The Treatment of Leprosy with the Sulfones

I. Faget's Original 22 Patients. A Thirty-Year Follow-up on Sulfone Therapy for Leprosy[1]

R. R. Jacobson and J. R. Trautman[2]

Nearly three decades have now passed since the sulfones were first employed in the treatment of leprosy by Faget *et al.* (5) at Carville. Their reports on the results of this trial in 1943 (5) and 1945 (4) helped establish these drugs as the treatment of choice in leprosy—a position they have not relinquished. This in some ways was a rather fortuitous occurrence. Leprosy, especially in its lepromatous form, often requires many years of therapy before it is arrested, yet drug trials in this disease tend to be reported in the literature (as were Faget's) after a relatively short period of observation. This is nearly always less than five years and usually as little as 12 to 24 months. Such trials are in some ways akin to reporting on the value of a new drug for the treatment of tuberculosis after it has been in use only a few months, or one for pneumococcal pneumonia after using it only a few days. One could probably clearly decide whether a drug has some degree of effectiveness after such a short period of observation, but the ultimate value or place of the drug in the chemotherapy of the disease in question, and even more important its limitations, would remain unknown quantities. This is not intended as a criticism of all leprosy drug trials *per se* but rather of the paucity of information on the long-term follow-up of such trials. In the case of the sulfones, the experience gained with the passage of time has clearly established their value for the chemotherapy of leprosy and justified their position as the treatment of choice for this disease. It seems appropriate however, to look once again at the case histories of those patients who were treated in the early years of the "sulfone era" to see if we can now more fully assess the limitations of these drugs, granting that no other medications seriously challenge their preeminence at this time.

Carville's extensive records span the "sulfone era" and indeed date back long before to the turn of the century. More important, however, is the fact that the sulfones were first used here, and since this is the major leprosy treatment center in the United States, follow-up reports are available on a majority of the patients treated in this country. We are therefore in an excellent position to evaluate the long-term results of sulfone therapy and are now in the process of reviewing the case histories of most of the patients treated here since 1941. It will be some time before this study is completed; therefore the results will be the subject of several future articles. The present report will concern itself only with the first 22 patients to receive Promin, who were described in the article published by Faget *et al* in 1943 (5). We believe these findings are of sufficient interest to make such a report desirable since it is becoming more apparent that they are also applicable to many other patients treated with the sulfones over long periods of time.

CASE HISTORIES AND TABULATION OF DATA

In a manner similar to the outline of the original report on these patients, brief case histories are presented below. Table 1 summarizes some of the pertinent data on the group as a whole.

Case 869. A 55 year old Oriental male whose lepromatous leprosy probably began about a year prior to his first admission in 1932. He was started on Promin in March 1941, and although his disease was declared inactive in 1945 he continued on therapy until a month after his discharge in 1950. A year later he returned with active disease once again, and sulfones were reinstituted. The disease was apparently ar-

[1] Received for publication February 11, 1971.

[2] Robert R. Jacobson, M.D., Chief of Medicine, and John R. Trautman, M.D., Director, U.S. Public Health Service Hospital, Carville, Louisiana, 70721.

TABLE 1. *Results of Promin therapy.*

Case number	Type of disease	Onset of disease to start of Promin therapy (Years)	Start of Promin to negativity (Yrs)	Years negative	ENL	Progression of neurologic deficits after the start of Promin	Status of disease currently or at the time of death
869	Lepromatous	10	4	6(2)[d]	No[e]	Yes[g]	Active
864	Lepromatous	10	5	3	No[e]	Yes[g]	Active
714[a]	Lepromatous[b]	13	9	0	Yes	No	Inactive
1206[a]	Lepromatous[b]	13	5	5	Yes	No	Inactive
661	Lepromatous	12	13	13	Yes	Yes[f]	Active
1229[a]	Dimorphous[h]	5	3	5(3)[d]	No	Yes[g]	Inactive
1366	Lepromatous[b]	9	8	17	Yes	Yes[f,g]	Active
1294	Lepromatous	15	5	5(4)[d]	No[e]	Yes[g]	Active
1413[a]	Lepromatous[b]	7	—[c]	0	No	No	Active
1078[a]	Lepromatous	9	15	8	No	Yes	Inactive
953	Lepromatous	8	5	19	Yes	Yes[g]	Active
1032	Lepromatous[b]	9	8	20	Yes	No	Inactive
1293	Lepromatous	15	5	4	Yes	Yes[g]	Active
1195	Lepromatous	12	—[c]	0	Yes	Yes	Active
575	Dimorphous	17	4	25	No	No	Inactive
1033	Lepromatous	9	—[c]	0	Yes	Yes	Active
576[a]	Lepromatous[b]	15	10	14	No	Yes	Inactive
689[a]	Lepromatous[b]	18	7	5	Yes	No	Inactive
1148	Lepromatous[b]	11	7	14	Yes	Yes[g]	Active
1196	Lepromatous	7	4	10(13)[d]	No	Yes[g]	Inactive
918[a]	Lepromatous[b]	11	—[c]	0	Yes	No	Active
1399[a]	Lepromatous	3	3	3(7)[d]	No[e]	Yes[g]	Active

