

THE TREATMENT OF LEPROSY WITH  
TB1/698.

A REPORT BASED ON 38 MONTHS' EXPERIENCE.

JOHN LOWE, C.B.E., M.D. (F'HAM), F.R.C.P.

*Late Specialist, Nigeria Leprosy Service,*

*Medical Secretary, British Empire Leprosy Relief Association, London.*

The use of TB1 698 (para-acetamidobenzaldehyde thiosemicarbazone) in leprosy started here in October 1950 in a small group of cases, and it has been used continuously since then on an increasing scale. It has now (Dec. 1953) been used in 273 cases for periods up to 38 months. A preliminary report (1) covering 12 months' treatment, and an interim report (2) covering 30 months' treatment, have already been published. The present report in general confirms and amplifies the findings made and the views expressed in these previous reports, but modifies them in certain

respects, since the earlier promise of this treatment has not been entirely fulfilled.

#### MODE OF ADMINISTRATION.

TBI/698 has been given orally twice a day for six days a week. A break of one day a week has been made, for administrative reasons, and because previous experience with other forms or prolonged chemotherapy of leprosy has shown that this break has many advantages and no obvious drawbacks.

The initial dose is usually either 50 or 100 mg. a day according to the weight and physical condition of the patient; in small children it has been 25 mg. a day. After a few days the dose has been increased to 100 or 150 mg. a day, and after another few days to 150, and in some cases later to 200 mg. a day. 200 mg. a day is the maximum we have used. Treatment has been continuous except (a) for short breaks of about 2 weeks once or twice a year for patients leave and (b) when intercurrent disease or complications have made a temporary stoppage of treatment advisable.

#### TOXIC EFFECTS OF TBI.

Under this head I discuss the bad effects apparently produced directly by the drug itself. The complications arising from the interaction of the drug and the leprosy processes are discussed later.

Many reports of the toxic effects of T.B.I have been published. The early German work on the use of TBI in tuberculosis was done with doses much higher than those now used, and toxic effects were more common and serious than now. Even with the lower doses at present used, some workers, particularly in the United States, regard the drug as too toxic for the treatment of tuberculosis:

The toxic effects on record include anorexia, headache, epigastric discomfort, vomiting, jaundice and other evidence of disturbed liver function; fever and rashes; a severe anaemia; and agranulocytosis.

In the present series of cases numbering 273, the following complications definitely or possibly due to the direct toxic action of the drug have been seen.

The following definite toxic effects have been seen:—

Acute agranulocytosis	...	...	5 cases.
Severe anaemia	...	...	6 cases.
Allergic dermatitis	...	...	1 case.
Drug fever	...	...	1 case.
Acute hepatitis	...	...	3 cases.

The following possible toxic effects have been seen:—

Subacute nephritis	...	...	...	2
Psychosis	...	...	...	1
Severe gastro-enteritis	...	...	...	4
				—
				7
				—

#### DEFINITE TOXIC EFFECTS.

(a) *Acute agranulocytosis.* Five definite and severe cases have been seen, in addition to others showing mild or moderate degree of granulopenia. Four of these serious cases have previously been reported (3). Since then one further case has been seen.

The following are the main features.

All occurred within the first three months of treatment, the number of weeks treatment being 5, 3, 6, 3, 12.

In two cases the patients first complaint was of inflammation of the gums, and of fever with rigors. The other three complained of malaise and fever, and were suspected of malaria; blood examination showed no malaria parasites but revealed the agranulocytosis.

One of the five cases was relatively mild, but four were severe. In the four severe cases, the granulocytes count fell from normal levels before treatment started to very low levels, to 500 or below; the actual lowest counts were 500, 40, 120, and 70, and nearly all granulocytes remaining were eosinophils. In one case, neutrophil polymorphonuclear leucocytes completely disappeared, and in another case they fell to a count of 25.

In one case the agranulocytosis was accompanied by severe hepatitis and jaundice.

In all five cases, TB<sub>1</sub> treatment was stopped and one million units of penicillin a day was given until the granulocyte count rose to normal levels, which usually took about seven days; during these seven days the fever (which in some cases was very high, 106) was controlled, but local sepsis developed, in two cases in the mouth, in two in lymph nodes which suppurated, and in one in the nail bed, with necrosis of the end of a toe.

When granulocytes reappeared in the peripheral blood, they were often immature, and sometimes grossly immature.

