The Efficacy of Sulfone Therapy in Leprosy[1]

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The history of the introduction of the sulfones, and particularly of dapsone (4,4′-diaminodiphenyl sulfone), into the chemotherapy of leprosy has been thoroughly reviewed by Chang and his co-authors ([1]), by Doull ([4]), and by Wade ([17]) in the correspondence pages of the INTERNATIONAL JOURNAL OF LEPROSY. Briefly, Faget and his co-workers at Carville explored a variety of substituted dapsones beginning in 1941 with Promin ([5]), the *bis* (N-glucose sodium sulfonate) of dapsone. Dapsone in a rather large parenteral dose was first employed in 1946 by Cochrane ([2]), who found it too toxic for routine use. During the next year, Lowe ([10]) began its use as an oral agent in more moderate dosage.

During the succeeding twenty years, sulfones have become firmly established in the chemotherapy of leprosy. Although there is now no serious question regarding the status of sulfones in the therapy of leprosy, it seems important, nevertheless, to review the evidence for the efficacy of sulfones. After all, for many years before the intro-

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duction of sulfone therapy, chaulmoogra oil preparations were firmly established in the treatment of leprosy, and their use was as widespread—although perhaps not as unquestioned—as is that of the sulfones today.

The scientific literature relating to sulfone therapy is now quite extensive. Only a very small number of published studies, however, yield evidence that withstands critical scrutiny. The discussion that follows will deal with the efficacy of sulfone therapy only in lepromatous leprosy. Most of the discussion will deal with dapsone therapy; therapy with dapsone derivatives will be much more briefly considered. Finally, some evidence relating to the mimimal therapeutic dose of dapsone will be summarized, and a few comments will be made regarding clinical trials of therapy in lepromatous leprosy.

EARLY CLINICAL STUDIES

The earliest study requiring careful consideration is that of Lowe ([8]) in 1954, who reviewed the status of 123 consecutive patients with lepromatous leprosy whose dapsone therapy was initiated between March 1946 and May 1948. Fourteen patients were excluded from analysis, including two patients who died, three who left the leprosarium against medical advice, and nine who were transferred elsewhere for treatment. The results of therapy in the remaining patients are summarized in Table 1. Of the 109 patients available for analysis, 97 (89%) had achieved the status of arrested disease, defined by a minimum of 24 months of treatment, and smears made from lesions, at an unstated interval, that had remained negative "in most cases" for 12 months. The remaining 12 patients appeared clinically to have arrested disease, but smears of lesions continued to demonstrate a few bacilli "so abnormal in morphology that they appear to be the remains of bacilli disintegrating rather than living bacilli" ([9]). In none of these patients did Lowe observe the phenomenon of initial improvement followed by deterioration.

Lowe's study was uncontrolled, and very likely he included patients with borderline leprosy (one presumes that among the patients with the smaller bacterial loads were patients with BB and BL disease according to the classification of Ridley and Jopling ([14]). Despite these reservations, Lowe's data seem to offer incontestable proof of the efficacy of dapsone therapy in lepromatous leprosy.

TABLE 1. *Results in lepromatous leprosy after 6 to 8 years of dapsone therapy.*[a]

Patients	No.
Arrested and discharged	77
Arrested, awaiting discharge	17
Arrested, but died or absconded before discharge	3
With clinical arrest, but smears showing a few bacilli	12
TOTAL	109

[a] Adapted from Lowe ([8]).

As impressive as the data on response to original treatment with dapsone are Lowe's data relating to relapse ([8]). Of 162 patients with lepromatous leprosy whose disease had become arrested after an average of 28 months of dapsone treatment, 148 had been discharged for an average of 22 months preceding Lowe's review. The data from the 94 per cent of these patients who had been reexamined at least once are presented in Table 2.

Of 130 patients available for analysis in this study of relapse, 124 (95%) demonstrated no evidence of relapse; two with symptoms of neuritis were felt to represent mild clinical relapse, while 13 in whom smears revealed a few bacilli were said to represent mild bacteriologic relapse.

