

Follow-up Study of Nerve Lesions in Leprosy Using the Time Intensity Curve Test^{1,2}

Alexander Magora³

Peripheral nerve lesions play an important role in leprosy because of resultant muscular weakness and sensory loss, which may cause contractures, deformities and physical disability. The damage may occur in the trunk or branches of the nerve and depends on the spread, activity, progress and stage of leprosy.

The nerve lesion may appear, or become worse, at any stage of the disease unless adequate therapy is instituted. Sometimes, however, not even adequate treatment is able to prevent superimposed nerve damage; this may be seen, for example, in leprosy reactions. It is not known whether inconspicuous nerve lesions can occur while the patient remains in good clinical condition and the laboratory examinations remain negative.

The nerve lesions vary in degree and localization, and little is known about their rate of progress or regression under adequate therapeutic conditions. A long term follow-up study of nerve lesions, therefore, would be significant.

The present investigation was carried out by means of repeated examinations of the time-intensity curve (TIC). This test has already proven reliable both as a diagnostic and prognostic aid in the evaluation of peripheral nerves in a variety of lesions (1, 3, 5, 6, 8, 10, 11, 14, 16, 17, 18). It has the additional advantage of making possible selective examination of nerve branches localized within individual muscles.

MATERIALS AND METHODS

Twenty-one patients with lepromatous leprosy were chosen for the study. For various reasons six of them did not attend regularly and were, therefore, subsequently excluded. The remaining 15 patients were followed for a period of six years. The main criteria for their selection were: negative bacteriologic smears for at least two years prior to this study, good response to maintenance therapy, no obvious vacillations in their clinical condition, and good cooperation. Their ages varied between 23 and 61 years and the disease had first been detected 6 to 28 years before the start of this investigation.

All the patients were on maintenance therapy of sulfone, 25-100 mgm. per dose. No other drugs were administered during the investigation. During the six year period of study none of the patients showed any signs of clinically detectable neurologic deterioration, and their histologic and bacteriologic examinations remained negative. With the exception of brief periods of mild to moderate pain along the ulnar nerve, none of the patients exhibited clinical signs of leprosy reaction.

No mention will be made of the patients' specific age, sex and country of origin as these data are irrelevant to the present report; the same applies to the sensory status which, except when there was extensive damage, did not parallel the motor condition.

Each patient underwent a thorough general and neurologic examination, histologic and bacteriologic evaluation and TIC determination approximately every six months.

In order to standardize the results of the clinical and electric evaluations, and for purposes of comparison, the following three

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³ A. Magora, M.D., Department of Physical Medicine and Rehabilitation, Hadassah University Hospital, P.O. Box 499, and Government Hospital for Hansen's Disease, Jerusalem, Israel.

muscles were examined bilaterally in each patient. They were chosen as being representative of the three most commonly damaged long peripheral nerves; opponens pollicis (OP) (median nerve), abductor digiti quinti (ADQ) (ulnar nerve) and peroneus longus (PL) (common peroneal nerve). Another reason for their selection was, that of the muscles innervated by these nerves, they appear to be among the first to be damaged and also because two of them are small, intrinsic (OP and ADQ) and one a large (PL) muscle. Ease of technical approach was another factor in the choice of these muscles.

The clinical muscle power was considered normal (grade 5) if the muscle was able to counter maximal resistance; grade 4 if it was able to withstand some degree of resistance; grade 3 if able to carry out its full range of motion against gravity, but without additional opposition; grade 2 if motion was possible only when gravity was eliminated; grade 1 if some muscular contraction was observed, and 0 if no volitional muscular contraction could be detected.

