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The Condition of the Peripheral Nerve in Leprosy Under Various Forms of Treatment

Conduction Velocity Studies in Long-Term Follow-Up[1]

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Peripheral nerve lesions are common in leprosy. They may be of two basic types: infiltrative, with inflammation and fibrosis along the nerve, or constrictive, in a patchy form, with signs of compression or strangulation. The nerve lesions may have an insidious, gradual onset with mild clinical signs or they may occur suddenly, especially during leprosy reactions. In many instances therapy may arrest the progress of the nerve damage.

The question arises, however, as to whether, in the absence of leprosy reaction (LR), the fibrosis of the nerve does not sometimes cause an insidiously progressive lesion, without immediately apparent clinical symptoms or signs. An additional problem to be considered is the type of therapy that most effectively influences the nerve lesion.

The sulfones (derivatives of 4,-4'-diaminodiphenylsulfone) were first introduced in 1937 by Buttle *et al.* [7] and Fourneau *et al.* [15] as agents against streptococcal infections, and later by Rist *et al.* [37] and Feldman *et al.* [13] against animal tuberculosis. In 1941, after further assessment [10] they were tried in human leprosy [12]. The good results obtained warranted their wide acceptance as the most commonly used therapeutic agent in leprosy. It should, however, be stressed that among other toxic effects, the sulfones may cause mild neuritis, manifested by paresthesias and dysesthesias [43].

A second group of drugs, mostly used in recalcitrant cases of LR, are the steroids, mainly prednisone and triamcinolone. These drugs may cause, in addition to their metabolic effects, obvious histologic, electromyographic and clinical signs of myopathy or polymyositis. This has been demonstrated experimentally in animals [3, 11, 25] and has been observed in human subjects suffering from various clinical conditions [5, 8, 20, 35]. It would also seem that the addition of fluor in position 9 (as in triamcinolone) further enhances the appearance of steroid myopathy [2, 26, 31, 44].

In 1965, thalidomide (alpha-(N-phthalimido)-glutarimide or N-phthaloyl-glutarimide), first investigated by Kunz *et al.* [29] and previously used as a powerful, non-depressant hypnotic, was introduced as a therapeutic agent with dramatic effects on the neuritis encountered in leprosy reaction of the lepromatous type [40, 41]. However, nothwithstanding its influence on the polyneuritis of leprosy and lack of neurotoxic effects in animals [28], thalidomide has been incriminated as the cause of polyneuropathy in human beings, especially if administered for prolonged periods of time [9, 14, 16, 17, 21, 38].

The question therefore arises in any long-term follow-up of leprosy, as to whether the condition of the peripheral nerve deteriorates, with or without LR and, if it does, whether the pathological process is primarily caused by the basic disease, by the various drugs employed or by a combined effect of both factors.

The parameter selected for the investigation of the nerves in leprosy is the conduction velocity of the motor fibers (MCV), a test whose value and reliability in a variety

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of clinical conditions involving the peripheral nerve has been proven [18, 19, 33, 42].

In the following report we present the results of a six-year follow-up study of leprosy patients who received various therapeutic regimes.

MATERIAL AND METHODS

The investigation was carried out on 103 leprosy patients, of whom 61 were men and 42 women. Sixty-seven were of the lepromatous, 8 of the tuberculoid and 20 of the indeterminate type; 8 had the dimorphous form. These 103 leprosy patients were followed for a period of six years. After the initial evaluation, they underwent repeated medical and bacteriologic examinations at 6-12 month intervals. The medical investigation consisted of a general, dermatologic and neurologic examination; the latter included examination of the muscle power, sensory status, tendon and periosteal reflexes and the presence of the Tinel sign, atrophy or nerve thickening.

The relationship between the type of disease and age appears in Table 1, and between type of disease and duration since onset in Table 2. Table 3 shows the relationship of the disease to the clinical and bacteriologic status. Fifty-two cases were in an arrested state, and all were negative bacteriologically. Fifty-one were clinically active, and of these, 23 were bacteriologically negative and 25 positive.

