INTERNATIONAL JOURNAL OF LEPROSY

VOLUME 19, NUMBER 3 JULY-SEPTEMBER, 1951

SULFOXONE SODIUM (DIASONE) IN THE TREATMENT OF LEPROSY
A SUMMARY ANALYSIS OF FIELD REPORTS

EUGENE R. KELLERSBERGER, M. D.
General Secretary, American Leprosy Missions, Inc.
New York City, N. Y.
AND WILLIAM RULE, M. D.
Superintendent, Bibanga Leprosy Colony
Belgian Congo

For the past several years the American Leprosy Missions, Inc. have furnished sulfoxone sodium (diasone) tablets to the medical departments of a number of missionary societies and certain other institutions throughout the world for the treatment of leprosy patients. From time to time reports have been received concerning the results obtained with this drug. The present article is an attempt to correlate and analyze these reports and to record the aggregate findings.

Thirty-two reports which bear on the subject have been received, involving a grand total of 2,176 patients treated, but ten of them have had to be eliminated from the analysis because of insufficiency of data. The most common deficiencies are with respect to the dosage given or the duration of treatment. All cases treated for less than 3 months have been eliminated. The material as a whole illustrates the difficulties involved in obtaining uniform and comparable data on work done under varying conditions and without standardization with respect to observation and recording.

The twenty-two reports on which this report is based have to do with a total of 1,430 cases which were able to take the treatment for the periods indicated in the tables. The specific areas from which the reports came include Central Africa, Central and Southern Asia, the Middle East, the West Indies, South America, and Oceania. The actual countries, and the

number of cases reported from each country, are as shown in Table 1.

TABLE 1.—*Sources and numbers of reports, and numbers of cases included.*

Countries	Number of reports	Number of cases	Percentage of cases
Belgian Congo	7	162	11.3
Nigeria	4	132	9.2
Angola	2	52	3.6
China	2	82	5.7
India	1	53	3.7
Thailand	1	76	5.3
Burma	1	3	0.2
Palestine	1	18	1.3
Haiti	1	2	0.1
Surinam	1	81	5.7
Philippines	1	769	53.8
Totals	22	1,430	99.9

For the sake of comparison and evaluation the cases involved have, so far as possible, been grouped in summary according to the length of time they had been taking the drug before the clinical estimate of their condition was made. On this basis three groups have been set up: patients who had taken sulfoxone for from three to six months, those who had taken it for from seven to twelve months, and those who had taken it for from thirteen to twenty-four months. The report from the Culion Sanitarium in the Philippines, which deals with more than one-half of all the cases, was not broken down on this basis and consequently has to be dealt with separately.* As to dosage, not all of the patients were given the same amount of the drug. Most of the investigators worked up to a maximum dosage of three tablets a day, or one gram of drug. A number of others used four tablets a day. One reported using five a day, and one other forced the dosage up to eight, then dropping back to a maintenance dosage of six. None of the investigators whose reports have been used gave less than three tablets a day as the sus-

* Not all of the treatment represented by this report was with the drug supplied by us.

tained dosage. Most of them interpersed periods of treatment with periods of rest.

In judging the improvement or lack of it of their patients, the investigators concerned have relied almost entirely on observation of the clinical course of the disease. Such evidences as the flattening and shrinking of nodules, diminution of swelling and edema, granulation and healing of ulcerations, relief of nasal obstruction, improvement of laryngitis and iridocyclitis, and subsidence of polyneuritis have been used to gauge the clinical results. In the tabulation of the observations we have indicated whether the patients were improved by treatment, unchanged, or grew worse. In our primary analysis the "improved" and "worse" groups were subdivided by the degrees of those changes reported, but because of undoubted differences of criteria of evalution that subdivision is regarded as of questionable value. The findings of this analysis are shown in Table 2.

