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CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY SECOND SERIES: ISONIAZID AND DIASONE (DIAMIDIN) ISONIAZID AND DIHYDROSTREPTOMYCIN ALSO A PILOT STUDY WITH STREPTOHYDRAZID

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In the first series of these studies (1), diasone (diamidin), 4-4'diaminodiphenyl sulfone (DDS) and dihydrostreptomycin (DHSM) were shown to be of definite and apparently of equal value in the therapy of lepromatous leprosy, insofar as could be judged by physical examination after 48 weeks of treatment. A combination of DHSM and diasone showed no advantage over either given singly, and addition of sodium-*p*-aminosalicylate (PAS) to the therapy did not increase the effectiveness of DHSM. No significant differences in bacteriologic effect could be demonstrated between any of these therapies. However, at the only institution for which the data permitted a comparison at the end of 48 weeks, the

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bacteriologic improvement was somewhat greater for all therapy groups combined than for a control group that received only a placebo (Ceslu) containing inositol and glycine. The dosages used were: diasone, 1 gm. daily; DDS, 0.2 gm. daily, and DHSM, 1 gm. three times a week.

In 1952, while the first series was under way, announcement was made of highly favorable results in treatment of pulmonary tuberculosis with isoniazid (INH). As soon as supplies of this drug could be obtained one of us (J.N.R.), at the Central Luzon Sanitarium, placed three carefully matched groups of lepromatous patients, 25 each, on treatment respectively with DDS, INH, and Marsilid (Hoffmann-LaRoche; an isopropyl derivative of INH), for a period of 24 weeks. The clinical condition of the patients was appraised before and after treatment by Dr. C. B. Lara of the Culion Sanitarium. The proportions improving, or worsening, were almost the same for the three groups. Bacteriologic results, likewise, showed no significant differences. A similar study by another of us (J.G.T.), in which 21 lepromatous patients were matched against the same number on Ceslu, was conducted at the same time at the Eversley Childs Sanitarium (assessor, J.N.R.). At the end of 32 weeks the patients receiving INH were in better clinical condition than those on Ceslu, but the results appeared to be inferior and were certainly no better than those obtained with diasone or with DDS.

The specific objectives of the second series, here reported, were: to compare in the effectiveness in lepromatous leprosy of diasone (diamidin), given singly, with that of diasone plus INH, and of DHSM plus INH. A supplemental pilot study of a combined compound containing streptomycin (SM) and INH in one molecule (Streptohydrazid, Pfizer) was carried on concurrently at Eversley Childs and at Westfort.

## PROCEDURES, METHODS AND MATERIALS

Organization.—Three large institutions were selected to participate in the second series. Two of these are operated by the government of the Philippines: the Central Luzon Sanitarium, situated about 30 miles north of Manila, and the Eversley Childs Sanitarium, situated about 8 miles northeast of Cebu City. The third is the Westfort Institution, operated by the government of the Union of South Africa and located near Pretoria. At each institution a resident research leprologist, nurses, technicians, and clerks were assigned to the work. A visiting consulting leprologist was appointed to make independent examinations at each institution, as in the first series.

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

Duration of treatment.—At each institution there was a preliminary period of at least 30 days for examinations, during which time treatment was withheld from those patients who had been previously treated with sulfones. The duration of the experimental treatment was fixed at 48 weeks. The actual periods were: at Central Luzon Sanitarium, 12 October 1953 to 8 September 1954; at Eversley Childs Sanitarium, 19 October 1953 to 15 September 1954; and at Westfort, where two rest periods were permitted, 22 September 1953 to 25 October 1954. Therapies .- The therapies included were as follows:

Regular Second Series:	Group A:	Diasone (or diamidin)
	Group B:	Diasone (or diamidin) plus INH
	Group C:	INH plus DHSM <sup>2</sup>
Supplemental Pilot Study:	Group D:	Streptohydrazid <sup>3</sup>

For diasone (diamidin) (Groups A and B), the initial dose was one tablet containing either 0.3 or 0.33 gm., given orally every second day for the first three weeks, one tablet daily for the second three weeks, two tablets daily for the third three weeks, and thereafter three tablets daily. No tablets were given on Sundays. The INH (Groups B and C) was given orally in tablet form in a dosage of 10 mgm. per kgm. body weight. The DHSM (Group C) was given intramuscularly, 1 gm. twice weekly. Streptohydrazid was given intramuscularly, twice weekly; the weekly equivalent dosage was 2 gm. of DHSM and 472 mgm. of INH.

*Physical examinations.*—Dermatologic and neurologic examinations were made by the consultant during the preliminary period, at the end of 24 weeks of treatment, and at the end of 48 weeks. The patients were presented for examination in a sequence unrelated to their therapy groups. In addition to being recorded on prescribed forms, the findings were depicted graphically on dermatologic and neurologic charts. The nature of the treatment being given to a patient was not disclosed to the consultant until his examination had been completed.

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

Other examinations.—Hemoglobin determinations were made during the preliminary period at all institutions, at 8-week intervals thereafter at Central Luzon and Westfort, and at the 24th and 48th weeks at Eversley Childs. Erythrocyte counts and packed cell volume estimations were made before and after treatment at Central Luzon and Eversley Childs. Hemoglobin, erythrocyte, leukocyte, and differential studies for the Westfort patients were made on preliminary and post-treatment specimens at the South African Institute for Medical Research, Johannesburg. At all institutions sulfone determinations were made at the 16th and 32nd weeks on patients of Groups A and B, and routine urine examinations on three or more occasions. The lepromin test was performed on all patients before and after treatment. The antigen used at the Philippine institutions was lepromin prepared by the Hayashi-Mitsuda method; the antigen used at Westfort was made by Dharmendra's method. Readings were made at 48 hours and 22 days.

*Photographic records.*—Color and black-and-white photographs were made during the preliminary period and after 48 weeks therapy.