TABLE 1. *Relationship between type and form of leprosy and age of patient.*

Age	Type				Total
	Lepromatous	Tuberculoid	Indeterminate	Dimorphous	
Up to 20 years	1	—	—	—	1
21–30 "	13	1	6	—	20
31–40 "	15	2	5	1	23
41–50 "	10	1	2	2	15
51–60 "	18	2	2	3	25
61 or over	10	2	5	2	19
Total	67	8	20	8	103

TABLE 2. *Relationship between type and form of leprosy and time interval after onset of disease.*

Onset of disease	Type				Total
	Lepromatous	Tuberculoid	Indeterminate	Dimorphous	
1–5 years	1	—	—	1	2
6–10 "	13	—	3	1	17
11–15 "	13	—	2	2	17
16–20 "	12	5	8	—	25
21–25 "	8	3	4	4	19
26–30 "	5	—	—	—	5
31 or over	15	—	3	—	18
Total	67	8	20	8	103

TABLE 3. *Relationship between type and form of disease and clinical activity and bacteriologic status.*

Clinical status	Bacteriologic status	Type				Total
		Lepromatous	Tuberculoid	Indeterminate	Dimorphous	
Arrested	Negative	25	8	18	1	52
		25	8	18	1	—
	Positive	—	—	—	—	
Active	Negative	19	—	2	5	26
		42	—	2	7	—
	Positive	23	—	—	2	25
Total		67	8	20 —	8	103

The patients received three types of treatment: sulfones alone or sulfones in combination with either prednisone or thalidomide. Table 4 presents the various therapeutic combinations according to the type of disease. All patients received sulfones: 15 received steroids (prednisone) and 27 thalidomide in addition to the sulfones. Prednisone and thalidomide were never administered together, but some patients who had repeated LR received either prednisone or thalidomide in their recurrent attacks. The basic indication for the use of either prednisone or thalidomide was the presence of a LR; in some instances, as will be seen, the patient continued with the same combination of sulfone and either prednisone or thalidomide for longer periods. The usual dose of sulfone was 100 mgm., which was gradually decreased to an average of 25 mgm. daily. The daily dose of prednisone was 5-30 mgm and of thalidomide 300-500 mgm. initially, with a gradual decrease to a main-

TABLE 4. *Relationship between type of disease and therapy.*

Therapy	Type				Total
	Lepromatous	Tuberculoid	Indeterminate	Dimorphous	
S.[a]	42	8	17	4	71
S. + P.[b]	4	—	1	—	5
S. + T.[c]	13	—	1	3	17
S. + P. + T.	8	—	1	1	10
Total	67	8	20	8	103

[a] S. = Sulfone.
[b] P. = Prednisone.
[c] T. = Thalidomide.

TABLE 5. *Type of disease, age, sex and time interval after onset of disease in patients with leprosy reactions.*

Type of disease	Age	Sex	Period since onset of disease
LL 31	21–30 yrs. 9	Male 21	1– 5 yrs. 1
LT 1	31–40 " 8	Female 17	6–10 " 7
LI 2	41–50 " 4		11–15 " 7
LD 4	51–60 " 11		16–20 " 6
	61 & over 6		21–25 " 8
			26 & over 9
Total patients with LR 38	38	38	38

tenance dose of 50-100 mgm./day.