The TIC examinations were carried out with a constant current stimulator of high output impedance. This method was used because it apparently avoids fluctuations of voltage between the electrodes thereby minimizing the importance of skin resistance and allowing a brief preparatory period. According to the experience of others^(12, 13) this method is also more accurate in scattered nerve lesions of the polyneuritis or polymyositis type which are also

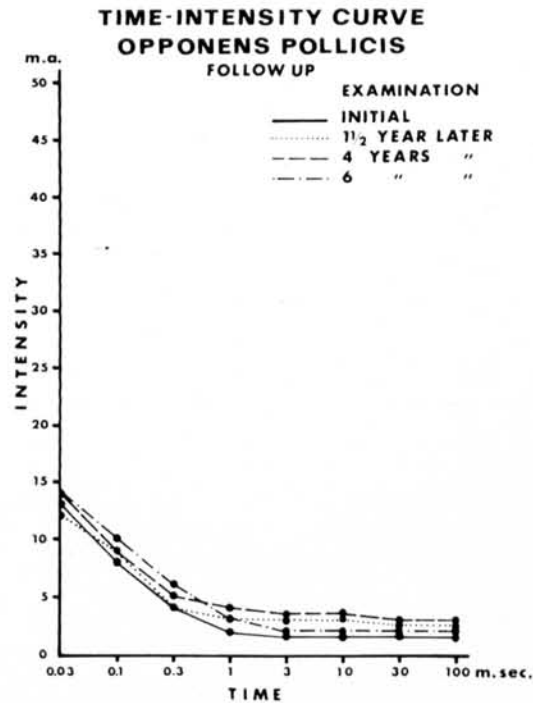


FIG. 1. TIC from a representative opponens pollicis muscle, over a period of six years. The TI curve is normal, as demonstrated by the regular slope and mild, gradual leftward rise. The clinical muscle power was grade 5 in all the examinations.

seen in leprosy. The pulse frequency was one per second. The apparatus was inspected every three months for any change in the amplitude, form or duration of its pulse. The examinations were all carried out in a constant temperature room, and always by the same investigator. To ensure

TABLE 1. Muscle power^a and atrophy. Initial examination.

| Muscle | Clinically determined grade of muscle power | | | | | | Atrophy | | Total |
|------------------------|---|---|---|---|---|---|---------|--------|-------|
| | 5 | 4 | 3 | 2 | 1 | 0 | Present | Absent | |
| Opponens pollicis | 26 | 2 | 1 | — | — | 1 | 2 | 28 | 30 |
| Abductor digiti quinti | 21 | 2 | 3 | 1 | 1 | 2 | 5 | 25 | 30 |
| Peroneus longus | 24 | 1 | 1 | 3 | — | 1 | 4 | 26 | 30 |
| Total | 71 | 5 | 5 | 4 | 1 | 4 | 11 | 79 | 90 |

^a Definition of grading given in text.

TABLE 2. Relationship between muscle power and the initial TIC examination.

| Clinically determined muscle power | Time intensity curve indication of denervation | | | | Total muscle examinations |
|------------------------------------|--|---------|--------|-----------------------|---------------------------|
| | Normal | Partial | Severe | Unobtainable response | |
| Normal ^a | 66 | 5 | — | — | 71 |
| Weak ^b | 2 | 7 | 1 | — | 10 |
| Very weak ^c | — | 1 | 3 | 5 | 9 |
| Total | 68 | 13 | 4 | 5 | 90 |

^a Grade 5.^b Grade 3-4.^c Grade 0-2.

exactitude each TIC examination was repeated twice, always using the same technic.

Before the TIC examination, the skin was thoroughly cleaned and dried. No heating of the skin was used mainly because some of the patients had anesthetic

lesions and because there was always ample time for adaptation to the room temperature. The electrodes were placed at the ends of the small muscles (OP and ADQ) and with a distance of 10.0 cm. between them for the PL (large muscle).

The TIC examination was performed according to the technic described by Wynn Parry (17, 18, 19, 20). The intensity of current, measured by milliamperes (ma) necessary to elicit the slightest visible muscular contraction was observed at eight preset times (measured in milliseconds (ms); 100 (rheobase), 30, 10, 3, 1, 0.3, 0.1 and 0.03 respectively). The results were plotted on a curve whose shape, slope and shift were analyzed. Each additional follow-up TIC was superimposed on the previous one and compared with it.

According to this technic, a normal curve (implying normally innervated muscle) is indicated by a regular shape, low slope and a leftward rise (Fig. 1); irregularities, kinks or sharp discontinuities, a steep slope and shift of the rise to the right, indicate partial or complete denervation (Fig. 2-5).

