

INTERNATIONAL
JOURNAL OF LEPROSY

And Other Mycobacterial Diseases

Volume 35, Number 1

January-March 1967

The Etiology of Erythema Nodosum Leprosum¹John H. S. Pettit and M. F. R. Waters²

It seems to be generally accepted that the term erythema nodosum leprosum (ENL) was coined by Murata in a paper entitled "Ueber Erythema Nodosum Leprosum,"⁽²¹⁾ which was recently translated by Hayashi and published in *Leprosy Review* by Jopling⁽¹¹⁾. Murata made it clear that ENL was found in lepromatous leprosy, that it was not an initial event, and concluded a detailed description of the disease by pointing out that he recommended the name "erythema nodosum leprosum" because the term "erythema nodosum" was already approved as a clinical entity and ENL was a characteristic syndrome appearing in the course of leprosy. The English translation concludes "ENL is a term which reasonably may be adopted for this singular and independent clinical syndrome, which also has its own histological features."

Although the original paper was written more than 50 years ago it took a surprising-

ly long time for ENL to be recognized outside Japan; e.g., the INTERNATIONAL JOURNAL OF LEPROSY in 1942, 1943 and 1944 made no mention of this condition or indeed of any form of reaction. Many papers that appeared before or immediately after World War II, when referring to erythema nodosum not infrequently seemed to confuse ENL with the different, classic condition, even though de Souza Lima and Maurano⁽³⁸⁾ had written in 1939 that the erythema nodosum seen as the most frequent cutaneous symptom of the lepra reaction, differed from classic erythema nodosum, in which lesions seldom affected the face or the nerves. They emphasized that ENL was associated with acute reactional phenomena of the nerves, lymph nodes, eyes and testicles, and also that the duration was very long, with not infrequent suppuration of the lesions. In 1942 Pecoraro⁽²²⁾ made a particular attempt to separate the differences between ENL and erythema nodosum of other etiologies, and stated that ENL was considered the most frequent acute skin manifestation of the "lepra reaction," and was seen usually in advanced cases, possibly signifying im-

¹Received for publication 20 June 1966.

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provement in prognosis. In 1946 an article entitled "Erythema nodosum in leprosy" by Pogge and Ross (²⁸) showed continued uncertainty as to the differentiation of reactions and said "leprosy is a chronic disease in which there are at times acute manifestations, the local lesions of which may be those of erythema nodosum or less often, erysipeloid reactions of the skin, painful neuritis, or painful lymphadenopathy." The authors pointed out that erythema nodosum did not seem to be a manifestation of the modern treatment of leprosy with sulfone derivatives, and said that among their 27 patients who were being treated with Promin and suffered from erythema nodosum, 52 per cent improved on the drug. They concluded, therefore, that the erythema nodosum seen with leprosy was neither caused by nor cured by the treatment.

As active treatment of leprosy became more readily possible with the spread of treatment with sulfones and their relatives, greater interest was taken in the different forms of lepra reaction. Wolcott, for example (⁴⁵), was one of the first to attempt to differentiate erythema nodosum from the other acute reactions; in an analysis of 248 cases in which erythema nodosum had occurred in Carville he pointed out that the condition usually started six to 12 months after treatment began, and stated that "although it has been seen in the course of several different regimens of treatment which have been employed in the past years, it is the consensus of the staff that erythema nodosum has become much more common since the initiation of sulfone therapy." In his summary he pointed out that there was a correlation between antileprosy treatment and the appearance of erythema nodosum as indicated by the observation that 7 per cent of cases occurred before treatment and 93 per cent afterward. He suggested also that the presence of erythema nodosum indicated an increasing resistance to the disease.

Schujman (³³) believed in a beneficial influence of the lepra reaction on the evolution of lepromatous cases and pointed out that, however frequent, intense and prolonged the reactions were, they were beneficial to the patient. He said that the favorable effects were greatest when they ap-

peared in the early stages of the disease, and continued with the statement that "reactions may sometimes cause clinical and bacteriological clearing of the lesions." It is presumed that the early occurring reactions are the same as those that show bacteriologic clearing, and that these represent the other form of acute lepra reaction, while the reactions clearing later were probably ENL cases.