Of the 103 patients, 38 had a total of 127 LR during the six-year follow-up period. Most of the LR were spontaneous, but some were provoked by discontinuation of the sulfone therapy. The type and duration of the disease, and the age and sex of the patients who had LR are presented in Table 5. The clinical manifestations and the clinical and bacteriological status appear in Table 6. From these two tables it can be seen that the most common manifestations were erythema nodosum and neuritis, either separately or together. The clinical manifestations of recurrent LR in the same subject were similar. Of the 38 patients, 12 were clinically in an arrested state and 11 of them were negative bacteriologically. Twenty-six were clinically active and these were all positive bacteriologically. The general data for the 28 patients in whom neuritis was the prominent manifestation of LR appear in Table 7 and the clinical condition and bacteriologic status in Table 8. From these tables it is clear that none of these factors (type of disease, age, sex, period since onset of disease, clinical condition and bacteriologic status) bears any relation to the appearance or development of neuritis as part of the LR.

As already mentioned, either prednisone or thalidomide was administered, in addition to sulfone, at the time of appearance of the LR, sometimes for prolonged periods. Tables 9 and 10 present the accumulated periods of treatment with prednisone and thalidomide respectively, over the six year period of follow-up. Nine patients received prednisone and 21 thalidomide for more than four months; 15 received thalidomide for more than one year and 7 for more than three years. From Table 11, in which only the longest, uninterrupted period of therapy is considered, it can be seen that prednisone was most commonly administered for one to six months while thalidomide was used for more than five

TABLE 6. *Clinical manifestations and condition and bacteriologic status in patients with leprosy reactions.*

Clinical manifestations of LR	Clinical condition	Bacteriologic status
Erythema nodosum 18	Arrested 12	Negative 11
Neuritis 28	Active 26	Positive 27
Other[a] 2		
Erythema nodosum and neuritis 19		
Total LR 38	38	38

[a] Iritis, epididymitis.

TABLE 7. *Type of disease, age, sex and time interval after onset of disease in patients with leprosy reaction manifested by neuritis.*

Type of disease		Age		Sex		Period since onset of disease	
LL	25	21–30 yrs.	8	Male	17	1– 5 yrs.	0
LT	1	31–40 "	6	Female	11	6–10 "	6
LI	1	41–50 "	2			11–15 "	7
LD	1	51–60 "	8			16–20 "	6
		61 & over	4			21–25 "	4
						26 & over	5
Total LR	28		28		28		28

months in 15 patients and for periods of more than three years in 3 patients.

Each patient underwent, in addition to the medical and bacteriologic examination, an investigation of the motor conduction velocity (MCV) at the time of each visit, so that there were at least five follow-up tests per patient. In addition, in the patients with LR, the MCV was examined at least three additional times if the manifestations were dermatologic only, and daily or at two-day intervals if neuritis was

TABLE 8. *Clinical condition and bacteriologic status in patients with leprosy reaction manifested by neuritis.*

Clinical condition		Bacteriologic status	
Arrested	7	Negative	6
Active	21	Positive	22
Total LR	28		28

TABLE 9. *Relationship of prednisone therapy to type of disease and period of administration.*

Period[a]	Type				Total
	Lepromatous	Tuberculoid	Indeterminate	Dimorphous	
15–30 days	2	—	—	—	2
1–2 months	1	—	1	—	2
3–4 "	1	—	1	—	2
5–6 "	4	—	—	1	5
7–9 "	2	—	—	—	2
10–12 "	1	—	—	—	1
1–2 years	1	—	—	—	1
Total	12	—	2	1	15

[a] Not continuously—in accumulated periods.

TABLE 10. *Relationship of thalidomide therapy to type of disease and period of administration.*

Period*	Type				Total
	Lepromatous	Tuberculoid	Indeterminate	Dimorphous	
15–30 days	2	—	—	1	3
1–3 months	2	—	1	—	3
4–6 "	5	—	—	—	5
7–9 "	—	—	—	1	1
10–12 "	—	—	—	—	—
1–2 years	7	—	—	1	8
3 or more years	8	—	1	1	10
Total	24	—	2	4	30

* Not continuously—in accumulated periods.

the prominent sign. In most cases the MCV was also examined 3-5 days and 10-15 days after the signs of LR had subsided.

