INTERNATIONAL JOURNAL OF LEPROSY

Volume 35, Number 2
Printed in U.S.A.

Clinical Evaluation Studies in Lepromatous Leprosy

Sixth Series: Effect (on Lepra Reaction) of Supplementing DDS with Dexamethasone, Methandrostenolone, or Mefenamic Acid[1]

James A. Doull, Jose G. Tolentino, Ricardo S. Guinto, Jose N. Rodriguez Leopoldo M. Leano, Juan V. Fernandez, Jose N. Rivera and T. T. Fajardo, Jr.[2]

Lepra reaction, usually in the form of erythema nodosum leprosum (ENL), is a frequent and often serious complication in lepromatous leprosy. Lepra reaction develops in untreated patients, but is widely believed to have greatly increased with the advent of sulfone therapy and to be precipitated by abrupt initiation of treatment or unnecessarily large doses of DDS. In consequence, DDS is given very cautiously over induction periods of as long as six months, and maximum dosage is kept at low levels ([11, 12]), perhaps at some risk of giving rise to resistant strains of *Mycobacterium leprae*. DDS therapy, furthermore, is suspended during periods of reaction, which are very often protracted. The effectiveness of DDS is thus greatly hampered by lepra reaction.

The main objective of this series of investigations ([2, 3, 4, 5, 6]) heretofore has been to find a drug or drugs superior to the sulfones in the treatment of lepromatous leprosy. Inasmuch as DDS remains the drug of choice, it became expedient to try to increase its therapeutic action by supplementing regular DDS therapy with drugs presumed to be capable of preventing or reducing lepra reaction. Anti-inflammatory drugs were naturally considered and two were chosen for trial, dexamethasone and a non-steroid drug, N-(2,3-xylyl) anthranilic acid, also known as mefenamic acid. Despite extensive experience, opinion remains divided regarding the value of corticosteroids in the treatment of actual lepra reaction. Their possible value as preventive agents has apparently not been determined. Mefenamic acid is known to have an anti-inflammatory potency five times that of acetylsalicylic acid, though somewhat less than that of phenylbutazone ([10]).

A third drug also was selected for trial, viz., methandrostenolone (17 alpha-methyl-17 beta-hydroxy-androsta-1, 4-dien-3-one), an anabolic steroid possessing little if any anti-inflammatory or corticoid property. It was thought that the protein-utilizing anabolic action of this drug would increase the strength and resistance of the patients sufficiently to overcome lepra reaction. Methandrostenolone was also credited with enough of a steroid-sparing effect to permit some rheumatoid patients to be maintained

[1]Received for publication 6 September 1966.

[2]J. A. Doull, M.D., Medical Director, Leonard Wood Memorial, Washington, D. C., deceased 6 April 1963; J. G. Tolentino, M.D., Chief, Clinical Branch, R. S. Guinto, M.D., Chief, Epidemiology Branch, J. N. Rodriguez, M.D., Consultant, Philippine Division, Leonard Wood Memorial, P.O. Box 117, Cebu, Philippines; L. M. Leano, M.D., Medical Officer, J. V. Fernandez, M.D., Associate Research Leprologist, J. N. Rivera, M.D., Assistant Research Leprologist, Leonard Wood Memorial and Philippine Department of Health, Central Luzon Sanitarium, Tala, Philippines; T. T. Fajardo, Jr., Assistant Epidemiologist, Epidemiology Branch, Philippine Division, Leonard Wood Memorial, Cebu, Philippines. *Requests for reprints* should be addressed to Leonard Wood Memorial, 1200 - 18th Street, N.W., Washington, D. C. 20036.

on it for prolonged periods ([1]). Gokhale and associates ([7]) have already reported some reduction of lepra reaction in six lepromatous patients during the first few months of treatment with anabolic steroids.

MATERIALS AND METHODS

Therapy scheme. As stated, our new objective was to prevent or limit the occurrence of lepra reaction by supplementing DDS with various drugs. The study was conducted in duplicate at two Philippine leprosaria, the Eversley Childs Sanitarium in Cebu and the Central Luzon Sanitarium near Manila. It was a strictly double-blind experiment, involving an elaborate system of placebos to match the trial drugs. The actual period of therapy was limited to 24 weeks. The complete therapy scheme was as follows:

Group	*Drugs given*	*Daily dosage*	*Tablets taken daily (except Sundays)*
A	DDS alone	2.5 mgm./kgm.	DDS by body weight 1 control for dexamethasone 2 control for methandrostenolone 3 control for mefenamic acid
B	DDS Dexamethasone	2.5 mgm./kgm. 1.5 mgm.	DDS by body weight 1 dexamethasone 2 control for methandrostenolone 3 control for mefenamic acid
C	DDS Methandrostenolone	2.5 mgm./kgm. 10 mgm.	DDS by body weight 2 methandrostenolone 1 control for dexamethasone 3 control for mefenamic acid
D	DDS Mefenamic acid	2.5 mgm./kgm. 750 mgm.	DDS by body weight 3 mefenamic acid 1 control for dexamethasone 2 control for methandrostenolone

Selection of patients and matching of therapy groups. A total of 400 volunteer patients were first selected, 160 at Eversley Childs and 240 at Central Luzon. All patients were lepromatous, heavily positive and lepromin-negative. The majority were new and untreated, but a small proportion with some prior DDS therapy were included after being kept completely without DDS for an average period of eight weeks. Those chosen were initially without lepra reaction, although a few with slight ENL on preliminary examination were included, as were a small number who developed ENL during the interval between enrollment and the start of therapy. The patients were assigned to the four therapy groups by a sampling method used and already described in the previous series of these studies ([8]).