[a] Deceased.
[b] Classified as "mixed" in the original article but on the basis of history, physical, and biopsy, should be considered lepromatous.
[c] This patient's disease never became negative.
[d] The leprosy reactivated in this case but responded once more to sulfones, and the figures in parentheses refers to the years it remained negative after a second course of therapy.
[e] This patient had ENL when his disease reactivated and was treated again but not during the initial course of therapy.
[f] During the initial course of therapy with Promin.
[g] When the disease reactivated.
[h] Though originally probably dimorphous, his leprosy was clearly lepromatous when it reactivated in 1949.

rested within one and a half years, and he was discharged in 1953. He returned 16 months later with reactivated leprosy. The disease has remained active since then. He is now apparently infected with sulfone-resistant bacilli but has steadfastly refused B663 (Lamprene®). Although he had only a few areas of decreased sensation at the time his disease first became "inactive" in 1945, he now has sensory loss involving most of his skin surface. Surprisingly, the disease has produced little in the way of motor or visual defects. He had no *erythema nodosum leprosum* (ENL) until he was given streptomycin in 1965. This complication was a recurrent problem for several years thereafter.

Case 864. A 67 year old white male with the onset of lepromatous leprosy about a year before admission here in 1932. He was given a four-month trial of sulfanilamide in 1940 with slight improvement. In March 1941 he was started on Promin and was discharged with inactive disease in 1946. He discontinued therapy after discharge and returned in 1950 with active leprosy. It

has remained active up to the present, and since his bacilli are now apparently sulfone-resistant, he is being treated with B663. Although he had only minimal sensory and no motor or visual defects on discharge in 1946, he now has extensive sensory and motor deficits and complete loss of vision in his right eye. He had ENL occasionally during the 1960's but none prior to that.

Case 714. A white male who died in 1950 at the age of 47 of carcinoma of the stomach. His disease apparently began about 1928, and he was first admitted here in 1930. On the basis of the history, physical examination, and a biopsy report, his disease should be considered lepromatous though it was referred to as "mixed" in the original report. He had progressive motor, sensory, and visual defects until Promin was begun but no further progression thereafter. He had only one short severe episode of ENL, and his disease could be considered inactive at the time of death since he had had a year of negative skin scrapings and no acid-fast bacilli were found in nerve and skin biopsies obtained at autopsy.

Case 1206. A white male who died in 1951 at the age of 67 of uremia secondary to renal amyloidosis. The patient's disease probably began about 1928 and he was first admitted to Carville in 1934. His disease was apparently lepromatous in type. By the time Promin therapy was begun he had far advanced disease with severe motor, sensory, and visual defects. These deficits did not progress after treatment was initiated. He had occasional mild ENL until his disease became inactive in 1946.

Case 661. A 54 year old white female with the onset of lepromatous leprosy in 1929. She was admitted to Carville at that time and treated with chaulmoogra oil until started on Promin in 1941. She had no significant motor deficit but moderate sensory and visual defects which progressed slowly until she had been treated with Promin for about two and a half years. She had occasional mild ENL, and her disease finally became inactive in 1954. It reactivated in 1967, however, perhaps because she had discontinued sulfone therapy two years earlier. It is now quite likely that her bacilli are sulfone-resistant, but this has yet to be confirmed in mouse foot-pad studies.

Case 1229. A Negro male who died in 1967 at age 78 of chronic lymphocytic leukemia. His leprosy began about 1936, and on admission to Carville in 1937 it was dimorphous in type. He had only minimal sensory and motor defects, but these did not progress once Promin therapy was begun. He was discharged in 1944 when his disease became inactive, and treatment was discontinued. The disease recurred in 1949, and before he returned for further treatment in 1952 he had far advanced lepromatous disease with severe motor, sensory, and visual deficits. These progressed slightly in spite of sulfone therapy, but his disease finally became inactive again in 1964 and remained so until his death.