RESULTS

Because the 15 patients included in the present report may be considered similar in most respects, and for simplicity of comparison, the figures presented are chosen as representative.

The degree of muscle power and atrophy found at the initial examination are detailed in Table 1. Of the 90 muscles, 71 had

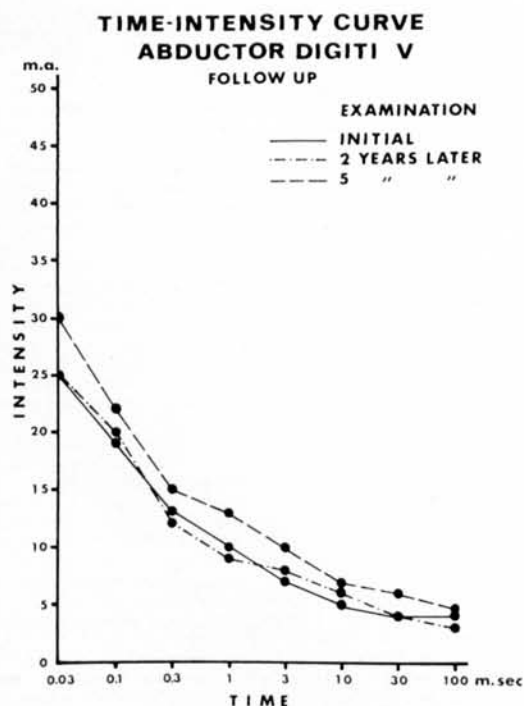


FIG. 2. TIC from an abductor digiti quinti, over a five-year period. The irregular slope, early rise and shift to the right indicate partial denervation. There is no change of the TIC during the follow-up period. The muscle power was grade 3 in all the examinations.

TABLE 3. Relationship between muscle power and the TIC two years after initial examination.

| Clinically determined muscle power | Time intensity curve indication of denervation | | | | Total muscle examinations |
|------------------------------------|--|---------|--------|-----------------------|---------------------------|
| | Normal | Partial | Severe | Unobtainable response | |
| Normal ^a | 64 | 4 | 1 | — | 69 |
| Weak ^a | 1 | 7 | 1 | — | 9 |
| Very weak ^a | — | 2 | 5 | 5 | 12 |
| Total | 65 | 13 | 7 | 5 | 90 |

^a See Table 2 for grades.

normal (grade 5) strength and the remaining 19, various degrees of weakness; ADQ (ulnar nerve) was the most commonly damaged muscle. In the following tables, the muscle power is redivided into three main groups: normal (grade 5), weak (grade 3-4), and very weak (grade 0-2). The TIC examination is presented in four main groups: normal (Fig. 1); partial denervation (Figs. 2, 3) as indicated by kinking of the curve, a slight shift to the right and a somewhat higher slope; severe denervation, as indicated by a sharp rise of the slope, discontinuity and a shift to the right (Figs. 4-5), and unobtainable (no response to an intensity of 50 ma).

The relationship between muscle power and TIC at the time of the initial examination is presented in Table 2. Sixty-six of the 71 normal muscles had a normal TIC, while five showed signs of partial denervation. On the other hand, two of the weak group had normal curves while seven showed partial and one, severe denervation. In the very weak group, four showed partial or severe denervation and in five, no response was elicited. This absence of response indicates complete denervation and atrophy of the muscle (especially if small).

Table 3 shows the same relationship two years after the initial examination. As no striking changes were found at shorter time intervals, the following tables present the results from two year intervals. There were 69 normal, 9 weak and 12 very weak muscles. Comparison with Table 1 shows that the number of normal and weak muscles

decreased. The decrease in muscle power followed a pattern of slow, gradual weakening without signs of general neurologic deterioration. Of the 69 normal muscles, five had abnormal curves. Of the nine weak muscles, one had a normal TIC (a PL, see Discussion), seven showed signs of partial, and one of severe denervation. The very weak group showed denervation in seven,