Particular effort was made to match the groups with respect to various characteristics known to influence the occurrence of lepra reaction ([9]), such as the preexistence of ENL in the patient, prior sulfone therapy, and the advancement of the disease. Although all the patients were basically lepromatous, i.e., with symmetrically distributed infiltration, some had localized lesions (plaques) of doubtful borderline nature and were possibly less subject to ENL than those with more frankly lepromatous lesions. As shown in Table 1, the four therapy groups were initially well matched in all possible respects.

Dropped patients. Discontinuance of therapy is always a problem in long-term studies. As in previous series, the greatest loss was caused by patients leaving the institution without permission. Of the 400 enlisted patients, 45 absconded, three died from causes unrelated to therapy, five were dropped for failure to continue treatment, and one was transferred to Culion before

TABLE 1. *Pretherapy status of original patients with respect to factors of possible influence on the occurrence of lepra reaction or the effect of therapy, by institution and therapy group.*

Pretherapy characteristic	Institution and therapy group							
	Eversley Childs				Central Luzon			
	A	B	C	D	A	B	C	D
Number of patients	40	39	40	41	60	59	59	62
Average:								
Age(years)	32.4	32.8	33.0	31.5	29.8	30.2	30.4	30.9
Weight in lbs.	107.2	107.8	107.0	105.0	104.8	106.3	106.2	105.3
Bacteriologic score for 8 sites	28.5	28.3	27.1	28.0	32.8	33.7	34.2	34.0
Percentage:								
Male sex	82.5	79.5	80.0	78.0	71.7	72.7	74.6	74.6
Clinically advanced (L3 class)	47.5	48.7	50.0	51.2	48.3	47.5	52.5	49.2
Lepromatous-borderline in type[a]	17.5	17.9	20.0	14.6	10.0	10.1	15.5	9.5
With preexisting ENL	5.0	2.6	2.5	4.9	16.7	15.3	15.3	19.0
With prior sulfone therapy[b]	32.5	40.3	27.5	39.0	8.3	10.2	8.5	15.9

[a]Essentially lepromatous, with symmetric diffuse infiltration, but with circumscribed lesions (plaques) of possible borderline nature.
[b]All patients with 5 grams or more of total prior DDS therapy.

the end of the study. The final results are thus based on the findings in 346 patients considered to have completed 24 prescribed weeks of therapy with DDS and the trial drugs. The final therapy status of the patients is given in Table 2.

Because of dropped patients, a reappraisal was made at the end of the study to determine the comparability of the groups with respect to pretherapy factors considered important in the original matching. As shown in Table 3, the therapy groups remained fairly well matched, except for a chance increase in patients with preexisting ENL in the mefenamic acid group (Group D).

Average amounts of drugs prescribed and taken. Patients sometimes asked to have therapy temporarily suspended when they were not feeling well; this resulted in a lowering of total dosage in one institution, Central Luzon. Table 4 gives the average prescribed amounts and the actual proportions taken at each institution. Eversley Childs patients took approximately 94 per cent of all prescribed drugs, a high

TABLE 2. *Final status of patients, with reasons for failure to complete 24 weeks of therapy, by institution and therapy group.*

Final status	Institution and therapy group								
	Eversley Childs				Central Luzon				
	A	B	C	D	A	B	C	D	Total
Therapy complete	36	35	39	38	45	53	47	53	346
Therapy incomplete (dropped):									
Absconded	3	3	1	3	13	4	11	7	45
Died	1	1				1			3
Refused treatment					1	1	1	2	5
Transferred to Culion					1				1
Original total	40	39	40	41	60	59	59	62	400

Deaths: Eversley Childs, Group A, #61-240, cancer of jaw, 15th week of study.
Group B, #61-136, coronary thrombosis, 22nd week.
Central Luzon, Group B, #658-10-60, leprous cachexia, 13th week.

TABLE 3. *Relevant pretherapy characteristics of patients who completed 24 prescribed weeks of therapy and observations, by therapy group, both institutions combined.*

Therapy group	Number of patients	Average bacteriologic score, 8 sites	Per cent clin. advanced (L3 degree)	Per cent lepromatous-borderline	Per cent with pre-existing ENL
A	81	38.3	30.0	11.1	16.0
B	88	39.8	31.5	13.6	11.4
C	86	39.5	31.4	10.5	16.3
D	91	38.5	31.5	15.4	29.6
Total	346	39.0	31.1	12.7	18.5

record for a study of 24 weeks. The patients at Central Luzon, however, took only about 80 per cent of the total prescribed drugs.

