REPRINTED ARTICLE

OBSERVATIONS ON ERYTHEMA NODOSUM LEPROSUM[1]

CLINICAL EVALUATION STUDIES IN LEPROMATOUS LEPROSY

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The characteristic lesions of erythema nodosum leprosum (ENL) have been described by many leprosy workers, the first known description being that of Murata ([11]).[2] It is the most common reactional manifestation of lepromatous leprosy and may take an acute, subacute or chronic course. It occurs in lepromatous patients as crops of discrete erythematous nodules, more rarely as raised patches, varying in size from a few millimeters to four or five centimeters in diameter. The nodules are generally found on the face and extremities, less frequently on the trunk, and are usually tender to touch. The individual ENL nodules last from three or four days to a week or longer. Larger lesions take much longer to clear up, and they may even undergo vesiculation or abscess formation with subsequent ulceration. Multiple or recurrent attacks of ENL sometimes occur with great frequency, although some patients experience only a few short attacks. Moderate to severe ENL is frequently accompanied by intermittent fever, joint or bone pains, neuritis, and occasionally by iritis and lymphadenitis. Severe and prolonged attacks of this complication bring much discomfort and pain to the patient, and result in definite worsening of his condition.

The histopathology of ENL has been studied by, among others, Wade ([14]) who reported the lesser acute ENL lesions as consisting mostly of focal round-cell infiltrates, predominantly monocytic and with only slight edema and vascular changes; by Wolcott ([15]) who found slight change in the subcutaneous blood vessels and edema of the corium; and by Pepler *et al.* ([12]) who reported the most important feature of ENL to be a panniculitis and called it "panniculitis nodosa leprosa." In addition to infiltration by monocytes, leucocytes and plasma cells,

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[2] F. de P. Barrera and A. P. Chavaria, in the first description of lepra reaction as a syndrome, entitled The acute exanthem in leprosy [*Bull. Johns Hopkins Hosp.* **35** (1924) 147-153], discussed primarily the erythema nodosum leprosum condition.

Mitsuda ([9]) also found in ENL lesions lepra cells swollen with lipoid granules and containing lepra bacilli which were almost all in granular form, but such old cells exist in the site before the reaction occurs and are not an essential feature of it. In a recent study Helwig ([8]) reported that acute ENL lesions and classical erythema nodosum do not show identical pathologic features. The consensus seems to be that the pathologic changes seen in acute ENL are slight in relation to the rather violent inflammatory appearance of the lesions, but more marked changes occur in persistent lesions or after repeated reactions in the same site.

The true nature of the ENL reaction is still a matter of speculation. The prevailing opinion is that it is an allergic reaction resulting from sudden circulation of the bacilli or more probably of their breakdown products, the latter possibly as a consequence of therapy, particularly with sulfones. Although ENL occurs in untreated patients, it is widely believed that the occurrence of this complication has greatly increased since the advent of sulfone therapy. Among those of the opinion that ENL may be induced by sulfone treatment are Wolcott ([15]), Muir ([10]) and Davison ([2, 3]). Another prevalent belief is that the occurrence of ENL is of good prognostic significance. This view is apparently shared by Mitsuda ([9]). Wolcott ([15]), Muir ([10]) and Cochrane ([1]) have reported greater frequency of clinical and bacteriologic arrest following therapy in patients with ENL as compared to those in whom ENL was absent. Davison ([2, 3]) on the other hand, found the occurrence of ENL to be of definitely unfavorable prognosis to the underlying disease. Sometimes there are deep-seated subcutaneous nodules and chronic fibrous masses, a form of reaction called "erythema induratum leprosum" by Rodriguez ([13]).

PRESENT STUDY

The clinical evaluation studies in lepromatous leprosy (controlled drug trials conducted by the Leonard Wood Memorial and the Department of Health, Philippines), carried on at the Eversley Childs Sanitarium in Cebu since 1952, made possible this study of the more general aspects of ENL.

