

CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY

THIRD SERIES: NICOTINAMIDE, AND BCG VACCINATION AS SUPPLEMENTS TO DIAMINODIPHENYL SULFONE (DDS)

JAMES A. DOULL, M.D.¹

*Medical Director, Leonard Wood Memorial
(American Leprosy Foundation)
Washington, D. C.*

JOSE N. RODRIGUEZ, M.D.

*Director, Bureau of Disease Control
Department of Health, Manila, Philippines*

ARTHUR R. DAVISON, M.D.

*Medical Superintendent, Westfort Institution
Pretoria, Union of South Africa*

JOSE G. TOLENTINO, M.D.

*Research Leprologist, Leonard Wood Memorial
Eversley Childs Sanitarium, Cebu, Philippines*

AND JUAN V. FERNANDEZ, M.D.

*Assistant Leprologist, Leonard Wood Memorial
Central Luzon Sanitarium, Rizal, Philippines*

In the first series of these studies (⁵), Diasone (Diamidin), 4-4'-diaminodiphenyl sulfone (DDS) and dihydrostreptomycin (DHSM) were shown to be of definite and apparently of equal value in treatment of lepromatous leprosy, insofar as could be judged from clinical changes during 48 weeks of therapy.² A combination of DHSM and Diasone showed no advantage over Diasone given singly, and the addition of sodium *p*-aminosalicylate (PAS) did not increase the effectiveness of DHSM. At two institutions where a control group was given a placebo of inositol and glycine (CESLU), the bacteriologic improvement was greater for all therapy groups than for the control group. Other than this, none of the groups at any institution was significantly different from any other in respect to bacteriologic changes.

In the second series (⁶), treatment with both isoniazid (INH) and Diasone (Diamidin), or with both INH and DHSM gave no better clinical results than were observed with Diasone alone. Bacteriologic improvement likewise occurred in all therapy groups at each institution, and was more or

¹Other participants in the third series studies were: R. S. Guinto and Y. T. Chang, Leonard Wood Memorial; R. Kooij, Westfort Institution, Pretoria; C. H. Binford, U.S. Public Health Service. Other persons and entities which contributed in one way or another are mentioned in the acknowledgments at the end of the report.

²Diasone (Abbott Laboratories) and Diamidin (Parke, Davis and Co.) are registered trademarks for sulfoxone sodium U.S.P.

less the same in each group. Very few patients became negative at all of the eight required sites, and in this respect also there was no association with any therapy.

The maximum dosages used were: In the first series, Diasone (Diamidin), 1 gm. daily; DDS, 0.2 gm. daily, and DHSM, 1 gm. three times a week; and in the second series, Diasone (Diamidin), 1 gm. daily; INH, 10 mgm./kgm. of body weight daily; and DHSM, 1 gm. twice a week. No treatment was given on Sundays.

The results obtained with nicotinamide in other mycobacterial infections, and the relatively high tolerance of the human subject to this drug, indicated the desirability of its trial in leprosy. As early as 1945, Chorine⁽³⁾ and Huant⁽⁷⁾ reported that this drug, also known as niacinamide and as nicotinic acid amide, possesses moderate tuberculostatic activity. In 1948 McKenzie *et al.*⁽¹⁰⁾ confirmed this finding. The discovery of the much greater tuberculostatic power of pyrazinamide and of isoniazid subsequently diverted attention from nicotinamide. Chang⁽²⁾, however, in 1954, found that nicotinamide has a highly suppressive action in mice inoculated with *M. leprae murium*.

In a preliminary trial one of us (J.G.T.), at Eversley Childs Sanitarium, placed 10 patients with lepromatous leprosy on both nicotinamide and INH and compared their progress over a period of six months with the same number of patients given DDS. Each of the latter group was matched against a member of the nicotinamide-INH group, taking into account age, sex, bacteriologic findings and prior sulfone treatment. Nicotinamide and INH were given intramuscularly five days a week, and orally on the other two days. The maximum daily doses, reached after a two-weeks induction period, were 1 gm. of nicotinamide and 0.3 gm. of INH. The dosage of DDS was the same as that used in the first series, that is, a maximum of 0.2 gm., reached after an induction period of 8 weeks. The results at the end of 24 weeks were inconclusive as regards both clinical and bacteriologic changes. The patients given nicotinamide and DDS, however, were in at least as good condition, in both respects, as those who received DDS only.

Several workers have treated lepromatous leprosy by vaccination with BCG. Azulay *et al.*⁽¹⁾ found that BCG vaccination by the oral route caused 7 of 20 lepromatous patients, who were already negative bacteriologically, to develop reactivity of the Mitsuda type but in all of them the reactions were small. Jonquieres and Masanti⁽⁸⁾ reported that of 39 lepromatous patients, 8 developed doubtful positivity which was not maintained. Lowe and McNulty⁽⁹⁾ obtained definite lepromin conversions in 10 per cent of 104 lepromatous patients following one vaccination, but they did not detect accelerated clinical improvement in a short subsequent period of observation. Convit *et al.*⁽⁴⁾ found that the Mitsuda reaction became positive in 25.5 per cent of 51 lepromatous patients fol-

lowing a single vaccination with BCG. All of their patients had received prolonged treatment with sulfones and were free from dermatological lesions prior to vaccination. The authors assumed that acquirement of reactivity to lepromin was beneficial, but it is not stated whether bacteriologic improvement followed vaccination.

