

## THE LATE RESULTS OF SULPHONE TREATMENT OF LEPROSY IN EAST NIGERIA

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It is now thirteen years since sulphone treatment of leprosy was first used in the United States.<sup>(1)</sup> Sulphone treatment in various forms has now become the standard treatment of leprosy throughout the world. Many reports have been published covering the early results; a few reports<sup>(2, 3 & 4)</sup> cover a few years treatment, but the only report on late results of treatment available to me is that of Erickson,<sup>(5)</sup> which is discussed later.

The object of the present report is to present the late results of sulphone treatment of leprosy as seen in Uzuakoli, East Nigeria, in a large series of cases studied intensively for periods up to eight years.

### THE CONDITIONS IN WHICH THE STUDIES HAVE BEEN MADE.

In assessing the value of any study of this nature, it is important to know the conditions in which the work has been done. The Ibo people of Eastern Nigeria are intelligent and progressive; they have known and feared leprosy for many generations and they can usually recognise the disease in its early stages; their village and clan organisations have greatly aided detection and treatment. Moreover leprosy has carried a great social stigma, and patients are prepared to go to much trouble and often expense to get cured of the disease, and to get rid of the stigma. The people have great faith in modern medicine and in those who administer it; they insist on having treatment, and are reluctant to stop treatment even if complications arise. With modern chemotherapy of leprosy at any rate, the patients usually persist in the treatment until they can receive a medical certificate that the disease is arrested, although in some cases this has taken several years. Of well over 1,000 patients treated and accurately recorded by me during the last six years, not more than one dozen have left without permission; although about one hundred have for various reasons been transferred to treatment centres elsewhere.

Further, and most important, when treatment ceases on the patient's discharge, they are instructed to come for examination every 3 months for a year and, after that, every 6 months for a year or more, and most of them do this for a time at any rate.

If any relapse occurs, it is almost sure to be detected either at periodical re-examination, or at home by the patient himself or his relatives, in which case the patient comes demanding more treatment.

For these reasons I think that it is very doubtful if there is any other centre in the world where conditions are so favourable to the successful treatment of leprosy, or for the assessment of late results of treatment, and of relapse rates.

#### THE FORMS OF SULPHONE TREATMENT USED.

Sulphone treatment of leprosy was started here by Dr. T. F. Davey in March 1946, exactly eight years ago, in a small group of 43 patients, "diasone" being the drug used. Later that year another small group was treated with "sulphetrone." Later still diamino-diphenyl-sulphone (D.D.S., dapsone) treatment became established, first in the Research Unit, and later as the routine treatment in the settlement and its many clinics, as well as in other settlements and clinics in Nigeria. No attempt is made here to assess the results of this widespread treatment. Our present discussion deals only with those patients studied thoroughly and treated in our small Research Unit which was established in December 1947, took over the patients and records of Dr. Davey's previous work, and continued and developed it.

#### THE PATIENTS TREATED.

The patients treated by the Research Unit, which form the basis of this study, have been selected from the Settlement and from its many clinics because of the severity and activity of their leprosy or because of complications arising during treatment. They do not represent the ordinary leprosy of the area; they are selected as the most marked cases of leprosy we have been able to find, or as those most difficult to treat, with the exception that we have usually not selected patients so crippled and disabled that they could not attend our clinic for all the many examinations which our research work demanded.

#### The Late Results of Treatment.

In assessing the late results of treatment of leprosy, two questions are of paramount importance. These questions are (1) What is the present condition of those patients who were being treated several years ago, and in how many of them has the arrest of the disease been produced? (2) In those in whom the disease has been arrested, how many have later shown relapse? The present paper attempts to answer these two questions in relation to our patients here.

THE PRESENT CONDITION OF PATIENTS WHO STARTED  
TREATMENT BETWEEN MARCH 1946 AND MAY 1948.

These patients number 131, and we here account for the whole number, taking them exactly as they appear on our books with no omissions whatever. Of the 131 patients, 9 were bacteriologically-negative tuberculoid cases, and 122 were bacteriologically-positive lepromatous cases. The patients fall into three groups according to the time when they started treatment, and the form of treatment used.

(a). *Patients starting treatment in March 1946.*

These patients number 43. Of these, two died from gastro-enteritis before the disease was arrested, one patient absconded, and one was transferred for treatment elsewhere. 39 cases remained for analysis — 35 lepromatous cases and 4 tuberculoid cases.

Of the 35 lepromatous cases, 34 became and remained bacteriologically negative. Of these 34, 2 died, one from pneumonia and one from unknown causes, before discharge, 30 have been discharged, and 2 are bacteriologically negative and clinically inactive and awaiting discharge. Only one of the 35 is still bacteriologically positive, and that very slightly, although the disease is clinically inactive.

