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CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY FIRST SERIES: DIASONE (DIAMIDIN), 4-4′-DIAMINODIPHENYL SULFONE, DIHYDROSTREPTOMYCIN

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There is urgent need for critical evaluation of drugs used in the treatment of leprosy. The sulfones are now by far the most widely used, having largely replaced all others including time-honored chaulmoogra and its derivatives. This reflects an equally widespread opinion among leprologists that the sulfones are not only beneficial, but superior to all other drugs.

It is not disputed that this view may be correct. It is pointed out, however, that the popularity of drugs at times exceeds their established therapeutic value. In the case of the sulfones, there is still lacking the sound pharmacologic support which can come only from studies which are controlled adequately and which include sufficient numbers of patients.

Only one study, by Faget *et al.* (1) in which patients considered comparable were left untreated as controls, has come to attention. This report gives limited information concerning clinical progress, nothing relating to bacteriology, and the number of patients was small. Promacetin (Parke, Davis & Co.), then called Internal Antiseptic No. 307, was given to 20 patients in oral doses of 0.3 to 1.0 gm. daily. A placebo was given by mouth to the same number of patients, matched as to type and stage of disease. After eight months the condition of the promacetin group was considered to be superior, especially as regards ulceration, rhinitis, and laryngitis.

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The need of adequate control of therapeutic trials can scarcely be stronger for any disease than for leprosy. Its natural course is usually prolonged over many years. The trend is not progressively downward, but subject to exacerbation and remission. Objective measurements of clinical and bacteriologic changes are crude and, to a greater or lesser extent, subject to the judgment of the observer. Rapid changes sometimes occur, especially in macules, ulcers and infiltration, and are readily demonstrable. Clinical changes of slow evolution are much more frequent, however, and may be detected only by most careful observation and photography. Moderate or slight variations in numbers of bacilli can be demonstrated only by painstaking and repeated examinations of several sites. Changes in viability of *Mycobacterium leprae* cannot be determined.

It is conceivable that a specific drug will be discovered which will be rapidly and universally effective. This is the ultimate objective, but its advent cannot be awaited with complacency. In the meantime, progress can be made by careful evaluation of those drugs which offer promise, based either upon opinions of clinicians of long experience or on theoretical grounds. Convincing evidence of value can be obtained only by impartial and technically equivalent observations, repeated after sufficient intervals, on adequate numbers of patients divided into at least two groups comparable in every characteristic that may affect prognosis insofar as these characteristics are known, one group being treated with the drug in question, the other left untreated or given some other therapy.

In determining the type of disease and the number of patients to be included in the present studies, two factors were given prime consideration. In the first place, the lepromatous type is universally regarded by leprologists as much more malignant, and much less subject to natural remission, than the tuberculoid type. Secondly, clinical improvement of lepromatous patients is slow even under intensive sulfone therapy. According to Faget and Pogge (2), approximately four months of treatment with diasone is usually necessary before any clinical improvement is observed; after 12 months they noted improvement in 70 per cent of the cases. Bacteriologic changes are even slower; e.g., at the end of one year Faget *et al.* (3) found no appreciable change in the average findings. Consideration of these facts led to a decision to include in these studies only bacteriologically positive cases of the lepromatous type.[2] It was decided also to conduct parallel experiments in several institutions in different countries, and at each of them to include as many suitable lepromatous patients as were available and willing to participate.

PROCEDURES, METHODS AND MATERIALS

Organization.—After obtaining approval by the respective governments, and assurance of support from staffs and patients, four institutions were selected for

[2] Seven of the Westfort patients, although previously bacteriologically positive, were negative at the sites chosen when admitted to the study; all, however, were lepromin negative.

participation. There were: in Japan, Aisei-en and Komyo-en, contiguous institutions on Nagashima Island in the Inland Sea; in the Philippines, Eversley Childs Sanitarium, near the city of Cebu; and in the Union of South Africa, Westfort Institution, near Pretoria. Statistics for the two Japanese institutions are combined in this report.

At each of the four institutions a resident research leprologist, nurses, technicians, and clerks were assigned to the work. Two visiting consulting leprologists were appointed to make independent preliminary and post-therapy examinations at the Japanese institutions, and one each at Eversley Childs and Westfort. The Memorial undertook to pay salaries for personnel specially employed, and to provide all drugs, supplemental equipment, record forms and other supplies.

Technical procedures were discussed by the medical director and Dr. L. F. Badger with a special committee for the project set up by the Japanese government, with the Leprosy Advisory Council in South Africa, and with an informal committee of experts in the Philippines. These were later printed as a Manual for Collaborating Investigators. In this Manual detailed information was given on dosage and modes of administration of the drugs, on various laboratory techniques, and on methods of recording clinical and laboratory observations. It was agreed that completed record forms would be dispatched to the Medical Department of the Memorial in Washington, D. C., for statistical analysis.

Specific objectives.—The primary objective was to determine the effectiveness of one of the higher sulfones in the treatment of lepromatous leprosy. Diasone (Abbott Laboratories), and the identical preparation diamidin (Parke, Davis & Co.), was chosen as representative because it has been so widely used. Secondary purposes were to ascertain whether or not diasone is superior to 4-4′-diaminodiphenyl sulfone (DDS) or to dihydrostreptomycin, and whether a combination of dihydrostreptomycin and diasone might be superior to either used singly. Since there is evidence that in the treatment of tuberculosis with streptomycin the addition of *p*-aminosalicylate delays emergence of bacilli which have acquired resistance to the antibiotic, the effectiveness of a combination of dihydrostreptomycin and sodium *p*-aminosalicylate was also studied.

Duration of therapy.—At each institution there was a preliminary period of at least 30 days for examinations, during which therapy was withheld from those patients being treated with sulfones. The original plan contemplated only 32 weeks of treatment, and this was adhered to at the Japanese institutions. At Eversley Childs and Westfort the period was extended to 48 weeks. At these institutions a rest of 2 weeks was permitted at the end of 32 weeks, and at Westfort an additional 12 days after 41 weeks of therapy. The calendar period of therapy at Aisei-en and Komyo-en was April 14, 1952 to November 24, 1952; at Eversley Childs, March 3, 1952 to February 16, 1953; and at Westfort, February 25, 1952 to February 23, 1953.

Therapies.—The therapies included, therefore, were as follows:

Group A: Diasone (or diamidin).
Group B: 4-4′-diaminodiphenyl sulfone (DDS).
Group C: Dihydrostreptomycin sulfate.
Group D: Drugs A and C.
Group E: Drug C plus sodium *p*-aminosalicylate (PAS).
Group F: Control "Ceslu" or PAS; see later).

The two sulfones (Groups A and B) were supplied as tablets identical in appearance. Diasone was labelled as Sulfone A (or 1), DDS as Sulfone B (or 2). Each diasone tablet contained 0.3 or 0.33 gm., and each DDS tablet 0.065 gm. For both sulfones the initial dose was one tablet 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.

Patients of Groups A and D at Aisei-en and Komyo-en received approximately 150 gm. of diasone, and those of Group B received 31 gm. of DDS. Patients at

Eversley Childs and Westfort belonging to these groups received, respectively, 241 gm. of diasone and 50 gm. of DDS.

Dihydrostreptomycin (Groups C, D, E) was given intramuscularly, 1 gm. three times weekly. Thus, patients completing therapy at Aisei-en and Komyo-en each received 96 gm., and those at Eversley Childs and Westfort, 144 gm.

PAS was given in tablets of 0.5 gm. each, in a daily (except Sundays) dosage of 12 tablets for the first week, 18 for the second, and 30 thereafter. Thus, patients of Group E at Aisei-en and Komyo-en receiving full therapy were given 2,790 gm., and at Eversley Childs and Westfort, 3,540 gm.