In three of the five cases of agranulocytosis, after recovery, no attempt was made to resume TB<sub>1</sub> treatment; in the other two cases, after a break of about a month, TB<sub>1</sub> treatment was cautiously resumed, and has now been continued for many months with no recurrence of the agranulocytosis.

In addition to the five definite cases recorded above, moderate degrees of leucopenia attributable to TB<sub>1</sub> treatment have been seen in many other cases, occasionally accompanied by an anaemia apparently due to the same cause, but in none of these has the leucopenia been serious.

(b) *Anaemia.* In several cases during the first few months of TB<sub>1</sub> treatment, marked falls in the haemoglobin and red cell content of the blood have been observed. The most marked cases are here summarised.

A young woman before treatment showed haemoglobin 88% (Sahli), red cell count 4.2 millions, and white cell count 6.2 thousands (granulocytes 2000). Treatment was started with 100 mg. a day; three weeks later the dose was increased to 150 mg. a day. After 8 weeks treatment she complained of great and rapidly developing weakness and she was found very anaemic. (R.B.C. 1,050,000; Hb 25%: red cells showed hyperchromia, macrocytosis and poikilocytosis.)

Treatment was stopped and vitamin B<sub>12</sub> was given empirically. A week later the red cell count had risen to nearly 2 millions and the haemoglobin to 44%. A few normoblasts were seen and hyperchromia was marked. Slow but steady improvement was seen, and after three more weeks red cells had risen to 3,200,000 and haemoglobin to 78% (Sahli). TB<sub>1</sub> treatment was resumed at a low dosage, 50 mg. a day, but after a few days the low granulocyte count (650) caused a stoppage of treatment. Later, sulphone treatment was instituted with no trouble.

A second case had a tragic ending. After four weeks on TB<sub>1</sub> treatment the patient was admitted to hospital for a minor operation under another section, and owing to an oversight was temporarily lost sight of by the Research Unit. After the operation he developed fever and sepsis of a foot, and was treated with penicillin. After a few days the Research Unit traced and examined him and found that the haemoglobin had fallen from 90% to 30% and the red cells from 5 millions to 1.2 millions. The white cells were numerous but grossly immature. The blood picture indicated a severe toxic anaemia and probably a recovering agranulocytosis. Death occurred a day later. This case illustrates the need for continued close observation during the first few weeks of treatment, and perhaps for the avoidance of all surgical operations during this period.

Four similar but less marked cases have been seen. In some of these also, leucopenia has accompanied the anaemia. In some, TB<sub>1</sub> treatment was abandoned, but in others, after an interval it has been resumed with caution and continued without serious difficulty,

(c) *Hepatitis*. In many of our patients, during the first few weeks of treatment, a complaint has been made of loss of appetite, "heaviness" in the upper right abdomen, and other symptoms suggestive of mild degrees of hepatitis; in some, laboratory tests have given confirmatory evidence. These symptoms usually subside in a week or two without cessation of treatment.

In three cases, severe hepatitis has developed during TB<sub>1</sub> treatment.

In one case it accompanied agranulocytosis as already described, and subsided with recovery. In the second case severe hepatitis and jaundice occurred after six weeks treatment. All the usual laboratory tests for toxic hepatitis gave strongly positive results. The jaundice subsided in a month and a month later TB<sub>1</sub> treatment was resumed with no trouble. In the third case, the early months of treatment passed without incident, but in the 7th month a marked enlargement of the liver and spleen was recorded and treatment was stopped for a month and then resumed. During the next few months there were several attacks of malaria. In the 20th month of treatment there was an attack of abdominal discomfort with marked liver enlargement and jaundice, and three weeks later death occurred from subacute liver necrosis.

*Comment.* These three toxic effects, all of them serious, (a) leucopenia sometimes going on to agranulocytosis, (b) anaemia which may develop rapidly and be very severe, and (c) hepatitis, indicate that the most important toxic effects of TB<sub>1</sub> are on the bone marrow and on the liver. During TB<sub>1</sub> treatment, especially during the first few weeks, patients should be carefully observed for signs of these complications.

In our experience, clinical observations are more important than laboratory tests. Frequent blood examinations may fail to

detect the impending acute anaemia or agranulocytosis, for these changes may develop quickly after one satisfactory examination and before the next is due. If the patient reports at once if unwell, proper clinical examination will usually detect them promptly, and recovery should occur.