All observations were made and recorded by one of us (J.G.T.) over a period of nine years, 1952 to 1961, in the course of five series of these studies on four of which reports have been published ([4-7]). The findings are based on the experience of more than 1,100 patients, of whom 1,025 completed 48 weeks of observation and intensive treatment with sulfones, other drugs (dihydrostreptomycin, para-aminosalicylic acid, isonicotinic acid hydrazide, niacinamide, thiourea compound CIBA-1906, amodiaquin and Etisul, a mercaptan compound), and various combinations of drugs.

All patients in the five studies were clinically lepromatous, bacteriologically positive and lepromin (Mitsuda) negative at the outset. A small proportion were basically lepromatous (all had diffuse infiltrations) but had lesions which are now considered to have been of "borderline" nature. It was observed, however, that the patients with borderline lesions also developed ENL.

Together with detailed clinical and bacteriologic appraisals which were carried out in a uniform manner throughout the five series, the patients were examined for ENL dur-

ing the preliminary (pre-therapy) period and subsequently at regular intervals every eight weeks for six examinations, the last after the forty-eighth week of therapy. Between the periodic examinations, daily medical consultations were held in which patients were encouraged to report any untoward manifestations, including ENL. A review of the daily treatment records of the 1,025 patients concerned showed only some 30 instances of ENL occurring in patients in whom that condition was absent during the regular observation periods, an indication that relatively few transient or mild attacks occurring between the regular observation periods were missed.

The ENL reaction was graded and recorded as slight, moderate or severe in degree, according to well-defined but arbitrary criteria, defining the number and extent of skin lesions and other manifestations. The same criteria were applied in all the five series. In this report the relative severity of ENL observed during the therapy-observation period of 48 weeks has been determined by simply adding the numerical values of the ENL scores (0, 1+, 2+ and 3+) for the six regular observation periods (after 8, 16, 24, 32, 40 and 48 weeks of treatment) and dividing the scores into negative (0), slight (1- to 4-plus values), moderate (5- to 8-plus values) and severe (9- to maximum 18-plus values).

RESULTS

Broad features of ENL.—To determine possible factors predisposing to the occurrence of ENL, a series of tabulations was made of the frequency and relative severity of this complication in relation to sex and age, to the clinical and bacteriologic status of the patients at the outset, and to various clinical findings on preliminary examination. To avoid duplication, the figures in Tables 1 and 2 were limited to 859 lepromatous patients joining any one of the five drug-evaluation series for the first time and who completed the 48 weeks of therapy-observations to which this study was limited.

The figures of Table 1 show that ENL was definitely more frequent and more severe in the clinically and bacteriologically more-advanced patients than in those with slight lesions or low bacteriologic scores at the outset. ENL was present initially or occurred during the therapy period in 49.7 per cent of L1 cases, in 64.6 per cent of L2 cases, and in 77.4 per cent of L3 cases. ENL was likewise more severe in L2 and L3 cases (28.3%) than in L1 cases (10.6%). Similarly, with regard to bacteriologic scores (smears from eight sites, 2 nasal and 6 skin), ENL occurred in 48.5 per cent of patients with average scores of 1+ degree, in 59.1 per cent of those with 2+, in 69.1 per cent of those with 3+, and in 76.8 per cent of the patients with heavily positive 4+ smears. The degree of severity of ENL is likewise shown in Table 1 to have increased in direct proportion to the degree of bacteriologic advancement. A high positive correlation was thus established between the occurrence of ENL, both in frequency and severity, and the degree of clinical and bacteriologic advancement of the underlying lepromatous condition.

As is also to be seen in Table 1, there appears to be a small but appreciable sex difference in both the frequency and relative severity of ENL. Of 247 female patients, 182 or 73.7 per cent had ENL at the outset or developed it during the therapy period, compared to 371, or 61.9 per cent, with similar findings among 612 male patients. Similarly, 33.6

TABLE 1.—*Frequency and relative severity of erythema nodosum leprosum in relation to clinical and bacteriologic status on preliminary examination, and to sex. Five clinical evaluation series combined, Eversley Childs Sanitarium, Cebu, 1952 to 1961.*

