

THE TREATMENT OF LEPROSY WITH DIPHENYL THIOUREA COMPOUND SU 1906 (DPT)

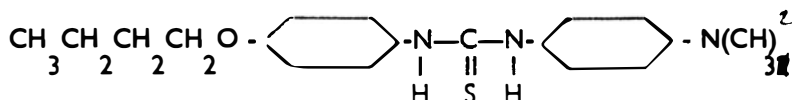
A REPORT ON EXPANDED TRIALS IN NIGERIA

I. A SECOND REPORT ON THE PROGRESS OF THE PILOT TRIAL WITH A REVIEW OF THE FINDINGS IN EXPANDED TRIALS

DR. T. F. DAVEY

Introduction

SU 1906 is the research reference number given in the CIBA laboratories to a relatively simple compound of diphenyl thiourea, also becoming known as DPT. It is 4 butoxy-4' dimethylamino-diphenyl thiourea, and has the following structural formula.



This substance was found to have outstanding bacteriological activity against *M. tuberculosis* both *in vitro* and *in vivo* by Mayer, Eisman and Konopha (1953) and Konopha, Gisi, Eisman and Mayer (1955), and this prompted its clinical trial in leprosy. Pilot trials in the treatment of leprosy with this substance were undertaken both in East and West Africa. In a progress report written after 16 months' experience of the drug in Nigeria, Davey and Currie (1956) found that it combined a noteworthy freedom from toxicity with chemotherapeutic activity similar to that of DDS. These findings were confirmed in East Africa by Ross Innes, Smith and Harden-Smith (1957).

Another sixteen months have now elapsed since the first progress report was written, and the further progress of the pilot trial in Nigeria is here reported, together with additional information gained from the wider use of DPT. The promising short term findings made it desirable to expand the trials of the drug in three directions, (a) to test its therapeutic activity in larger numbers of lepromatous cases of leprosy, (b) to examine its usefulness in patients whose response to sulphones was unsatisfactory, and (c) to explore its use in combination with other drugs. After preliminary work at the Uzuakoli Research Unit on the second and third of these projects, leprologists in charge of six Settlements in Nigeria were invited to co-operate in expanded trials of the drug, and all willingly agreed to do so. The centres concerned with

numbers of trial patients at each are as follows—

Leprosy Service, Oji River	Dr. A. S. Garrett Dr. K. Ellis	25 patients
Leprosy Service, Ossiomo	Dr. B. Nicholson Dr. S. Healy	8 patients
Leprosy Service, Rivers	Dr. M. Corcos	5 patients
Catholic Mission Settle- ment, Abakaliki	Dr. E. Fern	10 patients
Presbyterian Mission Settlement, Itu	Dr. M. Phillips Dr. R. Matheson	12 patients
Presbyterian Mission Settlement, Uburu	Dr. A. Macdonald Dr. L. Hogerzeil	10 patients

With 97 patients in various categories at the Research Unit, the additional 70 rapidly brought the numbers of patients receiving DPT either alone or in combination to 167. Apart from a few patients unable to tolerate sulphones all the additional patients were lepromatous cases previously untreated. At all centres laboratory work followed the same routine, and uniformity was sought by providing periods of study for the laboratory technicians of co-operating Settlements at the Research Unit, and by periodic visits to each centre by Mr. S. E. Drewett, Senior Laboratory Superintendent, when independent bacteriological tests were undertaken. Co-ordination in the choice of patients and their controls and in the clinical assessment of progress was maintained through similar visits to each centre by the writer.

Dosage

The drug was originally prepared in the form of coated tablets containing 0.25 gm. It was later found more convenient to use uncoated compressed tablets containing 0.5 gm.

An initial dose of 1.0 gm. daily in the case of adults and 0.5 daily in the case of children has been found generally satisfactory, subsequent increases depending on the weight and liability of the patient to reaction. For the average adult an increase in the initial daily dose by 0.5 gm. at fortnightly intervals is convenient up to a maintenance dose of between 25 and 40 mg. per kilo. At first a rather higher dosage than this was given, adults receiving 3.0 gms. daily as routine, but experience proved that this dose, which represents about 50 mg. per kilo is unnecessarily high, and few adults need more than 2.0 gms. daily, given in a single dose. In practice the lack of toxicity displayed by the drug makes it unnecessary to calculate dosage within narrow limits, but there is nothing to be gained therapeutically by exceeding the suggested

dosage. With prolonged treatment at a higher level than this the antithyroid action of the drug may begin to show itself.

Children tolerate DPT extremely well in the same dosage per kilo as is suggested for adults, which in practice means a daily dose ranging from 0.5 to 1.5 gms. in accordance with age.

The suggested routine for treatment is based on clinical experience. As yet it has not been found possible to establish a rationale of treatment which is based on studies of the absorption and excretion of the drug. For a long time no satisfactory method of estimation was available, and although in recent months we have been advised of two possible methods, technical difficulties have prevented any speedy assessment of their value. The drug has been used in sufficient numbers of patients and in a range of dosage sufficiently wide to enable an opinion on suitable dosage to be expressed with confidence.

Toxicity

The freedom from toxic side effects found in both West and East Africa in the pilot trials of DPT has also been experienced at each of the six new centres where the drug has been used. In the range of dosage used the drug is very well tolerated and causes no gastric or intestinal irritation, promoting on the other hand tranquility and a sense of well-being. Among Nigerian patients there has been no indication of any disturbance of bone marrow, liver, or kidney function for which the drug could be held responsible. No case of dermatitis or drug fever has arisen, the drug has indeed been well tolerated by patients hypersensitive both to sulphones and to thiosemicarbazone. Psychosis has not been seen. It has in fact not been necessary at any centre to remove any patient from treatment with DPT for any cause. The lack of toxicity displayed by DPT is one of its outstanding virtues, and has been the experience not only of leprosy workers, but also of those undertaking clinical trials in tuberculosis. Two conditions which may arise during treatment call for comment.

(a) Hypothyroidism

Thiourea and some of its compounds are potent antithyroid substances, which are believed to act by preventing the combination of iodine with tyrosine and consequently inhibiting the synthesis of thyroxine. The action of DPT in this direction is evidently feeble. Throughout the trial a careful watch has been kept for signs of hypothyroidism in patients receiving DPT, but on the dosage recommended there has been no evidence of any depressant action on thyroid activity. In the earlier stages of the pilot trial the standard dose was maintained at a rather higher level, and during the second year signs of hypothyroidism did

appear in one adolescent patient who had been receiving 3.0 gms. of DPT daily for 15 months. It was not possible to determine the basal metabolic rate with accuracy, but signs of impaired thyroid activity which developed in this patient included increase in weight, bradycardia, constipation, dry skin and mental dullness. With a reduction in dose to 1.5 gms. daily and the administration of small doses of thyroid extract these symptoms gradually disappeared and have not recurred. On the same high dosage another patient during the third year began to complain of amenorrhoea which might possibly have been related to the DPT. It has not recurred following a reduction in dose. There is thus some evidence that at a dosage of 50 mg. per kilo there is some risk of mild degrees of hypothyroidism developing after long administration of the drug. This dose appears to be unnecessarily high.

