CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY: A 48-WEEKS' STUDY OF CYCLOSERINE THERAPY

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Cycloserine is an antibiotic produced by *Streptomyces orchidaceus*, discovered and isolated by Harned *et al.* (7) of the Commercial Solvents Corporation. It is apparently identical with oxamycin, which was extracted from *Str. garyphalus* by Harris *et al.* (8). It is water soluble and of low molecular weight. Its wide but relatively low antibacterial activity was demonstrated by Welch *et al.* (13). In a strength of 10 to 20 mcgm. per cc. it has been shown to completely inhibit growth of various strains of *Mycobacterium tuberculosis*, by Cummings *et al.* (2) and Barclay and Russe (1). Patnode *et al.* (10) found that it has little or no antituberculosis effect in mice, guinea-pigs, and rabbits, but Schmidt (11) noted that it delayed death of monkeys with established tuberculosis.

Cycloserine is well tolerated by a variety of small animals, signs of toxicity appearing only with large doses and being confined to the central nervous system. In man, a dosage of 1 gm. daily is usually well tolerated, but lethargy and somnolence occasionally appear and if the drug is not withdrawn the patient may become disoriented. In extreme cases, convulsions may occur. For reviews of the subject, reference is made to Modave (9), and Storey and McLean (12).

EXPERIMENTAL

Following a favorable preliminary report on the use of cycloserine in treatment of pulmonary tuberculosis by Epstein *et al.* (6), it was decided to make a limited trial in lepromatous leprosy.

At each of two Philippines institutions, Central Luzon Sanitarium and Eversley Childs Sanitarium, 20 patients suffering from lepromatous leprosy were selected. No

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known epileptic or mentally ill patient was included. At each institution the patients were divided into groups of 10 each, pairs of patients being matched as closely as possible in respect to sex, age, body weight, prior sulfone therapy, bacteriologic findings and current clinical status. One group at each institution was placed on cycloserine (CS) and the other on 4-4′-diaminodiphenyl sulfone (DDS).

All patients were seen by a physician at least three times weekly for several weeks, especially to detect evidence of somnolence, dizziness or mental confusion. Laboratory tests included examination of the urine for urobilinogen by the Wallace-Diamond method and for bilirubin by use of Ictotest. Index cards and records of clinical and bacteriologic examinations were prepared in the same manner as for the first, second and third series of clinical evaluation studies ([3, 4, 5]).

The trial was limited to 48 weeks. At Eversley Childs, treatment was commenced on June 22, 1955, and continued until May 23, 1956. At Central Luzon treatment was started on July 5, 1955, and continued until June 5, 1956. Both CS and DDS were given orally, six days weekly. The initial dose of CS was one capsule (250 mgm.) daily. This was increased in the third week to 500 mgm., in the fifth week to 750 mgm., and in the seventh week to a maximum of 1 gm. daily. The actual total number of capsules taken by patients completing treatment averaged 973 at Eversley Childs and 530 at Central Luzon. Blood level determinations were made by a colorimetric method described in a mimeographed circular of Eli Lilly and Co. entitled Seromycin (cycloserine, Lilly).[2] During the 40th week patients at Eversley Childs showed blood levels from 8.0 to 40.5 megm. per cc. During the 12th week at Central Luzon the blood levels varied from 9.5 to 34.2 megm. Later observations were not made at Central Luzon.

The initial dose of DDS was 50 mgm. three times weekly for the first two weeks. This was increased progressively to a maximum of 200 mgm. daily at the ninth week. The actual amounts taken by patients who completed treatment averaged 47 gm. for those at Eversley Childs and 27 gm. for those at Central Luzon. The sulfone blood levels at the 16th week and at the 32nd week averaged 0.5 mgm. per cent at Eversley Childs. Blood levels were not obtained at Central Luzon.

A detailed record was kept for each patient, of both groups, with entries made at least four times during the course of treatment, showing occurrence or nonoccurrence of a list of signs and symptoms referring to the gastrointestinal and nervous systems, auditory loss, fever, anemia and jaundice, and cutaneous eruption.

