Streptomycin Combined with Sulfones in the Treatment of Relapsed Lepromatous Leprosy [1]

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Since the sulfones were introduced for the treatment of leprosy in 1941 ([8]), a number of cases have been reported that have relapsed despite adequate and continuous sulfone therapy. The first case was reported in 1950 ([6]), and three additional cases were reported in 1953 ([28]). More recently, there seem to have been more and more such cases ([3, 11, 14, 20]). The precise mechanism of relapse remains obscure in most cases. The phenomenon of true sulfone-resistant *Mycobacterium leprae* has been demonstrated ([17-19]), but this is apparently quite uncommon even in cases of leprosy that are progressive despite many years of sulfone treatment ([22]).

The clinical management of relapsed lepromatous leprosy continues to be a problem. In our experience, which is contrary to that recorded in a recent report by Browne ([3]), continuing sulfone therapy alone has not been rewarding. The present paper deals with the authors' experience with the combination of streptomycin and sulfones in the management of relapsed lepromatous leprosy.

MATERIALS AND METHODS

Ten cases of lepromatous leprosy were selected, all of which had relapsed despite what was regarded to be adequate as well as continuous sulfone therapy. Relapse was taken to be the appearance of new, progressive leprosy lesions from which skin scrapings and/or biopsies revealed numerous bacilli with a high percentage of solidly staining forms, in patients previously either inactive or showing regressive disease. The clinical data are summarized in Table 1.

It is of interest that all of these cases were of long-term leprosy, the patients having had the disease for an average of almost thirty years. Each had been on long-term sulfone therapy with an average duration of treatment of 14.7 years prior to relapse. Several patients were followed on sulfone alone for extended periods of time following relapse, and without exception these patients continued to deteriorate clinically and bacteriologically.

Each case was treated with streptomycin 1.0 gm. intramuscularly three times weekly, and their sulfone was continued in a dosage of 600-700 mgm. of DDS (dapsone) per week, or what is considered its equivalent dose of Sulfoxone (Diasone), i.e., six or seven 330 mgm. tablets per week by mouth. The dosage of streptomycin employed is similar to that recommended for long-term maintenance therapy of tuberculosis ([16]), particularly in patients over 50 years of age ([9]). In order to determine that the prescribed oral sulfones were being taken, random blood-sulfone determinations were performed during the course of the study on each patient by the method described by Simpson ([15]).

Clinical examinations, supplemented by color photography, were carried out at approximately monthly intervals. An estimation was made of each patient's progress at these examinations, regarding his skin lesions, the status of his peripheral nerves, and the presence or absence of erythema nodosum. At each examination the patient was also checked for the presence or absence of Romberg's sign in an effort to

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TABLE 1. *Clinical data.*

Case No.	Age (yrs.)	Sex	Duration of			
			Leprosy (yrs.)	Sulfone therapy prior to relapse (yrs.)	Relapse before streptomycin (mos.)	Observation on combined treatment with sulfones & streptomycin (mos.)
1	56	F	32	23	1	21
2	39	M	25	8	3	22
3	61	M	29	14	71	22
4	64	M	33	13	65	23
5	49	M	24	19	8	23
6	51	M	30	16	25	20
7	52	M	36	13	133	21
8	38	M	23	13	16	13
9	62	M	37	22	5	24
10	43	M	26	6	4	22
Mean	51.5		29.5	14.7	33.1	21.1

detect any vestibular damage, and each patient had audiograms during the course of the study to detect any auditory toxicity of streptomycin.

Skin scrapings for acid-fast bacilli were made at monthly intervals from a single site on each patient. The sites of the skin scrapings were usually earlobes, although in several patients with nodular lepromatous leprosy scrapings were made regularly from lepromata on the extremities. Skin scrapings were evaluated independently and blindly by an experienced technician as to the numbers of bacilli present and the percentage staining solidly on routine acid-fast staining. Quantitation of the numbers of bacilli was done by the method in use at Carville for over 20 years, viz.,

Numerous—Hundreds of acid-fast bacilli per oil immersion field.

Moderate—Ten to 100 bacilli per oil immersion field.

Few—Fewer than 10 bacilli per oil immersion field.

Rare—Fewer than 10 bacilli per entire smear.

None found—No bacilli in 50 oil immersion fields.

Skin biopsies were obtained every six months from the same site in each patient and evaluated independently by the Chief of Pathology at this hospital. A biopsy index ([23]) was calculated and comparison made with subsequent biopsies.

