THE SULFONE TREATMENT OF TUBERCULOID LEPROSY

JOHN LOWE, M. D., M. R. C. P.
Specialist, Nigeria Leprosy Service
Uzuakoli, Nigeria

The application of the sulfones to leprosy, which has revolutionized the therapy of this disease, originated at the United States national leprosarium at Carville, Louisiana, where forms other than the lepromatous are apparently uncommon; and the early reports by Faget and his coworkers (5, 6, 7, 8, 11) dealt only with lepromatous cases. The early reports of Muir (18, 19) and of others on sulfone treatment in other parts of the western hemisphere also dealt with cases of that kind. These reports showed that the nerve lesions responded to treatment less rapidly than did the lesions of skin and mucous membrane. Faget, for example, stated (5): "Episodes of acute leprous neuritis also are not prevented or abated by sulfone therapy." Others reported that sulfones had little beneficial effect on trophic lesions caused by the destruction of nerves; and, indeed, Erickson and Johansen (4) have found that bone changes of trophic nature may increase while lepromatous lesions of the skin and other tissues concurrently improve.

The early reports of sulfone treatment appear to have been interpreted, for some reason not apparent, by some workers as indicating that sulfones are of no value in the treatment of the nonlepromatous forms of leprosy; and one worker (3) has stated categorically that, "No case showing neural macules, tuberculoid or neural anaesthetic lesions should be given sulphone therapy." If this view of the matter were correct, then in many countries the value of these drugs in the treatment of leprosy would be limited. In large parts of Africa and Asia, particularly India, nonlepromatous forms, particularly the tuberculoid ones, greatly predominate. In such places, any kind of treatment suitable only for lepromatous cases would be useful in only a minority of those requiring treatment.

When I started observations on sulfone treatment of leprosy here in Nigeria, in December 1947, I had been informd that these drugs were of little or no use in nonlepromatous cases. At that time no report of their use in such cases had appeared, and there was no evidence of any serious attempt to study their action in them, although I presumed there must be evidence unpublished.

This position seemed to me unsatisfactory. I argued that the sulfones were selected for study in leprosy because of their activity against acid-fast bacilli *in vitro* and in animals; that all active leprous lesions are due to the presence of acid-fast bacilli; that the action of sulfones in lepromatous cases is probably a direct one on the bacilli; and that a similar antibacterial action might be expected in nonlepromatous cases, including the tuberculoid ones, with corresponding clinical improvement in the lesions.

It was anticipated that the differences between tuberculoid and lepromatous leprosy might influence the action of sulfone drugs. The tuberculoid lesion is believed to be the result of the reaction, largely allergic, of the tissues to the presence of a small number of bacilli or the products of their disintegration, this allergy being probably accompanied by or constituting a part of an immunity response. These circumstances should favor the action of the sulfones, and perhaps make it more rapid than in lepromatous cases. It also seemed likely that if sulfone treatment in tuberculoid cases induced destruction or acceleration of destruction of bacilli, that effect might be followed by a temporary increase in the signs of activity in the lesions because of increased tissue response to the products of increased disintegration of the bacilli, and that such increased inflammation occurring in nerves might produce severe neuritis with an increase in trophic lesions.

Early in 1948 I began to treat a few active tuberculoid cases with sulphetrone. It was expected that, as in lepromatous cases, any response would be slow. The work was somewhat upset in its early phases by the fact that attempts to start at larger doses, or to increase the dose more rapidly, than in the treatment of lepromatous cases gave rise to sulfone dermatitis in a few cases. Within a few weeks, however, it became clear that the good expectations were being fulfilled and the bad ones were not. Gradually this work was continued and extended, until now (June 1950), we have studied closely the effects of sulfone treatment in over fifty cases for periods up to 24 months. Previous publications (13, 14, 16) have contained preliminary reports of this study. Here are recorded the results of this treatment of the first fifty active tuberculoid cases.

