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IS ERYTHEMA NODOSUM LEPROSUM A FAVORABLE OCCURRENCE?

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Erythema nodosum leprosum (ENL), which Pepler, Kooij and Marshall (8) concluded is a form of panniculitis and have called "panniculitis nodosa leprosa," occurs only in patients with the lepromatous type of leprosy as an acute, subacute or chronic skin eruption, with or without fever. It is characterized by showers of dusky red nodules, 0.5 to 4 cm. in diameter, on the limbs, the face, and less often the trunk. They last in acute cases from a few hours to several weeks. Recurrent attacks are the rule. Although ENL occurs in untreated patients it is much more common after treatment, and its incidence has greatly increased since the advent of sulfone therapy.

It is a widely held belief that the occurrence of ENL is a favorable sign. This opinion is chiefly based on the following observations.

Wolcott (9), on analyzing 248 cases of leprosy in which ENL occurred, found an obvious correlation between the institution of the sulfone treatment and the appearance of the reaction: 7 per cent occurred before that treatment was inaugurated, and 93 per cent afterward. In several instances the clinical and bacteriological arrest of leprosy following closely upon repeated and severe attacks of ENL was striking. On these grounds Wolcott suggested that the occurrence of ENL indicates an increasing resistance to the disease.

Muir (7) found that in reacting cases the bacilli are phagocytosed by monocytes and in the more severe reactions by polymorphonuclear leucocytes, while sometimes small abscesses full of lepra bacilli and pus cells are discharged, thus bringing about much more rapid elimination of bacilli than in the nonreacting cases. He points out that the reaction caused by DDS should be distinguished from the ordinary classical form of leprosy reaction, for while the latter results in deterioration of the patient's condition, the former leaves him better off after each successive attack. Muir does not use the term erythema nodosum leprosum, although it is obvious that he is discussing chiefly that condition. He recommends that the reaction be deliberately induced by means of sufficient amounts of DDS or iodides.

Erickson (3) takes the same view. The committee on classification of the Madrid Congress (6) stated: "Erythema nodosum leprosum is characterized by the appearance of erythematous nodular skin lesions, accompanied at times by fever, and as a rule has a favourable prognosis".

Gramberg (4), however, has not supported this view. According to his experience ENL is an annoying complication.

In observing our patients with ENL some doubt arose about the favorable significance of the condition, and the investigations here reported were made.

PERIOD BEFORE NEGATIVITY IN PATIENTS WHO DID AND
WHO DID NOT SHOW ENL

For the purpose of this investigation the term "period before negativity" is used to signify the period from the beginning of treatment until the disease is declared arrested. We do not use the term "cured" in reference to our leprosy patients, but if signs of clinical activity are absent the disease is declared "arrested" when bacteriological examinations have been negative for a minimum period of twelve months. It is difficult to define clinical activity, as the usual stigmata of lepromatous leprosy do not always resolve completely. A patient who is entirely negative bacteriologically may still show pendulous ears and an apparently infiltrated face, including rugae of the forehead (Fig. 1). Obviously, the development of new lesions or the swelling or extension of old lesions is taken as a sign of clinical activity. We now consider that the occurrence of acute ENL is also a sign of clinical activity, though we have had two instances where that condition developed and bacilli could not be demonstrated. That is very exceptional.

The patients selected for this present study comprised the lepromatous cases that were involved in the Leonard Wood Memorial Clinical Evaluation Studies, first and second series. The results of these studies have been reported on by Doull (1) and Doull and associates (2). There was a total of 342 Westfort patients in these studies, of whom 97 had been declared arrested by August 1955. As shown in Table 1, the 97 arrested cases

TABLE 1.—Average period before negativity in 97 arrested
lepromatous cases, without and with ENL.^a

Treatment series and sex	Without ENL		With ENL	
	No. of arrested cases	Average period (months)	No. of arrested cases	Average period (months)
First, males	11	64	36	76
First, females	4	51	29	73
Second, males	5	55	6	66
Second, females	3	58	3	71
Totals	23	57	74	72

^a Period before negativity signifies the time between beginning of treatment and the time when the disease was declared arrested.

comprised 23 who had never shown the ENL reaction, and 74 who had had ENL. The average period before negativity of the former group was 57 months, and that of the latter group 72 months.