Findings on preliminary examination	Number of new patients	Per cent with erythema nodosum leprosum (ENL present initially or developing during treatment period of 48 weeks.)			Mean bacteriologic score, preliminary examination
		Slight	Moderate to severe	Total	
Clinical status:					
Slight (L1)	169	39.1	10.6	49.7	13.8
Moderate (L2)	447	36.2	28.4	64.6	18.4
Advanced (L3)	243	49.4	28.0	77.4	21.0
Bacteriologic status (bacteriologic scores for 8 sites,[a] denoting degree of advancement):					
0.5 - (+)	130	38.5	10.0	48.5	5.7
8.5 - 16.0 (2+)	237	38.0	21.1	59.1	12.6
16.5 - 24.0 (3+)	259	41.7	27.4	69.1	20.6
24.5 - 32.0 (4+)	233	42.9	33.9	76.8	28.5
Sex:					
Male	612	40.7	21.2	61.9	18.7
Female	247	40.1	33.6	73.7	17.1
Total	859	40.5	24.8	65.3	18.2

[a] Bacteriologic scores for 8 sites, 2 nasal and 6 skin, were determined by giving each smear an arbitrary numericail rating. Smears marked very scanty (v.s.) were given a grade of 0.5, those marked 1+ a grade of 1, 2+ a grade of 2, 3+ a grade of 3, and 4+ a grade of 4, thus ranging from 0.5 (v.s., 1 site) to a possible 32 (4+, 8 sites). Total scores were then divided into quartiles to denote the approximate degree of bacteriologic advancement of each patient.

Because of the high positive association between bacteriologic status and occurrence of ENL, mean bacteriologic scores have been added to Table 2 and ensuing tables to show comparability of the various groups of patients with regard to bacteriology.

per cent of the females had moderate to severe ENL, as against 21.2 per cent of the males. The excess frequencies in the females, 11.8 per cent for total ENL and 12.4 per cent for the greater severities, are 3.3 and 3.8 times their standard errors, respectively, and are thus significant in the statistical sense. Furthermore, the sex differences were observed separately in four of the five series. In one series, the fourth, the figures showed no difference between the sexes in total frequency, but there was a slight tendency towards greater severity in the females (68.6% total ENL and 31.4% severe ENL for 35 female patients vs. 67.1% total ENL and 28.2% severe ENL for 131 male patients).

Because of the high positive association between the occurrence of ENL and the clinical and bacteriologic advancement of the underlying disease, it was necessary to determine whether the sex differences seen in Table 1 might have been attributable to more advanced stages of lepromatous leprosy in the female patients as compared with the males. Among the 612 male patients, 50.0 per cent were L2 cases and 31.2 per cent were L3 cases, while among the 247 females the corresponding figures

were 57.1 per cent and 24.3 per cent. Similarly, the male patients were a shade more heavily positive bacteriologically at the outset; the mean bacteriologic scores were 18.7 for the male patients and 17.1 for the female patients. It thus appears that female lepromatous patients may be more susceptible than males to the development of ENL, either because of some inherent factor or some cause related to occupation or other feature of the environment.

No appreciable differences in frequency or severity of ENL were observed among the different age groups in the 859 patients, whose ages ranged from 10 to more than 50 years.

Table 2 shows the possible relationship between occurrence and relative severity of ENL attacks and various clinical findings on preliminary examinations of the patients. There is a definite positive correla-

TABLE 2.—*Frequency and relative severity of erythema nodosum leprosum in relation to various clinical findings on preliminary examination.*

Score denoting degree of clinical findings on preliminary examination	Number of new patients	Per cent with erythema nodosum leprosum (ENL present initially or developing during treatment period of 48 weeks.)			Mean bacteriologic score, preliminary examination
		Slight	Moderate to severe	Total	
Diffuse infiltration:					
0 (Neg.)	-----	-----	-----	-----	-----
1 - 5 (1+)	117	33.3	8.5	41.9	11.0
6 - 10 (2+)	520	41.5	25.4	66.9	17.8
11 - 15 (3+)	222	41.9	32.0	73.9	23.1
Macules:					
0 (Neg.)	521	40.7	30.5	71.2	18.5
1 - 4 (1+)	212	43.9	20.7	64.6	18.6
5 - 8 (2+)	113	36.3	8.8	45.1	16.5
9 - 12 (3+)	13	15.4	-----	15.4	16.4
Plaques:					
0 (Neg.)	540	40.7	28.3	69.0	17.4
1 - 4 (1+)	168	43.5	23.8	67.3	18.1
5 - 8 (2+)	98	35.7	15.3	51.0	20.8
9 - 12 (3+)	53	37.7	9.4	47.2	22.3
Atrophies:					
0 (Neg.)	676	42.2	25.3	67.5	18.4
1 - 2 (1+)	149	38.3	22.8	61.1	17.4
3 - 6 (2+ & 3+)	34	17.6	23.5	41.1	18.4
Contractures:					
0 (Neg.)	668	42.1	25.3	67.4	18.5
1 - 2 (1+)	145	39.3	22.8	62.1	17.1
3 - 6 (2+ & 3+)	859	21.7	23.9	45.6	18.4
Total	46	40.5	24.8	65.3	18.2