The average weight of the Filipino patients in this study was 106 pounds, or 48.2 kilograms. At 15 mgm. per kgm. of body weight weekly, the average maximum DDS dose came to 700 mgm. a week, and was reached after an induction period of eight weeks. The "prophylactic" daily doses of dexamethasone (1.5 mgm.) and mefenamic acid (750 mgm.) were approximately the maintenance doses of these drugs. Methandrostenolone was given in the full anabolic dose (10 mgm.).

Measurement of results. The standardized methods of five previous series were followed in measuring the usual clinical and bacteriologic changes effected by DDS therapy. Regular dermatologic and neurologic examinations of the whole body were made every eight weeks and recorded on prescribed forms, which included giving numerical values to infiltration, nodules, plaques, anesthesia, etc. Clinical photographs in color and black and white were taken before and after therapy. Each patient was graded as improved (slight, moderate or marked), stationary, or worse (slight, moderate or marked).

Smears from eight sites (2 ear lobes, 2 nasal and 4 skin) were taken and examined by the same technicians throughout the study. Each smear was given a numerical rating: those marked scanty a grade of 1, + a grade of 2, ++ a grade of 3, +++ a grade of 4, and ++++ a grade of 5; thus the highest score was 40, 10 for the two nasal and 30 for the six skin sites. Bac-

TABLE 4. *Average amounts of drugs prescribed and taken, by institution and therapy group.*

Group	Drugs given	Eversley Childs				Central Luzon			
		Number of patients	Average amount in grams		Per cent taken	Number of patients	Average amount in grams		Per cent taken
			Prescribed	Taken			Prescribed	Taken	
A	DDS alone	36	14.00	13.22	94.4	45	13.85	11.34	81.9
B	DDS	35	14.17	13.21	93.2	53	13.93	10.97	78.8
	+								
	Dexamethasone		0.216	0.203	94.0		0.216	0.173	80.1
C	DDS	39	14.04	13.17	93.8	47	13.78	10.89	79.0
	+								
	Methandrostenolone		1.44	1.36	94.4		1.44	1.14	79.2
D	DDS	38	14.33	13.26	92.5	53	13.79	11.18	81.1
	+								
	Mefenamic acid		108.00	103.15	95.5		108.00	88.23	81.7

TABLE 5. *Basic clinical and bacteriologic improvement after 24 weeks of therapy, by institution and therapy group.*

Therapy group	Eversley Childs			Central Luzon			Both institutions		
	Number of patients	Per cent clinically improved	Average percentage reduction in bact. score	Number of patients	Per cent clinically improved	Average percentage reduction in bact. score	Number of patients	Per cent clinically improved	Average percentage reduction in bact. score
A	36	33.4	16.1	45	35.6	14.6	81	34.6	15.2
B	35	40.0	20.1	53	41.5	12.7	88	40.9	16.3
C	39	35.9	11.8	47	29.8	13.8	86	32.6	13.0
D	38	31.6	18.3	53	32.1	10.8	91	31.9	13.6
Total	148	35.1	17.1	198	34.8	12.9	346	35.0	14.5

Clinical improvement: all patients classified as slightly, moderately or markedly improved.

teriologic improvement was expressed as average reductions from the pretherapy scores.

A detailed study was naturally made of lepra reaction. Patients were examined once a week, on the same day, for all possible signs and symptoms of reaction. A numerical rating (1+, 2+ or 3+) was given for the extent or degree of each reactional manifestation at each weekly examination. The findings were recorded on special forms which allowed comparisons between individuals or in terms of "person-weeks" of observation. Each patient was regarded as attacked by any reactional manifestation if found positive in two or more of the 24 weekly examinations.

The patients were also examined weekly for drug intolerance or side-effects due to prolonged medication with the trial drugs, i.e., gastrointestinal or psychic disturbances, moon-face or edema, undue weight change, hypertension, hirsutism, voice change or menstrual irregularity in females, etc. These were likewise recorded on special forms.

RESULTS

Clinical and bacteriologic changes. These are summarized in Table 5 by insti-

TABLE 6. *Frequency of attacks of erythema nodosum leprosum (ENL) during 24 weeks of therapy, according to results of weekly examinations, by institution and therapy group.*

Therapy group	Eversley Childs				Central Luzon			
	Patients		Person-weeks of observation		Patients		Person-weeks of observation	
	Total in group	Per cent attacked[a]	Total in group	Per cent positive for ENL	Total in group	Per cent attacked[a]	Total in group	Per cent positive for ENL
A (DDS alone)	36	47.2	857	14.1	45	60.0	1,065	33.7
B (DDS + dexamethasone)	35	62.9	831	28.9	53	67.9	1,245	32.4
C (DDS + methandrostenolone)	39	46.2	924	24.5	47	61.7	1,084	31.9
D (DDS + mefenamic acid)	38	44.7	904	30.1	53	73.6	1,229	42.1
Total	148	50.0	3,516	24.4	198	66.2	4,623	35.2

[a]Each patient was considered attacked by ENL, or any other reactional manifestation, if found positive for this manifestation in two or more of the 24 weekly examinations for signs and symptoms of reaction.