Assignment of patients to groups.—At the Central Luzon Sanitarium 213 patients, at Eversley Childs 234, and at Westfort 119, were selected for the experiment. At each institution approximately two-thirds were males, and all were between 12 and 50 years of age. An index card was prepared for each patient on which were entered a code name, age, sex, previous sulfone therapy (if any), year of onset, date of admission,

<sup>2</sup> At Westfort, the patients of Group C were given sodium p-aminosalicylate (PAS) in addition to INH and DHSM. The PAS was started on 26 October 1953 in daily oral dosage of 12 tablets of 0.5 gm. each. In the second week the dose was increased to 18 tablets daily and from the third week on 30 tablets daily were given. PAS was not given on Sundays.

<sup>3</sup> At the Eversley Childs Sanitarium and the Westfort Institution.

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stage of disease, presence or absence of infiltration, nodules and certain other signs, height, weight and miscellaneous items. These cards were airmailed to the office of the medical director in Washington, D. C. Essentially the same procedure was followed in assigning patients to groups as that described by Prof. W. G. Cochran in the report of the first series.

A minor deviation from that procedure was as follows: In order to select 25 young adult male patients at Eversley Childs and 10 at Westfort for the pilot study of Streptohydrazid (Group D), the cards for 100 male patients at Eversley Childs and for 40 at Westfort were first removed. Those removed included all males in ascending order of age beginning at 20 years and continuing until the required numbers were reached. These male patients were assigned each to one of four groups (A, B, C, and D) using a table of random numbers. Thus at each institution, in Groups A, B, and C, there was a reference or control group for that on Streptohydrazid, consisting at Eversley Childs of 75 patients and at Westfort of 30 patients. The remaining patients at Eversley Childs and Westfort and the patients at Central Luzon were then assigned each to one of the aforementioned three groups A, B, and C in the same manner as in the first series. A few changes were made to achieve better balance of the groups, especially with respect to stage of disease and duration of previous sulfone therapy. Lists of patients to be included in each treatment group were then airmailed to each institution.

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 the date of withdrawal were taken as final.

The numbers of patients originally selected and completing the therapy are shown for all institutions and groups in Table 1, those dropped being classified as to reasons for that action.

These states	Central Luzon	Eversley	Childs	Westfort		
I nerapy status	Regular series	Regular series	Group D	Regular series	Group D	
Therapy completed	187	202	20	111	9	
Therapy incomplete: Drug intolerance Complicating diseases Dosage insufficient	$\frac{2}{24}$		 5	1 4 3		
Total selected	213	234	25	119	10	

TABLE 1.—Numbers of patients selected at the Central Luzon and the Eversley Childs Sanitaria, and at the Westfort Institution, classified according to therapy status at the end of 48 weeks.

The principal reason for discontinuance of treatment was departure from the institution without permission. Any patient absent for 60 days or more was classified as having insufficient treatment and dropped. At Central Luzon there were 24 of these patients, at Eversley Childs 34, and at Westfort 4.

In a few instances, discontinuance was attributable to medical reasons not associated with leprosy or with specific therapy. Thus at Eversley Childs there was 1 death caused by lymphosarcoma; severe asthma necessitated discontinuance in 1 case; and pregnancy, complicated by severe morning sickness, in another. At Westfort there were 2 deaths from chronic nephritis; 1 patient discontinued treatment because of tuberculosis, and 1 because of edema and epistaxis.

In 3 instances, the causes for discontinuance are considered to be side effects of one or another of the drugs being tested. At Central Luzon there were 2 patients dropped from Group B because of severe and persistent anemia, a contributing factor in 1 of these being epistaxis caused by ulceration of the septum. At Westfort 1 patient of Group C was forced to discontinue treatment because of exfoliative dermatitis.

With a dosage of 10 mgm. per kgm. of body weight it was anticipated that some patients might show signs of intolerance to INH. It is possible that peripheral neuritis, which has been reported as occurring in tuberculous patients treated with this drug, passed unnoticed because of pre-existing damage to the peripheral nerves. At no institution was there any indication of nervous system involvement that might be attributed to any of the therapies except in 3 cases at Eversley Childs. In these patients, 2 in Group B and 1 in Group C, mental symptoms developed which were not immediately attributed to therapy. The fact that in each case full recovery took place after withdrawal of INH is suggestive that this drug was responsible. In each of these cases, however, there was other evidence of worsening, and the disease was classed as worse.

In 1 Westfort patient belonging to Group C the disease was classed as worse because of increase in ulceration at the time he was dropped. In this instance drug intolerance might have been taken as the cause for discontinuance; there was a notation on the record that treatment was discontinued because the patient could not tolerate PAS.

To determine the effect of dropping of patients on the comparability of the groups completing treatment at each institution, an analysis was made of certain group characteristics for patients selected and for those completing therapy. As far as can be judged, the comparability of Groups A, B, and C at each institution remained unaffected. At Eversley Childs 5 patients were dropped from Group D, 6 from the 25 matched patients of Group A, 5 from those of Group B, and 2 from those of Group C. Only 1 patient was dropped from Group D at Westfort, and 1 each from the 10 matched patients of Groups A, B, and C.

## CLINICAL RESULTS, REGULAR SECOND SERIES

On completion of the final examination the clinical status of each patient was summarized in relation to the pretreatment condition as either improved (slight, moderate or marked), or stationary, or worse (slight, moderate or marked). Differences between patients classed by the consultant as "stationary" and those regarded as "slightly worse" or "slightly improved" may be regarded as of minor significance. In Table 2, therefore, which includes only the regular Groups A, B, and C of this second series, the slightly changed and the unchanged have been combined into one central class, which is contrasted on the one hand with the moderately or markedly improved and on the other hand with the moderately or markedly worse.