Of the 4 tuberculoid cases, all have long been discharged with the disease inactive.

To summarize: of these 39 cases, 2 died just before discharge, 34 have been discharged, two are awaiting discharge and only 1 remains positive.

(b). *Patients starting treatment during 1947.*

These cases number 36, 35 being lepromatous and 1 tuberculoid.

Of the 35 lepromatous cases, 31 are now clinically inactive and bacteriologically negative, 22 having already been discharged. Eight are awaiting discharge and 1 went away just before discharge. The remaining 4 lepromatous cases are clinically inactive, but still show a few bacilli in the lesions. Treatment is continuing.

The one tuberculoid case has long been discharged.

(c). *Patients starting treatment early in 1948.*

These number 52. Eight were transferred for treatment elsewhere, and 2 absconded, leaving 42 for analysis, 39 being lepromatous cases, and 3 tuberculoid. Of the 39 lepromatous cases, 32 are clinically arrested and bacteriologically negative, 25 of these having already been discharged and 7 are to be

discharged shortly. The remaining 7 cases, though clinically inactive, still show a few bacilli.

All the 3 tuberculoid cases have been discharged.

These three groups are below taken together and the findings recorded in tabulated form.

TOTAL CASES	...	...	...	...	...	...	...	131
Died before disease arrested	...	...	...	...	...	...	...	2
Absconded	...	...	...	...	...	...	...	3
Transferred for treatment elsewhere	...	...	...	...	...	...	...	9
Remaining for analysis	...	...	...	...	...	...	...	117
<i>Lepromatous</i> cases arrested and discharged	...	...	...	...	...	...	...	77
<i>Lepromatous</i> cases arrested awaiting discharge	...	...	...	...	...	...	...	17
<i>Lepromatous</i> cases arrested but died (2) or absconded (1) before discharge	...	...	...	...	...	...	...	3
<i>Lepromatous</i> cases showing clinical arrest but smears still show a few bacilli	...	...	...	...	...	...	...	12
<i>Tuberculoid</i> cases arrested and discharged	...	...	...	...	...	...	...	8
								117
<i>Discussion.</i>								

From these observations one broad conclusion stands out. The response of leprosy to sulphone treatment is very slow, but amazingly 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 finally to bacteriological negativity. It is true that in many of these cases there have been periods, and sometimes quite long periods, when improvement has appeared to become negligible, and one has begun to wonder whether the lesions would ever become bacteriologically negative. The indications are that in time they all do.

Another most encouraging fact should be recorded. In none of these patients treated with sulphone have we observed the phenomenon of improvement occurring only up to a point, and then deterioration setting in; this phenomenon probably indicates the development of drug resistance, and is not infrequently seen in the chemotherapy of other infections—for example, in tuberculosis—and even in the chemotherapy of leprosy with agents other than sulphones. The fact that we have not seen this phenomenon does not prove that sulphone resistance of the leprosy bacillus is not seen at all, but it does indicate that, in East Nigeria at any rate, such drug resistance is mild in degree, and not sufficient to enable the infection to get out of the control of the continued administration of the drug in the usual doses.\*

\* See note at end of this paper.

I have, in fact, attempted to speed up the response to sulphones by giving doses larger than normal at different stages of treatment, including the later stage, and by combining sulphones with some other chemotherapeutic agent such as a thiosemicarbazone, but with no clear benefit.

Thus we conclude that the action of sulphones in leprosy is slow, sometimes very slow, but also very sure, and that the development in the bacilli of drug resistance is not a major factor in slowing up the response to sulphone treatment.

#### **The Relapse Rate in Patients Discharged after Sulphone Treatment.**

During these eight years, many different forms of treatment have been the subject of experiment in our Research Unit, and many of our patients have had more than one form of treatment. We here discuss only those who have had sulphone treatment only. Moreover our work with different sulphones has not shown conclusively the greater efficacy of one form of sulphone treatment over another, and the present report below makes no differentiation between the patients treated with different forms of sulphone.

We here consider only those who have continued treatment till the disease was considered arrested and inactive, the treatment had been stopped and the patient discharged. Every such case appearing on our records is included in the present study, with no selection and no omissions. The cases number 252.

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 12 months, with a *minimum* total period of treatment of 24 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 18 months).