tion between ENL and the degree of diffuse infiltration. This finding is to be expected, however, because the degree of infiltration is also directly associated with advancement of the disease, as shown in Table 2 by the sharp increases in the mean bacteriologic score with each increasing degree of infiltration in the patients.

Of perhaps greater interest are the figures in Table 2 which show a fairly defiinte but inverse relationship between ENL and the presence in essentially lepromatous patients of macules and plaques, lesions which apparently tend more to the tuberculoid side of leprosy than to the lepromatous. The frequency and severity of ENL attacks were observed to decrease as the number of macules and plaques increased, but without a corresponding significant decrease in the bacteriologic scores, showing that this inverse relationship was not necessarily related to the underlying lepromatous condition. There was also a slight tendency for patients with atrophies and contractures of the extremities to develop less ENL than patients in whom these deformities were absent, again seen in Table 2, without being related to any decrease in the mean bacteriologic scores.

Association between prior sulfone therapy and presence of ENL on preliminary examination.—The drug evaluation trials could not be limited to previously untreated lepromatous patients. All patients treated previously with sulfones, however, were kept without treatment for a minimum period of two months before the start of each series. As a first approach to the inquiry into the possible effect of sulfone therapy on the occurrence of ENL, the exact amount of total sulfones previously taken by each patient was determined in particular relation to the presence of ENL in these patients at the outset. The results are given in Table 3.

TABLE 3.—*Frequency of erythema nodosum leprosum on preliminary examination in relation to total prior sulfone therapy.*

Clinical evaluation series	Number of patients	Without prior sulfone therapy[a]		With prior sulfone therapy					
				Little[b]		Much[c]		Total	
		No.	Per cent with ENL	No.	Per cent with ENL	No.	Per cent with ENL	No.	Per cent with ENL
First (1952)	360	65	10.8	139	22.3	156	29.5	295	26.1
Second (1953)	259	93	32.3	53	26.4	113	43.4	166	38.0
Third (1955)	209	85	16.5	32	37.5	92	39.1	124	38.7
Fourth (1957)	226	33	6.1	72	20.8	121	30.6	193	26.9
Fifth (1960)	126	110	7.3	16	23.1	.....	.....	16	23.1
Total	1180	386	15.8	312	24.0	482	34.9	794	30.6

[a] Without prior sulfone therapy: includes a few patients with less than 1 gm. DDS or 5 gm. Diasone as total prior therapy.

[b] Little prior sulfone therapy: 1 gm. to maximum 10 gm. DDS or 5 gm. to 50 gm. Diasone.

[c] Much prior sulfone therapy: more than 10 gm. DDS or 50 gm. Diasone.

No positive association was observed between prior sulfone therapy and the degree of clinical or bacteriologic advancement of the disease on preliminary examination.

In the five series combined, ENL was present on preliminarly examination in 25.8 per cent of the 1,180 patients entering the study. As seen in Table 3, this reactional condition was present at the outset in 15.8 per cent of 386 patients who had never received treatment with sulfones, and in 30.6 per cent of 794 patients who had been previously treated with this drug. Dividing the latter group into those with *little* or *much* prior therapy, 24.0 per cent of 312 patients with *little* prior therapy and 34.9 per cent of 482 patients with *much* prior therapy were found with ENL initially. The increases in frequency of ENL which might be attributed to prior sulfone therapy are therefore not very large (8.2% little, 19.1% much and 14.8% total), although, in view of the large number of observations, the two larger differences are highly significant from a statistical standpoint, being well over three times their standard deviations. It thus appears that even if prior sulfone therapy had effected an increase in the frequency of ENL observed on preliminary examination of the patients, the increase was not as much as is generally attributed to sulfone treatment.