It can be seen from the foregoing that by the end of the 1940's the phrase "erythema nodosum leprosum" did not yet come trippingly to the tongue of most leprologists. In 1951 Montel (¹⁹) was provoked into writing a letter criticizing the frequent use of the words "erythema nodosum" in leprosy writings. He emphasized that erythema nodosum had specific characteristics, while the condition under discussion was clinically totally different. Unfortunately his letter did not stimulate very much clearer thought, and writings on the lepra reactions continued to use the words erythema nodosum, acute lepra reaction, and ENL without any clarification as to whether they were the same or different conditions. This confusion makes it exceedingly difficult to follow the papers that were written at this time. Some persons, as noted by Roche *et al.* (³²), thought that the lepra reaction was essentially a useful thing, and that its occurrence in a patient represented a favorable sign. Contreras *et al.* (⁵) early in 1952, took the opposite view as to the importance of lepromatous lepra reaction, considering it a grave syndrome with serious changes that might lead to generalized amyloidosis and a fatal ending. Davison (⁶) pointed out that, the lower the original bacteriologic index (BI), the less likely it was that ENL would develop; because 24 patients with low BIs took 57 months to become negative, whereas 76 patients with low BIs and ENL took 65 months or more, he concluded that ENL had a bad prognostic significance.

De Souza Lima (³⁷) had been so disgusted with the "chaotic situation with respect to views of lepra reaction prior to the establishment of the South American classification" that he stated that it would be best to discard all previous concepts and re-examine the matter on the basis of the cri-

teria of that classification, and, although he included in his paper a form of "reaction" that occurred as the first manifestation of the disease, his other definitions are accepted. He allows room for tuberculoid and lepromatous lepra reaction as "exacerbation of pre-existing lesions and appearance of new ones, structurally identical, in the course of chronic evolution of the disease," and also for erythema nodosum leprosum, which "only occurs in the L type and where superimposed new elements which are structurally different occur at a time when there is apparent quiescence of the specific lesions." In this way de Souza Lima anticipated by some years the differentiation that has been made by Jopling (¹²), who refers to "type 1" and "type 2" reactions in lepromatous leprosy.

SULFONES AND THEIR CONNECTION WITH ENL

It can be seen that ENL was not unknown to careful observers many years before any sulfone treatment was developed. Although chaulmoogra oil was used extensively, Muir (²⁰) questioned its value and stated that other leprologists had the same dubious opinion as to its success. This suggests that at that time leprosy was not really effectively treated, and although at least some patients improved (indeed the phrase "burnt-out case" was coined especially to describe them) it should not be believed that this was necessarily due to successful therapy.

The sulfones dramatically altered this picture, and when at last persons were cured of leprosy an increasing number of reactions were seen. As early as 1950 Floch and Destombes (⁷) pointed out that sulfone therapy had fixed attention on the reactions of leprosy, "for these drugs unquestionably favour their occurrence." "They are very frequent," they said, "in the first few months of treatment. While in some patients the first reaction appears only after the beginning of treatment, there exists in others a veritable threshold about which the reaction is precipitated." Although they claimed that reactions appeared only after the institution of sulfone therapy, they

pointed out also (⁸) that tuberculoid reactions were susceptible to sulfone treatment. De Souza Araujo (³⁶) spoke, in his summary, of "cases of lepra reaction due to the indiscriminate use of sulphone," while in an account of the Seventh International Congress of Leprology (⁴) the following sentence occurs: "ENL is a well known complication in lepromatous patients during chemotherapy and may require a decrease in dosage, or if severe, withdrawal of the drug for a period of time."