(b) *Skin eruptions*

When used in the treatment of tuberculosis in doses of 6.0 to 9.0 gms. daily, DPT has been found to cause an irritating skin eruption in some patients. This has not been encountered to any appreciable extent among patients receiving the lower dosage used in leprosy treatment even after prolonged administration. Incidental skin eruptions have occurred from time to time but it has not been possible definitely to implicate DPT as the agent responsible. Other possible causes have always been present, and their treatment brought relief without there being any need to modify the dose of DPT.

THE PROGRESS OF LEPROSY

A. DPT given alone

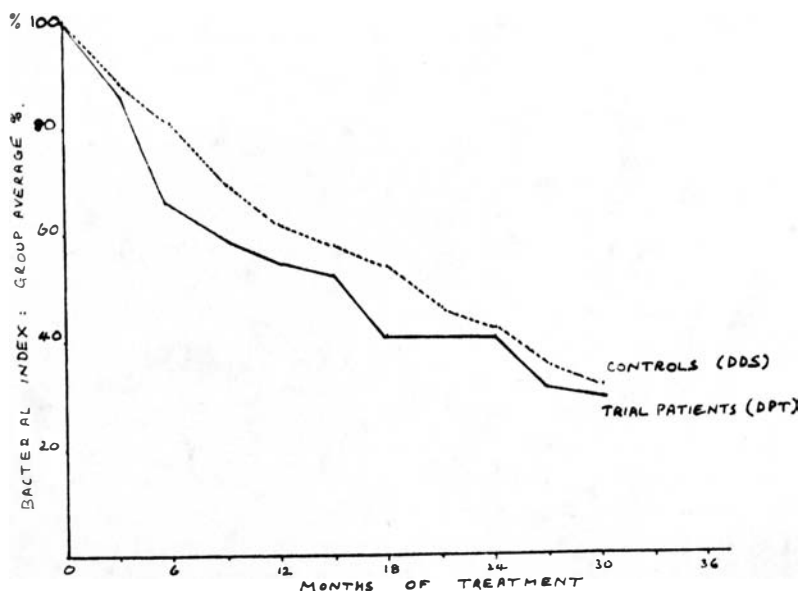
Here we have to consider the progress of the pilot trial group of patients at the Research Unit, comprising all three main types of leprosy, up to the 32nd month of treatment, with in addition the findings in supplementary groups of 25 lepromatous patients treated for one year at centres other than the Research Unit.

(a) *Tuberculoid cases*

The eight tuberculoid cases in the pilot trial are all in a residual condition. Four were discharged from treatment after two years, and having been followed up for six months are all fit and well. The other four are being retained under observation, two because of the persistence of neuritis for some time after macules became residual. Additional tuberculoid cases placed on DPT treatment because of severe neuritis have made satisfactory clinical progress and are discussed later in relation to neuritis.

(b) *Indeterminate and Borderline cases*

After two years or longer, five out of six patients in this group are clinically also in a residual condition. Their progress was, how-



Relative Decline in Bacterial Index. Trial Patients and Controls.

ever, not uneventful. As commonly happens in any form of chemotherapy the immunological instability of this group showed itself in the appearance of recurrent macules in three of these patients at various times between the 7th and the 21st month. Such new lesions were of short duration and tended to be closer in appearance to tuberculoid than the original lesions. Nerve involvement was prominent but not serious in its effects. The sixth patient had a short-lived eruption of similar type at the 24th month.

(c) *Lepromatous cases*

FIRST YEAR

The pilot trial covered 17 patients. In the first progress report it was stated that these all exhibited an early response to treatment, with satisfactory clinical and bacteriological progress, particularly marked during the first nine months, but with a perceptible falling off in bacteriological improvement in a few cases after that time. This effect proved to be temporary only, and at the end of the first year of treatment it may be said that all cases showed satisfactory progress, particularly gratifying in some individuals, while the group as a whole displayed a degree of resolution, both clinical and bacteriological, rather greater than was found among controls on routine DDS treatment. The same is true of eight other lepromatous cases added later to the original group.

Expanded trials have added a further 25 cases at three centres, and among these identical results have been obtained during the first year of treatment. Resolution has been satisfactory in all respects, and is considered by the experienced leprologists respon-

sible to be at least as good as that encountered in controls on normal DDS treatment, and in some cases to be better.

SECOND YEAR

During the second year of treatment the slowing down in decline in bacterial index which is familiar in the chemotherapy of leprosy became apparent in the pilot trial group of patients, as did the variation in the rate of progress between one patient and another which is also a common experience. Clinical progress was, however, uninterrupted, and in several patients biopsies exhibited the continued shrinking of lepromatous infiltration in the skin, which as Ridley has noted (1956) accompanies satisfactory resolution. As long as this shrinking layer of infiltration contains acid-fast material positive results will be obtained in routine smears, and the appearance of a negative smear is thus evidence of a very advanced degree of resolution. By the end of the second year 3 patients had become negative to routine bacteriological tests, and in all patients with persistently positive smears the proportion of bacilli showing degenerative changes steadily increased with the passage of time. In the group as a whole the advantage gained over controls during the first year was maintained.

THIRD YEAR

Twelve patients in this group have now completed eight months in their third year of treatment, and progress continues to be satisfactory. In a majority of them the skin is beginning to assume a normal appearance, with surprisingly little loss of elasticity, while bacteriological progress continues to be gratifying. There are as yet no signs of drug resistance developing.

The group progress in bacterial index of trial patients and their controls is illustrated graphically in Figure 1. This shows that during the first year trial patients showed greater progress than their controls, and that ground gained then has not subsequently been lost.

Complications during Treatment

(a) *Erythema nodosum*

This common complication in the chemotherapy of lepromatous cases has not been a serious problem in patients receiving DPT. During the first year it was rare, occurring in 3 cases out of a total of 44 treated with DPT alone. Such a finding is not unusual in Nigerian practice, where this condition tends to be more a late than an early complication of chemotherapy, being most prevalent when the Bacterial Index has fallen to the neighbourhood of 1.0 or less. During the second year in the pilot trial group it occurred more frequently, and has again been encountered during the third year. As generally seen it has been mild and easily controlled by

a short course of treatment with Fantorin (Stibophen). No case has yet been encountered of persistent erythema nodosum; indeed patients in such a condition following DDS treatment have done very well when the DDS treatment has been replaced by DPT. In one patient severe erythema nodosum was associated with the rare phenomenon of a change in type from lepromatous to borderline leprosy and was associated with a severe neuritis with ulnar paralysis which, however, was only temporary. In this patient the reactive condition led rapidly to the disappearance of bacilli from routine smears in the skin. Erythema nodosum is thus not prominent during DPT treatment and has tended to occur rather earlier among trial patients than among their controls.

(b) *Neuritis*

Apart from the example mentioned above no serious case of neuritis has arisen. Phases of mild or moderately severe neuritis occurred in tuberculoid and borderline cases mostly during the first fifteen months of treatment. In lepromatous cases, neuritis, like erythema nodosum, has not been prominent, and when it has occurred it has not been persistent. It has indeed been found that patients presenting severe nerve involvement when DPT treatment was instituted have made calm and steady progress in their nerve condition as well as in their general infection.