The evidence as regards the efficacy of nicotinamide and BCG being inconclusive, it was considered worthwhile to obtain additional information by means of a clinical trial conducted on a sufficiently large scale to permit measurement of any advantage which supplemental treatment with either of these agents possesses over treatment with DDS alone.

OBJECTIVES, ORGANIZATION AND PROCEDURES

Specific objectives.—The specific objectives of the third series were to compare the effectiveness in lepromatous leprosy of DDS with that of DDS plus nicotinamide; and the benefit, if any, of supplementing either of these therapies by vaccination with BCG.

Organization.—The institutions selected were the three which participated in the second series. Two of these are operated by the Philippine government: Central Luzon Sanitarium, situated near Caloocan, Rizal Province, about 30 miles north of Manila, and Eversley Childs Sanitarium, situated in Mandawe, in Cebu Province, about 8 miles northeast of Cebu City. The third was 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 consultant leprologist was appointed to make independent examinations at each of the institutions in the Philippines. These examinations were entrusted to a resident research leprologist at Westfort.

Assignment of patients to therapy groups.—At the Central Luzon Sanitarium 185 patients, at Eversley Childs 210, and at Westfort 101, were selected for the study. In all cases a clinical diagnosis of lepromatous leprosy had been made. At each institution approximately two-thirds of the patients were males. At the Philippine institutions all were between 10 and 40 years of age; at Westfort all were over 10 years but there were 16 who were over 50 years of age. An index card was prepared for each patient, on which were entered a code name, age, sex, dates and amounts of prior sulfone treatment, year of onset, date of admission, stage of disease, presence or absence of infiltration, nodules, and certain other signs, and the results of a tuberculin test using PPD in a maximal dose of 0.0001 mgm. (5 TU). These cards were airmailed to the office of the medical director in Washington.

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 (⁵). The cards for male and female patients, respectively, were arranged in descending order of age. A coin was tossed to determine whether the first male patient would be assigned to receive DDS (Group A) or DDS plus nicotinamide (Group B), and the following cards were then assigned alternately to each group. The same procedure was followed with the cards for the female patients. The cards for tuberculin-positive patients of Group A were classed as Subclass A-1 and those for tuberculin-positive patients of Group B as Subclass B-1. The cards for the patients of Group A who were tuberculin negative were rearranged by sex and descending order of age and assigned alternately to Subclasses A-2 and A-3, the disposition of the first card being again settled by coin tossing. A similar procedure resulted in separation of the tuberculin negatives of Group B into Subclasses B-2 and B-3. Except that the tuberculin-positive patients

proved to be on the average slightly older than the negatives, the subclasses were very well balanced with one another in respect to the various items included on the index cards. At each institution, however, a few transpositions were made to improve the comparability of Subclass A-1 with B-1, and A-2, A-3, B-2 and B-3 with one another. Lists of patients to be included in each subclass were then air-mailed to each institution.

In summary, the two major groups at each institution were divided into three subclasses, the arrangement being as follows:

Group A. To be treated with DDS.

- A-1 Reactors to tuberculin. Not to be vaccinated with BCG.
- A-2 Nonreactors to tuberculin. To be vaccinated with BCG.
- A-3 Nonreactors to tuberculin. Not to be vaccinated with BCG.

Group B. To be treated with DDS plus nicotinamide.

- B-1 Reactors to tuberculin. Not to be vaccinated with BCG.
- B-2 Nonreactors to tuberculin. To be vaccinated with BCG.
- B-3 Nonreactors to tuberculin. Not to be vaccinated with BCG.

Laboratory and other examinations.—All patients entering the study were required to be negative to lepromin. In the Philippines, the lepromin used was prepared by the Mitsuda-Hayashi method; at Westfort, it was prepared by Dharmendra's technique. Tuberculin testing was done with commercial PPD preparations. Patients were tested first with PPD in a dosage of 0.00002 mgm. (1 TU), and if negative were retested immediately with 0.0001 mgm. (5 TU). Retesting with tuberculin and lepromin was done at the end of the 12th, 24th, 36th, and 48th weeks.

Patients who were negative to 0.0001 mgm. of PPD and assigned to Subgroups A-2 and B-2 were vaccinated with BCG, and if still negative to tuberculin were re-vaccinated at the end of the 12th and at the end of the 24th weeks. BCG was given by intradermal inoculation. That used in the Philippines was fresh, living vaccine prepared at the Alabang Laboratory. That used at Westfort was fresh living vaccine from the Statens Seruminstitut, Copenhagen.

Bacteriologic examinations.—Separate smears were examined from eight sites, as in the first and second series, viz.: 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. All entering patients were positive at two or more skin sites.

Other laboratory 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 week at Eversley Childs. Erythrocyte counts and packed cell volume estimations were made before and after treatment at Central Luzon and Eversley Childs. Hemoglobin estimations, erythrocyte and leukocyte counts, and differential leukocyte studies for the Westfort patients were made on preliminary and post-treatment specimens at the South African Institute for Medical Research, Johannesburg. At the Philippine institutions serum sulfone determinations were made at the 16th and 32nd weeks, and at Westfort at the 16th and 40th weeks. Routine urine examinations were made on all patients on three or more occasions.

