A BACTERIOLOGIC STUDY OF ERYTHEMA NODOSUM LEPROSUM

D. S. Ridley, M.D.

Hospital for Tropical Diseases
London, England

Among the various episodes which punctuate the course of lepromatous leprosy there is an eruption which, on account of its clinical appearance, was compared by Danielssen and Boeck [2] with erythema nodosum as early as 1848, and by Hansen and Looft [7] in 1894. In 1912, Murata [15] gave a clear description, with histologic report, of the condition which he designated erythema nodosum leprosum (ENL). Because of objections to this name, or lack of familiarity with it, many other terms have been used none of which has gained general acceptance. For many years, ideas on the subject were imprecise, as shown by the general application of "lepra reaction" or the like to all of the reactional conditions of leprosy. The fullest description of the "acute exanthem" of leprosy is that of Barrera and Chavarria [1], and in it many of the features of ENL are to be recognized. The literature of the earlier period is reveiwed by Klingmüller [9], and Green [6] gives some references. Other noteworthy papers include one by Stein [23], and some to be mentioned later.

Despite differences in emphasis, there is a measure of agreement on many points. It is agreed that ENL occurs only in lepromatous leprosy; that it is liable to be precipitated by chemotherapy, potassium iodide or emotional shock; that the reactions occur at the sites of small pre-existing lepra-cell granulomata, sometimes in subcutaneous tissue, sometimes in the dermis; and that bacilli are present in these lesions, although they are both few and granular. In addition to general inflammation there may be also on occasion fibrinoid necrosis of collagen [17] and vascular necrosis. Few would disagree with Pepler, Kooij and Marshall [16] that, in spite of points in common, ENL and erythema nodosum are not the same condition; and there would be much support for the view that ENL is probably an allergic condition the nature of which is not understood, although it may be connected in some way with the dissemination of bacilli from skin lesions. It is disputed whether or not these reactions are beneficial to the patient [24], Davison [4] and Davison and Kooij [5] especially being convinced that they are not beneficial.

ENL has not always been distinguished from the acute lepra reaction which is an exacerbation of lepromatous leprosy [25], or from the reactions of other types of leprosy [22]. The literature is further confused by different interpretations of the nomenclature of classification.

For the purposes of this paper a few generalizations must suffice: (*a*) Reactions are probably symptomatic of an alteration in the immunologic balance. The nature of the upset in ENL is unexplained, since in many cases there is neither an exacerbation of the infection nor any appreciable alteration in the resistance of the patient. (*b*) In ENL the lesions show an inflammatory reaction with infiltration of polymorphonuclear leucocytes, whereas in most other reactions—except the ulcerations of Lucio leprosy ([10])—there is only edema and no infiltration of cells other than those which are characteristic of the leprous granuloma. The ENL inflammation is not due to any known extraneous infection ([8]). (*c*) ENL differs from most other reactions in that the skin eruption does not occur predominantly in clinically apparent, pre-existent leprosy lesions.

It was thought that further light might be shed on the ENL phenomenon by (1) a study of the number and condition of the bacilli in the ENL lesions, and in the other leprosy lesions (lepromata), before and during the reaction; and by (2) a bacteriologic comparison of patients with ENL and others with a similar period of treatment who had not developed ENL.

MATERIALS AND METHODS

Bacterial indices.—(*a*) "Numerical index" in lepromata: At the Jordan Hospital, Redhill, all patients as a routine have had skin biopsies made at 3-month intervals. Assessment of the quantities of bacilli in the biopsy specimen have been made by a method previously described ([20]). The density of the bacilli in a granuloma (i.e., number per field expressed as an index) is multiplied by the size of the lesion (i.e., the fraction of the dermis occupied by the granuloma); this is thought to give a good index of the total number of bacilli and is referred to hereafter as the "numerical index." The maximum possible figure is 6.0.

(*b*) "Bacterial index" of ENL biopsy specimens: Unfortunately, the numerical index cannot be employed since the ENL lesion is swollen by inflammatory reaction and does not correspond exactly with the area of the section occupied by bacilli. The best that can be done is to assess the density of bacilli in different parts of the section and take the average. This is the familiar "bacterial index." It is less accurate than the numerical index and less responsive to variations of granuloma size. It was used to compare the ENL biopsies (made, at different times, on 21 lesions) with any biopsies of lepromata made within 3-month intervals. This interval is longer than desirable, but since one-half of the leprosy biopsies were taken before and one-half after the ENL biopsies it is thought that bias is avoided.

