CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY FOURTH SERIES:

4,BUTOXY-4′DIMETHYLAMINODIPHENYL THIOUREA (DPT), AMODIAQUIN, AND 4-4′DIAMINODIPHENYL SULFONE (DDS) 2.5 MGM. AND 4 MGM. PER KG. OF BODY WEIGHT

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INTRODUCTION

In 1955 Buu-Hoï *et al.* (1) reported improvement in 11 of 13 cases of leprosy treated for 6 months with a thiourea, 4,4′diethoxythiocarbanilide. A few months later a preliminary report was published by Davey and Currie (2) stating that another thiourea, 4,butoxy-4′dimethylaminodiphenylthiocarbanilide, had been found "to have negligible toxicity at the dosages used and to possess activity against *M. leprae* during the first year of treatment very similar to that displayed by DDS." The latter drug was originally labeled SU 1906 and later CIBA 1906 by the manufacturer, CIBA Pharmaceutical Products, and is sometimes called DPT. In 1953, Mayer *et al.* (7) had shown that SU 1906 and certain other thioureas exhibited antituberculosis activity greater than that of streptomycin and approaching that of isoniazid, both *in vitro* and in the mouse, and, in 1954, Schwartz *et al.* (8) had reported promising results in pulmonary tuberculosis in man. Because of these reports, SU 1906 was selected for trial in the fourth series of our clinical evaluation studies.

In a personal communication to Dr. E. P. Payne of Parke, Davis and Co., Dr. Mario Lujan Fernandez of Costa Rica reported favorable results with the anti-malarial drug amodiaquin (Camoquin, Parke, Davis and Co.) in the reactions of lepromatous leprosy. No untoward effects, and for the most part beneficial results, had been observed in a large number of patients. Because of the possibility that it might be effective against the basic disease, either by direct action against *M. leprae* or by aiding the natural processes of recovery through reduction of the frequency and severity of reactions, it was decided to include amodiaquin also in the fourth series.

As in our third series, 4,4′diaminodiphenyl sulfone (DDS) was chosen as the reference drug. To ascertain the relative value of higher and lower doses of DDS, a daily dosage of 2.5 mgm. per kgm. of body weight was prescribed for one group of patients and 4.0 mgm. per kgm. for another. Since the average weight of the adult Filipino male patient has been found to be about 50 kgm. these dosages were equivalent to about 125 mgm. daily for the average adult male on the lower schedule and 200 mgm. on the higher. Another purpose of using two levels of dosage of DDS was to study the correlation of the dosage with the frequency and the severity of reactions. There is a widespread opinion among leprologists that the reactions of lepromatous leprosy are more frequent and severe when higher dosages of sulfones are used than when the doses are smaller, but as far as we are aware this question had never been subjected to a controlled study.

PROCEDURES, METHODS AND MATERIALS

Organization.—Volunteers for the study were obtained at the Central Luzon Sanitarium, situated about 20 miles north of Manila, and at the Eversley Childs Sanitarium, situated 8 miles north of Cebu City. At each institution a leprologist, nurses, technicians and clerks were assigned to the work.

Technical procedures were standardized as far as possible. These included the dosages and methods of administration of drugs, various laboratory techniques, photography of patients, and recording of clinical and laboratory observations.

Physical examinations.—Regular dermatologic and neurologic examinations were made by the research leprologists prior to therapy and at bimonthly intervals thereafter. Special examinations were made when indicated by worsening of signs or symptoms. The nose and throat examinations were made with the aid of a head mirror, and one of us (J.G.T.) was responsible for these examinations at both institutions. In addition to being recorded on prescribed forms, the findings were depicted graphically on dermatologic and neurologic charts. One of us (J.G.T.), in the capacity of a nonresident consultant, examined all patients at Central Luzon prior to therapy and at the end of 24, 48, 72 and 96 weeks. Another of us (J.N.R.) examined the patients on these occasions at Eversley Childs.

Bacteriologic examination.—Separate smears were examined from eight sites: right and left sides of the nasal septum, right and left earlobes, and four optional skin sites. These examinations were made on at least five occasions—during the preliminary period, and at the end of 24, 48, 72 and 96 weeks of treatment.

Photographic records.—Several black-and-white and color photographs of each patient were made prior to therapy, at the end of 72 weeks, and at the end of 96 weeks.

Other examinations.—Hemoglobin values, packed red-cell volume, erythrocyte

counts, sedimentation rates, total leukocyte and differential counts, levels of sulfone in blood serum, and presence of albumin, sugar, casts, urobilinogen and bile in the urine were determined prior to therapy and at intervals throughout the study. Lepromin tests were made three times, prior to therapy and at the end of the 72nd and the 96th weeks. The blood protein pattern was studied by the method of paper electrophoresis prior to therapy, and at the end of 12, 24, 48, 72 and 96 weeks of treatment. The patients were weighed prior to therapy and at the end of 48, 72 and 96 weeks of therapy.

Selection of patients and assignment of groups.—At the Central Luzon Sanitarium, 250 patients were selected for the experiment, and 250 at Eversley Childs Sanitarium. As in the previous three series of these studies, an index card was prepared for each patient on which was entered a code name, date of birth, sex, previous therapy (if any), year of onset, date of admission, stage of disease, bacteriologic findings, and presence or absence of infiltration, nodules and certain other signs, height, weight and some miscellaneous items. These cards were airmailed to the medical director, Leonard Wood Memorial, in Washington, D.C.

The plan that was adopted required the arrangement of the patients at each institution into four groups: SU 1906, designated A/F; amodiaquin, B/K; higher sulfone (4 mgm.), C/W; and lower sulfone (2.5 mgm.), D/Y. Sufficient drugs were available for only about 225 patients at each place. Twenty-six patients were therefore dropped from the Central Luzon list and 24 from that for Eversley Childs, those dropped being ones with the greatest amount of previous sulfone therapy.

The method of assignment to groups was that used in the preceding three series. The index cards for each institution for patients of each sex were arranged in order of decreasing age. The four oldest males were each assigned to a group using a table of random numbers, then the second lot of males, and so on through the rest of the males and females. Frequency distributions were prepared for the groups at each institution for such items as lengths of previous sulfone treatment, duration of stay, and stage of disease. After examination of these distributions a few changes were made to achieve better balance, especially in respect to stage of disease and previous sulfone treatment. The names of the patients selected for each group were then airmailed to the respective institutions.

Eight patients at Central Luzon and 22 at Eversley Childs were lost from the study for various reasons after they were selected but before the preliminary examination. At Central Luzon, 2 had been transferred to Culion, 2 refused to enter the study and 4 left the institution. Each of these was replaced by a new patient matched against the original one in various ways and of almost exactly the same weight. At Eversley Childs, 20 had left the institution, 1 had become seriously ill, and 1 had become clinically inactive. Each of these was replaced by another exhibiting clinical signs closely similar to those present in the replaced patient at the time the original selection was made. After these replacements were made the frequency of various characteristics in each group was again carefully studied. In addition to being comparable in age and sex distribution, the four groups remained remarkably alike with respect to average bacteriologic score, prior sulfone treatment, and percentages of patients in different stages of the disease. These characteristics are given for all entering patients in Table 1.

Double blind principle of therapy.—In setting up the study, the principle of the "double blind" experiment was adhered to. Neither physician nor patient knew the therapy to be given to any individual. For the protection of the patient, a sealed envelope containing a list of the patients in each therapy group at each institution was entrusted to one of us (R.S.G.) who was not responsible for therapy at either place and was not acquainted with any of the patients. The agreement was that if any patient should become worse to a point where in the opinion of two leprologists a change of treatment was desirable, he was to be discharged from the experiment and assigned to the care of a special consultant who was not connected with the clinical evaluation studies. The seal was to be broken only upon request of one of these consultants.

TABLE 1.—*Status of patients on admission to the fourth series, in respect to certain characteristics possibly related to prognosis, by therapy group and institution.*

Characteristic of therapy group	Central Luzon					Eversley Childs				
	A/F	B/K	C/W	D/Y	All groups	A/F	B/K	C/W	D/Y	All groups
No. of patients	56	56	56	56	224	56	57	56	57	226
Average										
Age (years)	29.8	30.5	30.5	30.3	30.3	25.4	24.0	24.3	23.4	24.4
Weight (lbs)	102.3	101.8	103.0	103.7	102.7	98.3	102.9	102.4	98.0	100.4
Bact. score	26.7	27.2	27.9	25.5	26.8	29.8	30.0	28.4	29.2	29.3
Percentage										
Male sex	64.3	64.3	64.3	64.3	64.3	78.6	77.2	76.8	75.4	77.0
L1 or L2 class	55.3	64.3	62.5	57.1	59.8	94.6	94.7	98.2	98.2	96.5
Prev. untreated°	66.1	75.0	66.1	71.4	69.6	32.1	17.5	21.4	26.3	24.3

° Includes all patients who had either received no DDS previously or a total of less than 10 grams.