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

Physical examinations.—Dermatologic and neurologic examinations were made by the consultant during the preliminary period, after 24 weeks of treatment, and at the end of 48 weeks. At these examinations 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 48-weeks examination had been completed and his findings entered on the records.

Dosages of drugs.—DDS was scheduled to be given in approximately the same doses as for Group B of the first series, i.e., one tablet (50 mgm.) every second day for the first two weeks, one tablet daily for the third and fourth weeks, two tablets daily for the fifth and sixth weeks, three tablets daily for the seventh and eighth weeks, and thereafter four tablets daily. Since no tablets were given on Sundays, full dosage for the period of the study was approximately 52 gm. The individual records for the Philippine institutions showed that the average amount actually taken by patients who completed treatment was 48 gm. for Eversley Childs and 26 gm. at Central Luzon. The average concentrations in the blood serum were: Eversley Childs, 16th week, 0.48 mgm. per cent; and 32nd week, 0.42 mgm. per cent. At Central Luzon, 16th week, 0.40 mgm. per cent, and 32nd week, 0.56 mgm. per cent. At the latter institution there was much greater difficulty in persuading the patients to take full and regular dosage than at Eversley Childs, but the serum levels for the two institutions corresponded much more closely than was expected from the average dosage of DDS as computed from the individual treatment records.

The starting dose of nicotinamide was 300 mgm. daily, except Sundays. This was increased to 500 mgm. daily after the end of two weeks. Full dosage for each individual was therefore about 142 gm. The detailed records for the Philippine institutions show that the average quantity actually taken at Eversley Childs was 131 gm. At Central Luzon, the average was 77 gm.

At Westfort, the actual dosages of DDS approximated the amounts prescribed. The average concentrations in the blood serum were: 16th week, 0.92 mgm. per cent; and 40th week, 0.88 mgm. per cent. Only 50 mgm. of nicotinamide was given daily during the first three weeks, 300 mgm. daily for the fourth and fifth weeks, and 500 mgm. daily from the sixth to the twelfth weeks. From that time to the end of the study the patients of Group B were given a tablet containing 100 mgm. of isoniazid (INH) and 100 mgm. of nicotinamide in a dosage of approximately 15 mgm. per kgm. of body weight of each drug daily.

Duration of treatment.—The duration of treatment was fixed at 48 weeks. The actual periods were: At Central Luzon Sanitarium, May 24, 1955, to April 24, 1956; at Eversley Childs Sanitarium, June 1, 1955, to May 2, 1956; and at Westfort Institution, where a rest period of about one month was allowed between December 15, 1955 and January 15, 1956, from May 23, 1955, to May 25, 1956.

As in the first and second series, various technical procedures and the record keeping were standardized as far as practicable. The completed records were sent to the office of the medical director in Washington for tabulation and study.

Dropped patients.—Patients whose treatment was discontinued because of worsening of the disease were considered to have completed treatment. The records of their physical condition and bacteriology for the examination closest in time to the date of withdrawal were taken as final. The number of patients originally selected are shown for each institution in Table 1, those dropped being classified according to reason for that action.

The principal reason for discontinuance of therapy was departure from the institution without permission, although some discontinued for other reasons. Any

patient absent for 60 days or more was classified as having insufficient treatment and was dropped. At Central Luzon there were 17 of these patients, at Eversley Childs 24, and at Westfort 5. In 3 instances at Eversley Childs and in 2 at Westfort discontinuance was attributable to medical reasons not associated with leprosy or with specific therapy. One patient at Eversley Childs was forced to discontinue treatment because of intolerance to nicotinamide. Treatment with this drug was repeatedly suspended but when resumed the patient invariably complained of anorexia, nausea and vomiting.

To determine the effect of dropping of patients on the comparability of the subgroups at each institution, an analysis was made of certain group characteristics for patients selected and for those completing treatment. As far as can be judged the comparability of these subclasses remained unaffected.

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

Treatment status	Central Luzon	Eversley Childs	Westfort	Total
Complete (examined)	166	175	93	434
Complete (no final examination)	1	4	—	5
Incomplete				
Drug intolerance ^a	—	1	1	2
Erythema nodosum leprosum	—	—	—	—
Complicating diseases ^b	—	3	2	5
Dosage insufficient ^c	17	24	5	46
No treatment ^d	1	3	—	4
TOTAL SELECTED	185	210	101	496

^a Eversley Childs, to nicotinamide (B-1; DDS + nicotinamide); Westfort, exfoliative dermatitis (A-1; DDS).

^b Eversley Childs, 3 died of chronic nephritis, acute enteritis, broncho-pneumonia; at Westfort 2 died of cirrhosis of liver, laryngeal stenosis.

^c Central Luzon, absconded, 14; transferred to Culion, 2; trouble in family, 1. At Eversley Childs, absconded, 21; refused, 3. At Westfort, mentally ill, 1; repatriated, 1; became tuberculoid, 1; absconded, 2.

^d Central Luzon, absconded before therapy started, 1. At Eversley Childs, absconded before therapy started, 3.

RESULTS

CHANGES IN REACTIVITY TO LEPROMIN AND TO TUBERCULIN

1. *In Subgroups A-1 and B-1.*—All patients of these subgroups were positive to tuberculin and negative to lepromin on preliminary examination. Tuberculin reactivity was very stable. At the Philippine institutions, only 3.6 per cent, and at Westfort only 3.2 per cent, failed to react to the same dosage of tuberculin when tested at the end of 48 weeks. At the Philippine institutions, 2 patients showed 1+ lepromin reactions at the end. At Westfort all patients remained negative to lepromin.