TABLE 7. *Relative frequency, duration and severity of attacks of ENL during 24 weeks of therapy (and weekly observations), by therapy group, both institutions combined.*

Therapy group	Total patients in group	Patients attacked during therapy		"Person-weeks" positive for ENL	
		Number	Per cent	Average duration of attacks	Per cent 3+ or more in severity[a] (severe ENL)
A (DDS alone)	81	44	54.3	10.9	23.7
B (DDS + dexamethasone)	88	58	65.9	11.1	33.4
C (DDS + methandrostenolone)	86	47	54.7	12.2	19.5
D (DDS + mefenamic acid)	91	56	61.5	14.1	22.5
Total	346	205	59.2	12.1	24.8

[a]Severity of ENL in terms of the numerical ratings (1+, 2+ or 3+) for extent or degree of one or more clinical varieties of ENL lesions in the same patient, i.e., the classical papulo-nodules or the "multiforme" type, including blebs or bullae, pustules, ulceration, etc.

tution and therapy group. No appreciable improvement in the lepromatous disease was expected after 24 weeks of DDS therapy, even if the trial drugs should prove effective in reducing lepra reaction. At both institutions, there was recognizable clinical improvement in about 35 per cent of the patients, with no therapy group showing significantly greater or lesser change than the average for all groups. Small average reductions of 17.5 per cent (Eversley Childs) and 12.9 per cent (Central Luzon) in total bacteriologic scores were noted, also without any definite difference among therapy groups. None of the drugs on trial appeared to have enhanced the therapeutic action of DDS after 24 weeks of treatment.

Prophylactic effect of trial drugs on ENL. As expected, the weekly examinations revealed ENL as the commonest reactional manifestation in the 356 lepromatous patients of this study. ENL was the only specifically reactional condition observed with enough frequency for an adequate comparison of attack rates among therapy groups. The occurrence of ENL is shown in Table 6 by institution and therapy group, both in terms of individuals attacked and in the proportions of the weekly observations that were found positive for this complication. It is obvious from this table that none of the trial drugs prevented or shortened the attacks of ENL in the course of 24 weeks of regular therapy with DDS at either institution. At the Eversley Childs Sanitarium, the patients under DDS alone even had shorter attacks (14.1% of the total weekly observations) than those under DDS + dexamethasone (28.9%), DDS + methandrostenolone (24.5%) or DDS + mefenamic acid (30.1%). Among the greater number of patients at the Central Luzon Sanitarium, however, there was no appreciable difference between therapy groups both as to numbers of persons affected or to "person-weeks" positive for ENL.

After combination of the findings of both institutions, the therapy groups are compared in Table 7 as to average duration and relative severity of the attacks of ENL. The figures in Table 7 confirm the obvious lack of any prophylactic value attributable to supplementary therapy with dexamethasone, methandrostenolone and mefenamic acid in the manner used in this experiment. Paradoxically, 58 patients who were given 1.5 mgm. of dexamethasone daily, together with DDS, appeared to have developed more severe attacks of ENL (3+ grade, 33.4%) as compared with those under DDS alone (23.7%) or with the average for all patients (24.8%).

Factors favoring ENL. In a report based on findings in the five previous series of these studies ([9]), it was noted that during treatment, whether with sulfone or non-sulfone drugs, ENL developed with greater frequency and severity among patients in

TABLE 8. *Comparative occurrence of ENL during the therapy period, for patients with preexisting ENL and those without ENL at the outset, by therapy group, both institutions combined.*

Therapy group	ENL present at outset				ENL absent at outset			
	Patients		Person-weeks positive for ENL		Patients		Person-weeks positive for ENL	
	Number in group	Attacked during therapy	Average per patient (duration)	Per cent 3+ or more in severity	Number in group	Attacked during therapy	Average per patient (duration)	Per cent 3+ or more in severity
A	13	12 (92.3%)	16.5	21.6	68	32 (47.1%)	8.8	2.8
B	10	10 (100.0)	18.9	47.2	78	48 (61.5%)	9.5	6.0
C	14	12 (85.7)	16.6	10.8	72	35 (48.6)	10.5	4.3
D	27	24 (88.9)	18.9	22.6	64	32 (50.0)	10.5	2.5
Total	64	58 (90.6%)	17.9	23.7	282	147 (52.1%)	9.8	4.1

whom this complication was already present initially than among those in whom it was still absent. The occurrence of ENL is thus compared by therapy group in Table 8 for patients with and without ENL at the commencement of therapy.