MATERIAL AND METHODS

Cases treated.—The cases were taken as they came provided only that they showed active tuberculoid lesions of the skin; usually, too, there was obvious involvement of superficial nerve

trunks. There was no selection of cases, every available one being treated; and all of them are here presented, with no omissions. They are divided into three groups, according to the Cairo Conference classification, as follows: "major" with marked thickening and inflammation of the skin lesions and almost always of nerves (21 cases); "medium" with less inflammation than "major" and more than "minor" (19 cases); "minor," with only slight thickening and inflammation of the skin lesions, often confined to the margin (10 cases).

Sulfones used.—Two forms of sulfone were used in treating these cases, sulphetrone and diaminodiphenyl sulfone (DDS). Both were given orally. Sulphetrone was given in daily doses increasing in steps of 1 gm. every week from 1 gm. to 5 gm. over a period of five weeks, and then continued at that level. DDS was given in daily doses increasing in steps of 100 mgm. every two weeks from 100 mgm. to 300 mgm., and then continued at that level. Both forms of the drug produced similar results, but there was some evidence that the response to DDS was more rapid than that to sulphetrone.

Details regarding the cases treated and the results obtained are given in Table 1.

RESULTS OF TREATMENT

(*a*) *The phase of early response.*—The possibility of an early exacerbation of the lesions in skin and nerve had been envisaged before the work started. In actuality this activation occurred much earlier than was expected. In some of the first cases it was missed, but it soon became clear that, particularly in the major tuberculoid lesions, there generally was a phase of increased inflammation, occasionally accompanied by slight superficial ulceration. This phase usually occurred about three weeks after the beginning of treatment, but in some cases as early as the first week. The patches became slightly thicker and redder, and there soon was seen scaling and desquamation which lasted for several weeks. In cases classed as "medium" and "minor" these changes were far less marked, and sometimes they were not observed.

This early increase of inflammation in the skin lesions was, very fortunately, usually not accompanied by a change in the nerves sufficient to cause symptoms such as severe pain, or increase in trophic lesions.

(*b*) *The phase of subsidence.*—Following quickly on the early response and desquamation, particularly in major tuber-

TABLE 1.—*Details of tuberculoid cases before and after treatment.*

Case No.	Before treatment: Skin lesions No. & site *a*	Before treatment: Nerve lesions degree *b*	Before treatment: Trophic lesions degree *b*	Treatment: Drug used *c*	Treatment: Time treated (weeks)	After treatment: First visible response (weeks)	After treatment: Subsidence of skin lesions (weeks)	After treatment: Nerve thickening (change) *d*	After treatment: Nerve tenderness (change) *d*	After treatment: Trophic lesions (change) *d*	Remarks
1. *Major tuberculoid cases*											
1	50 L	Mkd	Slt	Spt	7	?	24	Less	Gone	Gone	
2	50 L	Slt	Nil	Spt	48	?	24	Less	Gone	Nil	Dermatitis, 5th week.
3	(C) S	Slt	Nil	Spt	96	3	24	Gone	Gone	Nil	Originally B + *f*
4	60 L	Slt	Nil	Spt	60	3	26	Gone	Gone	Nil	
5	6 L	Mkd	Mkd	DDS	50	2	15	Less	Gone	Unch.	
6	16 L	Mod	Nil	DDS	48	3	20	Unch.	Gone	Nil	Reactivation, 2 months. *g*
7	12 L	Mkd	Mod	DDS	66	3	30	Less	Gone	Unch.	
8	15 L	Mkd	Mkd	DDS	54	2	25	Less	Gone	Incr.	
9	(C) S	Slt	Slt	DDS	52	?	21	Unch.	Gone	Slt	
10	(C) S	Slt	Nil	DDS	52	2	24	Gone	Gone	Nil	
11	6 S	Mkd	Nil	DDS	52	2	28	Unch.	Gone	Nil	
12	(C) S	Slt	Nil	DDS	52	4	25	Less	Gone	Incr.	Developed psychosis.
13	50 L	Mkd	Nil	DDS	25	1	—	Unch.	Less	Nil	
14	(C) S	Mkd	Mkd	DDS	24	2	24	Less	Gone	Unch.	
15	20 L	Mod	Slt	DDS	24	3	24	Less	Gone	Unch.	
16	12 L	Mod	Nil	DDS	24	2	—	Unch.	Less	Nil	
17	10 L	Mod	Nil	DDS	20	1	20	Unch.	Gone	Nil	
18	50 L	Mkd	Mod	DDS	20	2	20	Less	Gone	Less	Originally B + *f*.
19	12 L	Mod	Slt	DDS	20	2	—	Unch.	Less	Unch.	
20	60 L	Mod	Nil	DDS	12	1	—	Less	Gone	—	
21	12 L	Mod	Nil	DDS	12	3	—	Unch.	Unch.	—	
2. *Medium tuberculoid cases*											
22	50 S	Mod	Nil	Spt	110	?	25	Gone	Gone	Nil	
23	12 L	Mod	Nil	DDS	67	3	12	Gone	Gone	Nil	
24	6 L	Slt	Nil	Spt	65	3	20	Gone	Gone	Nil	
25	9 M	Mod	Mod	Spt	61	?	24	Less	Gone	Unch.	
26	20 M	Slt	Nil	Spt	33	?	?	Gone	Gone	Nil	Treatment intermittent.
27	(C) S	Slt	Nil	DDS	53	2	17	Gone	Gone	Nil	
28	25 L	Slt	Slt	DDS	64	3	36	Gone	Gone	Incr.	Claw hand developed.
29	(C) S	Nil	Nil	DDS	5	3	24	Nil	Nil	Nil	Dermatitis, 5th week. *h*
30	(C) S	Mkd	Mod	DDS	70	3	28	Less	Gone	Unch.	
31	(C) S	Mod	Nil	DDS	21	3	20	Less	Gone	Nil	