The MCV investigations were carried out with a constant voltage stimulator, up to 200 V., duration of pulse one millisecond (m.sec.) and frequency of one pulse per second. The stimulator had very good ground isolation. The stimulus was given by a two pronged stimulator and the responses were recorded through a teflon-coated concentric needle inserted into the most distal muscle. The response was amplified from 400 to 1000 times; it was recorded on tape and later accumulated and measured by a computer of average transients (CAT). The CAT was triggered by the stimulus artefact and the responses were synchronously summated in the CAT memory. The results were obtained in analog form, displayed on an oscilloscope and were then either photographed or plotted on ultraviolet paper. The advantages of this technic are accuracy of measurement of the period of latency and duration of the evoked response and control over the consistency of response. An additional advantage is that processing and measurement can be undertaken after the patient has been discharged and that the procedure is not time-consuming. In cases in which the evoked response was of very low amplitude, or where it tended to be obscured by either spontaneous activity or lack of complete relaxation, the CAT was able to extract the real evoked response by exact, synchronous accumulation. The MCV examinations were carried out in a room with constant temperaure, always using the same technic. As it was found that the most commonly damaged nerve was the ulnar, all MCV tests were carried out on this nerve, on both sides in each patient. In patients with LR, only the most severely damaged ulnar nerve was followed up. Before the actual examination, the procedure was explained to the patient and a brief period was provided for relaxation. The ulnar nerve

TABLE 11. *Longest period of continuous administration of prednisone and thalidomide.*

Longes period	Prednisone	Thalidomide
Less than one month	2	2
1–2 months	4	6
3–4 "	4	4
5–6 "	3	1
7–9 "	1	1
10–12 "	—	3
1–2 years	1	7
3 or more years	—	3
Total	15	27

TABLE 12. *Results of initial examination of MCV[a] in 103 patients*

Nerve	Velocity		Distal latency		Duration of evoked response		Total examined
	N.[b]	A.[c]	N.	A.	N.	A.	
Ulnar							
No.	156	50	151	55	150	56	206
%	75.7	24.3	73.3	26.7	72.8	27.2	100.0
Median							
No.	68	9	66	11	66	11	77
%	87.0	13.0	84.4	15.6	84.4	15.6	100.0
Radial							
No.	43	3	43	3	43	3	46
%	93.5	6.5	93.5	6.5	93.5	6.5	100.0
Common peroneal							
No.	91	17	90	18	89	19	108
%	84.2	15.8	83.3	16.7	82.4	17.6	100.0
Total							
No.	358	79	350	87	348	89	437
%	81.9	18.1	80.0	20.0	79.6	20.4	100.0

[a] The results are considered according to the number of nerves examined.
[b] N. = Normal.
[c] A. = Abnormal, including complete lack of response.

was examined at at least three points: axillary, above the elbow, and at the level of the wrist.

Only supramaximal current was used. The distance was measured with an elastic tape, with the elbow in full extension and the wrist in the neutral position, special care being taken not to pull the skin. For MCV of the ulnar nerve the recording electrode was inserted in the abductor digiti minimi muscle. In a number of cases, according to the clinical condition, the median, radial, and common peroneal nerves were also examined (Table 12).

The interpretation of the MCV was based on the analysis of three basic criteria: velocity, latency, and duration and form of the evoked response. The velocity was considered normal if the results obtained were between 50-69 m/sec. for the ulnar nerve, 47-66 for the median, 50-72 for the radial and 43-57 for the common peroneal nerve ([23, 24, 34, 39]). The latency was interpreted according to the segment of nerve examined and the distance to the recording electrode. The age of the patient and variations of temperature (either in the laboratory or of the patient) were also considered. The final interpretation of MCV was also based on comparison of values received on both sides: a difference in velocity of more than 10 m/sec., even if both results were within normal limits, was considered abnormal for the slower conducting nerve. Since a tendency to slower conduction on the non-dominant side has been observed ([4, 30]), the handedness of the patient was also taken into account. In order to avoid any diurnal variations of MCV ([22]), most investigations were carried out at approximately the same time of day.