The problem of concealment of the therapy given each of the groups was resolved as follows: A tablet resembling the yellow tablets of SU 1906 in size and taste, but differing in color, was given to patients of each of the three groups not receiving SU 1906. Two of these tablets, K and Y, were placebos but the third one, W, given to group C/W, contained the higher dose of DDS. Also, three additional placebo tablets were prepared, each resembling in appearance and taste that of amodiaquin (tablet B); these were designated, respectively, A, C and D and were given to the groups not receiving amodiaquin, that is, A/F, C/W and D/Y. To confuse the picture further the DDS tablet for the lower dose of DDS was a specially prepared one (Upjohn 55-C or 56-C) which was given as a pretended supplemental treatment to Group D.

Therapies used.—The rather complicated scheme of therapy may be summarized as follows:

Group	*Drug studied*	*Guide to therapy*
A/F	SU 1906	*Yellow* PD&Co. tablet (CID 842 "A") °*Yellow* CIBA tablet "F"
B/K	Amodiaquin	°*Yellow* PD&Co. tablet (CID 369 "B") *Light Blue* CIBA tablet "K"
C/W	DDS, 4 mgm.	*Yellow* PD&Co. tablet (CID 842 "C") °*Pink* CIBA tablet "W"
D/Y	DDS, 2.5 mgm.	*Yellow* PD&Co. tablet (CID 842 "D") *Dark Green* CIBA tablet "Y" °UPJOHN tablet 55-C or 56-C

° Indicates drug being studied.

Each patient was provided with a laminated plastic identification card, of the same color as his CIBA tablet, i.e., yellow, blue, pink or green, showing case number, name, sex, date of birth, weight and group.

In the case of group B/K the treatment became known through an untoward incident which is discussed below under the title "amodiaquin blueness." The treatment given

to other patients—although it was known that some were on sulfones and others on a thiourea—remained undisclosed until the end of the 96 weeks of therapy.

Unbiased appraisal of clinical and bacteriologic status.—Three working rules were adhered to in the physical examinations: (1) the patients were presented to the examiner in a sequence unrelated to therapy group; (2) the clinician was required to make his assessment of changes on clinical grounds only, that is, without knowledge of bacteriologic or other laboratory findings, and (3) the opinion of the examining clinician was obtained in writing at the conclusion of each examination. The laboratory findings in turn were made by personnel not engaged in the clinical work and to whom the treatment of the patients was not known, except when this was disclosed by chemical tests of the blood serum—the results of which were recorded on a different form from that on which bacteriologic results were entered.

Duration of treatment.—At each institution there was a preliminary period of at least 35 days for examinations, during which time no sulfone therapy was administered. The duration of the experimental treatment was originally fixed at 72 weeks; later this was extended to 96 weeks—except for the amodiaquin group in which therapy was terminated at the end of 72 weeks. The actual periods were: At Central Luzon Sanitarium, June 17, 1957, to April 20, 1959 and at Eversley Childs, June 3, 1957, to April 6, 1959.

SIGNIFICANT EVENTS DURING THERAPY

Dosages prescribed and actually taken.—The recommended dosages of SU 1906 and of the sulfones were carefully and individually calculated. The maximal doses were reached after an induction period of nine weeks and were for SU 1906, 60 mgm. per kgm. of body weight; for DDS, higher dose, 4 mgm. per kgm.; and for DDS, lower dose, 2.5 mgm. per kgm. The dose of amodiaquin (CID 369B) was 0.2 gm. daily for each patient. All drugs were taken orally, six days weekly, under supervision.

Chiefly because of the occurrence of erythema nodosum, the patients frequently asked to have their treatment temporarily suspended or to have the quantity reduced. This resulted in a lowering of dosage, especially at Central Luzon. At Eversley Childs, the proportions of the quantities prescribed which were actually taken were very high considering the duration of the experiment. The record for each group and each institution may be seen in Table 2.

TABLE 2.—*Average quantities of drugs per patient, prescribed and actually taken, for patients who completed 96 weeks of treatment (72 weeks for amodiaquin) by therapy group and institution.*

	Central Luzon			Eversley Childs		
	Average amount (gm.)			Average amount (gm.)		
Therapy	Prescribed	Taken	% Taken	Prescribed	Taken	% Taken
SU 1906	1474	661	44.8	1412	1237	87.6
Amodiaquin	83	56	67.5	83	76	91.6
DDS (4 mgm.)	102	43	42.2	97	85	85.6
DDS (2.5 mgm.)	64	44	68.7	62	52	83.9

Amodiaquin blueness.—The reason for discontinuance of amodiaquin at 72 weeks is an interesting story which has already been related in the JOURNAL (4). In the tenth week of therapy blueness of the skin, especially of the face, was reported in patients at Eversley Childs who were receiving amodiaquin. A short time later a similar observation was made at Central Luzon. The blueness (greenish blue) had an affinity for areas of diffuse or localized infiltration. None was observed in the conjunctivae, the buccal mucous membranes, or on the hard or soft palate. The blueness was not accompanied by constitutional symptoms, and no abnormalities were observed in the urine or in the results of the liver function tests.

Amodiaquin had never been known, as far as we were aware, to cause blueness,[1] and, thinking that the "light blue" placebo Ciba tablet "K" was to blame, this tablet was discontinued for several weeks. This did no good and it was learned from the manufacturer that the dark green tablet "Y" given to Group D/Y had about seventy times as much of the blue dye (FD Blue No. 1) as did the light blue tablet given to Group B/K. In the meantime, one of us (J.G.T.) had observed the blue discoloration in a small series of patients given amodiaquin alone, and not in patients given the light blue tablet alone.

A number of biopsy specimens from blue areas were examined at the Armed Forces Institute of Pathology, Washington, D. C., by histochemical methods by Dr. Frank B. Johnson and his associates. Their report states:

1. Histochemical studies were performed on 9 specimens from patients of B/K group, Central Luzon.
2. A strong reaction for iron was observed in subcutaneous tissue, particularly in association with foci of mononuclear inflammatory cells in one of the cases. This iron reaction is due to the presence of a brown granular pigment, which is presumably hemosiderin.
3. In two other cases, small traces of similar pigment were observed.
4. No iron positive pigment was observed in 15 sections of lepromatous skin lesions from AFIP files.
5. It is possible that the presence of the brown granules could account for the blue lesions in one case. The hemosiderin might be due to local hemorrhage or to increased permeability of blood vessels in the lesion, incident to therapy.
6. All tissue elements, with the exception of red blood cells, appeared well preserved by being shipped in the frozen state.

At the end of 72 weeks the clinical status of the patients of the B/K group at each institution was clearly not as good as that of the patients of the other groups, and it was decided to terminate the amodiaquin therapy. Most of the patients were placed on DDS, and nearly all remained in the study for clinical and bacteriologic observation until the end of 96 weeks. The fact that only a few B/K patients discontinued therapy prior to the end of 72 weeks was surprising. Of 113 patients

[1] Since this was written pigmentation following amodiaquin administration has been reported by others. See Addendum to references.

at both institutions who were assigned to this group, 89 completed 72 weeks of treatment. Three discontinued because of blueness; 2 refused to continue for unknown reasons; 16 absconded; 1 was transferred to Culion, and 2 died.

Dropped patients.—Patients whose treatment was discontinued because of worsening of the disease were considered to have completed therapy. The records of their physical condition and bacteriology for the examination closest in time to date of withdrawal was taken as final.

At Central Luzon, 8 deaths occurred of which 6 were attributed to leprosy, 1 to gastric or duodenal ulcer and 1 to suicide; at Eversley Childs there were 2 deaths, 1 of which was charged to leprosy and the other to pulmonary tuberculosis. Autopsies were not obtained. The patients whose deaths were attributed to leprosy are counted among those becoming worse at the examination next following the date of death and at each subsequent examination.

The principal cause of leaving the study was departure from the institution without permission. The numbers of patients originally selected and completing various periods of treatment are shown for both institutions and for all groups in Table 3, those dropped being classified as to reasons for that action.

TABLE 3.—*Numbers of patients selected at Central Luzon and Eversley Childs classified according to treatment status at 24 weeks, 48 weeks, 72 weeks and 96 weeks.*

	24 weeks		48 weeks		72 weeks		96 weeks [a]	
Therapy status	C.L.	E.C.	C.L.	E.C.	C.L.	E.C.	C.L.	E.C.
Therapy complete	199	208	182	187	180	171	170	160
Died (leprosy) [b]	—	—	2	—	4	1	6	1
Not examined	3	3	6	4	—	—	—	—
Therapy incomplete								
Dosage insuff. (absc.)	14	12	28	28	33	33	40	42
Refused	6	2	2	4	2	4	2	4
Died (other causes) [b]	—	1	2	1	2	1	2	1
Transferred	1	—	1	2	2	16	3	18
Removed by parents	1	—	1	—	1	—	1	—
TOTAL	224	226	224	226	224	226	224	226

[a] Patients of B/K who were examined at 96 weeks are included although amodiaquin was discontinued at the end of 72 weeks.