The control groups (F) at Aisei-en and Komyo-en and at Eversley Childs were given a preparation which was named "Ceslu." This resembled dihydrostreptomycin in appearance, and was given intramuscularly three times weekly. The composition of Ceslu was not disclosed until the end of the therapy. Each dose contained 0.15 gm. of glycine (aminoacetic acid) and 0.15 gm. of inositol. At Westfort, Group F received PAS in the same dose as for Group E.

Assignment of patients to groups.—At Aisei-en and Komyo-en taken together 364 patients, at Eversley Childs 360, and at Westfort 240, were selected for the experiment. At each institution approximately two-thirds were males, and all were between 15 and 50 years of age. An index card was prepared for each patient on which were entered a code name, age, sex, prior sulfone therapy, year of onset, date of admission, stage of disease, presence or absence of infiltration, nodules, and certain other signs, height, weight and some miscellaneous items. These cards were air-mailed to Professor W. G. Cochran at Johns Hopkins University. The method of assignment to groups is thus described by him:

"In assigning patients to therapy groups, the objective was to obtain six groups each of which would show, on the average, the same degree of responsiveness to a specified therapy. The preliminary items of information noted above—age, sex, prior sulfone therapy, and so on,—were recorded because each of them might be to some extent an index of prognosis. However, it was not feasible to make all six therapy groups exactly comparable on all of these indices, and the experts had differing opinions as to which index would be the most successful in predicting prognosis. After studying various methods of construction of the therapy groups, it was decided to give the chief emphasis to age and sex.

"Cards for patients of each sex were arranged in order of decreasing age; the six oldest males were each assigned to a group using a table of random numbers, then the second lot of males, and so on through the rest of the males and females. With a view to revision of the lists to obtain a better balance on the other relevant items, frequency distributions were prepared for the groups at each institution for such items as length of previous sulfone treatment, duration of stay, stage of disease, height, and weight. After examination of these distributions, it was decided not to make any revisions for Westfort but some changes were made for the other institutions in order to obtain better balance, especially with respect to stage of disease and previous sulfone treatment. Code names of the patients selected for each of the six groups were then telegraphed or airmailed to the respective institutions."

Physical examinations.—Dermatologic and neurologic examinations were made by the research leprologists at monthly intervals. The consultants made independent examinations during the preliminary period, at the end of 16 weeks therapy, and at the end of 32 weeks at all institutions; also at the end of 48 weeks at Eversley Childs and Westfort. In addition to being recorded on prescribed forms, the findings were depicted graphically on dermatologic and neurologic charts. Emphasis was placed on unbiased appraisal. The patients were presented to the consultants in a sequence unrelated to their groups, and the nature of the treatment being given to a patient was not disclosed to the consultant until his examination had been completed.

To test the comparability of clinical examinations made by various observers,

188 of the study patients at Aisei-en and Komyo-en were examined by seven international teams during a Working Clinical Conference held at Aisei-en in September 1952 (4). The conference was timed to fall between the 16-week and 32-week examinations at all institutions. The findings of these teams were compared with those of the Japanese consultants as recorded at the 16-week examinations completed a few weeks before. In 70 per cent there was practically complete agreement; in 20 per cent some disagreement, and in 10 per cent substantial disagreement.

As a further effort to secure uniformity, Dr. Millar was present at the 32-week examinations at Aisei-en and Komyo-en and Eversley Childs and at the 48-week examinations at Westfort, and the writer was present at the 32-week examinations at Eversley Childs.

Bacteriologic examinations.—Separate smears were made from at least eight sites—right and left earlobes, right and left sides of the nasal septum, and four optional sites—on each patient at the time of the consultants' examinations at Aisei-en and Komyo-en and at Eversley Childs. At Westfort six smears were examined from seven sites, one earlobe being chosen, and the two smears from the nasal septum being combined.

Photographic records.—Color and black-and-white photographs were made during the preliminary period, at the end of 32 weeks therapy at the Japanese institutions and at Eversley Childs, and at the end of 48 weeks at Eversley Childs and Westfort. Altogether, 9,144 kodachromes and 14,940 black-and-white photographs were taken.

Biopsies.—Arrangements were made for examination of biopsy specimens at the Leprosy Registry of the Armed Forces Institute of Pathology, Washington, D. C. Preliminary and post-therapy specimens from more than 70 per cent of the patients are now being examined.

Other examinations.—Hemoglobin determinations were made on all patients during the preliminary period, after 16 and 32 weeks of therapy at all institutions, and after 48 weeks at Eversley Childs and Westfort. A Tallqvist scale was used at Eversley Childs, and hemoglobinometers at the Japanese institutions and at Westfort. Red- and white-cell counts were made at the same time. Urine examinations were required before and after therapy. Supplemental blood and urine examinations were made when indicated.

Lepromin tests were made before and after therapy. At Aisei-en and Komyo-en and at Eversley Childs, the Mitsuda-Hayashi lepromin was used and readings were made at 22 days. At Westfort, Dharmendra's lepromin was used and readings were made at 48 hours.

Quantitative determinations of sulfones and *p*-aminosalicylate in the blood were made on one-quarter of the patients receiving these drugs on at least four occasions during the period. The patients were selected by lot. This expedient was adopted because personnel and facilities were insufficient to permit checking the blood levels of all patients.

Because dihydrostreptomycin has been reported to cause damage to the eighth nerve, audiometric measurements were made at the Japanese institutions and at Westfort on patients receiving this drug, and, for a control, on a number of patients on other drugs. At Eversley Childs, dependence was placed upon tests with the spoken voice and watch tick. No serious loss in hearing at speech frequencies was reported.

Dropped patients.—In any prolonged study of a chronic disease a number of patients will drop out. It is most important to record in every instance the reasons for withdrawal and the date. In these studies a rule was adopted that any patient showing intolerance to a drug or worsening of the disease should be withdrawn immediately from the experiment, if this was considered necessary by two leprologists. Those dropped because of worsening of the disease are regarded as having completed therapy, and the records of their physical condition and bacteriology for the date closest to time of withdrawal were taken as final.

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

TABLE 1.—*Numbers of patients selected at Aisei-en and Komyo-en, Eversley Childs, and Westfort classified according to therapy status at end of 48 weeks (32 weeks in Japan).*

Therapy status	Aisei-en and Komyo-en	Eversley Childs	Westfort
Therapy complete (examined)	312	307	233
Therapy complete (no final examination)	0	5	1
Therapy incomplete			
Drug intolerance	15	1	0
Erythema nodosum	14	3	0
Complicating diseases[a]	9	6	0
Dosage insufficient[b]	3	38	4
No therapy[c]	11	0	2
Total selected	364	360	240

a Includes 2 who died from causes other than leprosy.

b All missing 30 days or more of treatment at Aisei-en and Komyo-en, and 60 days or more at Eversley Childs and Westfort, are regarded as receiving insufficient therapy.

c Did not commence treatment for various reasons.

It will be seen that 52 of the patients originally selected at Aisei-en and Komyo-en are not included among those regarded as completing therapy. Eleven of these actually did not begin treatment at all, for various reasons. Of the 41 others, 15 were dropped because of drug intolerance, which was in no case very serious: anemia, Group A, 1; B, 2; anorexia and arthralgia, B, 2; anorexia, B, 2; C, 1; D, 1 and E, 3; vertigo, C, 1 and E, 1; and loss of hearing, E, 1; 14 were dropped because of erythema nodosum leprosum (A, 4; B, 1; C, 1; D, 3; E, 4; F, 1), and 9 because of complicating diseases. Three were not included in the final tabulation because they had missed 30 days or more of treatment. The total number that completed therapy and examinations, therefore, was 312.

At Eversley Childs the chief difficulty was departure of patients from the institution without permission. Forty-eight did not complete treatment, while another 5 completed it but were not present for the final examination; 38 of the former group missed 60 days or more of treatment. One patient (Group B) was dropped because of anemia, and 3 (B, 1; E, 2) because of erythema nodosum; 6 discontinued treatment

because of complicating diseases. The total completing therapy and examinations, therefore, was 307.