(c) *Exacerbation of the disease*

Reference has already been made to the appearance of fresh skin lesions during the treatment of borderline cases. These are considered to reflect a changing immunological state rather than indicate an exacerbation of the disease, for without exception the subsequent progress of those concerned on continued DPT treatment was quite satisfactory.

A watch has been kept for any signs of exacerbation of the disease in lepromatous cases. In the first progress report the case was mentioned of a patient who showed some exacerbation at the sixth month following severe influenza. He was the only example of such an occurrence; indeed after the first year there was less variation in consecutive bacterial findings among individual trial patients than among their controls, and no evidence of seasonal influences.

Treatment in special cases

An important aspect of the use of DPT is its value in the treatment of patients in whom sulphone treatment is either difficult or impossible. It has now been used for adequate periods in a number of the conditions which complicate treatment with the sulphones, and the following results have been obtained.

(a) *Drug sensitivity*

In three patients hypersensitive both to sulphones and to

thiosemicarbazone, DPT has provided an entirely satisfactory form of chemotherapy. No case of drug sensitivity to DPT has been encountered yet in Nigeria.

(b) *Psychosis*

Three patients with psychosis have tolerated DPT much better than they tolerated DDS. One of them, who developed psychotic signs after only short courses of DDS, has had several months of complete normality during treatment with DPT.

(c) *Persistent erythema nodosum*

Seven patients transferred to treatment with DPT after long periods of recurrent erythema nodosum during DDS treatment, have settled down very well and been able to tolerate therapeutic doses without difficulty.

(d) *Severe neuritis*

When it was noticed that neuritis was not prominent during DPT treatment, a number of patients with severe neuritis occurring during DDS treatment were transferred to the new drug, and have in general made satisfactory and more tranquil progress. The same is true of patients presenting severe neuritis on first consultation. For patients with this complication of leprosy DPT has proved itself an acceptable form of chemotherapy. Among 13 patients suffering from neuritis who have received it, no case has arisen of any extension of paralysis which has been more than temporary. The tendency has been in the opposite direction, relief from pain and improvement in motor nerve involvement being commonly encountered.

(e) *Unsatisfactory response to DDS*

DPT has also been found of value in eight patients whose response to DDS was slow and unsatisfactory. In all of them resolution was expedited.

DPT given twice weekly

The need for daily administration is a serious disadvantage from the standpoint of the wider use of DPT. The study of its absorption and excretion will in due course give information on which a sound rationale of treatment can be based, but it has been thought desirable not to wait for this, but to observe directly the effects in patients of administration on a twice weekly basis. Sixteen patients at the Research Unit have now had twice weekly treatment for periods up to seven months, the dose employed commencing at 1.0 gm. and rising by 1 gm. at fortnightly intervals up to a maximum of 4.0 gms. twice weekly. This is a little less per week than the dosage recommended above, but 4.0 gms. was considered to be as much as patients could be expected to take as routine.

ILLUSTRATIONS TO ELECTRONMICROSCOPY

Article by R. KOOU, M.D. on page 56



Fig. 1. Lepromatous Leprosy. Untreated Leprosy bacillus attached to a saline crystal. Magnification 36,000 x.

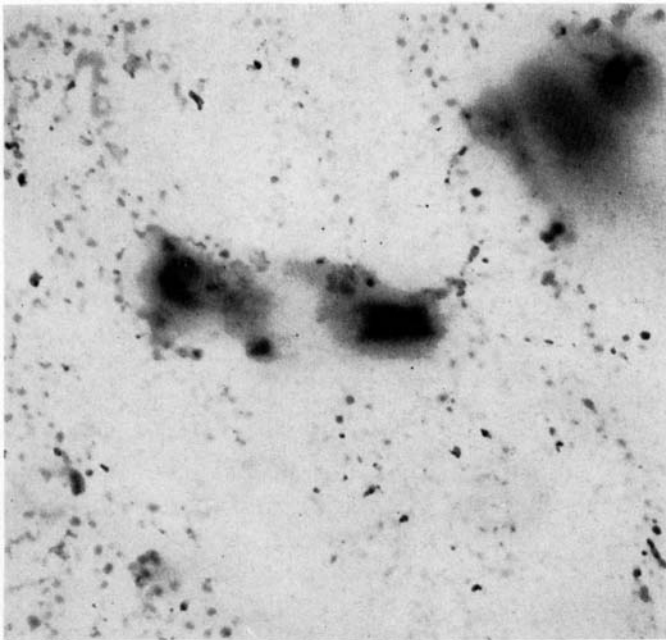


Fig. 2. Lepromatous Leprosy. Treated with DDS and Isonicotinic acid hydrazide during 2½ years. Magnification 27,000 x.

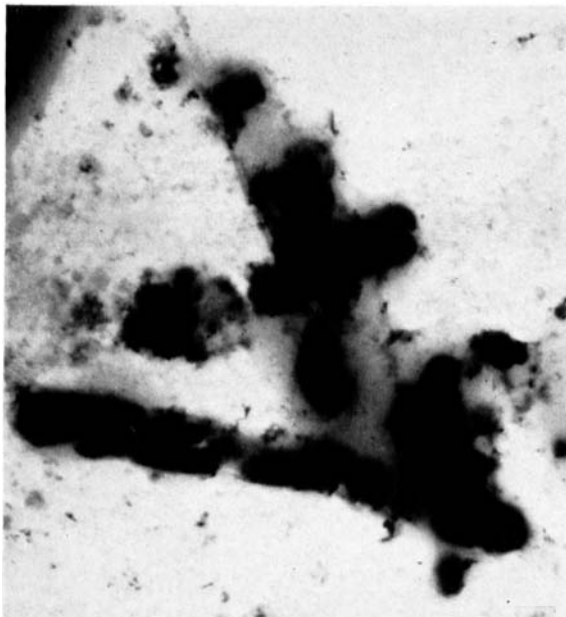


Fig. 3. Lepromatous Leprosy. Untreated. Magnification 17,200 x.



Fig. 4. Lepromatous Leprosy. Untreated. Shadow cast. Magnification 13,000 x.

