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THE CHEMOTHERAPY OF LEPROSY

LATE RESULTS OF TREATMENT WITH SULPHONE, AND WITH THIOSEMICARBAZONE ¹

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This paper is based on the results of treatment of leprosy observed in over 1000 carefully selected patients in the research unit attached to the Leprosy Settlement, Uzuakoli, East Nigeria, in the eight years from March, 1946 to March, 1954.² As described in reports made during various phases of the work (1, 3-12, 14, 15,) the chemotherapeutic agents have included various sulphones—diasone, sulphetrone, promin, diaminodiphenlysulphone (dapsone) [DDS]—p-aminosalicylic acid, streptomycin, thiosemicarbazone, isoniazid, and other agents. By far the best results have been obtained with sulphones (particularly dapsone) and TB1/698 (p-acetamidobenzaldehyde thiosemicarbazone).

The findings of these therapeutic studies have in general supported, and been supported by, the findings of workers in other countries. Sulphone and thiosemicarbazone are now widely used. From evidence so far available, it appears that the other agents mentioned can play only a small part in the treatment of leprosy, although isoniazid, in combination with other agents, may be worth further study.

Little information has been published, however, on late results. In this paper I shall present results observed as long as eight years after the beginning of treatment with sulphone, and thirty-eight months after the beginning of treatment with thiosemicarbazone.

SULPHONE TREATMENT

The methods, toxic effects, and earlier results of treatment with

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¹ Reprinted from the Lancet (London) 2 (1954) 1065-1068 (Nov. 20), with the consent of the editor, without change except in the list of references. This article is a summary of the author's late results with the two drugs indicated at the time he ended his work in Nigeria to go to London. They were reported separately and more fully in articles in Leprosy Review 25 (1954) 113-124 and 186-199. Abstracts of those articles, and one of a communication from Dr. T. F. Davey telling of the results of a subsequent examination of the TB-1 cases, appear in this issue.—EDITOR.

² The therapeutic research was started by Dr. T. F. Davey, from whom I took over in January, 1948.

sulphone have already been described (14). The toxic effects are the results of allergy, the most serious being exfoliative dermatitis and sometimes hepatitis. With prompt diagnosis, followed by stopping of sulphone, and treatment with corticotrophin or cortisone (9), recovery is complete

The late results of treatment exclusively with sulphone are discussed in detail in a recent report (13) which endeavours to answer two questions: (1) in how many of the patients treated for several years has the disease been arrested; and (2) in how many such cases has the arrest been maintained?

ARREST OF INFECTION

In March, 1954, I reviewed the 131 cases in which treatment started between March, 1946, and March, 1948. Of these patients, 2 had died, 3 had absconded, and 9 had been transferred for treatment elsewhere, before the disease was arrested. This left 117 for study:

Treatment started in March, 1946: All 39 cases were clinically inactive. In 1 there were still a few bacilli in the lesions.

Treatment started during 1947: All 36 cases were clinically inactive. In 4 there were still a few bacilli in the lesions.

Treatment started early in 1948: All 42 cases were clinically inactive. In 7 there were still a few bacilli in the lesions.

The series may be summarised as follows:

Lepromatous cases arrested and discharged	77
Lepromatous cases arrested awaiting discharge	17
Lepromatous cases arrested but died (2) or absconded (1) before dis- charge	3
Lepromatous cases showing clinical arrest but smears still showed a few bacilli	12
Tuberculoid cases arrested and discharged	8

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From these observations one broad conclusion stands out. The response of leprosy to sulphone treatment is very slow, but very sure. In not one of these 117 cases has the treatment failed to produce a definite and progressive improvement leading, in the course of years, to clinical inactivity and (it appears) finally to bacteriological negativity. It is true that in many of these cases there have been periods, and sometimes quite long periods, when improvement seemed negligible, and one has wondered whether the lesions would ever become bacteriologically negative. The indications are that in time they all do.

Another very encouraging fact should be recorded. In none of these patients treated with sulphone have we observed the phenomenon of improvement followed by deterioration. This phenomenon probably indicates the development of drug resistance, and is not infrequently seen in the chemotherapy of other infections—e.g., tuberculosis—and even in the chemotherapy of leprosy with agents other than sulphones. The fact

and rapid.

that we have not seen it does not prove that the leprosy bacillus never becomes resistant to sulphones, but it does show that, in East Nigeria at any rate, such drug resistance is insufficient to enable the infection to escape control by the drug administered in the usual doses.