Granularity index.—Davey ([3]) has found that progressive degrees of bacterial degeneration of the leprosy bacillus can be assessed in stained smear preparations. In the method used in this study bacilli were divided into 3 classes: "solid" (S), meaning solid-staining, unbroken rods; "fragmented" (F), meaning bacilli in which the acid-fast element was interrupted at one or more points but at least one fragment displayed an elongated form (also single, very short rods); and "granular" (G), meaning round granules, either in line or in clumps. To each class (S, F and G) a value was assigned: 2 if bacilli of the given class appeared to be numerous (>30% of the total bacillary population), 1 if few (5-30% of the bacilli) or 0 (if <5%). The resulting values, 2-1-0 and its permutations, are a convenient representation of the relative proportions of solid, fragmented and granular bacilli. These values from 2-0-0 (all solid) to 0-0-2 (all granular) were placed in order and numbered to give a granularity index, as shown in the tabulation below.

S-F-G value	*Granularity index*
2-0-0	0
2-1-0	1
2-2-0	2
2-1-1 (= 1-2-0)	3
2-2-1	4
2-2-2 (= 1-2-1, 0-2-0)	5
1-2-2	6
1-1-2 (= 0-2-1)	7
0-2-2	8
0-1-2	9
0-0-2	10

The precise order in some cases is not obvious, but the ratio of solid to granular can be determined in each instance by plotting the crude distribution curve (the 2-1-0 value) on squared paper and counting the squares on each side of the center (fragmented) line. It is generally possible to obtain agreement between different observers to within 1 unit of the index, provided prior agreement has been obtained on the classification of every form of bacillus. With earlier attempts to assess granularity by direct counts of bacilli in each of the classes, agreement had been difficult to obtain.

Selection of cases.—All lepromatous patients admitted to the Jordan Hospital during the last 7 years were used, provided the records of biopsy examinations were complete, i.e., sections were available of lesions before the commencement of treatment, and at 3-month intervals thereafter until the onset of ENL or until the patient was considered to be beyond the stage when ENL might develop. Most cases fell into homogeneous groups (see Table 2); the others (Cases 19-26) are considered separately. The term "lepromatous" is used strictly, but some patients who were not typically lepromatous in all respects were investigated for comparison. Altogether the results are based on the analysis of 223 biopsies apart from those of the 21 ENL lesions; some of them were double biopsies involving two lesions of a given case, and it is these cases which account for the occasional appearance of a half-figure in the granularity indices. Any two biopsies made within one month of each other were considered as one, but if the interval was longer they were assessed separately.

RESULTS

ENL lesions and lepromata.—The results of comparative examinations of ENL lesions and lepromata, as regards the numbers of bacilli and their granularity, are shown in Table 1. The ENL lesions were classified as "deep": large nodules, predominantly subcutaneous, which tended to persist for many days ([21]); "superficial": small, transient, pink nodules affecting the dermis; and "necrotic": superficial nodules which, unlike the majority, showed vascular necrosis and a tendency to ulcerate. Commonly, lesions of more than one type occur together in the same person. As the group with deep nodules was small, two cases without any corresponding biopsy of a leproma are included in the series of 21 ENL biopsies.

When the means, all cases, are estimated it is found that the bacterial index for the lepromata is only slightly higher than that for the ENL lesions, i.e., 3.2 against 2.9, which difference is insignificant statistically. Furthermore, the difference in the mean granularity of bacilli in the two lesions is also insignificant, 7.7 against 8.1. When lesions are paired, the differences in numbers and granularity are still insignificant.

