ORAL "SULFON-CILAG" IN THE TREATMENT OF LEPROSY

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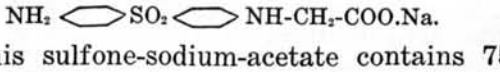
It is common knowledge that, in the modern treatment of leprosy, disubstituted derivatives of diaminodiphenyl sulfone (Promanide, Solapsone, Sulphonal sodium) have to a great extent been replaced by the parent substance (DDS).

The monosubstituted derivatives have also been shown to be effective (1). Floch and associates (4) concluded that succinyaldiaminodiphenyl sulfone (1500F) owed its therapeutic activity principally to its unchanged molecule. They (5) investigated another monosubstituted derivative, aminohydroxyethylaminodiphenyl sulfone (1087 MM), and found similar therapeutic activity; this substance is found unchanged in the blood, and is partly excreted unchanged in the urine. Herrera (6) believed that Propriosulphone was preferable to DDS for the treatment of infectious cases of leprosy, although 93 per cent of it is eliminated in the urine in the first 24 hours. The monosubstituted sulfones so far investigated are safe and effective in the treatment of leprosy (1), but more evidence is needed before their final therapeutic value can be assessed.

PRESENT REPORT

The present report is of the use of a sulfone of this monosubstituted class, of Swiss manufacture, called in French "Sulfon-Cilag." Chemically it is the sodium salt of 4-carboxymethylamino-4′-aminodiphenyl sulfone, and its structural formula is as follows:



The molecule of this sulfone-sodium-acetate contains 75.6 per cent of DDS. It is freely soluble in water, and may be administered parenterally by injection. Ramanujam (8) has reported a short series of cases treated with it, given by intramuscular and subcutaneous injection.

The clinical trials here reported were carried out at the Yalisombo Leprosarium.[1] The subjects were 67 inpatients of the leprosarium, who had presented themselves voluntarily for segregation and treatment. They represented several tribes in the clinical catchment-area of Yalisombo: Topoke, 17; Bambole, 14; Lokele, 12; Foma, 10; Bamanga, 7; Torumbu, 4; Bakumu, 2; Balengola, 1.

Of this group, 42 were males and 25 females; 61 were adult, the other 6 being children aged from 11 to 16 years. The weights of the adult patients ranged from 42 kgm. (92.4 lb.) to 58 kgm. (127.6 lb.), the average being 52 kgm. (114.4 lb.).

Clinically the cases were classified as lepromatous, 57, tuberculoid, 9, and inde-

[1] The necessary quantities of the drug were kindly supplied by the manufacturer, Cilag Société Anonyme, Schaffhausen, Switzerland, in the form of tablets for oral administration each containing 0.2 gm. of active substance.

terminate, 1. The degree of advancement of the disease in the lepromatous cases, as shown in Table 1, was marked in 31, moderate in 23, and slight or early in only 3. As is also shown in that table, 41 of the 57 lepromatous cases showed neural involvement, and 22 had nodules; almost all of them had marked macules, only the three early cases having slight macules. Of the 22 patients classed as "nodular," all but 4 had macules, usually widespread and advanced.

TABLE 1.—*Classification, clinical features and treatment of the 67 cases receiving Sulfon-Cilag.*

Type and group	No. of cases	Clinical features (lepromatous cases)							Treatment		
		Form				Advancement			Duration (weeks)		Total dose (gm.)
		Macular		Nodular	With neural	Slt.	Mod.	Mkd.	Range	Ave.	
		Slt.	Mkd.								
Lepromatous 1	18	1	17	4	14	1	6	11	12	12	15.1
Lepromatous 2											
Group *a*	6	—	23	12	18	0	3	3	13–24	16.5	17.2
Group *b*	10					0	4	6		17.4	30.8
Group *c*	6					0	4	2		18.7	47.7
Group *d*	4					0	2	2		22.3	72.6
Lepromatous 3	6	1	4	3	3	1	2	3	25–36	30.2	33.4
Lepromatous 4	7	1	6	3	6	1	2	4	36	46.0	75.5
Subtotal	57	3	50	22	41	3	23	31			
Tuberculoid	9	—	—	—	—	—	—	—	—	30	38.8
Indeterminate	1	—	—	—	—	—	—	—	—	19	15.2

Material for the bacteriological examination was obtained by the "scraped incision" method from each of the following sites: right earlobe, forehead, right cheek, margin of an active lesion, apparently healthy skin, nasal mucosa, and edge of an ulcer if present ([7, 9]). The material so obtained was stained by the Ziehl-Neelsen method. The bacterial index was calculated, after the examination of fifty typical oil-immersion fields, according to the formula suggested by Dharmendra ([3]) and Cochrane ([2]):

1. Slight. Bacilli in occasional fields, not more than 2 or 3 per field; 1 or 2 small globi in 50 fields.

2. Moderate. Bacilli in every field, but not more than 10 per field; a few globi here and there.

3. Heavy. Numerous bacilli and globi in every field.

4. Massive. Innumerable bacilli, and large numbers of globi in every field. The first and last indices are reported in this paper, the intermediate three-monthly records being omitted.