TABLE 2.—*Results obtained, by duration of treatment.*

Duration of treatment	Number of cases	Results of treatment							
		Improved		Unchanged		Worse		Died	
		No.	%	No.	%	No.	%	No.	%
3- 6 months	187	155	82.8	14	7.5	7	3.7	11	5.9
7-12 months	415	307	74.0	42	10.1	60	14.4	6	1.4
13-24 months	59	33	56.0	24	40.6	2	3.4	0	0
6 months to 2½ years /a	769	576	74.9	190	24.7	3	0.4	/b	--
Totals	1,430	1,071	74.8	270	18.8	72	5.2	17	1.2/c

/a Philippine data. Twenty-two of these cases, or 2.9 per cent, had improved to the stage of bacteriological negativity.

/b Deaths not recorded; the data refer to patients living at the time of the last examination in 1949.

/c Deaths were recorded only in the twenty-one reports comprising 661 patients, of whom they represent 2.6 per cent.

It will be noted in the totals that an over-all of practically 75 per cent of the patients treated were reported as being clinically improved. At the same time 18.8 per cent had remained unchanged, while 5.2 per cent had grown worse. Among the 661 patients involved in the reports in which deaths were recorded, a total of 17, or 2.6 per cent, had died. In general these results do not differ greatly from those of Sloan and co-

workers in Hawaii (3), who reported that 83 per cent of patients treated with sulfoxone had improved, 15 per cent had remained unchanged, and only 2 per cent had become worse. Their patients had been treated for three years, in a single well-equipped institution.

There is some interest in a comparison on the results obtained in the single large leprosarium in the Philippines from which we have data, the parties treated for six months to two and one-half years, with the totals for the 644 living patients treated in the twenty-one other institutions, where the treatment had been given for from three to two years. In the latter group 76.8 per cent had improved, 12.4 per cent had remained unchanged, and 10.7 per cent had grown worse, against 74.9, 24.7 and 0.4 per cent respectively in the former place.

Further considering the data of the former group of institutions, it is interesting, and unexpected, to find that the improvement rates seem to have decreased materially with prolongation of treatment, from 82.8 per cent for the 3-6 months group to only 56.0 per cent for the relatively small 13-24 months group. These figures would seem to support the observation of one of the investigators that there was an initial improvement in all of his patients, but thereafter often a regression. On the other hand this is not the experience of Johansen and Gray (2), who are accustomed to seeing definite improvement after three to six months of treatment with very few relapses. A factor which perhaps influenced our data may have been that the cases put under treatment first, and that hence were treated longest, were on the average relatively advanced, and that, later, patients whose disease on the average was earlier and therefore more favorable were attracted for treatment. It should be mentioned that most of the deaths occurred early in treatment, which suggests improvement of the general condition of the patients as time went on.

At this point we may break down our statistics according to the parts of the world from which the reports came. The results are given in Table 3, in which Central Africa includes reports from the Congo, Nigeria, and Angola; Southern Asia includes India, Burma, and Thailand; Central Asia represents the reports from China; and West Indies-Guiana comprises Haiti and Surinam. The Middle East has only one report, from Palestine, and Oceania the one from the Philippines.

It would appear that the best response to sulfoxone therapy was observed in Central Africa where, contrary to the trend

TABLE 3.—*Regional distribution of the data.*

Duration of treatment	Number of cases	Results of treatment							
		Improved		Unchanged		Worse		Died	
		No.	%	No.	%	No.	%	No.	%
Central Africa									
3- 6 months	173	148	85.6	11	6.4	7	4.0	7	4.0
7-12 months	160	155	97.0	2	1.2	2	1.2	1	0.6
13-24 months	13	13	100.0	--	--	--	--	--	--
Totals	346	316	91.4	13	3.7	9	2.6	8	2.3
Southern Asia									
7-12 months	132	71	53.8	--	--	57	43.2	4	3.0
Central Asia									
3- 6 months	6	1	16.6	3	50.0	--	--	2	33.4
7-12 months	30	5	16.6	23	76.6	1	3.4	1	3.4
13-24 months	46	20	43.5	24	52.2	2	4.3	--	--
Totals	82	26	31.8	50	61.0	3	3.6	3	3.6
West Indies-Guiana									
3- 6 months	2	2	100.0	--	--	--	--	--	--
7-12 months	81	64	79.0	17	21.0	--	--	--	--
Totals	83	66	80.0	17	20.0	--	--	--	--
Middle East									
3- 6 months	18	16	88.8	--	--	--	--	2	11.2
Oceania									
6 months—2½ years	769	576	74.9	190	24.7	3	0.4	--	--/*a*