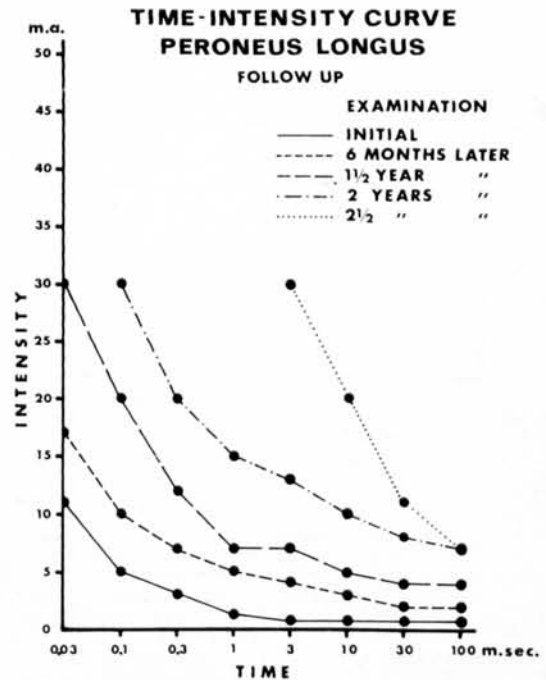


FIG. 3. TIC from a peroneus longus muscle, over a five-year period. The follow-up demonstrates a gradually developing partial denervation. The initial muscle power was grade 5; it was grade 4 after one year and in all the ensuing examinations, grade 3.

TABLE 4. Relationship between muscle power and the TIC four years after initial examination.

| Clinically determined muscle power | Time intensity curve indication of denervation | | | | Total muscle examinations |
|------------------------------------|--|---------|--------|-----------------------|---------------------------|
| | Normal | Partial | Severe | Unobtainable response | |
| Normal ^a | 62 | 5 | — | — | 67 |
| Weak ^a | — | 10 | 1 | — | 11 |
| Very weak ^a | — | 1 | 4 | 7 | 12 |
| Total | 62 | 16 | 5 | 7 | 90 |

^a See Table 2 for grades.

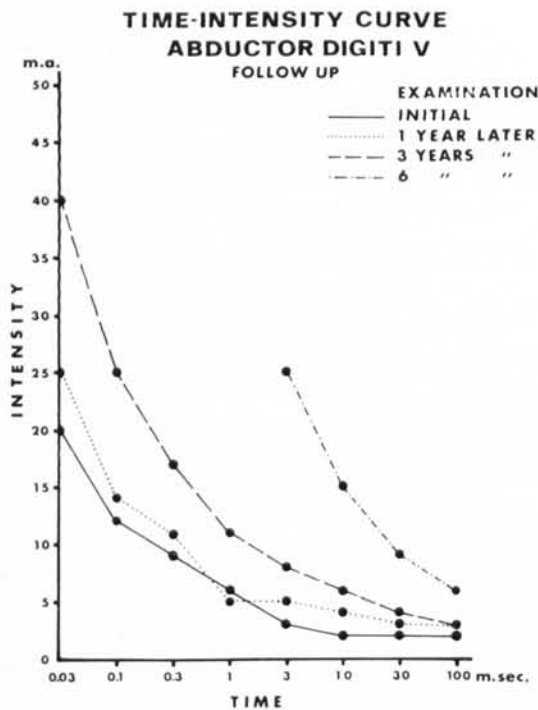


FIG. 4. TIC from an abductor digiti quinti, over a six-year period. The initial TIC examination shows partial denervation, with gradual worsening. The muscle power was initially grade 5 and decreased to grade 2.

and the same five muscles as previously were completely denervated and atrophied.

The same trend is evident at four (Table 4) and six years after the initial examination (Table 5). Of the initial 71 normal muscles, only 65 were still normal after six years and three of these showed a TIC of partial denervation. At the same interval

six of the 12 previously very weak muscles showed severe denervation, and in the remaining six it was impossible to elicit any response.

From Figure 3 it is evident that the deterioration of some of the muscles occurred insidiously (never abruptly as in a lepra reaction) and within variable, but always protracted, periods of time. From Figure 4 it is noted that a muscle with normal power and a TIC showing any degree of partial denervation, gradually deteriorated, while a normal TIC in a grade 5 muscle (Fig. 1) indicates that the muscle will remain normal.