Therapy group <sup>b</sup>	Central Luzon		Eversley Childs				Westfort					
		Per cent		No. pts.	Per cent		N	Per cent				
in the	pts. Impr. Stat. Worse	Worse	Impr.		Stat.	Worse	pts.	Impr.	Stat.	Worse		
A	62	17.7	77.4	4.8	64	12.5	85.9	1.6	35	42.9	57.1	-
в	62	14.5	85.5	-	70	10.0	82.9	7.1	39	61.5	38.5	-
c	63	20.6	77.8	1.6	68	7.3	91.2	1.5	37	62.2	35.1	2.7
A, B	124	16.1	81.5	2.4	133	11.3	85.0	3.7	74	52.7	47.3	-
B, C	125	17.6	81.6	0.8	138	8.7	87.0	4.3	76	61.8	36.8	1.3
Total	187	17.6	80.2	2.1	202	9.9	86.6	3.5	111	55.9	43.2	0.9

 TABLE 2.—Percentages of patients who had completed treatment, classed as improved, stationary, or worse on final clinical examinations, by institutions and therapy groups.<sup>a</sup>

a Impr. = moderately or markedly improved; Stat. = stationary, slightly improved, or slightly worse; Worse = moderately or markedly worse.

b For the drugs used in these treatment groups, see p. 175 of the text.

Inspection of Table 2 shows that the proportions classed respectively as improved, stationary, and worse did not differ significantly as between therapy Groups A, B, and C at any of the three institutions. For Groups A and B taken together, i.e., for all patients given diasone (diamidin), the results were not very different from those for Groups B and C, in which all patients received INH.

There was a wide difference in the proportions classed as improved at Westfort and at the Philippine institutions. At Westfort 55.9 per cent of all patients were so classed, against 17.6 per cent at Central Luzon and only 9.9 per cent at Eversley Childs. The explanation is not obvious; it may be that some unknown factor renders the disease more amenable to treatment in South Africa than in the Philippines. Part of the explanation, however, is probably variation in the concept of improvement held by the various consultants, together with the great difficulty of forming a judgment as to clinical changes in many cases. Evidence of this difficulty is seen in the variations in proportions improving on diasone therapy in the first series as compared to the present one. At Eversley Childs 29.6 per cent of Group A in the first series were recorded as improved, as compared to only 14.1 per cent in Group A of the second; and at Westfort 25.0 per cent were considered to have improved in (A) of the first series, and 42.9 per cent in the comparable group (A) of the second series.

The proportions recorded as definitely worse were small at all institutions, and there was no consistency between the institutions in this respect. At Central Luzon 4.8 per cent (3 patients) of Group A became worse, but at Eversley Childs only 1 patient in this group became worse and none at Westfort. At Eversley Childs 7.1 per cent (5 patients) of Group B became worse, but none of this group was recorded as worse at Central Luzon or at Westfort. In Group C 1 patient at each institution became worse.

Prognostic value of certain background factors.—Lacking definite information on factors that affect prognosis in leprosy we have, as noted above, taken into account especially sex, age, stage of disease and previous sulfone therapy in matching the groups. It is of interest therefore to see whether or not patients differing in respect to these factors differed also in the clinical improvement that was observed.

The proportions recorded as showing marked or moderate improvement did not differ significantly for males and for females at any institution. At Central Luzon the percentages were: males 17.0, and females 18.3; at Eversley Childs, males 10.5, and females 9.0; and at Westfort, males 52.3 and females 61.5. Younger patients benefited more than older at Eversley Childs, but the contrary was the case at Central Luzon and at Westfort.

The relationship to prior sulfone therapy was as follows: at Eversley Childs 41.6 per cent of the patients had had no prior sulfone therapy, 26.2 per cent had 1 year or less, 25.7 per cent 1 to 2 years, and 6.4 per cent more than 2 years. At Central Luzon the comparable percentages were 4.3, 42.8, 15.5, and 37.4; and at Westfort, 8.1, 29.7, 30.6, and 31.5. At Eversley Childs, significant clinical improvement was recorded in 12.4 per cent of those patients with no prior sulfone therapy or with treatment of less than one year, and in 4.6 per cent of those with one year or more of prior treatment. At Central Luzon, improvement was noted in 27.3 per cent of those with no prior treatment or with treatment of less than one year, and in 8.1 per cent of those with one year or more of treatment. At Westfort, improvement was noted in 64.3 per cent of those with no prior treatment or with treatment of less than one year and in 46.4 per cent of those with one year or more of prior treatment. Thus clinical improvement was recorded considerably more frequently in patients with little or no prior sulfone treatment than in others. Referring back to the first series, the evidence obtained at the different institutions was contradictory in this respect.

For those in different stages of the disease at the outset, the percentages that showed improvement were: at Central Luzon,  $L_1$  cases 10.0, and  $L_2$  and  $L_3$  combined, 19.3; at Eversley Childs,  $L_1$  cases 6.7, and  $L_2$  and  $L_3$ , 14.3; and at Westfort,  $L_1$  cases 52.2, and  $L_2$  and  $L_3$  taken together 61.4.

Thus the evidence is that lepromatous patients who have received little previous sulfone therapy, and also those in the more advanced stages of the disease, showed a better response to therapy than those with more previous treatment or those in the early stage of the disease, respectively. It is impossible from the data at hand to separate these factors satisfactorily. At all institutions a greater proportion of the  $L_2$  and  $L_3$  cases than of those

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classed  $L_1$  had received one year or less of sulfone therapy before entering the second series. For Eversley Childs the percentages were: for  $L_2$  and  $L_3$  cases, 78.6, and for  $L_1$ , 57.7; for Central Luzon and Westfort: for  $L_2$ and  $L_3$  cases, just one-half and for  $L_1$ , less than one-third. It may be argued that the important factor is lack of prior treatment, and that stage of disease is only incidental; or, on the other hand, that among patients in the more advanced stages clinical improvement occurs more frequently, or is more readily detectable, than in those in the early stage of the disease, and that prior sulfone therapy is not a pertinent point. A larger series in which the number of cases would be sufficient to permit comparison of improvement rates for patients in each stage of the disease, classified according to prior treatment, is necessary to throw light on this important question.

Occurrence and prognostic significance of erythema nodosum leprosum (ENL).—In the first series, this reactional condition was present at the outset in 23.5 per cent of the Eversley Childs patients and there was no difference between those who had been previously treated with sulfones and those who had not. At the Japanese institutions the prevalence of ENL at the outset was 47.4 per cent, and was much higher for the previously sulfone-treated cases than for the others. At Westfort the over-all frequency of ENL on enrollment in the first series was 57.9 per cent, and it was much the higher among the previously sulfone-treated patients.