TABLE 2. *Relapse after arrest of lepromatous leprosy with dapsone therapy.*[a]

Patients	No.
With no evidence of relapse	124
With recurrent "neuritis"	2
With a few bacilli in smears	13
Not reexamined	9
TOTAL	139

[a] Adapted from Lowe ([8]).

It is important to note that Lowe's patients were not discharged on chemotherapy. He states of the "neuritis" that it disappeared within a few weeks of the resumption of therapy. Of the 13 with bacteriologic relapse, three were readmitted for treatment and rapidly became negative, two were referred elsewhere for resumption of treatment, and the remaining eight were not retreated, but were observed at intervals. Of the six who reported for reexamination, five were negative, while the sixth again showed a few bacilli with no other evidence of relapse. In 12 of the 15 cases demonstrating relapse, less than 12 months had elapsed since discharge from the leprosarium, and no relapse occurred later than 23 months following discharge. Lowe questions the significance of the finding of a few bacilli without clinical evidence of relapse, and suggests that these bacteriologic relapses may not be of serious importance.

The work of Muir ([12]) with oral dapsone therapy in lepromatous leprosy must be mentioned in passing. In 1951 he reviewed the progress of 58 patients with lepromatous leprosy who had completed at least one year of treatment with dapsone. Although he noted "granulation" of bacilli in smears made after a few weeks of treatment, which progressed to fragmentation and "absorption"—meaning presumably, the disappearance of the acid-fast fragments—he employed the bacteriologic index (BI) to measure the response to therapy while stating his reservations with respect to the method. The average decrease of the BI in the 58 patients was 70 per cent. This study also was uncontrolled, and suffers from methodologic deficiencies not found in Lowe's study. Lowe ([8]), along with Muir ([12]) and more recent authors ([20]), recognized the slowness of the fall of the BI, which is at best imprecisely measured, but because Lowe studied his patients up to the point of bacteriologic negativity, he did not need to rely on small changes in the BI for evidence of response to therapy. In spite of the deficiences in Muir's study, the decrease of the BI in 39 of 58 patients (67%) in as short a time as one year compared with no change in 15 (26%) and a slight increase in only 4 (7%), suggests that a response to therapy had occurred.

CONTROLLED CLINICAL TRIALS

Remarkably few controlled clinical trials of sulfone therapy have been carried out. Noordeen, in his recent review of 104 treatment trials in leprosy ([13]), found only 10 that were adequately designed, not all dealing with sulfones.

Perhaps the first controlled trial of a sulfone is one carried out at Carville, in which Promacetin (sodium 4,4′-diaminodiphenyl sulfone-2-acetylsulfonamide) was administered for more than nine months to 20 patients with lepromatous leprosy, while an identical appearing placebo was administered to a control group of 20 patients matched for type and stage of the disease. These patients very likely had not previously received sulfones, since the trial is briefly described in Faget's original report of sulfone therapy published in 1943 ([5]). Assessment was made almost solely on clinical grounds; the results are summarized in Table 3.

TABLE 3. *Assessment nine months after initiation of Promacetin trial.*[a]

	Control	Promacetin
Total number of patients	20	20
Leprosy improved	1	6
" stationary	9	5
" worse	5	3
Complications only improved	0	5
Complications worse	5	1
Bacteriologically negative	0	2

[a] Adapted from Faget *et al.* ([5]).

It may be noted that six of the Promacetin patients experienced clinical improvement, and an additional five experienced improvement from "complications" defined as "chronic ulcerations, leprous rhinitis, leprous laryngitis, and iridocyclitis;" only four experienced worsening of the leprosy or its complications. Of the control patients, on the other hand, only one experi-

TABLE 4. *Assessment of a trial of dapsone* vs *placebo.*[a]

Treatment	Length of trial: 32 weeks — *Clinical assessment* — No. pts.	Per cent: Impr.	Stat.	Worse	Length of trial: 48 weeks — *Clinical assessment* — No. pts.	Per cent: Impr.	Stat.	Worse
Dapsone	49	16.3	88.7	—	47	27.7	68.1	4.2
Placebo	56	1.8	71.4	26.8	52	3.8	57.7	38.5
	Bacteriologic assessment							
		△ BI				△ BI		
Dapsone	49	0.89			47	0.93		
Placebo	56	0.62			52	0.53		

[a] Adapted from Doull (3).

enced improvement in his disease process, while 10 experienced worsening of their leprosy or its complication.