In our series of 13 patients showing these complications, 2 deaths occurred. In one case, the patient ceased to be under our supervision when the complication arose and it was not detected till too late. In the second case, TB<sub>I</sub> treatment was continued after one attack of hepatitis, and the second attack was fatal; this case would indicate the inadvisability of continuing TB<sub>I</sub> in any patient after an attack of hepatitis.

(d) *Allergic dermatitis*. In our 273 cases treated with TB<sub>I</sub>, only one severe case of allergic dermatitis has been seen.

After three weeks on TB<sub>I</sub>, the patient developed malaria which was treated with paludrine. One week later a generalised follicular dermatitis developed, the process involving the mucous membranes and there was a tendency to exfoliation. The condition was very similar to the exfoliative dermatitis due to sulphones, with which we here are very familiar. TB<sub>I</sub> treatment was stopped, and antihistamin treatment was given for 3 days, but the dermatitis got worse. Small doses of A.C.T.H. were given for three days with marked improvement, and in two weeks recovery was complete. No attempt was made to resume TB<sub>I</sub> treatment, sulphone treatment taking its place. Ten months have now passed with no recurrence of dermatitis.

In a few other cases, a mild follicular dermatitis has been seen on the trunk and arms, but it has not been severe and has soon subsided, in some cases with no stoppage in treatment; in others, TB<sub>I</sub> treatment was resumed with no difficulty. In one case, TB<sub>I</sub> treatment was abandoned for sulphone.

(e) "*Drug fever*". In one case, the administration of TB<sub>I</sub> for the first twelve months was without trouble, and then occurred a continued fever with no apparent cause; when TB<sub>I</sub> was stopped the fever stopped and when TB<sub>I</sub> was restarted the fever recurred. Finally TB<sub>I</sub> treatment was abandoned for sulphone treatment and no further trouble arose. Somewhat similar cases have been recorded by Dharmendra and Chatterji (4).

#### POSSIBLE TOXIC EFFECTS OF TB<sub>I</sub>.

Under this head are included three conditions, probably not caused by TB<sub>I</sub>, but TB<sub>I</sub> may have accentuated them. These three conditions are psychosis, subacute nephritis, and acute gastroenteritis.

*Acute psychosis* has been seen in only one case, after four months TB<sub>I</sub> treatment (carried on with little difficulty although the haemoglobin level was persistently low) the patient became morose, depressed and unmanageable, and this persisted for several months.

Finally the patient was taken home by relatives and has not been seen again.

*Subacute nephritis* has been seen in two cases. In one there was evidence of mild chronic nephritis before TB<sub>I</sub> treatment was started but this became markedly accentuated in the 6th month of treatment. In the second case there was no evidence of nephritis when treatment started, but an attack of subacute nephritis occurred in the 6th month. In both cases recovery occurred, and treatment was resumed.

*Acute gastro-enteritis* has been the cause of death of three patients during TB<sub>I</sub> treatment. This condition is seen in a few of our patients here every year, nearly always in the rainy season. The aetiology is obscure. No organism has been incriminated. It may be seen in patients who are on sulphone treatment, on TB<sub>I</sub> treatment, or even on no treatment. It is characterised by high fever, severe abdominal pain, sometimes diarrhoea, sometimes vomiting, (the vomit and the stools sometimes showing altered blood,) by collapse, a falling blood pressure, and in a high proportion of cases, death. At post mortem are seen a large fatty liver, and congestion of and often small haemorrhages into the walls of the stomach and small intestine. In a few cases a plastic peritonitis is seen.

Three fatal cases of gastro-enteritis occurred in our present series of 273 patients, one in the 7th month and one in the 16th month and one in the 18th month. All three cases were in adults, and all showed malaria parasites in the blood at the time of the illness; one had recently had an attack of malaria. It is probable that neither malarial infection nor TB<sub>I</sub> treatment contributed much to the fatal termination. In one, the abdominal symptoms suggested an abdominal catastrophe and laparotomy was performed, but nothing definite was found. In all three cases, death occurred within 48 hours of the onset of acute symptoms.

In two of the three cases, post mortem was performed with findings as outlined above.

[In one further case death occurred after a period of TB<sub>I</sub> treatment. An old very feeble ill-nourished woman became bed-ridden and incontinent, and died of cardiac failure.]