In the second series, ENL was present on initial examination in 38.9 per cent of the patients at Central Luzon, 37.1 per cent at Eversley Childs, and in 13.0 per cent at Westfort. At Central Luzon and at Westfort it was more frequent in those who had been receiving sulfones than in others; at Eversley Childs there was no difference in this respect.

ENL occurred during treatment in a considerable proportion of patients who were free from it on preliminary examination but, as in the first series, there was no clear relationship to the type of therapy. At Central Luzon it occurred in 28.2 per cent of patients in the diasone groups (A and B), and in 24.4 per cent of those in the INH groups (B and C). At Eversley Childs the comparable percentages were 13.2 and 12.4; and at Westfort, 34.5 and 25.9.

The relationship of ENL to prognosis is still a matter of speculation. In the present series, there was some evidence that clinical improvement was more frequent in those patients in whom ENL was not present on preliminary examination than in others. At Central Luzon, 22.6 per cent of 115 patients in whom ENL was absent on the preliminary examination were recorded as clinically improved at the end of treatment, as compared to 9.7 per cent of 72 patients in whom it was present. At Eversley Childs, the figures were 14.2 per cent of 127 patients without ENL at the outset, as compared to 2.7 per cent of 75 patients who had it. At Westfort, 56.1 per cent of 98 patients without ENL improved, and 53.8 per cent of 13 patients with the reaction. Too much weight should not be given to this

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comparison, because the groups that differed with respect to frequency of ENL may have differed also in other respects. A carefully controlled and especially designed study is necessary to determine the prognostic significance of ENL.

Effect of therapy on specified lesions.—As in the first series, and for lack of any better method, the consultants were asked to give 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. If any lesion on the list was not present in the designated part of the body, its absence was recorded. These ratings were added together for each type of lesion. The totals for successive examinations were compared with one another in an attempt to measure the effect of different therapies on specified lesions. A high degree of association would be expected with the changes in clinical status shown in Table 2, because changes in the various lesions would obviously constitute the basis for the judgment of the consultant as to the progress of the disease in the patient.

Infiltration : Infiltration was again the universal clinical feature, being noted at the outset in all patients at all institutions. A simple and useful index of change in infiltration was used in the first series, and has been applied here also. This index is based on the ratings for infiltration given by the consultants at the preliminary and 48-week examinations.

In calculating this index, the patients in each group at each institution were first divided into two classes according to the extent of infiltration present at the outset; that is, those graded from 0 to 7 and those graded from 8 to 15. For each class, a score was computed as follows: Patients whose infiltration disappeared during treatment were given a weight of 2; improved but not cleared up, 1; stationary, 0; worse, -1. For each class-i.e., 0 to 7 and 8 to 15 on preliminary examination-a mean improvement score was obtained for each therapy group by addition of the ratings and division of the total score by the number of patients. The proportions of patients with original infiltration ratings of 0 to 7 and of 8 to 15 varied somewhat as between the different groups and institutions.

To make the indices more comparable, an adjustment was made using the same factors as in the first series. In that series it was found that 61.6 per cent of all patients at all institutions had original infiltration ratings of 0 to 7 and 38.4 per cent had ratings of 8 to 15; i.e., the proportions were 0.616 and 0.384. The adjusted mean index for each group was obtained by multiplying the mean improvement score for the 0 to 7 class by 0.616, that for the 8 to 15 class by 0.384, and adding the products.

The highest possible value of any index is 2.0, which would signify that infiltration had disappeared from all patients in the group. The lowest possible is -1.0, which would occur if all patients showed increase of infiltration. If all remained the same the score for the group would be zero.

The indices for the groups of the second series, and for combinations of the groups receiving diasone (A and B) and INH (B and C), are shown in Table 3.

Improvement in infiltration was not very conspicuous in any group, and there was no significant difference between the therapy groups at any institution. It may be added that for Eversley Childs and Westfort, the

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institutions that participated in both series, improvement in infiltration was not as apparent in the second series as in the first one. For the diasone group (A) of each series the adjusted indices of change in infiltration

9	Central	Luzon	Eversle	y Childs	Westfort		
Group	Index	S.E.	Index	S.E.	Index	S.E.	
A	0.37	0.082	0.36	0.104	0.63	0.127	
в	0.40	0.089	0.47	0.095	0.58	0.130	
C	0.29	0.113	0.43	0.113	0.63	0.080	
AB	0.38	0.060	0.42	0.071	0.63	0.100	
BC	0.35	0.050	0.45	0.074	0.58	0.100	
ABC	0.36	0.054	0.42	0.060	0.62	0.081	

TABLE 3.—Adjusted mean indices for changes in infiltration, with standard errors, by institutions and therapy groups.\*

a The index for each group and combination of groups is adjusted to compensate for inequalities in proportions of patients with light (0 to 7) and heavy (8 to 15) infiltration on preliminary examination. The proportions of all patients with light and heavy infiltration, respectively, in the first series, were used as a standard. Highest possible index, 2; lowest possible index, -1.

were 0.66 for the first series and 0.36 for the second at Eversley Childs, and 0.81 for the first series and 0.63 for the second at Westfort.

Nodules: On preliminary examination, 17.8 per cent of the Central Luzon patients, 21.9 per cent of those at Eversley Childs, and 9.1 per cent at Westfort were recorded as having nodules. Improvement occurred quite generally at all institutions, without distinction as to therapy group. A few patients without nodules on preliminary examination developed them during the course of the treatment. At Central Luzon this happened in 3 of 49 patients in Group A, 2 of 53 in B, and none of 50 in C; at Eversley Childs in none of 47 in A, 1 of 58 in B, and none of 52 in C; at Westfort in 1 of 30 in A, 1 of 31 in B, and none of 30 in C.