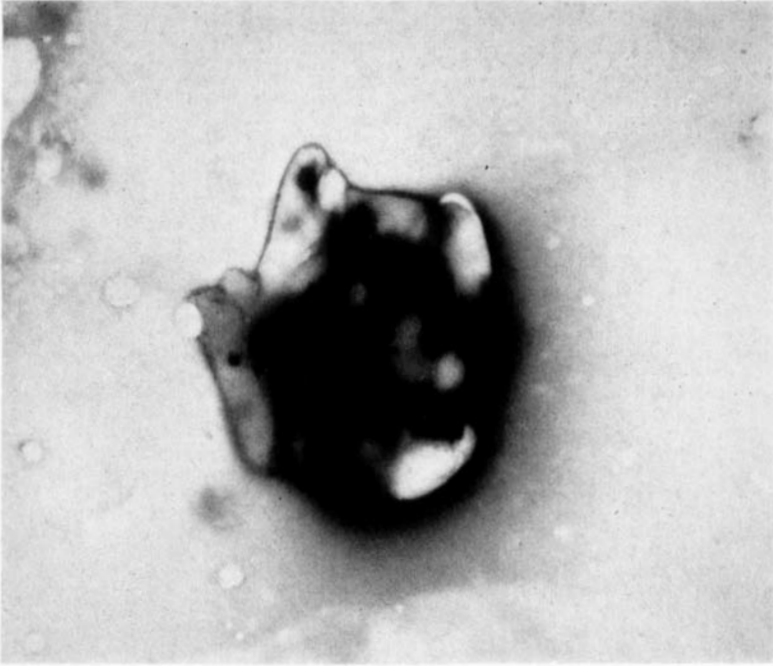


Fig. 5. Lepromatous Leprosy. Untreated Mass of bacilli. Magnification 12,000 x.

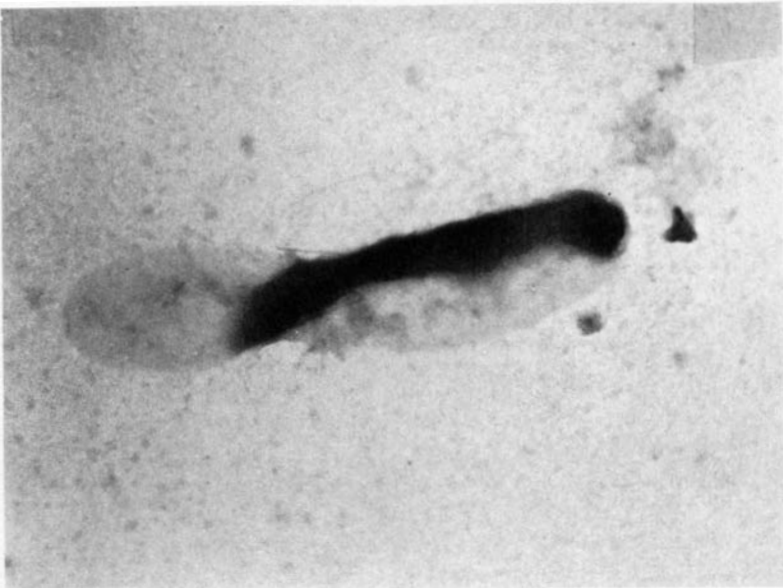


Fig. 6. Lepromatous Leprosy treated with DDS and thiosemicarbazone for 3½ years. Magnification 36,500 x.



Fig. 7. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Magnification 36,500 x.

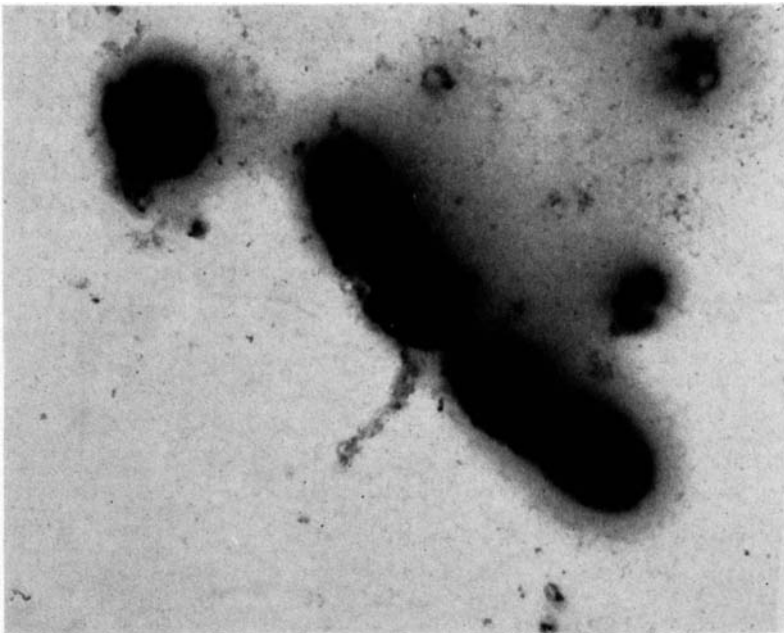


Fig. 8. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Magnification 13,200 x.



Fig. 9. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Magnification 17,200 x.

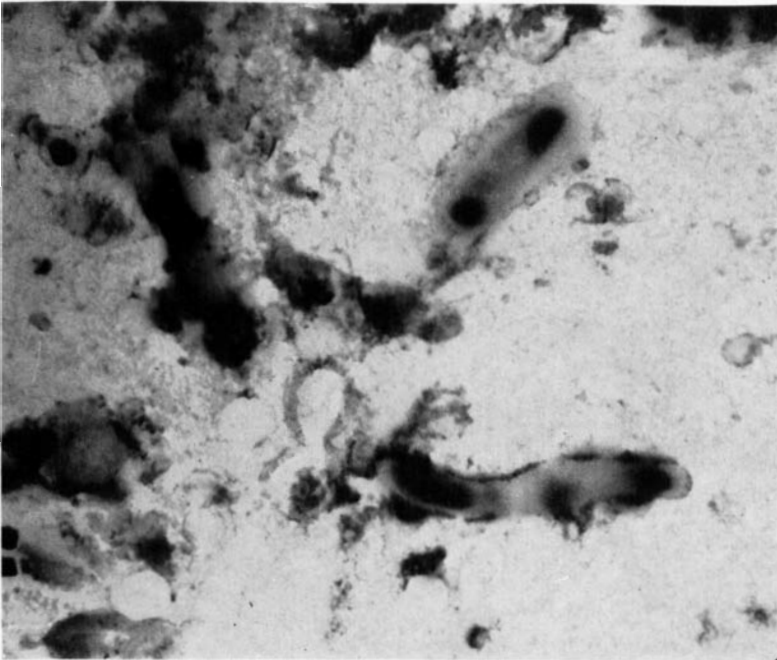


Fig. 10. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Magnification 13,200 x.

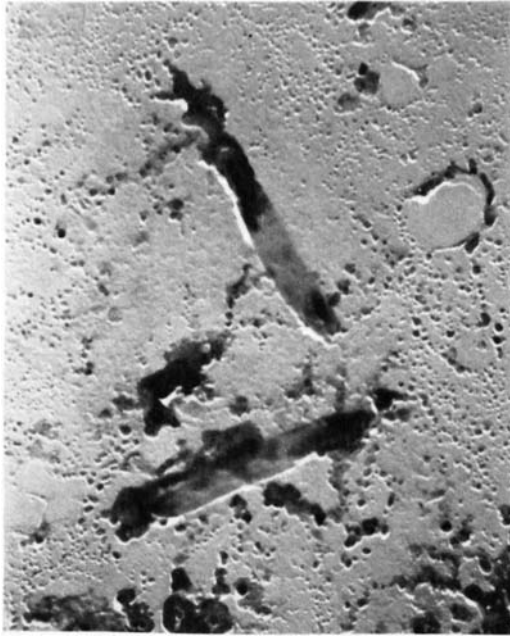


Fig. 11. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Shadow cast. Magnification 12,400 x.