Irrespective of the therapy group, more than 90 per cent of 64 patients with preexisting ENL continued to have recurrences of this complication during the therapy period. In some contrast, ENL occurred in only 52.1 per cent of 282 patients in whom it was absent initially. The attacks were, furthermore, almost twice as long (average duration 17.9 *vs* 9.8 weeks out of 24) and many times more severe (3+ grade 23.7% *vs* 4.1%) among those with preexisting ENL. The attack rates shown in Table 8 leave no further doubt that the three trial drugs had no prophylactic effect on ENL.

The results of an attempt to ascertain why some lepromatous patients were much more susceptible to ENL than the others are summarized in Table 9. The findings confirm our previous observation ([9]) that these patients tended to be more advanced clinically (L3 class 46.9% *vs* 37.2%), but not necessarily more heavily positive (average bacteriologic score 30.6 *vs* 31.5), less borderline-lepromatous in type (1.6% *vs* 15.2%), and with more previous sulfone therapy (31.3% *vs* 19.5%) than the latter. These relatively small differences seem hardly sufficient, however, to account entirely for the far greater frequency, duration and severity of the attacks in patients with preexisting ENL than in those initially without it, under equal conditions of therapy. It would appear that some lepromatous patients are inherently more susceptible to ENL than others for still unknown reasons.

TABLE 9. *Pretherapy characteristics of patients with preexisting ENL and those without ENL at the start of treatment, institutions and therapy groups combined.*

Pretherapy characteristic	ENL present at outset	ENL absent at outset
Number of patients	64	282
Average bacteriologic score (8 sites)	30.6	31.5
Per cent clinically advanced (L3 class)	46.9	37.2
Per cent borderline-lepromatous in type	1.6	15.2
Per cent with prior sulfone therapy[a]	31.3	19.5

[a]All patients with 5 grams or more of total prior DDS therapy.

TABLE 10. *Numbers of patients found positive for various signs and symptoms of lepra reaction during 24 weeks of therapy, with the average duration of each condition, by therapy group, both institutions combined.*

Therapy group	Total patients	Number attacked and average duration in "person-weeks" of observation					
		ENL	Fever	Neuritis	Conjunctivitis or iritis	Acute leprom. infiltration	Confined in infirmary
A	81	44 (10.9)	27 (3.5)	14 (1.6)	5 (9.5)	1 (4.0)	11 (4.3)
B	88	58 (11.1)	46 (4.8)	16 (2.9)	10 (5.0)	1 (24.0)	26 (5.1)
C	86	47 (12.2)	29 (4.0)	13. (4.6)	6 (5.5)	1 (2.0)	14 (5.7)
D	91	56 (14.1)	40 (4.8)	10 (3.2)	7 (7.0)	—	16 (4.9)
Total	346	205 (12.1)	142 (4.4)	53 (2.8)	28 (6.4)	3 (10.0)	67 (5.0)

As stated (Tables 1 and 3), a special effort was made to match the therapy groups in number of patients with borderline-lepromatous lesions, because they were possibly less subject to attacks of ENL and could differ from more frankly lepromatous patients in response to treatment. It is shown in Table 9 that only one of 44 such patients had preexisting ENL. During the therapy period, however, ENL developed in 15 (34.9%) of the 43 remaining patients of this particular clinical type, as compared to 52.1% for all patients without preexisting ENL in the entire study. ENL is known to occur, almost diagnostically, only in patients with lepromatous leprosy.

Other signs and symptoms of lepra reaction. Table 10 gives the relative occurrence of various other reactional or presumably reactional complications as compared to ENL. The more severe episodes of ENL were often accompanied by fever. Fever occurred in 142 or 41.0 per cent of the 346 patients in the study for an average of 4.4 person-weeks of observation out of 24. As seen in Table 10, fever was even somewhat less frequent, and of shorter average duration, in the patients under DDS alone (Group A) than in those of the other groups.

Painful neuritis was recorded in 53 or 15.3 per cent of all the patients for an average duration of 2.8 person-weeks. This complication was likewise not more frequent (attack rate 17.3%), nor of longer duration (1.6 person-weeks), in the control group than in all the groups taken together.

Some 8.1 per cent of the patients developed acute or subacute eye lesions in the form of conjunctivitis or iritis, which were thought to be of allergic rather than infectious nature. These presumably reactional eye lesions were also not more frequent in the control group than in the other therapy groups.

Although of doubtful significance, the proportions of patients requiring hospitalization and the average periods of bed confinement are included in Table 10 as a rough index of the severity of the attacks of lepra reaction. Perhaps purely by chance, more patients in Group B (DDS + dexamethasone) were confined in the infirmary for lepra reaction (29.6%) than the general average (19.4%), although not for longer periods (4.3 *vs* 5.0 person-weeks).

"Acute lepromatous infiltration" is a rare complication, as judged solely from this series. This presumably reactional condition was recorded in the weekly charts of only three of the 346 total patients and was preexistent in one patient, in whom it persisted throughout 24 weeks of daily treatment with DDS and 1.5 mgm. of dexamethasone. One patient in Group A and another in Group C appeared to have developed mild and relatively short-lasting episodes of acute lepromatous infiltration during the therapy period.