[b] Deaths:

Central Luzon	A/F	49-80-57	Leprous cachexia and nephritis, 2/16/58, 35th wk.
	"	51-74-57	Lepra reaction and cachexia, 8/15/58, 61st wk.
	"	52-6-57	Gastric or duodenal ulcer, 12/10/57, 26th wk.
	B/K	48-78-57	Lepra reaction and cachexia, 7/15/58, 57th wk.
	"	56-19-57	Lepra reaction and nephritis, 3/19/59, 92nd wk.
	"	56-111-57	Leprous laryngitis, 12/8/57, 25th wk.
	D/Y	42-83-57	Suicide, 12/24/57, 28th wk.
	"	44-102-57	Lepra reaction and cachexia, 11/11/58, 74th wk.
Eversley Childs	A/F	55, 151	Lepra reaction and cachexia, 5/28/58, 52nd wk.
	C/W	54, 040	Pulmonary tuberculosis, 11/17/57, 24th wk.

As in the previous three series, comparison was made of the dropped patients with those remaining in the study with respect to those characteristics observed on preliminary examination that seemed probably related to prognosis. The average bacteriologic score, the percentage of cases classed as L2 and L3, and the percentage of the patients to whom no previous sulfone treatment had been given were investigated in particular. No significant differences were found with respect to the frequency of any of these characteristics between those who were examined and those not examined at 24, 48, 72 and 96 weeks, at either institution.

Since one of the most important of these characteristics, in our opinion, is the "heaviness" of the bacterial load, the average preliminary bacteriologic scores for patients who completed and who did not complete 96 weeks of observation are given in Table 4. Obviously the failure to be examined at the end of 96 weeks was not related to the degree of bacteriologic positivity at the commencement of the study.

TABLE 4.—*Average preliminary (before treatment) bacteriologic scores per patient (2 nasal sites, 6 skin sites) of each therapy group for patients who were examined and for those who were not examined at the end of 96 weeks, by institution.*

		Central Luzon Patients		Eversley Childs Patients	
Therapy group	Sites	Completing 96 weeks	Not completing	Completing 96 weeks	Not completing
A/F	Nasal	6.1	5.4	7.4	7.5
SU 1906	Skin	21.2	19.3	23.2	20.7
B/K	Nasal	6.1	7.3	7.8	8.3
Amodiaquin	Skin	20.5	21.4	21.8	23.2
C/W	Nasal	6.5	7.7	7.8	8.1
DDS 4 mgm/kgm.	Skin	20.8	23.7	20.4	20.6
D/Y	Nasal	6.1	4.9	8.8	7.2
DDS 2.5 mgm/kgm.	Skin	20.8	23.7	20.8	21.8
All groups	Nasal	6.2	6.2	8.0	7.7
	Skin	20.5	20.9	21.5	21.4
All groups	all	26.7	27.1	29.5	29.1

CLINICAL CHANGES

The difficulties of clinical appraisal of the value of drugs in leprosy have been discussed in previous reports. Essentially the same methods were used in the present study as before. The consultant was asked to give a numerical rating to the degree and extent of infiltration, nodulation and of a number of other lesions, for various regions of the body, at each physical examination. If any lesion was not present its absence was recorded. These ratings were added together for each type of lesion and used for comparison with results at later examinations. Neurologic and dermatologic charts of the patient's body, kodachrome transparencies, and black-and-white photographs made before therapy were used

to supplement the written record. On completion of each examination the consultant summarized in writing his opinion as to progress of the case, using the following grades: improved (marked, moderate or slight); stationary; or worse (slight, moderate or marked). Examination of the detailed ratings of the more significant cutaneous lesions has in nearly every instance provided support for the consultant's final opinion regarding progress of the disease.

A statistical summary of the clinical appraisals is given in Table 5, which shows the percentages of patients of each group falling into the respective grades on successive examination at each institution.

Inspection of Table 5 reveals several striking facts. The inferiority of amodiaquin to the other drugs is evident. The proportions of patients whose disease became worse were substantially higher for those treated with amodiaquin at the end of 72 weeks at both institutions, and the proportions of those improving were substantially lower. It is remarkable, however, that at Central Luzon 45.5 per cent and at Eversley Childs 33.3 per cent of the amodiaquin-treated patients were recorded as improved at that time. This raises the question as to whether this drug actually has some effect on leprosy. The bacteriologic findings will be discussed later, but it may be mentioned that in the first series of our studies as reported by Doull ([3]), the proportion of patients treated at Eversley Childs with the placebo Ceslu (inositol and glycine) and recorded as clinically improved after 48 weeks, was only 3.8 per cent. Central Luzon Sanitarium did not participate in the first series.

At both institutions, and especially at Eversley Childs, the clinical evidence of the superior position of the two sulfone groups over the amodiaquin one was clearly evident by the end of 72 weeks and was significant in the statistical sense at each institution, although the discoloration of the skin added to the difficulty of making an appraisal. At the end of 96 weeks, in spite of the fact that most of the amodiaquin patients had received DDS after the 72nd week, the difference in favor of the sulfone groups was even wider than it was at the 72-weeks examination.

The record of SU 1906 fell short of our hopes. At both institutions it showed superiority to amodiaquin at 72 weeks, especially as regards the proportion showing worsening of the disease, and it maintained this position at 96 weeks. In comparison with both higher and lower doses of DDS, however, SU 1906 showed consistently lower rates of improvement of all reexaminations except the first (24 weeks) at both institutions. It should be stated that the differences are small. In fact, at the end of 96 weeks, the proportion of patients classed as improved in the two sulfone groups taken together was not significantly higher than the proportion in the SU 1906 group at either institution. So we conclude that there may be a real difference in favor of the sulfones over SU 1906, but if so, further experiments are necessary to establish

TABLE 5.—*Percentages of examined patients classified by the consultants as improved, stationary, or worse at successive examinations at Central Luzon and Eversley Childs, by therapy groups.*

	Central Luzon				Eversley Childs			
	Weeks of treatment				Weeks of treatment			
	24 wks.	48 wks.	72 wks.	96 wks.	24 wks.	48 wks.	72 wks.	96 wks.
SU 1906								
No. of pts.	(50)	(45)	(45)	(45)	(51)	(43)	(40)	(37)
Improv.	44.0	46.7	53.3	51.1	15.7	53.5	47.5	64.9
Stat.	52.0	48.9	42.2	42.2	82.3	44.2	50.0	29.7
Worse	4.0	4.4	4.4	6.7	2.0	2.3	2.5	5.4
Amodiaquin [a]								
No. of pts.	(48)	(46)	(44)	(41)	(52)	(51)	(48)	(46)
Improv.	47.9	56.5	45.5	43.9	9.6	47.0	33.3	43.5
Stat.	43.7	34.8	29.5	19.5	88.5	43.1	50.0	43.5
Worse	8.3	8.7	25.0	36.6	1.9	9.8	16.7	13.0
DDS (4 mgm.)								
No. of pts.	(51)	(50)	(49)	(47)	(53)	(49)	(44)	(40)
Improv.	45.1	50.0	61.2	61.7	11.3	63.3	68.2	85.0
Stat.	47.0	48.0	38.8	36.2	84.9	32.6	31.8	15.0
Worse	7.8	2.0	—	2.1	3.8	4.1	—	—
DDS (2.5 mgm.)								
No. of pts.	(50)	(43)	(46)	(43)	(52)	(44)	(40)	(38)
Improv.	38.0	55.8	56.5	67.4	19.3	63.6	65.0	81.6
Stat.	50.0	37.2	43.5	30.2	78.8	31.8	32.5	18.4
Worse	12.0	7.0	—	2.3	1.9	4.5	2.5	—
Total								
No. of pts.	(199)	(184)	(184)	(176)	(208)	(187)	(172)	(161)
Improv.	43.7	52.2	54.3	56.3	13.9	56.7	52.9	67.7
Stat.	48.2	41.8	38.6	32.4	83.7	38.0	41.3	27.3
Worse	8.0	6.0	7.1	11.4	2.4	5.3	5.8	5.0
Both DDS groups								
No. of pts.	(101)	(93)	(95)	(90)	(105)	(93)	(84)	(78)
Improv.	41.6	52.7	58.9	64.4	15.2	63.4	66.7	83.3
Stat.	48.5	43.0	41.1	33.3	81.9	32.3	32.1	16.7
Worse	9.9	4.3	—	2.2	2.9	4.3	1.2	—

[a] Amodiaquin discontinued at 72 weeks; patients treated with DDS 72nd-96th weeks.