Fig. 12. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Shadow cast. Magnification 28,200 x.



Fig. 13. Tuberculoid Leprosy. Untreated. Magnification 30,000 x.

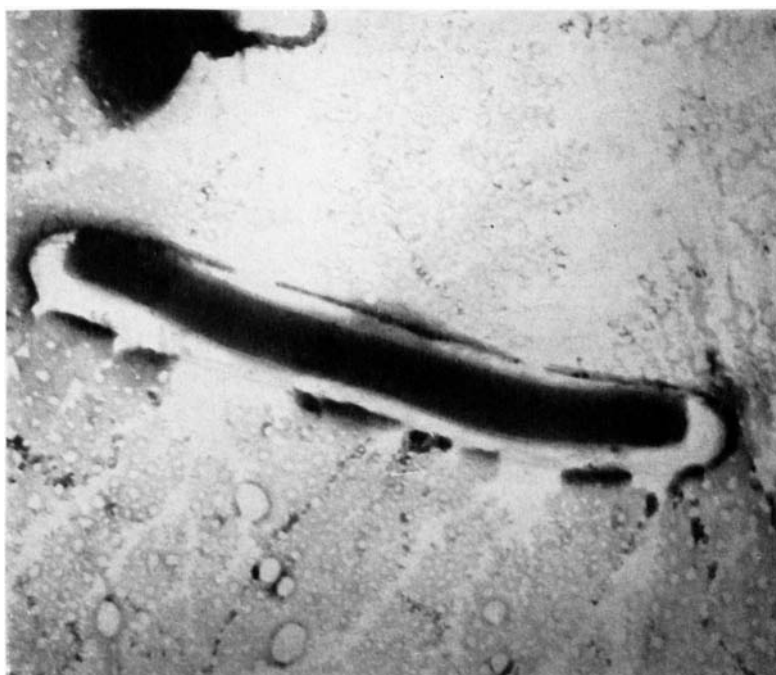


Fig. 14. Tuberculoid Leprosy. Untreated. Magnification 30,000 x.

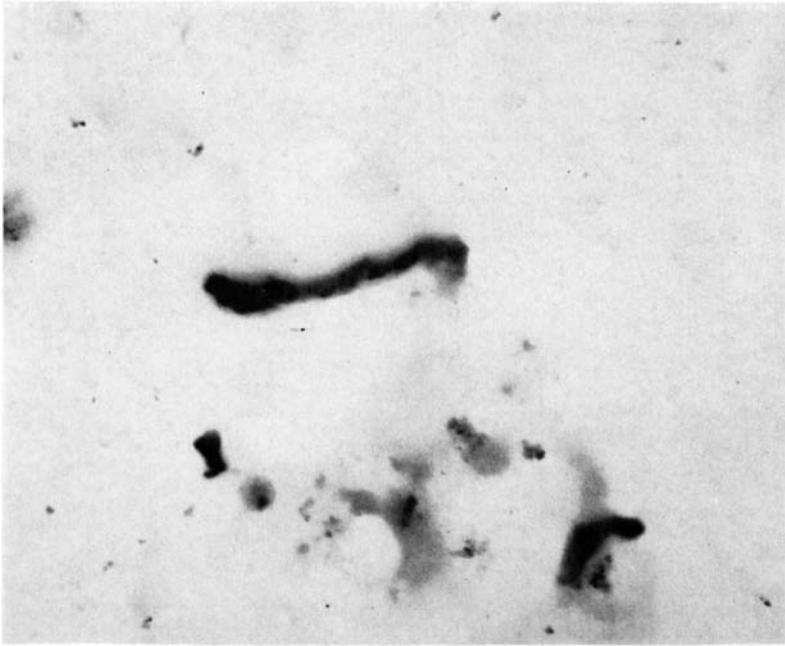


Fig. 15. Tuberculoid Leprosy. Treated with DDS for 5 months. Remnants of bacilli? Magnification 30,000 x.

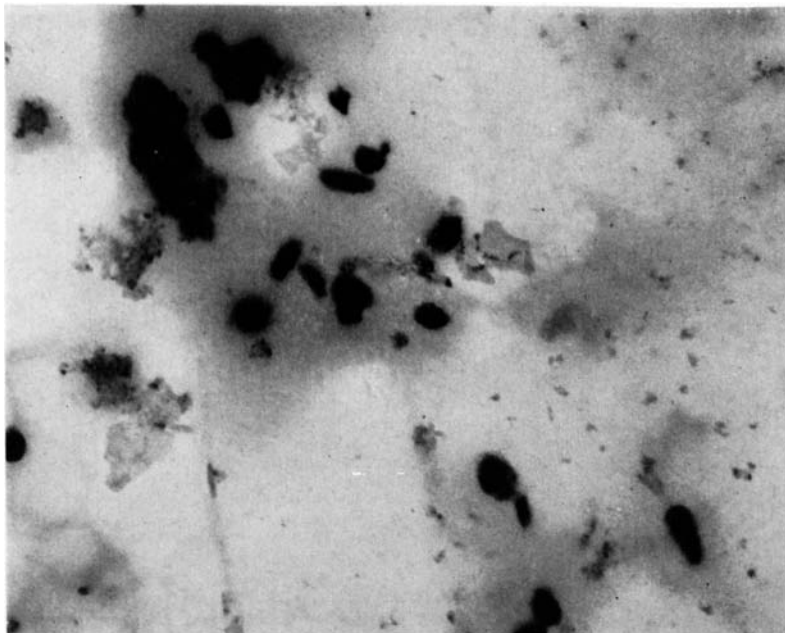


Fig. 16. Tuberculoid Leprosy. Treated with DDS for 5 months. Remnants of bacilli? Magnification 30,000 x.

One patient complained of some discomfort after this dose. The remainder have made no complaints and are quite satisfied with this form of treatment.

Therapeutically the results in some patients have been good, but an element of uncertainty has been encountered which is absent on daily administration. In five patients after three months, it was felt that progress was definitely less than would be expected on daily treatment, and they were transferred to daily treatment, after which enhancement of progress speedily became evident. The remainder, consisting of two lepromatous, six tuberculoid and three borderline cases, have continued to make satisfactory progress on twice weekly treatment. On the whole twice weekly treatment appears to involve some loss in the efficiency of the drug, though results in some patients may be entirely satisfactory.

B. DPT in combination with other drugs

Once the chemotherapeutic activity of DPT had been demonstrated, it became desirable to examine its usefulness in combination with other drugs. As the drug is not likely to be manufactured very cheaply, much of its practical usefulness may depend on whether it can be combined safely with a cheaper drug to produce materially improved results, particularly if thereby it could be used in rather lower dosage than appears to be necessary when given alone. Preliminary work on this subject has been undertaken in these expanded trials, and findings are here presented after one year's experience of DPT, used in combination with DDS and with INH.