RESULTS

The 103 leprosy patients underwent, during the six-year period of follow-up, a total of 1153 MCV examinations. Of these, 437 were carried out at the time of the initial examination, 308 in the follow-up of the 65 patients without signs of LR, and 408 in those with various signs of LR (Tables 5-8). The results of MCV were divided into two groups, i.e., normal and abnormal.

The results of the initial examination are presented in Table 12, in which they are related to individual nerves. The highest percentage of abnormal MCV was obtained from the ulnar (24.3%) and the lowest from the radial nerve (6.5%). In a few cases, while the velocity was within normal limits, both the latency and the duration of the evoked response were abnormal, indicating a lesion of the distal part of the nerve.

Table 13 presents the results of MCV in the 65 patients without leprosy reaction, at the end of the six-year follow-up period. A certain deterioration of the MCV, most prominent in the ulnar nerve, may be observed. While 121 ulnar nerves in these patients were conducting normally at the beginning of the follow-up period, only 112 were doing so at the end of this period. The same deterioration, but to a lesser degree, was noticed in the common peroneal nerve. This decrease of MCV was never abrupt; repeated examinations showed a gradual slowing down towards abnormal values, accompanied by an insidious clinical loss of motor power. In most instances the duration of the evoked response was the first parameter to change. Throughout the follow-up period these patients received only sulfone and their clinical condition and bacteriological status did not show any fluctuation.

TABLE 13. *Results of MCV after six years of follow-up in 65 patients without leprosy reaction.*

Nerve	Normal	Abnormal[a]	Total
Ulnar			
No.	112[b]	18	130
%	68.9	31.1	100.0
Median			
No.	25	5	30
%	84.2	15.8	100.0
Radial			
No.	14	1	15
%	93.3	6.7	100.0
Common peroneal			
No.	54[c]	14	68
%	79.4	20.6	100.0
Total			
No.	309	101	410
%	75.4	14.6	100.0

[a] According to latency, velocity and/or duration of evoked response.
[b] Of 121 ulnar nerves previously normal.
[c] Of 58 common peroneal nerves previously normal.

The situation was completely different in the 38 patients who had had at least one leprosy reaction (LR) and especially so in those with a resultant neuritis. The following tables, in which various relations are presented, refer only to the number of patients or of LR and not to the total number of nerves examined. The reason for this is that in many cases only one nerve, in general the most severely damaged (ulnar), was examined repeatedly, mainly because of pain and the apprehension of the patient. The clinical diagnosis of neuritis as the manifestation of LR was based on the appearance of severe pain in the distribution of at least one peripheral nerve, and possibly thickening of the nerve with or without a positive Tinel sign, dysesthesia, loss of sensation and motor deficit.

Table 14 presents the results of MCV in relation to the number of days since the appearance of clinical signs of LR treated by sulfones only. The value of "normal" CV was taken to be that found constantly in the previous examinations of the same nerve, regardless of whether this was within the usually accepted normal values or not. Only those values which, on comparison with the previous ones, showed a velocity slower by at least 10m/sec. and/or a prolonged latency period were regarded as

TABLE 14. *Results of MCV in relation to the time interval after onset of leprosy reaction—without antireactional treatment.*

MCV	Period in days				
	1–2	3–4	5–7	8–10	11–14
Normal[a]	27	9	8	7	7
Abnormal[b]	11	29	30	31	31
Total	38	38	38	38	38

[a] Previous MCV values considered as normal.
[b] Abnormal values considered only if MCV decreased by at least 10 m/sec.

