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## PRELIMINARY REPORT ON 4:4'DIAMINODIPHENYL SULFONE (DDS) TREATMENT OF LEPROSY

ERNEST MUIR

*Purulia Leper Home and Hospital  
Purulia, Bihar, India*

Since the discovery of the effectiveness of the sulfones in the treatment of leprosy, those concerned with the welfare of the innumerable poverty-stricken sufferers from this disease throughout the world have been on the lookout for a form of sulfone which would be effective, safe, easily administered, and at the same time cheap enough to make it available to the poor.

In 1947, Dr. Wevill of Imperial Chemical Industries, Ltd., suggested to the writer that 4:4'diaminodiphenyl sulfone (DDS), the parent substance of the proprietary sulfones, might be worthy of trial. He mentioned its usefulness in tuberculosis of cows, but said it had so far been found too toxic for human use. As a result of our conversation, Wevill arranged that a supply of DDS should be sent out to Nigeria for experimental use by the staff of the Leprosy Research Unit at Uzuakoli, under Dr. John Lowe, who chose to administer it orally. The first results obtained there have already been published (3, 4).

It was not until April 1949 that the writer himself, by then working at the Purulia Leper Home in India, had an opportunity to test this drug. This paper describes certain findings after a year's trial by the oral route.

### THE MINIMUM EFFECTIVE DOSE

In testing DDS it was apparent that, because it is highly toxic, much smaller doses would have to be used than those of sulfone derivatives in use. It was therefore necessary to determine the minimum effective therapeutic dose and the maxi-

imum subtoxic amount. Information was received from Lowe (personal communication) that he had found a daily dose of 0.2 to 0.3 gm. to be tolerated by his patients, that there was nearly 100 per cent absorption from the alimentary canal, and that because excretion was slow minute doses produced what was apparently a therapeutic blood level (1 to 2 mgm. per 100 cc.).

My previous experience with diasone in Trinidad (6) and in England (7), and that of many other writers, has shown that in advanced lepromatous cases it sometimes takes years before a noticeable diminution in the numbers of bacilli occurs, but that certain early clinical signs of improvement are often observable within a few weeks or months. These signs are: control of lepra reaction, the healing of long-standing lepromatous ulcers, the clearing of the nose when blocked, the arrest of lepromatous invasion of the eye, and, later, the gradual flattening out of nodules and thickenings of the skin.

If DDS were to be effective in the same way as diasone, the first indications of improvement in advanced cases suffering from these complications would likely be of similar nature. Trying it out in several such cases, it was found that doses as small as 0.05 gm. daily, or even less, were at least as effective as the usual doses of diasone in ameliorating the conditions mentioned. Also, after a few weeks of treatment there was, in many cases, flattening of nodules with improvement of the clinical appearance. These favorable early effects encouraged the hope that the later results, especially the reduction and final disappearance of bacilli, would also be similar to those obtained with diasone.

#### METHOD OF ADMINISTRATION

Since the DDS was supplied to us in the form of fine powder which is almost insoluble in water, a 2.5 per cent suspension (i.e., containing 0.1 gm. in 4 cc.) was prepared in sweetened acacia mucilage. This preparation was administered by squirting it into the mouths of the patients with a syringe.

Cochrane (1, 2), and Molesworth *et al.* (5), have administered DDS as an oily suspension by subcutaneous injection and have obtained good results. Further experience will be necessary to show whether the oral or the parenteral method of administration is the better one. Against the oral method it has been urged that, because of the toxicity of the drug, tablets distributed to patients would be subject to abuse and that the treatment would thus come into disrepute. This has not been found the case in

my experience with diasone tablets. There is no reliable evidence that, used in proper dosage, DDS is any more toxic than diasone in the amounts ordinarily used.

#### TYPES OF PATIENTS CHOSEN

Three kind of patients were selected for this trial of DDS. (1) Advanced lepromatous cases with complications such as those mentioned, suitable for testing the earlier effects. (2) Uncomplicated lepromatous cases, some relatively early and others moderately advanced but all in good health and able to work and take exercise. (3) Tuberculoid cases with wide-spread lesions but with little or no deformity. The number of treated patients here considered, including 5 of the tuberculoid form, is 94 (see Table 1).

With the last two categories of patients it was possible gradually to work out the toxicity level and the maximum amount tolerated.

#### AVERAGE DOSE TOLERATED

The two important signs of intolerance of sulfones are the production of anemia and lepra reaction.