2. *In Subgroups A-2 and B-2.*—All were negative to tuberculin and lepromin on preliminary examination. At the Central Luzon Sanitarium, 16 patients of A-2 and 19 of B-2 were classed as having completed treatment, but 1 of each of these subgroups died as a consequence of a severe reactive process. Of the 33 surviving, 26 were vaccinated once with BCG and 7 twice. All but 1 were positive to tuberculin at the end of 48 weeks. None became positive to lepromin.

At Eversley Childs, 19 patients of A-2 and 21 of B-2 completed treatment, a total of 40. Of these, 18 were vaccinated once, 12 twice, and 10 three times. All but 3 were positive to tuberculin at the end of 48 weeks. Three patients, 1 belonging to A-2 and 2 belonging to B-2, showed small Mitsuda reactions (1+) when the lepromin test was repeated at the end of 48 weeks.

At Westfort, 9 patients of A-2 and 7 of B-2 completed treatment. All were vaccinated twice with BCG. Of the 16, 13 were tuberculin positive at the end of the study. None became positive to lepromin.

In the total experience in these subgroups, at the three institutions, among 89 patients who completed treatment, there were 44 who were vaccinated once with BCG, 35 twice, and 10 three times. All but 7 were tuberculin positive at the end of 48 weeks. Only 3 became lepromin positive, and these had only 1+ reactions.

3. *In Subgroups A-3 and B-3.*—All were negative to tuberculin and to lepromin on preliminary examination. Although these patients were not vaccinated with BCG, nevertheless 53.5 per cent at both of the Philippine institutions taken together and 53.3 per cent at Westfort became positive to tuberculin. The greater part of these changes were observed at the end of the first 12 weeks at all institutions. The only known factor which may have contributed was the repeated application of the lepromin test. Unfortunately, we do not have controlled observations on the development of reactivity to tuberculin following lepromin testing in patients with lepromatous leprosy. It may be added that the tuberculin reactions which were observed at the end of 48 weeks in patients of A-2 and B-2 and in those of A-3 and B-3 were of definitely lower intensity than those observed at the end of the study in the initially positive Subgroups A-1 and B-1.

At the two Philippine institutions, 1 patient of 73 who completed treatment in these subgroups showed a 1+ reaction to lepromin when finally tested. At Westfort none of 16 patients in A-3 and B-3 became lepromin positive.

Thus, of 434 patients who completed treatment at all institutions and who were tested both before and at the end of treatment, only 6 became reactive to lepromin and in all of these the size of the papule produced by the lepromin was small.

CLINICAL CHANGES

The percentages of patients completing treatment, classed as improved, stationary, or worse on final clinical appraisal is shown by institutions and therapy groups in Table 2.

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

Therapy group ^b	Central Luzon				Eversley Childs				Westfort			
	No. pts.	Per cent			No. pts.	Per cent			No. pts.	Per cent		
		Imp.	Stat.	Worse ^c		Imp.	Stat.	Worse ^c		Imp.	Stat.	Worse ^c
A-1	49	42.8	53.1	4.1	46	67.4	32.6	—	30	60.0	30.0	10.0
B-1	53	50.9	45.3	3.8	45	55.5	42.2	2.2	31	54.8	35.5	9.7
A-2	16	25.0	68.7	6.3	19	68.4	31.6	—	9	88.9	11.1	—
B-2	19	57.9	31.6	10.5	21	61.9	33.3	4.8	7	57.1	28.6	14.3
A-3	15	46.7	53.3	—	23	60.9	39.1	—	8	75.0	25.0	—
B-3	14	42.9	50.0	7.1	21	61.9	33.3	4.8	8	75.0	25.0	—
A-1, B-1	102	47.0	49.0	3.9	91	61.5	37.4	1.1	61	57.4	32.8	9.8
A-2-3)	64	43.7	50.0	6.3	84	63.1	34.5	2.4	32	75.0	21.9	3.1
B-2-3)	35	42.9	48.6	8.5	40	65.0	32.5	2.5	16	75.0	18.8	6.2
A-2, B-2	29	44.8	51.7	3.4	44	61.4	36.4	2.2	16	75.0	25.0	—
A-3, B-3												
TOTAL	166	45.8	49.4	4.8	175	62.3	36.0	1.7	93	63.4	29.0	7.5

^a Imp.=markedly, moderately, or slightly improved; Stat.=stationary; Worse=slightly, moderately, or markedly worse. (In the reports for the first and second series, the "slightly" changed were classed as "stationary.")

^b For the drugs used in these treatment groups, see p. 6 of the text.

^c The numbers becoming worse are in all instances too small to be of significance. The percentages are shown only for balancing.

As far as can be judged from these figures, supplementation of DDS therapy by nicotinamide was not advantageous. For all "A" subgroups (DDS) the average percentages of patients showing improvement was 40.0 at Central Luzon, 65.9 at Eversley Childs, and 68.1 at Westfort. For all "B" subgroups (DDS plus nicotinamide) the comparable percentages were 51.1, 58.6 and 58.7.