Because of the high positive association seen in Table 1 between occurrence and severity of ENL and clinical or bacteriologic advancement of the disease, an effort was made to determine if the underlying lepromatous condition was less advanced in the untreated patients than in those who had already received treatment. On preliminary examination of 386 untreated patients, 17.4 per cent were classed as L1, 45.1 per cent as L2, and 37.5 per cent as L3 in degree of clinical advancement, and 67.9 per cent had total bacteriologic scores of 3+ and 4+ degree. The corresponding figures for 794 previously treated patients were 24.3 per cent L1, 54.3 per cent L2, and 21.4 per cent L3; and 49.1 per cent had bacteriologic scores of 3+ and 4+ magnitude. This shows that the higher frequency of ENL at the outset in the previously-treated patients was not due to more advanced stages of the disease or to heavier loading with bacilli.

Frequency and relative severity of erythema nodosum leprosum occurring during the therapy period in relation to type of antileprosy drug.—The results of a more direct approach to the possible effect of therapy on the development of ENL are given in Table 4. A total of 752 lepromatous patients in whom ENL was *absent* on preliminary examination completed 48 weeks of therapy and observations in the five clinical evaluation series. Table 4 gives frequencies and relative degrees of severity of ENL occurring during the therapy period according to therapy groups.

It is seen that of the two most commonly used sulfones, DDS appeared to have induced somewhat more ENL than Diasone, although not necessarily of greater severity. Of 77 patients under Diasone therapy (6 gm. weekly), 48.1 per cent developed ENL as against 65.2 per cent of 138 patients under maximum DDS therapy (1.2 gm. weekly) for

TABLE 4.—*Frequency and severity of erythema nodosum leprosum developing during the therapy period (48 weeks) in patients* without ENL *on preliminary examination in relation to type of therapy.*

Therapy groups and maximum weekly doses of drugs on clinical trial for 48 weeks	Patients without ENL on preliminary examination	Per cent developing ENL during therapy period			Mean bacteriologic score, preliminary examination
		Slight	Moderate to severe	Total	
(a) *Sulfones, alone or in combination with other drugs:*					
Diasone (6 gm.)	77	29.9	18.2	48.1	15.2
Diasone (6 gm. & DHSM (3 gm.); Diasone (6 gm.) & INH (3.5 gm.)	83	37.4	8.4	45.8	15.0
DDS (1.2 gm.)[a]	138	48.6	16.7	65.2	17.4
DDS (1.2 gm. & nicotinamide (3 gm.)[b]	60	50.0	16.7	66.7	16.3
DDS (reduced dose, 0.75 gm.)	80	32.5	20.2	52.5	22.3
DDS (0.75 gm.) & Etisul (15 gm. by inunction)	47	36.1	25.6	61.7	24.7
Total, sulfone group	485	40.0	16.9	56.9	18.0
(b) *Nonsulfones:*					
Dihydrostreptomycin (3 gm.)	45	33.3	8.9	.42.2	14.6
DHSM (3 gm.) & PAS (90 gm.); DHSM (3 gm.) & INH (3.5 gm.); Streptohydrazide	110	39.1	11.8	50.9	15.5
Thiourea compound CIBA-1906 (18.0 gm.)	31	35.5	19.3	54.8	21.2
Amodiaquin (1.2 gm.)	40	42.5	12.5	55.0	23.0
Total, nonsulfone group	226	38.0	12.4	50.4	17.4
(c) *Untreated control group:*					
CESLU (placebo group, first series)	41	39.0	7.3	46.3	14.2
Totals	752	39.4	15.0	54.4	17.6

[a] Includes 14 patients given BCG vaccination in addition to DDS.