(a) *DPT used in combination with DDS*

A total of 32 patients have received the two drugs in combination for one year or longer. They fall into three groups.

1. Full dosage of DPT with full dosage of DDS. 2.0 gm. DPT daily with 600 mg. DDS weekly (given daily or twice weekly) 11 patients
 2. Full dosage of DPT with low dosage of DDS. 2.0 gm. DPT daily with 400 mg. DDS weekly 12 patients
 3. Low dosage of DPT with low dosage of DDS weekly 9 patients
- DDS. 1.0 gm. DPT daily with 200 mg.

All the patients in the third of these groups were at the Research Unit. Most of the patients in the other two groups were at other centres. In all cases DDS treatment followed standard routine, and was given daily in some patients, twice weekly in others. DPT was given daily at the same time.

Without exception all patients have tolerated the two drugs

very well, and at the dosage levels used no toxic effects have been observed over and above the minor disturbances attendant on DDS therapy. At these dosages the two drugs may safely be combined. There was also the possibility that a combination of drugs might delay the onset of drug resistance should this be encountered in the later stages of the trial.

Where chemotherapeutic activity is concerned, the progress of these groups has not been the same. Both the first and second groups have made very good clinical and bacteriological progress, better than would be expected under DDS treatment alone, and better than was encountered in controls receiving DDS on its own. In the third group progress was satisfactory but not outstanding, certainly not as marked as in the other groups, but decidedly better than would have been expected on the dosage of DDS alone.

That is all that can be said at present. The combination of drugs appears to give results during the first year superior to those obtained when DDS is given alone, but it is not yet clear whether the combination is superior to DPT alone. Larger numbers, additional groups, and observation over a longer period will be needed before sound judgment on this matter is possible. The important point at present is that when combined with DDS, DPT still contributes both its freedom from toxicity and enhanced therapeutic action.

(b) *DPT in combination with INH*

DPT has been used in combination with INH in 20 patients for periods of 7 to 20 months at 4 centres. INH alone has not been found generally useful in the chemotherapy of leprosy as its effects are unpredictable. This, however, does not rule it out as a possibly useful member in a drug partnership, and its use in conjunction with DPT commended itself as a possible means of using DPT economically in a combination of low toxicity. The two drugs have been given in doses of 1.0 to 1.5 gms. DPT with 100 mg. and 200 mg. INH daily.

Once again the combination has been extremely well tolerated, and no toxic effects of any description have been detected, patients continuing cheerful and in very good physical condition.

The therapeutic effects have not been quite the same at all centres. All eight patients at the Research Unit have made excellent progress, better than would be expected with DDS treatment, and with little if any difference from that expected with larger doses of DPT alone. At other centres results have been outstandingly good in some individuals but not so good in others, and generally not quite as good as that seen when DPT is used alone in full dosage. Further study is again needed, but results so far make this a promising combination of drugs.

Conclusions

It is the opinion of all those taking part in these trials that in DPT we have an anti-leprosy drug of considerable potential importance, a drug which combines a noteworthy freedom from toxic side effects with chemotherapeutic activity of a high order. In a dosage of 25-40 mg. per kilo its activity is quite as great as that of DDS and sometimes surpasses it, and after 32 months of experience there is no evidence of the development of drug resistance.

Complications during treatment have hitherto not been important, one of the virtues of DPT being the favourable course often taken by patients with neuritis. Drug hypersensitivity and psychosis have not been encountered. On the basis of experience so far DPT is considered to be the drug of choice when an alternative is needed to DDS.

DPT can be combined safely with both DDS and INH, the combination having a very satisfactory chemotherapeutic action during the first year of treatment.

In the treatment of the individual patient DPT promises to be a serious rival to DDS, for it combines an activity, at least as great with the promise of a relatively smooth course uninterrupted by major upsets. It is particularly valuable in children. For large scale use, however, something more is needed than high therapeutic activity and lack of toxicity. The dose of DPT is relatively large, and apart from its inconvenience this adds to the cost of treatment. When given twice weekly results though often adequate are not generally as good as when daily treatment is given. For these reasons DPT is not applicable to many situations. A drug with such outstanding qualities should, however, be within the reach of patients everywhere, particularly those in whom DDS has failed to be all that could be desired. Further study both of it and of closely related compounds is urgently needed with the object of promoting ease of manufacture and greater economy and simplicity in administration.

Acknowledgements

Many workers have co-operated in these expanded trials on DPT, and it is a pleasure to acknowledge the help given not only by medical officers who agreed so willingly to take part and have given most careful attention to this work, but also Mr. S. E. Drewett, Senior Laboratory Superintendent, the laboratory staff at the various settlements, and perhaps above all the patients who so readily volunteered at all centres to take what to them was an unknown drug, and faithfully carried out all that was required of them.

Thanks are also due to the Directors of Medical Services, East and West Nigeria, for permission to publish this paper.

Grateful thanks are due to Messrs. Ciba Ltd. for continued generous supplies of DPT.

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2. FINDINGS AT OJI RIVER SETTLEMENT

DR. A. S. GARRETT

At Oji River we have carried out our small section of research on DPT under the close guidance of Dr. Davey.

We have had 25 patients, the first of whom started in July, 1956. They have been on a standard dose of 2 gm. daily as with Dr. Davey's other patients.

The previously untreated lepromas have all shown clinical and bacterial resolution as fast as that in their controls and also faster in all cases but one.

Reactions of neuritis and erythema nodosum have been almost absent and no eye reactions have occurred.

The group of patients given DPT because of previous reactions on dapsone have all had less reactions and some markedly less than before.

The group given DPT to accelerate slow resolution of tuberculoïd leprosy has succeeded in its aim.

No case of toxicity to mind or body has been noted.

These few notes are to stress that my findings are identical with what Dr. Davey reports. There is nothing to add to his findings.

It has previously been strongly held by some people, that all effective anti-leprosy treatment commonly causes reactions. DPT points to a reversal of that view. Investigation of the biochemistry of DPT and *Mycobacterium leprae* may reveal that, in killing the bacterium, DPT fixes a toxin.

3. FINDINGS AT OSSIOMO SETTLEMENT

DR. B. NICHOLSON

Eight patients have been treated at Ossiommo Settlement with DPT for periods ranging from 12½ to 15½ months. Of the eight, four had diffuse lepromatous leprosy, three had macular leproma, and one was a borderline case with areas of diffuse infiltration. They include four adult males, one adult female, one male child and two female children.

On admission the Bacterial Indices ranged from 2.2 to 3.8 with an average of 3.2.

Dosage

Started in all cases at 0.25 gm. daily. In adults it was increased to 1.5 gm. daily over a period of four weeks and in the children to maxima of 1 gm. Recently doses in a few cases have been increased to maxima of 2.0 gm. daily.

These doses have been maintained without difficulty, except in the cases referred to below.

Attitude of Patients

All patients who have been treated with DPT have welcomed it at all stages of the test. No patient has made any complaint about it.

Toxicity

No toxic effect of any kind has been noted in any patient. A sense of well-being has been evident in several cases.

Progress of Leprosy

Every one of the eight cases has shown marked improvement. Clinically there has been general resolution of infiltration and nodules have disappeared.