The Sulfon-Cilag tablets were administered in the mornings. The dose for the first week in all adult cases was 200 mgm. on alternate days, i.e., thrice weekly; thereafter, a daily dose was given six days a week. The size of the dose varied according to the general condition, weight, and therapeutic response of the individual: 100 mgm., 150 mgm., or 200 mgm., daily for six days a week. After three weeks' treatment, a week's rest was allowed.

The amount of treatment given the several groups is also shown in Table 1. In this matter, it will be noted, the lepromatous cases have been divided into four groups according to the duration of the treatment: Group 1, 12 weeks; Group 2, 13-24 weeks; Group 3, 25-36 weeks; and Group 4, more than 36 weeks. The second group has been subdivided according to the dosage; (*a*) low, (*b*) low-moderate, (*c*) high-moderate, and (*d*) high.

RESULTS

Clinical changes.—In judging the clinical results, the criteria adopted were subjective well-being, general health, retrogression of macules with cicatrization and repigmentation, diminution in size of nodules, and healing of trophic ulcers. The findings are given in Table 2. The "improvement index" given in the last column is a rough clinical yard-stick, useful for comparative purposes when the same observer examines the patients over the same range of time. It is calculated as follows:

Stationary, ... 1 point;
Slight improvement, ... 2 points;
Moderate improvement, ... 3 points;
Marked improvement, ... 4 points.

Thus, cases that become worse during treatment do not affect this improvement index; they are apparently resistant to treatment by the particular drug used in the doses administered.

TABLE 2.—*Results of treatment, by type, and group, and by degree of advancement of the disease.*

Type and group	No. of cases	Worse	Stationary	Improved			Improvement index
				Slt.	Mod.	Mkd.	
All cases, by type and group							
Lepromatous 1	18	0	3	6	6	3	2.4
Lepromatous 2							
Group *a*	6	1	0	2	1	2	3.0
Group *b*	10	0	3	2	5	0	2.2
Group *c*	6	1	3	1	1	0	1.6
Group *d*	4	1	1	0	2	0	2.3
Lepromatous 3	6	0	1	4	0	1	2.2
Lepromatous 4	7	0	0	3	3	1	2.7
Subtotal	57	3	11	18	18	7	2.4
Tuberculoid	9	0	0	1	6	2	3.1
Indeterminate	1	0	1	0	0	0	1.0
Lepromatous cases, by degree of advancement							
Early	3	0	2	0	1	0	1.7
Moderate	23	3	3	7	9	1	2.4
Marked	31	0	6	11	8	6	2.5

It is recognized that the figures in Table 2 are not statistically valid, for the groups are much too small. That factor doubtless explains at least in part some of the apparently anomalous findings, notably the higher improvement index of the Group 2*a* cases, treated with low doses, than those of the groups receiving larger doses.

There is, therefore, no warrant to draw any but the broadest conclusions. However, there was among these patients improvement attributable to treatment greater than could be expected in cases that had been clinically stationary at the beginning of treatment and for some time previously. In some instances there was a halting and a reversal of the steady deterioration seen before the beginning of treatment. It is evident that improvement may be more marked in the more advanced cases of lepromatous leprosy than in the earlier cases. The patients who will eventually respond to treatment will show amelioration in their clinical condition within three months. The presence, as in all such series, of unknown factors determining unpredictable changes in clinical state and variable response to therapy forbids further analysis.

Bacteriological changes.—The changes in the bacterial index accompanying the treatment are indicated in Table 3, which gives the indices calculated both before and immediately after the conclusion of the treatment.

TABLE 3.—*Bacteriological and hematological changes in the patients treated.*

Type and group	No. of cases	Bacteriological[a]					Hematological[b]		
		Index		Patients			No. pats.	Decrease	
		Before	After	Impr.	Stat.	Worse		Hb	RBC
Lepromatous 1	18	2.7	0.9	15	3	0	10	11	786
Lepromatous 2	(26)						12	10	865
Group *a*	6	1.7	0.7	4	0	2			
Group *b*	10	1.6	0.6	8	1	1			
Group *c*	6	2.2	1.0	4	1	1			
Group *d*	4	2.6	1.0	4	0	0			
Lepromatous 3	6	2.8	1.5	5	1	0	2	—	735
Lepromatous 4	7	2.5	0.4	7	0	0	3	5	650
Subtotal	57	2.3	0.8	47	6	4	27	10	792
Tuberculoid	9	0.9	0.1	9	0	0	6	8	670
Indeterminate	1	0.7	0.0	1	0	0	1	10	220

a The bacteriological index is Dharmendra's (see text), calculated before and after treatment.

b The hematological changes were of the hemoglobin only, or of the red blood cells only, or of both, but for consideration of space these are combined in the figures in the Number of Patients column. The decrease data are average, percentages for the hemoglobin (Hb), thousands for the red blood cells (RBC).

