patients during the first two months of treatment. Progress was recorded as "much improved," "slightly improved," "unaltered," or "worse."

DOSAGE

The sulfone was used in the form of avlosulfon (I.C.I.). The maintenance dose was 200 mgm. daily by mouth, with a maximum dose of 250 mgm. for the few patients over 140 lb. in weight and a minimum of 100 mgm. for children. Thiosemicarbazone was given in the form of neustab (Boots), in a maintenance dose of 150 mgm. daily by mouth for adults down to 25 mgm. for small children. After six months treatment the maintenance dose for adults was increased to 200 mgm.

RESULTS

THE FIRST GROUP

The first group, the 10 patients who had had previous treatment, consisted of 5 lepromatous cases, 4 tuberculoid and 1 borderline.[1] Three of the lepromatous cases were classified as L2, and two as L3. All five were subject to frequent reactions. The tuberculoid patients all had extensive leprids and marked neural lesions with mutilations. At the end of six months treatment with thiosemicarbazone, the results were moderately successful, considering the resistant nature of the cases. Table 1 sets out the results. All patients appeared to be in better general health than before. Reactions were fewer, and the tuberculoid patients had less extensive and less active lesions.

TABLE 1.—*Group 1, 10 previously treated cases, after 6 months treatment with thiosemicarbazone.*

Type	Total	Much improved	Slightly improved	Unaltered	Worse
Lepromatous	5	-------	2	3	-------
Tuberculoid	4	-------	3	1	-------
Borderline	1	-------	1	-------	-------
Totals	10	-------	6	4	-------

At the end of twelve months treatment, however, the position was altered. The borderline case and 3 of the lepromatous

[1] In the original manuscript this case was called "indeterminate." In correspondence the author states that cases so classified included not only children with early flat macules but two cases—this one and one other mentioned later—with "lesions which resembled both tuberculoid and lepromatous types," called "indeterminate" for lack of another name. The term "borderline" has been substituted with the author's permission.—EDITOR.

ones had all slipped back to their original state, and the remaining two lepromatous cases were listed as worse. One of the latter two was a full-blooded aboriginal boy who suffered such a severe reaction as to appear moribund, with enlarged liver and spleen, albuminuria, and large ulcerating nodules. The other was a young adult full-blood whose reactions became worse, the nodules ulcerating for the first time; his attacks of neuritis were severe. Smears remained positive in all cases.

Of the 4 tuberculoid cases, 3 showed some lessening of activity in the leprids. The fourth, after an initial period of marked improvement, relapsed to the previous active state.

THE SECOND GROUP

The second group consisted of 14 new patients, these also treated with thiosemicarbazone. Among them were 4 lepromatous cases, 2 classified as L2 and 2 as L3. In 3 of these cases, after twelve months, no detectable alteration had occurred. The fourth patient (L3) died after an acute illness, 10 weeks after the commencement of treatment, when he was receiving 150 mgm. of the drug daily. He developed acute pain in the large joints, high fever and enlarged liver; there was no skin desquamation. The urine contained much albumin; it was not tested for liver damage. A postmortem examination was not made, the writer unfortunately being absent on leave at the time. The diagnosis of the condition, and the question of whether or not toxic effects of thiosemicarbazone played a part, remain uncertain.

There were 7 tuberculoid cases in this group, of which 5 were moderately severe, with extensive leprids and neural signs, while the other 2 were less severe with no obvious neural lesions. At the end of twelve months, 3 of the more severe cases were listed as slightly improved and 2 as unaltered. One of the milder cases was much improved and 1 slightly improved.

The remaining 3 cases in this group were children with early indeterminate skin lesions. After twelve months, 2 were much improved and 1 slightly improved.

THE THIRD GROUP

This group consisted of the 14 new patients put under DDS treatment. Of the 6 lepromatous cases, 5 were classified as L2 and 1 as L3. After twelve months, the L2 cases were listed as 1 much improved, 3 slightly improved, and 1 unaltered. The L3 case was much improved. The 5 tuberculoid cases in this group

were all moderately advanced and active. After twelve months, 3 were much improved and 2 slightly improved. There were two indeterminate cases, children with early lesions. One was much improved while the other remained unaltered. The remaining case was borderline, a child with infiltrations suggesting the lepromatous type but with some skin lesions resembling leprids. The infiltrations subsided considerably, the leprid-like lesions looked less active, and he was listed as much improved.