Case No.	Before treatment: Skin lesions No. & size[a]	Before treatment: Nerve lesions, degree[b]	Before treatment: Trophic lesions degree[b]	Treatment: Drug used[c]	Treatment: Time treated (weeks)	After treatment: First visible response (weeks)	After treatment: Subsidence of skin lesions (weeks)	After treatment: Nerve thickening (change)[d]	After treatment: Nerve tenderness (change)[d]	After treatment: Trophic lesions (change)[d]	Remarks
	2. *Medium tuberculoid cases*										
32	(C) S	Mod	Slt	DDS	20	3	20	Unch.	Unch.	Unch.	
33	30 M	Mod	Mod	DDS	17	4	—	Unch.	Unch.	Unch.	
34	12 M	Slt	Nil	DDS	5	3	17	Unch.	Less	Nil	Dermatitis, 5th week. [h]
35	60 S	Slt	Nil	DDS	17	4	16	Gone	Gone	Nil	
36	6 L	Mod	Mod	DDS	13	4	—	Unch.	Unch.	Unch.	
37	10 L	Nil	Nil	DDS	13	3	12	Nil	Nil	Nil	
38	12 M	Mkd	Nil	DDS	12	3	—	Unch.	Less	Nil	
39	(C) S	Mkd	Slt	DDS	10	3	—	Unch.	Less	Unch.	
40	30 M	Mkd	Mod	DDS	9	4	—	Unch.	Unch.	Unch.	
	3. *Minor tuberculoid cases*										
41	50 S	Mkd	Mkd	Spt	68	?	24	Less	Gone	Less	Drop-foot recovered.
42	60 S	Mod	Nil	Spt	98	?	30	Less	Gone	Nil	
43	12 L	Nil	Nil	Spt	67	?	30	Nil	Nil	Nil	
44	(C) S	Slt	Nil	DDS	38	?	24	Gone	Gone	Nil	
45	3 L	Nil	Nil	DDS	55	3	42	Nil	Nil	Nil	
46	(C) S	Mod	Mkd	DDS	28	4	—	Unch.	Less	Unch.	
47	50 M	Slt	Nil	DDS	18	2	16	Unch.	Less	Nil	
48	35 S	Mod	Slt	DDS	22	2	20	Unch.	Less	Nil	
49	36 M	Mod	Slt	DDS	18	?	16	Unch.	Less	Unch.	
50	40 S	Nil	Nil	DDS	18	?	—	Nil	Nil	Nil	

a Approximate number and relative size on the whole. (C) signifies "hundreds" of lesions. L = large; M = medium; S = small.