Case 1366. A 64 year old white male whose lepromatous leprosy probably began about 1932 but was not diagnosed until 1940 at which time he was admitted to Carville. He had moderate motor and sensory loss at the time Promin was begun, and these impairments progressed slightly during his first year of therapy, in association with recurrent ENL. He was discharged in 1950, a year after his disease became inactive. His intake of Diasone was quite irregular over the next 18 years, and he returned in 1968 with active disease and severe motor and sensory deficits together with some visual impairment. His condition has improved somewhat on regular sulfone intake but his leprosy remains active.

Case 1294. A 62 year old white male with the onset of lepromatous leprosy in the mid 1920's. He was first admitted to Carville in 1927, and over the next 13 years his disease slowly progressed. He developed mild motor and moderately severe sensory impairments, but these stabilized after initiation of sulfanilamide therapy in 1940 followed by Promin in 1941. Therapy was discontinued, and he was discharged when his disease became inactive in 1946. It had reactivated by the time of his return in 1951 but responded once more to sulfones. However, in 1959 it was found to be active again and has remained so since then. He is now on B663 because his bacilli are thought to be sulfone-resistant. Severe motor and sensory deficits have developed since 1950, but

he has no serious eye problems. He had no ENL prior to 1960 but has had it occasionally since then.

Case 1413. A white male who died in 1944 at age 57 of "heart failure and a tuberculous empyema." His leprosy appears to have been essentially lepromatous in type though it was called "mixed." He had severe motor, sensory, and visual deficits before therapy was started, but these did not progress thereafter. Although he died before his leprosy became inactive, there seems to have been a definite favorable response to Promin, which was given from March 1941 to August 1942, and to sulfathiazole, which he took from June to October 1941 and October 1942 to June 1943. The sulfathiazole was used because severely "sclerosed" veins made the intravenous administration of Promin difficult.

Case 1078. A white male who died in 1964 at age 62 of aspiration of blood during a massive nasopharyngeal hemorrhage. His leprosy probably began in the early 1930's, and on admission to Carville in 1935 he had moderately advanced lepromatous disease. He had moderate sensory loss when Promin therapy was begun in 1941 which slowly progressed until his disease became negative in 1956. He had no significant motor deficit or ENL but lost part of the vision in his left eye. His relatively irregular intake of sulfones may have accounted for the long period of treatment necessary to arrest his disease. He continued to take Diasone, and his condition remained unchanged from 1956 until his death in 1964.

Case 953. A 56 year old white male, admitted here in 1933 shortly after skin lesions first appeared and were diagnosed as lepromatous leprosy. His disease and the associated sensory loss progressed until Promin treatment was begun in 1942. It became inactive in 1946 but reactivated in 1965 with further progression of the sensory loss. During that nineteen-year interval he had taken Diasone fairly regularly until 1961 but took it only occasionally thereafter. He has improved again on sulfone therapy, but his disease remains active. He had mild ENL during his first two years on Promin but none since then, and no significant motor or visual deficits have developed.

Case 1032. A 55 year old white male with the onset of leprosy about 1933. It seems to have been essentially lepromatous in type though called "mixed" in the original report. By the time he was started on Promin in 1942 he had severe motor and sensory deficits which neither improved nor progressed with treatment. He had also lost most of his vision, and though it improved temporarily on Promin, he eventually became completely blind. He had "severe ENL" before therapy but only mild reactions thereafter. His treatment was changed from Promin to Diasone in 1950 when his leprosy became inactive, and it has remained so to the present.

Case 1293. A 62 year old white female admitted here in 1928 about a year after the onset of lepromatous leprosy. The mild degree of sensory loss and infiltration of her skin noted on admission progressed very slowly until Promin therapy was begun in 1942. In 1947 her leprosy became inactive, and she discontinued therapy after discharge. It reactivated in 1951, and possibly because of irregular therapy it has continued to be active to the present. She has developed extensive sensory loss but no significant motor or visual defects. She has had relatively mild intermittent ENL since beginning the use of Promin. Clinically her disease is now sulfone-resistant, but she is doing well on B663.

Case 1195. A 60 year old white male whose lepromatous leprosy began about a year before his first admission here in 1932. He had only a mild degree of sensory loss at the time, but it slowly progressed in spite of eventual sulfone therapy to the point where nearly all of his skin surface was involved. His disease has never become negative although he had negative skin scrapings for nearly a year during the early 1950's. Irregular intake of treatment may account for his relatively poor response, and clinically his disease is now sulfone-resistant. He has improved markedly on B663, however, and has no significant motor or visual defects. He had intermittent ENL during the 1940's but none since then.