Note: There are slight differences in the numbers examined between these figures and those of Appendix A. Patients dying from leprosy are included above. In a few instances also the examination was complete in respect to clinical signs and not to bacteriology, or vice versa.

the fact. This refers only to clinical measurement; the bacteriologic one is discussed later.

Another observation which is of great practical importance is that the patients on the higher dosage of DDS (4 mgm./kgm.) did not im-

prove in greater proportion than those receiving the lower dose (2.5 mgm.), as far as the clinical evidence goes. It is suggested also that the higher rates of improvement in both the sulfone groups at Eversley Childs than at Central Luzon may have resulted from the fact that the patients at the latter institution did not receive on the average as great a proportion of the prescribed amount of DDS.

Effect of treatment on specified lesions.—As mentioned above, the consultants gave a numerical rating to the degree and extent of infiltration, nodules, and other lesions for different regions of the body (face, ears, trunk, buttocks and extremities) at each physical examination. These ratings were added for each type of lesion, and the totals for successive examinations were compared in an attempt to measure the effect of different therapies on specified lesions.

Infiltration: Infiltration was the one universal sign—as in the three previous series. Measurement of changes is highly subjective, especially when the preliminary findings indicate only a slight degree of infiltration. The recorded changes are shown in Table 6 for each therapy group at each institution.

TABLE 6.—*Numbers and percentages of the patients of each therapy group classed as improved with respect to infiltration, Central Luzon and Eversley Childs, after 96 weeks treatment.*

	Central Luzon			Eversley Childs		
	Number		%	Number		%
Therapy	Examined	Improved	Impr.	Examined	Improved	Impr.
SU 1906	42	30	71.4	36	24	66.7
Amodiaquin [a]	38	18	47.4	46	23	50.0
DDS 4 mgm.	47	33	70.2	40	32	71.4
DDS 2.5 mgm.	42	30	71.4	37	29	78.4
Total	169	111	65.7	159	108	67.9

[a] Treated with DDS from the 73rd through the 96th week.

Note: To reconcile the numbers examined with those shown for 96 weeks in Table 5, add the deaths from leprosy shown in footnote to Table 3. For one patient at Central Luzon (on SU 1906) the degree of infiltration was not recorded for the preliminary examination, and for one at Eversley Childs, on DDS 2.5 mgm., the degree was not recorded for the final examination.

It is evident from Table 6 that the amodiaquin group did not do as well as the other groups at either institution with respect to improvement of infiltration. When comparisons were made of the results for the sulfone groups taken together versus the amodiaquin group significant chi-square values were found at each institution. The difference between the sulfone groups and the SU 1906 one was not significant at either place.

Nodules: At Central Luzon, of 168 patients who were examined after

96 weeks of treatment, 29 (17.3%) were recorded as having nodules on the preliminary examination. Four patients developed nodules during therapy, and in 10 the existing nodules disappeared. There was no significant difference between the therapy groups with respect to occurrence of new nodules or to disappearance of old ones, except that disappearance did not occur in any patient treated with amodiaquin. At Eversley Childs, of 159 patients who were examined after 96 weeks of treatment, 22 (13.8%) were recorded as having nodules on the preliminary examination. One patient (in the amodiaquin group) developed nodules during therapy and in 14 the nodules disappeared. There was no difference between the therapy groups at Eversley Childs with respect to disappearance of nodules.

Lepromatous ulcers: (*a*) Nasal septum. As already mentioned, all nose and throat examinations were made by one of us (J.G.T.), using a head mirror and reflected light. At Central Luzon, of 166 patients who were examined after 96 weeks of treatment, ulceration of the septum was recorded on the preliminary examination in 74 (44.6%). There were 2 patients for whom the results of preliminary examination were not recorded. In the SU 1906 group there were 20, and in 3 of these healing took place before the end of 96 weeks. Of 21 other patients of this group, in whom no ulceration had been observed on preliminary examination, 8 developed ulceration during therapy. In the amodiaquin group, there were 17 patients in whom ulceration was noted prior to therapy, and healing took place in 4. Ulceration occurred in 5 of 20 who were negative at the beginning. In the DDS (4 mgm.) group there were 19 on the preliminary examination, and healing took place in 8. Ulceration developed in 8 of 28 who were free at the outset. In the DDS (2.5 mgm.) group there were 18, and healing took place in 9. New ulceration occurred in 5 of 23 in whom it had not previously been observed. Thus, in the two sulfone groups taken together, the record at Central Luzon showed healing in 46 per cent and new ulceration in 25 per cent. This is a poor record for a drug that is commonly supposed to heal such ulcerations fairly promptly. It is, however, a better record than that of the SU 1906 or the amodiaquin group. Taken together, these two groups showed healing in 19 per cent of patients and new ulceration in 32 per cent.

At Eversley Childs, ulceration of the nasal septum was noted on preliminary examination in 39 (24.8%) of the 157 patients who completed 96 weeks of therapy. There were 2 patients for whom the results of the 96 weeks examination were not recorded. In the SU 1906 group, ulceration was present in 8 patients; in 5 of these healing took place, and ulceration occurred in only one of 28 in whom it had been absent. In the amodiaquin group, ulceration was present in 11 patients, and in 6 healing took place. Ulceration occurred, however, in 4 of 35 in whom it had been absent. The sulfone groups had a better record, and did not

differ from one another; in both taken together, ulceration was present in 20 patients and healing took place in 18 (90.0%). New ulceration was observed in only 3 of 55 patients in whom it was not present at the beginning. It is of interest that 2 of the Eversley Childs patients who developed ulceration of the nasal septum while under treatment were receiving 4.0 mgm. of DDS per kgm. of body weight. One is known to have taken 91 per cent of the prescribed dosage; the other, 88 per cent. The third patient was receiving 2.5 mgm. per kgm. and actually took two-thirds of the prescribed dosage.

Healing of ulceration of the nasal septum thus takes a much longer time than is usually supposed and new ulceration may occur under continuous sulfone therapy. It is evident, however, that sulfone-treated patients did better in this respect than others at both institutions. At Eversley Childs, where the treatment schedules were more closely adhered to than at Central Luzon, the value of sulfone treatment is indicated also by a higher percentage of healing, and a lower frequency of patients developing ulceration, than were observed at Central Luzon. The findings on the preliminary and 96-weeks examinations are summarized in Table 7.

TABLE 7.—*Numbers and percentages of patients with ulceration of the nasal septum on preliminary and 96 weeks examination by institution and therapy group for patients completing 96 weeks of therapy.*

Institution	Therapy Group	Preliminary examination			96 weeks examination			
					Present			
		Present	Absent	% Present	Old	New	Absent	% Present
Central Luzon	SU 1906	20	21	48.8	17	8	16	61.0
Eversley Childs	"	8	28	22.2	3	1	32	11.0
Central Luzon	Amodiaquin	17	20	45.9	13	5	19	48.6
Eversley Childs	"	11	35	23.9	5	4	37	19.6
Central Luzon	DDS (4 mgm.)	19	28	40.4	11	8	28	40.4
Eversley Childs	"	11	28	28.2	0	2	37	5.1
Central Luzon	DDS (2.5 mgm.)	18	23	43.9	9	5	27	34.1
Eversley Childs	"	9	27	25.0	2	1	33	8.3
Central Luzon	All	74	92	44.6	50	26	90	45.8
Eversley Childs	"	39	118	24.8	10	8	139	11.5

(*b*) Other lepromatous ulcerations. At Central Luzon, lepromatous ulceration of the skin was present at the beginning in 19 patients, 4 each in the SU 1906, amodiaquin and DDS (2.5 mgm.) groups, and 7 in the DDS (4 mgm.) group. Healing took place in all patients except for one each in the SU 1906 and DDS (2.5 mgm.) groups and 2 in the amodiaquin group. New ulceration, however, was observed in 12 patients, 4 each in the SU 1906 and amodiaquin groups and 2 each in the sulfone groups. At Eversley Childs, only 4 patients showed lepromatous ulceration at the beginning, 2 in the SU 1906 group and one each in the

amodiaquin and DDS (2.5 mgm.) groups. In all but one of these (in the SU 1906 group) the ulcerations healed. New ulceration was observed in one patient belonging to the DDS (2.5 mgm.) group. This patient had actually taken 78 per cent of the prescribed amount of DDS.

Keratoconjunctivitis: At Central Luzon this complication was recorded on preliminary examination in 26 patients, 6 each in the SU 1906 and amodiaquin groups, 9 in the DDS (4 mgm.) group, and 5 in the DDS (2.5 mgm.) group. The condition cleared up in 4 patients treated with SU 1906, 5 treated with amodiaquin, 8 treated with DDS (4 mgm.), and 4 treated with DDS (2.5 mgm.). It occurred during therapy in 4 patients in whom it was absent at the beginning, in one belonging to the SU 1906 group and in 3 of the amodiaquin group.