The report of the Panel on Lepra Reaction of the Eighth International Congress of Leprology (³) (in the words of an Editorial in *Leprosy in India* approvingly quoted by Wade (⁴²)) "instead of clarifying the situation tended to make the confusion worse confounded." Not only is the phrase "erythema nodosum leprosum" almost entirely overlooked and the words "erythema nodosum" used instead, but in the discussion of therapy it states "specific treatment should be maintained, lessened or stopped altogether according to the severity of the reactional state." As recently as 1965 Trautman (⁴⁰) suggested that in severe cases of erythema nodosum sulfone dosage should be discontinued, and Jopling (¹⁴), in October 1965, also hinted that reducing the sulfone dosage to 5 mgm. twice a week would be taking the first step in getting the reaction under control and would permit steady improvement in smears and biopsies.

OTHER CAUSES OF ENL

The selection of papers by well respected authorities, noted above, would seem to the newcomer to offer overpowering evidence that sulfones are the cause of ENL.

A deeper investigation, however, demonstrates that it is well recognized that ENL does not occur only when a patient is given sulfones. The whole history of leprosy prior to the advent of sulfones is studded with case reports that may or may not have used the diagnosis under discussion, but are, all the same, clear evidence that ENL was being seen, and the other causes of ENL are well recognized. Teichmann (³⁹) said "most patients in reaction could not

stand more than few ccs of hydnicarpus oil injection without getting worse," Melamed and Fiol (¹⁷) pointed out that smallpox vaccination may precipitate reactional phenomena in the lepromatous form, and Schujman (³⁴) reported that he was so convinced of the favorable influence of lepra reaction in the ultimate evolution of lepromatous leprosy that he provoked these reactions artificially with potassium iodide or smallpox vaccination. He pointed out that although reactions cannot be induced in all lepromatous cases, when they are obtained the condition is exactly the same as the spontaneous reaction. Other authors have reported ENL in patients who were being treated with diphenylthiourea (^{9, 10}) and sulfamethoprazine (¹⁶).

ENL AND THE MORPHOLOGIC INDEX

It is apparent that even if sulfones do cause ENL, this cannot be the whole story; for many years some workers, believing that the incrimination of sulfones is as yet unproven, have not found it necessary in a doctrinaire way to stop the drug because of a severe outbreak of ENL. This was for three basic reasons.

First, it seemed to have been overlooked that, even if the reaction did follow sulfone therapy, it might easily have been a manifestation of clinical improvement in the disease. Second, in large settlements it is quite clear that long term residents, although continuing sulfone therapy, do not continue with ENL when bacterial negativity has been attained. This has been confirmed by Wade (⁴¹), largely on the basis of information in issues of the *Carville Star* for January and March 1955. He noted that negative patients were classified in Carville in three categories, viz., (1) physically able-bodied and capable of working outside, (2) partially disabled, and (3) permanently disabled, but he made no mention of any patient in any form of reaction when smear-negative. Similarly, Lara and Tiong (¹⁵) pointed out that about 25 per cent of the inmates in Culion were smear-negative, and in a study of the reasons why such patients were not prepared to leave the settlement, did not suggest that the

continuation of any form of reaction was a reason for hospital retention. The third reason for suspicion that previous theories have not been entirely convincing is the recent demonstration (²⁴) that careful observation of ENL under controlled conditions does not confirm that cessation of sulfones has any real importance in modifying its progress.

Recent work of Shepard (³⁵) has shown that the *Mycobacterium leprae* can be cultivated, and Rees and Valentine (²⁹) have demonstrated that viable and nonviable bacilli may be recognized under the light microscope by the presence or absence of granularity in the bacilli, so that it is now possible to tell whether leprosy bacilli are alive or dead. It seems worthwhile, therefore to consider whether or not ENL may be a simple manifestation of some factor connected with the death or disintegration of *M. leprae*, and so be more common now because successful treatment has at last become possible. As long ago as 1953 Mitsuda (¹⁸) pointed out that, after treatment with Promin or other drugs, leprosy bacilli are destroyed and take a granular form; he suggested that as a result of this breakdown of the leprosy bacilli products would enter the blood stream and cause ENL in the skin, iridocyclitis in eyes, and neuritis in nerves. Ridley (³⁰), in a bacteriologic study of ENL, stated that his cases did not develop a reaction until the bacilli had become granular.