Case 575. A 76 year old white male with the onset of dimorphous leprosy about 1925. On admission here in 1928 he was in good condition except for moderate sensory loss, but in the fourteen-year interval before the start of Promin therapy he developed severe sensory and motor deficits and became blind. His disease became inactive on Promin in 1945, and he has taken Diasone since then.

Case 1033. A 52 year old Chinese male with the onset of lepromatous leprosy about 1933. He had a mild degree of sensory loss and bilateral ulnar paresis prior to the start of Promin. His disease improved with therapy to the point where skin scrapings were showing either no or rare numbers of bacilli, but in 1952 he developed tuberculosis and simultaneously the leprosy became progressively worse. Treatment for tuberculosis (INH and streptomycin) also led to improvement of his leprosy, but it exacerbated again in 1960 and has remained active. His disease is clinically sulfone-resistant, but he is slowly improving on B663, and there has been no further progression of his various neurologic deficits which include extensive sensory loss and bilateral ulnar and median paralysis. His vision remains essentially normal. He had only mild ENL while on Promin, but there were multiple severe episodes while taking Ciba 1906 or streptomycin in the 1960's.

Case 576. A white male who died at the age of 43 in 1966 of renal failure secondary to chronic glomerulonephritis. His leprosy was essentially lepromatous when Promin was started in 1942, though it had had some dimorphous characteristics on admission in 1928. It became negative in 1952, and treatment was continued until he died. He had no significant neurologic deficits on admission, but by the time Promin was begun he had extensive sensory loss, bilateral ulnar paralysis, and was almost blind. He noted some progression of the sensory loss on therapy but no further paralysis. At no time did he experience ENL.

Case 689. A white male who died in 1954 at age 61 of a myocardial infarct. He had lepromatous leprosy which probably began about 1924. He had only a moderate degree of sensory loss on admission here in 1930, but by the time Promin was begun he had extensive sensory loss, bilateral ulnar and median paralysis, a right below-the-knee amputation, and was almost completely blind. His disease became inactive in 1949, but he continued on Diasone until his death. He had moderately severe ENL during his first few years on Promin but no further progression of his already severe neurologic deficits.

Case 1148. A 67 year old white male with the onset of lepromatous leprosy about 1931. Prior to beginning with Promin in 1942 he had moderately severe sensory loss and was slowly losing his eyesight. With treatment his condition stabilized and his vision improved somewhat. His leprosy became inactive in 1949, and he was discharged in 1954. Over the next ten years his Diasone intake was irregular, and he returned in 1964 with active disease which had produced extensive sensory loss in the previously uninvolved areas of his body, together with ulnar and median paralysis and a significant loss of visual acuity. He also had bilateral weakness in dorsiflexion of the feet. With regular therapy his various neurologic deficits stabilized. Currently he is on B663 because his bacilli are thought to be sulfone-resistant. He had ENL only during his first three years on Promin and while on streptomycin in the 1960's.

Case 1196. A 56 year old white male who developed lepromatous leprosy about 1935. He had an excellent response to Promin with no evidence of ENL. His disease became inactive in 1946, was found to have reactivated in 1956, but became inactive again in 1957 after only 18 months on Diasone. At the start of Promin therapy he had a mild to moderate degree of sensory loss and right ulnar weakness, but these deficits did not progress during his initial treatment. However, after his leprosy reactivated he developed bilateral ulnar and median paralysis with considerable extension of the sensory loss. His condition is now stable, and recent skin scrapings and a biopsy remain negative. He has continued on Diasone up to the present.

Case 918. A Filipino male who died in 1944 at age 21 of "tuberculous peritonitis and bronchopneumonia." At autopsy the patient also had amyloidosis involving the

kidneys and other organs. Prior to the start of Promin therapy he had extensive sensory loss and clawing of the right hand. There was no further progression of these deficits thereafter, and the ENL which he had had intermittently since 1935 was reportedly less severe. He received Promin for only slightly more than a year, and the numbers of bacilli in his skin scrapings were unchanged at the time of his death.