Plaques: Plaques were present at the outset in 46.5 per cent of the Central Luzon patients, 39.3 per cent of those at Eversley Childs and 20.0 per cent at Westfort. At Eversley Childs and Westfort, improvement in plaques was the rule in all three groups. At Eversley Childs 3 patients of Group A who had no plaques at the beginning developed them, as did also 1 patient in B. At Westfort 1 patient of this category in each group developed plaques during the treatment. At Central Luzon the picture was not quite so favorable, but there was no significant difference between the groups. In Group A, 2 patients with plaques at the beginning worsened in this respect, and 2 others who had been free from plaques developed them. In Group B the original lesions became worse in 4 patients and 3 new instances occurred, and in Group C plaques became worse in 2 patients and developed in 2 others.

Lepromatous ulcers: (a) Nasal ulcers: In studying the effectiveness of the therapy on ulceration of the nasal septum the diasone groups (A and B) have been compared with the INH groups (B and C) at each institution. (It should be noted that in this comparison Group B is counted as both a diasone and an INH group.) At Central Luzon, ulceration of the septum was noted on preliminary examination in 98 patients, or 53.3 per cent. In the diasone groups there were 64; in 32, or 50.0 per cent, of these patients the ulcers were healed on final examination. In the INH groups there were likewise 64; in 30, or 46.9 per cent, healing took place. The other facet is that new ulceration of the nasal septum was observed in 1 patient of Group A, 3 of B, and 6 of C. At Eversley Childs, septal ulceration was present at the outset in 59 patients, or 29.4 per cent. In the diasone groups there were 36 such patients; in 30 of these, or 83.3 per cent, the ulcers healed. In the INH groups there were 42, and the percentage in which healing took place was 78.6. New ulceration was observed at the end in 1 patient each in Groups A, B, and C. At Westfort, septal ulceration was present at the beginning in 49 patients, or 44.1 per cent. There were 33 with ulceration in the diasone groups, and healing occurred in 39.4 per cent. There were 35 in the INH groups, and healing took place in 54.3 per cent. New ulceration occurred in 5 patients of Group A, 9 of B, and 1 of C.

(b) Other lepromatous ulceration: At Central Luzon, lepromatous ulceration of the skin was recorded in 9 patients; 5 in Group A, and 2 each in Groups B and C. In all, except 2 in Group A, healing took place. New ulceration was noted in 1 patient of Group B and in 2 of Group C. At Eversley Childs, lepromatous ulceration was noted in 11 patients at the beginning: 6 in A, 2 in B and 3 in C. In all these, except 2 in A, healing occurred. In 1 patient of Group B new ulceration was recorded. At Westfort, ulceration was present in 1 of Group A, 2 of B, and 1 of C. Healing occurred in 1 of A and 1 of B. New ulceration was not observed.

Keratoconjunctivitis: This important complication was not recorded either on preliminary or final examination in any patient at Westfort. At Central Luzon it was recorded at the outset in 12 patients; 4 in each of the three groups. One new case occurred during treatment in Group A and 3 cleared up, leaving 2 at the end. Three new cases occurred in B and 4 cleared up, leaving 3. Two new cases occurred in C and 2 cleared up, leaving 4 at the end. The condition was observed at Eversley Childs in 40 patients at the beginning: 16 in Group A, 13 in B, and 11 in C. Probably milder degrees of inflammation were recorded at the beginning at Eversley Childs than at Central Luzon, because at the end of treatment there were recorded only 5 cases: 1 each in Groups A and C, and 3 in B. Only 1 case (in B) developed during treatment.

Neurologic findings: There were no significant changes in the extent

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of anesthesia, as recorded by the consultants, associated with any of the therapies.

General health: The general health of the patients on the average remained good in all groups at the three institutions. The average weights of both males and females increased in all groups at Central Luzon and Eversley Childs. At Westfort, the average weights for the groups were more or less the same after the treatment as before. Erythrocyte counts showed a slight fall in all groups and in both sexes at Central Luzon and Eversley Childs; at Westfort a slight fall occurred in Groups A and B, but not in C. The average hemoglobin values remained more or less the same for all groups at Central Luzon; at Eversley Childs there was a slight fall in all groups; at Westfort there was a slight fall in Groups A and B.

#### CLINICAL RESULTS, PILOT STUDY OF STREPTOHYDRAZID

At Eversley Childs, 20 of the 25 patients placed on Streptohydrazid completed treatment. Of these, 2 were graded as clinically improved, and 18 as stationary. Of the 75 patients in Groups A, B and C who were selected for reference, 62 completed treatment. Of these, 5 were graded as improved, 54 as stationary and 3 as worse. Of the improved, 2 were in Group A, 2 in B, and 1 in C. The 3 patients becoming worse were in Group B (diasone plus INH).

At Westfort, 9 of the 10 patients on Streptohydrazid completed treatment. Of these, 6 were graded as improved, 1 as stationary and 2 as worse. Of the 30 patients in Groups A, B and C who were selected as controls for those on Streptohydrazid, 27 completed treatment; and of these, 16 were graded as improved, 3 in Group A, 7 in B, and 6 in C, and none as worse.

Thus, from the viewpoint of clinical opinion, the patients treated with Streptohydrazid showed about the same progress as those on diasone, diasone plus INH, and DHSM plus INH.

#### BACTERIOLOGIC FINDINGS, REGULAR SECOND SERIES

The bacteriologic procedures adopted for the first series (1) were adhered to in the second. As has been noted, smears were required from both sides of the nasal septum, both earlobes, and four optional skin sites. For the optional sites the most marked or active lesions were selected, and subsequent smears were made from approximately the same areas. The present analysis deals only with the preliminary and final (48-weeks) results.

Status on preliminary examination.—Preliminary bacteriologic findings for all sites, and for all excepting the nasal septum, are given for each institution in Table 4.