In a series of drug trials (^{25, 27, 43, 44}) workers in Malaysia have shown convincingly that the morphologic index (MI) (percentage of solid-staining bacilli) falls dramatically under several forms of therapy, and is less than 5 per cent within six months of the commencement of the treatment. As experience in Sungei Buloh confirms the claim (⁴⁵) that previously untreated lepromatous cases do not normally develop erythema nodosum leprosum within less than six months of active antileprosy treatment, an investigation was carried out to study what the MI was at the onset of ENL.

RESULTS

Although many more patients are admitted to the Sungei Buloh Leprosarium

than are taken into the Research Unit, it was decided that only lepromatous cases that had been studied fully should be investigated. Nearly all of these cases had been in a drug trial and so were more intensively investigated than an average patient; e.g., not only was the initial diagnosis histologically confirmed by Ridley, using a pair of biopsies, but the bacterial index and the morphologic index were studied at regular intervals while the patients were in our care. It was possible, therefore, to discover the type of lepromatous leprosy in each patient, and also to find what the MI was on admission and just prior to the appearance of the symptoms of ENL. It must be pointed out that sometimes the MI had not been studied for a time before the symptoms first appeared, but this period was rarely if ever more than six weeks. Because of the rapid fall in the MI that follows treatment, it is obviously true that the recorded MI in such cases will be somewhat higher than the actual MI at the onset of reactions, but it is also probable that many patients did not report the first few mild lesions and so the hospital notation on ENL is often later than the actual onset. It is believed, therefore, that the indices quoted below are, if anything, rather higher than the true findings would be.

During the period January 1960 to December 1964, 130 lepromatous patients were admitted to the Research Unit, of whom 84 were pure lepromatous (LL) and 46 near-lepromatous (13 BL/LL and 33 BL) ⁽³¹⁾. The investigation here reported was carried out at the end of March 1966

when all patients had been followed for at least 15 months, and most of them for a longer period. At that time 74 had already been discharged from the hospital, to continue treatment as outpatients. Thirty-six were living in the patients' housing section and 17 were still in the Research Unit wards. Three patients had died.

Table 1 shows the incidence of ENL in the various types of lepromatous leprosy and also the average MI on admission and shortly before the onset of ENL. Of the 84 LL cases 46 (54.7%) had at some time or other developed ENL, and 14 (30% of the 46 near-lepromatous cases) had also developed reaction of the same sort. It can be seen that, although the MI was on the average about 30 per cent when the patients were admitted to the hospital, the ENL did not appear until the MI had fallen to almost zero. The MI of the smear taken most recently before the onset of ENL was recorded in all but three cases and showed an average of 1.9 for all LL cases (two were not recorded) and of 0.8 for the BL cases (one was not recorded). Among the 57 cases where the MI had been recorded, only six had MI's of 5 or more, and when these cases were graded in retrospect according to Waters' classification of ENL ⁽⁴³⁾, which ranges from 1+ to 4+, the higher number showing the severest form of reaction, it was noted with interest that two of the patients with high MI's developed the most severe grade of ENL (4+) while three others developed 3+ reactions and one a 2+ reaction. This raised a question that we had not considered pre-

TABLE 1. *Erythema nodosum and the morphologic index (MI).*

Type of leprosy (Ridley scale)	Number of cases	ENL reaction		Average MI	
		Number of cases	Per cent	On admission	Prior to onset of ENL
LL	84	46	54.7	32.8 6 not traced	1.9 2 not recorded
BL/LL	13	7	53.9	37.0 2 not traced	0.8 1 not recorded
BL	33	7	21.2	21.9 2 not traced	0.8
All types	130	60	46.2	30.4 10 not traced	1.8 3 not recorded

TABLE 2. Association of grade of erythema nodosum leprosum with the morphologic index (MI).