At Westfort, only 7 patients on the original list were dropped. Two of these did not commence therapy; 4, including a patient repatriated to Portuguese East Africa, missed 60 days or more of treatment and 1 completed therapy but did not have a final examination. The total completing therapy and examinations, therefore, was 233.

To determine the effect of dropping of patients on the comparability of the groups completing therapy at each institution, an analysis was made of certain group characteristics for patients selected and for those completing therapy. Taking both sexes together it was found that at all institutions the groups remained remarkably alike as regards these characteristics. For example, the proportions of males in all groups were not significantly affected by dropping of patients. This was true also of the proportions of L_2 cases and of percentages of sites in each group with 2 + or higher bacteriology. Examining the sexes separately it was found that the average ages, weights, hemoglobin determinations, and red cell counts were likewise not significantly affected. At Aisei-en and Komyo-en and at Westfort the patients had previously received a considerable amount of sulfone therapy, but at these institutions those who completed therapy in each group had received approximately the same quantities as those who had been dropped. As Eversley Childs the amount of previous sulfone therapy received by patients entering the experiment was negligible.

CLINICAL RESULTS

In planning the studies the difficulties of clinical appraisal were recognized. Descriptive accounts of individual cases have their place, but are insufficient for the purposes envisaged. Quantitative data are required of sufficient reliability to be used as indices of the condition of individual patients and of groups.

Lacking any better method, the consultant was asked to give a numerical rating to the degree and extent of infiltration, nodulation and other lesions for various body sites, at each physical examination. If any lesion on the list was not present its absence was recorded These ratings were added together for each type of lesion and used for comparison with results at later examinations.

Infiltration was the most prominent clinical feature, being noted at the preliminary examination in all the Japanese, all the Filipino, and all but two of the South African patients. There were wide differences in frequency of nodules. At Aisei-en and Komyo-en, they were recorded in 91.3 per cent; at Eversley Childs in 31.6 per cent, and at Westfort only in 13.3 per cent. Part of these differences are doubtless attributable to variations in nomenclature. Localized corrugations of the skin of the upper eyebrows or of the intersupercilial space, for example, which would be termed

infiltration at Westfort were sometimes recorded as nodules at Eversley Childs. At Aisei-en and Komyo-en there was a tendency to classify certain lesions as flattened nodules which would be called plaques at Eversley Childs and Westfort. At Aisei-en and Komyo-en, 7.7 per cent of patients completing therapy were recorded as having plaques at the preliminary examination, whereas the percentages were 23.1 at Eversley Childs and 80.3 at Westfort. The recorded differences, however, are too great to be satisfactorily explained by differences in terminology. At least it appears to be quite certain that nodules and plaques, taken together, were much more frequent among the patients selected at Aisei-en and Komyo-en and at Westfort than at Eversley Childs. At the conference in Japan which has been mentioned it was agreed that no changes in nomenclature would be made during the study; i.e., a lesion called a nodule or a plaque at the beginning was so designated at the final examination, if still present.

On completion of the final examinations the clinical status of each patient was summarized by the consultant as one of the following: improved—slight, moderate or marked; stationary, or worse—slight, moderate or marked. Examination of the detailed records has in nearly all instances provided adequate support for the consultants' opinions. On tabulating them, the writer included as "moderately improved" one West-

TABLE 2.—*Percentages of patients completing therapy classed as improved, stationary, or worse on final clinical examinations, by institutions and therapy groups.*[a]

Therapy group[b]	Aisei-en and Komyo-en (32 weeks)				Eversley Childs (48 weeks)				Westfort (48 weeks)			
	No. pts.	Per cent			No. pts.	Per cent			No. pts.	Per cent		
		Impr.	Stat.	Worse		Impr.	Stat.	Worse		Impr.	Stat.	Worse
A	53	24.5	71.7	3.8	54	29.6	70.4	—	40	25.0	75.0	—
B	49	16.3	83.7	—	47	27.7	68.1	4.2	39	28.2	66.7	5.1
C	54	18.5	75.9	5.5	52	28.8	69.2	1.9	40	30.0	67.5	2.5
D	55	18.2	78.2	3.6	53	15.1	83.0	1.9	38	39.5	60.5	—
E	45	26.7	71.1	2.2	49	30.6	69.4	—	39	30.8	69.2	—
A, B, D	157	19.7	77.7	2.5	154	24.0	74.0	1.9	117	30.8	67.5	1.7
C, D, E	154	20.8	75.3	3.9	154	24.7	74.0	1.3	117	33.3	65.8	0.9
A-E	256	20.7	76.2	3.1	255	26.3	72.1	1.6	196	30.6	67.9	1.5
F	56	1.8	71.4	26.8	52	3.8	57.7	38.5	37	16.2	83.8	—
Total	312	17.3	75.3	7.4	307	22.5	69.7	7.8	233	28.3	70.4	1.3

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

b For the drugs used in these treatment groups, see p. 379 of the text.

fort patient who was discharged from the institution during therapy for whom the consultant's opinion was not given. In all other cases the opinions regarding the degree of improvement were given on the records and have been accepted as final. There were a few patients, dropped because of worsening of the disease, for whom the degree was not graded by the consultant. These have been regarded as markedly worse.

Differences between patients classified as "stationary" and those classified as "slightly worse" or "slightly improved" may be regarded, on the average, as of minor significance. Similarly, the differences between "moderate" and "marked" may be taken as small. In Table 2, therefore, 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.

For Aisei-en and Komyo-en the proportion improved in Groups A to E combined was 20.7 per cent as compared to 1.8 per cent in Group F, a difference which is highly significant in the statistical sense. At Eversley Childs the percentage improved in Groups A to E combined was 26.3 as compared to 3.8 in Group F, again a highly significant difference. At Westfort, where the control drug was PAS, the percentage improved in Groups A to E was 30.6 as compared to 16.2 in Group F, a difference which would usually not be considered significant by the statistician, but which is great enough to warrant further investigation.

Table 2 also shows that, at all institutions, the proportions of the patients becoming clinically improved were approximatey the same for those receiving sulfones (Groups A,B,D) as for those receiving dihydrostreptomycin (Groups C,D,E). It will be noted that the patients who received both diasone and dihydrostreptomycin (Group D) are included in both of these combinations.

For individual therapy groups at Aisei-en and Komyo-en, the proportions of patients becoming clinically improved were highest in Groups E (26.7%) and A (24.5%), and lowest in B (16.3%). At Eversley Childs the percentages for Groups A (29.6), B (27.7), C (28.8) and E (30.6) are about equally high; that for D (15.1) is the lowest. The fact that the proportion of improved patients in Group D was not significantly low at Aisei-en and Komyo-en and was high at Westfort detracts from any significance which the Eversley Childs observation might otherwise have. At Westfort the widest difference, that is, between Groups A and D, is not significant.

At Aisei-en and Komyo-en, one patient receiving Ceslu (Group F) was recorded as moderately improved, and at Eversley Childs one as moderately and another as markedly improved. At both places large proportions of this group, 71.4 per cent and 57.7 per cent, respectively, were recorded as stationary, slightly improved or slightly worse. At Westfort, in the control group (PAS), 83.8 per cent were so classed.

The proportions recorded as definitely worse were small in all groups at all institutions, except in the control groups at Aisei-en and Komyo-en and at Eversley Childs. With this important exception there are no significant differences between individual groups at any of the institutions. In the control group at Aisei-en and Komyo-en, 15 patients, or 26.8 per cent, became worse, and 12 of them had to be dropped. At Eversley Childs, where as already noted the amount of sulfone received by patients prior to the experiment was negligible, 20 patients, or 38.5 per cent, of the controls became worse, and 15 of these patients were dropped. It is remarkable, in the light of present opinion as to the lack of effectiveness of PAS, that at Westfort no patient in the control group was recorded as becoming moderately or markedly worse.