/*a* Not stated.

of the total figures which has been noted, the improvement rates increased with the duration of treatment. The nearly equal rate of the Near East (Palestine) group can be accorded little

significance because the cases were few and the period of treatment short. The results in the West Indies-Guiana group were also satisfactory, as were those assigned to Oceania, especially when it is considered that the patients in the Culion leprosarium are all there because they are of the persistently bacteriologically-positive kind and that most of them had been long under segregation. It may be a question if type of case and average duration of the disease may not have been a factor in the more favorable results in Africa. Those recorded in Southern and Central Asia are less favorable, especially those in China, where a nutritional factor perhaps may interfere. In the latter area the best results were observed in the patients who had been treated for more than a year, and the workers there stressed the importance of continuing treatment for long periods of time.

The investigators were in accord in observing that sulfoxone is particularly effective in clearing the nasal passages and in promoting the healing of ulcers. Next most effective was its action upon nodules, causing them to shrink and flatten out. They were also encouraged by the good effect of sulfoxone on lesions of the eye and larynx. All agreed that the least effect was on the nerve lesions, and that paresthesias and neuritis were seldom helped.

Not all of the reports included in this study contained information on the bacteriological status of the patients. Those that did so reflected conflicting impressions. Several of the observers saw little or no change; for instance, Bosler in Nigeria treated 57 cases for a year with no patient becoming bacteriologically negative in that time. Of the Philippine group, only 2.9 per cent had become negative. On the other hand, one report states that of 76 positive cases 20 had become negative after ten months of treatment, which indicates a 26 per cent conversion in that period. The most remarkable result was reported by Price in the Belgian Congo, whose 19 patients were all bacteriologically positive at the beginning and all negative after a year of therapy. His experience led him to comment that sulfoxone may exhibit its greatest virtue in its ability to reduce infectivity and so become a valuable public health adjunct in those countries with hyperendemic leprosy.

These reports would have more meaning if the types of cases were known, to say nothing of the methods of examination, but unfortunately too few of the investigators reported the classification of their cases as lepromatous or neural to make a valid analysis on this basis, and the statistics when drawn up are

confusing. It is possible that both of the above favorable findings may be compatible with others already published. Johansen and Erickson (1) state that clinical improvement precedes the reduction and disappearance of bacilli in the tissues. They also state that the mucous membrane becomes bacteriologically negative rapidly, the nasal mucosa in particular sometimes clearing in six to twelve months; but the nodules in the skin, on the other hand, do not become negative until after three to five years of treatment. This relatively rapid clearing of the mucous membranes may tend to uphold the opinion expressed by Price, since it would seem reasonable that bacilli in the mucous membranes can more readily transmit the disease than those in the deeper and more fixed tissues, excepting, of course, the ulcerative and draining nodules. But even here sulfoxone has a definitely healing effect.

Not all of our collaborators gave information about reactions of the patients to the drug, but most of them did, and the consensus is that reactions of varying severity are relatively common. From actual figures given we find that, among 359 patients, 102 suffered some sort of reaction once or repeatedly. This is an incidence of 28.4 per cent. In most of these cases it was not necessary to stop administration of the drug, but in a few of them it was. Lepra reactions were frequently encountered, but in only two or three cases was it necessary to stop treatment. Likewise, mild microcytic anemias were not uncommon. In three or four instances the anemia was more profound, and it was deemed dangerous to continue sulfoxone. In one instance the drug was discontinued when an alarming leucopenia developed.