[b] Includes 17 patients given BCG vaccination in addition to DDS and nicotinamide.

the same length of time. The observed difference, 17.1 per cent, is 2.4 times its standard error. A reduced dose of DDS (0.75 gm. weekly) given to 80 patients resulted in a slightly lower ENL attack rate of 52.5 per cent, in spite of the fact that this group was more heavily positive bacteriologically than the group of 138 patients under maximum DDS therapy and therefore could have been more prone to develop ENL. Drugs other than sulfones (dihydrostreptomycin, isonicotinic acid hydrazide, nicotinamide and Etisul) given in combination with sulfones did not appear to have an appreciable effect on the resulting attacks of

ENL; nor did BCG vaccination, which was given to 31 patients under DDS therapy.

It is also evident in Table 4 that the nonsulfone drugs used singly or in various combinations in the five series (DHSM, PAS, INH, CIBA-1906 and amodiaquin) did not seem to have provoked the occurrence of ENL to a degree significantly different from that observed in patients under Diasone therapy, although the relatively small number of 31 patients under therapy with the thiourea compound CIBA-1906, and the 40 patients under the antimalarial drug amodiaquin, were both more heavily positive as shown by their mean bacteriologic scores, and thus could have been more inherently susceptible to ENL than the groups with lower bacteriologic scores. Although the number is small, it should be particularly noted in Table 4 that ENL occurred in no less than 46.3 per cent of 41 patients kept untreated for 48 weeks (placebo group, first series, 1952), making possible an important comparison between treated and untreated patients.

The clinical and bacteriologic appraisals at the end of the therapy period showed beyond doubt that the antimalarial drug amodiaquin was more or less inactive as an antileprosy drug, so that the patients under amodiaquin therapy might, in effect, almost be considered another untreated control group. The ENL attack rate for 40 patients under amodiaquin therapy was, nevertheless, as high as 55.0 per cent. In view of the above observations, a finding of this study bears emphasizing: even at maximal doses the sulfones may not necessarily induce as much ENL as is generally believed.

Course of pre-existing erythema nodosum leprosum in patients undergoing therapy.—Of 1,025 patients completing 48 weeks of various therapies, 273 already had ENL at the outset but were well enough to continue with the drug trials. Among these patients in whom ENL was present on preliminary examination, 59.0 per cent had ENL lesions of slight degree, 36.6 per cent of moderate degree, and only 4.4 per cent had this reactional condition in a severe degree. Table 5 gives the results of an attempt to show the effect of various therapies on the course of the pre-existing ENL.

As in the preceding table, it would appear from the findings in Table 5 that, in patients with pre-existing ENL, this reactional condition underwent a somewhat more severe course under DDS therapy than under Diasone. The course of ENL in such patients under Diasone was also comparable and not appreciably more severe than for those in the nonsulfone therapy groups. The experience of only 14 patients (with ENL on preliminary examination) in the untreated control group is very limited, but it would appear that the pre-existing ENL had a milder course in this untreated group than in the others. On the other hand, all of the 12 patients under amodiaquin continued to have attacks of ENL during the therapy period in spite of the fact that amodiaquin was in-

TABLE 5.—*Frequency and relative severity of erythema nodosum leprosum during the therapy period (48 weeks) in patients with ENL on preliminary examination, by therapy groups.*

Therapy groups	Patients with ENL on preliminary examination	Per cent with ENL during therapy period			Mean bacteriologic score, preliminary examination
		Slight	Moderate to severe	Total	
(a) *Sulfone groups:*					
Diasone, alone or combined with DHSM & INH	86	30.2	58.1	88.3	16.5
DDS, alone or combined with nicotinamide and Etisul	101	22.8	70.3	93.1	17.8
Total, sulfone group	187	26.2	64.7	90.9	17.2
(b) *Nonsulfone groups:*					
DHSM, alone or combined with PAS & INH	47	25.5	63.9	89.4	14.1
Thiourea compound (CIBA-1906)	13	23.1	69.3	92.4	22.8
Amodiaquin	12	58.3	41.6	100.0	21.6
Total, nonsulfone group	72	30.6	61.1	91.7	16.9
(c) *Untreated control group:*					
CESLU (placebo group, first series)	14	21.4	28.5	50.0	13.9
Totals	273	27.1	61.9	89.0	17.0

effective as an antileprosy drug.