Grade of ENL	Number of cases	Average MI prior to onset	Range	
			Maximum	Minimum
4+	5	8.5	25	0.7
3+	15	2.3	9.3	0
		1 not recorded		
2+	19	1.4	5.0	0
1+	21	0.3	1.6	0
		1 not recorded		

viously, viz., whether or not the most severe attacks of ENL developed in patients who had a higher MI at the start of the reaction. Although it is realized that at the onset of a chronic disease the future severity cannot be assessed, in retrospect it was interesting to find out (Table 2) that of the five patients in the series who developed a 4+ reaction the average MI at the onset was 8.5 (respectively 25, 7.2, 1 and 0.7, with one case not recorded). Among those patients who developed 3+ ENL, the maximum severity had an average MI at the start of reaction of 2.3 (range 9.3-0), while cases with 2+ ENL had an average MI at onset of 1.4 (5.0-0), and the 21 patients whose ENL was never more than 1+ severity showed an average on onset of only 0.3 (range 1.6-0).

The few confirmed cases of sulfone-resistant leprosy that have been reported to date (²⁶) were all from Sungei Buloh Leprosarium and had had high MI's after many years of treatment. As all of these were in the lepromatous range and five of them have now been reported, it would seem, according to the findings of Table 1, that at least one or two of the patients should have developed ENL in the past if it were due simply to a combination of sulfone and leprosy. It is interesting to point out that none of these patients had at any time suffered from such reaction during the whole of their period of unsuccessful treatment.

As a corollary to the study described above it was hoped to find out if patients treated with diphenylthiourea (DPT) also developed ENL only when the MI was low. Only one of the Research Unit patients admitted between 1960 and 1964 had been treated with DPT, but in the settlement

we found another nine patients who had received Ciba 1906 since admission, in a dosage of two tablets twice a day. Sometimes the reason for giving this treatment was not particularly clear, but several of the cases, including our own, had shown one or another form of sulfone sensitivity and had not been treated further with DDS. Unfortunately these patients had not been studied in the detailed way outlined above, and so no information was available concerning their MI's. It is worth mentioning that of the ten lepromatous cases only three gave a history of complete freedom from ENL at all times. Three had occasional mild attacks (grade 1+) and four others needed occasional doses of prednisolone to suppress their symptoms (2+). It is obvious that these figures are not in any way sufficient for statistical treatment analysis, but they show that patients who do not receive sulfone are liable to ENL and so confirm the work of Harter *et al.* (¹⁰).

DISCUSSION

In the past 20 years a wave of misconception has swept through the leprosaria of the world and unclear thinking has led to three problems concerning erythema nodosum leprosum that urgently need clarification. First, there is a persistent tendency for authors to use the word "erythema nodosum" when they are considering ENL. A wide range of authorities have now shown that ENL is a specific condition both clinically and histologically different from the classic erythema nodosum, and it is most strongly to be hoped that in the future all articles concerning ENL will use the name of the disease and not further complicate an already unhappy story.

The second problem that must be solved is for all leprosy workers to realize that ENL is a condition with a wide range of clinical severity. The confusion surrounding thinking concerned with the clinical aspects of ENL is exemplified in the second edition of *Leprosy in Theory and Practice* edited by Cochrane and Davey (¹), where the statement is made that "generally speaking, erythema nodosum is not an unfavorable sign and . . . represents a nuisance factor in the progress of the lepromatous type of leprosy," and in the later statement (¹³) stressing that erythema nodosum leprosum may cause severe constitutional symptoms. In some parts of the world leprosy workers tend to confine the definition of ENL to the mild rose spots that Waters would call 1+ or 2+, and many physicians, when faced with a patient suffering from a more severe attack, complicate matters by producing an additional diagnosis, e.g., "progressive reaction." Although Cochrane (²) believes that it is extremely important to differentiate between the erythema nodosum and progressive reactional phases, the only differentiation that is offered is that in the former condition the reaction is temporary. Such statements only confuse newcomers to leprosy and not infrequently lead them to suspect that their predecessors' logic was imperfect.

The third and most severe problem is the "love-hate" relationship that leprologists have developed with sulfone therapy in the belief that it causes ENL and that the drug must be stopped in order to help the therapy of the reaction. It is believed that studies of patients with this reaction will persuade workers that ENL does not occur until most of the leprosy bacilli have been rendered nonviable, as shown by the MI, and that there is no doubt that those workers (^{18, 23}) were right who suggested that ENL was the result of the death or disintegration of leprosy bacilli.