Case 1399. A white male who died in 1968 at age 46 of a myocardial infarct. His disease began in 1939, and though called "maculoanesthetic" in the original report, a biopsy taken prior to the start of Promin showed lepromatous leprosy. All subsequent biopsies were consistent with lepromatous disease except for a few years in the early 1960's when they demonstrated some dimorphous characteristics. His response to Promin was excellent, but when discharged as having inactive disease in 1945 he did not continue therapy and returned three years later with active lepromatous leprosy. He responded once more to Promin and was discharged with inactive disease in 1951. Over the next nine years his Diasone intake was extremely irregular, and when he returned in 1960 he had far advanced active disease with a biopsy showing the histoid variety of lepromatous leprosy. His bacilli had apparently become sulfone-resistant, and though he had good temporary responses to both Ciba 1906 and streptomycin, he eventually had to be given B663. He had shown an excellent clinical and bacteriologic response to this drug prior to his death in 1968. At no time were there significant problems with his eyes, and no motor loss, but progressive sensory loss which developed during periods when his disease was highly active eventually led to nearly total cutaneous anesthesia. He had ENL only in the early 1960's, but it was relatively mild.

COMMENTS

All of the patients (even the four whose disease never became negative) improved on Promin, often with nearly complete clearing of their various skin lesions. The lesions recurred in those whose leprosy reactivated and in whom the bacilli apparently became sulfone-resistant. In most of these latter instances the cutaneous infiltration was more marked than it had been initially. In addition, all of the patients had varying degrees of neurologic deficits (sensory, motor and/or visual) at the initiation of therapy; and, as shown in Table 1, these progressed in six of the 22 cases during the initial course of Promin and ultimately in 15 of the 22. This progression was in the form of a markedly increased sensory loss in most instances. Further motor loss was less common, and fortunately serious loss of eyesight occurred in only a few cases. The extensive sensory loss sometimes led to further deformity via the usual cycle of injury, infection, and absorption or a need for surgical amputation of digits common to such cases. Thus, in one way or another many of the 22 cases were ultimately severely deformed by the disease in spite of sulfone therapy, though the deformity would probably have been much more widespread and severe without it.

A detailed discussion of the pattern of therapy in each of these patients is not included here since this would make all of the case histories prohibitively long. One aspect of therapy does deserve further elaboration at this time, however, and that concerns the use of the sulfonamides in some of these patients. Fourteen of the 22 received them, six before Promin was utilized and eight being on this drug for some time. Table 2 summarizes the details of these trials. In only three cases was any improvement noted, probably because serious side effects severely limited the duration of most of the trials. Three of the patients were given these preparations for infections other than leprosy, and most of those receiving sulfathiazole had already shown at least clinical improvement on Promin. Sulfathiazole was apparently tried as part of a search for an oral alternative to the intravenous Promin. Also of possible interest is that two of the patients (case numbers 576 and 714) were involved in lengthy combined Promin-penicillin trials in the mid 1940's. They had already shown marked improvement on Promin alone; there is no evidence that penicillin had any effect on the course of the disease.

TABLE 2. *Trials with sulfonamides.*

Case Number	Drug	Dates Given	Response	Promin started	Comment
869	Sulfathiazole	21 days in 8/41	None	3/41	He had already improved on Promin
864	Sulfanilamide	11/40 to 12/40 and 12/40 to 3/41	"Slight improvement in some lesions"	3/41	Case 7 in reference 3
714	Sulfathiazole	10 days in 8/41	None	5/41	
1206	Sulfathiazole	10 days in 8/41	None	5/41	He had already improved on Promin
1229	Sulfathiazole	3/43 to 6/43	None	10/41	Already markedly improved on Promin
1366	Sulfathiazole	4/41 to 7/41	None	10/41	
1294	Sulfanilamide	7/40 to 8/40 and 11/40 to 12/40	Slight improvement	10/41	Case 4 in reference 3
	Sulfathiazole	22 days in 6/41	None		
1413	Sulfathiazole	6/41 to 10/41 and 10/42 to 6/43	Improved	3/41	
1078	Sulfathiazole	20 days in 8/41	None	5/41	He had already improved on Promin
1032	Sulfathiazole	10 days in 1/42	None	1/42	Given for a non-leprous infection
1195	Sulfanilamide	5 days in 7/40	None	4/42	Case 2 in reference 3
1033	Sulfanilamide	11/40 to 1/41	None	4/42	Case 12 in reference 3
918	Sulfapyridine	13 days in 1/41	None	5/42	Given for a non-leprous infection
1399	Sulfathiazole	7 days in 3/42, 9/42, and 8/43	None	2/42	Given for a non-leprous infection in each instance