There was likewise no clinical evidence of value of vaccination with BCG. The percentages showing improvement in Subgroups A-2 and B-2 taken together were 42.9 at Central Luzon, 65.0 at Eversley Childs, and 58.7 at Westfort. For the unvaccinated tuberculin negatives, Subgroups A-3 and B-3, the comparable percentages were 44.8, 61.4 and 75.0.

The proportions of all patients showing improvement at the respective institutions were: 45.8 per cent at Central Luzon, 62.3 per cent at Eversley Childs, and 63.4 per cent at Westfort. The differences between the Philippine institutions on the one hand and Westfort on the other may reflect variations in standards. The difference between the two Philippine institutions may have been caused by the failure of the patients at

Central Luzon to take DDS regularly and in the prescribed dosage. To obtain further information on the latter point, the patients at Central Luzon and Eversley Childs were classified into two groups, representing higher and lower total dosage of DDS. At Central Luzon the range was from a minimum of 2.3 gm. to a maximum of 50.3 gm., the median being 28.0 gm. At Eversley Childs the range was much narrower, being from 36.0 to 50.0 gm., with a median of 49.0 gm. At Central Luzon, 54.0 per cent of 82 patients receiving the higher dosage and 40.0 per cent of 81 receiving the lower dosage improved, and 3 of each group became worse. At Eversley Childs the proportions recorded as improved were the same (62.0%) for 88 patients receiving the higher and 87 receiving the lower total dosage. Three patients who became worse were in the lower dosage group, but all had taken more than 46.0 gm. Obviously, the relationship between dosage of sulfones and clinical improvement requires further study.

Effect of treatment on specified lesions.—As in the first and second series, 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.

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 two 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 weeks examinations. For the method of calculation of this index reference is made to the publication (⁵).

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 subgroups of the third series and for the totals of A and of B are shown in Table 3.

Improvement in infiltration was not conspicuous in any subgroup, and there was no consistency in the rank of the indexes for the subclasses at different institutions. The index for all Group A patients was almost exactly the same as that for all of Group B at Central Luzon and Eversley Childs, and the difference between the indexes for these groups at Westfort was not a significant one.

Nodules: On preliminary examination 22.9 per cent of the Central Luzon patients, 19.0 per cent of those at Eversley Childs, and 20.4 per cent of those at Westfort were recorded as having nodules. Comparing the totals of Group A and Group B it was found that improvement occurred in 4 of A and 10 of B at Central Luzon; in 5 of A and 7 of B at Eversley Childs; and in 6 of each group at Westfort. In 1 patient of Subgroup B-2 at Central Luzon in whom nodules were absent on preliminary examinations, they appeared during treatment. This did not happen in any patient at the other two institutions.

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

Therapy group	Central Luzon		Eversley Childs		Westfort	
	Index	S.E.	Index	S.E.	Index	S.E.
A-1	0.44	0.125	0.45	0.168	0.22	0.095
B-1	0.50	0.108	0.58	0.171	0.35	0.100
A-2	0.06	0.070	0.72	0.121	0.53	0.149
B-2	0.52	0.153	0.72	0.059	0.00	0.000
A-3	0.60	0.228	0.55	0.162	0.31	0.126
B-3	0.16	0.029	0.59	0.125	0.46	0.094
A-1, 2, 3	0.42	0.102	0.58	0.085	0.54	0.105
B-1, 2, 3	0.45	0.083	0.57	0.107	0.32	0.079

^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 and second series were used as a standard.

Lepromatous ulcers: (a) Nasal ulcers: In studying the effect of treatment on ulceration of the nasal septum, Group A (DDS) has been compared with Group B (DDS plus nicotinamide). At Central Luzon, ulceration of the septum was noted on preliminary examination in 72 patients, 31 of A and 41 of B. In Group A, 32.3 per cent were healed on final examination, and in Group B, 41.5 per cent. New ulceration was observed in 4 patients of Group A and in 1 of Group B. At Eversley Childs, ulceration was present on preliminary examination in 25 patients, 13 of A and 12 of B. In Group A, 53.8 per cent healed, and in B, 33.3 per cent. New ulceration was observed in 4 patients of A and 2 of B. At Westfort, ulceration of the septum was recorded as absent in all patients on both preliminary and final examinations.

(b) Other lepromatous ulceration: At Central Luzon, lepromatous ulceration of the skin was present at the beginning in 24 patients, 10 of Group A and 14 of Group B. In 9 of A and 8 of B healing occurred. New ulceration occurred in 2 patients in B. At Eversley Childs, ulceration was noted in only 6 patients, 2 in A and 4 in B. Healing took place in all. In 3 patients of Group A, but in none of B, ulceration occurred during

treatment. At Westfort, ulceration was present in 2 patients of A but in none of B. In both patients healing occurred. New ulceration was not observed.

Keratoconjunctivitis: At Central Luzon, this serious complication was present on preliminary examination in 21 patients, 10 in A and 11 in B. Three new cases occurred in A and 6 cleared up, leaving 7 at the end. In B no new cases occurred during therapy, 3 cleared up leaving 8. At Eversley Childs, the condition was observed in only 4 patients at the beginning, 1 in A and 3 in B. No new cases occurred during treatment and 3 cleared up, leaving 1 at the end (in B). At Westfort, none of the patients had keratoconjunctivitis at the beginning but during treatment this complication occurred in 1 patient of Group A.