The estimation of hemoglobin with the Sahli hemoglobinometer gives a simple and adequate index of the state of the patient as regards anemia, and, along with the clinical signs and symptoms, a safe guide to the amount of DDS tolerated. The ordinary uncomplicated case, whether lepromatous or tuberculoid, was found to tolerate 4 milligrams per kilogram of body weight. The average weight of the adult male was about 50 kilograms, so that the average dose for such patients was 0.2 gm. The initial hemoglobin percentages of these patients ranged from 65 to 85. An increase of even .05 gm. over the tolerated amount was attended by a fall in hemoglobin, followed by a rise again as soon as the dose was reduced to the former amount. The accuracy with which this occurred showed that absorption must be fairly uniform, and not a matter of chance circumstances which would have caused a fluctuating blood concentration. This was taken to confirm the information received regarding the high absorption and slow excretion of DDS.

Patients with hemoglobin percentages lower than 65, or with lepra reaction, were given smaller doses; or, if these signs were severe, treatment was suspended temporarily. Careful regulation of the bowels was found necessary, as constipation often gave rise to reaction and sometimes to lowering of the hemo-

globin. Tablets of ferrous sulfate were given to anemic patients, the average adult dose being 3 tablets of 3 grains each. It was found, however, that if the administration of iron was not followed within one or two weeks by a very definite increase in the hemoglobin, it was a mistake to continue it for a longer period because it tended to cause reaction and had an otherwise unfavorable effect. It was better to give it in short courses, and only if the hemoglobin percentage was low or had a tendency to fall.

#### MARGIN BETWEEN EFFECTIVE AND SUBTOXIC DOSES

These clinical experiments showed that in healthy patients the subtoxic maximum dose was, as said, 4 mgm./kgm., and that in advanced and complicated cases an effective dose was one-fourth of that amount. This smaller dose suffices to control the above-mentioned complications, but to what extent it may be effective in gradually eliminating bacilli we do not yet know. It has been found, however, that a patient who at first could not tolerate more than the smaller amount gradually became able to stand larger doses as treatment proceeded. This does not necessarily mean that he acquires tolerance in the ordinary sense of the word, but rather that the initial small doses, by removing the complications, improved his general health and made him able to stand larger amounts.

Observations so far made show clearly that, in healthy uncomplicated cases, there is a safe margin between the maximum subtoxic dose and the minimum effective one, and that such patients, if on a fairly well balanced diet, can continue on a daily dose of 4 mgm./kgm. without interruption over an indefinite period. In contrast, in weak or complicated cases much care has to be exercised during the early period of treatment. The diet has generally to be improved, and particularly vitamin B supplements provided by yeast or some other preparation. Treatment may have to be interrupted for two or three weeks at a time to allow febrile reactions to subside; but as a rule each reaction as it passes off leaves the patient in better condition than before, and nearer the stage at which treatment may be continued without interruption.

#### IMPROVEMENT UNDER TREATMENT

The clinical and bacteriological changes observed in the 94 patients under treatment, the treatment periods varying from 12 months to less than 3 months, are shown in Table 1.



TABLE 1.—Results of treatment, by duration.

Period of treatment	Number of cases	Clinical changes			Bacteriological changes		
		No change	Im-proved	Much improved	No change	Im-proved	Much improved
12 months	26	1	11	14	10	9	7
9 "	24	1	13	10	13	8	3
6 "	19	6	11	2	10	9	----
3 "	8	5	3	----	6	2	----
3 "	17	15	2	----	17	----	----
Total	94	28	40	26	56	28	10

In assessing the clinical changes such factors as the healing of ulcers, control of reaction, inactivation of eye lesions, clearing of the nose, improvement in general health, flattening and disappearance of nodules, have been taken into account. No case is reported as "worse," but it should be noted there were three unrecorded patients who died, with whom DDS treatment was begun tentatively with minute doses when all other remedies had failed. Two of these cases were complicated by advanced pulmonary tuberculosis, and one had uncontrollable lepra reaction with anorexia.

Another eight patients given DDS but not recorded absconded from the institution for social reasons. Five of them had made remarkable clinical improvement, while the other three had not been under treatment long enough to show improvement. Only one patient remaining in the institution stopped the treatment voluntarily.

The five tuberculoid cases all show considerable improvement, and in four of them the lesions have almost entirely disappeared. It is difficult to assess these results since tuberculoid cases so often have a tendency to heal spontaneously, but the results are better than one would have expected on hydncarpus treatment.