b Degrees of nerve and trophic changes: Mkd = marked, severe; Mod = moderate; Slt = slight; Nil = none.

c Spt = sulphetrone; DDS = diaminodiphenyl sulfone.

d Unch. = unchanged, as before; Nil = no lesion before treatment.

e Unch. = unchanged, as before; Incr. = increased; Nil = previous condition cleared up (the minus sign used where there was "nil" before treatment).

f This patient was bacteriologically positive at the outset of treatment but rapidly became negative.

g This patient was discharged after 12 months of treatment and had a reaction 2 months later (see text).

h Treatment stopped in the 5th week on account of the sulfone dermatitis.

culoid lesions, there was a phase of progressive subsidence of thickening and of inflammation which started usually after about one month. By the end of six months, as a rule, these lesions were no longer elevated, and on being picked up between thumb and finger they were found no thicker than the surrounding skin. Moreover, there was definite visible evidence of shrinkage and subsidence, the epidermis being wrinkled and thin and atrophic. Loss of pigment was usually still obvious, and loss of sensation persisted. In "medium" and "minor" lesions the signs of subsidence, though present, were much less obvious; the lesions slowly became inactive and "residual."

During the same period, the tenderness usually disappeared from the affected nerves, although thickening was usually undiminished.

(*c*) *The later phases.*—After subsidence of signs of inflammation of the skin lesions, further changes in them were slight and very slow in developing. Observations during the following six months or one year showed a gradual return of pigment in some cases. This change was most marked in the "minor" lesions, which might become almost invisible, and least marked in the "major" lesions, which remain visible for an indefinite period. The same is to be said of the return of skin sensation, which in "minor" lesions may be complete but in "major" lesions is partial or does not occur.

During this same period, improvement in the affected nerves usually becomes obvious. Any residual tenderness disappears, and the nerves become thinner, but severely affected ones rarely return to normal size.

The effect of these nerve changes on any paralytic lesions in their distribution is very variable. In a few cases, trophic lesions have diminished or disappeared. We have seen recovery of facial palsy in one case, and of drop foot in two. In most cases, however, paralytic lesions remain unchanged by treatment, while in some they actually increase during treatment. For example, in two cases with very thick ulnar nerves but no deformity of the hands, the nerve thickening gradually became less but at the same time the hand became deformed by ulnar palsy.

Trophic ulcers of the feet associated with damage to the tibial nerve were present in a few of the cases here recorded, and they showed no marked tendency to healing under sulfone treatment. There was, however, a beneficial effect in controlling secondary bacterial infection.

Case report.—The following case report (Case No. 1) records

a marked response to treatment, but it is fairly characteristic of the response seen in major tuberculoid cases.

Examination made on March 16, 1948: Female, aged 10. The general condition is very poor; emaciation. There are numerous large major tuberculoid lesions, thick, red and inflamed, widely scattered throughout the body. Smears show no acid-fast bacilli. The following nerves are thick and tender: right great auricular; right ulnar; branches of the medial cutaneous nerve of forearm, of the right radial, right ulnar, and right median at the wrist; both external peroneals; both superficial peroneals; both superficial peroneals at the ankle; both posterior tibial nerves at the ankle; and cutaneous nerves on inner and outer sides of both feet. The left arm nerves are normal. There is wasting of the small muscles of the right hand.

Comments: Extensive active major tuberculoid lesions, with marked and extensive nerve involvement, apparently the result of a "tuberculoid reaction." Because of the marked nerve damage—the right ulnar and both posterior tibial nerves are enormous—trophic lesions appear inevitable. Sulfone treatment in this case must be carefully watched and regarded as experimental.