The question remains as to whether or not it is advisable to reduce or terminate dosage of sulfones, not because they are believed to be the causative agent of the reaction, but for one of two other reasons. These are that diminution of sulfones as suggested by Jopling (¹³), will slow down

the process whereby the patient's tissues have been destroying leprosy bacilli too rapidly, or that ENL is neither a reaction to the sulfone drug nor to the disintegrating bacilli but to an unknown material compounded from these two sources. It remains to be proven that sulfones have any stimulating effect on the tissues that destroy the leprosy bacilli, and it is not believed that this suggestion is tenable, while the other possibility would be more convincing if other antileprosy drugs did not also precipitate reactions.

It is believed that in our present state of knowledge there is no reason to consider that diminishing or stopping sulfones will have any effect on erythema nodosum leprosum, because by the time ENL has become severe almost all the bacilli are no longer viable and consequent cessation of sulfone therapy can neither diminish the speed of death nor alter the tissue reaction to the dead bacilli. No physician can be blamed for seeking any method to alleviate the distressing symptoms of ENL, but it is feared that the emotional desire to help such patients has led to a misunderstanding of the etiology. It is recommended that further consideration be given before a patient is deprived of the major necessity in his life, i.e., a drug that kills the causative organism of the disease. Such a cessation cannot help a patient who may still have a number of viable organisms, as these will be able to multiply and so lead to relapse of the disease.

SUMMARY

An appeal is made for recognition of cases of erythema nodosum leprosum and designation as such. A study of 60 cases of ENL has confirmed earlier suggestions that the reaction appears only when the great majority of leprosy bacilli in the patient's tissues are no longer viable. This, in conjunction with other findings, emphasizes the fact that incrimination of the sulfone drugs as the causative agent of the reaction is untenable. Therefore the cessation of sulfone treatment during the course of ENL is not only illogical but is potentially

dangerous to the patient's progress in that it allows any residual viable bacilli to propagate and extend a previously controlled infection.

RESUMEN

Se hace un llamado para el reconocimiento de casos de erythema nodosum leprosum y su designación como tal. Un estudio de 60 casos de ENL ha confirmado las primeras indicaciones que la reacción aparece solo cuando la gran mayoría de bacilos de la lepra en los tejidos del enfermo no están vivos. Esto, en conjunto con otros hallazgos, acentúa el hecho que culpar a las drogas sulfónicas como el agente causante de la reacción es insostenible. De consiguiente la suspensión del tratamiento de sulfona durante el curso de ENL es no solamente ilógica sino es potencialmente peligrosa para el progreso del paciente en que permite cualquier bacilo viviente residual propagarse y extenderse en una infección controlada previamente.

RÉSUMÉ

Dans cet article, on plaide pour qu'enfin les cas d'erythème noueux soient reconnus et désignés comme tels. Une étude de 60 cas d'ENL a confirmé ce que l'on soupçonnait déjà à la suite d'études antérieures, à savoir que la réaction n'apparaît que lorsque la grande majorité des bacilles de la lèpre présents dans les tissus du malade ne sont plus désormais viables. Ensemble avec d'autres observations, cela indique nettement qu'il n'est plus possible de tenir les sulfones comme l'agent responsable des réactions. Dès lors, l'interruption du traitement sulfoné au cours de l'ENL est non seulement illogique, elle peut également être dangereuse pour le pronostic du malade du fait qu'elle permet aux quelques bacilles qui continuent à être viables de se propager et d'étendre une infection qui jusqu'alors était sous contrôle.

Acknowledgments. This work was carried out in the Sungei Buloh Research Unit, which is jointly administered by the Malaysian Ministry of Health and the British Medical Research Council. Thanks are due to Dr. D. S. Ridley of the Hospital for Tropical Diseases in London for his help with the histology and also to the patients and staff of the Leprosarium for their cooperation.

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