At Eversley Childs keratoconjunctivitis was recorded on preliminary examination in 5 patients, 2 in the SU 1906 group, and 1 each in the amodiaquin, DDS (4 mgm.) and DDS (2.5 mgm.) groups. The condition cleared up in all patients except the one treated with amodiaquin and in this patient it improved. In 1 patient of the DDS (2.5 mgm.) group, in whom this condition was absent on preliminary examination, it was present at the 96-weeks examination.

Neurologic changes: There were no significant changes associated with any of the therapies in the extent of anesthesia.

BACTERIOLOGY

The bacteriologic procedures adopted in the first, second and third series were adhered to in the fourth. As has been noted, smears were required from both sides of the nasal septum, both earlobes, and four optional skin sites. The most marked or active lesions were selected as optional sites, and subsequent smears were made from approximately the same places. The present analysis deals with the comparison of the changes that took place in the four therapy groups in respect to nasal and skin sites, considered separately and together, between the preliminary examination and those made after 24, 48, 72 and 96 weeks of treatment.

At Central Luzon, of 165 patients completing 96 weeks of treatment, 40 (24.0%) became negative at all 8 required sites. Of these 40, 7 had been treated with SU 1906, 4 with amodiaquin, 16 with DDS (4 mgm.), and 13 with DDS (2.5 mgm.). Thus of 88 patients treated with DDS, 29 (33.0%) became negative at all required sites, while of 77 treated with SU 1906 or amodiaquin, 11 (13.4%) became negative. This difference is a highly significant one in the statistical sense.

At Eversley Childs, of 158 patients completing 96 weeks of treatment, 32 (20.3%) became negative at all required sites. Of these 32, 5 had been treated with SU 1906, 6 with amodiaquin, 13 with DDS (4 mgm.), and 8 with DDS (2.5 mgm.). Thus, of 76 patients treated with DDS, 21 (27.6%) became negative, whereas of 82 treated with either SU 1906 or amodiaquin, 11 (13.4%) became negative. This difference is

not as conspicuous as that observed at Central Luzon; nevertheless, a difference of this size would be expected in random sampling less frequently than once in twenty trials.

When the results at both institutions are considered together it is a fair conclusion that DDS was more effective than the other drugs in producing negativity. Of the total receiving DDS, 30.5 per cent became negative at the required sites, as compared to 15.6 per cent for SU 1906 and 12.2 per cent for amodiaquin. In both instances the differences are of statistical significance. The difference between SU 1906 and amodiaquin may be a real one, but larger numbers would be needed to answer this question. It should be emphasized that negativity at eight sites does not imply complete negativity of the patient.

Much bacteriologic improvement, short of negativity at eight sites, occurred in all the groups at each institution. In studying this matter, the usual practice of giving each smear an arbitrary numerical rating was followed. Smears marked V.S. were given a grade of 1; those marked 1+, a grade of 2; 2+, 3; 3+, 4; and 4+, 5. The scores for the nasal septum sites and those for the skin sites were studied separately. The averages for each patient of each therapy group, for preliminary and subsequent examinations, are shown by institution in Table A of the Appendix.

On the advice of Professor William G. Cochran the bacteriologic results were studied by the method of variance analysis. The variance is the square of the standard deviation. This method provides a basis for comparing not only two treatments but as many as may be desired. In essence, it is a comparison of the variation of the scores for the individual patients from the means of their respective groups—which is not related to specific therapy—with the variation of the means of the therapy groups from their grand mean. If the variation of the means of therapy groups is significantly greater than that of individuals from the means of their own groups, the conclusion must be that the therapies vary in effectiveness, because the only known difference between the groups is with respect to therapy. The ratio of the variation between means of therapy groups to the variation within groups has been called the F (Fisher) value by Snedicor, and its significance is determined from tables available in textbooks of statistics. Because of the long duration of the experiment and for technical reasons a modification known as the method of covariance was used in comparing the preliminary bacteriologic scores with those at each later examination.

Comparisons were made of the scores obtained at 24, 48, 72 and 96 weeks with those on preliminary examination. Data for Central Luzon and Eversley Childs were considered separately and in combination. Likewise the results for nasal septum and skin sites were studied separately and together. Six comparisons were made: all therapy

groups *vs* the mean of all the data; DDS 4.0 mgm. *vs* DDS 2.5 mgm.; SU 1906 *vs* amodiaquin; both DDS groups combined *vs* SU 1906; both DDS groups combined *vs* amodiaquin, and the DDS and SU 1906 groups combined *vs* amodiaquin. These procedures necessitated 216 computations, but the net results can be expressed briefly.

Judging from the reexaminations at 24 weeks and at 48 weeks, there was no clear evidence that any therapy was better than another. The differences for both septum and skin appeared to be in favor of DDS over SU 1906, and of DDS over amodiaquin, but the findings were not uniformly consistent at the two institutions. By the end of 72 weeks, the superiority of the sulfones over amodiaquin was evident from both nasal and skin sites at both institutions, and this was even more definitely established at the end of 96 weeks. At 72 weeks, the nasal sites indicated superiority of DDS over SU 1906 at both institutions, but the skin sites did not. At 96 weeks improvement in the nasal sites indicated superiority of DDS over SU 1906 at both institutions. This was true also of the skin sites at Central Luzon, but at Eversley Childs the reduction in scores for skin sites was practically the same for both drugs. That is, we were unable to demonstrate to our satisfaction that DDS was more effective than SU 1906 in reducing the bacteriologic score for the skin sites, but DDS was more effective on the nasal sites at both institutions. SU 1906 was more effective than amodiaquin on the skin, but not on the nasal septum sites. The lower dose of DDS was just as effective as the higher one, in both nasal septum and skin sites, as indicated by the results at all examinations at both institutions. The average bacteriologic scores for both institutions taken together for successive examinations, expressed as percentages of the scores on preliminary examination, are given for each therapy group in Table 8 and shown graphically in Figure 1.

TABLE 8.—*Average bacteriologic scores for nasal septum and skin sites after 24, 48, 72 and 96 weeks of therapy, expressed as percentages of the pretherapy scores. Central Luzon and Eversley Childs combined, by therapy group. (The numbers of patients are shown in parentheses.)*

	2 Nasal septum sites				6 Skin sites			
	Weeks of therapy				Weeks of therapy			
Therapy group	24 (413)	48 (369)	72 (348)	96 (323)	24 (413)	48 (369)	72 (348)	96 (323)
A/F	82.0	74.7	60.8	50.4	69.6	59.6	46.7	34.3
B/K	78.7	74.5	68.6	56.1	75.0	65.3	63.1	54.8
C/W	70.4	65.2	47.5	26.5	67.8	53.2	43.3	25.7
D/Y	73.7	67.5	50.9	32.2	66.9	52.2	38.3	20.9
Total	76.0	70.3	56.8	41.1	69.9	57.7	48.1	34.4

In the first series of these studies, a group of patients at Eversley Childs suffering from lepromatous leprosy were treated with a placebo

(Ceslu) for a period of 48 weeks. The bacteriologic findings for this group of patients are also shown in Figure 1 because it indicates what may happen without therapy.

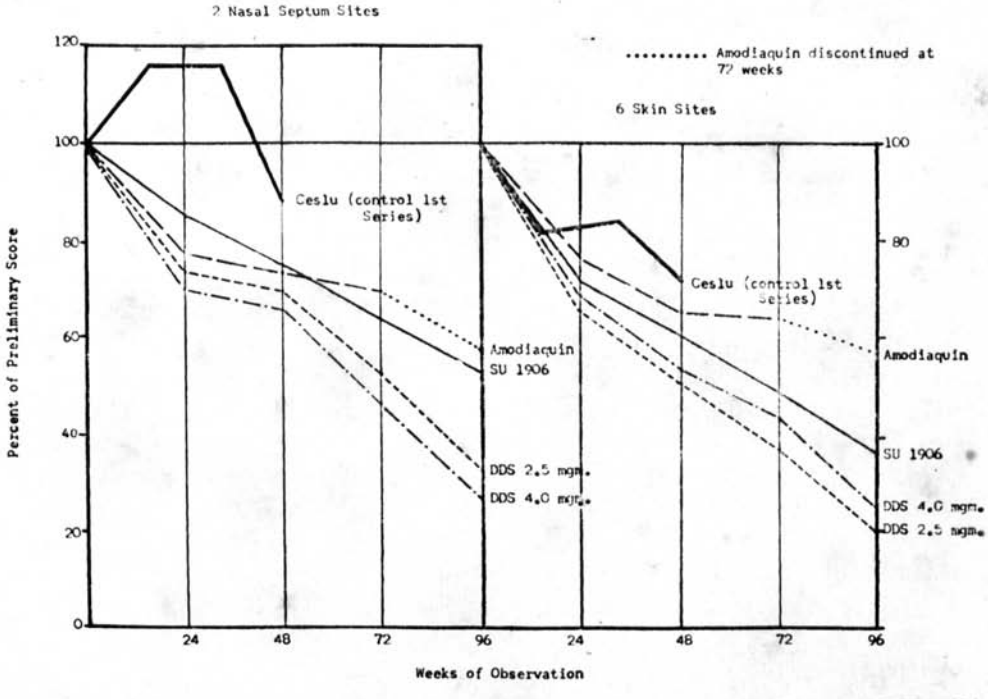

FIG. 1. Bacteriologic scores, fourth series, by therapy group; Central Luzon and Eversley Childs data combined, and Ceslu (placebo control, first series) Eversley Childs.