These data leave much to be desired. The initial BI's are not stated. That changes in the BI are not reliable indications of response to therapy when these changes are measured over a period as short as one year, has already been suggested, and one year is certainly insufficient if the criterion of response is to be "conversion" of the skin smears. Changes in the clinical appearance of the patient, the primary criterion of response employed in this trial, are at best difficult to quantitate, and may certainly be misleading.

The first extensive controlled trial of sulfones in lepromatous leprosy was that carried out by the Leonard Wood Memorial in the Philippines and elsewhere, and reported by Doull (3). The trial included among the six treatment groups a group of patients on dapsone and another on placebo. The trial was carried out for 48 weeks at two institutions, and for 32 weeks at two others. The data relating to a comparison of dapsone and placebo are presented in Table 4.

Patients were assessed both clinically and bacteriologically. The clinical status at the end of the trial was determined to be improved, stationary, or worse. The change in the BI was averaged for each group by a complicated scoring technic; possible scores ranged from —1 to 2; the higher the score, the more favorable was the change in the BI. Differences between the dapsone and placebo groups were found to be statistically significant, although the clinical assessment yielded far more striking results than did the bacteriologic. Here, also, then, is evidence of the efficacy of sulfone therapy.

Several inadequacies of experimental design are evident. The trial was conducted in "single-blind" rather than "double-blind" fashion. The majority of the patients in each group had had prior sulfone therapy, and bacteriologic assessment was by means of changes in the BI.

There seems *a priori* a disadvantage in identifying to the clinical investigators conducting a trial the patients included in the placebo group. Although the investigators may have no particular preference for one of the drug-containing regimens over any of the others, it seems likely that the lack of efficacy of the placebo regimen may be prejudged. Since the design of the trial permitted immediate withdrawal of any patient showing intolerance to the drug or worsening of the disease, at the discretion of two clinicians, at which point the trial

was considered completed, one suspects that knowledge of the trial regimen may have permitted some bias in judging results of therapy. Many double-blind clinical trials including a placebo regimen have demonstrated virtually as much intolerance to the placebo as to the active drugs. And it seems likely that, in a situation that might possibly represent worsening, the anxiety of the responsible clinicians would be much greater if the patient were known to have been included in the placebo group than if the nature of his treatment were unknown.

Doull's report ([3]) describes as "insignificant" the prior sulfone therapy at the Eversley Childs Sanitarium in Cebu—the institution in which placebo and dapsone were compared for 48 weeks. And indeed, if one regards the therapeutic dose of dapsone to be 50 to 100 mgm. daily, only insignificant sulfone therapy had been experienced by these patients prior to the initiation of the trial. But in the light of accumulating evidence, to be considered later, that the therapeutic dose of dapsone is much smaller than 50 to 100 mgm. daily, the lack of significance of prior sulfone therapy in this group of patients seems less certain. Of the more than 300 patients in all treatment groups who completed the trial at Eversley Childs, only about 30 had had no prior sulfone therapy.

The most recent controlled clinical trials that yield evidence of efficacy of the sulfones are those carried out in Sungei Buloh by Waters ([18]) and Waters and Pettit ([19]). These trials were designed and conducted after the relationship between the morphology and viability of *M. leprae* had been suggested, and, in fact, their results have provided strong support for this hypothesis. Their recency, in one way advantageous to the success of these trials, has also resulted in one disadvantage. By the time these trials were initiated, the efficacy of sulfones had become so widely accepted that it was no longer possible to compare dapsone with a placebo. Despite this handicap, these trials have produced gratifying evidence of efficacy of sulfones in the form of a uniform fall in the ratio of solidly stained to nonsolidly stained *M. leprae*, which occurred during the first few months of therapy with dapsone. These data, taken together with the demonstration by Shepard and McRae ([15]) of the relationship between the morphology of *M. leprae* and the ability of the organisms to multiply in the mouse foot pad, provide additional evidence for a therapeutic effect of sulfones in leprosy.