The clinical changes for which cases were classified as moderately or markedly worse, as recorded by the consultants, were as follows:

Aisei-en and Komyo-en (23 cases): Increase of or new infiltration, plaques, or nodules, 11 cases (Group C, 1; F, 10). Increase in lepromatous ulceration, 1 case (F). Progress of eye lesions, 9 cases (A, 2; C, 1; D, 1; E, 1; F, 4). Increase in neuritis, 2 cases (C, 1; D, 1).

Eversley Childs (24 cases): Increase of or new infiltration, plaques, or nodules, 19 cases (Group B, 1; C, 1; D, 1; F, 16). Increase in lepromatous ulceration, 2 cases (both in F; one with ulceration of pharynx and larynx). Progress of eye lesions, 2 cases (both in F; one had also laryngeal ulceration). Increase in neuritis, 1 case (B; case severe, patient hospitalized).

Westfort (3 cases): Increase of or new infiltration or plaques, 2 cases (B, 1; C, 1). Increase in neuritis, 1 case (B).

Clinical improvement according to stage.—At Aisei-en and Komyo-en the cases in Groups A to E classed as L_1, L_2 or L_3 did not show significant differences in proportions moderately or markedly improved. The single case in Group F which improved was classed as L_2 at the outset.

At Eversley Childs the proportions improved in Groups A to E, combined, for those in different stages at the outset were: L_1, 16.7 per cent; L_2, 19.7 per cent, and L_3, 40.2 per cent. Two cases in Group F which improved were classed as L_3 at the outset.

At Westfort the proportions improved in Groups A to E for stages were: L_1, 30.9 per cent; L_2, 27.1 per cent, and L_3, 35.5 per cent. Of 6 which improved in Group F, 4 were classed as L_2 and 2 as L_3 at the outset.

Clinical improvement according to prior sulfone therapy.—The amount of prior sulfone therapy at Eversley Childs was insignificant, at Aisei-en and Komyo-en it was moderate, and at Westfort it was considerable. For all groups of patients at Eversley Childs there was no significant difference with respect to the proportion significantly improved as between those who had received no sulfone therapy and the others who had received only small quantities. At Aisei-en and Komyo-en the proportion showing improvement was 13.1 per cent for those with more than two

years prior treatment, as compared with 21.7 per cent for those with less than two years. At Westfort on the other hand, a much higher proportion (35.9%) of patients with more than two years of prior sulfone treatment improved than of other patients (9.2%).

Effect of therapy on specified lesions.—An attempt has been made to evaluate the effect of the different treatments on infiltration, nodules, plaques and ulcers. A high degree of association would be expected with the clinical status as given in Table 2, because changes in these lesions constituted the principal basis for clinical judgment. The effect of treatment on erythema nodosum leprosum has also been studied.

Infiltration: Five areas on each patient, that is, face, ears, trunk, buttocks and extremities, were each graded from 0 to 3 according to amount of infiltration present. Thus, the total rating of any patient could vary from 0 to 15. Studying the institutions separately, a correlation table was prepared for each therapy group to show the frequency of patients at each rating from 0 to 15 at preliminary and at final examinations.

At the Japanese institutions, in all therapy groups, a high proportion of patients improved in respect to infiltration. The differences were small between Groups A, B, D and E, the percentages ranging from 75.5 for B to 81.8 for D. For Group C the percentage was 70.4, and for the control group, 62.5. At Eversley Childs the differences between Groups A, B, D, and E were likewise small, the percentages ranging from 75.5 for E to 81.5 for A. For Group C the percentage was 65.4, and for F, 32.7. At Westfort, the range for Groups A, B, D and E was from 72.5 per cent for B to 86.8 for D. For Group C, which was the lowest, the percentage was 67.5 and for the control group it was 73.0.

Change in infiltration may be more readily detectable in persons in whom infiltrated lesions are marked than in those in whom they are slight. Also, infiltration may be more amenable to treatment at certain stages of the disease than at others. Although the groups were fairly well balanced at the outset in respect to the proportions with various degrees of infiltration, there were some differences. To make all groups comparable in this respect, and also to give due weight not only to the number of patients of each group in whom infiltration improved but also to the number in whom it remained stationary or became worse, a simple arithmetic index of variation in infiltration was adopted.

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 percentages of all patients at all institutions with original infiltration ratings of 0 to 7 and of 8 to 15, respectively, were next computed. It was found that 61.6 per cent had grades of 0 to 7 and 38.4 per cent grades of 8 to 15, i.e.,

the proportions were 0.616 and 0.384. An 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 maximum possible value of any index is 2, which would signify that all infiltration had disappeared in all patients of the group. The minimum is -1, which would occur if all patients showed increase of infiltration. The indices for groups, for combinations of groups receiving a sulfone, and for combinations of groups receiving dihydrostreptomycin, are shown by institutions in Table 3.

TABLE 3.—*Adjusted mean indices for changes in infiltration, with standard errors, by institution and therapy group.*[a]

Group	Aisei-en and Komyo-en		Eversley Childs		Westfort	
	Index	S.E.	Index	S.E.	Index	S.E.
A	0.78	0.070	0.66	0.101	0.81	0.065
B	0.72	0.070	0.53	0.116	0.82	0.080
C	0.63	0.091	0.31	0.127	0.66	0.102
D	0.75	0.073	0.61	0.105	0.92	0.056
E	0.74	0.073	0.67	0.108	0.79	0.082
ABD	0.75	0.041	0.61	0.062	0.85	0.039
CDE	0.71	0.046	0.53	0.066	0.79	0.047
A-E	0.72	0.034	0.56	0.050	0.80	0.035
F	0.49	0.093	—0.17	0.124	0.73	0.075
Total	0.68	0.032	0.44	0.047	0.79	0.032

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, were used as a standard. Highest possible index, 2; lowest possible index, –1.

For Aisei-en and Komyo-en, there are no differences between Groups A to E sufficiently great to be emphasized, except to note that the index for Group C is the lowest. The difference between the highest index (Group A) and that for the control group is 0.29, which is 2.5 times its standard error (0.116). For Eversley Childs, the indices are all on a lower level than for the other institutions. The striking fact is the negative index for Group F. The difference between the next lowest index (Group C) and that for F is 0.48, which is only 2.7 times its standard error (0.177), but the differences between the indices for other therapy groups and that for F are all highly significant. The index for Group C is lower than those for Groups A, B, D and E, but the difference is in no case

larger than 2.1 times its standard error. For Westfort, the difference between the highest index (Group D) and that for F is 0.19, which is 2 times its standard error (0.094). The difference between the index for Group D and the lowest group (C) is 0.26, which is 3 times its standard error (0.087).

Judging by this method of appraisal, therefore, improvement in infiltration was about the same under the higher sulfone as with DDS; dihydrostreptomycin was slightly less effective than either sulfone at all institutions; and the combination of dihydrostreptomycin with diasone was not advantageous. The control groups which received Ceslu showed less improvement than other groups, markedly less at Eversley Childs. The control group at Westfort, which received PAS, showed about the same improvement as Group C.

Nodules: At the Japanese institutions and at Eversley Childs those patients who had nodules at the outset showed improvement in this respect without significant differences between the groups. The proportions in whom nodules became worse were, however, much higher in the control groups than in the others. At the Japanese institutions, of 236 patients in Groups A to E combined with nodules at the beginning, only 5, or 2.1 per cent, became worse as compared to 7, or 14.3 per cent, of 49 patients in Group F. At Eversley Childs the comparable figures were: for Groups A to E combined, 2 of 76, or 2.6 per cent, and for Group F, 6 of 21, or 28.6 per cent. At Westfort, as already noted, only 31 patients had nodules at the outset. In all but 4 of these, in which the condition remained stationary, improvement was recorded.

At Aisei-en and Komyo-en there was a total of 20 patients without nodules at the outset in Groups A to E combined and 7 in F. Of these, 3 had nodules on final examination: one each in Groups C, E and F. At Eversley Childs, nodules were absent on preliminary examination in 178 patients in Groups A to E and 31 in F. Of these, 11 or 6.2 per cent in A to E and 6, or 19.3 per cent, in F developed nodules. At Westfort only one patient originally without them (in Group C) had nodules at the final examination.