RESULTS

With one exception, all blood-sulfone determinations indicated that the patient was indeed taking the prescribed sulfone. One value was 0.07 mgm. per cent, which in our laboratory is approximately the value obtained on persons not receiving sulfones. For the remainder of the determinations there was a mean value of 0.20 mgm. per cent (0.24 mgm.% for the DDS group and 0.19 mgm.% for the Sulfoxone group, with a range of 0.12-0.37 mgm.%).

No patient developed significant, clinically detectable vestibular damage during the course of the study. Several patients showed high frequency hearing loss on audiograms, but in no instance was this symptomatic, and in no case was it necessary to stop streptomycin.

The results of clinical evaluations are summarized in Table 2.

TABLE 2. *Clinical evaluation.*

Case No.	Onset of improvement (mos.)	Rate of improvement	Erythema nodosum leprosum	Months after streptomycin that ENL appeared
1	1	Moderate	Yes	5th onward
2	1	Moderate	No	—
3	5–6	Slow	Yes	ENL throughout, more severe from 4th month onward
4	1	Dramatic	Yes	15th onward
5	3	Slow	Yes	12th onward
6	2	Moderate	Yes	14th onward
7	1	Moderate	Yes	2nd onward
8	2	Moderate	Yes	5th onward
9	2	Moderate	Yes	10th onward
10	2	Moderate	No	—

The onset of clinical improvement was quite early in most cases. In general, the rate of improvement was comparable to that seen in previously untreated lepromatous cases beginning sulfones for the first time. It is interesting that eight of the 10 patients under observation developed erythema nodosum leprosum.

The results of monthly skin scrapings and determinations of morphologic index ([19, 27]) are summarized in Table 3.

The fall in the morphologic index with the combined treatment with sulfones and streptomycin was satisfactory and comparable to that seen in previously untreated lepromatous cases started for the first time

TABLE 3. *Morphologic indices of skin scrapings.*

	Streptomycin				
		After			
Case No.	Before	3rd month	6th month	9–13th month	14–21st month
1	50	1	1	1	1
2	90	10	1	1	1
3	25	1	1	1	1[a]
4	90	5	5	1	1[b]
5	99	5	1	1	1[b]
6	25	5	1	1	1
7	75	25	1	1	0–1
8	75	50	5	1	[c]
9	90	1	1	1	1[d]
10	50	1	1	1	1[a]
Mean	66.9	10.4	1.8	1	1

[a] Morphologic index 1 through 22nd month.
[b] " " 1 " 23rd "
[c] Not available.
[d] Morphologic index 1 through 24th month.

TABLE 4. *Biopsy indices of serial biopsies.*

Case No.	Streptomycin			
	Before	After		
		6 months	12 months	18 months
1	1.50	0.60	0.13	0.15
2	1.24	1.24	1.00	0.88
3		Biopsies not made		
4	4.81	3.71	3.30	2.63
5	2.93	1.51	0.88	0.63
6	3.38	2.10	1.38	0.70
7	4.68	2.44	1.35	1.24
8	4.13	3.99	3.58	[a]
9	1.58	0.50	0.88	0.45
10		Biopsies not made		
Mean	3.03	2.01	1.56	0.95
Decrease since previous biopsy (per cent)		33.6	22.5	25.1[b]

[a] Not available.
[b] Compared to same seven patients at the 12th month.

on sulfones. In general, there has been no significant change in the numbers of bacilli present in skin scrapings, although several patients now show moderate numbers of bacilli, whereas before streptomycin all cases were showing numerous bacilli.

A biopsy index was calculated for each of the serial biopsies. These are summarized in Table 4.

The mean decreases in biopsy index obtained with the combined treatment compare favorably with the average rate of fall of the biopsy index of from 25 per cent ([23]) to 30 per cent ([24]) expected in uncomplicated lepromatous cases for each six-month period of sulfone treatment.

DISCUSSION

It cannot be claimed that the bacteria from the 10 cases making up the present study were sulfone-resistant in the absence of mouse foot pad inoculations and the demonstration that bacilli taken from these patients multiply in animals receiving sulfones ([18-19]). It is unfortunate that this method was not utilized to test for true sulfone resistance in these cases.

In any case, in the early work on this project, it was assumed that relapse in spite of sulfone therapy represented sulfone resistance, and for this reason another antileprosy drug was prescribed. Streptomycin has been used in the treatment of leprosy at Carville since 1945 ([7]), particularly for mucous membrane lesions ([12]), with generally good results. Streptomycin inhibits the multiplication of *M. leprae* in mouse foot pad infections ([25]), and a number of other clinical studies ([5, 21, 26]) have demonstrated the effectiveness of streptomycin in human leprosy. When the drug is used alone, however, relapses are frequent ([28]), and improvement is not sustained. It has been postulated that this may well be due to development of resistance of the leprosy bacillus to streptomycin ([4]).