Neurologic findings: There were no significant changes in the extent of anesthesia, as recorded by the consultants, associated with any of the therapies.

General health: The general health of all patients remained good at all institutions. The average weights of both males and females remained approximately the same in all subgroups at Central Luzon and increased in all at Eversley Childs. At Westfort, the average weight for male patients of both major groups remained about the same; the average weight of females showed a gain in both groups. Erythrocyte counts showed a fall for both sexes in all subgroups at all institutions except for males of Subgroup A-2 at Westfort. The fall was of about the same extent for those of patients of Group A as for those of B. The average hemoglobin values likewise fell in both sexes in all subgroups at Central Luzon and Eversley Childs, except in females of B-3 at Eversley Childs. The values for the Westfort patients were approximately the same at the end as on the preliminary examination.

PROGNOSTIC SIGNIFICANCE OF ENL AND BACKGROUND FACTORS

Erythema nodosum leprosum.—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 in its frequency between those who had been treated previously with sulfones and those who had not. At the Japanese institutions, the prevalence of ENL at the outset was 47.4 per cent, and at Westfort it was 51.9 per cent; in both places it was much higher in those previously treated with sulfones. The proportion of patients in whom ENL developed during therapy was about 40 per cent at each institution, and was about the same for those on sulfones as for those on DHSM.

In the second series, the initial frequency was 38.9 per cent at Central Luzon, 37.1 per cent at Eversley Childs, and only 13.0 per cent at Westfort. At Central Luzon and 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 con-

siderable proportion of patients who were free from it on preliminary examinations, but, as in the first series, there was no clear relationship to the type of therapy.

In the present series, ENL was present on preliminary examination in 28.9 per cent of the patients entering the study at Central Luzon, 29.4 per cent at Eversley Childs, and 23.9 per cent of those entering at Westfort. There was a positive relationship to prior sulfone treatment at the Philippine institutions. At Central Luzon, 38.3 per cent of 81 patients who had been previously treated showed ENL on preliminary examination as compared to 20.0 per cent of 85 who had received no treatment. At Eversley Childs, 36.0 per cent of 111 previously treated patients showed this complication but only 18.2 per cent of 66 who had never received sulfones. At Westfort, there were too few untreated patients to permit a comparison. During treatment of the third series, ENL was recorded at Central Luzon in 73 patients, or 44.0 per cent of those in whom it was not present on preliminary examination; at Eversley Childs it was observed in 72 patients, or 40.7 per cent; and at Westfort in 31, or 33.3 per cent.

The relationship of ENL to prognosis is still a matter of speculation. In the first series there was no evidence of greater or lesser clinical or bacteriologic improvement in patients in whom ENL occurred than in others. In the second series, there was some evidence that patients in whom ENL was *absent* on preliminary examination improved clinically somewhat more frequently than other patients. In the present series, also, the proportion graded as improved was higher at each institution for patients in whom ENL was absent both on preliminary and later examinations than for other patients. As stated in the report of the second series, groups that differed in respect to ENL may have differed in other ways. A controlled and specially designed study is needed to determine the prognostic significance of ENL.

ENL and reactivity to tuberculin.—It was thought possible that there might be some relationship between reactivity to tuberculin and the presence or occurrence of ENL. It was found, however, that there was no significant difference, either at the Philippine institutions or at Westfort, between the originally tuberculin-positive patients and the originally negative ones in respect to the frequency of occurrence of ENL during treatment. Nor was any evidence found that vaccination with BCG evoked the occurrence of ENL.

Various background factors.—As in the first and second series, as noted above, we took into account especially sex, age, stage of disease and previous sulfone therapy in matching the groups. The clinical improvement which occurred has therefore been studied in respect to these factors.

At Central Luzon, a greater proportion of male than of female patients showed improvement; at Eversley Childs the proportion of females was slightly in excess; and at Westfort the male patients had the advantage.

There was therefore no consistency in the results. There was likewise no consistent relationship between the age of the patients and recorded clinical improvement.

A feature which we think is not significant in itself but which illustrates the difficulty of measurement of clinical improvement in early cases is that, as in the second series, the recorded percentages showing improvement were much greater at each institution for L_2 and L_3 cases than for those classed as L_1 . This fact is obviously of importance in assigning patients to groups, but it may have no bearing on the actual response to treatment of early and advanced cases respectively.

As in the second series, clinical improvement in this series was recorded more frequently in those with little or no prior sulfone therapy than in others. In the first series the evidence obtained at the different institutions was contradictory in this respect.

BACTERIOLOGIC RESULTS

Many statistical analyses have been made of the bacteriologic findings in the search for evidence of some advantage of one treatment over another. No such evidence was found.

At Central Luzon, 16 patients of 166 completing treatment, or 9.6 per cent, became negative at all required sites. Of the 16 becoming negative, 8 were in Group A and 8 in Group B. At Eversley Childs, 22 patients of 175 completing treatment, or 12.6 per cent, became negative at all eight sites. Eleven of the negatives were in Group A and 11 in Group B. At Westfort, 11 patients of 93 completing treatment, or 11.8 per cent, became negative at all required sites. Five were in Group A and 6 in Group B. The average bacteriologic scores for skin and nasal septum sites on preliminary and 48 weeks examinations are shown in Table 4.