Plaques: At Aisei-en and Komyo-en, plaques were recorded as improved in 19 out of 21 patients in Groups A to E and in 1 of 3 in F. One patient (in Group B) originally negative for plaques had some on final examination. At Eversley Childs, plaques were recorded as improved in 38, or 63.3 per cent, of 60 patients in Groups A to E but only in one of 11 patients in F. Plaques were present on final examination in 24, or 12.4 per cent, of 194 patients belonging to Groups A to E in whom they were not present on preliminary examination, and in 15, or 36.6 per cent, of 41 such patients of Group F. At Westfort all plaques were recorded as improved except in one patient in Group B, while none of the originally negative patients had plaques on final examination.

Lepromatous ulcers: (*a*) Nasal ulcers: At Westfort, ulceration of the

nasal septum was noted in only a few cases. At Aisei-en and Komyo-en ulcers were recorded on preliminary examination in 102, or 32.7 per cent of the patients who completed therapy. In the sulfone groups (A,B,D) there were 57; in 38 of these, or 66.7 per cent, the ulcers were healed on final examination. In the dihydrostreptomycin groups (C,D,E) there were 48; in 35 of these, or 72.9 per cent, healing took place. Group D, which is included in both of these subtotals, had 23 patients with such ulcers; in 15 of these, or 65.2 per cent, there was healing. In the control group there were originally 20 with nasal ulcers; in 10 of these, or 50 per cent, healing occurred. The other aspect of the picture is that new nasal ulceration occurred in only 6, or 3.4 per cent, of 174 patients of Group A to E combined who were originally negative, but in 7, or 19.4 per cent, of 36 such patients in Group F.

At Eversley Childs the picture was very similar. Nasal ulceration was noted at the outset in 112 patients, or 36.5 per cent, but for one of these there was no entry on the final record. In the sulfone groups (A,B,D) there were 55 such patients; in 36, or 65.5 per cent, the ulcers were healed on final examination. In the dihydrostreptomycin groups (C,D,E) there were also 55 patients, and the percentage in which healing occurred was exactly the same as for the sulfone groups. Group D had 18 patients with such ulcers, and in 13, or 72.2 per cent, there was healing. In the control group there were 19 with ulcers; healing occurred in 7, or 36.8 per cent. At the final examination, however, new nasal ulceration was recorded in 22, or 13.6 per cent, of 162 patients originally negative in Groups A to E combined and in 8, or 24.2 per cent, of 33 such patients in Group F.

(*b*) Other lepromatous ulceration: At Aisei-en and Komyo-en, lepromatous ulceration of skin areas was recorded in 17 patients, 14 in Groups A to E and 3 in F. In all except one (in F), healing took place during the treatment period. Small ulcers occurred in 4 of 295 patients who were negative for them at the outset, one each in Groups A and B and 2 in E.

At Eversley Childs, ulceration of skin areas was present initially in 39 patients, 33 in Groups A to E and 6 in F. In one patient without ulceration at the beginning, there was no final entry. In all groups except F, healing took place in all instances. In 3 of the 6 in Group F, ulceration was still present on final examination. In Groups A to E, ulceration was present on final examination in only 3 patients (B, 2; C, 1) among 221 who had no ulcers at the outset. In Group F, new ulcerations were noted in 8, or 17.3 per cent, of 46 negative on preliminary examination.

At Westfort, skin ulcers were recorded for 11 patients, 9 in Groups A to E and 2 in F. Complete healing occurred in only 3, all in Group D. One, also in Group D, who was negative at the outset had ulceration on final examination.

Erythema nodosum leprosum: This reactional condition (ENL) was reported present on preliminary examination in 47.4 per cent of the patients at Aisei-en and Komyo-en, in 23.5 per cent at Eversley Childs,

and in 57.9 per cent at Westfort. At Aisei-en and Komyo-en it was most persistent in Groups A and E; at Eversley Childs in Group E, and at Westfort in Group A. As regards patients in whom ENL was not present at the outset, it is of interest that at each of the centers the proportion—about 40 per cent—who developed such lesions during therapy was approximately the same for those on sulfones (Groups A,B,D) as for those on dihydrostreptomycin (Groups C,D,E). Group F was low in comparison with the other groups at Aisei-en and Komyo-en and at Westfort, but at Eversley Childs the proportion of patients in Group F developing ENL was approximately the same as in Groups A and C, although lower than in Groups B, D and E.

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

General health: Although there were individual variations, the average health of all groups of patients remained good at all institutions. At Aisei-en and Komyo-en there was some loss of weight in both males and females in all groups except Group F, in which the weights remained stationary. For Groups A to E combined the average loss for males was 1.8 kgm., and for females 2.0 kgm. At Eversley Childs the final average weights for males and for females of all groups were approximately the same after therapy as at the outset. At Westfort both sexes in every group showed slight gains in average weight.

At Aisei-en and Komyo-en the average red blood cell counts were somewhat lower for each sex in all groups at the final than at the preliminary examination. The hemoglobin values did not fall correspondingly, but were down somewhat for males of Groups A and B and for females of Groups A to D, inclusive. For males at Eversley Childs, the average red blood cell counts and hemoglobin values were slightly higher for all groups on the final examination and for females for all groups except B, which showed a slight reduction in cell count without change in hemoglobin. At Westfort there were no significant changes either in red cell counts or in hemoglobin values.

BACTERIOLOGIC FINDINGS

An important feature of this study was the adoption of standard bacteriologic procedures. The methods used make it reasonably certain that the preliminary and post-therapy results are comparable, at least at the same institution.

Smears were made by the scraped incision method except from the nasal septum. For that site a sharp instrument, either a tenotomy knife or a periosteal elevator, was recommended but not always used. As noted above smears were required from both earlobes, both sides of the nasal septum and from four optional skin sites except at Westfort where only one earlobe was included. For the optional sites the most marked or active lesions were selected, and subsequent smears were made from approximately the same areas in each examination. Although intermediate examin-

ations were made, and other sites examined in many instances, the present analysis deals only with preliminary and final results, with respect only to the required sites.

Staining was by the conventional Ziehl-Neelsen method, using a standard lot of basic fushsin, with acid alcohol (3% HCl in 95% C_2H_5OH) as decolorizer.

Findings were reported as follows: 4+, hundreds of bacilli to a field; 3+, 20-100 bacilli to a field; 2+, 10-20 bacilli to a field; 1+, fewer than 10 bacilli to a field; VS, very scanty bacilli, fewer than 10 to a slide; 0, no bacilli in 50 fields.

Status on preliminary examination.—Preliminary bacteriologic findings for all sites, and for all sites except the nasal septum, are shown in Table 4 for patients completing therapy at the different institutions. The Eversley Childs patients were the "heaviest" bacteriologically, having the smallest proportion of negative sites and the highest proportion of 3+ and 4+ results. The Westfort patients were somewhat "lighter" bacteriologically than those at Aisei-en and Komyo-en. Omission of the results on smears from the nasal septum—i.e., including only the findings for skin sites—brings the preliminary bacteriologic findings at Aisei-en and Komyo-en closer to those of Eversley Childs; the Westfort results still indicate lighter infection. Approximately 90 per cent of nasal sites were negative at Aisei-en and Komyo-en, 80 per cent at Westfort, but only 31 per cent at Eversley Childs. Because of these variations the following analysis is restricted to results on skin sites, that is, the earlobes and the four optional sites.

TABLE 4.—*Bacteriologic findings on preliminary examination by institutions; percentages for all sites and for all sites excluding nasal septum.*

Results	Aisei-en and Komyo-en		Eversley Childs		Westfort[a]	
	8 sites	6 sites	8 sites	6 sites	6 sites	5 sites
Negative	34.8	19.1	17.0	12.3	36.3	27.5
VS, 1+ & 2+	47.7	57.6	53.6	60.1	56.3	63.9
3+ & 4+	17.5	23.3	29.4	27.6	7.4	8.6
No. of sites[b]	2,328	1,707	2,456	1,842	1,380	1,151
No. of patients	312	312	307	307	233	233

a At Westfort smears were made from 7 sites, but those from both sides of the nasal septum were combined.

b All observations are omitted from the table unless satisfactory preliminary and final reports were received. Hence, the totals are slightly less than the number of patients multiplied by the numbers of sites.