RELAPSE

During the period under review 252 patients, treated exclusively with sulphone, were rendered fit for discharge.

The criteria for cessation of treatment and discharge varied with the type of case. In lepromatous cases (all bacteriologically positive) treatment was continued until the disease had been clinically inactive, and until "smears" from the lesions had been found and remained bacteriologically negative, for, in most cases, twelve months, with a *minimum* total period of treatment of twenty-four months. In non-lepromatous cases (nearly all tuberculoid and nearly all bacteriologically negative) six months' clinical inactivity, and a *minimum* treatment period, in most cases, of one year (later extended to eighteen months).

Relapse in lepromatous cases.—Lepromatous cases in this series numbered 162. They varied widely in severity. Before treatment they were classified, on the results of bacterial examinations of smears taken from the lesions, as:

Heavy infections $(4+, 3+)$	46
Moderate infections (2+)	52
Mild infections (1+)	64
The second second second second second	100

The period of treatment necessary to render the disease clinically inactive and the lesions bacteriologically negative varied between a few months (in a few mild cases) and seventy-four months, the average being twenty-eight months. The total period of treatment before discharge varied between twenty-four months and eighty-two months (average forty-one months). The period between discharge and my review varied from a few weeks to sixty-one months (average twenty-two months).

Of these 162 patients, 14 had only recently been discharged and were not yet due for re-examination. Of the remaining 148, 139 (94%) had been examined since discharge, some of them only once, most of them more than once, and some as many as nine times at intervals of several months for periods up to five years. The findings at the re-examinations were:

No sign of relapse, clinical or bacteriological	124
Slight clinical signs of relapse (neuritis only)	2
Slight bacteriological relapse (a few acid-fast bacilli found in smears)	13
Clinical and bacteriological signs of relapse	0
	139

Thus in not a single case has there been any really serious relapse. In 15 (11%) there was some evidence of relapse, but it was always slight.

In the 2 patients showing neuritis, this finding was very recent; treatment was resumed, the neuritis subsided in a few weeks, and no other signs appeared.

Of the 13 showing a few bacilli in smears (often in the ear lobe), 3 were readmitted for treatment and rapidly became negative. Of the other 10, 2 were referred elsewhere for treatment, and 1 of these, recently examined, was found negative three months later; the other was not seen again. The striking finding, however, is in the remaining 8 cases showing a few bacilli on re-examination. They were sent away with no resumption of treatment, and told to report again later; 6 of them did so, and 5 of the 6 were then found negative; the 6th still showed a few acid-fast bacilli in smears, but no other evidence of relapse.

It may be that further studies will show that, in the absence of clinical evidence of the relapse, the finding of a few bacilli is of no serious importance.

The average time from the cessation of treatment to the detection of relapse was seven and a half months. In 12 of the 15 cases, the relapse occurred within one year. In not a single case was relapse detected at more than two years after cessation of treatment, although in some of the 139 cases the period of observation was as long as five years. Our finding, therefore, is that "relapse" occurs early or not at all. If this is confirmed, it is a very important finding. In answer to the suggestion that late relapse may present a real problem, we can say that in Nigeria, so far, it has not done so.

These results are almost better than one had dared to hope.³

Relapse in tuberculoid cases.—The tuberculoid cases treated with sulphones only and then discharged numbered 90. Nine of these were not due for re-examination. Of the remaining 81, 69 (85%) had been examined since discharge, most of them more than once, and some up to eight times, for periods up to four years.

Among these 69 cases there were 8 (12%) with reactivation of the disease. This reactivation was clinical only; in none had smears from the lesions become positive.

Of these 8 relapses, 7 occurred between three and twelve months after cessation of treatment; the other was detected twenty-eight months after cessation of treatment.

Six of the 8 patients had received less than the usual period of treatment. In the light of this experience, a minimum period of eighteen months (preferably two years) treatment is recommended in tuberculoid cases, although clinical inactivation is common within one year.