#### *Findings in lepromatous cases.*

Lepromatous cases in this series number 162. They have varied widely in severity. Before treatment they were classified, on the results of bacterial examination of smears taken from the lesions, as:

Heavy infectious	(4 + 3 +)	...	46
Moderate	„ (2 +)	...	52
Mild	„ (1 +)	...	64
			<hr/>
			162

The period of treatment necessary to render the disease clinically inactive and the lesions bacteriologically negative varied between a few months (in a few very mild cases) and 74 months, the average being 28 months. The total period of treatment before discharge varied between 12 months and 82 months and averaged 41 months. The period that has elapsed since discharge varies between a few weeks and 61 months, and averages 22 months.

Of these 162 patients, 14 have only recently been discharged and are not yet due for re-examination. For the present purposes these may be ignored, and 148 remain.

Of these 148, 139 (94%) have 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.

The findings at the re-examinations of these 139 patients are here summarised.

No sign of relapse, clinical or bacteriological	...	124 cases
Slight <i>clinical</i> signs of relapse (neuritis only)	...	2 "
Slight <i>bacteriological</i> relapse (a few acid fast bacilli found in smears)	...	13 "
Clinical <i>and</i> bacteriological signs of relapse	...	Nil "
		139 "

Thus in not a single case has there been any really serious relapse.

In only 15 (10.8%) there was some evidence of relapse, in all cases slight.

In the two patients showing neuritis, this finding has been very recent. Treatment has been resumed and the neuritis has subsided in a few weeks, and no other signs have appeared.

Of the 13 showing a few bacilli in smears (often in the ear lobe), 3 were re-admitted for treatment and rapidly became negative. Of the other 10, two were referred elsewhere for treatment, and one of these, recently examined, was found negative 3 months later; the other has not been seen again.

The striking finding however is in the remaining 8 cases showing a few bacilli. They were sent away with no resumption of treatment, and told to report again later; six of them have done so, and five of the six are found negative on re-examination; the sixth still shows a few acid-fast bacilli in smears, but no other evidence of relapse.

Thus the significance of these findings of a few bacilli with no clinical evidence of relapse is not by any means clear. It may be that further studies will show that such "relapses" are of no serious importance.

Some further facts about these 15 cases of relapse may be of some interest.

The time that elapsed between the cessation of treatment and the detection of the relapse varied between 3 months and 23 months, and averaged only  $7\frac{1}{2}$  months; in 12 of the 15 cases, the relapse occurred within one year. In not a single case has relapse been detected at more than two years after the cessation of treatment, although in some of the 148 cases the period of observation has been up to 5 years. Our findings, therefore, are that "relapse" occurs early or not at all. If this is confirmed, it is a most important finding, for it has been suggested that late relapse may present a real problem. Our findings are that, in Nigeria so far, late relapse has presented no problem at all.

The bacteriological status of these 15 cases before treatment started was:—

Heavy infections	...	...	6
Moderate infections	...	...	4
Slight infections ...	...	...	5

The period of treatment of these 15 cases had varied between 35 and 78 months, and it appears that their response to treatment had been rather slow. These findings indicate that relapse is not confined to the cases originally with heavy infection.

To sum up. Of 148 lepromatous cases treated with sulphones until the disease had been clinically inactive and smears negative for one year, discharged and later examined between 1 and 9 times for periods up to 5 years after discharge, serious relapse has not been seen in a single case. In 2 cases, leprous neuritis was found, although skin smears were negative. In 13 cases, a few bacilli were detected in smears but there were no clinical signs of relapse and, moreover, in these 13 cases, whether treatment was resumed or not, the smears later became negative in all but one of those re-examined later. All the relapses occurred early, usually within one year and all within two years of the cessation of treatment.

These results are extremely encouraging; in fact almost better than one had dared to hope.

#### *Findings in tuberculoid cases.*

The tuberculoid cases treated with sulphones only and then discharged number 90. The period of treatment in these cases has varied between 9 months and 34 months, and has averaged 20 months; the period since discharge varies between a few weeks and four years, and averages 22 months. Of the 90 cases, at the present time, 9 are not yet due for re-examination and are ignored. Of the remaining 81, 69 (85%) have been examined since discharge,

most of them more than once, and some up to 8 times, for periods up to 4 years.

In these 69 cases, 8 (11.6%) cases of reactivation of the disease have been seen. In all these 8 cases, the reactivation was clinical only; in none had smears from the lesions become positive.

Of these 8 relapses, 7 occurred between 3 and 12 months after the cessation of treatment; the other one was detected 28 months after the cessation of treatment.