TABLE 1.—*Bacterial indices (bacterial index and granularity index) of ENL lesions and lepromata.*

Case No.	Type of ENL lesion	Duration of ENL (years)	Bacterial indices[a]			
			ENL lesions		Lepromata	
			B.I.	G.I.	B.I.	G.I
26	Deep		3	9		
27	"	1.5	2	10		
28	"	.5	4	7	(3)	(8)
29	"	2	3	9	4	8
					3	9
30	"	2.5	2	10	2.5	8
	Superficial	2.5	2	9	2.5	10
31	"	2.5	2.5	6	3	7
					3.5	5
8	"	1	4	9	4.5	9
	"	1.5	3.5	6	3	4
					4	4
32	"	1.5	2.5	7	3.5	7
		2	2.5	6	2.5	9
		2	3	9	2	8
6	"	1	3	10	2	10
					3	9
2	"	.5	3	6	3.5	8
					3.5	8
7	"	1	2.5	8	3	8
		1.5	2.5	9	3	5
33	Necrotic	2.5	3	5	2	7
19	"	1	2.5	9	4	9
	"	1.5	2	10	2	10
					2	10
27	"	4	2.5	7	(2.5)	(10)
34		1	5	8	5	5
					4.5	7
Mean		1.7	2.9	8.1	3.2	7.7

[a]B.I. = bacterial index; G.I. = granularity index. The figures in parentheses were from lepromas which in histologic examination showed some evidence of ENL reaction. These were discounted in calculating the means.

Biopsies of clinically normal skin in cases 30, 8 and 7 gave bacterial indices of 0, 3 and 2 respectively.

Although the bacterial index applied to sections is less accurate than one would wish it to be, the results suffice to show that the numbers of bacilli in ENL lesions are similar to those in nonreacting lepromata. They are, however, more numerous than in apparently healthy lepromatous skin. It was noticeable, however, that bacilli were fewer in the central area of reaction than around the periphery. As regards granularity, it can be concluded that in the aggregate there is no appreciable difference between the two types of lesions.

If these results do not shed much light on the situation in which ENL lesions are precipitated, they at least add interest to the study of lepromata in ENL and non-ENL cases which follows.

The onset of ENL.—In 8 cases in which the biopsy series was complete the number and condition of bacilli before and after the onset of ENL could be compared, with results shown in Table 2. The mean period of treatment at the onset of ENL was 8.5 months; but the preceding biopsies, used in the analysis, were made on the average at 7 months (there being a 3-month interval between biopsies).

In all 8 cases bacilli had become granular before the onset of ENL. The range of granularity from 5.5 to 9 indicated that in each case there was a preponderance of granular over solid forms. The mean granularity of 7.2 was close to that of the series in Table 1, 20 months later.

The most significant observation was that in each of the 8 individuals the fall in the numerical index up to the time of onset of ENL was higher than expected. The difference between the mean values before treatment and before the onset of ENL (3.6 *vs* 1.6) represented a fall of 55 per cent in the period of 7 months, the lowest individual figure being 44 per cent (Case 5). From past experience the expected figure would be 26 per cent in 6 months, and for all the lepromatous

TABLE 2.—*Bacterial indices (numerical index and granularity index) of lepromata, and response to treatment of ENL and non-ENL cases.*

Case No.	Treatment[b]	Bacterial indices[a]				Fall in N.I. with treatment		Period of treatment (in months)	
		Before treatment		Before onset ENL			at onset		at onset
		N.I.	G.I.	N.I.	G.I.	at G6	ENL	at G6	ENL
	Lepromatous with ENL								
1	S	3.0	3	1.4	7	1.6	1.6	5	5
2	S	4.0	1	1.5	6	2.5	2.5	10	11
3	S	2.2	3	0.7	9	1.2	1.5	8	16
4	S+V	2.2	3	1.0	5.5	1.2	1.2	6	8
5	S	3.9	5	2.2	8	1.4	1.7	2	10
6	S	4.8	0	1.8	8	3.9	3.0	7	10
7	I/S	2.9	4	1.1	8	1.8	1.8	2	3
8	I/S	5.5	1	2.8	6	2.7	2.7	4	4
Mean		3.6	2.6	1.6	7.2	2.0	2.0	5.5	8.5
	Lepromatous without ENL								
9	S	2.2	2			1.2		6	
10	S	1.0	2			0.25		5	
11	I/S	5.0	2			1.0		17	
12	S	1.3	3.5			0.8		6	
13	C	3.5	1			0.0		6	
14	V	3.3	3			0.9		3	
Mean		2.7	2.3			0.7		7	
	Borderline-lepromatous								
15	S	4.4	3			1.6		5	
16	S	0.9	1			0.65		8	
17	S	0.8	3			0.65		13	
18	C	1.5	5			0.5		3	
Mean		1.8	3.0			0.8		7	

[a]N.I. = numerical index; G.I. = granularity index; G6 = granularity index 6.
[b]C = Ciba 1906; I = isoniazid; S = sulfone; V = Vadrine.

cases in Table 2 during the first 2 years of treatment the mean fall was 26.5 per cent per 6 months. The exceptional fall in numerical index occurred in fact before the granularity index reached 6, in a period of 5.5 months. Thereafter there was no further fall in the numerical index before the onset of ENL.