abnormal. Table 14 shows that of the 38 patients, 11 had an abnormal CV at the end of the second day after the onset of clinical signs, 29 within four days, 30 at the end of one week and 31 after 8 days or more. A few remarkable facts emerge from the analysis of this group, which, not having received any antireactional therapy, may be considered as a control-group. Firstly, in the majority of cases the MCV became abnormal within four days after the onset of the LR. Secondly, of the 10 patients who had erythema nodosum as their only clinical manifestation of LR, without any clinical evidence of nerve involvement, 7 had a constantly normal MCV. On the other hand, in the remaining 3 patients who started their LR with erythema nodosum only, and exhibited an abnormal MCV by the end of one week, clinical evidence of nerve lesions developed in the following days. This finding will be discussed later. A third point of interest, not reflected in this table, is that in the great majority of LR the ulnar nerve was the one most frequently damaged, in general slightly more so on one side, but without relation to age, handedness or previous degree of damage. The common peroneal nerve was next in frequency, followed by the median. The radial nerve was only very rarely damaged, either clinically or electrically, in the present series of patients.

Of the 89 LR, in the 28 patients with neuritis as the major clinical manifestation, 63 were treated with thalidomide and 26 with prednisone. In recurrent LR these therapeutic trials were often carried out consecutively in the same patient. Antireactional therapy was instituted within two days of the onset of LR.

Table 15 shows the results of MCV in the 26 LR treated with sulfone and prednisone. The incidence of nerve lesions, as

TABLE 15. *Results of MCV in relation to the time interval after onset of LR—treated with prednisone*

MCV	Period in days						
	1–2	3–4	5–7	8–10	11–14	15–21	22–30
Normal	10	5	4	7	10	14	19
Abnormal	16	21	22	19	16	12	7
Total	26	26	26	26	26	26	26

manifested by abnormal MCV and parallel clinical signs, increased within the first week of the onset of LR. It was only after the first week and especially during the third and fourth weeks that the nerves returned to their previous state. It must however be stressed that in seven patients the nerve examined failed to return to its previous state in spite of relatively high dosages (30 mgm/d) of prednisone. The typical neuralgic pain tended to lessen and to disappear gradually after 4-7 days of prednisone therapy.

Table 16 shows the MCV in 63 LR cases treated with sulfone and thalidomide. It is obvious that after only four days the number of nerves affected started to decrease, and within two weeks the great majority of those examined had returned to their previous condition. The neuralgic pain tended to disappear two to five days after the thalidomide therapy was initiated. Only two patients failed to fully respond to this treatment.

Five patients received thalidomide for periods of one month to four years, without suffering from LR. None of these patients developed any signs of LR during this period. Furthermore, ten patients who had had at least one LR, continued the thalidomide therapy for periods of at least one year. During the thalidomide administration none of these patients suffered from a LR.

Of the 27 patients treated repeatedly with thalidomide, four complained of paresthesias and dysesthesias of the extremities which, after brief periods of time, disappeared spontaneously. It was not certain whether these symptoms had been present before the administration of thalidomide. In any case, it should be stressed that continued thalidomide therapy neither aggravated these complaints nor caused any other untoward effect. In a fifth patient, after three weeks of thalidomide therapy, and while the signs of a LR neuritis were receding, a widespread polyneuritis occurred, with severe neuralgic pain of the hands and feet, sensory loss and motor deficit of most of the limb muscles, more pronounced distally. A lumbar puncture carried out at this time showed a marked rise of the proteins in the cerebrospinal fluid without increase of cells; a diagnosis of Guillain-Barré syndrome was therefore obvious. The thalidomide was discontinued. Within three months all the neurological signs had almost disappeared. Thalidomide therapy was reinstated and the patient, who by this time had received doses of 100 mgm. daily for over one year, did not have any sign of LR or neuritis. It should also be stressed that none of the four previously mentioned patients suffered from any recurrence of dysesthesias or paresthesias, or any other neurologic sign, in spite of administration of thalidomide for prolonged (over one year) periods of time.