In all 8 cases, the original lesions became active again, sometimes with increase in their size and sometimes with neuritis of the previously affected nerves. In none did new lesions appear, although in similar cases not included in the present series

³ They were probably even better than indicated. In the official terminology used in the Philippines, the finding of a few bacilli under conditions here indicated has for many years been called an "interruption" (of the required negative period with continuous negative bacteriological findings), to avoid confusion in the use of the term "relapse." The latter is reserved for those cases in which the disease has definitely become reactivated, almost invariably evidenced by clinical as well as bacteriological findings; it is not applied to the chance finding of a small residual deposit of old bacilli that were probably there all the time. —EDITOR. this has occasionally been seen. The relapse had no serious effects, although it might have done so if undetected or untreated. In all 8 cases resumption of sulphone treatment was followed by subsidence of the activity. Six of the 8 patients had again been discharged, while 2 were still completing their second course of treatment.

A relapse-rate of 12 per cent (8 out of 69 cases) is perhaps higher than was expected, for tuberculoid leprosy is relatively mild, with characterised relative immunity to the infection. It should be noted, however, that after we increased the period of treatment in this condition relapses became far fewer.

DISCUSSION

Reports of late results of sulphone treatment have been few, but two have come from the National Leprosarium, Carville, Louisiana, U.S.A.

Erickson (²) reported that of 77 lepromatous cases arrested by sulphone treatment and discharged from the hospital, 33 had been re-examined and 6 cases of relapse had been detected. Of the 33 cases re-examined, 11 had ceased treatment on discharge, and 5 of these showed relapse; the remaining 22 had continued treatment after discharge and of these only 1 showed relapse. Erickson himself points out that these figures may be misleading, that routine re-examination was not made of all discharged patients, and that those who had relapsed were more likely to have come for re-examination than those who had not. Erickson says: "The fact that relapses have occurred does not brand the sulphones as failures in the therapy of leprosy. In fact, it detracts very little, if any, from the reported value of these drugs in this relentless disease."

The paper of Wolcott and Ross (16) does not deal with relapse after treatment, but with reactiviation of the quiescent or arrested disease during treatment. It states that several such cases have been seen, and it records and illustrates 3 of them.

One cannot ignore the fact that the findings in the United States have been less favorable than those here recorded from Nigeria. One hesitates to suggest that the Nigerian form of sulphone treatment (previously disubstituted sulphones and now diaminodiphenylsulphone [DDS], both given orally) is more effective than that most commonly used in the United States (intravenous promin); but there are theoretical and practical objections to intravenous promin (8). It may be that, for some unknown reason, patients in the United States—and, it is reliably reported, in Britain—respond to sulphone less well than patients in Nigeria. But we are justified in judging the efficacy of treatment mainly by the response observed in patients in the great endemic foci of the disease, rather than in countries where leprosy is a minor problem.

Erickson's recommendation that treatment should be continued indefinitely to prevent relapse is hardly justified by our experience in Nigeria; but, if further experience shows it to be advisable, such after-treatment with oral dapsone is so simple and economical that is presents no difficulty.

THIOSEMICARBAZONE TREATMENT

Our use of TB1/698 (*p*-acetamidobenzaldehyde thiosemicarbazone) in leprosy started in October, 1950, in a small group of cases, and has since continued on an increasing scale. By the end of last year, 273 patients had been treated, for periods up to thirty-eight months. I am now able

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to confirm in general the views expressed after twelve and thirty months' treatment (7, 12); but the earlier promise has not been entirely fulfilled.⁴

ARREST OF INFECTION

The methods of administration and the toxic effects have been discussed elsewhere (7, 11, 12). In our series of 273 cases three serious toxic effects have been seen; acute agranulocytosis (5 cases); severe and rapidly developing toxic anaemia (6 cases); severe hepatitis (3 cases). To these effects 2 deaths have been attributed. Three other patients died from fulminating gastro-enteritis probably not caused by the treatment, but possibly aggravated by it.

Period	Bacteriological status								
of treatment	Potor		After treatment						
	Deloi	e treatment	4+	3+	2+	1+	Negative		
	4+	10 cases	0	4	4 ·	2	0		
1/21	3+	7 cases	0	0	2	4	1		
24-38	2+	8 cases	0	0	2	3	3		
months	1+	5 cases	0	0	0	0	5		
		30 cases	0	4	8	9	9		
12-24 months	4+	3 cases	0	2	1	0	0		
	3+	3 cases	0	1	1	1	0		
	2+	5 cases	0	0	1	4	0		
	1+	3 cases	0	0	0	1	2		
	1.1.1	14 cases	0	3	3	6	2		
6-12 months	4+	2 cases	0	2	0	0	0		
	3+	2 cases	0	1	0	1	0		
	2+	15 cases	0	0	4	11	0		
	1+	6 cases	0	0	0	4	2		
	1	25 cases	0	3	4	16	2		

TABLE	1.—Bacteriological	results	of	thiosemicarbazone	treatment	of	69	cases	of
		lep	rom	atous leprosy.					