The Eversley Childs patients were the most heavily infected, having the highest proportion of 3+ and 4+ sites. The next heaviest infected were the patients at Central Luzon, and the "lightest" bacteriologically were those at Westfort. At Westfort 42.1 per cent of all sites were nega-

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tive at the outset, as compared to 12.6 per cent at Eversley Childs and 7.6 per cent at Central Luzon. The percentages of the nasal septum smears that were negative at the outset were: at Westfort, 91.2; at Eversley Childs, 28.2; and at Central Luzon, 4.5. One or the other, or both, of the

Desults	Central	Luzon	Eversle	y Childs	Westfort		
nesuts	8 sites	6 sites	8 sites	6 sites	8 sites	6 sites	
Negative	7.6	8.6	12.6	7.4	42.1	25.5	
VS, 1+ & 2+	61.6	60.0	49.3	52.6	37.5	47.4	
3+ & 4+	30.8	31.4	38.1	39.9	20.4	27.1	
No. of sites	1,504	1,128	1,616	1,212	808ª	604ª	
No. of patients	188	188	202	202	102	102	

 TABLE 4.—Bacteriologic findings on preliminary examination by institutions;

 percentages for all sites (8), and for all sites excepting nasal

 septum (6).

a Eight sites not examined.

earlobes were more uniformly positive; the percentages of negative smears from earlobes being for Westfort 14.2, for Central Luzon 9.6, and for Eversley Childs 8.7. Of the smears from the four optional skin sites, 31.3 per cent were negative on preliminary examination at Westfort, 8.1 per cent at Central Luzon, and 6.8 per cent at Eversley Childs.

Patients becoming negative.—Relatively few patients were negative at all required sites on the 48-weeks examination, and even these may have been positive at other than required sites. Of all who completed treatment, the proportions becoming negative were 10.7 per cent at Central Luzon, 8.4 per cent at Eversley Childs, and 12.6 per cent at Westfort. These conversions were not associated with any particular therapy. In the first series, negativity at all required sites at the end of the study had also occurred in a few cases, without relationship to the type of therapy; in fact, it was not significantly less frequent in the control groups than in the others.

Sites becoming negative.—It was thought possible the greater effectiveness of one of the therapies might be indicated by a higher proportion of negatives in the 48-week smears from the nasal septum. At Westfort the number of septum sites that were positive on preliminary examination was too small to yield significant results. At Central Luzon there were at the start 118 positive smears in Group A, 122 in B, and 119 in C. The proportions of these sites that were negative at the end of 48 weeks were: 67.8 per cent for A, 67.2 per cent for B, and 63.0 per cent for C. At Eversley Childs there were originally 97 positives in A, 98 in B, and 95 in C. The percentages negative at the end were 45.4 for A, 45.9 for B, and 29.5 for C.

It should be emphasized that the nasal septum, like the skin, may become negative without treatment. At Eversley Childs, in the two sulfone groups (A and B combined) of the first series, there were 143 septum sites that were positive on preliminary examination. Of these, 37.1 per cent were negative after 48 weeks of treatment. In the control (Ceslu) group there were 63 sites positive at the beginning, of which 27.0 per cent became negative.

In the second series, as in the first, smears from the earlobes that were positive at the beginning showed lower conversion rates than did those from the nasal septum. The differences between the groups in this respect were not consistent. The percentages of earlobe sites becoming negative were for institutions and groups as follows: at Central Luzon: A, 33.0; B, 27.1; and C, 23.0; at Eversley Childs: A, 19.8; B, 26.3; and C, 20.8; at Westfort: A, 20.0; B, 14.1; and C, 15.7.

For the four optional skin sites the percentages becoming negative were a little higher than for the earlobes at Central Luzon, but they were lower at the other institutions. There were no significant differences as between Groups A, B, and C in this respect at any institution.

Improvement in sites.—A detailed analysis was made of the results of smears from the earlobes, nasal septum, and four optional sites to ascertain the frequency, in each therapy group, of improvement short of complete negativity of the patient. Correlation tables were prepared showing the number of sites falling into each of the several categories—i.e., negative, very scanty, 1+, 2+, 3+, and 4+ at the preliminary and at the final examinations.

In considering the question of improvement of sites the results of the first series are pertinent. At the Japanese institutions, where the control group was given Ceslu, about 40.0 per cent of the sites improved by the end of 32 weeks, but there was no significant difference between any of the therapy groups or between these and the controls. At Westfort, where the controls were given PAS, approximately one-half of the sites showed improvement at the end of 48 weeks in both the therapy and control groups. At Eversley Childs, where also the control group received Ceslu, the proportion of sites that improved was 52.3 per cent for the therapy groups and 37.0 per cent for the control group. It can be concluded, therefore, that improvement in a considerable proportion of the sites that show improvement under any therapy is attributable not to the treatment but to other factors.

In the second series the proportions of sites showing improvement were, for all groups, 75.3 per cent at Central Luzon; 66.6 per cent at Eversley Childs, and 32.4 per cent at Westfort. There was remarkable uniformity in the percentages of sites that showed improvement, remained stationary, and became worse in the three groups at each institution. Bacteriologic improvement in relation to prior therapy.—At each institution the bacteriologic improvement of sites was somewhat, but not significantly, greater for patients who had received one year or more of sulfone therapy before entering the second series than for those who had received less than one year or no prior sulfone treatment. The comparison is rendered less valuable because the groups differed in other respects. Those who had received sulfones for a longer period had on the average longer periods of institutional care and probably earlier onsets.

At Eversley Childs there were 89 patients in the second series or the Streptohydrazid pilot study who had been in therapy groups A to E of the first series. Thirty of these patients received a sulfone in both series; these were in Group A, B, or D in the first series and in either A or B in the second. Twenty-two had received DHSM for two years; these were in Group C, D, or E in the first series and in C or D in the second. Thirtyseven additional patients had received a sulfone in one series and DHSM in the other; these were in Group A or B in the first and in C or D in the second, or in C or E in the first and A or B in the second.

In comparing these three classes, treatment other than with a sulfone or DHSM has been disregarded. Also patients in Group D of the first series were considered to have received only diasone in both series if they were in Groups A or B of the second; and as having only DHSM throughout if they were in Group C or D of the second.