The manifestations of toxicity seen included malaise, chilliness, anemia, leucopenia, eczema and lepra reactions. One report stated that headache was the most frequent and troublesome side-effect. Fully one-half of the patients involved in that report complained more or less regularly of headache after taking the drug.

Seventeen deaths were recorded, not including the Philippine report. Perhaps this is no more than might be expected from such a group of actively leprous patients. Unfortunately, we have no control group with which to compare this figure. Obviously not all of the deaths were due to sulfoxone. On the other hand, it is very likely that some of them were. In two instances it was definitely stated that the deaths were probably induced by the drug. Another case was reported as having died with

an exfoliative dermatitis and agranulocytosis, which almost surely indites the sulfoxone. Buker and his associates in Thailand saw some of the most frequent reactions, and they stated that they considered the drug too toxic to permit obtaining maximum benefit from it. It is possible that racial or other variables may be operative in this matter, but anyone using the drug must certainly remember that he is using a toxic and potentially dangerous agent.

SUMMARY AND CONCLUSIONS

From an analysis of 22 reports made to the American Leprosy Missions, Inc. by the medical departments of several missionary societies and other institutions in various parts of the world on the treatment of leprosy with sulfoxone sodium (diasone), and comprising a total of 1,430 cases, the following observations are made:

1. Because these reports were not uniform as to data contained, and because none of them included observations of control groups, we can present no dogmatic or statistically exact findings. However, since the series is a fairly large one, as well as geographically representative, the findings may be of value in themselves and for correlation with other published material on the same subject.

2. The 661 cases involved in twenty-one of the reports are divided into three groups: 187 which received sulfoxone therapy for three to six months, 415 which received it for seven to twelve months, and 59 which received it thirteen to twenty-four months. The report on 769 patients of one institution does not permit this grouping.

3. In total, 74.8 per cent of the patients improved clinically, 18.8 per cent remained unchanged, 5.2 per cent grew worse, and 1.2 per cent died. Deaths were recorded only in the twenty-one reports comprising 661 patients, of whom they represented 2.6 per cent. At least three, and possibly more, of the 17 deaths reported were probably ascribable to the drug.

4. In the groups that could be broken down on the basis of duration of treatment, the total improvement rates decreased with prolongation of therapy while the proportions of cases which were unaffected increased. This gives rise to the question whether the initial incidence of improvement may not be greater than its ultimate incidence; but that finding was not invariable, and some other explanation may be found.

5. The data have also been analyzed on the basis of the

various parts of the world from which the reports emanated. The improvement rates varied from 91.4 per cent in Central Africa to 31.8 per cent in China. Many unknown factors may have determined the differences found, and no conclusion is possible.

6. Sulfoxone treatment, as with the sulfones generally, is particularly effective in clearing the obstructed nasal passages and promoting the healing of ulcers. Its next most effective action is upon the nodules of the skin. Least effected by it are the neural lesions.

7. The reports vary widely with respect to the observed effects on the bacteriological status of the patients, and again no conclusion is possible.

8. Reactions to the drug are relatively frequent; usually they are mild, but they can be quite persistent and severe. Those most often encountered were lepra reactions, anemia, headache, eczema, leucopenia, malaise and chilliness. Among 359 patients for whom the actual figures were given, 102 suffered reactions, or 28.4 per cent.

9. It was the consensus of the collaborators that the treatment of leprosy with sulfoxone is very gratifying, and offers a greater incidence of clinical improvement than has been seen with any of the other drugs which antedate the sulfones. It should always be remembered, however, that sulfoxone is a potentially dangerous drug which should be used aggressively but carefully.

RESÚMEN

Las siguientes observaciones resultaron de un análisis de 22 reportes hechos a "American Leprosy Mission, Inc." por los departamentos médicos de varias sociedades missioneras y otras instituciones en varias partes del mundo relacionadas con el tratamiento de la lepra por medio del sulfoxono sódico (diasone), y que incluye un total de 1,430 casos.

1. Como no hubo series testigos y porque los datos no son del todo uniformes, no podemos presentar hechos de significado estadístico ni conclusiones dogmáticas.