Of the 8 cases of relapse, 3 occurred in a small group of patients who, for various reasons received less than 1 year's treatment; 3 occurred in a much larger group of patients who had received between 1 and 2 years' treatment; and 2 occurred in patients who had received between 2 and 2½ years' treatment. In the light of this experience, a period of at least 18 months to 2 years' treatment is recommended in such cases, although clinical inactivation of the disease is commonly seen within one year.

In all the eight cases, the relapse consisted in the recrudescence of clinical activity in the original lesions, sometimes with increase in size of these lesions, and sometimes with neuritis of the previously affected nerves. In none of these 8 cases did new lesions appear, although in similar cases not included in the present series, this has occasionally been seen.

In none of the 8 cases was the relapse serious, although it might have become serious if undetected or untreated. In all 8 cases, the resumption of sulphone treatment was followed by subsidence of the activity. Six of the 8 patients have again been discharged, while 2 are still completing their second course of treatment.

This incidence of relapse 8 (11.6%) out of 69 tuberculoid cases is unexpectedly high, for these tuberculoid cases of leprosy are relatively mild and are characterised by relative immunity to the infection. It is, however, noticeable that since we have increased the period of treatment in tuberculoid cases, relapses have been far fewer.

#### *Discussion.*

As previously stated, the only report of the late results of sulphone treatment available to me is that of Erickson.<sup>(5)</sup> He reported that of 77 lepromatous cases arrested by sulphone treatment, 33 had been re-examined and in 6 (18%) relapse had occurred, 3 of these relapses being clinical, and 3 subclinical, (smears from the lesions showed bacilli, but there was no definite clinical activity). Of these 6 cases of relapse, 5 patients had received intravenous promin for a period between 38 and 57 months, and one had received oral diasone for 18 months only.



Of the 33 cases re-examined, 11 had ceased treatment on discharge and of these 5 (45%) showed relapse; the remaining 22 had continued treatment after discharge and of these only 1 (4.5%) showed relapse.

In discussing these results, Erickson himself states:

- "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. Their ability to produce regression of leprosy lesions and to keep the ravages of the disease in check cannot be discounted."
- "The figures given for the probability of relapse are tentative and, in the final analysis, may not be representative of what the true incidence of relapse eventually will be. Since the number of patients followed is small, a great deal of significance cannot be placed on the statistical results obtained. Also, the duration of follow-up has been short in some instances. A factor of selection may have entered into the calculations particularly with reference to the patients representing clinical relapse. Two of these patients had been discharged from the hospital and returned when skin lesions appeared. Since patients who develop visible evidences of the disease are, undoubtedly, more likely to return for examination than those who do not develop them, it may be that the three cases of clinical relapse here reported are the only ones that have developed among all of the patients so far having their disease arrested on the sulphones. Should this be the case, the probability of clinical relapse would be much less at the present stage."

These comments are much to the point. The three patients who had clinical relapse with visible lesions were perhaps, as Erickson states, the only ones in the group of 77. If this is so, the clinical relapse would be 4%, and the subclinical relapse rate, 3 out of 30, would be 10%, giving a total relapse rate of 14%. These figures are comparable with those here recorded.

There is no ignoring the fact, however, that Erickson's report is, on the whole, much less favourable than the present one, and causes for this difference must be sought.

The following points have to be considered:

- (a). Our group of patients studied is much larger than that of Erickson (229 instead of 77), and moreover our re-examinations cover 90% of the discharged patients, whereas the figure for Erickson's group was only 44%. Our figures should be more reliable.
- (b). The period of treatment of the two series of cases is not dissimilar, and the difference cannot be attributed to this factor. The form of sulphone treatment used, however, has differed widely. Most of Erickson's cases received promin intravenously, a form of treatment which is open to theoretical and practical objections (6). In our series, disubstituted sulphones given orally, and later dapsone (D.D.S.) given orally, have been used. We might be tempted to believe that our treatment is more effective than that used in Erickson's series, but there is no proof of this.

- (c). It may be that in our Nigerian patients, the disease tends to be milder than in patients in the United States of America, and to respond more readily to chemotherapy, and also to relapse less readily. This idea is in accord with the experience of workers in different countries, who find that certain people tolerate sulphone treatment better and respond to it better than others. It may also be that our patients are treated earlier, and co-operate more fully in treatment and, therefore, respond better, and relapse less readily.

Of these possible factors, it appears that two may be important; our form of sulphone treatment may be more effective, and our patients may be peculiarly responsive to treatment.

In any case, we must maintain our sense of proportion. West Africa is a far more important focus of leprosy than the United States. We are justified in judging the efficacy of treatment of any disease by the response to treatment observed in patients in the great endemic foci of the disease.