These special classes of patients, namely, (1) those who received sulfones in both series, (2) those who received DHSM in both, and (3) those who received sulfone in one series and DHSM in the other, were roughly comparable to one another in respect to bacteriologic status on entering the first series. For all eight sites the average score at that time for each site (giving a value of 0.5 for very scanty, of 1 for 1+; 2 for 2+, etc.), was 1.85 for those who received a sulfone in both series, 2.15 for those who received DHSM in both, and 2.35 for those receiving a sulfone in one series and DHSM in the other. In respect to sex, age, body weight and length of stay in institution, the classes were not greatly different. The average duration of disease from the stated date of onset to enrollment in the first series was three years longer for those who had DHSM in both series (C, D, E, first series and C, D, second series) than for the other classes.

Only 5 of these 89 patients were negative at all required sites at the end of the second series. Of 30 given sulfones in both series, 1 became negative at all required sites. As far as is known this patient was never heavily positive; on preliminary and later examinations the highest grade recorded for any site was 2+. Of 22 patients given DHSM in both series, 3 gm. weekly in the first and 2 gm. weekly in the second, 3 became negative. These 3 would also be classed as light positives. In one the highest score at any site in all examinations was 2+; in the second the highest was 1+ except for one site, which on one occasion was 3+; and in the

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third the highest for any site was 2+ (except for one nasal 4+ and one nasal 3+) in all examinations over the two-year period. Of the 37 treated with a sulfone in one series and DHSM in the other, only 1 was negative at all sites at the end of the second year. This patient also was never heavily positive, as far as the records show.

Taking the preliminary examinations on entering the first series as the base, an estimate was made of improvement to the end of the first and to the end of the second series.

Indices of bacteriologic changes were calculated by the method used in the first series, with certain exceptions. Sites originally negative and remaining so were regarded as stationary and given no weight (zero); in the first series such sites were given a weight of 2.0. Also, it was considered unnecessary to adjust the indices for differences between the classes in respect to proportions of sites heavily and less heavily infected, respectively, at the outset. Another departure from the procedure of the first series was that the standard error of each index was based on the average change per site achieved by each *patient* rather than on the average score for *sites* of the class or group.

It was found, as was expected, that there were no significant differences between the three classes at the end of the first series. When the differences between the indices for the end of the first series and those for the end of the second series were studied, it was found that the greatest improvement during the second series apparently was made by those who were on a sulfone throughout. The average difference between the improvement for this class and improvement for those treated with DHSM in both series approached statistical significance—being approximately at the 5 per cent level.

The patients receiving a sulfone in one series and DHSM in the other fell between the sulfone and the DHSM classes with respect to bacteriologic improvement during the second series; that is, their average improvement was not significantly different from that for those receiving a sulfone in both series or from those given DHSM in both.

#### BACTERIOLOGIC FINDINGS, PILOT STUDY OF STREPTOHYDRAZID

At Eversley Childs only 2 of the 20 patients on Streptohydrazid who completed treatment became negative at all required sites. In 68.7 per cent of the sites, however, there was improvement. Of the 62 reference patients in Groups A,B, and C, 4 were negative at all required sites at the end of 48 weeks, and improvement occurred in 66.1 per cent of the sites in these patients. At Westfort, where 9 of the Streptohydrazid patients completed treatment, only 1 was negative at all sites as compared to 6 of the 27 reference patients in Groups A, B, and C. Improvement in sites occurred equally in the Streptohydrazid and reference groups.

### CHANGES IN LEPROMIN STATUS

None of the patients at Central Luzon or at Eversley Childs gave a positive Mitsuda reaction to the Hayashi-Mitsuda lepromin before or at conclusion of therapy. At Westfort there were in Group A at the outset 2

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patients with weakly positive reactions to the Dharmendra antigen, 3 mm. or 4 mm. in diameter; these patients remained unchanged. Six others developed weakly positive reactions. In B there was 1 patient who was weakly positive at the beginning but negative at the end; 5 developed weakly positive (3 mm.) reactions, one a reaction of 5 mm, in diameter and one a reaction of 8 mm. In Group C one patient was reactive (8 mm.) at the outset but negative at the end; 2 others were weakly positive, 1 remaining so, the other 1 becoming negative. Nine who were negative became weakly positive, 3 mm. or 4 mm., and 2 developed small positive reactions (5 mm.). One patient in D became weakly positive (3 mm.). Thus the changes that occurred at Westfort were relatively few, for the most part of questionable significance, and not associated with any particular therapy.

## SUMMARY

1. There is described a controlled therapeutic study of lepromatous leprosy which was carried out concurrently at the Central Luzon Sanitarium and the Eversley Childs Sanitarium in the Philippines, and the Westfort Institution in South Africa. At Central Luzon, 213 patients commenced and 187 completed 48 weeks of treatment; at Eversley Childs, 234 commenced and 202 completed; and at Westfort, 119 commenced and 111 completed.

2. At each institution the patients were divided into three matched groups, A, B, and C, taking into consideration sex, age, stage of disease, prior sulfone therapy and certain other factors. Group A received diasone (diamidin) in the standard dosage; Group B received diasone in the same dosage as A, plus isoniazid (INH), 10 mgm. daily per kgm. of body weight; Group C received the same dosage of INH as B, plus 1 gm. dihydrostreptomycin (DHSM) intramuscularly twice weekly.

3. All therapies were well tolerated. The principal cause for discontinuance of treatment was departure from the institution without permission. As the groups were constituted at the end, however, they were comparable to one another inasfar as this could be determined.

4. On completion of treatment the proportion of each group, at each institution, showing clinical improvement was approximately the same. This was true of general improvement and of improvement in specified lesions such as infiltration, ulcers, nodules and others. A very small proportion became worse, and in this respect there was no evident relationship to any particular therapy.

5. No evidence was obtained that clinical improvement may be related to age, sex or other background factors, except prior sulfone therapy and stage of the disease. At all institutions, patients who had received little or no sulfone therapy before entering the study showed a higher clinical improvement rate than those who had been treated for a year or more. Also at all institutions the  $L_2$  and  $L_3$  patients taken together showed higher proportions of improvement than those classed as  $L_1$ . The patients in whom the disease was more advanced, however, were likewise those who on the average had received less sulfones before entering the study. Unfortunately the numbers of cases were too small to yield improvement rates for patients in various stages of the disease classified as to amount of prior sulfone therapy.