Of the 15 patients who showed no clinical improvement at the conclusion of the treatment, 12 being clinically stationary and 3 worse, 11

nevertheless showed improvement in the bacteriological index. Three of these were in the first, and 4 in the second, of the lepromatous groups; the other case was the indeterminate one.

Of the 10 patients showing no bacteriological improvement during the treatment, 4 being worse and 6 stationary, 6 showed some improvement clinically. In 3 of them it was slight, but in the other 3 it was of moderate degree.

It is evident that patients who will eventually respond to the drug will show early evidence, by a reduction in the bacteriological index, of that ultimate response. Further treatment in such cases will confirm the earlier improvement, more of the bacilli showing irregular staining, fragmentation and disintegration.

Hematological changes.—Hemoglobin values were determined by the Tallqvist method at monthly intervals during the administration of the drug, and erythrocyte counts were made. Iron was administered in all cases, in the form of Blaud's pills. The numbers of cases in which there was diminution of the hemoglobin, or of the erythrocyte count or both, are shown in Table 3, together with the average decreases.

Thus, in spite of the administration of iron in theoretically adequate amounts, about one-half of the treated patients (34 of 67) suffered slight anemia. The erythrocytes were more vulnerable than the hemoglobin.

Toxic manifestations.—Albuminuria did not occur in any case under treatment. No case of jaundice was noted. Many patients complained of generalized aches, or pain confined to the small bones of feet and hands. In 13 patients with lepromatous leprosy (4 in Group 1, and 9 in Group 2), the pain was considered severe enough to warrant sedation.

Trophic ulcerations.—Local treatment of ulcers was continued unchanged in the individual cases, any amelioration being attributed to the effect, direct or indirect, of the specific therapy. There were 26 cases with such lesions; 2 were of the tuberculoid group, and the other 24 were lepromatous. There was no improvement in the 2 tuberculoid cases, or in 10 of the lepromatous ones, but of the 14 that were improved 11 showed almost complete healing of the ulcers.

Neural involvement.—No improvement was noted in the extent of anesthesia. In one of the tuberculoid cases neural involvement was first observed during the treatment, while the clinical condition generally and the bacteriological index were both showing improvement. One patient showed deterioration of the neural involvement during treatment.

Laryngitis.—Three patients improved greatly; another became worse.

Lepra reaction.—Three patients showed moderately severe lepra reaction in the course of treatment.

CONCLUSIONS

1. Sulfon-Cilag administered orally in small doses has shown definite therapeutic effect in lepromatous and active tuberculoid leprosy.

2. Active tuberculoid lesions, both major and minor, whether bacteriologically positive (*"poussées bacillifères"*) or negative, all responded to treatment; all of the tuberculoid patients were subjectively, clinically, and bacteriologically improved as the result of treatment. The raised, succulent edges of the lesions became inactive, and cicatrization and repigmentation progressed towards complete healing.

3. Lepromatous cases showed, in the main, both clinical and bacteriological improvement during the period of treatment. Clinical improvement was not generally maintained at the initial rate. The bacteriological index does not always change *pari passu* with amelioration in the clinical condition, but diminution in this index is a favorable indication. It suggests that if therapy could be continued for longer than was possible in the cases under review, it would result in both bacteriological and clinical amelioration.

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RESÚMEN

1. El Sulfón-Cilag administrado por vía oral a dosis pequeñas reveló efecto terapéutico bien definido en la lepra lepromatosa y tuberculoidea activa.

2. Todas las lesiones tuberculoideas activas, tanto mayores como menores, ya positivas (*"poussées bacillifères"*) o negativas bacteriológicamente, respondieron al tratamiento; todos los enfermos tuberculoideos mejoraron subjetiva, clínica y bacteriológicamente a consecuencia del tratamiento. Los bordes suculentos elevados de las lesiones se inactivaron y la cicatrización y la repigmentación avanzaron hacia la curacón total.

Los casos lepromatosos revelaron, en lo principal, mejoría tanto clínica cuanto bacteriológica durante el período de terapéutica. La mejoría clínica no se mantuvo generalmente a la velocidad inicial. El índice bacteriológico no se altera siempre *pari passu* con el mejoramiento del estado clínico, pero la disminución de este índice constituye una indicación favorable, sugiriendo que, si pudiera continuarse la terapéutica más tiempo de lo que fué posible en los casos en estudio, daría por resultado mejoramiento tanto bacteriológico como clínico.

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