Treatment was delayed for three months during which time the lesions increased rather than diminished. Treatment with sulphetrone was started on June 1st, 1948. In July: "Patches still thick and red; nerves thick and tender." In August: "Patches thinner, nerves less tender." In November: "Patches all flat and nerves less swollen and not tender. Activity much reduced since sulfone treatment, but this may be due to natural subsidence."

Nearly one year later, in October 1949, the following note was made: "Activity of patches gone. Nerve thickening much less; the right ulnar now only a fraction of its previous size; no claw hand or drop foot had developed." In November, however, the opinion was recorded that the fibrosis of the left peroneal nerve might lead to drop foot. Treatment was then stopped, after 18 months, and the patient was discharged, still showing depigmented but inactive patches in various parts of the body with some loss of sensation; while the other nerves were almost normal in size, the peroneal nerves were still thick but not tender.

The patient, who returned for reexamination in March and June 1950, shows no recurrence of activity, no trophic lesions, and a great improvement in general health and appearance. Though the patches on the buttocks and thighs are still easily visible, they are flat and residual; the patches on the face and arms have almost faded.

Permanence of the results of treatment.—The response of tuberculoid lesions to treatment was so striking and constant that, in view of the relative high degree of immunity believed to exist in patients with such lesions, it was decided to stop treatment of certain cases after 12 months and observe them for evidence of relapse. This has been done in 12 cases, and the periods of observation of these now vary between 2 and 15 months. So far, recurrence of clinical activity has been seen in only one case. That recurrence occurred within two months of

the cessation of treatment; moreover, there were no new lesions, the recurrence being confined to the sites of the old lesions. Upon resuming treatment this activity rapidly subsided.

TUBERCULOID CASES IN TESTING NEW DRUGS

The response of major tuberculoid cases to treatment is so marked that it appears justifiable to consider using this response as a test of the activity of new drugs, or of the effectiveness of varying dosages. This has been done to a certain extent, with interesting results here mentioned briefly.

Sulfones in normal doses produced a definite response within a month, sometimes within a few days. On the other hand sulphetrone in very small doses (.25 gm. a day) produced no response in six weeks.

Para-aminosalicylate, 15 gm. a day, produced no response in tuberculoid cases in six weeks. In lepromatous cases it gave no definite response in six months.

Hydnocarpus oil injections, intramuscular and subcutaneous, produced no definite response in two months.

Streptomycin, 1 gm. a day, produced a very definite response within one week. No trials have yet been made in lepromatous cases.

We think that these results give a clear indication that the two most active agents in leprosy are sulfones and streptomycin, and that the most effective treatment of leprosy is probably the use of these two drugs in combination. This matter is now being further studied.

It appears probable that any drug which does not produce a definite response in major tuberculoid cases in one month is unlikely to be of much value in the treatment of any form of leprosy.

DISCUSSION

I have previously recorded (11) that, in tuberculoid cases of leprosy, widespread clinical activity can arise, last a few months, and then subside for long periods without any treatment. In northeast India it was found (15) that tuberculoid activity frequently appeared in the hot season, and gradually subsided during the rainy season which followed. The question arises whether the subsidence of clinical activity here recorded under sulfone treatment may not have been a similar phenomenon.

In considering the matter there is, firstly, the fact that in this part of Nigeria tuberculoid activity is often persistent and

shows little or no tendency to vary with season, or to subside spontaneously (16). Secondly, there is the fact that a number of the cases here recorded were observed for some time before sulfone therapy was begun, and during that period they showed no tendency to subsidence; sometimes, indeed, there was an increase of activity, often in spite of treatment with injections of hydnocarpus oil. Thirdly, in the cases here recorded treatment was begun in all of the different seasons during a period of two years, and much the same response was seen at all seasons.