#### RESULTS OF TREATMENT.

##### (a) *Lepromatous cases with no previous treatment.*

86 such cases are included in our present study. The results may be considered from two points of view, clinical and bacteriological.

*The clinical results* will be considered first. In almost every case the early clinical results have been good. Slowly but surely the leprosy lesions have become less marked, the nodules and infiltrations less obvious, the neuritis less troublesome, the nerves sometimes less thick, eye inflammation less, and so on. Within twelve months in nearly all cases the clinical improvement has been definite or

marked. During the second twelve months, in most cases, improvement has been slower but steady and definite, though there have been some cases in which improvement during the second twelve months has been negligible. During the third twelve months, while there have been some cases in which improvement has continued, there have been others in which improvement appeared to cease, and still others in which definite deterioration has occurred, in a few cases quite rapidly.

To summarise; the early clinical results have been good; the late results have been disappointing in some cases. It seems probable that in some cases with prolonged treatment the drug loses its efficacy, possibly as the result of the bacilli becoming drug resistant.

The *bacteriological results* in these cases are summarised in the following table:—

#### 24-38 months treatment.

<i>Bacteriological status before treatment</i>	<i>Bacteriological status after treatment</i>				
	4+	3+	2+	1+	<i>negative</i>
4+ 10 cases	0	4	4	2	0
3+ 7 cases	0	0	2	4	1
2+ 8 cases	0	0	2	3	3
1+ 5 cases	0	0	0	0	5
<hr/> 30 cases <hr/>	<hr/> 0 <hr/>	<hr/> 4 <hr/>	<hr/> 8 <hr/>	<hr/> 9 <hr/>	<hr/> 9 <hr/>

#### 12-24 months treatment.

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
<hr/> 14 cases <hr/>	<hr/> 0 <hr/>	<hr/> 3 <hr/>	<hr/> 3 <hr/>	<hr/> 6 <hr/>	<hr/> 2 <hr/>

#### 6-12 months treatment.

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
<hr/> 25 cases <hr/>	<hr/> 0 <hr/>	<hr/> 3 <hr/>	<hr/> 4 <hr/>	<hr/> 16 <hr/>	<hr/> 2 <hr/>

17 cases with less than 6 months treatment are not analysed.

These results are rather disappointing. While nearly all the cases show improvement, the improvement in some cases is not very marked, even after 3 years treatment. Moreover (though this is

not shown in the table) there are some cases in which earlier improvement has not been maintained, and which are now showing more bacilli than they did a year ago. These results on the whole do not compare favourably with those shown by a similar analysis of similar cases treated with sulphones. The first part of this table may be compared with the following table reproduced from a previous report (5) on results of sulphone treatment for 30-38 months:—

<i>Bacteriological status before treatment</i>	<i>Bacteriological status after treatment</i>				
	4+	3+	2+	1+	<i>negative</i>
4+ 23	nil	2	7	10	4
3+ 4	nil	nil	nil	2	2
2+ 2	nil	nil	nil	nil	2
1+ 6	nil	nil	nil	nil	6
35	nil	2	7	12	14

Thus, judged from the bacteriological standpoint, the results, particularly the late results, of TBI treatment are disappointing, and correspond with the rather disappointing clinical results recorded above.

*Relapse.* 3 lepromatous cases have been classed as "disease arrested" and discharged 15 months, 5 months, and 3 months ago. On re-examination, one of these 3 cases has shown slight relapse, bacteriological but not clinical, a few bacilli only being found on routine examination.

(b) *Lepromatous cases previously treated with sulphone.*

In our present series there were 45 such cases. The reasons for the change from sulphone treatment to TBI treatment were:—

Severe and repeated "reaction" ...	23 cases
Severe neuritis ... ..	10 cases
Eye inflammation ... ..	3 cases
Sulphone psychosis ... ..	4 cases
Slow progress ... ..	5 cases

In the five cases in which progress on sulphone treatment was slow, the change to TBI treatment produced no apparent increase in the rate of progress.

In the other forty cases in which for varying reasons sulphone treatment was difficult and sometimes impossible, the change was beneficial in practically every case.

In the 4 cases in which psychosis had developed on sulphone treatment, TBI treatment presented no such difficulty. In the 36 cases in which complications, reaction, neuritis, iritis had made continuous sulphone treatment difficult or impossible, the change was beneficial in practically every case; these complications were not abolished at once but the attacks were rendered less frequent and less severe and finally disappeared, and



moreover the leprosy improved. In some of these patients, however, in the last few months, improvement has become negligible, and in some, sulphone treatment has now been resumed in the hope that recovery will be speeded up.