DISCUSSION

It is apparent from a review of the records that each of the 22 patients involved in this study considered Promin far superior to the chaulmoogra oil they had previously received. Their leprosy had been progressive and producing increasing deformity and disability when Promin halted the process in most cases and slowed it in the others. Optimism finally replaced the despair so prevalent among leprosy patients and those charged with their treatment from time immemorial. The fact that the therapy had to be given intravenously daily for years did not seem to bother most of the patients, possibly because they often rapidly "felt" better months before there was any objective improvement. There were relatively few side effects, with varying degrees of hemolytic anemia being most frequently observed. ENL occurred in 12 of the 22, a frequency not significantly different from that seen today—and in most instances it was relatively mild. As noted above, only six showed any progression of their various neurologic deficits during the initial course of therapy, and this progression was not marked except in one instance; however, with the passage of time and reactivation of the disease in many cases, the condition of the patient often deteriorated again.

Having acknowledged the obvious immediate benefits of Promin in these cases, it is now necessary to evaluate the results from a much longer range point of view to assess some of the very important limitations of sulfone therapy. Cases 1413 and 918 will not be included in this evaluation since both died less than three years after Promin was started of causes apparently unrelated to the treatment. Both received Promin somewhat irregularly, and their disease remained quite active at the time of death though some improvement was evident.

Considering then only the 20 who lived over three years beyond the initiation of the trial, 18 eventually became negative at an average of 6.7 years after Promin was begun, with a range of three to 15 years. Here negativity is defined as negative skin scrapings over a twelve-month period and no clinical evidence of activity. Half the patients also had a skin biopsy taken, and these were all negative. This 90% success rate is excellent considering the advanced disease present in most patients at the onset of therapy with the patient having had the disease for an average of 10.8 years at the time. On the other hand the leprosy has remained continuously active in two of the patients. Although both initially improved clinically and bacteriologically to the point where skin scrapings showed "rare" numbers of bacilli for several years, their disease eventually became progressive again in spite of continued therapy. Clinically their disease is now sulfone-resistant, and both are at present on B663.

Although the initial success rate was excellent, the long-term follow-up on the 18 who became negative has not yielded particularly encouraging results. The leprosy reactivated an average of nine years later in 11 of the 18. Only five of the 11 ever became inactive again, and three of these five reactivated a second time with their leprosy remaining active thereafter. Thus in only nine of the 20 patients under consideration did the leprosy become "permanently" inactive, and the results might have been even poorer had all of the nine survived longer. Four of the seven whose disease never reactivated (Cases 714, 1206, 1078 and 689) died earlier than reactivation was statistically likely to occur (nine years), and one of the two whose disease became "permanently" negative only after having reactivated once, died three years thereafter. To review this data in another way, only four of the 20 had an excellent long-term bacteriologic response to the sulfones; three of these four were seriously deformed by the disease; the other was moderately deformed by it.

Thirteen of the 20 are still living, and ten of these 13 have active disease. Eight of the ten are apparently infected with sulfone-resistant bacilli, and six of these are now receiving B663. Determinations of sulfone sensitivity were undertaken in two of the latter patients before B663 therapy was started, and such studies are planned in the four active cases who are not on it. All those on B663, whether or not their bacilli

were studied in mouse foot-pads, had progressive disease in spite of adequate sulfone intake either orally or by injection. Those taking oral sulfones had their intake monitored with random blood sulfones. Thus the bacilli infecting these patients were "clinically" sulfone-resistant, and this is also true of the one case (1399) who died while on the drug. That this concept is valid is indicated by the fact that up to the present time all bacilli obtained from patients who were classified "clinically" as sulfone-resistant have also been resistant when studied in the mouse foot-pad.

Another point of interest in these 20 patients is the evident advantage of continuing sulfone therapy once the disease has become negative. Five of the 20 discontinued therapy within a year after attaining negativity, and their leprosy reactivated an average of four years later. Two patients stopped therapy after four and 11 years respectively, and the disease reactivated two years later in both instances. Although their intake was somewhat irregular, the remaining 13 continued on sulfones indefinitely, and in the four whose leprosy reactivated it did so an average of 15 years after it had first become negative. Thus those who continued therapy were clinically free of disease over a decade longer on the average than those who did not. The number of cases is too small to offer statistically valid data regarding the relative merits of continuing therapy five or ten years beyond negativity and then stopping it as has been advocated ([6]) versus continuing it for life. However, a careful review of these and other Carville case histories suggests that regular intake of therapy for life is the wisest course to follow, and a statistical analysis of the course of the disease in all patients treated at Carville will be the subject of later articles.