Furthermore, certain control observations were made. In one case, treatment was accidently delayed for three months from the time the case was accurately recorded, and during this time clinical activity increased; the beginning of treatment was quickly followed by subsidence of activity. In three other cases, treatment with another drug, para-aminosalicylate, or with sulphetrone in the minute dose of .25 gm. a day, was given for several weeks with no appreciable response; but response followed at once on the institution of sulfone treatment with adequate dosage.

Finally, there is the finding that in fifty consecutive cases, unselected except for their activity, the institution of sulfone treatment was followed in every case by a response which within one year led to the disappearance of all signs of activity in skin and nerve, although nerves frequently remained hard and fibrous. These results are far too constant, too rapid and too striking to be attributable to spontaneous subsidence. Without treatment, in some patients the lesions may subside, in others they will remain active, and in still others they may increase. Subsidence in all of fifty cases can only be due to treatment.

It may be asked why other workers have not reported similar results. When this work was started, no favorable reports had been published. While this work was in progress, de Souza Lima (20) reported that sulfone treatment had a marked effect in producing subsidence of activity in active tuberculoid cases, but had no effect whatever on the nerve lesions. Our preliminary reports of good results in tuberculoid cases (13, 14, 16) are now supported by Molesworth (personal communication) and others (10).

The reason for the delay in establishing the value of sulfones in tuberculoid cases probably lies in the fact that in the leprosaria of the Western Hemisphere, where sulfones were first widely used, few active tuberculoid cases were available for

treatment, while in Africa and Asia, although many active tuberculoid cases are available for study, the very limited supplies of expensive sulfones were purposely reserved for the more severe infectious lepromatous cases. This was encouraged by the published statements that sulfones are of little or no value in nonlepromatous cases. It is also possible that some workers were led to interpret the early mild focal reaction in the lesions as an exacerbation or aggravation of the disease, and did not continue treatment long enough to observe the real results. The problem of making sulfone treatment available to all active cases of leprosy, irrespective of the type of the disease, has been solved it is believed by the introduction of the inexpensive mother substance diaminodiphenyl sulfone in treatment (1, 2, 9, 14, 17), and especially by the demonstration of the suitability of the oral route (14, 16) and that twice weekly treatment suitable for outpatients is effective (14, 16, 17).

The facts reported in this paper justify the conclusion that sulfone treatment is the one of choice in tuberculoid cases. It is already generally accepted that it is the one of choice for lepromatous cases. There remain only the so-called "medium" or "uncharacteristic" cases; and a few of these have been seen and treated here with good results. The conclusion, therefore, is that sulfone treatment should be employed in active leprosy of all forms, and that it can and should replace treatment with hydnocarpus oil and its derivatives.

Here in Nigeria it has one limitation: the cosmetic effect of the treatment is often not enough to obscure the "residual" depigmentation, which is often very obvious in our dark-skinned people. Moreover, the effect of the treatment on trophic lesions is preventive rather than curative. It may be difficult to persuade a patient, and even more difficult to persuade the people in his village, that a residual depigmented patch or a deformed hand does not mean that the disease is still active. To overcome one part of this difficulty, it may sometimes be necessary to adopt some form of cosmetic treatment to make the residual inactive skin lesions less obvious, as intradermal injections of some preparation which will darken the skin. Iodized oils, hydnocarpus oil, or any other available oil which is suitable, have been suggested for this purpose. But such treatment should be regarded only as cosmetic treatment. Active leprosy of any kind calls for sulfone therapy, until some more rapidly active therapy replaces it.

SUMMARY

At the outset of the use of the sulfones in leprosy they were used exclusively for the treatment of lepromatous cases, and in general they have continued to be so used. In consequence of this and other considerations the idea has grown that these drugs are not of value in other forms of the disease.

This view seeming illogical, we undertook to treat tuberculoid cases with sulphetrone and, especially diaminodiphenyl sulfone (DDS), and more than fifty have been so treated. The present report is of the first fifty cases, taken as they presented themselves with no selection except for the requirement that they should have active skin lesions.