To summarize, ENL did not develop until bacilli had become granular (index 6), which occurred on the average after 5.5 months of treatment. During this period the rate of fall in the numerical index was twice the average. In 6 out of 8 cases the onset of ENL followed shortly afterwards.

ENL cases and non-ENL cases.—The significance of these observations was tested further by comparing the bacteriologic findings in the ENL cases with those in 6 lepromatous patients who never developed ENL and also with 4 other patients, broadly lepromatous, with plenty of bacilli but with a few features which led to their classification as "borderline-lepromatous." Patients of this kind do not develop ENL, but it was thought that they might provide circumstantial evidence.

These results, also, are summarized in Table 2. The numerical indices before treatment appear to be lower in the non-ENL groups than in the ENL group, but there are wide individual variations and the differences in the means are not statistically significant. Nor do initial granularity indices differ significantly in any of the groups.

There is no event in the non-ENL groups with which the onset of ENL may be compared; but the point at which granularity 6 is attained, which is closely related to the onset of ENL as regards time and the number and granularity of bacilli, may conveniently be used as a substitute. At this point the mean period of treatment is 7 months for each of the non-ENL groups, against 5.5 months for the ENL group—a difference which is not statistically significant. In 7 months the mean fall in the numerical indices is 26 per cent (2.7 to 2.0) for the non-ENL lepromatous cases, and 45 per cent (1.8 to 1.0) for the borderline-lepromatous. Both these rates of decrease are the same as those of earlier comparable groups, whereas in the ENL group the fall had been double the amount expected. The results, as percentages, show some overlap between ENL and non-ENL groups (individual variation for the non-ENL lepromatous group ranges from 0% to 61%). The absolute figures, however, establish an absolute difference: the falls in the numerical index when granularity reaches 6 vary from 3.9 to 1.2 among lepromatous patients who subsequently developed ENL, and from 1.2 to 0 among those who did not. Furthermore, the figures for borderline-lepromatous cases lie in the same range as the non-ENL lepromatous, with one exception which will be discussed later.

The table also shows that in several of the non-ENL lepromatous patients the numerical index was still high when granularity 6 was

reached. Yet subsequent resolution of their lesions was not associated with ENL.

Other cases.—Before discussing these results it is necessary to examine the results of cases excluded from Table 2, and the validity of their rejection. These excluded cases, most of whom developed ENL, fall into three categories: (*a*) patients whose biopsy records were incomplete, usually because treatment had commenced prior to admission; (*b*) patients in whom the initial biopsy showed a granularity of 6 or higher, and (*c*) patients who "relapsed" by which is meant that there was a fall in the granularity index from 6 or more to 5 or less. Only the last two categories will be considered.

First, two patients with an initial granularity of 6 or higher: In Case 19 the granularity index was 8 before treatment, and ENL had already developed. Case 20 showed an initial granularity of 6 and ENL developed after 1 month of treatment. There is a possibility that in these two persons there had been spontaneous improvement before treatment was instituted; both gave an exceptionally long history of nontreatment (10 years, and 7 years or more, resp.), yet their initial numerical indices were not high (3.5 in one and 1.2 in the other, lower than in any of the 8 cases in the table). While these two cases cannot be included to support the previous findings, they are not inconsistent with them.

Secondly, patients who "relapsed": This is a common event after the onset of ENL, the course of which is often not affected. But when the relapse occurs before the onset (or expected onset) of ENL, expectations are upset, as shown by 5 patients on an experimental drug followed by sulfones. Because of their erratic progress, they can only be considered separately.

CASE 21: The numerical index fell by 2.0 by the end of 9 months, when the granularity was 6.5. At the next biopsy, granularity had fallen back to 5. At 18 months, a biopsy showed the granularity index to be 8, and immediately ENL developed.