This group of 45 patients illustrates what is felt to be the most important use of TBI, namely in the treatment of those cases in which sulphone treatment presents real difficulty. In such cases, after TBI treatment has been given with benefit for 1 or 2 years, after complications have died down and the disease become more quiescent, the resumption of sulphone treatment may be desirable.

(c) *Tuberculoid cases with no previous treatment.*

TBI treatment has been given to 110 cases of leprosy of the milder tuberculoid type. Almost all of these cases were bacteriologically negative when examined by ordinary methods, so improvement has to be judged on clinical grounds, by the subsidence of activity of the skin lesions as shown by the cessation of spread, by the disappearance of the thickening and erythema, by the diminution of depigmentation and sensory change, by the diminution in thickening and tenderness of nerves, and so on.

Judged on these grounds, the results of treatment have been good. Often within six months, and usually within twelve months, signs of activity have subsided, although depigmentation of the affected areas of skin, and thickening without pain and tenderness of the affected nerves have often persisted. Treatment has lasted for between 18 and 24 months in most cases before discharge. On the whole the results in these cases have been as good as those observed after a similar period of sulphone treatment.

While on the whole the subsidence tended to be slower than with sulphone, it has seemed more often to be accompanied by a return of pigment and sensation to the affected areas of skin. The subsidence of nerve thickening was also perhaps more marked.

*Relapse.* Of the 110 such cases so far treated, 39 have already completed their treatment and been discharged, the period since discharge now being up to 15 months. Of these 39, 33 have attended for re-examination at least once, and some several times since discharge, and of the remaining 6, 3 are not yet due for re-examination. Of the 33 actually re-examined, 3 have shown signs of re-activation of the disease, all of them at the first three-monthly examination after discharge. In one of these three, the treatment had been inadequate (for twelve of the standard eighteen months treatment, as an experiment, the TBI had been given twice weekly and not daily) but in the other two, full treatment had been given for 19 and 21 months. All three relapses were slight.

In similar tuberculoid cases, slight relapses have been seen

after a similar period of sulphone treatment; and these relapses also have usually occurred within a few weeks or months after the cessation of treatment; late relapses not having been seen.

These findings of relapse after TB<sub>1</sub> treatment are therefore not entirely unexpected, although they do indicate that in this respect TB<sub>1</sub> treatment appears no better than sulphone treatment.

(d) *Tuberculoid cases previously treated with sulphones.*

Thirteen such cases have been treated with TB<sub>1</sub>. The causes of the transfer from one drug to the other are here summarised:—

Sulphone psychosis ... ..	2 cases
Severe neuritis ... ..	1 case
Slow progress ... ..	5 cases
Severe tuberculoid reaction ...	1 case
Relapse after sulphone ...	1 case
Sulphone dermatitis ... ..	2 cases

—  
12 cases

All these cases responded in the usual way to TB<sub>1</sub> treatment, but there was no clear indication that the response was any better than continued sulphone treatment would have given (except of course in sulphone psychosis and dermatitis when continued sulphone treatment was impossible).

Thus TB<sub>1</sub> treatment of tuberculoid cases has given results which are considered good, about as good as, and in some respects perhaps better than the results of sulphone treatment. Relapses have occurred in some discharged patients, but a comparison of relapse rates is not yet possible for data are insufficient.

(e) *Other cases.*

Nine cases of "border line" type have been treated for periods up to 30 months. The clinical response has been good, and three have become bacteriologically negative. One was discharged after 25 months treatment, and 3 months later showed a bacteriological relapse with numerous bacilli in the nasal discharge. This was unexpected; during several years experience of sulphone treatment we have not made such a finding in discharged patients.

Only 2 cases of "indeterminate" type are included in our present series, and they have been treated for only a short time.

COMBINED TREATMENT WITH SULPHONE AND TB<sub>1</sub>.

Sulphone treatment, here used in the form of oral administration of diamino-diphenyl sulphone, is of established value and is now the routine treatment of leprosy in most centres. TB<sub>1</sub> treatment, though still experimental, appears to have a very definite

value in leprosy. It was therefore thought worth while to study the value of the two drugs given together. We were advised however that a synergistic action of the two drugs was unlikely, in spite of the fact that sulphone, and not TB<sub>1</sub>, is inactivated by para-amino benzoic acid, which fact would suggest that their modes of action are somewhat different.