Rebound effect upon withdrawal of dexamethasone. All patients were continued on routine DDS therapy after the 24 weeks of the experiment. As a delayed afterthought, the examinations for lepra

TABLE 11. *Occurrence of ENL during the last 12 weeks of the therapy period and the first 12 weeks after withdrawal of the trial drugs, by therapy group, second "batch" patients of the Central Luzon Sanitarium.*

Therapy group	Total patients	Last 12 weeks of therapy				First 12 weeks after therapy period			
		Number attacked	Per cent "person-weeks" positive for ENL			Number attacked		Per cent "person-weeks" positive for ENL	
			13-16 weeks	17-20 weeks	21-24 weeks	Former cases	New cases	1-4 weeks	5-8 weeks	9-12 weeks
A	22	12	31.0	30.7	25.3	10	2	28.7	39.1	36.0
B	27	14	34.9	32.4	29.6	12	7	61.9	43.2	32.3
C	24	12	34.4	30.4	30.5	10	2	43.0	35.0	29.1
D	27	18	50.9	52.8	47.7	18	5	52.4	69.4	65.6
Total	95	56	38.3	37.1	33.8	50	16	47.1	46.9	40.7

reaction were continued for 12 additional weeks, although only with the last of two "batches" of patients assembled in one institution, Central Luzon. The purpose was to ascertain any consequences of withdrawal of the trial drugs, particularly dexamethasone. The limited data in Table 11 compare the therapy groups as to occurrence of ENL during the last 12 weeks of treatment with the trial drugs and the 12 weeks immediately following, but only in some 27 per cent of the total patients.

The limited attack rates in Table 11 more than suggest a rebound effect on ENL upon the discontinuance of dexamethasone. During the last four weeks of daily therapy with 1.5 mgm. of dexamethasone, 29.3 per cent of the weekly observations in Group B were positive for ENL. This complication more than doubled within the first four weeks after withdrawal of the corticosteroid. No such increase was observed in the other therapy groups. ENL was absent in 13 patients of Group B during the last 12 weeks of the therapy period, but suddenly cropped up in seven within 12 days after stopping dexamethasone, a happening not observed in the other groups. There were five new posttherapy cases of ENL in Group D, but four occurred more than four weeks after mefenamic acid was discontinued.

The patients of Group D in Table 11 had more ENL throughout both the therapy

TABLE 12. *Changes in weight of patients after 24 weeks of supplementary treatment with methandrostenolone, compared to weight in other therapy groups, both institutions combined.*

Therapy group	Number of patients	Percentages of various changes in weight						
		Gain (lbs.)			Plus or minus 2 lbs.	Loss (lbs.)		
		11 over	7 to 10	3 to 6		3 to 6	7 to 10	11 over
A. (DDS alone)	81	6.2	9.9	19.7	27.2	24.7	11.1	1.2
B. (DDS + dexamethasone)	88	2.3	9.1	25.0	28.4	15.9	17.0	2.3
D. (DDS + mefenamic acid)	91	2.2	5.5	17.6	44.0	20.9	7.7	2.2
Groups A, B and D	260	3.4	8.1	20.8	33.5	20.4	11.9	1.9
C. (DDS + methandrostenolone)	86	14.0	11.6	27.9	30.2	9.3	3.5	3.5

and posttherapy periods than the others, including those of Group B. The probable explanation is that as a result of chance, 13 of the 27 patients in Group D happened to be of the innately hypersusceptible type with preexisting ENL. There were only seven such patients in 22 of Group A, eight in 27 of Group B and five in 24 of Group C.

Anabolic action of methandrostenolone. The anabolic steroid was given in the standard full dose (10 mgm.) for 24 weeks. The general anabolic effect on the lepromatous patients of this study is assessed in Table 12, which compares body-weight changes among therapy groups. Of 86 patients treated with methandrostenolone, 53.5 per cent gained three or more pounds and 25.6 per cent gained seven to 14 pounds, compared to 32.3 per cent and 11.6 per cent, respectively, in 260 patients of Groups A, B and D combined. The differences in favor of Group C are significant in a statistical sense, as evidenced by chi-square values of 12.4 and 10.0, respectively. Despite methandrostenolone therapy, 16.3 per cent of the patients in Group C lost three or more pounds in weight and 7.0 per cent lost seven to 14 pounds, but the correspondingly larger proportions of weight loss were 32.3 per cent and 13.8 per cent in the 260 other patients. Supplementary treatment with the anabolic steroid was thus of benefit to the lepromatous patients, even if it failed to reduce lepra reaction.

Lepromatous patients are subject to large fluctuations in body weight, as judged from the data in Table 12. These were often associated with prolonged or severe lepra reaction with attendant fever, malaise, loss of appetite and general worsening of the underlying lepromatous disease. Many patients who lost seven or more pounds during the therapy period suffered from severe ENL, and those gaining seven or more pounds tended to have recovered from attacks of severe reaction.