In summary, efficacy of sulfone therapy in lepromatous leprosy seems to have been established by the long term study of Lowe, which demonstrated the arrest of the disease process in almost all of a large number of leprosy patients by dapsone given over a long period of time, and also by the short term studies of Waters and Pettit, which demonstrated the uniform early change in the morphologic characteristics of the infecting organisms during dapsone therapy.

Except for the trial of Promacetin at Carville, all of the evidence for the efficacy of sulfones in lepromatous leprosy adduced thus far has come from trials of dapsone. Many clinical trials of dapsone derivatives and related compounds have been reported. Because with but few exceptions these compounds act through degradation to dapsone, little more needs to be said about them in terms of efficacy. Suffice it to say that both Muir ([11]) and Fernández and Carboni ([6]) have reported that increasing granularity of *M. leprae* accompanied the clinical improvement occurring with sulfoxone (Diasone) therapy. The use of these drugs in lepromatous leprosy is worthy of consideration in another context, viz., the therapeutic dose of dapsone.

Lowe has reported ([7]) some ingenious studies with Sulphetrone, Promin, and sulfoxone, which relate both to their mechanism of action and also to the matter of the therapeutic dose of dapsone. Sulphetrone was found in tablet or crystalline form to contain 0.25 to 0.3 per cent dapsone, a proportion that was increased 20-fold or more by autoclaving in dilute solution for one hour; dilute solutions were found, furthermore, to be unstable even at refrigerator temperature. When Sulphetrone was given orally, 1 gm. was found to yield a blood dapsone concentration equivalent to

that resulting from 14 mgm. of dapsone. Sulfoxone tablets were found to contain approximately 0.2 per cent dapsone, and the blood dapsone concentrations Lowe reported after various doses of sulfoxone suggest that a 300 mgm. sulfoxone tablet is roughly equivalent to 13 mgm. of dapsone. Thus, Muir's patients who took six sulfoxone tablets daily received the equivalent of 78 mgm. of dapsone daily. And the patient whose disease process responds to 300 mgm. of sulfoxone daily is receiving only about 90 mgm. of dapsone per week. Lowe's study of Promin gave similar results. The drug injected intravenously in a dose of 4 gm. daily yielded a blood dapsone concentration roughly equivalent to that produced by 30 mgm. of dapsone orally daily.

Shepard and his co-workers ([16]) have recently reported that a concentration of dapsone in the feed 1/10 of the least concentration giving detectable blood levels in the mouse, regularly inhibited the multiplication of *M. leprae* in the mouse foot pad. Shepard estimated that this intake of dapsone produced a blood dapsone concentration of 0.03 μgm./ml.; on the basis of calculation from Lowe's observation of 0.9 μgm. dapsone/ml. of blood as a result of a daily dose of 15 mgm. dapsone, a daily dose of only 0.5 mgm. is required for a blood dapsone concentration of 0.03 μgm./ml. It is unquestionably extremely hazardous to extend the results in the mouse to man. Shepard's work, on the other hand certainly suggests that doses of dapsone in man a good deal smaller than the traditional 300 to 600 mgm./week may well be therapeutic, a suggestion reinforced by observations of the efficacy of several dapsone derivatives in lepromatous leprosy.

Finally, it seems appropriate to comment on the general problem of chemotherapy trials in leprosy. The evidence for the efficacy of the sulfones in lepromatous leprosy has been hard-won; more than 25 years have passed since their first use in Carville. Earlier workers were certainly handicapped by the lack of precise methods for the measurement of chemotherapeutic efficacy, and none of the comments made here in retrospect should be construed as condemning these earlier workers because their experimental design, otherwise adequate, did not take into account knowledge that was not then available. One hopes, on the other hand, that it will not again be necessary to review so many inadequate trials to find evidence for the efficacy of some new compound 25 years hence. There is nothing magical about the double-blind and the control, and the incorporation of these features into a chemotherapy trial does not automatically insure that valid results will be obtained.