CASE 22: Granularity 6 was reached in 15 months, when the fall in numerical index was 2.1. The next biopsy showed a relapse, with a large rise of the numerical index, and solid forms. At 18 months, granularity had returned to 6, but ENL did not develop until 23 months, when the numerical index had fallen again.

CASE 23: The numerical index had fallen to 1.6 at 18 months, when granularity reached 5.5. Subsequently the latter was 5, but ENL eventually developed at 26 months.

CASE 24: Fall in the numerical index was only 0.4 when granularity reached 6 at 3 months. Subsequently there was a granularity of only 1, but it never again fell below 5. ENL never developed in a 3-year follow-up.

CASE 25: The fall in the numerical index was only 0.3 when, at 9 months, granularity 6 was reached. There was a subsequent relapse when granularity returned to 5.5; and, after a further fall in the numerical index of 1.4, ENL developed.

In general these cases support the findings that ENL is related to a fall in the numerical index of 1.2 or more before the granularity reaches 6 (or 5.5). A relapse at this point, however, delays the onset until the granularity again falls below 5.

Validity of the results.—The difference between ENL and non-ENL

groups, in the fall of numerical indices up to the time the granularity reaches 6, is highly significant from a statistical point of view. This holds whether the non-ENL lepromatous group is considered alone or in conjunction with the borderline-lepromatous group.

Are the results invalidated by bias in assessing the indices? The numerical indices were assessed some time before the present study was contemplated, and the figures have not been altered. The time of onset of ENL was obtained from the clinical records.[1] There was therefore no room for bias with respect to these factors. There was an opportunity for bias in assessing the granularity indices. All results in the critical region of 4 to 7 were therefore re-checked by comparing each one with a particular section of granularity 5 which was used as a standard. In 5 of the 25 cases assessment of granularity was made blind, not knowing whether or not the patients had developed ENL.

The fact that the period of treatment at granularity 6 was longer in the non-ENL groups than in the ENL group, suggests that the smaller falls in numerical indices were not due to abbreviation of the period by bias in assessing granularity. The rule appears to be established, but the small number of cases available does not permit one to say whether exceptions are rare.

Acute lepra reactivation.—There was bacteriologic evidence of such a reaction at 3 months, with fall in granularity or increase of numerical index or both, in Cases 1, 11, 21 and 23. In three of these cases ENL developed, not in the other. There was no evidence of any connection between the two types of reaction.

ENL and prognosis.—ENL follows a sharp fall in the numerical index. Thereafter, in Cases 1 to 8, progress was more erratic than in the non-ENL group. The mean rates of fall for the ENL group were 43 per cent for the 6 months prior to the onset, and 18 per cent per 6 months for the following 18 months, with a mean of 25 per cent for the first 2 years of treatment. For the non-ENL lepromatous cases the corresponding figure was 27 per cent, but progress was maintained at a steady rate throughout the period. In general, therefore, progress was slower after the onset of ENL, which was the view of Davison and Kooij ([5]) and of Davison ([4]), but in individual cases the erratic results give a favorable impression at certain stages.

Cytology of lesions.—Muir ([14]) refers to the breaking up of globi as a significant event in the initiation of the ENL reaction. In active lepromata, bacilli are engulfed in healthy-looking histiocytes or macrophages, which with maturation undergo lipoid degeneration. In older, less active lesions and in treated cases, many foam cells and globi fuse or disintegrate with the formation of a symplasm (the term [12] used in connection with Johne's disease seems appropriate) in which nuclei

[1]Records by Dr. W. H. Jopling.

are few and cell boundaries often not apparent. In the ENL specimens studied the underlying leproma was represented in all cases by a symplasm, partially or fully developed.

The serial biopsy specimens of lepromata were examined for the first appearance of symplasm similar to that seen in the ENL biopsies. In the 8 cases the first appearance occurred, on an average, 3 months before the onset of ENL, the interval ranging in individual cases from 7 months before to 3 months after the onset. Since formation of symplasm and granulation of bacilli are both indicative of aging and lessened activity, there is a broad correlation between the two which is probably fortuitous. The correlation of the onset of ENL with the appearance of symplasm is less exact and probably less significant than that with granularity of bacilli.