The earlier results having been fully recorded (7, 12), I shall concentrate here on the later results.

⁴ See Footnote 1, and especially the abstract referred to there of a more recent note by Dr. T. F. Davey. A reference to the fuller report of the results with thiosemicarbazone has been inserted (13a) in the original list. —EDITOR.

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Lepromatous cases with no previous treatment.—Eighty-six lepromatous cases were treated with thiosemicarbazone only, and in almost all of them the early clinical results were good. Slowly but surely the leprous lesions became less marked, the nodules and infiltrations less obvious, the neuritis less troublesome, the nerves sometimes less thick, the eye inflammation less, and so on. Within twelve months clinical improvement was nearly always definite or considerable. During the second twelve months, in most cases, improvement was slower but [it was] steady and definite in all but a few cases. During the third twelve months, however, though improvement sometimes continued, it did not always do so, and there were cases of definite deterioration, sometimes quite rapid.

Thus, though the early clinical results were good, the late results have on the whole been disappointing, and in some cases bad. It seems probable that, with prolonged use, the drug is liable to lose its efficacy, possibly through the bacilli becoming resistant.

The *bacteriological results* are summarized in Table 1. (Seventeen cases with less than six months' treatment are not analysed.)

These results, like the clinical ones, are rather disappointing. While nearly all the cases showed improvement, this was sometimes not very substantial, even after three years. Moreover (though this is not shown in the table) there were cases where the number of bacilli increased in the third year. It may be instructive to compare the first part of this table with Table 2, taken from a previous report (14) on the results of sulphone treatment for thirty to thirty-eight months.

Before	treatment		A	fter treatment	t	
Delote	ucaument	4+	3+	2+	1+	Negative
4+	23	0	2	7	10	4
3+	4	0	0	0	2	2
2+	2	0	0	0	0	2
1+	6	0	0	0	0	6
	35	0	2	7	12	14

 TABLE 2.—Bacteriological results of sulphone treatment of 35 cases of lepromatous

 leprosy for 30-38 months.

Relapse.—Three lepromatous cases classed as "disease arrested" had been out of the hospital for fifteen, five, and three months. On re-examination, 1 of these showed slight relapse, bacteriological but not clinical.

Lepromatous cases previously treated with sulphone.—Included in our 273 cases are 45 lepromatous cases previously treated with sulfone but

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with difficulty because of the following complications:

(ases
Severe and repeated "reaction"	23
Severe neuritis	10
Eye inflammation	3
Sulphone psychosis	4
Slow progress	5
	45
	40

In the 5 cases in which progress on sulphone treatment was slow, the change to TB1 treatment produced no apparent increase in the rate of progress. In the other 40 cases the change was beneficial in almost every case.

In the 4 cases in which psychosis had developed on sulphone treatment, TB1 treatment presented no such difficulty. In the 36 cases in which reaction, neuritis, or iritis had made continuous sulphone treatment difficult or impossible, the complications were not abolished at once under thiosemicarbazone therapy, but the attacks became less frequent and less severe and finally disappeared, and the leprosy improved. In some of these patients, however, improvement later became negligible, and in some of them sulphone treatment was resumed in the hope of speeding recovery.

This group of 45 patients illustrates what is felt to be the most important use of TB1—namely, for cases in which sulphone treatment presents real difficulty. In such cases, after TB1 treatment has been given with benefit for one year (or perhaps eighteen months) and complications have died down, the resumption of sulphone treatment is strongly recommended.

Tuberculoid and other cases.—Tuberculoid cases of leprosy treated with thiosemicarbazone numbered 110. Results on the whole were good as good as, and possibly sometimes slightly better than, with sulphone. Of these 110, 39 completed treatment and were discharged at the time of review. Thirty-six were due for re-examination and 33 had actually been re-examined, after periods of up to fifteen months. Three cases (9%) of relapse had been detected.