Although more data will be presented in future reports the present study suggests a number of limitations of sulfone therapy. These are as follows:

1. Though effective, the sulfones act too slowly. The average of 6.7 years to attain negativity in this group is probably an optimal sulfone response for leprosy as advanced as it was in these patients. Nevertheless, it is questionable whether the disease can ever be adequately controlled when such a long treatment period (often complicated by reactive episodes) is required. Comparatively more effective drugs are available for the treatment of tuberculosis and syphilis, and the necessary treatment period is much shorter, but these diseases have not been eradicated. Furthermore, none of the other drugs currently available has been shown to be significantly better than the sulfones for the treatment of leprosy. What may be needed is not more drugs that act in some way like the sulfones but rather a whole new approach to chemotherapy based on increasing knowledge of the physiology and biochemistry of *Mycobacterium leprae* and the host response to their presence.

2. The sulfones are not completely effective, i.e., treatment with these drugs will not inactivate the disease in all cases. Two of the 20 patients in this group never became inactive, and there are similar examples among other patients currently under study. In some cases irregular intake of the drugs may be responsible, but this apparently is not universally true. Also of significance is that the bacilli become sulfone-resistant relatively early in some patients as in the case reported recently by Browne (1). Whatever the reason for the unsatisfactory response, it is clear that these individuals must be identified early and their therapy altered as indicated.

3. Lifetime sulfone therapy is probably necessary for all patients with lepromatous leprosy. As for the patients discussed in this paper, discontinuation of therapy before the leprosy was inactivated was again followed by a progression of the disease, and stopping treatment within a few years after attaining a state of inactivity always resulted in "reactivation." Furthermore, the data suggests that reactivation can occur even if treatment is continued indefinitely, but it is much more likely to occur if treatment is discontinued. That this is reactivation of the disease and not reinfection cannot be proven at present. However, the demonstration of bacilli in some sural and other nerve biopsies ([2]) years after the disease was determined to be inactive by the usual criteria, and the fact that in many of these cases the bacilli

have become sulfone-resistant indicates that the problem is probably one of reactivation. This relatively high reactivation rate emphasizes the need for lifetime followup both as a public health measure and to prevent the development of still more deformity and other disabilities.

4. Reactional states frequently complicate sulfone therapy. This problem, of course, is not peculiar to sulfone therapy since reactions seem to accompany any effective treatment in some patients. B663 and thalidomide have been extremely helpful in the management of this problem, but the use of thalidomide is relatively restricted, and the cost of B663 (when compared with Dapsone) may be prohibitive in many areas. It is interesting that in the 20 patients under consideration here, most of those who did not have reactions when treated the first time did have them when their disease reactivated and was again treated. It is thus conceivable that the incidence of reaction might approach 100% if leprosy remains active for many years.

5. Sulfone-resistant leprosy bacilli eventually develop in a significant number of cases after prolonged treatment with the sulfones. This is apparently becoming a serious problem in patients with lepromatous disease who survive for more than two decades after the start of sulfone therapy, but its epidemiology has yet to be defined. For example, does irregular intake of therapy or giving it in low doses for long periods of time increase the likelihood of sulfone-resistance or accelerate its appearance? We hope to explore these and other possibilities in future reports on a much larger group of patients since the group under consideration in this paper is too small to yield definitely meaningful data.

6. Sulfone therapy is not uniformly successful in preventing further deformity and disability in patients with leprosy. Fifteen of the 20 patients studied had progression of their previous neurologic deficits or developed new ones while on sulfones. In six cases this occurred during the initial course of therapy and in nearly all cases when the disease reactivated. This may have been associated with reactions in some patients, but this was not usually the case, and four of the fifteen never had a reaction. Undoubtedly the end result is far better than it would have been without the sulfones but not as good as one would have hoped for—or perhaps expected. It would appear that much of this might have been prevented had all the patients continued to take therapy regularly after their disease was inactivated. Furthermore, today's patients are almost always started on treatment earlier in the course of their disease than this group was; effective alternative drugs such as B663 are now available when sulfone-resistant bacilli develop, and thalidomide can be used to suppress ENL associated with lepromatous leprosy. Taking all these factors into account it seems likely that most present and future patients will have a better long-term result in-so-far as deformity and disability are concerned.