Bacilli in blood and urine.—Leprosy bacilli are to be found sometimes in the urine of ENL patients, and in the blood stream on occasions ([1, 11]). In this series systematic observations have not been made, but acid-fast bacilli were present in the urine of 2 out of 6 ENL patients (numerous in Case 21). None were found in the urines of 6 nonreacting lepromatous patients. Blood was not examined.

Plasma protein and complement-fixing antibody.—It is known that the gamma globulin of the plasma is markedly raised during ENL reactions, more so than nonreaction periods (e.g., [13]). This has been confirmed in the present series of cases ([26]), in which a rise in the alpha-1 globulin also was observed in many of the ENL cases, but not in the others. Both these findings could be attributed to a nonspecific response to tissue damage, although part of the gamma globulin fraction might represent antibody.

The sera of lepromatous patients frequently fix complement in the presence of mycobacterial antigens. For a period, complement-fixation tests using lepromin as antigen were carried out on all our patients at various intervals. Over one-half of the results were positive, but there was no correlation between the antibody titer and ENL; the highest titer, 1 in 60, was obtained in a borderline-lepromatous case (Case 17).

DISCUSSION

The principal findings are: (*a*) that the bacilli in skin lesions are relatively granular before the onset of ENL; (*b*) that the development of ENL is correlated with a large fall in the numerical index before, but not after, the bacilli have become granular; and (*c*) that ENL is correlated with the absolute value of the fall, rather than the fall expressed as a percentage of the initial value. The onset of ENL appears to be delayed by a relapse of the infection beforehand, but not to be inhibited by a relapse subsequently.

It has been found previously ([19]) that the fall in the numerical index during treatment is relative to the value of the index at the time. That

the onset of ENL is related to fall in absolute value points to the conclusion that it depends, not on the rate of clinical progress under therapy, but on the actual number of solid or fairly intact bacilli which disappear from the skin.

This disappearance of bacilli is associated either with shrinkage of the leproma or with reduction of the density of bacilli within the surviving parts of the granuloma ([18]). During the early and middle stages of treatment of lepromatous leprosy, when ENL is most frequent, the first process alone is observed in most cases; the second is witnessed in borderline leprosy or in the later stages of treatment in the lepromatous type.

Shrinkage of the granuloma accounted almost completely for the fall in numerical indices in all cases of Table 2 except Case 15, which was the only exception to the finding that ENL follows when the index fall exceeds 1.2 before the granularity reaches 6. If the falls in the numerical index are calculated solely on the basis of shrinkage of granuloma, discounting any alterations in bacterial density, none of the estimates is altered significantly except for this case, which becomes 0.5 instead of 1.6. On this basis the only discrepancy in the results would disappear. The absence of histologic signs of resolution, apart from replacement fibrosis, points to the probability that this shrinkage of lepromata consists in the absorption of both granuloma cells and bacilli into lymphatics and blood stream.

Patients who do not develop ENL fall into two groups: (*a*) those with a heavy or moderate infection in whom removal of bacilli from skin is slow (Cases 11 and 13), or in whom such progress is perhaps above average yet slow in relation to the rapid development of granularity (Case 14); and (*b*) patients who make good bacteriologic progress but in whom removal of bacilli from skin amounts to little because there are relatively few bacilli in the initial lesions. The latter group includes a few of the lepromatous patients (Cases 10 and 12), besides most of the borderline-lepromatous and all truly borderline patients, in whom ENL would not be expected. If a drug could be found which would make bacilli granular before any significant absorption from the skin should occur, the incidence of ENL would probably be very low. But delayed treatment may predispose to ENL (Cases 19 and 20).

Since the present findings were based on a small series of cases, it is not certain that a larger series would produce such clear-cut results. For one thing, it is known that ENL may occasionally develop at a very late stage of treatment ([5]). It is notable that the two ENL cases in which there was significant delay in the onset of ENL after the granularity 6 point showed two of the lowest falls in numerical index at this point (Cases 3 and 5). This suggests that there may be cases in which a relatively small fall in the numerical index is followed by the onset of ENL after considerable delay. Another unexplored situation

is that of ENL precipitated by intercurrent infection, potassium iodide or emotional crisis. During the preparation of this paper ENL developed in a recently-admitted leprosy patient coincidentally with the onset of sarcoidosis of the liver; the bacterial granularity was only 3. It may be that adrenal exhaustion and other influences on the immunologic state of the patient precipitate ENL when otherwise it would not be expected.