6. Eight sites on each patient were examined bacteriologically prior to treatment, at the end of 24 weeks of treatment, and at the end of 48 weeks. Very few patients became negative at all required sites, and in this respect also there was no relationship to any therapy.

7. Bacteriologic improvement occurred, however, in a high percentage of sites at Central Luzon and Eversley Childs, and in a lower percentage at Westfort. At each institution these percentages were more or less the same for Groups A, B, and C. Reference is made to the fact that during the first series a considerable proportion of sites improved bacteriologically in the control group at each of the participating institutions. The conclusion is reached that in all probability much of the bacteriologic improvement observed in the second series was not attributable to any therapy but to unknown causes which were equally operative in all groups.

8. There was some evidence, based on rather small numbers of patients that sulfone therapy continued over a period of two years may produce greater bacteriologic improvement than DHSM therapy for the same length of time. At Eversley Childs, 30 patients who had received either diasone or DDS in the first series were given diasone in the second, either alone or combined with INH. Likewise, 22 patients who received DHSM in the first series, either singly or combined with diasone or with sodium *p*-aminosalicylate (PAS), received in the second one DHSM together with INH. Only 1 of the sulfone-treated class and 3 of the DHSM-treated one were negative at all required sites at the end of the second series. The total improvement in bacteriologic status of sites, however, was somewhat greater for the sulfone-treated class.

9. A small pilot study of Streptohydrazid (Pfizer) was carried on concurrently with the regular second series. At Eversley Childs 25 patients were entered, of whom 20 completed 48 weeks treatment; and at Westfort 10, of whom 9 completed. The patients who received this therapy did no better, and no worse, either clinically or bacteriologically, than comparable patients in Groups A, B, and C of the regular series.

## RESUMEN

Preséntanse aquí los hallazgos correspondientes a la segunda series de estudios de justipreciación clínica, llevados a cabo por este grupo de investigadores. Los establecimientos interesados y el número de enfermos comprendidos fueron: Sanitario Central de Luzón, cerca de Manila, 213 (descendió a 187 al terminar el período de 48 semanas de trataminento); Sanitario Eversley Childs, Cebú, 234 (bajó a 202); e Institución Westfort, Pretoria, 119 (bajó a 111).

En cada uno de estos sitios se dividieron los casos en tres grupos equiparados para comparación de tres terapéuticas: A, diasona solamente; B, diasona más isoniacida (INH) y C, INH más dihidroestreptomicina (DSHM). En dos de los sitios, se asignaron además grupos más pequeños a un estudio explorador de la Estreptohidracida (Pfizer), compuesto ésta de estreptomicina e isoniacida. Todas las terapéuticas se toleraron bien, consistiendo la causa principal de la disminución del número de enfermos durante el período de tratamiento en la partida de los sujetos sin autorización.

Al cabo del período de tratamiento do 48 semanas, la proporción de enfermos mejorados en cada uno de los grupos regulares (A, B  $\Upsilon$  C) en el mismo establecimiento, era approximadamente idéntico; y esto rezó no sólo con respecto a la mejoría general sino también con las alteraciones observadas en las varias clases de lesiones. En cambio, hubo considerables diferencias en los porcentajes de enfermos mejorados en los distintos establecimientos: Eversley Childs, 9.9; Central Luzón, 17.6; Westfort, 55.9. Las proporciones muy pequeñas fueron aun peores (3.5%, 2.1% y 0.9%, respectivamente), sin ninguna relación evidente con ninguna terapéutica dada.

No se observaron signos de relación de los resultados con ninguno de los factores fundamentales, exceptuando la sulfonoterapia anterior y el período de la enfermedad. En todos los puestos, los enfermos que no habían recibido antes sulfonoterapia o que habían recibido poca acusaron mejores resultados que los tratados antes con sulfonas durante un año o más. Los casos más avanzados ( $L_2$  y  $L_3$ ) lo pasaron mejor que los menos avanzados ( $L_1$ ), sunque en conjunto los más avanzados habían recibido menos sulfonoterapia anteriormente.

La existencia de ENL, observada en más de la tercera parte de los enfermos filipinos al hacerse el examen inicial, pero solamente en la octava parte de los pacientes de Pretoria, se considera, con suma cautela, con respecto al pronóstico. Los coeficientes de mejoría clínica en los filipinos fueron más bajos entre estos enfermos que entre los que no manifestaban tal situación al ingreso, en tanto que entre los enfermos africanos los coeficientes eran muy semejantes en ambos grupos. Los porcentajes de los que manifestaron ENL durante el tratamiento, sin haberlo tenido al principio, variaron considerablemente, pero no hubo la menor prueba de que ninguna de las drogas fuera en particular susceptible de precipitar tal situación.

Relativamente pocos enfermos se volvieron bacteriológicamente negativos en todos los 8 sitios de examen exigidos por los procedimientos prescritos (10.7% en Central Luzón, 8.4% en Eversley Childs y 12.6% en Westfort) y aquí tampoco hubo la menor relación con ninguna terapéutica. No obstante, hubo mejoría clínica en los sitios examinados en porcentajes altos en los establecimientos filipinos, y algo menores en Sudáfrica; en todos los sitios, las cifras fueron aproximadamente idénticas para cada uno de los tres grupos terapéuticos. Considerando estos y anteriores resultados, parece probable que gran paete de la mejoría bacteriológica observada no fuera debida a ninguna terapéutica dada, sino más bien a causas desconocidas que obraron por igual en todos los grupos. Sin embargo, hay datos de que el tratamiento con sulfona durante dos años puede producir mejores resultados que la terapética con DHSM durante el mismo tiempo.

Los enfermos del estudio explorador con Estreptohiracida no lo pasaron mejor, ni tampoco peor, que los comparables de los tres grupos de la serie regular.

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