INITIAL DOSAGE OF DIAMINODIPHENYL SULFONE IN THE TREATMENT OF TUBERCULOID LEPROSY

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During the last fifteen years or so the sulfone drugs have almost entirely replaced chaulmoogra oil and its products in the treatment of leprosy. More recently there has been a trend away from the more expensive sulfone derivatives after it was found (3) that the parent compound, diaminodiphenyl sulfone (DDS), could be used safely. General acceptance of this compound came when it was shown that doses of 100 to 200 mgm. daily would suffice, thus avoiding the toxic effects which occur when larger doses are employed (2).

Regardless of the sulfone drug selected for use, it has been the custom to employ small doses at the outset of treatment and to wait some time before each successive increment in the daily dose. Thus the Expert Committee on Leprosy of the World Health Organization (4) has stated that, ". . . treatment should be started at levels considerably lower (about one quarter) than the dose ultimately attained, and the increase should be gradual and last several weeks." For example, in the clinical evaluation studies carried out by the Leonard Wood Memorial (1), patients were given 65 mgm. of DDS on alternative days for the first three weeks of treatment, 65 mgm. daily in the 4th-6th weeks, 130 mgm. daily in the 7th-9th weeks, and only in the 10th week was the full dose of 200 mgm. daily given.

Although this schedule of dosage appears paradoxical from the viewpoint of chemotherapy, there may be sound reasons for its use. Thus it might be argued that the direct toxic effect of DDS would be less if the patient were given a chance to develop a tolerance. However, that development is unlikely in view of the cumulative toxic effect of the drug which was seen when large dosages were employed. A more plausible explanation for using a low initial dose and gradual increments thereof is the supposition that lepra reaction in lepromatous patients and reactional states of tuberculoid cases might be less frequent.

We have made a study of the latter point, comparing the course of patients with tuberculoid leprosy when treated with several weeks of low dosage as compared with patients receiving the full dose at once.

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MATERIAL AND METHODS

From among the ambulatory patients coming to the Special Skin Clinic of the Rangoon General Hospital, those who had the tuberculoid type of the infection in clear-cut form were accepted for this therapy experiment. Those patients who had previously been given specific treatment, or who lived at great distances from the clinic, were rejected. There was no discrimination on the basis of sex or age. At the beginning cases with very active lesions were avoided, but later on these, too, were taken into the series. Alternate cases were assigned to one of two treatment series. Each of them originally consisted of 100 patients, both containing a large proportion of children.

The patients in one of these groups, the "ascending-dose series," were begun with an initial dose of 25 mgm. DDS daily and increased at weekly intervals to 75 or 100 mgm. daily for adults, depending on the body weight. The adult patients in the other group, the "maximal-dose series," were given at the start the maximal dose of 75 or 100 mgm. daily, depending on weight. In both series the maximum for the children was 25-50 mgm. daily.

Follow-up examinations were made at weekly intervals in the beginning and later at monthly intervals. In total, 122 patients were followed for an average of six months and a minimum of three months. Of these, 63 were in the ascending-dose group and 59 in the maximal-dose group. The two series are compared in the following tabulation.

	Ascending series	Maximal series	Total
Cases followed	63	59	122
Males	36	33	69
Females	27	26	53
Age, average	29	25	27
Classification:			
Minor Nm1	18	26	44
Minor Nm2	20	16	36
Major	11	6	17
Reaction	5	2	7
Active	9	9	18
Bact. positive	8	4	12

It will be seen that the ratio of male to female patients was similar in the two groups. The number of "active" cases was the same in both groups, although there was a greater proportion of major tuberculoid cases in the ascending group than in the maximal one. The average maximal dose reached in the ascending series (70 mgm.) was almost identical with the average dose (68 mgm.) given in the series which was started on the full amount. The average follow-up of these patients was 6 months in each group.

RESULTS

It is most interesting to compare the incidence of neuritis in the two groups. As shown in Table 1, neuritis was noted in 17 cases, with practically equal distribution between the two groups, and 14 of them were treated. Of the 14 treated cases, 3 had neuritis before the treatment with DDS was started, and were serious enough to warrant a series of injections with chaulmoogra oil or sulphetrone. In the 14 cases in which the neuritis developed after the DDS treatment was initiated, it was severe enough in 11 to warrant injections along the affected nerve trunk. Of these severe

cases coming on after the start of the treatment there were 6 in the ascending-dose group and 5 in the maximal-dose group. It is an interesting fact that 5 of these severe neuritic complications were noted during the first two weeks of the treatment; the other 6 came on later, between 6 and 30 weeks after the institution of treatment.