SUMMARY

Numbers and granularity of leprosy bacilli have been compared by the use of appropriate indices in lesions of erythema nodosum leprosum (ENL), and in lepromata. On the basis of serial biopsies, the bacteriologic progress of patients who develop ENL has been compared, before and after the onset of the reaction, with that of patients who never developed ENL. The principal findings were:

(1) There were more bacilli in ENL lesions than in apparently normal skin areas ("inapparent" infiltrations). The number and granularity of bacilli in the ENL lesions were similar to those in non-reacting lepromata biopsied at the same time. But in the actual foci of reaction, bacilli were fewer.

(2) Bacilli in lepromata were granular before the onset of ENL in all cases.

(3) The onset of ENL was preceded by an exceptional fall in the number of bacilli in the skin, which occurred before bacilli had become granular. Similar falls subsequently were not associated with the onset of ENL.

(4) The occurrence of ENL was closely connected with the actual quantity of nongranular bacilli to be absorbed from the skin, and with the timing of this event. The effect of bacteriologic relapses was to abort the onset of ENL.

The cytology of lesions, the urinary excretion of bacilli, the plasma proteins and complement-fixing antibody against lepromin, were all studied in relation to ENL. After the onset of ENL the progress of patients was more erratic than that of non-ENL patients. On balance, ENL was not beneficial.

RESUMEN

Se han comparado las cantidades y la granularidad de los bacilos leprosos, usando indices apropiados en las lesiones del eritema nudoso leproso (ENL) y en los lepromas. A base de biopsias seriadas, se ha comparado la evolución bacteriológica de los enfermos que manifiestan ENL, antes y después de iniciarse la reacción, con la de los enfermos que jamás manifestaron ENL. Los principales hallazgos fueron:

(1) Hubo más bacilos en las lesiones de ENL que en las zonas cutáneas aparentemente normales (infiltraciones "inaparentes"). El número y la granularidad de los bacilos en las lesiones de ENL fueron semejantes a los de los observados en los lepromas irreactivos biopsiados al mismo tiempo. Sin embargo, en los focos reales de reacción, eran menos los bacilos.

(2) Los bacilos de los lepromas eran granulares antes de la iniciación del ENL en todos los casos.

(3) La iniciación del ENL fué precedida de una baja excepcional del número de bacilos en la piel, lo cual sucedió antes de granularse los mismos. Las bajas de bacilos observadas después no se relacionaron con la iniciación del ENL.

(4) La aparición de ENL se relacionó íntimamente con la cantidad real de bacilos no granulares que había que absorber de la piel y con la fecha de este acontecimiento. El efecto de las recidivas bacteriológicas consistió en abortar la iniciación del ENL.

La citología de las lesiones, la excreción urinaria de bacilos, la proteína del plasma y el anticuerpo fijador del complemento contra la lepromina, todos estos factores fueron estudiados en relación con el ENL. Después de iniciarse el ENL, la evolución de los enfermos fué más caprichosa que la de los enfermos sin ENL. Todo considerado, el ENL no resultó beneficioso.

ACKNOWLEDGMENTS.—I acknowledge with gratitude my indebtedness to Sir George McRobert, Prof. A. W. Woodruff, and Dr. J. H. Walters for their cooperation and permission to report on their patients; to Dr. W. H. Jopling for much advice and clinical information, and for taking the biopsy specimens; and to Miss Marian Wise for the histologic preparations.

I am grateful to Dr. J. H. Hanks and Dr. J. Ross Innes for much useful criticism and many suggestions.