Twelve other tuberculoid cases previously treated with sulphones, but with difficulty because of complications, were treated with thiosemicarbazone with much less difficulty and with results similar to those described above.

Nine cases of "borderline" type, and 2 of "indeterminate" type were treated with thiosemicarbazone for periods up to thirty months, with similar results. One of the borderline cases, treated for twenty-five months with clinical arrest, and with negative smears for twelve months before discharge, showed clinical and bacteriological relapse within three months.

DISCUSSION

Compared with sulphone, thiosemicarbazone has more limitations in the treatment of leprosy. It is more expensive and more troublesome to

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administer (twice daily instead of once daily or less); its toxic effects are about as common but more serious and more often fatal; and it is liable to lose its therapeutic action. For these reasons we have thought it unjustifiable to continue thiosemicarbazone therapy for a long time, and hence we have no really late results which we can compare closely with the late results of sulphone therapy.

In my view TB1 treatment of leprosy should be confined (a) to patients who become allergic to sulphones,⁵ (b) to those who suffer serious toxic effects of sulphones (e.g., psychosis), and (c) to those in whom for any other reason sulphone administration presents difficulties (e.g., severe or repeated reaction, neuritis, or eye inflammation). When the patient has improved sufficiently on TB1 treatment, sulphone treatment should be resumed if possible.

Experiments have been made in treating leprosy with sulphone and thiosemicarbazone given together. Toxic effects increased, and the results were no better than with either drug given alone.

SUMMARY

Sulphone treatment.—Of 131 patients who started sulphone treatment in the research unit of the Nigeria Leprosy Service between March, 1946, and March, 1948, 117 were available for analysis in March, 1954. In all of these the disease had been rendered clinically inactive, and in most of them the lesions were bacteriologically negative. The numbers positive were: after eight years' treatment, 1 out of 39 treated; after seven years, 4 out of 36 treated; and after six years, 7 out of 42 treated. Most of the 117 patients had long been discharged.

Sulphone treatment appears to arrest the disease in every case, but may take a very long time to do it. Deterioration has never followed improvement; nor has there been any other indication of serious drug resistance.

Of 252 patients discharged from the unit after sulphone treatment, 229 should have returned for re-examination by last March and 208 (92%) had done so. Of 148 discharged lepromatous cases, 94% had been re-examined, and 15 (11%) of these showed slight evidence of relapse. Of 81 discharged tuberculoid cases, 85% had been re-examined, and 8 (12%) showed slight evidence of relapse.

Relapse occurred early-often within six months, usually within one year, and almost always within two years. Late relapse has not been

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⁵ In patients allergic to sulphones, desensitisation can be effected by daily administration starting at very low levels (1 mg.) and increasing slowly over a period of several weeks till therapeutic doses are reached. Any recurrence of skin irritation must be carefully watched for, and necessitates a temporary cessation of the course, and a reduction of dose. The use of anti-histamine, corticotrophin, or cortisone in small doses may facilitate desensitisation.

seen. All relapses were slight and responded to resumed treatment; some slightly positive relapses became negative with no resumption of treatment.

Less favourable late results of sulphone treatment recorded elsewhere are discussed. The findings recorded here strengthen the view that sulphone treatment constitutes a major revolution in the treatment of leprosy.

Thiosemicarbazone treatment.—The results of treatment of leprosy with TB1/698 (p-acetamidobenzaldehyde thiosemicarbazone) for periods up to thirty-eight months are compared with those of sulphone therapy.

Serious toxic effects, although no more common, are more serious than those of sulphone.

While the earlier results are comparable with those obtained with sulphone, the late results are not so good. In the third year of treatment, some cases showed evidence of drug resistance, with exacerbation of the disease. Arrest of the disease was produced in a smaller proportion of cases, and some of these relapsed.

For these reasons, thiosemicarbazone has been abandoned for the long-term treatment of leprosy in patients who can tolerate sulphone. It remains an alternative remedy, useful temporarily for those few patients who cannot tolerate sulphones.

Thanks are due to many members of the staff of the Nigeria Leprosy Service for very valuable help given during the eight years covered by this study; particularly to Dr. T. F. Davey, O. B. E., who started the work, and to Miss F. McNulty and Mr. G. Okezie for laboratory work. To the patients, who have cooperated so well, thanks are also due.

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