STATISTICAL ANALYSIS OF THE RESULTS

Because of the great number of ties among the observations, Wilcoxon's nonparametric test was used for a statistical analysis.¹ Testing the hypothesis that no difference (null) exists in the time before the arrest of the disease between the patients without ENL and those with ENL, the following results were found.

For the first group of males the null hypothesis could be rejected on a 1 per cent level, and for the first group of females it could be rejected on a 1.5 per cent level of significance. The second groups of males and females consist of too few observations to find any significant deviation from the null-hypothesis on the 5 per cent level. Testing the four groups of no ENL against each other, no indication of any difference between the groups could be found. Also, no difference could be found between the four groups with ENL.

Thus, testing all the 23 observations with no ENL against the 74 observations with ENL, a highly significant difference was found ($P = 0.00001$). In this case Student's t -test was also applied, and by that method the null-hypothesis could be rejected at the 0.000,000,1 per cent level of significance.

Consequently, there exists a highly significant difference in the period before negativity between the patients with no ENL and the patients with it.

It appears, therefore, that ENL retarded the elimination of the bacilli in the cases involved in this investigation. Moreover, four deaths occurred in the group of patients with ENL, and none in the group without it.

We also find that the period before negativity influences the incidence of ENL. In the cases under review, the first series group had been under observation for an average of 6 years, and the incidence of ENL was 63 per cent. Those in the second series group were under observation for an average of 3-½ years, and they had an incidence of 50 per cent.

INFLUENCE OF THE DEGREE OF ENL ON THE PERIOD BEFORE NEGATIVITY

Regarding the degree of ENL, the outcrops of lesions may last, as previously stated, from a few hours to several weeks. The severity of the condition varies between mild, moderate and severe. In mild ENL we may find a few transient spots whose presence is often unknown to the patient.

¹ H. R. van der Vaart, Gebruiksaanwijzing voor de toets van Wilcoxon, Rapport S.32(M4) 1950, Statistische Afdeling, Mathematisch Centrum, Amsterdam. D. Wabeke and C. van Eeden, Handleiding voor de toets van Wilcoxon, Rapport S.176(M 65 en M 65a) 1955, Statistische Afdeling, Mathematisch Centrum, Amsterdam.

In the moderate degree the lesions are of longer duration, are more nodular in character, and sometimes—but not necessarily—they are tender on palpation (Fig. 2). In the severe degree the lesions are painful, even crippling to the patient; they are tender to touch, and are accompanied by neuritis and sometimes arthritis. The nodules may vary in size from 5 to 40 mm. in diameter. They occasionally have flattened, dusky centers, suggestive of erythema multiforme (Fig. 3). The liver, spleen and testes may be tender. Temperature is elevated, and the patient is unable to sleep. The lesions may break down to extrude a pus-like material. Puckered scars remain. An examination of this so-called pus shows that the extruded matter is mostly liquefied fat. This substantiates the conclusion that ENL is really a panniculitis.

In the process of resolution the mild degrees may resolve without any residue. In the moderate and severe degrees the skin over the lesions usually desquamates. Resolution may then become complete, or a slightly tender erythematous infiltrate may be left. This is the subacute stage, and these infiltrations are frequently the sites of recrudescence. The chronic stage is reached when firm subcutaneous nodules are palpable, but often invisible, or when the indurations remain as dusky or often blackened, infiltrated, coalesced masses which are very resistant to treatment.

Analysis of the data of the cases which exhibited ENL with respect to the influence of the degree of the condition on the period before negativity results in the figure shown in Table 2. From these it is evident that ENL had little if any effect in that respect.

THE PART OF DRUGS IN THE EVOLUTION OF ENL

It has been suggested that ENL may be an allergic reaction to the sulfones, and that the production of allergy in an anergic individual (an-

TABLE 2.—*Influence of the degree of ENL on the length of the period before negativity.*

Degree of ENL	Number of patients	Average period (months)
Mild	26	74
Moderate	21	72
Severe	17	76

ergic to *M. leprae*) may be the cause of the efficacy of the sulfones in the treatment of leprosy.