The Bacterial Index now ranges from 1.1 to 3.2 with an average of 2.1.

Complications

One extremely severe case of diffuse lepromatous leprosy in rather poor general condition suffered repeated attacks of low fever in the early months of treatment. The dose of DPT was reduced but not abolished and the attacks subsided after about six months. They may not have been directly due to the treatment.

The single patient with borderline leprosy had typical erythema nodosum leprosum after having been free of complication during treatment for 12 months. This subsided in a short time after reducing the dose. He is now again on full dose.

Comments

Improvement was seen in every case clinically and bacteriologically. This was distinctly better than is to be expected from similar patients treated with Dapsone in this area. The psychological calmness of these patients while on treatment with DPT is especially noteworthy.

4. EXPERIENCE AT RIVERS SETTLEMENT

DR. M. CORCOS

Five patients have now been on DPT for the following periods.

No. 1	Male	Adult	18 months
No. 2	"	"	18 months
No. 3	"	"	17 months
No. 4	"	"	16 months
No. 5	"	"	14 months

All were lepromatous cases previously untreated. The dosage in all cases has been:—

Weeks 1—2	...	0.5 gm. daily
„ 3—4	...	1.0 gm. daily
„ 5 onwards	...	1.5 gm. daily

Raised after 3 months to 2.0 gms. daily.

All the patients liked the drug and there have been no complaints of any symptoms attributable to it. No case of toxicity attributable to the drug has been noted at any time.

Therapeutic activity has been as follows:—

- No. 1. Severe diffuse leproma with some nodulations of ears. Marked clinical resolution after 18 months. Smears at the beginning of treatment were all 4+. After 18 months of treatment, skin smears were 2+ though ears were still 3+ and left side of nose 4+.
- No. 2. A moderate diffuse leproma. Has much improved clinically. Skin smears at the beginning of treatment were all 2+. After 18 months' treatment, only scanty bacilli were found except in ear lobes which still showed 2+.
- No. 3. Active diffuse leproma with early nodulation. Extremely marked clinical improvement after 17 months of treatment. Skin smears at beginning of treatment 3+—present time 2+ and 1+.
- No. 4. Diffuse leproma. Steady clinical improvement. At beginning of treatment skin smears 3+. After 16 months of treatment from 2+ to scanty.
- No. 5. Diffuse leproma with faint maculation—much improved after 14 months of treatment. Skin smears at beginning of treatment 4+ and 3+. After 12 months' treatment 2+.

Complications during treatment have been notably absent so far. Case No. 5 who complained of nerve pain in the left ulnar nerve (which was grossly thickened) when starting treatment lost this in a few weeks without any radical local treatment. The pain has not recurred though the nerve is still somewhat thickened. There have been no true lepra reactions, but case No. 1, after 15 months' of treatment, showed a slight almost symptomless erythema-nodosum-like reaction which lasted for about two months. Treatment has not been interrupted.

It was not at all easy to match exactly these patients with control of the same severity. Moreover, since all the controls had received previous Dapsone treatment the state of their leprosy at the beginning of their treatment did not necessarily correspond with the state of the leprosy of the experimental cases at the beginning of the experiment **and** of the treatment; the controls were selected on the basis of similarity to the experimental cases, of clinical condition and bacteriology at the time of matching.

Thus the controls were usually more severe cases of leprosy than the experimental cases, but as mentioned had already been under treatment. Controls 1 and 3 particularly were considered unsatisfactory.

- Control 1. Diffuse leproma—relapsed in 1953 following *Hydnocarpus* treatment. Treated with Dapsone since then. Smears 2+ and 3+ at beginning of experiment, and unchanged 10 months later.
- Control 2. Previous treatment 15 months. Diffuse infiltrated leproma. Steady clinical improvement. Skin smears at beginning of treatment 2+. At beginning of experiment 2+. After 15 months experimental period smears very scanty + and acid fast granules.
- Control 3. Nodular leproma, 1 year and 11 months previous treatment with DDS. Smears at beginning of treatment were 4+, at beginning of experiment 2+ and after 9 months very scanty +.
- Control 4. Previous treatment 1 year 11 months. Diffuse leproma with slight maculation—steady clinical improvement on Dapsone. Skin smears at beginning of treatment 4+. beginning of experiment 3+. After 14 months smears were -ve and very scanty +ve.
- Control 5. Treatment with *hydnocarpus* oil from 1948 to 1949. Very irregular treatment with DDS, thereafter until beginning of experiment. Skin smears in 1949 were 1+, at the beginning of the experiment they had become 4+. After 12 months of regular DDS, although there was marked clinical improvement, skin smears were still 3+ and 2+.

Within the limits of the experiment it was considered that the progress made by the five experimental cases in the 1st year of treatment was fully up to that made by DDS treated cases.

5. EXPERIENCE AT ABAKALIKI SETTLEMENT

DR. E. FERN

It is now 16 months since 3 of our 10 trial patients began receiving DPT. Two started treatment 14 months ago and the remaining 5 began treatment this year.

1. Dosage

Six patients are receiving DPT and DDS. The initial dose of DPT was 1.0 gm. daily (6 days a week) with low dosage of DDS, 200 mg. twice weekly. This dosage was given for a month. It was then raised to 1.5 gm. daily and continued for three months. Thereafter, it was raised to 2.0 gm. daily. This dosage, along with 200 mg. of DDS twice weekly, has been maintained throughout.

Four patients are receiving DPT in combination with INH. Three of these patients showed hypersensitivity to sulphones and to thiosemicarbazone. After consultation with the specialist they were transferred to treatment with DPT. The fourth patient had

received no treatment previously.

2. **Attitude of patients to DPT**

All patients have continued cheerful and in fairly good physical condition. All are satisfied with the treatment. Several who are hypersensitive to DDS and thiosemicarbazone desire to be transferred to the new drug, after seeing the promising results in the above three cases.

3. **Toxicity**

The drug has been well tolerated. There have been no complaints of headache, nausea or malaise. No dermatitis and no drug fever have been noted. Two patients who showed hypersensitivity to thiosemicarbazone and DDS were transferred to treatment with DPT and INH while they were still in acute lepra reaction. No untoward effects were observed. One was given Cortisone. Both recovered from the reaction and have continued in fairly good condition. Blood and urine examinations have shown no pathological changes in all cases.

4. **Therapeutic activity, clinical and bacteriological**

Clinical improvement was noted as early as 6 months in some cases, but after 8 months when a second report was submitted clinical and bacteriological improvement was seen in most cases. In the two cases of macular lepromatous group, the patches had faded considerably, more so than in the control patient. Two cases of the nodular group and one of the infiltrative group showed resolution earlier than did the control patients.

The earlier bacteriological response was better, as changes were noted sooner. Now, however, the bacteriological picture changes slowly and although still positive in all cases, the bacteria show degenerative changes in most cases.