Three young men in good physical condition were selected for the first trial. Their leprosy was completely untreated. The dose used was 100 mg. of each drug daily. In one of the three cases in 3½ weeks fever and a generalised dermatitis developed. Treatment was stopped. Later observations showed that he had become intensely allergic to sulphone. In the other two cases the combined treatment continued for longer but the patients complained of headaches and malaise and there was no obvious advantage of the combination of the two drugs over either drug given alone. The trial was stopped.

Later a further attempt was made to study combined treatment. 9 patients were selected who had been receiving one or other treatment for widely varying periods and who were showing a poor response to that treatment. In the first case, previously on TB<sub>1</sub> treatment 150 mg. a day, the dose used for combined treatment was 100 mg. of each drug daily. Within four weeks he developed fever and allergic dermatitis, and a few days later an acute psychosis. Treatment was stopped and the toxic manifestation subsided. Later, sulphone treatment alone was used with no trouble.

Thus of 4 cases in which sulphone had not previously been used, when it was given in combination with TB<sub>1</sub>, serious toxic effects were seen in 2. The TB<sub>1</sub> appeared to enhance the toxicity of the sulphone.

In the remaining eight cases, the previous treatment had been with sulphone and had been well tolerated, but response had been unusually slow or inadequate. The dosage used was in most cases 150 mg. of TB<sub>1</sub> daily and 400 m.g. of DADPS twice weekly; in two cases daily DADPS was used instead of twice weekly, the dose being 100 m.g. in one and 200 m.g. in the other.

In one of the eight cases, severe anaemia caused the abandonment of the combined treatment in 2 months. In two others, severe reaction at the 3rd and 4th month caused its cessation. In the five others, though complaints of headache and malaise were not uncommon, the combined treatment caused no serious trouble and was continued for 6, 6, 15, 22, and 28 months in the five different cases. No obvious benefit was seen from the combined treatment, progress appearing no quicker than with either drug given alone.

Combined treatment was therefore abandoned.

#### TB<sub>1</sub> IN PREGNANCY, THE PUERPERIUM, AND LACTATION.

Previous experience with sulphone has shown its value in maintaining the health of the mother during pregnancy and in preventing the aggravation of leprosy so often seen in untreated cases during the puerperium. It has been found possible to continue sulphone treatment during the whole of pregnancy, the puerperium and lactation. Further, sulphone is excreted in the mothers milk and may be of value in combating possible leprosy infection of the baby. (In East Nigeria as in many parts of Africa, there is no real alternative to breast feeding because there are no cows). Moreover serious toxic effects in the baby have not been seen.

The question arises whether the same is true of TB<sub>1</sub>. The

toxic effects of TBI are such that if they occurred during pregnancy they would be very serious. It may be unwise to start TBI treatment during pregnancy and we have not done it. Some women already on TBI treatment have become pregnant, and have continued the treatment with benefit through pregnancy the puerperium and lactation, with no untoward results to themselves\* or in most cases to the child. In one case however, a child has shown signs and symptoms which appeared to be those of the toxic effects of TBI, a marked anaemia of toxic type which recovered promptly when the mother's TBI was stopped. It was perhaps significant that in this case the TBI treatment was started when the child was a few months old.

Chatterji and Bose (6) have shown that if a mother receives TBI, her milk contains TBI but in such small amounts that toxic effects to a baby would appear unlikely. Nevertheless on general grounds, and on our limited experience of TBI, we regard sulphone treatment as preferable during and after pregnancy.

#### TUBERCULOSIS DEVELOPING DURING TBI TREATMENT OF LEPROSY.

Both the drugs used in the treatment of leprosy, sulphones now being used as the routine treatment, and TBI now being used experimentally, were originally introduced into medicine for the treatment of tuberculosis, although they are not now widely used for this purpose.

A study of the incidence and severity of tuberculosis in those receiving these drugs for leprosy may be of interest.