There was definite improvement in bacteriologic status in each subgroup at each institution, but no subgroup was significantly different from another in this respect. At Central Luzon, for six skin sites, the percentage reduction was 26.5 for all patients of Group A and 29.6 for all of Group B; at Eversley Childs, the comparable figures were 62.9 and 63.5, and at Westfort, 32.1 and 29.6. At Central Luzon, for two nasal septum sites, Group A patients showed a reduction of 28.0 per cent and those of B, 27.8 per cent; at Eversley Childs, the percentage reduction for A was 45.9 and for B, 40.9. The number of nasal-septum positives on preliminary examination at Westfort was too few to warrant further analysis. Clearly the addition of nicotinamide to the therapy had no advantage.

Having in mind the possibility that the nasal septum sites might have shown more rapid improvement than the skin sites, the preliminary results were compared to those obtained at the end of 24 weeks treatment. It was found that at Eversley Childs the improvement at that time was

much greater for the nasal septum sites than for the skin sites. At Central Luzon, the difference was not great but was in favor of the skin sites.

Significant differences in respect to reduction in the average bacteriologic score were not found between patients originally tuberculin positive (5 TU) and those originally negative. Likewise, no differences were found between patients in whom ENL was present on preliminary examination or developed it during treatment and those in whom ENL was not present at any time.

TABLE 4.—*Bacteriologic scores; on preliminary examination and after 48 weeks treatment, for 6 skin sites and 2 nasal septum sites, by institution and therapy group.^a*

Therapy group	Central Luzon		Eversley Childs		Westfort	
	Prelim.	48 weeks	Prelim.	48 weeks	Prelim.	48 weeks
<i>Skin sites (6), average</i>						
A-1	14.67	10.82	17.56	6.69	11.20	7.50
B-2	16.22	11.54	17.96	5.72	10.00	6.97
A-2	20.60	14.67	16.00	3.26	11.33	7.78
B-2	16.44	11.28	20.33	9.00	12.71	7.71
A-3	16.07	12.20	20.57	9.48	12.13	8.50
B-3	19.93	14.00	20.57	7.81	9.13	7.75
Total	16.48	11.85	18.59	6.83	10.83	7.47
<i>Nasal septum sites (2), average</i>						
A-1	3.16	2.29	4.19	2.17	(Numbers too few)	
B-1	4.57	3.41	4.19	2.74		
A-2	4.40	2.93	4.21	2.31		
B-2	4.22	3.50	5.38	3.52		
A-3	3.47	2.73	5.57	3.09		
B-3	5.21	3.21	5.19	2.48		
Total	4.05	2.96	4.63	2.65		

^a Scoring system: 4+ = 5; 3+ = 4; 2+ = 3; 1+ = 2; VS = 1.

Neither the age of the patients nor the stage of disease upon entrance into the study was related to the amount of bacteriologic improvement which took place at any of the institutions.

Bacteriologic improvement was much greater at Eversley Childs than at the other institutions. The average score of the Westfort patients was much lower at the beginning than that of the patients at Eversley Childs, and this fact may be related to the lesser improvement at Westfort. At Central Luzon and Eversley Childs, however, the starting levels were not greatly different. Yet the fall in the average bacteriologic score for all patients at Eversley Childs was for six skin sites, 63.3 per cent and for two nasal septum sites, 42.8 per cent; whereas at Central Luzon the comparable percentages were only 28.1 and 26.9.

These differences between the two Philippine institutions were considered to be possibly related to the failure of the Central Luzon patients to take treatment regularly and in the prescribed dosage. In a further exploration of this matter, the bacteriologic improvement in patients receiving higher total dosage of DDS was compared to that of those receiving lower dosage at Central Luzon and Eversley Childs taken separately. At each institution the percentage reduction in average score for skin sites was the same for higher and lower dosages. At Central Luzon the improvement in score for nasal septum sites was greater for the higher dosage patients, but at Eversley Childs the reverse was true. Thus, as with clinical improvement, a clear relationship between bacteriologic improvement and dosage of DDS was not demonstrated in this study.

SUMMARY

In a triplicate therapeutic experiment on lepromatous leprosy carried out at two leprosaria in the Philippines and one in the Union of South Africa, two major groups of patients at each institution were treated respectively with diaminodiphenyl sulfone (DDS), and with DDS plus nicotinamide. Tuberculin-negative patients of each group were divided into two subclasses. The patients of one subclass were vaccinated at least once with BCG; those of the other were left unvaccinated. Treatment was continued for 48 weeks.

No evidence was found that either supplementary therapy with nicotinamide or vaccination with BCG was advantageous. Patients of all subclasses showed clinical and bacteriologic improvement, but those treated only with DDS and not vaccinated showed about the same progress as others. Observed clinical improvement was limited to dermatologic lesions; there were no significant changes in the extent of anesthesia associated with any of the therapies.

Only 6 of 434 patients at all institutions developed lepromin reactivity of the Mitsuda type, and in all of these the size of the reaction was small.

The occurrence of the reactional condition, erythema nodosum leprosum, was not associated with either clinical or bacteriologic improvement. It was equally frequent in the two principal therapy groups, was not evoked by BCG vaccination, and was not associated with reactivity to PPD (0.0001 mgm.).