Our experience in East Nigeria with sulphone treatment of leprosy on a very big scale has been far more favourable than that of Erickson in the United States. If it were found here, as he has reported in the U.S.A., that if treatment is stopped on discharge, the relapse rate may be as high as 45%, we should indeed be facing a serious problem. On the other hand, even if the relapse rate is only 10% as we have found it, Erickson's recommendation that, after discharge, treatment should be continued for a long period, and perhaps indefinitely, may still be worth consideration. Such continued treatment, if oral dapsone is used, can be carried out with very little trouble and at very low cost. All that is needed is the swallowing of a few tablets of dapsone every week; a tablet of 100 mg. may be swallowed daily; three or four similar tablets twice weekly, or even four or six tablets once weekly, at an annual cost of not more than four shillings per patient. This provides a simple and effective after treatment. Surely this is a very small price to pay for the maintenance of the arrest of leprosy.

#### SUMMARY AND CONCLUSIONS.

1. The late results of sulphone treatment of leprosy are studied from the patients and records of the Research Unit of the Leprosy Settlement, Uzuakoli, E. Nigeria.
2. As far as possible, the present condition (March, 1954) of every patient whose treatment started between March, 1946 and March, 1948 is studied, with the following findings:—
  - (a) of 131 such cases on the records, 117 are available for analysis.

Disease inactive and smears negative. Discharged	88
Disease inactive and smears negative.	
Awaiting discharge	17
Disease inactive but smears still positive ... ..	12*
	<hr/> 117

(\*Of these 12, only one has had eight years treatment, 4 seven years treatment, and 7 six years treatment.)

- (b) Sulphone treatment is found to be very sure, but sometimes very slow in its action. It appears to produce arrest of the disease in every case, but may take a very long time to do it.
  - (c) Improvement up to a point, followed by deterioration, has not been seen, nor other finding indicating serious drug-resistance.
3. The relapse rate after the cessation of sulphone treatment is studied in the Research Unit patients with the following findings:
- (a) Of 252 such patients discharged from the Settlement with instructions to return for re-examination, 23 are not yet due to return, and of the remaining 229, 208 (92%) have returned at least once and some up to 9 times, for periods up to 5 years.
  - (b) Of 148 discharged lepromatous cases, 139 (94%) have been re-examined, and of these 139, 15 (10.8%) have shown slight evidence of reactivation of the disease. No serious case of relapse has been seen.
  - (c) Of 81 discharged tuberculoid cases, 69 (85%) have returned for examination, and of these 69, 8 (11.6%) have shown signs of reactivation of the disease in the "tuberculoid" form. In none has the lepromatous form developed, and in none have positive "smears" been found.
  - (d) In both tuberculoid and lepromatous cases, reactivation occurred early, usually within one year, and almost always within two years of the cessation of treatment. Later relapse has not been seen.
  - (e) The cases of relapse with clinical manifestations rapidly responded to resumed treatment; and, in the rest, with only slightly positive smears, the smears have again become negative, in some cases with, but in some cases without, resumed treatment.
  - (f) Thus the relapses have been few, mild, and readily controlled. These findings are considered very satisfactory.
  - (g) The report of Erickson in the United States, of higher relapse rates, is considered, and also his recommendation of prolonged after-treatment as routine in discharged patients.

- (h) The present findings in Nigeria hardly justify this routine after treatment; if however by further study it is shown to be advisable, it is so simple and economical that it should present no difficulty.
4. The findings of this study of the late results of sulphone treatment of leprosy reveal the main weakness of the treatment, namely the extreme slowness of its action; but also reveal its strong points, the sureness of its action and the permanence of results in most cases. These findings strengthen the view that is steadily gaining ground, that sulphone treatment constitutes a major revolution in the treatment of leprosy.

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#### Later Note.

Since the above paper was written, I have seen the report of Wolcott & Ross (*International Journal of Leprosy* 1953, No. 4, pages 437-440) on "Exacerbations of leprosy during present day treatment." They report three cases, all lepromatous cases, treated, with marked improvement, and in two of the three cases, clinical inactivity and repeatedly negative smears. While treatment was still going on, there was severe reactivation of the disease, clinical and bacteriological.

In all these three cases sulphones had been given for a long time (apparently intravenous promin in all three cases, sometimes in "small amounts"), but other drugs were given, in one case isoniazid, and in the other, thiosemicarbazone, isoniazid, dihydrostreptomycin, P.A.S.; and in one case aureomycin and other medications were added.

They state that in recent years at Carville, Louisiana, U.S.A., a number of similar cases of exacerbation have been seen.

This experience is very different from mine in Nigeria. It is difficult to explain this difference.

The matter is briefly discussed above.