5. **Complications during treatment**

One case of the nodular group, on DPT and DDS, developed erythema nodosum. The first attack was mild and prolonged. The second attack began four weeks ago, and was associated with neuritis of the ulnar nerve. This has since subsided. He is receiving Anthiomaline injections. The patient has been afebrile and ambulatory. DPT and DDS were continued throughout.

Another case of the nodular group, on DPT and INH, developed neuritis of the ulnar nerve, not as mild as the former. He is receiving Fantorin injections. Treatment with DPT and INH is being continued.

The patient, who was transferred to treatment with DPT because of repeated lepra reactions, had yet another reaction last month. It was not as prolonged nor of such severity as marked his previous attacks. He responded to a course of antimony injections. He is now afebrile, ambulatory, in fairly good con-

dition and quite cheerful, whereas formerly he was always apathetic.

6. **Comments**

From the foregoing it will be seen that all ten patients have tolerated the drug well, apart from the three just mentioned, who developed complications. Even then, these were mild, compared to those patients who are being treated with sulphones and thiosemicarbazone. No toxic effects have been observed so far. In conclusion, it may be said that these 10 patients have benefited by the use of the new drug.

6. **EXPERIENCE AT ITU SETTLEMENT**

DR. R. MATHESON

Comments on Drug Trials with DPT

There were twelve patients in all treated. Seven were treated with DPT and DDS for fifteen months, while one was treated similarly for eleven months. Dosage was—DPT 2 gms. daily and DDS 100 mgs. daily. Three patients were treated with DPT and INH for nine months, while one was treated with DPT and INH for eight months. Dosage was DPT 2 gms. and INH 100 mgs. daily. Patients seemed happy and there were no complaints about treatment.

Toxicity was nil.

All patients progressed markedly while on treatment. Those on DPT and DDS made faster progress than their controls.

There was little difference for a long time between those on DPT and INH daily and their controls. In fact the controls seemed to be making better progress. In the last few weeks the trials have been making greater progress.

There was little in the way of complications. One of the DPT and DDS groups had slight erythema nodosum after a year on treatment, but soon recovered. Another, after a year on treatment developed macules of the borderline variety and has made good progress since.

DPT has certainly proved very effective in the cases here.

7. **EXPERIENCE AT UBURU SETTLEMENT**

DR. A. MACDONALD

Report of a trial of DPT used in combination with Dapsone and INH.

Selection of Trial Cases

At this centre six lepromatous cases were chosen for the trial of combined DPT and Dapsone treatment, and five for the trial of combined DPT and INH treatment. All were patients previously untreated for leprosy, and all were of active lepromatous type in varying degrees of severity. At the outset all were lepromin negative.

Controls

Controls, who on first admission corresponded closely in respect of type and severity of the disease and bacterial index, were selected for each patient in the experiment. All controls had for

TABLE I

	I	2	3	4	5	6
Name	Nneze	Nwokporo	Odum	Ivo	Nwochulo	Ori
Duration of Treatment (months)	16	16	16	15	15	9
Clinical effect of therapy	Rapid early improvement maintained.	Excellent response apparent after six months.	Excellent response apparent after six months.	Slow steady improvement.	Slow, not dramatic improvement.	Good, steady response.
Compared with control	More rapid response.	Much better response.	Better.	Not much better.	Not better.	Not better.
Bacteriological effect of therapy	After 6 months rapid reduction in bacilli.	Steady slow reduction in No. of bacilli.	Steady slow reduction in No. of bacilli.	Satisfactory.	Satisfactory.	Steady reduction in No. of bacilli.
B.I. fall	2.7—0.3	3.3—2.0	2.7—1.0	4.0—2.5	3.3—1.2	3.3—2.0
Compared with control	Better response.	Better.	Better.	Parallel response	Parallel response	Parallel response
Control's B.I.	3.0—1.7	3.7—3.3	3.0—2.3	3.0—1.3	4.0—1.3	2.7—2.0

TABLE II

Name	1	2	3	4	5
Duration of Treatment (months)	Otu	Uho	Emmanuel	Amos	China
	14	14	11	6	10
Clinical effect of therapy	Excellent rapid response.	Rapid early response.	Excellent response.	Response evident after six months.	Good response apparent after six months.
Compared with control	More rapid response.	Better.	Better.	Not better.	Not better.
Bacteriological effect of therapy	Rapid reduction in No. of bacilli maintained.	Rapidly became negative.	Very good.	Slow effect.	Steady good response.
B.I. fall	4.0—0.6	2.0—0	3.6—0.7	3.0—2.4	4.0—2.0
Compared with control	Much better.	Better.	Better.	Not better.	Not better.
Control's B.I. fall	3.0—2.3	2.3—0.6 —	2.3—1.3	2.3—1.0	3.6—1.3 (in 15 months)

the corresponding period of treatment received 3 mg. oral Dapsone twice weekly.

Reactions, Toxicity, Complications, etc.

None of those taking DPT showed any dislike of the drug. (One, No. 10, absconded for reasons unknown after 7 months' treatment.) Nearly all were appreciative of the steady improvement effected in their condition. None showed any signs of toxicity due to the drugs. Only one (No. 3) showed any of the complica-

tions of leprosy during the period of treatment; this man developed erythema nodosum leprosum in the fifth month, which was quickly controlled by the administration of Fantorin. His control, a case of very similar type, began to have frequent recurrent erythema nodosum leprosum after fifteen months with increase in the Bacterial Index and polyneuritis. Case No. 6 died of cerebral malaria after nine months of treatment.

Combined DPT/Dapsone treatment

(a) Dosage

Cases Nos. 1—5 were after 2 to 3 months gradual increase in dosage receiving 2.0 gm. DPT daily with 300 mg. Dapsone twice weekly. Case No. 6 (a girl) received a maximum dose of 1.0 gm. DPT daily with 200 mg. DDS twice weekly.

(b) Therapeutic Effect

In all these severe cases the response to therapy was good—excellent in cases 1, 2 and 3 as compared with the much slower response of their controls on Dapsone. Cases 4, 5 and 6 showed a response to treatment very similar to that of their controls on Dapsone alone.

Combined DPT/INH Treatment

(a) Dosage

In all cases the dosage was quickly increased to a maximum of 2.0 gm. DPT daily with 200 mg. INH daily.

(b) Therapeutic Effect

This was excellent in cases 7, 8 and 9 as compared with that of their controls. Cases 10 and 11 showed a slower response not better than that of their controls.

Conclusions

All the patients treated with DPT in combination either with Dapsone or INH showed a satisfactory response to the therapy. More than half showed excellent rapid improvement which compared favourably with that of their controls who received Dapsone only. The general impression from this small series is that DPT used in conjunction with other active drugs in this way evokes a very satisfactory response both clinically and bacteriologically, and prevents residual scarring of the skin and disfigurement.

Acknowledgements

We are grateful to Dr. Davey of the Research Unit, Uzuakoli, for the opportunity of taking part in the extended trial of these drugs, and for his encouragement and advice. Mr. Drewett undertook the training of one of our laboratory assistants and we thank him for this valuable help. Dr. L. M. Hogerzeil was responsible for selecting the patients for DPT treatment and their controls, and we are grateful to him for his careful recording of the initial findings in each case.