Patients becoming negative.—An unexpected feature of the findings is the proportion of patients negative at all required skin sites on final examination. Such patients, however, were not necessarily bacteriologically negative; in fact, some were still positive at other than the required sites. Of all patients completing therapy, 10.3 per cent at Aisei-en and Komyo-en,

8.5 per cent at Eversley Childs, and 22.6 per cent at Westfort were negative at the required sites on final examination. Such conversions occurred in each group at each institution, including the controls, and their frequency was not associated with any particular form of therapy. The percentages for Groups A to E combined and for Group F, respectively, were: Aisei-en and Komyo-en, 10.1 and 10.7; Eversley Childs, 9.0 and 5.8, and Westfort, 23.3 and 18.9. As would be expected, those patients with fewest bacilli at the outset had the greatest probability of becoming negative.

Improvement in sites.—To ascertain whether any therapy resulted in bacteriologic improvement short of complete negativity of the patient, a detailed analysis was made of the results for the skin sites. Correlation tables were prepared showing the frequency of sites falling into each of the several categories—i.e., negative, very scanty, 1+, etc.—at preliminary and final examinations. Study of these tables shows that the proportion of sites which had improved, moving at least as far as the next lower category, was substantial in each group at each institution. At Aisei-en and Komyo-en it varied from a high of 51.8 per cent in Group C to a low of 41.4 per cent in Group F; at Eversley Childs, from 59.9 per cent in A to 41.3 per cent in F; and at Westfort, from 62.9 per cent in E to 50.5 per cent in D. At Aisei-en and Komyo-en there was no difference between all patients receiving a sulfone (Groups A, B and D) and all receiving dihydrostreptomycin (Groups C, D and E). At Eversley Childs there was a slight difference in favor of the sulfones, and at Westfort a slight difference in favor of dihydrostreptomycin; in neither case was the difference significant from the statistical point of view.

As a convenient measure of the extent of bacteriologic changes in the groups, an arbitrarily weighted index of improvement was adopted, similar in mode of calculation to that described above for measurement of changes in infiltration.

This index takes into account bacteriologic improvement, lack of change, or worsening at any of the skin sites. Sites moving from positive to negative were each given a value of 2; those showing improvement but not becoming negative, 1; remaining stationary, 0; and becoming worse, -1. Sites negative at the outset and remaining negative were each given a value of 2, and those becoming positive, -1. The absolute values of this index are limited by the rules of the study. That is, a smear negative at outset, which could not improve, was defined as "no bacilli in 50 fields," and the upper limit of worsening was taken as 4+.

To make the indices more closely comparable, as between groups and institutions, an adjustment was necessary because of differences in proportions of light and heavy infections. The degree of infection on preliminary examination was reduced from six classes to three: (1) negative; (2) very scanty, 1+ and 2+; and (3) 3+ and 4+. The adjustment factors used were the proportions of the skin sites falling into each of these subclasses, prior to therapy, at all institutions combined. For the respective subclasses these proportions were: 0.185, 0.601, and 0.214.

The method of obtaining the adjusted index for each group was therefore as follows: The sites were divided into the three subclasses mentioned, and a mean index was obtained for each by dividing its total score, as calculated from the weights given above, by the number of sites. The mean score for each subclass was then multi-

plied by its appropriate adjustment factor. The adjusted index for any group is the sum of the adjusted mean scores for its three subclasses. The higher the index, the greater the average bacteriologic improvement. The maximum value is 2 and the minimum -1.

The indices for groups and certain combinations of groups for each institution are given in Table 5. At the Japanese institutions the indices for Groups A, B and C are higher than those for D, E and F. The difference between the highest index (B) and the lowest one (D) is 0.34, which is 3.3 times its standard error (0.103). The indices for Groups E and F are only slightly higher than that for D. After 32 weeks of therapy, therefore, the bacteriologic improvement, thus measured, in patients treated with dihydrostreptomycin combined either with diasone (Group D) or with PAS (Group E), was approximately the same as that in the group receiving only a placebo. There is, however, evidence, which is suggestive only, of bacteriostatic or bactericidal action of diasone (Group A), DDS (Group B), and dihydrostreptomycin used singly (Group C).

TABLE 5.—*Adjusted mean indices for changes in bacteriologic findings, with standard errors, by institutions and therapy groups.*[a]

Group	Aisei-en and Komyo-en		Eversley Childs		Westfort	
	Index	S.E.	Index	S.E.	Index	S.E.
A	0.83	0.064	0.97	0.066	0.99	0.071
B	0.89	0.071	0.93	0.059	1.17	0.056
C	0.81	0.067	0.87	0.065	1.35	0.056
D	0.55	0.074	0.78	0.073	1.18	0.067
E	0.59	0.079	0.79	0.062	1.18	0.061
ABD	0.75	0.040	0.90	0.038	1.11	0.037
CDE	0.65	0.042	0.81	0.039	1.23	0.035
A-E	0.73	0.032	0.87	0.029	1.17	0.028
F	0.62	0.068	0.53	0.074	0.99	0.066
Total	0.71	0.029	0.81	0.025	1.14	0.026

a The index of improvement for each group and each combination of groups is adjusted to compensate for inequalities in proportions of sites negative; VS, 1+ and 2+, and 3+ and 4+, respectively, on preliminary examination. The comparable proportions of all sites in all patients completing therapy were used as a standard. Highest possible index, 2; lowest, -1.

At Eversley Childs, where therapy was for 48 weeks, the index for each of the Groups A to E is substantially higher than for F. In the case of the highest (Group A), the difference is 0.44, which is 4.4 times its standard error (0.099); and of the lowest (Group D), the difference is 0.25, or 2.4 times its standard error (0.104). Thus, there is suggestive

evidence of bacteriostatic or bactericidal effect of each of the sulfones and of dihydrostreptomycin used singly; also, to a lesser degree, of diasone plus dihydrostreptomycin and dihydrostreptomycin plus PAS. The difference between the index for Groups A to E combined and that for F is 0.34, which is 4.3 times its standard error (0.079).

At Westfort, the indices of improvement are higher in every group than at the other institutions. This is in part due to the fact that the method of calculation of the index did not fully compensate for the better average bacteriologic status at Westfort on preliminary examination. The differences between the highest index (Group C) and those for Groups A and F are significant in the statistical sense. The explanation of this fact is not obvious. If it were attributable to superior effectiveness of the drug given Group C, the dihydrostreptomycin group at Eversley Childs should have been in a similar position, which it was not. The other differences between groups are not significant. Groups C, D and E combined are significantly higher than Groups A and F because of the high position of Group C. The difference between the index for the total of Groups A to E and that for F is 0.18, which is 2.5 times its standard error (0.072). Again, the results with combined therapies indicate no advantages over the single drugs. The fact that the index for the control group is as high as that for Group A and not significantly lower than the others, with the exception of that for C, suggests that PAS may possess some bacteriostatic or bactericidal capacity against *M. leprae.*

Association between clinical progess and change in bacteriologic status.—To determine the relationship between final opinion on clinical progress and bacteriologic change, bacteriologic indices were calculated for patients at each of the centers classed as markedly or moderately improved in Groups A to E combined. These were compared with the indices for other patients in these groups. The results are shown in Table 6.