SUMMARY

Although sulfones have been employed in the treatment of leprosy since Faget's historic trial of Promin at Carville in 1941 and the first use of dapsone by Cochrane and his co-workers in India about 1946, surprisingly little evidence for the efficacy of these drugs has been produced which will withstand scientific scrutiny. Although it may seem unnecessary now to consider such evidence, because there is so widely held an impression of efficacy, it must be remembered that a similar impression of the efficacy of chaulmoogra oil in leprosy was held by some very influential proponents of its use.

Good studies of the efficacy of sulfone therapy have been few. Noordeen, who recently reviewed 104 clinical trials in leprosy, found only 10 studies, not all dealing with sulfone therapy, which were statistically well-designed, and from which valid data could be obtained. And many of the studies well-designed from the statistical viewpoint are inadequate because they were carried out before adequate methods for measuring the effects of the drugs were available. Because of the confused state of the literature, one may be tempted to accept clinical impressions in place of evidence.

There is, now, interest in defining the optimal sulfone regimen, and in comparing the efficacy of other drugs with that of the sulfones. A critical review of the evidence for efficacy of sulfone therapy in leprosy is therefore in order.

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DISCUSSION

Dr. Binford. I would like to make a few remarks in opening the discussion of Dr. Levy's paper. We who treated leprosy in the presulfone days saw the unremitting progress of lepromatous leprosy when it was treated with chaulmoogra oil; in two or three years the manifestations of lepromatous disease changed from mild lesions to extensive nodulation with all of the complications of the terminal stages of lepromatous leprosy. Now the efficacy of the sulfone drugs has changed that picture. At this point I would like to pay tribute to Dr. Faget, and his group at Carville, as Dr.

Levy has done. Dr. Faget went to Carville in 1940 after developing an intense interest in tuberculosis work in Public Health Service hospitals. Shortly after he reached Carville, his attention was called to a report by W. H. Feldman and others on the efficacy, in experimental tuberculosis, of Promin, a sulfone drug developed by Parke, Davis and Company. Dr. Faget made arrangements with Dr. E. A. Sharp, head of the Department of Clinical Investigation at Parke, Davis and Company, for trial in leprosy. Dr. Faget and his associates started with 22 patients in March 1941, trying Promin first by mouth. They found that patients could not tolerate it that way and from then on gave it intravenously. Results were assessed at the end of a year. This was not a double-blind experiment by any stretch of the imagination. There were no controls.[1] The clinicians knew what would have been expected under chaulmoogra therapy. We do not know the classification of all the patients. A number were recorded as mixed; so probably there were some borderline cases. About 10 were classified as purely lepromatous. At the end of the year 15 of the group had improved. Five were bacteriologically negative; i.e., repeated skin scrapings showed no bacilli. There were no bacterial indices at the time, and no assessments of solid versus nonsolid forms. Out of this uncontrolled experiment, however, a revolution was started in the treatment of leprosy. Last year, 25 years after Dr. Faget and his associates began their experiment, their original article, which was originally published in *Public Health Reports* in 1943, but not widely circulated among leprosy workers around the world, was reprinted in the INTERNATIONAL JOURNAL OF LEPROSY.

Dr. Hanks. Dr. Binford's remarks have caused me to reminisce. Dr. Faget once told me that before he and his group started the work on Promin they had made a trial run with sulfonamides. Dosages were incorrect and results not good. In any event, when they started the Promin work they included some patients who had been on sulfonamides for a period of four to six months. Dr. Faget told me that the patients in the Promin trials who first showed convincing improvement were those who had been on sulfonamides. It would be of interest for the eventual record if someone with access to the Carville records would check into this; perhaps a note could be incorporated officially in the record of factors contributing to early successes in the Promin trials.

Dr. Long. An ingenious retrospective study has been made by Dr. Levy himself on some of the early work. It would be interesting if he would tell the group something more about it.