2. De unos 661 casos relatados en 21 de los reportes, se han hecho tres grupos: 187 recibieron diasone de 3 a 6 meses, 415 lo recibieron de 7 a 12 meses, y 59 lo recibieron de 13 a 24 meses. Una institución reportó 769 casos que no pudieron agruparse en ésta forma.

3. En total, el 74.8% de los pacientes mejoró clínicamente,

el 18.8% permaneció igual, y el 5.2% empeoró. El 1.2% murió. Muertes fueron debidamente registradas en los 21 reportes que sumaron 661 casos. Por lo menos 3, y posiblemente más de entre los 17 casos que fallecieron, murieron como consecuencia de la droga administrada.

4. En los grupos que no pudieron separarse de acuerdo con la duración del tratamiento, la mejoría disminuyó a medida que el período de tratamiento aumentó, y por el contrario, los casos no mejorados aumentó correspondientemente. Esto sugiere la cuestión de si la mejoría inicial aparente no es en realidad mayor que la mejoría permanente; pero como ésta observación no fué invariable, se debe buscar otra explicación.

5. Los datos también se analizaron de acuerdo con su origen geográfico. Los promedios de mejoría variaron desde el 91.4% en el Africa central al 31.8% en la China. Muchos factores deben haber intervenido, pero no se puede llegar a conclusión alguna.

6. El tratamiento con sulfoxono, iqual que con otros derivados sulfones, es especialmente eficáz en mejorar las obstrucciones nasales y estimular la cicatrización de las úlceras. Luego es más efectivo en las lesiones nodulares de la piel, y son afectadas menos favorablemente las lesiones neurales.

7. Los reportes denotaron gran variación en los efectos sobre el status bacteriológico de los pacientes, lo cual no permitió conclusiones positivas.

8. Las reacciones a la droga fueron relativamente frecuentes, por lo regular benignas, pero a veces persistentes y severas. Las mas frecuentes fueron: reacción leprosa, anemia, cefalea, éczema, leucopenia, malestar general y escalofríos. De 359 pacientes en quienes se reportó adecuadamente, 102 (28.4%) sufrieron reacciones.

9. El concenso de los colaboradores en éste estudio es que el tratamiento de la lepra con el sulfoxono es alagador, y ofrece una mayor frecuencia de mejoría clínica que ninguna droga antes del advenimiento de las sulfonas. Debe recordarse, sinembargo, que el sulfoxono es potencialmente peligroso y debe usarse con cuidado aunque agresivamente.

ACKNOWLEDGEMENTS

Appreciative acknowledgement is made to the following, upon whose reports the data in this study is based: Drs. C. K. Becker, H. T. Knights, E. W. Price and R. E. Klienschmidt in the Belgian Congo; A. B. Macdonald, H. A. Bosler, J. A. Dreisbach, and C. W. J. Morris in Nigeria; W. S. Gilchrist

in Angola; L. S. Kaufman in India; J. Edwards in Burma; R. S. Buker and co-workers in Thailand; N. D. Fraser, D. Harris and W. E. Braisted in China; W. D. M. Harris in Haiti; S. J. B. de Mesquita in Surinam; and C. B. Lara, chief physician of the Culion Sanitarium in the Philippines. The following nurses have also helped us in collecting the above data: Misses Stober and Alumbaugh in the Belgian Congo, Miss Cottier in Angola, and Sister Norgaard in Palestine.

REFERENCES

1. JOHANSEN, J. A. and ERICKSON, P. T. Current status of therapy in leprosy. J. American Med. Assoc. **144** (1950) 925-929.
2. JOHANSON, F. A. and GRAY, H. H. The modern treatment of leprosy. Med. Woman's J. **56** (1949) 19-24.
3. SLOAN, N. R., CHUNG-HOON, E. K., GODFREY-HORAN, M. E. and HEDGCOCK, G. H. Sulfone therapy in leprosy; a three year study. Internat. J. Leprosy **18** (1950) 1-9.