None of the 15 patients who received prednisone developed signs of either neuropathy or myopathy. On the other hand, some of those who received the drug for periods of over six months developed diabetes, and signs related to sodium retention.

No relationship was found between the effect of thalidomide and prednisone and

TABLE 16. *Results of MCV in relation to the time interval after onset of LR—treated with thalidomide.*

	Period in days						
MCV	1–2	3–4	5–7	8–10	11–14	15–21	22–30
Normal	19	18	29	46	59	61	61
Abnormal	44	45	34	17	4	2	2
Total	63	63	63	63	63	63	63

the type or form of leprosy, although the number of tuberculoid and dimorphous patients is admittedly too small for valid, significant conclusions. No relationship was found with regard to the age of the patient, the time interval since the onset of the disease, clinical activity, bacteriologic status or the number of nerves damaged. It should, however, be stressed that while both antireactional drugs influenced the course of LR, thalidomide had a dramatic effect, especially when neuritis was the prominent manifestation.

DISCUSSION AND CONCLUSIONS

A number of important conclusions can be drawn from this investigation, but at the same time several questions and problems are raised.

First, as already demonstrated in a previous study ([32]), it is apparent that leprosy patients may, while under sulfone therapy and without LR, show a gradual, insidious deterioration of the condition of the peripheral nerve. This finding probably indicates that the peripheral nerve is subjected to increasing pressure, with resultant hypoxia from the presence of even a few adhesions. The MCV tests show that this damage may occur either in the trunk or distal branches, and that it is most common in the ulnar nerve.

With regard to LR, it is obvious that sulfones have no beneficial effect whatsoever upon its course, and that without antireactional therapy the nerve lesion progresses as if no therapy was being provided. On the other hand, both prednisone and thalidomide had a marked effect upon the LR. The effect of prednisone is slower, and that of thalidomide faster and often dramatic when nerve lesions are present. The mechanism of action of these two drugs is still unexplained. While it may be assumed that the antiphlogistic, analgesic, fibrinolytic and antiimmune effects of prednisone play a role, it is so far unknown whether thalidomide possesses such modes of action.

In this connection it should be mentioned also that while LR occurred under combined therapy with sulfone and prednisone, it did not do so when thalidomide was being used. Although the number of patients is too small for evaluation of statistical significance, it is remarkable that the few patients who had suffered from numerous repeated LR (with lepromatous leprosy) in the past, had no new LR for periods of over three years while under thalidomide treatment.

The problem of thalidomide polyneuropathy also raises some questions. Although reports were found in the literature that thalidomide may cause nerve lesions ([9, 14, 16, 17, 21, 38]), it is very difficult to understand the mechanism of this process. It has been stressed that the thalidomide polyneuropathy usually occurs after a minimum of three to six months of administration, often after 18-24 months ([6, 14, 17, 36]), and only after the intake of large amounts ([17]). If a direct toxic action is considered likely, the neuropathic effect of thalidomide should have occurred more frequently in leprosy patients, in whom the nerves may already be partially damaged and who receive the drug for long periods and in large doses. Of the five patients in our series who developed additional signs of polyneuropathy, one almost certainly had a Guillian-Barré syndrome, while in the remaining four the signs were probably caused by the underlying disease. This opinion is strengthened by a number of facts. First, the symptoms of neuropathy were observed in these patients after only three to five weeks of thalidomide therapy and after the intake of relatively small quantities of the drug; furthermore it is not sure whether these complaints were not present before the administration of the drug. Secondly, the signs and symptoms disappeared completely within a few weeks or months; this is in contrast to the descriptions of thalidomide neuropathy in the literature ([17, 21]) which stress that, in most cases, even partial amelioration may take years after the discontinuation of the drug. Thirdly, the same five patients who developed signs of neuropathy again received thalidomide after the neurological signs had receded, sometimes for periods of more than one year, and yet none of them developed further signs of neuropathy. The few histologic studies carried out in thal-

idomide polyneuropathy ([17, 27]) have reported degeneration of axis cylinders and of the myelin sheath, without segmental demyelination, and a selective loss of nerve fibers with large diameter; these findings indicate only that neuropathy is present, without however, being specific for any particular type ([1]).