Drug intolerance or side-effects. None was recorded in the weekly charts of the 346 patients in the four therapy groups, except for one case of "moon-face" among 88 patients treated with DDS and 1.5 mgm. of dexamethasone. The latter became evident after 14 weeks, but disappeared upon withdrawal of the corticosteroid. No side-effects of androgenic nature were noted in 22 female patients treated with 10 mgm. of methandrostenolone for 24 weeks. There were also no signs of intolerance to mefenamic acid, which was given to 91 patients in a dose of 750 mgm. daily for 24 weeks in addition to regular DDS therapy.

SUMMARY

In a double-blind study conducted in duplicate at two Philippine leprosaria, 346 lepromatous patients divided into four matched groups were treated for 24 weeks with (A) DDS alone, (B) DDS + dexamethasone, (C) DDS + methandrostenolone and (D) DDS + mefenamic acid, to determine whether these drugs could prevent or reduce lepra reaction and thus increase the therapeutic action of DDS.

The maximum daily DDS dose (2.5 mgm. per kgm. of body weight) was reached after eight weeks. Daily doses of the trial drugs were: dexamethasone 1.5 mgm., methandrostenolone 10 mgm., and mefenamic acid 750 mgm. No treatment was given on Sundays. Average proportions taken of the total prescribed drugs were approximately 94 per cent for patients at Eversley Childs and 80 per cent for those at Central Luzon.

After 24 weeks of therapy, 35 per cent of the patients in both institutions were regarded as clinically improved and there was an average reduction of 14.5 per cent in total bacteriologic scores, without any significant difference in favor of any therapy group.

No reduction was observed in the frequency, duration of severity of ENL or any other reactional manifestation in the patients under supplementary therapy for 24 weeks with dexamethasone, methandrostenolone or mefenamic acid as compared with manifestations in patients under DDS therapy alone.

Treatment with methandrostenolone resulted in a moderately appreciable increase in body weight of the lepromatous patients in Group C over those of the other therapy groups.

Except for one temporary instance of moon-face, there were no signs of intolerance or side-effects attributable to DDS and supplementary therapy with dexamethasone, methandrostenolone or mefenamic acid in this study.

RESUMEN

En un estudio doble ciego conducido en forma duplicada en dos leprosarios en Filipinas, 346 pacientes lepromatosos divididos en cuatro grupos semejantes fueron tratados durante 24 semanas con (A) DDS solo, (B) DDS + dexamethasona, (C) DDS + methandrostenolone y (D) DDS + ácido mefenámico, para determinar si estas drogas podrían prevenir o reducir la reacción leprosa y esta forma aumentar la acción therapeútica de DDS.

La maximum dosis diaria de DDS (2.5 mgm. por kgm. de peso corporal) fué alcanzada al término de ocho semanas. Las dosis diarias de las drogas de ensayo fueron: dexamethasona 1.5 mgm., methandrostenolone 10 mgm., y ácido mefenámico 750 mgm. No se trató a los enfermos en Domingos. La proporción promedia que se tomó del total de drogas prescritas fué aproximadamente 94% en los pacientes de Eversley Childs y 80% para aquellos en Central Luzon.

Después de 24 semanas de tratamiento, 35% de los enfermos en ambas instituciones se consideraron como clinicamente mejorados y hubo una reducción promedio de 14.5% en los resultados bacteriológicos totales, sin ninguna diferencia significativa en favor de ninguno de los grupos therapeúticos.

No se observó disminución en la frecuencia, duración de la severidad de ENL o de cualquiera otra manifestación reaccional en los enfermos bajo tratamiento suplementario por 24 semanas con dexamethasona, methandrostenolone o ácido mefenámico comparados con manifestaciones en enfermos tratados solamente con DDS.

El tratamiento con methandrostenolone resultó en un aumento moderadamente apreciable del peso corporal de los enfermos lepromatosos del Grupo C sobre aquellos enfermos de los otros grupos de tratamiento.

Excepto por un momento transistorio de edema (moon face), no hubo signos de intolerancia o manifestaciones colaterales atribuibles al DDS y tratamiento suplementario con dexamethasona, methandrostenolone o ácido mefenámico en este estudio.

RÉSUMÉ

Dans une étude menée par la méthode du double incognito, et répétée dans deux léproseries des Philippines, 346 malades lépromateux ont été séparés en quatre groupes présentant les mêmes caractéristiques. Ces malades ont été traités pendant 24 semaines avec: (A) de la DDS seulement, (B) de la DDS et de la dexaméthasone, (C) de la DDS et du méthandrostenolone, (D) de la DDS et de l'acide mefénamique. Cette étude avait pour but de déterminer si ces médicants pouvaient prévenir ou réduire la réaction lépreuse et, dès lors, accroître l'action thérapeutique de la DDS.