Reports from the National Leprosarium Carville Louisiana U.S.A. (7) state that since the introduction of sulphone as the routine treatment for leprosy, the incidence, severity and mortality of tuberculosis of the lungs in leprosy patients has markedly diminished. Experience here at Uzuakoli Nigeria has been similar, and it should be emphasized that in our Africans, tuberculosis often arises acutely and develops rapidly. In several hundreds of cases of leprosy I have observed, no case of tuberculosis arising after sulphone treatment has been well established and maintained for several months. Two or three cases have been detected during the first few weeks or months of sulphone treatment, and it appeared likely that the disease had originated before sulphone treatment was introduced. Moreover the severity of the disease seems to be modified by the sulphone treatment. There is evidence that sulphone is exerting a suppressive action on tuberculous infection,

---

\*Since this paper was drafted, one case has been seen of exacerbation of leprosy during the puerperium in a woman receiving TBI treatment.

and in combination with streptomycin and isoniazid we have used it with apparently some effect in treatment. Is the same true of TBI?

Here again our experience is limited. In our 273 patients treated up to 38 months with TBI, two new cases of tuberculosis have arisen, one in a patient after 9 months treatment and the other in the 6th month of treatment. There was no evidence that the disease had been present before TBI treatment started. In neither case was the disease severe.

So far our experience suggests that the suppressive action of TBI on tuberculosis is less marked than that of sulphone.

#### DISCUSSION AND CONCLUSIONS.

An attempt has been made to present the relevant facts of our experience of TBI in the treatment of leprosy during the last 38 months, with a view to assessing the part it should play in the treatment of leprosy.

There is no doubt that TBI has a beneficial action in most active cases of leprosy, but many questions arise regarding toxicity and efficacy, and the simplest and most useful way of discussing these questions is to make a comparison between TBI treatment and sulphone treatment of similar cases.

Compared with sulphone treatment TBI has two advantages:

(1) In patients who have difficulty with sulphone treatment because of the severe and repeated attacks of reaction erythema nodosum, neuritis, iritis, etc. which it may provoke, TBI is almost always better tolerated, and is beneficial.

(2) In some patients, clinical improvement under TBI treatment appears for a time at any rate more marked than in similar patients on sulphone treatment.

On the other hand TBI treatment has several disadvantages compared with sulphone.

(1) While toxic effects of the two drugs are seen in about the same proportion of cases, TBI is more dangerous, since it has a toxic effect on bone marrow and on the liver. It should not be used except under close medical supervision.

(2) While the early results, judged clinically and bacteriologically, of TBI treatment appear to equal those of sulphone treatment, the late results of TBI treatment appear less satisfactory. A considerable proportion of patients after 2 years or more TBI treatment with good progress, reach a stage where the drug seems to lose its action, and further progress is not seen; moreover in several

such patients, definite clinical and bacteriological deterioration has set in; in our experience with sulphone treatment this has not occurred. We are gradually being forced to the view that in the long run TBI treatment is less effective than sulphone treatment.

(3) Sulphone treatment while it can be given daily, can also be given twice weekly, once weekly, or according to some workers, once fortnightly. In our experience, TBI treatment has to be given daily and preferably twice daily to be effective. This renders the treatment much less widely practicable.

(4) The cost of TBI treatment is several times as great as oral treatment with diamino-diphenyl sulphone. With several thousands of patients to be treated, this difference may be important.

For these reasons it is considered that TBI treatment of leprosy should be confined (a) to patients who become allergic to sulphones (b) to patients who suffer serious toxic effects of sulphone e.g. psychosis and (c) to those patients in whom for any other reason sulphone administration present difficulties e.g. severe or repeated reaction neuritis, eye inflammation etc. In this third group of cases, when the patient improves sufficiently on TBI treatment, sulphone treatment should be resumed if possible.

#### REFERENCES

1. LOWE, J. (1952) *Lancet* 1 p. 436.
2. LOWE, J. (1953) *Leprosy in India* 25 No. 3 p. 188
3. LOWE, J. (1952) *Leprosy Review* 23 3 & 4 p. 109.
4. DHARMENDRA and CHATTERJI, K. R. (1952). *Leprosy in India* 24 p. 93.
5. LOWE, J. and DAVEY, T. F. (1951). *Trans. of Roy. Soc. of Trop. Med. and Hyg.* 44 p. 633.
6. CHATTERJI, K. R., and BOSE, R. (1953). *Leprosy in India* 25 p. 199.
7. GRAY, H. H., and BANCROFT, H. (1952). *Internat. Jour. of Lep.* 20 p. 463.