#### COMPARISON OF CLINICAL AND BACTERIOLOGICAL IMPROVEMENT

The rapidity of clinical and bacteriological improvement depends on different factors:

(1) As has been said, early clinical improvement is rapid in patients with certain complications: lepromatous ulcers, blocked nose, eye conditions, and especially lepra reaction; whereas in such cases bacteriological improvement is slow.

(2) Some patients with the diffuse lepromatous form display little abnormality of appearance, although bacteriological examination may show a massive infection all over the body. Obviously, in such cases little or no apparent clinical change can be expected.

(3) When bacteriological examinations show a massive infection, even a reduction in the number of bacilli by 75 per cent may still leave a massive infection. It is obvious that in these cases a *noticeable* bacteriological improvement may be delayed until long after a marked clinical improvement has taken place. But in milder cases a 75 or even 50 per cent reduction is much more noticeable.

#### METHOD OF ASSESSING BACTERIOLOGICAL IMPROVEMENT

Bacteriological examinations of all patients are made every three months. Five skin points are chosen where the clinical features indicate that the most bacilli are likely to be found. From these points smears are made in the usual manner by the scraped incision method, all being placed on one slide. Care is taken to search for, and include smears from, cutaneous and subcutaneous nodules. Cases have been found which had been marked as bacteriologically negative for years, but in which careful palpation detected nodules which were found still to retain a massive infection.

When few bacilli are found the smear is marked as slight, or "+1"; when the concentration is massive, as "+4"; while "+2" and "+3" indicate intermediate amounts. The average of the readings of the five smears is taken as the "bacillary index." Thus the bacillary index of a case with smears rated at +4, +2, +1, +3 and +3 would be +2.6.

As mentioned above, it is difficult in massive infections to assess reduction until the bacilli have become very much fewer than at first. Consequently, in Table 1 some of the 10 cases recorded as "no change" after a year's treatment may in reality have had a considerable reduction which could not be perceived. In fact, too much weight should not be laid on apparent bacteriological improvement in a given case unless that improvement has been maintained over several examinations. Even in the most skilled hands the finding of bacilli and the estimation of the numbers found are to a considerable extent subject to chance variation. On the other hand there seems to be significance in finding, as in the table, 27 per cent of cases bacteriologically "much improved" in those treated for 12 months, 13 per cent in those treated for 9 months, and an absence of "much" improvement in those with less than 9 months treatment.

## THE AIM IN TREATMENT

In the treatment of leprosy two main things are aimed at: the destruction of the bacilli, and their elimination. We do not know in what way sulfones act on the bacilli. We cannot, therefore, tell to what extent bacilli found in patients treated with sulfones are dead and awaiting elimination, or are still alive.

With most pathogenic microorganisms their destruction implies their removal from the tissues. That is not always the case with *M. leprae*. It is possible for dead lepra bacilli to remain in the tissues for a considerable length of time; it is known that dead bacilli injected into rats can sometimes be found eighteen months later.

In a case with massive infection extending throughout the skin and the mucosa of the upper respiratory tract, are we justified in hoping for a drug which will eliminate all the bacilli in a few months time? It seems likely that, because of the danger of inducing excessively severe reactions, the process of elimination, at least in advanced lepromatous cases, should be spread over a long period of time.

## SULFONE REACTIONS

Writers experienced in the sulfone treatment of leprosy almost invariably refer to the crops of fugitive nodules or skin thickenings which appear for a day or two and then spontaneously disappear, called by some "erythema nodosum." In other cases the reaction is more severe, and there is also severe pain referred to the bones. In most cases, if the reaction is at all severe, it is accompanied by fever which may last for a few days or extend over weeks.

Is this sulfone-induced reaction the same as the ordinary lepra reaction so well known in leprosy without treatment? The main difference seems to lie not in the symptoms, which are practically the same, but in the results. Whereas the ordinary lepra reaction leaves the patient worse than before, the sulfone reaction usually leaves him in a better condition. In many patients there is a succession of reactions, each less in duration and severity than the one before, until at last the reactive phase is passed. This is illustrated by the following case:

CASE 20.—A boy of 11 years had been suffering from frequent and almost continuous reactions for about 18 months in spite of all forms of treatment. His weight was about 42 lbs. From May 11 to 15, 1949, he was given 0.05 gm. a day of DDS by mouth. Fever and other signs of reaction disappeared, lepromatous ulcers healed rapidly, and the general health improved. One eye had been destroyed and the cornea of the other

was severely invaded, the prognosis being complete blindness; this condition quickly subsided leaving a useful eye though with reduced vision. Daily doses of 0.05 gm. were continued till May 28th, when there was a reaction with a rise of temperature lasting 10 days, during which DDS was stopped. It was then given in 0.05 gm. doses on alternate days until October 7th, when there was a reaction lasting 19 days during which DDS was again stopped. Then 0.05 gm. was given daily for 15 days, after which there was another reaction lasting 12 days. Thereafter, except for a break of 2 weeks at Christmas, he was given 0.05 gm. daily for 8 weeks. There was then an attack of leprous orchitis with fever, interrupting treatment for 7 weeks. Then again 0.05 gm. was given daily for 2 weeks, after which there was a recurrence of orchitis and interruption of treatment for 12 days. Since then treatment has proceeded without stopping. During all this time, in spite of the frequent reactions and interruptions of treatment, there was steady clinical improvement, and bacteriological improvement from +4 to +1.8.

In this case, which is typical of many in this institution, the signs of reaction before and after the beginning of DDS treatment were very similar. The difference lay in the effect on the patient. Under the treatment he was less toxic during the attacks, picked up strength again as soon as the fever subsided, and showed clinical and bacteriological improvement instead of deterioration.

Some workers recommend persisting in the treatment during reactions. Experience in this institution shows that it is better to diminish the dose or, if there is a considerable rise of temperature, to interrupt treatment entirely until the reaction passes off.

#### DRUG-FASTNESS

Those who advocate the continuance of treatment in spite of reactions do so also because they fear that small doses might encourage the formation of drug-fast strains of *M. leprae* such as occurs with streptomycin in tuberculosis (2). This may occur, but as yet we have no evidence that there is more than one strain of *M. leprae*, or that resistant strains can develop. Obviously, such evidence would be difficult to obtain with a microorganism which will neither grow in cultures nor produce disease in experimental animals.

#### SUITABILITY OF DDS FOR OUTPATIENT TREATMENT

It having been found that in strong, well nourished lepromatous inpatients DDS was well tolerated and could be continued indefinitely without toxic signs, some suitable outpatients were selected and given the drug in 0.2 gm. tablets. To begin with they presented themselves for inspection at weekly intervals,



and later sometimes every two weeks. It is still too soon to report on these cases, but some of them already show satisfactory clinical improvement. There have been no untoward toxic effects. Debilitated or anemic outpatients, or those with a history of recent reactions, are not considered suitable for this form of treatment.

#### SUPPLEMENTAL TREATMENT

A number of DDS patients are under supplementary treatment with intradermal injections of hydnocarpus oil. The injections are given on the right side of the body, leaving the left side as a control with a view to finding out if the injections speed up elimination of bacilli. There has not yet been time to ascertain results.

An interesting side-effect of the treatment of the main group of 94 cases lies in the fact that three of them had, in addition to leprosy, been suffering for some years from periodic filarial attacks accompanied by fever and local swellings. Within a few weeks of the beginning of DDS treatment these attacks entirely ceased. This may of course be a coincidence, but at least it merits further investigation.

#### CONCLUSIONS

While it is still too soon to come to any definite conclusions regarding the effectiveness of diaminodiphenyl sulfone (DDS) in the treatment of leprosy, there is evidence that it gives results similar in many respects to those obtained with the compound sulfone derivatives. There is, apparently, a sufficient gap between the minimum effective dose and the maximum subtoxic dose to make treatment safe in the ordinary lepromatous case, although great care has to be exercised at first in the treatment of very advanced and debilitated patients. Although further evidence is required, there are indications that it is useful in tuberculoid cases, especially those with extensive lesions. The oral method of administration has been used and is recommended, but further evidence is required as to whether this route or the injection of an oily suspension into the tissues holds the greater advantage. Possibly a combination of the two methods may turn out better than either alone. There is reason to believe that we have in DDS an effective, easily administrable, and—with reasonable precautions—safe drug, which from the small size of the effective dose and the relative simplicity of its structure can be made available to the poor.

## SUMMARY

1. The clinical and bacteriological results obtained so far in 94 patients treated by the oral administration of diaminodiphenyl sulfone (DDS) are described.

2. Definite clinical improvement has been obtained in 96 per cent and much improvement in 48 per cent of the 50 cases which have been treated for over 9 months.

3. In these same patients there has been bacteriological improvement in 20 per cent.

4. There is evidence that DDS may prove as effective as the other sulfones used in leprosy, while its relative cheapness should make it available to much larger numbers of patients.

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