TABLE 6.—*Bacteriologic indices and their standard errors for patients classed clinically, as moderately or markedly improved, and for other patients, Groups A to E combined, by institutions.*

Therapy Groups A-E	Aisei-en and Komyo-en[a]		Eversley Childs[a]		Westfort[b]	
	32 weeks therapy		48 weeks therapy		48 weeks therapy	
	Index	S.E.	Index	S.E.	Index	S.E.
Clinically improved	0.71	0.072	0.81	0.060	1.36	0.060
Other patients	0.74	0.035	0.89	0.033	1.08	0.034

a Six sites.
b Five sites.

At Aisei-en and Komyo-en, and at Eversley Childs, where clinical and bacteriologic results were independently recorded, the differences are small and in the opposite direction from that expected; that is, the clinically improved patients have slightly lower indices of bacteriologic improvement than other patients. Apparently clinical improvement progressed, on the average, without corresponding bacteriologic improvement. Conversely, bacteriologic improvement occurred without corresponding clinical improvement. At Westfort, on the other hand, where clinical judgment was affected to some extent by bacteriologic status, the difference in indices is in favor of the clinically improved and is 4.1 times its standard error (0.069).

For patients recorded as moderately or markedly worse, clinical opinion and the bacteriologic index are in agreement for all institutions. At Aisei-en and Komyo-en, the index for such patients is 0.47, with a standard error of 0.117. At Eversley Childs, the corresponding index is 0.60, with a standard error of 0.115. For Westfort, only 2 patients were classed as moderately or markedly worse.

CHANGES IN LEPROMIN STATUS

Lepromin tests were done at all institutions before and after therapy. As already noted, Mitsuda-Hayashi lepromin was used at Aisei-en and Komyo-en and at Eversley Childs, and final readings were made at 22 days. A reaction of 4 mm. in diameter or greater was regarded as positive. At Westfort, where the Dharmendra antigen was used readings made at 48 hours, a reaction over 5 mm. in diameter was regarded as positive.

At Komyo-en, all the 111 patients who completed therapy were recorded as lepromin negative before and after therapy. At Aisei-en, where 201 patients completed therapy and testing, some changes in reactivity occurred. The results are summarized in Table 7. Of 154 patients belonging to Groups A to E and giving negative or doubtful reactions on entering the study, 25, or 16.2 per cent, were positive after 32 weeks of therapy. In all of these, reactions were 1+ except in 1 patient of Group

TABLE 7.—*Late lepromin results before and after therapy, Groups A-E combined, and Group F, Aisei-en.*

Reaction before therapy	Reaction after 32 weeks therapy							
	Positive		Doubtful		Negative		Total	
	A-E	F	A-E	F	A-E	F	A-E	F
Positive (17)	3	2	3	0	7	2	13	4
Doubtful (27)	9	0	2	2	12	2	23	4
Negative (157)	16	2	18	2	97	22	131	26
Total (201)	28	4	23	4	116	26	167	34

B, who developed a 2+ reaction. In Group F, of 30 originally negative or doubtful, 2 gave 1+ reactions. Of 13 in Groups A to E who were 1+ before therapy, only 3 remained positive; and this occurred also in 2 of 4 patients of Group F who were originally positive.

At Eversley Childs there were 305 patients who completed therapy and had preliminary and final lepromin tests. Of 233 belonging to Groups A to E, with negative or doubtful readings before therapy, only 2 (1 in A and 1 in E) were positive after 48 weeks of therapy. In both the reactions were 1+. In the control group, none of 50 with similar original reactions became positive. One patient in Group A had a 1+ reaction before therapy, and one in F a 2+; both were negative at the final test.

At Westfort, there were 229 patients eligible for this analysis. All were negative at first. Of 192 in Groups A to E, 34, or 17.7 per cent, became positive. Of 37 in Group F, 4, or 10.8 per cent, became positive. All reactions were 1+, except for one patient of Group B, in whom it was 2+. It should be noted that most observers would consider these one plus reactions as doubtful and only those of 10 mm. or larger as positive.

A comparison has been made between patients who became bacteriologically negative at all required skin sites and those who did not. As mentioned above, the former were not necessarily negative elsewhere. On the average, however, those who became negative at required skin sites had certainly eliminated many more bacilli than those who did not.

At Aisei-en, of 20 patients who were lepromin negative or doubtful and bacteriologically positive at the outset, and who became bacteriologically negative at all required skin sites, 3, or 15 per cent, had 1+ final reactions. Of 164 originally similar patients who remained bacteriologically positive, 24, or 14.6 per cent, became positive to lepromin, only one having larger than a minimal positive reaction.

At Eversley Childs, none of 25 lepromin-negative patients who became negative bacteriologically developed reactivity to lepromin. Of 278 who remained bacteriologically positive, 2 had reactions graded as 1+ at the end of 48 weeks.

At Westfort, there were 50 patients originally negative to Dharmendra's lepromin (48-hour reaction) and positive bacteriologically who became negative at all required skin sites. Of these, 7, or 14 per cent, had 1+ reactions after 48 weeks therapy. Of 172 who remained bacteriologically positive, 30, or 17.4 per cent, developed reactivity, but only one had a reaction larger than 1+.

SUMMARY

A study of leprosy therapy was conducted at four institutions: Aisei-en and Komyo-en, on Nagashima Island in the Inland Sea of Japan; Eversley Childs Sanitarium, Cebu, Philippines, and the Westfort Institution, Pretoria, Union of South Africa. In the study of the results, the statistics for the two Japanese institutions have been combined.

At each institution, patients with lepromatous leprosy were selected and assigned in equal numbers to six therapy groups by a method which gave priority to comparability in sex and age, but also took into account other characteristics possibly relevant to prognosis. These groups were subjected to impartial appraisal after 32 weeks therapy at Aisei-en and Komyo-en, and after 48 weeks at the other institutions. The drugs and combinations used were: (A) diasone (diamidin); (B) 4-4′-diaminodiphenyl sulfone (DDS); (C) dihydrostreptomycin sulfate; (D) A plus C; (E) C plus sodium *p*-aminosalicylate (PAS), and (F) a placebo (Ceslu) at the Japanese institutions and Eversley Childs, and PAS at Westfort.

The results given are based upon study of the records of patients who completed therapy and examinations, 312 at Aisei-en and Komyo-en, 307 at Eversley Childs, and 233 at Westfort. As far as can be determined, the patients of each group who completed therapy did not at the start of the experiment differ from the others in any characteristic which might have affected prognosis.

With respect to clinical changes, the proportions of patients definitely improved at all institutions were substantially higher for Groups A to E combined than for the control groups (F). At Aisei-en and Komyo-en and at Eversley Childs, judging from the detailed records, the principal factors which influenced clinical judgment were lessening of infiltration, diminution in size or disappearance of nodules and plaques, and healing of lepromatous ulcers. At Westfort the major factor was improvement in infiltration, but there the difference between Groups A to E and the control group in this respect was much smaller than at the other institutions, and clinical judgment was influenced to some extent by changes in bacteriologic status.

The proportions definitely worse were likewise much higher for Group F than for the other groups at Aisei-en and Komyo-en and at Eversley Childs. The factors indicating worsening were increase in infiltration, nodules, plaques and ulceration, in eye lesions, and in neuritis. At Westfort only 2 patients, 1 each in Groups B and C, showed increase in infiltration or plaques, and in only one of these, in C, was this conspicuous. A large proportion of the control group here remained stationary, a fact which is tentatively attributed to suppressive capacity of the PAS used instead of Ceslu.

No evidence was found of superiority of the higher sulfone over DDS, of either sulfone over dihydrostreptomycin, or of the combinations used over the individual sulfones or dihydrostreptomycin. At Aisei-en and Komyo-en 2 patients receiving diasone became worse, but none of those receiving DDS. At Eversley Childs and at Westfort no patient on diasone became worse, whereas 2 on DDS did so at each institution. There is suggestive evidence that dihydrostreptomycin was not as effective as the sulfones in reducing infiltration.

Possibly because of greater difficulty in assessment, L_1 and L_2 cases

did not show greater clinical improvement than did those classed as L_3; less improvement, in fact, at Eversley Childs and Westfort.