Relationship of clinical to bacteriologic improvement.—Since the commencement of these studies the clinicians have been asked to make their appraisals of changes in clinical condition without knowledge of the bacteriologic findings. At times we have had the impression that there was a high positive correlation between the two indexes. In the first series ([3]), however, it was found that the bacteriologic improvement of patients classified as clinically improved was only slightly more than that of "other patients" at two of the institutions in the study. A check made at Eversley Childs, and including the 48 weeks results of the first four series, brought out the facts shown in Table 9.

As seen in Table 9 there is a positive correlation between the bacteriologic and clinical appraisals. Nevertheless, it is of a much lower order than was anticipated—as is evident from the fact that, of the patients regarded as clinically unchanged or worse, 47.1 per cent had a reduction of 50 per cent or more in the bacteriologic score whereas of those classed on clinical findings as moderately or markedly improved only 60 per cent showed as great a reduction in their bacteriologic score.

TABLE 9.—*Numbers of patients showing 50 percent improvement in bacteriologic score, and less than 50 per cent, according to clinical status at the end of 48 weeks therapy, Eversley Childs Sanitarium, four series combined.*

Reduction in bacteriologic score (8 sites)	Improved		Worse or Stationary	Total
	Moderately or Markedly	Slightly		
50% or more	81	240	171	492
Less than 50%	54	185	192	431
Total	135	425	363	923
Percent reduced 50% or more	60.0	56.3	47.1	53.3

ERYTHROCYTE SEDIMENTATION BEFORE AND AFTER TREATMENT

Increase in the rate of sedimentation of the erythrocytes is a well-known phenomenon of a nonspecific nature which is frequently observed in lepromatous leprosy. In the present study, red-cell sedimentation was studied to determine whether a trend towards normality would be more evident with any of the therapies than with the others. Readings were made at the end of one hour on specimens of blood taken prior to therapy and after 24, 48, 72 and 96 weeks of treatment. At the end of 72 weeks, the combined data for both institutions showed that the average fall for all patients was only 10.3 per cent less than it was on preliminary examination. The average improvement was about the same for the patients of each group, except that the patients receiving the higher dose of DDS showed on the average slightly less reduction in the rate than the others. At the end of 96 weeks, the average fall from the preliminary readings was 12 per cent; that is, about the same as at 72 weeks. The least improvement was in the amodiaquin group; the other groups were not markedly different from one another. The conclusion may be drawn that, insofar as abnormal sedimentation is an indication of active disease, none of the drugs used in the study showed a noteworthy effect by the end of 96 weeks. The comparison between the readings on preliminary examination and those at 96 weeks is given in Table 10.

GAMMA GLOBULIN IN RELATION TO THERAPY

In a comparison of the sera of apparently healthy persons with those from patients suffering from lepromatous leprosy, using the method of paper electrophoresis, we have found that the range of the gamma globulin fraction was 21 to 29 per cent of total proteins for normals and 32 to 46 per cent for the lepromatous patients. It was hoped that the gamma fraction would return to more or less normal levels as clinical and bacteriologic improvement progressed. Our findings have not been entirely satisfactory in realizing this expectation. A

TABLE 10.—*Average erythrocyte sedimentation readings (uncorrected) in mm. (60 min.) for bleedings before therapy and after 96 weeks, by therapy group for Central Luzon and Eversley Childs patients taken together. Westergren method.*[a]

Group	No. of Pts.	Average fall		Per cent Reduction
		Prelim.	96 wks.	
SU 1906	76	76.6	63.6	17.0
Amodiaquin	85	74.2	70.5	5.0
DDS 4 mgm./kgm.	85	78.3	66.9	14.6
DDS 2.5 mgm./kgm.	80	73.9	64.5	12.7
Total	326	75.7	66.6	12.0

[a] Information incomplete for 11 patients, 7 of whom died from leprosy.

lowering of the overall gamma globulin percentage was observed at both institutions which was somewhat greater in each of the DDS groups than in the thiourea one and definitely greater than in the amodiaquin group. The average percentage at the end of 96 weeks, however, even in the DDS groups, was still much higher than in normal persons. A detailed study of these electrophoresis findings will be published later.

ERYTHEMA NODOSUM

This reactional condition was present at the outset in 44.5 per cent of the Central Luzon patients and in 24.8 per cent of those at Eversley Childs. Because of the disability caused by these reactions and of their great frequency in lepromatous leprosy it is hoped that their various aspects can be reported on more fully at some future time. The present discussion is restricted to the frequency and severity of reactions of which ENL was a manifestation in relation to the various therapies employed.

As shown in Table 11, the percentage of patients having one or more attacks of ENL in the fourth series was the same at Central Luzon as at Eversley Childs. At each institution the patients receiving the lower dose of DDS (2.5 mgm. per kgm.) had a slightly lower attack rate than other patients. At neither leprosarium was this difference statistically significant but when the figures for both institutions are combined the size of the difference is larger than would be expected to occur in random sampling once in twenty times. While therefore the group receiving the lower dose of DDS cannot be said to have had fewer attacks of ENL, there was a trend in this direction of which the significance must be determined by future studies.

An attempt was made to estimate the severity of ENL attacks by computing the proportion of the total period of observation that was spent in the infirmary. At Central Luzon the proportion for all patients was 3.7 per cent, and at Eversley Childs it was 2.5 per cent. At Central

TABLE 11.—*Percentages of patients having one or more attacks of ENL during a maximum therapy period of 96 weeks, by institution and therapy group.*

Therapy group	Central Luzon			Eversley Childs		
	No. of Pts.	Average observation (wks.)	Per cent attacked	No. of Pts.	Average observation (wks.)	Per cent attacked
SU 1906	55	82.1	74.5	55	77.2	74.5
Amodiaquin	56	79.5	80.4	57	84.9	77.2
DDS 4 mgm.	54	89.4	81.5	55	81.7	81.8
DDS 2.5 mgm.	55	82.3	67.3	56	79.0	67.9
Total	220	83.3	75.9	223	80.7	75.4

Note: At Central Luzon 4 patients and at Eversley Childs 3 patients who absconded after examination but before treatment are excluded.

Luzon the patients receiving the lower dose of DDS spent much less time in the infirmary, 0.6 per cent of their total, than did the other three groups. At Eversley Childs, however, there was no appreciable difference between the groups in this respect.

In regard to the occurrence and severity of ENL, we are forced to the conclusion that clear and significant differences between the different therapies employed did not emerge in this study.

LEPROMIN TESTS

As noted previously, all patients were negative to Mitsuda-Hayashi lepromin on admission to the study. At Central Luzon, 165 were retested at the end of 96 weeks; 3 had reactions 4 mm. in diameter or larger (actually all were 5 mm.). At Eversley Childs, 158 were retested at the end of 96 weeks; 2 had reactions 4 mm. in diameter and 3 had reactions measuring 5 mm. Thus, of the total of 323 patients who were retested only 3 per cent developed significant reactivity of the Mitsuda type during an observation period of about two years. Six of these patients had received DDS, one SU 1906 and 3 amodiaquin. Of these 10 patients, 7 showed clinical improvement, 2 were regarded as stationary in this respect, and 1 was worse. Six of the 10 had become negative bacteriologically at all eight sites, a higher proportion than was the case in patients who did not develop reactivity to lepromin (21%), but the number becoming reactive is too small to give significance to this difference. Three others who had developed reactivity to lepromin improved markedly in their bacteriologic scores, but one was still moderately heavily infected on the 96 weeks examination.

VARIOUS BACKGROUND FACTORS

As has already been discussed, and as was done in the first, second, and third series of these studies, the age and sex of the patients, stage

of disease, and previous sulfone therapy were taken into account in matching the groups, because of the possible importance of some or all of these factors in prognosis. The clinical and bacteriologic improvement that occurred has therefore been carefully studied in respect to these factors.

Sex and age.—In the previous three series ([3, 5, 6]) no consistent relationship was found between the age or sex of the patients and either the clinical or bacteriologic changes occurring during therapy. In the present study, the proportions of each sex showing clinical improvement at 96 weeks, were: at Central Luzon, males, 58.3 per cent, and females, 56.3 per cent; and at Eversley Childs, males, 69.8 per cent, and females 64.3 per cent. The reductions in the average bacteriologic scores for the same patients were, at Central Luzon, males, 66.6 per cent, and females, 74.9 per cent; and at Eversley Childs, males, 69.2 per cent, and females, 68.7 per cent. Thus there is no evidence in this study of any association between clinical or bacteriologic change and the sex of the patients.