Dr. Levy. Dr. Binford provided unstained sections from both pre- and post-48 week treatment patients in the placebo and DDS groups from the original trial at the Eversley Childs Sanitarium, Cebu, Philippines. These were stained and examined for bacterial morphology. The results, however, were rather disappointing, although they did seem to prove that DDS was better than the placebo. Many of the patients before treatment had had no demonstrable solidly staining leprosy bacilli. Furthermore, one group of females in the placebo group had a response to the placebo that was in every way identical with that of the DDS-treated patients. One might question the precision of the solid counting. Solid counts are much more difficult to perform on sections than on smears. The sections were of varying thickness and, although they were all stained at the same time and under standard conditions, they were sometimes quite difficult to examine. It was suspected that perhaps several factors might account for the initial solid counts of 0, and for the prompt response to placebo observed in a few patients. The discussion of the trial by Doull in his article in the INTERNATIONAL JOURNAL OF LEPROSY states that DDS concentrations were to be measured in the blood in random patients at random intervals. But there is no record of

[1] *Editor's note*: A brief account, however, of a controlled trial with another sulfone drug (later designated Promacetin) was recorded in the article. This controlled study apparently was started after the efficacy of Promin was demonstrated in the first 22 patients.

such determinations. I can, therefore, freely speculate that some of the patients may have had access to an illicit supply of DDS or sulfoxone. This is known to occur. Probably everywhere in the world patients have access to sulfone in some form or another. The Leonard Wood Memorial records contained rather complete notes regarding the amount of prior sulfone therapy. However, if sulfones were taken illicitly, these records would not be accurate. It would appear that a rather small number of tablets of sulfoxone taken at some unknown interval prior to the initiation of the trial were sufficient to produce a zero solid count. I had hoped to obtain some results striking enough to give further evidence of the efficacy of small doses of sulfones. I speculate that 44 tablets, on the average, were enough to result in a zero or very low solid count in otherwise untreated patients. And those who started with higher solid counts had taken a much smaller number of sulfoxone tablets, on the average.

Dr. Shepard. I feel that future chemotherapeutic trials in leprosy should incorporate regular measurements of blood and urine sulfones. The procedures are not difficult to carry out and do not require a specialized laboratory. In assessing a trial it is important to know the sulfone measurements in patients who are supposed to receive sulfone and in patients who are supposed to receive other drugs, so that two possible sources of error can be evaluated. One is that patients do not take their medication. Right in the middle of the trial one can find patients without detectable sulfones even though there is a recorded daily intake of DDS. The other source of error is that patients who nominally belong to a nonsulfone group do, in fact, take sulfones surreptitiously. If there are regular measurements of sulfones in blood or urine, at least once a month, one can assess the magnitude of these sources of error.

Dr. Levy. At a tuberculosis sanatorium in the Indian Service, the shower drains occasionally became clogged with PAS tablets. The patients were hospitalized, taking their medication, presumably, under the observation of the nurse. Dr. Rees and his group at Sungei Buloh have solved the problem by injecting the drug. There are alternatives, e.g., watching the patient actually swallow the pill and searching the mouth afterward. Finally—in response to Dr. Binford's comments—there are dangers in proving the efficacy of a drug by clinical impression alone. For example, if at some later date it became necessary to compare the efficacy of some other drugs with that of dapsone, one would need to have some carefully measured data for evaluation.

Dr. Rees. I would like to reinforce Dr. Levy's remarks. The collection of quantitative data, including those coming from the mouse foot pad model, becomes of the greatest importance if we are going to make DDS a more practical drug in the control of leprosy. It is necessary to know whether the drug can be given intermittently, or if it can be given as a depot. An important point in Dr. Levy's message is that all new trials must be planned in such a way that we can get valid answers as rapidly as possible.

Dr. Binford. This scientific review is very timely. The fact that this whole day is going to be spent on sulfones shows the need for the critical work that Dr. Rees has just mentioned. I would like to confirm Dr. Shepard's comments about the need for following patients to see whether or not they actually are getting DDS. In a study recently carried out in the Philippines, comparing another drug with DDS, the conclusion at the end of a year was that there was no significant difference in the two groups. On looking critically at the findings, it was realized that no precautions were taken to determine whether or not the patients who were on the experimental drug were taking dapsone (DDS) on their own. Because of failure to make spot checks for DDS in the experimental group we have hesitated to report this trial. We are much pleased that the U. S. Panel is developing a protocol to guide further drug studies so that valid conclusions can be made from the results of a study.