We agree with Wolcott's findings that the incidence of ENL has been greatly increased since the introduction of the sulfones. As said, he reported that in the presulfone days its incidence was 7 per cent, and that afterward it was 93 per cent.

Our patients under discussion had been divided among various treatment groups. The drugs used were diasone, DDS, streptomycin, PAS, INH, and combinations of these drugs. No particular treatment group produced results superior to those of the other groups. None of the treatments was inert. No significant differences in occurrence of ENL in the various treatment groups were found.

In our institution we have approximately 500 lepromatous and borderline patients, and 500 other patients of nonlepromatous types. We group the borderlines with the lepromatous. All of the patients have been subjected to the various lines of treatment under review. No kind of treatment has ever produced ENL in our nonlepromatous patients, despite the fact that approximately 50 per cent of them give negative skin reactions to the Dharmendra antigen (Mitsuda reaction). On the other hand, we have instances of new, untreated lepromatous patients showing ENL.

Our experience leads to the conclusion that ENL is not a reaction to one class of drugs, but is provoked by all drugs which are not inert against *M. leprae*; and that the longer these drugs operate, the greater is the likelihood that ENL will occur.

BACTERIOLOGICAL INDEX OF CASES WITH AND WITHOUT ENL

By August 1955 the first series had been under special observation and treatment for 32 months, and the second series for 24 months. The patients were divided into two groups: (1) those who entered the project with ENL or who developed it later, and (2) those who never showed ENL. The combined bacteriological index of each group was calculated for the first six months of the project and for the six months ending September 1955.

The period of six months was chosen because our routine bacteriological examinations ("bacteriological checks") are done at two-monthly intervals. Skin smears are taken from various sites, and the degree of positivity of each smear is estimated from 4+ down to negative, as detailed by Doull (1). The bacteriological index is the sum of the degrees of positivity at each examination.

These findings are by no means consistent, owing to various sources of error, e.g.: (a) the technique of the person making the smear, (b) the selection of the particular site for the incision, (c) the staining and decolorizing of the slide, and (d) the acumen of the person reading the slide. It is for this reason that an average of three bacteriological examinations was used in this analysis.

The bacteriological indices of the patients without ENL and those with the condition, in each series, are shown in Table 3.

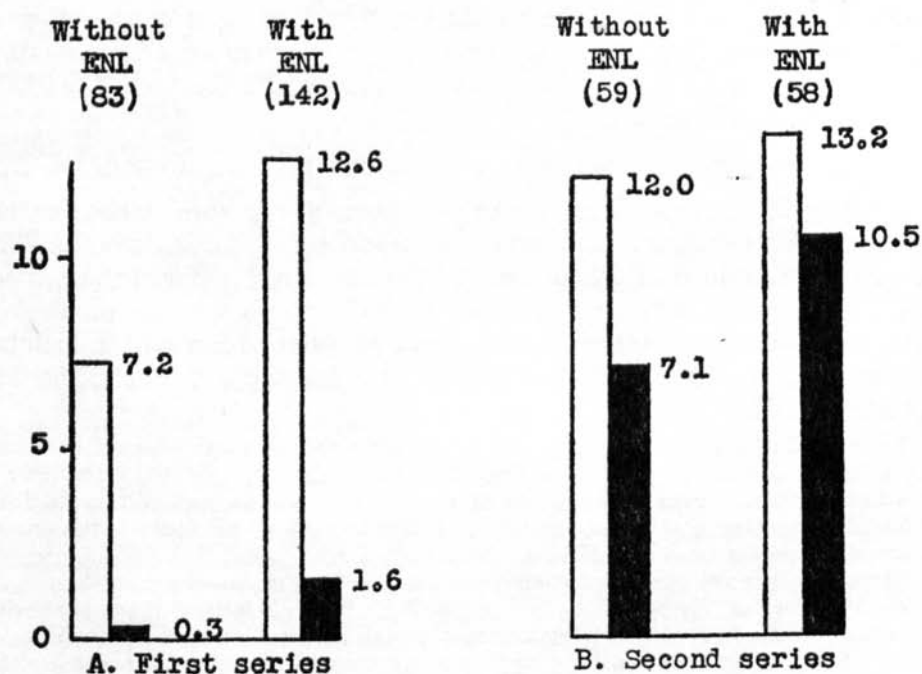
It will be noted that in each series the cases without ENL commenced with fewer bacilli on the average than did those in the ENL group. The difference was most marked in the first series cases, as is shown graphically in Text-fig. 1.