All of these cases responded to the treatment. After a preliminary phase of focal reaction in the skin lesions, best seen in the major tuberculoid cases, the signs of activity slowly subsided, and usually within six months the lesions became inactive and "residual," showing only varying degrees of atrophic wrinkling, loss of pigment and of cutaneous sensibility. The signs of activity in the nerves—thickening, tenderness, and sometimes pain —subsided much more slowly, and while tenderness and pain disappeared thickening often persisted.

The sulfone drugs constitute the therapy of choice in tuberculoid as well as lepromatous cases, and there is reason to believe that they are more effective than other drugs in simple macular cases as well.

REFERENCES

1. COCHRANE, R. G. A comparison of sulphone and hydnocarpus therapy of leprosy. Internat. J. Leprosy **16** (1948) 139-144.
2. COCHRANE, R. G., RAMANUJAM, K., PAUL, H. and RUSSELL, D. Two-and-a-half years' experimental work on the sulphone group of drugs. Lep. Rev. **20** (1949) 4-64.
3. COCHRANE, R. G. General principles in the treatment of leprosy with particular reference to the sulphones. Lep. India **21** (1949) 83-86.
4. ERICKSON, P. T. and JOHANSEN, F. A. Bone changes in leprosy under sulfone therapy. Internat. J. Leprosy **16** (1948) 147-156.
5. FAGET, G. H. Chemotherapy of leprosy. Internat. J. Leprosy **15** (1947) 7-14.
6. FAGET, G. H. and ERICKSON, P. T. Chemotherapy of leprosy. J. American Med. Assoc. **136** (1947) 451-457.
7. FAGET, G. H., POGGE, R. C. and JOHANSEN, F. A. Present status of diasone in the treatment of leprosy; brief clinical note. Pub. Hlth. Rep. **61** (1946) 960-963.
8. FAGET, G. H., POGGE, R. C., JOHANSEN, F. A., DINAN, J. F., PREJEAN, B. M. and ECCLES, C. G. The promin treatment of leprosy; a progress report. Pub. Hlth. Rep. **58** (1943) 1729-1741.

9. FLOCH, H. and DESTOMBES, P. Traitement de la lèpre par la "sulfone-mère" (diamino-diphenyl-sulfone). Internat J. Leprosy **17** (1949) 367-377.
10. HAMERS, A. L. T. M. and HERMANS, E. H. Lepratherapie met sulfonamides. Nederlandsche Tijdschr. v. Geneesk. **93** (1949) 2345-2350.
11. JOHANSEN, F. A. and ERICKSON, P. T. Promizole treatment of leprosy; a progress report. Internat. J. Leprosy **15** (1947) 378-379.
12. LOWE, J. A study of macules in nerve leprosy with particular reference to the "tuberculoid" macule. Lep. India **8** (1936) 97-112.
13. LOWE, J. Sulphone treatment of leprosy. Lep. Rev. **9** (1948) 129-138.
14. LOWE, J. Treatment of leprosy with diamino-diphenyl-sulphone by mouth. Lancet **1** (1950) 145-150.
15. LOWE, J. and CHATTERJEE, S. N. Seasonal variations in leprosy in Calcutta. Internat. J. Leprosy **7** (1939) 137-148.
16. LOWE, J. and SMITH, M. The chemotherapy of leprosy in Nigeria. Internat. J. Leprosy **17** (1949) 181-195.
17. MOLESWORTH, D., NARAYANASWAMI, P. S. and SIMPSON, I. A. Treatment of lepromatous leprosy with 4:4′-diaminodiphenyl sulfone in oil; findings in 100 cases treated for one year; with a note on the technique of sulfone determination. Internat. J. Leprosy **17** (1949) 197-210.
18. MUIR, E. Diasone in the treatment of leprosy. Lep. Rev. **17** (1946) 87-95.
19. MUIR, E. The sulphone treatment of leprosy. British Med. J. **1** (1947) 798-801.
20 DE SOUZA LIMA, L. Present status of sulfone therapy at the Padre Bento Sanatorium. Internat. J. Leprosy **16** (1948) 127-137.