In an effort to deal with any remaining sulfone-sensitive organisms or any strains of sulfone-sensitive bacilli that might arise

from the presumed sulfone-resistant population of leprosy bacilli under streptomycin therapy, sulfones were continued in the present study along with the streptomycin. On combined therapy, no evidence of relapse has been noted to date, whereas relapse has been seen in 25 per cent of 100 patients followed for two years on streptomycin or dihydrostreptomycin alone ([26]).

It is interesting that Karat *et al.* ([13]) have recently reported good results in "acute lepromatous ulceration of the skin" with a combination of streptomycin and isoniazid. One of the patients in the present study (case No. 4) had a similar clinical picture of a number of ulcerating lepromatous skin lesions. Dramatic, rapid improvement followed the addition of streptomycin to the sulfone therapy, all ulcerations healing in the first month.

The high proportion of patients developing erythema nodosum leprosum in the present study is noteworthy in that the work of several investigators ([1, 10, 27]) may be interpreted as associating erythema nodosum leprosum with effective antileprosy treatment.

It is evident therefore that the combination of streptomycin with sulfones is effective in lepromatous leprosy that relapses despite continuous sulfone treatment alone. Improvement thus far appears to be sustained and is comparable to that seen in previously untreated cases started on sulfones for the first time. In the present study a high proportion of patients have developed erythema nodosum leprosum on the combination of streptomycin with sulfones.

SUMMARY

As the years pass since sulfone therapy of leprosy was initiated in 1941, more and more cases are being seen that relapse despite continuous sulfone treatment. Ten cases of lepromatous leprosy are reported in which relapse occurred despite adequate sulfone therapy. All cases responded well to a combination of streptomycin and continued sulfone therapy. Objective improvement was documented clinically, bacteriologically, and histopathologically, and the rate of improvement was comparable to that seen in uncomplicated lepromatous cases beginning sulfone therapy for the first time. During the combination treatment an unusually large number of patients (8 out of 10) developed erythema nodosum leprosum. The authors feel that the combination of streptomycin with sulfones is useful in the treatment of cases of lepromatous leprosy that relapse despite regular and adequate sulfone therapy.

RESUMEN

Con el correr de los años desde el comienzo de la terapia con sulfonas de la lepra en 1941, mas y mas casos se ven que recaen a pesar de un tratamiento continuado con sulfonas. Se comunican diez casos de lepra lepromatosa en los cuales la recaída se produjo a pesar de un tratamiento sulfónico adecuado. Todos los enfermos respondieron bien a una combinación de estreptomicina y tratamiento con sulfona continuado. La mejoría objetiva se probó en forma clínica, bacteriológica, e histopatologicamente, y el grado de mejoría fué comparable con lo que se observa en enfermos lepromatosos sin complicación que inician el tratamiento sulfónico por primera vez. Durante el tratamiento combinado un no habitual gran número de enfermos (8 en 10) desarrollaron erythema nodosum leprosum. Los autores creen que la combinación de estreptomicina con sulfonas es útil en el tratamiento de los casos de lepra lepromatosa que recaen a pesar dè un tratamiento regular y adecuado con sulfona.

RÉSUMÉ

A mesure que les années passent depuis que la thérapeutique sulfonée de la lèpre a été lancée en 1941, on voit de plus en plus de cas qui récidivent malgré un traitement sulfoné continu. On rapporte ici dix cas de lèpre lépromateuse chez lesquels une récidive est survenue malgré un traitement adéquat par les sulfones. Tous les cas ont bien répondu à une combinaison thérapeutique consistant en l'addition de streptomycine à la continuation du traitement sulfoné. L'amélioration objective a été documentée par des examens cliniques, bactériologiques, et histopathologiques. Le taux d'amélioration a été comparable à celui que l'on constate dans les cas de lèpre lépromateuse non compliquée, mis en traitement sulfoné pour la première fois. Au cours de ce traitement combiné, un nombre inhabituellement élevé de malades (8 malades sur 10) ont

développé un érythème noueux lépreux. Les auteurs estiment que la combinaison de streptomycine et de sulfones est utile pour le traitement des cas de lèpre lépromateuse qui récidivent malgré une thérapeutique sulfonée régulière et adéquate.

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