Regarding reactions, it is also shown in Table 1 that 11 such occurrences were noted—again with practically equal distribution between the

TABLE 1.—*Episodes of neuritic and reactional nature occurring in the two treatment groups, and effects on the lesions.*

Group	No. of cases	Neuritis		Reactions		Lesions[a]	
		Noted	Treated	Noted	Treated	Reduced	Faded
Ascending-dose	63	9	8	6	5	41	11
Maximal-dose	59	8	6	5	2	36	11
Total	122	17	14	11	7	77	22

a Total cases improved, 81 per cent.

two groups—and that in 7 of them the condition was severe enough to justify the use of cortisone or potassium antimony tartrate. Since the reactional condition had been present in 1 of these cases before treatment, there were 6 such cases that occurred during the course of the treatment, 4 in the ascending group (the dose in three instances only 25 mgm., in the other one 100 mgm.) and 2 in the maximal series (doses 50 and 75 mgm., respectively). Again it may be noted that 3 of the reactions occurred during the first two weeks of treatment, the other 3 coming on later, 8-12 weeks after the beginning of treatment.

Finally with regard to Table 1, it can be seen that during the brief period of treatment with DDS the infiltration of the lesions was reduced in more than one-half of the cases in each series, and that the lesions had faded in 11 cases in each of the two series. In no instance was it felt that the patient's lesions had become worse.

Mention may be made of the toxic reactions to DDS itself, details of which are shown in Table 2. The most frequent symptom was giddiness, which was noted by 3 of the patients in the ascending group and 5 in the maximal group. Insomnia and weakness were unusual complaints. In 2 instances anemia developed in the ascending series, and 1 instance of skin rash in the maximal group.

DISCUSSION

It is obvious that the two series of tuberculoid cases involved in this experiment were quite similar at the outset, and that the results of the two methods of initiation used in the treatment—including neuritis, re-

actions, drug reactions and control of the lesions—were also similar. None of the small differences found has any statistical significance. Nor does it seem worth while to extend the number of observations with tuberculoid cases in an attempt to bring out significant differences. It seems quite

TABLE 2.—*Side effects of the drug in the two treatment groups; numbers of patients complaining.*

Group	No. of cases	Giddiness	Insomnia	Anemia	Weakness	Rash	Total with reactions
Ascending-dose	63	3	2	2	1	0	8
Maximal-dose	59	5	1	0	0	1	7
Total	122	8	3	2	1	1	15

clear that no harm was done, in any respect, by starting the treatment with the maximal dose, and that nothing is served in such cases by the customary gradual induction of treatment.

It might be interesting, however, to repeat this experiment with cases of the simple or indeterminate type, and also with caution to extend the same investigation to the treatment of lepromatous cases. Until such experiments are carried out it would be hazardous to recommend that all leprosy patients be given the maximal dose of DDS at the start of their course of therapy. However, it has been the personal observation of one of the authors (R.E.) that lepromatous patients are less prone to develop erythema nodosum leprosum reactions when continued on a reasonable dose of DDS, than when treatment is discontinued and, after a rest period, started again with a gradually increasing dose.

SUMMARY

Two hundred cases of leprosy of the tuberculoid type were treated with DDS, one-half receiving gradually-increasing doses and the other half starting with the full dose at once. Some 122 of these cases (63 of the ascending-dose group and 59 of the maximal-dose group) were followed for an average of six months. The results were the same with regard to neuritis, reactions, side-effects of the drug, and beneficial effect of the treatment. Until a similar trial is carried out with lepromatous cases, however, it would not be wise to alter the conventional plan of therapy with DDS in cases of that form of the disease.

RESUMEN

Doscientos casos de lepra de forma tuberculoidea fueron tratados con DDS, recibiendo la mitad dosis cada vez mayores y comenzando la otra mitad con la dosis completa en seguida. Unos 123 de estos casos (63 del grupo de dosis ascendente y 59 del grupo de dosis máxima) fueron mantenidos en observación durante un promedio de seis meses. Los resultados fueron idénticos con respecto a neuritis, reacciones, efectos

colaterales de la droga y efecto beneficioso del tratamiento. Sin embargo, hasta que se lleve a cabo un ensayo semejante con casos lepromatosos, no sería prudente alterar el plan vigente de tratamiento con DDS en casos de esa forma de la enfermedad.

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