RESUMEN

En un triple experimento terapéutico sobre lepra lepromatosa, llevado a cabo en dos leproserías de las Filipinas y una de la Unión de Sudáfrica, dos grandes grupos de enfermos fueron tratados en cada establecimiento con diaminodifenilosulfona (DDS) y con DDS más nicotinamida, respectivamente. Los enfermos tuberculinonegativos de cada grupo fueron divididos en dos subclases. Los enfermos de una subclase fueron vacunados a lo menos una vez con BCG; a los della otra se les dejó sin vacunar. El tratamiento prosiguió por 48 semanas.

No se encontraron pruebas de que la terapéutica complementaria con nicotinamida o la vacunación con BCG fueran ventajosas. Los enfermos de todas las subclases revelaron mejoría clínica y bacteriológica, pero los tratados exclusivamente con DDS y dejados sin vacunar mostraron más o menos el mismo adelanto que los demás. La mejoría clínica observada se limitó a las lesiones dermatológicas; no hubo alteraciones importantes en la intensidad de la anestesia que se relacionaran con las distintas terapéuticas.

Unicamente 6 de los 434 enfermos de todos los establecimientos manifestaron reactividad de la forma Mitsuda a la lepromina, y en todos ellos el tamaño de la reacción fué pequeño.

La aparición del estado reactivo, eritema nudoso leproso, no se vinculó ni con la mejoría clínica ni con la bacteriológica. Alcanzó frecuencia igual en los dos principales grupos de terapéutica, no lo provocó la vacunación con BCG y no se asoció con la reactividad al PPD [DPP] (0.0001 mgm.).

ACKNOWLEDGEMENTS

The third series of studies was a joint enterprise of the Leonard Wood Memorial, the Department of Health of the Republic of the Philippines, and the Ministry of Health, Social Welfare, and Education of the Union of South Africa. Generous assistance was received from Dr. A. C. Jovellanos, director of Eversley Childs Sanitarium, Dr. A. Runez, director of the Central Luzon Sanitarium, and their staffs, and from the staff of the Westfort Institution of which Dr. A. R. Davison is medical superintendent. Miss D. Derrom of the Leonard Wood Memorial was responsible for checking the records and for the tabulations.

The studies received financial support from research grants from the U.S. Public Health Service, National Institutes of Health (E-199-C2 and E-199-C3); U.S. Veterans Administration; Leonard Wood Memorial; Abbott Laboratories; Lederle Laboratories, Division of American Cyanamid Co.; Parke, Davis and Co.; Eli Lilly and Co. Nicotinamide was donated by Eli Lilly and Co. and Merck and Co.; the BCG used in the Philippines was donated by the Alabang Laboratory, and that used at Westfort by the Statens Seruminstitut, Copenhagen. DDS was supplied by the respective governments. Acknowledgment is made also of generous assistance from shipping companies of the Far East Conference in transporting drugs, and from the Maron Shipping Agency in packing and expediting shipments.

REFERENCES

1. AZULAY, R. D., MOURA, A. and MOURÃO, G. A viragem da reação lepromínica pelo BCG administrado aos doentes lepromatosos em condições clínico-bacterioscópico-histopatológicas de "transferência para dispensário." *Rev. brasileira Leprol.* **20** (1952) 178-182.
2. CHANG, Y. T. Chemotherapy of murine leprosy. III. The effects of nicotinamide and pyrazinamide (aldinamide) on mouse leprosy. *Internat. J. Leprosy* **22** (1954) 331-346.
3. CHORINE, V. Action de l'amide nicotinique sur les bacilles du genre mycobacterium. *Compt. Rend. Acad. Sci.* **220** (1945) 150-151.
4. CONVIT, J., RASSI, E., CANTO RODRIGUEZ, F. and CONTRERAS, R. Changes in the lepromin and tuberculin reactions of lepromin negative leprosy patients after vaccination with BCG. *Internat. J. Leprosy* **20** (1952) 347-354.
5. DOULL, J. A. Clinical evaluation studies in lepromatous leprosy. First series: Diasone (diamidin), 4-4'-diaminodiphenyl sulfone, dihydrostreptomycin. *Internat. J. Leprosy* **22** (1954) 377-402.

6. DOULL, J. A., RODRIGUEZ, J. N., DAVISON, A. R., TOLENTINO, J. G. and FERNANDEZ, J. V. Clinical evaluation studies in lepromatous leprosy. Second series: Isoniazid and diasone (diamidin), isoniazid and dihydrostreptomycin. Also a pilot study with streptohydrazid. *Internat. J. Leprosy* **25** (1957) 173-192.
7. HUANT, E. Note sur l'action de très fortes doses d'amide nicotinique dans les lésions bacillaires. *Gaz. Hôp.* **118** (1945) 259-260.
8. JONQUIERES, E. and MASANTI, J. Vacunación con el BCG y viraje de la leprominorreacción en enfermos de lepra. *Rev. argentina Dermatosif.* **38** (1954) 137-143.
9. LOWE, J. and McNULTY, F. Tuberculosis and leprosy; immunological studies. *Leprosy Rev.* **24** (1953) 61-90.
10. MCKENZIE, D., MALONE, L., KUSCHNER, S., OLESON, J. J. and SUBBAROW, Y. The effect of nicotinic acid amide on experimental tuberculosis of white mice. *J. Lab. & Clin. Med.* **33** (1948) 1249-1253.