The results obtained in these three groups are shown in Table 2.

TABLE 2.—*Results after 12 months treatment, groups 1 and 2 with thiosemicarbazone, Group 3 with DDS.*

Group	Type	Total	Much improved	Slightly improved	Unaltered	Worse
1	Lepromatous	5	-------	-------	3	2
	Tuberculoid	4	-------	3	1	-----
	Borderline	1	-------	-------	1	-----
	Totals	10	-------	3	5	2
2	Lepromatous	4	-------	-------	3	1 died
	Tuberculoid	7	1	4	2	-----
	Indeterminate	3	2	1	-------	-----
	Totals	14	3	5	5	1
3	Lepromatous	6	2	3	1	-----
	Tuberculoid	5	3	2	-------	-----
	Indeterminate	2	1	-------	1	-----
	Borderline	1	1	-------	-------	-----
	Totals	14	7	5	2	-----

DISCUSSION

All reports on the use of thiosemicarbazone that I have seen, from Hohener and Ryrie onwards, have been favorable. The most recent one at the time of writing is that of Schujman (5), which is also favorable. It will be seen, however, that our results with this drug have not been encouraging. The preparation used came from the same firm as that for Ryrie's series, and the same dosage (150 mgm.) was used for the first six months and then increased to 200 mgm. Progress was moder-

ately satisfactory for the first six months, but the improvement shown at that time was not maintained. Results were distinctly better among tuberculoid cases than among lepromatous cases. Each lepromatous case continued to have reactions, and two of them had much severer reactions than previously. No patient on this drug showed appreciable alteration in the bacteriological smears. The improved mental outlook of patients on thiosemicarbazone, mentioned by Ryrie, was not noted, but this would be difficult to assess in a primitive people.

The patients treated with DDS showed considerably more improvement, as is apparent from comparison of Groups 2 and 3 in Table 2. In addition, the positive smears of four of these patients became negative after twelve months treatment. All patients were constantly under the observation of the nursing staff, who were emphatic in their opinion that the patients on DDS enjoyed better general health than those on thiosemicarbazone. The average gain in weight which they showed was greater.

With the possible exception of the patient on thiosemicarbazone who died, there was no evidence of toxicity from either drug.

The five children with early indeterminate lesions were not suitable subjects for the trial, as it could be expected that some would improve without any treatment.

In the Northern Territory, leprosy has been present among the aborigines for only 60 years. It has now reached an incidence of 56 per mille, with 50 per cent of lepromatous cases and a high incidence among children.[2] The disease is therefore virulent, and hereditary immunity must be small. The existence of hereditary immunity is said to be doubtful, and if the disease is virulent enough to withstand thiosemicarbazone it would, presumably, also withstand sulfone.

SUMMARY

Ten patients who had failed to respond to other methods of treatment were given a year's trial on thiosemicarbazone, with disappointing results.

Fourteen new patients also gave disappointing results on thiosemicarbazone.

Fourteen new patients on sulfone (DDS) gave distinctly better results.

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[2] An abstract of a report by the author on this matter appears in this issue.

No satisfactory explanation is evident for the relative failure of thiosemicarbazone in the treatment of Australian aborigines.

RESÚMEN

Se comparan los resultados de thiosemicarbazone con los de DDS en el tratamiento de 38 leprosos aborígenes en Darwin, Australia, durante el período de un año. Cada uno de tres grupos de pacientes contenía casos lepromatosos, tuberculoides y de otros tipos. Un grupo de 10 eran pacientes que no habían respondido al sulphetrone. Al finalizar el año bajo el semicarbazone solo 3 casos (tuberculoides) demostraron mejoría mientras que 2 casos empeoraron. En un grupo de 14 casos nuevos sin tratamiento previo, y sometidos a ésta droga, los resultados fueron mejores, pero no tan buenos como en un grupo semejante tratados con DDS. Com el thiosemicarbazone los resultados en general fueron mejores despues de 6 meses que despues de 12 meses, y mejores en casos tuberculoides que en lepromatoso, pero ningún caso demostró mejoría bacteriológica, mientras que 4 de 14 casos tratados con DDS se tornaron bacteriológicamente negativos. El autor nota que sus resultados con thiosemicarbazone son contrarios a los de otros investigadores.

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