We have tentatively concluded, therefore, that at least in our patients, no neurologic signs of thalidomide toxicity were observed. However, even if mild paresthesias and dysesthesias were to occur because of thalidomide, it is our impression that this should not constitute a contraindication to use of the drug, because of the excellent effect it has on the LR and because all other drugs presently used in leprosy and LR have similar or worse side effects. Our opinion, based on reported experience with the drug, is that until absolute objective and well controlled proof that thalidomide has toxic effects upon the peripheral nerve is presented, the drug should be further used in leprosy.

The MCV has been proven to be a good, reliable tool for following the condition of the nerve trunk in leprosy, and it is our impression that it is an accurate indicator of the effect of any drug used. While it has, on one hand, the disadvantages of being influenced by many intrinsic and extraneous factors and of having wide normal limits, it is, on the other hand, almost the only tool that allows comparative studies of the nerve trunk. This is important in leprosy, and especially in LR, because the main clinical manifestations are often related to the nerve trunk alone, and may sometimes be only subjective.

In the present investigation of LR, the MCV showed decreased velocity and increased latency within 48 hours of the appearance of pain, often before nerve thickening was apparent. As such, it is of value in the objective determination of the presence of LR neuritis. Moreover, while in some cases MCV showed only a mild decrease in velocity, in others it was unrecordable or of extremely low velocity. If many more cases are studied, and the findings correlated with sensory conduction and histologic studies, it should be possible to quantitate, to a certain extent, the degree of nerve damage. MCV studies have been shown to be of value not only in patients in whom neuritis was evident clinically, but also in a few instances in which the dermatologic lesions were predominant. A slowing of velocity, prolonged latency and increased duration of the evoked response, indicated the possibility of a subclinical neuritis, which was proven by the appearance of clinical signs a few days later.

The fact that the nerve may undergo progressive constriction, can be demonstrated only with the help of electrical tests and, if the changes are in the nerve trunk, by MCV. Clinical examination cannot distinguish mild changes in the sensory or motor status, and the patient may even be unaware of them because of their insidiousness and his own ability to adapt to the changes produced.

The significance of MCV as a prognostic tool was demonstrated by the degree of improvement on treatment which, except for pain, always preceded any clinical improvement by 2-5 days. This is important in assessing the value of the drug used, in deciding whether the most effective drug has been administered, and in determining the degree of residual damage after the leprosy reaction.

Finally, it should be stressed again that, regardless of its many advantages, the MCV is useful only if the test is carried out under standardized conditions and if provisions are made for the elimination of as many causes of error or artefacts as possible.

SUMMARY

A total of 103 leprosy patients were followed-up for a period of six years. During this time they underwent regular clinical, bacteriologic and motor conduction examinations.

Of the 103 patients, 38 had 127 leprosy reactions, 89 of them with neuritis. Sixty-three of the latter were treated with thalidomide and 26 with prednisone. These two antireactional drugs were evaluated with regard to their effect upon the neuritis (by clinical and electrical means) and to their possible toxic effects.

In some of the patients without leprosy reaction the MCV demonstrated a slow deterioration of the nerve trunk. In a few cases of leprosy reactions manifested by erythema nodosum, the presence of subclinical neuritis was demonstrable.

All the means of evaluation used showed thalidomide to have a more rapid effect than prednisone. Thalidomide, in low therapeutic doses for long periods, also apparently succeeded in preventing recurrence of leprosy reactions. The complications observed in five patients could not be related to thalidomide and were probably caused by the underlying disease in four instances, and by a Guillain-Barré syndrome in the fifth case.

The significance and possible pitfalls of MCV are discussed.

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