A comparison of the findings in Tables 4 and 5 will show that, regardless of the type of therapy, ENL occurred with much greater frequency and severity in patients in whom this reactional condition was already present at the outset than in those in whom it was absent. Among the 752 patients without ENL on preliminary examination this complication occurred in 54.4 per cent, and in 15.0 per cent the attacks were classed as moderate to severe in degree. For the 273 patients with pre-existing ENL lesions, this reactional condition continued during the therapy period in 89.0 per cent, and in 61.9 per cent the attacks were of moderate to severe degree. In the experience of five clinical evaluation series, the occurrence and course of ENL during the therapy period was therefore influenced more greatly by the presence of this complication at the outset than by the type of therapy, whether of sulfone or nonsulfone nature.

Association between occurrence of ENL and clinical or bacteriologic improvement after 48 weeks of therapy (prognostic significance of ENL).—The observed association between the occurrence of ENL and the degree of clinical or bacteriologic improvement after 48 weeks of various therapies is shown in Table 6.

TABLE 6.—*Association between occurrence of erythema nodosum leprosum and observed clinical and bacteriologic improvement after 48 weeks of various therapies.*

Clinical evaluation series	Patients completing 48 weeks' therapy	With ENL			Without ENL		
		Number of patients	Per cent showing clinical improvement[a]	Per cent showing definite bacteriologic improvement[b]	Number of patients	Per cent showing clinical improvement[a]	Per cent showing definite bacteriologic improvement[b]
First (1952)	328	204	71.1	36.3	124	71.8	54.8
Second (1953)	228	153	43.1	52.3	75	58.7	70.1
Third (1955)	175	132	57.6	81.8	43	79.1	88.4
Fourth (1957)	192	130	46.2	34.6	62	74.2	41.9
Fifth (1960)	102	63	39.7	14.3	39	76.9	50.0
Five series combined	1025	682	54.5	46.3	343	70.8	60.1

[a] Clinical improvement: all patients slightly, moderately or markedly improved, according to the consultant leprologist's final appraisal.
[b] Definite bacteriologic improvement: all patients showing a reduction of 50 per cent or more in total bacteriologic scores.

Of 682 patients in whom ENL occurred, 372 or 54.5 per cent were found to have shown definite clinical improvement after the period of therapy, according to the impartial final appraisal of the consultant leprologist (Dr. J. N. Rodriguez). Among the 343 patients, on the other hand, without ENL at any time, 243 or 70.8 per cent showed the same degree of clinical improvement.

Similarly, considering a reduction of 50 per cent or more in the bacteriologic scores as definite bacteriologic improvement, 46.3 per cent of the 682 patients with ENL improved bacteriologically as against 60.1 per cent of the 343 patients without ENL.

The difference in favor of patients without ENL, 16.3 per cent for the clinical and 13.8 per cent for the bacteriologic factors, though not large, are significant in the statistical sense, each being more than four times its standard error. Contrary to prevailing opinion, our findings agree with those of Davison in that the occurrence of ENL, at least for the duration to which this study is limited, is definitely not of good prognosis. Except for the clinical appraisals for the first series, as seen in Table 6, our findings were consistent in this respect in all the five series.

SUMMARY

A study is reported of the frequency and relative severity of erythema nodosum leprosum observed in an appreciable number of essentially lepromatous patients in five clinical evaluation series conducted at the Eversley Childs Sanitarium, Cebu, from 1952 to 1961.

A preliminary study of the broad features of ENL showed that female patients were slightly more subject to attacks of this reactional condition than were male patients. No age differences in frequency or severity occurred. There was a definite positive association between the occurrence of ENL and the degree of the clinical and bacteriologic advancement of the underlying lepromatous condition. An inverse relationship was also shown between the occurrence of ENL and the presence in the patients of macules and plaques, and also of atrophies and contractures.

A positive relationship was observed between prior sulfone therapy and the presence of ENL at the time of preliminary examination, but the increase in frequency of ENL attributable to prior treatment with sulfones was not as large as is commonly reported.

In patients without ENL on preliminary examination, this complication occurred with slightly greater frequency under DDS therapy than under Diasone. The frequency of ENL occurring in patients under treatment with various nonsulfone drugs was not appreciably different from that observed under Diasone therapy.