The first-series patients had had extensive sulfone treatment prior to the commencement of the project, and this probably accounts for the overall more rapid decrease in their bacillus counts. It will be noted, also, that the average duration of treatment in the second series was shorter.

TABLE 3.—Average bacteriological indices of patients with and without ENL.

Series	Treatment (months)	Without ENL			With ENL		
		No. of cases	Bact. index		No. of cases	Bact. index	
			Before	After		Before	After
First	32	83	7.2	0.3	142	12.6	1.6
Second	24	59	12.0	7.1	58	13.2	10.5

From these findings it is clear that the bacilli took longer to be eliminated in the ENL groups than in the others, and we may therefore conclude that ENL is of bad prognostic significance.



TEXT-FIG. 1. Average bacteriological indices of patients without and with erythema nodosum leprosum, before treatment (open columns) and after treatment (solid columns). A, first series; B, second series. (For duration of treatment, see Table 3.)

COMMENT

The longer period before negativity and the higher bacteriological index for the group of patients with ENL show that the occurrence of ENL is *not* a favorable sign.

The occurrence of four deaths in the group of patients with ENL is in agreement herewith. These findings differ from the generally-expressed opinion that ENL is a favorable occurrence.

The cause of ENL is obscure. It resembles the Herxheimer reaction, although the attacks last longer and may recur for years.

As said, Pepler *et al.* have recently shown that ENL is a kind of panniculitis. In the literature (e.g., Kooij (5)) there are several reports of cases of panniculitis that ended fatally. It is therefore not surprising to find that ENL is an unfavorable reaction which should be controlled, not promoted.

SUMMARY

1. The average period of treatment until the disease could be declared arrested, in these cases in which that came about, was 57 months in the 23 patients without ENL, but 72 months in the 74 such patients with ENL. Statistically this difference in time is highly significant. There were more of these arrested patients with ENL than without it.

2. The average bacteriological index of the whole lot of ENL cases (200 patients) was higher than that of the whole group without ENL (142 patients), and the time required for the elimination of the bacilli was longer for the ENL group.

3. A mild degree of ENL retarded the arrest of the disease as much as did a severe degree of the condition.

4. The incidence of ENL increased with the duration of the disease.

5. There seems to be no great differences in occurrence of ENL among the various treatment groups (diasone, DDS, streptomycin, PAS, INH).

6. ENL is not a reaction to the drug treatment alone, as it does not occur in nonlepromatous cases under any type of treatment.

7. ENL is not a favorable sign.

SUMARIO

1. El período medio de tratamiento hasta poder declarar la enfermedad estacionada en los casos en que sucedió esto, fué de 57 meses en los 23 enfermos sin ENL, pero de 72 meses en los 74 con ENL. Estadísticamente, esta diferencia en tiempo es muy importante. Hubo más de estos enfermos estacionados con ENL que sin él.

2. El índice bacteriológico medio de todo el lote de casos con ENL (200 enfermos) fué más alto que el de todo el grupo sin ENL (142 enfermos) y el tiempo requerido para la eliminación de los bacilos fué más largo para el grupo con ENL.

3. Un grado leve de ENL retardó el estacionamiento de la enfermedad tanto como una forma grave de la dolencia.

4. La incidencia de ENL aumentó con la duración de la enfermedad.

5. No parece que haya mucha diferencia en la ocurrencia de ENL entre los varios grupos terapéuticos (diasona, DDS, estreptomicina, PAS, INH).

6. ENL no es una reacción a la farmacoterapia sola, pues no se observa en casos no lepromatosos con ninguna forma de tratamiento.

7. ENL no es un signo favorable.

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DESCRIPTION OF PLATE

PLATE 4

FIG. 1. Residual infiltration of the face of a lepromatous leprosy patient who has become clinically and bacteriologically negative (arrested case).

FIG. 2. Nodules on the face of a patient with acute erythema nodosum leprosum of moderate degree.

FIG. 3. Erythema nodosum leprosum lesions on the back resembling erythema multiforme.



PLATE 4