REFERENCES

1. BARRERA, F. DE P. and CHAVARRIA, A. P. The acute exanthem of leprosy. Johns Hopkins Hosp. Bull. **35** (1924) 147-158.
2. DANIELSSEN, D. C. and BOECK, W. Traité de la Spédalskhed, ou Eléphantiasis des Grecs. Paris: J. B. Baillière, 1848, pp. 206-209.
3. DAVEY, T. F. Progress with new anti-leprosy drugs. Trans. VIIth Internat. Congr. Leprol., Tokyo, 1958; Tokyo (Tofu Kyobai), 1959, pp. 252-259.
4. DAVISON, A. R. Erythema nodosum leprosum. Leprosy Rev. **30** (1959) 112-113.
5. DAVISON, A. R. and KOOIJ, R. Is erythema nodosum leprosum a favorable occurrence? Internat. J. Leprosy **25** (1957) 91-98.
6. GREEN, R. Some observations on the leprous reaction. (Synonyms: Leprotic fever; the acute exanthem of leprosy; lepra reaction, etc.) Trans. Roy. Soc. Trop. Med. & hyg. **22** (1929) 367-380.
7. HANSEN, G. A. and LOOFT, C. Leprosy: In its Clinical and Pathological Aspects. Transl. by N. Walker, M.D. Bristol: John Wright & Co., 1895.
8. ITO, M. and OHIRA, K. Bacteriological investigations of suppuration in the lesions of erythema nodosum leprosum. La Lepro **23** (1954) 279-281 (in Japanese; English abstract).
9. KLINGMÜLLER, V. Die Lepra. Handbuch der Haut- und Geschlechtskrankheiten, Vol. 10. Berlin: J. Springer, 1930, pp. 493-504.
10. LATAPÍ, F. and CHEVEZ ZAMORA, A. The "spotted" leprosy of Lucio. An introduction to its clinical and histological study. Internat. J. Leprosy **16** (1948) 421-430.
11. LOWE, J. Leprous reaction. Indian Med. Gaz. **64** (1929) 438-441.
12. M'FADZEAN, J. The histology of the lesions of Johne's disease. J. Comp. Path. **13** (1918) 73-87.
13. MIGUEL, S., ROLDAN, A., GUILLEN, J., TERENCIO, J. and PONCIANI, J. Proteínas plasmáticas en la lepra. Internat. J. Leprosy **22** (1954) 47-54.
14. MUIR, E., LANDEMAN, E., ROY, T. N. and SANTRA, I. The treatment of leprosy in the light of the nature of its spread through the body. Indian J. Med. Res. **11** (1923) 543-578.
15. MURATA, M. Ueber erythema nodosum leprosum. Japanische Ztschr. Dermat. & Urol. 12 (1912) 1013; *reprinted by W. H. Joplin in English translation,* Leprosy Rev. **29** (1958) 116-118.
16. PEPLER, W. J., KOOIJ, R. and MARSHALL, J. The histopathology of acute panniculitis nodosa leprosa (erythema nodosum leprosum). Internat. J. Leprosy **23** (1955) 53-60.

17. Richter, R. Bemerkungen zur Histologie der Leprareaktion nach Conteben. Dermat. Wchnschr. **134** (1956) 1071-1077.
18. Ridley, D. S. The bacteriological interpretation of skin smears and biopsies in leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. **49** (1955), 449-452.
19. Ridley, D. S. The use of biopsies in therapeutic trials in leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. **51** (1957) 152-156.
20. Ridley, D. S. Therapeutic trials in leprosy using serial biopsies. Leprosy Rev. **29** (1958) 45-52.
21. Rodriguez, J. N. Erythema induratum leprosum. A deep nodular form of reaction in lepromatous leprosy. Internat. J. Leprosy **25** (1957) 313-322.
22. De Souza Campos, N. and Rath de Souza, P. Reactional states in leprosy. Lepra reaction, tuberculoid reactivation (tuberculoid lepra reaction), reactional tuberculoid leprosy, borderline (limitantes) lesions. Internat. J. Leprosy **22** (1954) 259-272.
23. Stein, A. A. Zur morphologie der Leprareaktion. I. Mitteilung. Histologische Veranderungen bei de I. Typus von Leprareaktionen. Internat. J. Leprosy **7** (1939) 149-160.
24. Wade, H. W. Effect of reactions in lepromatous leprosy. Internat. J. Leprosy **25** (1957) 399-400 (editorial).
25. Wolcott, R. R. Erythema nodosum in leprosy. Internat. J. Leprosy **15** (1947) 380-388.
26. Woodruff, A. W., Jopling, W. H. and Ridley, D. S. Plasma proteins in erythema nodosum leprosum. (To be published.)