The proportions of various age groups showing clinical and bacteriologic improvement in the fourth series are shown, by institution, in Table 12.

TABLE 12.—*Numbers and percentages of patients completing 96 weeks of therapy, classified by institution according to age group at time of entry and clinical and bacteriologic changes.*

Age group on entry	Central Luzon			Eversley Childs		
	No. of Pts.	Clinical Per cent improved	Bacteriologic Per cent reduction in score	No. of Pts.	Clinical Per cent improved	Bacteriologic Per cent reduction in score
10-19 yrs.	40	47.5	58.7	58	72.4	65.3
20-29 yrs.	53	49.1	64.3	55	63.6	67.1
30 and over	74	78.9	69.1	45	68.9	65.7
Total	167	57.5	65.1	158	68.3	69.1

Note: Information incomplete for 9 patients at Central Luzon, 6 of whom died of leprosy, and for 3 patients at Eversley Childs, 1 of whom died of leprosy. In order that bacteriologic and clinical findings shall refer to the same patients, the percentages of clinical improvement are based on totals minus patients who died. This applies also to Table 13.

As is to be seen, clinical improvement was observed in a higher proportion of older than of younger patients at Central Luzon, but that was not the case at Eversley Childs. Similarly, the reduction in bacteriologic score was slightly greater in older than in younger patients at Central

Luzon, but not at Eversley Childs. It is concluded therefore that there was no established relationship between the age of the patients and either clinical or bacteriologic improvement.

Stage of disease.—In the report of the third series ([6]), it was noted that the recorded percentages of patients showing improvement was greater at each institution for those whose disease was classed as L2 and L3 than for those in whom it was classed as L1. The explanation which was offered is that clinical improvement is more difficult to detect in early than in advanced cases of lepromatous leprosy. In the present series, at Central Luzon, the proportions showing improvement were the same for the three categories; at Eversley Childs the lighter cases had an advantage: of 73 L1 cases, 76.7 per cent improved, and of 87 L2 and L3 cases, 60.9 per cent.

Prior sulfone therapy.—As far as we are aware there is no support for the opinion that prior sulfone therapy is an important factor in determining the outcome of treatment in such experiments as this series of trials. Nevertheless, the possibility was kept in mind and a careful record was obtained of the previous treatment, if any, that each patient had received. In tabulating the results it was found that among the sulfone-treated groups (C/W and D/Y) at each institution the proportions recorded at 96 weeks as clinically improved did not differ significantly from one another for (*a*) patients who had received no prior sulfones, (*b*) those who had had some treatment but less than 10 gm. of DDS, (*c*) those who had received 10 gm. but less than 20 gm., and (*d*) those who had received 20 gm. or more. The pertinent bacteriologic results were irregular. At Central Luzon there was an apparent tendency towards greater bacteriologic improvement among those who had previously received the most sulfones, but the difference is not a significant one statistically. At Eversley Childs there was no consistent trend. A summary of these findings for both institutions combined is given in Table 13.

TABLE 13.—*Clinical and bacteriologic improvement after 96 weeks for patients receiving sulfones (C/W and D/Y) in relation to the quantity of sulfones received prior to commencement of the study. Central Luzon and Eversley Childs combined (8 sites).*

Prior sulfone treatment	No. of patients	Clinical findings. Per cent improved	Bacteriologic findings Per cent reduction in score
None	49	73.5	72.2
Less than 10 gm.	22	63.6	71.3
10-20 gm.	26	76.9	71.6
20 gm. or more	67	76.1	80.5
Total	164[a]	73.8	75.1

[a] Information incomplete for 4 patients. The total completing 96 weeks in these therapy groups was 168, including one who died from leprosy.

SUMMARY

In a duplicate experiment on lepromatous leprosy carried out at two leprosaria in the Philippines, Central Luzon Sanitarium near Manila and Eversley Childs Sanitarium near Cebu City, four groups of patients were treated respectively with 4 butoxy—4′dimethylamino-diphenyl thiourea (SU 1906), amodiaquin (Camoquin), a higher dose of DDS (4 mgm. per kgm. of body weight) and a lower dose of DDS (2.5 mgm. per kgm.). Treatment was continued for 96 weeks, except in the amodiaquin group in which the drug was discontinued at 72 weeks; most of the patients of this group were continued on DDS.

At both institutions the superiority of DDS over amodiaquin was evident from the physical examinations at 72 weeks, and this was confirmed at 96 weeks in spite of the fact that most of the amodiaquin patients had received DDS from the 73rd week. SU 1906 likewise was superior to amodiaquin. In comparison with both higher and lower doses of DDS, however, SU 1906 showed consistently lower rates of improvement at each examination, but the differences were small. The patients on the higher dosage of DDS did not improve in greater proportion than those in the lower dose, as far as the clinical evidence goes.

As has been found in our previous studies, healing of ulceration of the nasal septum took longer than is usually supposed, and new ulcerations occurred under continuous therapy with either DDS or SU 1906. At Eversley Childs, where the treatment schedules were more closely adhered to than at Central Luzon the value of sulfone treatment was indicated by a higher percentage of healing and a lower frequency of patients developing new ulcerations.

With regard to bacteriologic findings, judging from the reexaminations at 24 weeks and at 48 weeks, no therapy was significantly better than another. By the end of 72 weeks, however, the superiority of DDS over amodiaquin was evident from both nasal and skin sites at both institutions. At 72 weeks the nasal septum sites indicated superiority of DDS over SU 1906, but the skin sites showed no differences; at 96 weeks this situation had not materially changed. That is, we were unable to demonstrate to our satisfaction that DDS was more effective than SU 1906 in reducing the bacteriologic scores for the skin sites; DDS was more effective on the nasal sites. SU 1906 was more effective on the skin sites than was amodiaquin, but not on the nasal septum sites. The lower dose of DDS was just as effective as the higher one, on both nasal and skin sites.

Determination of the rate of sedimentation of erythrocytes and of the gamma globulin fraction of the serum proteins did not prove helpful in measuring the efficacy of the various therapies.

Reactions of which erythema nodosum was a manifestation were about equally frequent in all therapy groups.

As in our previous studies there was no evidence that any of the

background factors studied, including age, sex, stage of disease or prior sulfone therapy, was associated with either clinical or bacteriologic improvement. It is probable that the difficulty of detecting clinical improvement in patients whose lesions are slight is the explanation of our failure to observe better results with early than with late treatment.

Only about 3 per cent of the patients developed significant lepromin reactivity of the Mitsuda type during an observation period of about two years, and all the reactions were small.

RESUMEN

En un experimento en duplicado sobre lepra lepromatosa, llevado a cabo en dos leproserías de las Filipinas, el Sanitario Central de Luzón cerca de Manila y el Sanitario Eversley Childs cerca de la ciudad de Cebú, cuatro grupos de enfermos fueron tratados, respectivamente, con 4-butoxi-4'dimetilaminodifenil tiourea (SU 1906), amodiaquina (Camoquín), una dosis más alta de DDS (4 mgm. por kg. de peso vivo) y una dosis más baja de DDS (2.5 mgm. por kg. de peso). El tratamiento continuó por 96 semanas, excepto en el grupo de la amodiaquina en el que se discontinuó la droga a las 72 semanas; en la mayoría de los enfermos de este grupo se continuó con DDS.

En ambos establecimientos, la superioridad de la DDS sobre la amodiaquina resultó evidente a base de los exámenes físicos a las 72 semanas, lo cual se confirmó a las 96 semanas, a pesar de que la mayoría de los enfermos a amodiaquina había recibido DDS desde la 73a. semana. El SU 1906 fué también superior a la amodiaquina. Sin embargo, en comparación con las dosis más altas y más bajas de DDS, el SU 1906 reveló constantemente tasas más bajas de mejoría en cada examen, aunque las diferencias fueron pequeñas. En lo que muestran los datos clínicos, los enfermos que recibieron la dosis más alta de DDS no mejoraron en mayor proporción que los de la dosis más baja.

Según se observó en los estudios anteriores, la cicatrización de la ulceración del tabique nasal exigió más tiempo que lo que se suele suponer, y se presentaron nuevas ulceraciones bajo terapéutica continua ya con DDS o con SU 1906. En el Eversley Childs, en el que se adhirieron más a los regímenes terapéuticos que en el Central de Luzón, el valor de la sulfonoterapia quedó indicado por un porcentaje más alto de curación y una frecuencia menor de enfermos que manifestaron nuevas ulceraciones.