La dose quotidienne maxima de DDS, soit 2.5 mgm. par kilogramme de poids, a été attiente après huit semaines. Les doses quotidiennes des médicaments expérimentés ont été: dexaméthasone 1.5 mgm., méthandrostenolone 10 mgm., et acide mefénamique 750 mgm. Aucun traitement n'a été administré de dimanche. La proportion moyenne prise pour chacun des médicaments prescrits a été approximativement de 94% chez les malades de Eversley Childs de 80% pour ceux de Central Luzon.

Après 24 semaines de traitement, 35% des malades dans les deux institutions ont été considérés comme améliorés cliniquement. Il s'est produit une diminution moyenne de 14.5% dans les indices bactériologiques totaux sans qu'on puisse mettre en évidence aucune différence significative en faveur de l'un ou l'autre des groupes thérapeutiques.

Chez les malades recevant un traitement additionnel de 24 semaines avec la dexaméthasone, la méthandrostenolone ou l'acide mefénamique, il n'a été observé aucune diminution dans la fréquence, la durée ou la gravité de l'ENL ou d'aucune autre manifestation réactionnelle, lorsqu'on les comparait avec les manifestations survenues chez les malades auxquels la thérapeutique par la DDS seule était prescrite.

Le traitement avec la méthandrostenolone a entrainé une augmentation modérée, mais appréciable, du poids corporel chez les malades lépromateux du groupe C, par rapport à ceux affectés aux autres groupes thérapeutiques.

A part un exemple de faciès lunaire temporaire, il ne s'est produit aucun signe d'intolérance ou aucun effet secondaire attribuable à la DDS ou à la thérapeutique additionnelle par la dexaméthasone, la méthandrostenolone ou l'acide mefénamique utilisés dans cette étude.

Acknowledgments. This is the sixth major series of joint therapeutic studies in leprosy by the Leonard Wood Memorial and the Department of Health of the Republic of the Philippines. Generous assistance was received at the time of the study from Dr. A. C. Jovellanos, director of Eversley Childs Sanitarium, and Dr. A. Runez, director of the Central Luzon Sanitarium, and their staffs.

Financial support was received from U.S. Public Health Service grant E-199, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, and from the Leonard Wood Memorial.

Ciba Pharmaceutical Products, Inc. donated the dexamethasone, methandrostenolone (Dianabol) and the corresponding control tablets. Parke, Davis and Co. donated the drug and control tablets for mefenamic acid. 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. Bornhold, H. J. Personal communication and unpublished data from Ciba Research Laboratories.
2. 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.
3. 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) 173-182.
4. Doull, J. A., Rodriguez, J. N., Davison, A. R., Tolentino, J. G. and Fernandez, J. V. Clinical evaluation studies in lepromatous leprosy. Third series: nicotinamide and BCG vaccination as supplements to diaminodiphenyl sulfone (DDS). Internat. J. Leprosy **26** (1958) 219-235.
5. Doull, J. A., Rodriguez, J. N., Tolentino, J. G., Fernandez, J. V., Guinto, R. S., Rivera, J. N. and Mabalay, M. C. Clinical evaluation studies in lepromatous leprosy. Fourth series: 4,butoxy-4'dimethylaminodiphenyl thiourea (DPT), amodiaquin, and 4,4'-diaminodiphenyl sulfone (DDS) 2.5 mgm. and 4 mgm. per kg. of body weight. Internat. J. Leprosy **29** (1961) 291-317.
6. Doull, J. A., Tolentino, J. G., Rodriguez, J. N., Guinto, R. S., Rivera, J. N., Fernandez, J. V. and Mabalay, M. C. Clinical evaluation studies in lepromatous leprosy. Fifth series: diethyl dithiolisophthalate (Etisul) as a supplement to 4-4'diaminodiphenyl sulfone DDS). Internat. J. Leprosy **33** (1965) 186-205.
7. Gokhale, B. B., Kotnis, M. G., Kasbekar, P. V. and Marathe, S. V. Leprotic reactions and anabolic and anti-diabetic drugs. Leprosy Rev. **35** (1964) 91-96.
8. Guinto, R. S., Tolentino, J. G. and Doull, J. A. Clinical evaluation studies of the Leonard Wood Memorial. Objectives, methods and conclusions. Internat. J. Leprosy **32** (1964) 168-176.
9. Guinto, R. S., Tolentino, J. G. and Mabalay, M. C. Observations on erythema nodosum leprosum. Clinical evaluation studies in lepromatous leprosy. J. Philippine Med. Assoc. **38** (1962) 929-940. (*Reprinted in* Internat. J. Leprosy **31** (1963) 81-94.)
10. Reutner, T. F., Disken, R. A., Weston, K. and McAlpine, R. J. Clinical Investigation Bulletin, Experimental Compound CI-473, Parke, Davis and Co., 1960.
11. [World Health Organization] A guide to leprosy control. 1965, pp. 13-17.
12. [World Health Organization] WHO Expert Committee on Leprosy. Third Report. Tech. Rept. Series No. 319, 1966, pp. 7-10.