There were no serious manifestations of intolerance. Vertigo was recorded once or oftener in 6 patients at Central Luzon in the CS group and in 1 of those given DDS. At Eversley Childs, vertigo was recorded only once—in a patient receiving CS. Erythema nodosum leprosum occurred in patients of both groups and was at least as severe, if not more so, in those receiving CS as in those given DDS.

RESULTS

Of the original 10 patients on cycloserine at Eversley Childs, 3 absconded or were not available for final examination, and 7 completed therapy. Of the 10 on DDS, 2 absconded and 8 completed therapy. Of the original 10 on CS at Central Luzon, one died in September from leprous cachexia, 2 absconded, and 7 completed therapy. Of those on DDS, all completed therapy. So, for both institutions, 14 of those on CS and 18 of those on DDS completed the 48-weeks therapy.

Clinical.—In the opinion of the consultant examiners, based upon assessment of changes in infiltrations, nodules, plaques, ulcers and a variety of other signs, 4 of the 14 on CS showed improvement, and 14

[2] Seromycin (Eli Lilly and Co.) is the registered trade mark for cycloserine.

of the 18 on DDS. Although the numbers are small it is clear that CS showed no advantage over DDS as far as could be judged by clinical observations—aided by black-and-white and color photographs taken during the preliminary examinations.

Bacteriologic.—Smears from eight sites—each side of the nasal septum, right and left earlobes, and four optional skin sites—were examined on at least three occasions: before starting therapy, at the end of 24 weeks, and at the end of 48 weeks.

On preliminary examination, all patients were positive in smears from two or more of the skin sites. Bacteriologic improvement occurred in both therapy groups, at both institutions, but no patient was negative at all sites at the end of 48 weeks' therapy. Following the same criteria as in previous studies ([3, 4, 5]), positivity was graded from very scanty (vs) to 4-plus. Counting "vs" as 1.0, 1+ as 2, 2+ as 3, etc., the average scores for patients of both institutions who completed treatment were as shown in Table 1.

TABLE 1.—*Average bacteriologic scores, for patients treated with DDS and CS respectively, before therapy and after 24 and 48 weeks of treatment.*

Sites and Group	Preliminary	24 weeks	48 weeks
Skin sites ([6])			
DDS Group	25.0	20.4	16.2
CS "	24.0	20.8	18.2
Nasal septum sites ([2])			
DDS Group	7.2	5.1	4.2
CS "	7.9	5.6	5.7

As is evident from the table, the records show little difference between the groups in respect to either the rapidity or the extent of bacteriologic improvement. There is certainly no indication of superiority of CS over DDS.

CONCLUSIONS

1. In matched groups of patients suffering from lepromatous leprosy, there was no evidence, clinical or bacteriologic, of superiority of cycloserine over 4-4′-diaminodiphenyl sulfone in a trial lasting 48 weeks.
2. Cycloserine was well tolerated by these patients.

CONCLUSIONES

1. En grupos equiparados de enfermos que padecían de lepra lepromatosa, no se observaron signos, ya clínicos o bacteriológicos, de superioridad de la cicloserina sobre la 4,4-diaminodifenil-sulfona en una prueba que duró 48 semanas.
2. La cicloserina fué bien tolerada por los enfermos.

Acknowledgments.—This study was a joint enterprise of the Leonard Wood Memorial (American Leprosy Foundation) and the Department of Health of the Republic of the Philippines. Generous assistance was received from Dr. A. Runez, director of the Central Luzon Sanitarium, from Dr. A. C. Jovellanos, director of the Eversley Childs Sanitarium, and from the staffs of these institutions. Financial support was received from Research Grant E-199, National Institute of Allergy and Infections Diseases, National Institutes of Health, U.S. Public Health Service; U.S. Veterans Administration; Leonard Wood Memorial; Abbott Laboratories; Lederle Laboratories, Division of American Cyanamid Co.; Eli Lilly and Co.; and Parke, Davis & Co. Cycloserine (Seromycin) was donated by Eli Lilly and Co. Generous assistance was also received from the shipping companies of the Far East Conference in transporting drugs, and from the Maron Shipping Agency in packing and expediting shipments.

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