Con respecto a los hallazgos bacteriológicos, a juzgar por los re-exámines a las 24 y a las 48 semanas, ninguna terapéutica fué significativamente mejor que otra. Sin embargo, para el final de las 72 semanas, era manifiesta la superioridad de la DDS sobre la amodiaquina por las localizaciones nasales y cutáneas en ambos establecimientos. A las 72 semanas, las lesiones del tabique nasal indicaban superioridad de la DDS sobre el SU 1906, pero las localizaciones cutáneas no mostraban diferencias; a las 96 semanas, esta situación no había variado mayor cosa. Es decir, no era posible demostrar, a la satisfacción de los AA., que la DDS era más eficaz que el SU 1906 para rabajar los índices bacteriológicos para los sitios cutáneos; la DDS era más eficaz para las localizaciones nasales. El SU 1906 fué más eficaz en los sitios cutáneos que la amodiaquina, pero no en los del tabique nasal.

La determinación de la velocidad de la erito-sedimentación y de la fracción de globulina gamma en las ser proteínas no resultó útil para medir la eficacia de las varias terapéuticas.

Las reacciones para las cuales el eritema nudoso es una manifestación fueron más o menos igualmente frecuentes en todos los grupos terapéuticos.

Lo mismo que en los estudios anteriores, no hubo pruebas de que ninguno de los factores circunstanciales, incluso edad, sexo, período de la enfermedad o sulfonoterapia anterior, se vinculara con mejoría clínica o bacteriológica. Es probable que lo difícil que es descubrir mejoría clínica en enfermos cuyas lesiones son leves explique el no haberse podido observar mejores resultados con el tratamiento temprano que con el tardío.

Sólo aproximadamente 3 por ciento de los enfermos manifestaron importante reactividad a la lepromina de la forma Mitsuda durante un período de observación de dos años, y todas las reacciones fueron pequeñas.

RESUMÉ

Au cours d'une double expérimentation menée dans deux léproseries des Philippines, au Central Luzon Sanitarium près de Manile et à l'Eversley Childs Sanitarium près de Cebu City, quatre groupes de malades ont été traités respectivement par la 4-butoxy-4′ dimethylaminodiphényl thiourée (SU 1906), l'amodiaquin (Camoquin), et des doses relativement plus élevées (4 mg par kg) et plus faibles (2.5 mg par kg) de D.D.S. Le traitement a été poursuivi pendant 96 semaines, sauf en ce qui concerne l'amodiaquin qui n'a été administrée que pendant 72 semaines, la plupart des sujets compris dans ce groupe ayant été alors repris en traitement avec la D.D.S.

Dans les deux institutions, la supériorité de la D.D.S. sur l'amodiaquin est clairement apparue à l'examen physique des malades après 72 semaines. Cela fut confirmé à la 96e semaine, en dépit du fait que chez les plupart de ces sujets l'amodiaquin avait été remplacée par la D.D.S. à partir de la 73e semaine. Le SU 1906, de même, a donné de meilleurs résultats que l'amodiaquin. Comparé aux posologies différentes, plus élevées ou plus basses, de la D.D.S., le SU 1906 a régulièrement entraîné une amelioration moins marquée; les différences, toutefois, sont faibles. Les malades traités par les doses de D.D.S. les plus hautes n'ont, pour autant qu'en témoigne l'aspect clinique, pas été améliorés davantage que ceux auxquels ont été administrées des doses plus faibles.

Ainsi qu'il est apparu de nos études antérieures, la cicatrisation des ulcérations du septum nasal prend plus de temps qu'on ne le croit généralement. De nouvelles ulcérations apparaissent même durant le cours d'un traitement continu par la D.D.S. ou le SU 1906. A Eversley Childs, où la régularité du traitement est plus stricte qu'à Central Luzon, la valeur des sulfones est soulignée par le plus grand pourcentage de guérison des ulcérations, ainsi que par la fréquence plus faible de cas d'ulcérations nouvelles.

En ce qui concerne les résultats bactériologiques, établis d'après les examens répétés après 24 et 48 semaines, aucune thérapeutique n'est significativement supérieure aux autres. Après 72 semaines, toutefois, les examens de prélèvements de la muqueuse nasale des deux côtés et de divers endroits de la peau indiquent, dans les deux institutions, une supériorité évidente de la D.D.S. sur l'amodiaquin. Après 72 semaines également, les prélèvements nasaux témoignent d'une supériorité de la D.D.S. sur le SU 1906, alors que les prélèvements cutanés par contre n'en indiquent pas; après 96 semaines, la situation est analogue. Ainsi, nous n'avons pas pu démontrer d'une manière qui nous satisfât, une supériorité de la D.D.S. sur le SU 1906 pour ce qui regarde l'examen bactériologique de la peau; la D.D.S. est cependant plus efficace si l'on considère les prélèvements de la muqueuse nasale. Par ailleurs, le SU 1906 est plus efficace que l'amodiaquin si l'on envisage les prélèvements cutanés, mais non si l'on se réfère à la muqueuse nasale.

Les déterminations de la vitesse de sédimentation des erythrocytes, ainsi que du taux des gamma globulines dans les protéines sériques, ne se sont pas révélées fort utiles pour mesurer l'efficacité des diverses thérapeutiques.

Les réaction, dont l'érythème noueux est une manifestation, sont apparues avec une fréquence analogue dans les divers groupes.

Comme dans nos études précédentes, nous n'avons pas constaté que l'amélioration clinique ou bactériologique est associée avec un quelconque des facteurs accessoires que nous avons considérés, tels que l'âge, le sexe, le degré d'avancement de la maladie, ou un traitement antérieur par les sulfones. Il est probable que la difficulté de détecter une amélioration clinique chez des malades dont les lésions sont minimes explique le fait que nous n'ayons pas noté de meilleurs résultats avec un traitement précoce que lors d'un traitement tardif.

3% seulement des malades ont développé une réactivité notable, du type Mitsuda, a la lépromine, au cours d'une période d'observation qui s'est prolongée durant environ deux ans; toutés les réactions étaient faibles.

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Appendix A

Average bacteriologic scores per patient on preliminary and subsequent examinations for 2 nasal septum and 6 skin sites, by therapy group and institution.

Group	No. Pts.	Average Prelim	Average 24 wks	No. Pts.	Average Prelim	Average 48 wks	No. Pts.	Average Prelim	Average 72 wks	No. Pts.	Average Prelim	Average 96 wks
Central Luzon: 2 nasal sites.												
A/F	51	6.1	4.5	44	6.1	4.2	43	5.9	2.8	41	6.0	3.2
B/K	49	6.2	3.9	45	6.1	4.0	41	6.1	4.1	36	6.6	3.6
C/W	51	6.6	4.3	50	6.6	3.7	49	6.5	2.4	47	6.5	1.5
D/Y	50	5.8	3.6	43	6.0	3.0	45	5.7	2.2	41	6.1	1.5
Total	201	6.2	4.1	182	6.2	3.7	178	6.1	2.8	165	6.3	2.4
Central Luzon: 6 skin sites.												
A/F	51	21.4	14.8	44	21.8	12.9	43	21.2	9.5	41	21.1	7.9
B/K	49	20.3	13.3	45	20.4	11.1	41	20.5	12.4	36	21.7	11.6
C/W	51	21.1	13.0	50	21.2	10.3	49	21.1	9.2	47	20.8	5.0
D/Y	50	19.5	11.9	43	19.5	8.7	45	19.1	7.6	41	19.5	4.4
Total	201	20.6	13.3	182	20.8	10.8	178	20.5	9.6	165	20.8	7.0
Eversley Childs: 2 nasal sites.												
A/F	52	7.3	6.6	43	7.0	5.6	39	7.5	5.6	36	7.4	3.6
B/K	53	8.0	7.1	50	7.9	6.4	48	7.9	5.6	46	7.8	4.5
C/W	53	7.8	5.9	49	7.8	5.7	43	7.8	4.5	39	7.9	2.4
D/Y	54	8.3	6.7	45	8.3	6.6	40	8.4	5.3	37	8.6	3.2
Total	212	7.9	6.5	187	7.8	6.1	170	7.9	5.2	158	7.9	3.5
Eversley Childs: 6 skin sites.												
A/F	52	22.2	16.4	43	21.8	13.1	39	22.4	10.9	36	23.0	7.2
B/K	53	22.3	18.7	50	22.2	16.4	48	22.0	14.4	46	21.9	12.2
C/W	53	20.5	15.1	49	20.4	11.8	43	20.4	8.8	39	20.4	5.6
D/Y	54	21.5	15.6	45	21.0	12.3	40	20.7	7.6	37	20.5	3.9
Total	212	21.6	16.4	187	21.3	13.5	170	21.4	10.6	158	21.4	7.5

Therapies: A/F, SU 1906; B/K, amodiaquin (Camoquin) to the end of 72 weeks, thereafter most of the patients received DDS; C/W, DDS 4 mgm. per kgm. of body weight; D/Y, DDS 2.5 mgm. per kgm. of body weight.

In respect to the numbers included see note to Table 5 of the text.