The occurrence and course of ENL attacks observed during the 48-week therapy period was apparently influenced more greatly by the

presence of this reactional condition at the start of the experiments than by the type of therapy.

Clinical and bacteriologic improvement after 48 weeks of various therapies was appreciably higher for patients in whom ENL was absent than in those in whom ENL occurred.

RESUMEN

Preséntase un estudio de la frecuencia y relativa gravedad del eritema nudoso leproso observado en una proporción apreciable de enfermos esencialmente lepromatosos de cinco series de justipreciación clínica dirigidas en el Sanitario Eversley Childs, de Cebú, de 1952 a 1961.

Un estudio preliminar de las características más destacadas de ENL reveló que las mujeres eran ligeramente más propensas que los varones a accesos de ese estado reactivo. No hubo diferencias en freuencia o gravedad de acuerdo con la edad. Se observó una asociación positiva bien definida entre la existencia de ENL y la intensidad de la agravación clínica y bacteriológica notada en el subyacente estado lepromatoso. También se mostró una relación revés entre la existencia de ENL y la presencia en los enfermos de manchas y placas, y además de atrofias y contracturas.

Se observó una relación positiva entre la sulfonoterapia previa y la presencia de ENL at hacer el examen preliminar, pero el aumento en la frecuencia de ENL imputable al tratatemiento anterior con sulfonas no es tan elevado como se ha comunicado.

En los enfermos sin ENL en el examen preliminar, sobrevino esta complicación con una frecuencia ligeramente mayor bajo la terapéutica con DDS que bajo la Diasona. La frecuencia de ENL observada en los enfermos bajo tratamiento con varias drogas que no son sulfonas no fué apreciablement distinta de la revelada bajo terapéutica con la Diasona.

La ocurrencia y la evolución de los accesos de ENL observados durante el período de 48 semanas de terapéutica fueron aparentemente más afectadas por la presencia de este estado reactivo al iniciarse los experimentos que por la forma de terapéutica.

La mejoría clínica y bacteriológica al cabo de 48 semanas de varias terapéuticas fué apreciablement mayor para los enfermos en quienes no existía ENL que en aquéllos en que lo hubo.

RESUMÉ

Cette étude relate la fréquence et la sévérité relatives de l'erythème nouveux lépreux observé sur un nombre important de malades lépromateux lors de cinq séries d'essais thérapeutiques poursuivis à l'Eversley Childs Sanatarium, à Cebu, de 1952 à 1961.

Une étude préliminaire des caractéristiques générales de l'ENL a montré que les malades de sexe féminin étaient légèrement plus prédisposées à souffrir de réactions que les malades masculins. On n'a pas noté de différence quant à la fréquence des épisodes ni quant à leur sévérité, par rapport l'âge. Il y a eu association positive nette entre l'apparition d'ENL et le degré de sévérité des symptômes cliniques et bactériologiques de la lèpre lépromateuse. On a également mis en évidence une relation entre l'apparition d'ENL et la présence, chez les malades, de macules et de plaques, ainsi que d'atrophies et de contractures.

Un rapport existe entre la présence d'une thérapeutique sulfonée dèjà entamée et l'observation d'ENL au moment du premier examen. Néanmoins, l'augmentation dans la fréquence d'ENL attribuable à un traitement sulfoné antérieur n'a pas été aussi marquée qu'il n'est généralement rapporté. Chez les malades sans symptômes d'ENL lors de l'examen préliminaire, cette complication est apparue un peu plus fréquemment au cours du traitement par la DDS que lorsque la Diasone a étó utilisée. La fréquence de l'ENL chez des malades traités avec diverses médications non-sulfonées n'a pas montré de différence appréciable par rapport à celle enregistrée avec la diasone.

L'apparition et l'évolution des épisodes d'ENL enregistrés durant la période thérapeutique de 48 semaines ont, semble-t-il, été davantage sous la dépendance d'antécédents réactionnels semblables au début de l'observation que determinées par la sorte de traitement administré.

L'amélioration clinique et bactériologique après les 48 semaines de traitements de divers genres a été nettement plus marqué chez les malades sans épisodes d'ENL que chez ceux qui en ont souffert.

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