The results of this study clearly demonstrate that the battle against leprosy is far from being won and that the weapons currently available are not as effective as they once appeared to be. Also, they strongly suggest that lifetime follow-up of lepromatous patients is as important as case finding, and treatment with the sulfones must be regular and probably should be continued indefinitely to assure the best possible results. A return to isolation is not necessary to accomplish this, but follow-up must be considered an essential part of any leprosy control program, both to see that therapy is continued and for the periodic evaluation of the patient's clinical and bacterial status. It would appear that the chemotherapy of lepromatous leprosy should be approached in the same way as the therapy of diabetes or epilepsy, i.e., it is a lifetime problem and this fact must be acknowledged if truly effective leprosy control is to become a reality. The present series of patients is admittedly small, but it is also unique since these were the first patients treated with sulfones and thus the longest possible follow-up is available. Our future reports will cover a much larger group and hopefully will provide more definitive answers to some of the questions which now lack them. Such retrospective studies are admittedly inferior to prospective ones, but in a disease such as leprosy where data are ex-

tremely slow to accumulate, it is the only way to obtain it within a reasonable period of time.

SUMMARY

The case histories of the first 22 patients to receive sulfones for the treatment of leprosy are reviewed. Initially nearly all of the patients improved markedly, and in 18 instances the disease eventually was determined to be inactive. The long-term follow-up on these patients, however, has shown that despite such an excellent initial response, sulfone therapy has a number of serious limitations. Most of those whose disease became inactive eventually reactivated, and as might be expected the various neurologic deficits in these patients have increased, especially while the disease was progressive and either untreated or ineffectively treated. Further aggravating the problem has been the appearance of sulfone-resistant leprosy. Of major concern, however, is the fact that 30 years after they were started on sulfone therapy ten of the 13 patients still living continue to have active disease. Some of the implications of these findings as they pertain to leprosy control are discussed. It would appear that at present successful control of this disease is possible only if adequate follow-up and treatment are maintained on all lepromatous patients for life.

RESUMEN

Se revisan las historias clínicas de los primeros 22 pacientes que recibieron sulfona como tratamiento para la lepra. Inicialmente casi todos los pacientes mejoraron en forma notable, y en 18 casos se determinó eventualmente que la enfermedad se había vuelto inactiva. El seguimiento prolongado de estos pacientes, sin embargo, ha demostrado que a pesar de tan excelente respuesta inicial, la sulfonoterapia tiene una serie de limitaciones importantes. La mayor parte de los pacientes en los cuales la enfermedad se hizo inactiva tuvieron eventualmente una reactivación, y, como era de esperarse, las distintas fallas neurológicas de estos pacientes han aumentado, en especial mientras la enfermedad era progresiva y no tratada o tratada en forma inefectiva. Lo que agrava aún más el problema ha sido la aparición de lepra sulfonoresistente. Sin embargo, lo que es aún más grave es el hecho de que 30 años después que comenzaron sulfonoterapia, 10 de los 13 pacientes que aún viven siguen teniendo la enfermedad activa. Se discuten algunas de las implicaciones de estos hallazgos en lo que se refiere al control de la lepra. Parecía que por el momento es posible obtener un control adecuado de esta enfermedad solamente si se continúa controlando y tratando en forma adecuada a todos los pacientes lepromatosos durante toda su vida.

RÉSUMÉ

On a relaté l'histoire des vingt-deux premiers malades qui aient reçu des sulfones en vue de traiter la lèpre. Au début du traitement, presque tous les malades ont présenté une amélioration notable; dans 18 cas, la maladie est en fin de compte devenue inactive. La surveillance à long terme de ces malades a pourtant montré que, malgré cette réponse initiale excellente, la thérapeutique sulfonée présentiat un certain nombre de limitations graves. La plupart de ceux chez lesquels la maladie était devenue inactive, ont, à l'occasion, récidivé; ainsi qu'on pouvait s'y attendre, les divers troubles neurologiques présents chez ces malades se sont aggravés, particulièrement lorsque la maladie était évolutive, et que ces malades étaient inefficacement traités ou non traités. L'apparition d'une lèpre résistant aux sulfones a encore compliqué davantage le problème. Toutefois, un fait d'importance primordiale est l'observation que 30 ans après qu'ils aient commencé leur thérapeutique sulfonée, 10 des 13 malades encore en vie présentent toujours une affection active. On discute certaines des implications de ces observations, en ce qui concerne le problème du contrôle de la lèpre. Il semble qu'à présent le contrôle efficace de la maladie n'est possible qu'à la condition qu'une surveillance adéquate et un traitement approprié de tous les malades lépromateux soient maintenus pour toute la vie.

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