Erythema nodosum leprosum was a troublesome complication which contributed to difficulty of clinical appraisal. The proportions of patients in whom this condition developed during therapy was about 40 per cent at each institution, and was about the same for those on sulfones as for those on dihydrostreptomycin. In this respect Group F was low in comparison with other groups at Aisei-en and Komyo-en and at Westfort, but about the same as Groups A and C at Eversley Childs. Further study of the frequency of this complication and of its prognostic implications would be of great interest.

As regards bacteriologic changes, an analysis has been made of the findings in smears obtained before and after therapy from six skin sites on the patients at Aisei-en and Komyo-en combined and Eversley Childs, and five sites at Westfort. To describe the changes an arbitrary index was devised. This was weighted to adjust for variations between the groups in the proportions of lightly and heavily infected sites existing before therapy. The index has a maximum value of 2 and a minimum value of –1. The higher the index the greater the average bacteriologic improvement of the group.

For the Aisei-en and Komyo-en patients the index is higher for Groups A to E combined than for F, but the difference is not great. Likewise, there is no substantial difference between the index for the sulfone groups (A,B,D) combined and that for the groups on dihydrostreptomycin (C,D,E). Indices for Groups A, B and C, however, were higher than those for D and E, and those for D and E were approximately as low as that for F. Thus, after 32 weeks therapy, there was suggestive evidence of some bacteriostatic or bactericidal capacity of diasone, DDS, and dihydrostreptomycin. The combined therapies, on the other hand, were no better than the placebo in this respect.

At Eversley Childs the results suggest that after 48 weeks of therapy there was a higher degree of bacteriologic improvement in all Groups A to E than in F. There was, however, no advantage of one sulfone over the other, or of either sulfone over dihydrostreptomycin, or of the combinations used over diasone, DDS or dihydrostreptomycin used singly.

At Westfort there are no significant differences between the bacteriologic indices of the various groups, except that the index for Group C is substantially higher than those for the lower groups, A and F. The reason for this is not evident. The observation is in disagreement with the results obtained at the other institutions, where the indices for Group C were not higher than those for Groups A and B.

The bacteriologic index for patients of Groups A to E combined who were classed as moderately or markedly improved is compared with that for other patients of these groups. At Aisei-en and Komyo-en and at Eversley Childs no differences are found. This is not true of patients

classed as worse, for whom the indices are low. At Westfort, the patients who improved have a definitely higher index, attributable in part to the fact that clinical opinion as to improvement was influenced to some extent by bacteriologic changes.

In the lepromin testing, the classical lepromin was used at the Japanese institutions and at Eversley Childs, and readings were made on the 22nd day. Dharmendra's lepromin was used at Westfort, and readings were made at 48 hours. Some changes in reactivity were recorded.

At Aisei-en, 14.7 per cent of 184 patients who had given negative or doubtful results on preliminary examination became positive. This conversion occurred in all groups. No changes were recorded at Komyo-en. At Eversley Childs only 2 or 0.7 per cent of 303 patients originally giving negative or doubtful results became positive. One was in Group A and the other in E. At Westfort, of 229 patients lepromin negative on entry, 38, or 16.6 per cent, were classed as positive after therapy. There was no relationship between lepromin conversion and any specific therapy. At both Aisei-en and Westfort, change of lepromin status from negative to positive was about equally frequent in patients remaining bacteriologically positive as in those who became negative at all skin sites. It should be added that all patients who developed reactivity to lepromin had only 1+ reactions on final testing, except for 2 patients, one at Aisei-en and the other at Westfort in whom the reaction was graded as 2+.

CONCLUSIONS

1. Under the conditions of these studies, diasone (diamidin), 4-4′-diaminodiphenyl sulfone (DDS), and dihydrostreptomycin proved of definite and approximate equal value in the treatment of lepromatous leprosy. A combination of dihydrostreptomycin and diasone showed no advantage over either given singly, and addition of *p*-aminosalicylate (PAS) to dihydrostreptomycin did not augment its effectiveness. The proportion of patients who, on clinical grounds, were considered to be moderately or markedly improved was one-fifth at Aisei-en and Komyo-en after 32 weeks, and one-quarter at Eversley Childs and three-tenths at Westfort after 48 weeks. At the Japanese institutions and at Eversley Childs very few patients improved in the control groups given a placebo. At Westfort, there was improvement in about one-sixth of a control group given PAS, suggesting that this drug may have some beneficial effect.

2. A few patients in every group at each institution, *including the controls*, became bacteriologically negative at six required skin sites. At Aisei-en and Komyo-en the proportion was almost exactly the same for the total of all other groups as for the control group (10.1% *vs* 10.7%). The comparable figures for Eversley Childs were 9.0 per cent and 5.8 per cent; and for Westfort, 23.3 per cent and 18.9 per cent (for the PAS control).

3. A detailed examination of the preliminary and post-therapy findings in each of the six skin sites was made to measure bacteriologic

improvement short of attainment of negativity of the patient. At Aisei-en and Komyo-en the single therapies showed much the same results, each ranking somewhat higher than the combinations used and the placebo, which were about equal. At Eversley Childs, greater bacteriologic improvement occurred with all the therapies than in the control group. None of the treatments used, however, was remarkable in its effect in this respect, and none was significantly better than any other; i.e., the sulfones were about equal to one another, to dihydrostreptomycin and to the combination treatments given. At Westfort, the greatest bacteriologic improvement occurred in the group receiving dihydrostreptomycin only, a finding of doubtful significance; otherwise the results at Westfort did not show significant differences between any of the groups, including the control. There is, therefore, suggestive evidence that PAS had some beneficial effect not only on the clinical course but possibly also on bacteriologic status.

4. Changes in lepromin reactivity, from negative or doubtful to positive, were observed in a number of patients at Aisei-en and Westfort, but in only two at Eversley Childs. These changes were not associated with any particular therapy, or with attainment of bacteriologic negativity in the six required skin sites. In almost all instances the positive reactions in the final test were of the 1+ grade; only two patients, one at Aisei-en and one at Westfort, gave 2+ reactions.

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ABSTRACTO

Se hizo un estudio de la terapia anti-leprosa en cuatro instituciones: Aisei-en y Komyo en el Japón; Eversley Childs Sanitarium en Filipinas, y en Westport Institution en la Unión de Sud-Africa. Las siguientes drogas fueron empleadas, solas o en combinacion en grupos comparables de pacientes con lepra lepromatosa: Diasone, D.D.S., dihydrostreptomycin, y PAS (p-aminosalicilato sódico). Grupos testigos fueron administrados PAS en Westfort, y en otras instituciones un placebo. Los pacientes fueron observados por 32-48 semanas.

Se juzgó el resultado terapéutico por medio de hallazgos clínicos, incluyendo disminución de las infiltraciones, del tamaño de los nódulos o placas, y la cicatrización de las úlceras. Cambios bacteriológicos fueron evaluados por la comparación de frotas de 5 o 6 sitios hechos antes y después del tratamiento. Todos los pacientes fueron tambien sometidos a la prueba de la lepromina.

Bajo las condiciones de este estudio, diasone, D.D.S. y dihydrostreptomycin fueron de efectividad definitiva aunque aproximadamente igual. De la quinta a los tres décimas parte de los pacientes demostraron mejoría. Combinaciones de las drogas no aumentaron su efectividad. Algunos pacientes mejoraron con el placebo, pero hubo mejoría en la sexta parte del grupo que recibió PAS.

En algunos pacientes en cada grupo, incluyendo los testigos, los resultados bacteriológicos cambiaron hacia negatividad, la proporción variando del 5.3 al 23.3%. El indice bacteriológico indicativo de mejoría no fué consistente.

Cambios en la reacción a la lepromina de negativos o dudosos a positivos, se observaron en un número de pacientes en el Japón y en Sud-Africa, pero solamente en dos en Eversley Childs.

(Para detalles de este bien planeado y bien ejecutado estudio, es necessario leer el artículo en su totalidad. EL EDITOR).

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