DISCUSSION

The TIC determination evaluates the excitability of the nerve in relation to that of the muscle, and the proportion of normal and abnormal innervation (^{2, 17}). It actually relates, in curve form, the intensity of the stimulus and its duration. Through the application of an electrical stimulus between two electrodes, it permits the examination of the whole of small (in the present instance the OP and ADQ) or part of large muscles (PL).

Even though the examination of rheobase and chronaxy is less time consuming, we cannot agree with Walthard(¹⁵) that for this reason and because they are not painful, these procedures should be preferred to TIC. First, both in our experience and that of others(⁹), the TIC examination may be uncomfortable, but never painful if employed at times less than 300 ms. This

TABLE 5. Relationship between muscle power and the TIC six years after initial examination.

| Clinically determined muscle power | Time intensity curve indication of denervation | | | | Total muscle examinations |
|------------------------------------|--|---------|--------|-----------------------|---------------------------|
| | Normal | Partial | Severe | Unobtainable response | |
| Normal ^a | 62 | 3 | — | — | 65 |
| Weak ^a | — | 12 | 1 | — | 13 |
| Very weak ^a | — | — | 6 | 6 | 12 |
| Total | 62 | 15 | 7 | 6 | 90 |

^a See Table 2 for grades.

may be due to the use of a constant current technic. Furthermore, the TIC has the obvious advantages of demonstrating partial denervation (1, 2, 4, 5, 7, 20) and of indicating the trend of the nerve lesion.

There is no doubt that electromyography (EMG) is by far a more delicate and accurate explorative diagnostic tool but the TIC permits evaluation of a whole muscle and, through repeated comparison of curves, has value in assessing the prognosis of the lesion (7, 11). Similarly, measurement of motor conduction velocity allows evaluation of the nerve trunk but not of nerve branches localized within individual muscles (7).

The present study, though based on a small number of patients for such a broad spectrum disease, presents a number of important findings.

First, a number of muscles have clearly shown an insidious, gradual deterioration. Contrary to general belief, this may be a fairly common occurrence in spite of apparent inactivity of disease, good response to therapy, negative laboratory tests and lack of lepra reaction. The progressive weakness of the muscle may be detected only through careful examinations of individual muscles (not groups), always carried out by the same investigator, using the same technic. In most instances, the patient was not aware of the deterioration, mainly because the gradual progression of the weakness provided sufficient time for adaptation. The neuropathic origin of the deterioration, either in the nerve trunk or nerve

branch, was demonstrated. It may be assumed that at some time or another there was infiltration of the nerve and the resultant mild pressure caused neurapraxia. Supportive evidence for this assumption is given by the TIC examination which, in a

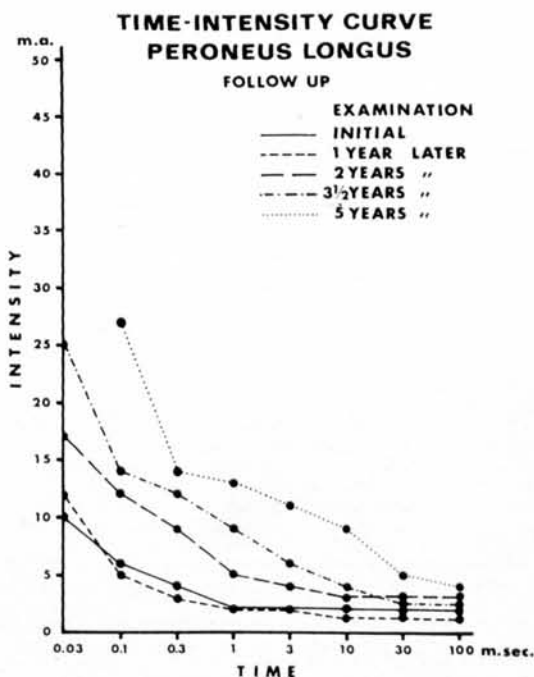


FIG. 5. TIC from a peroneus longus muscle, over two and a half years. The initial TIC examination was normal, although the muscle strength was grade 4. The second TIC examination showed partial denervation; later, there was gradual worsening of both the TIC and muscle power.

number of instances, was initially indicative of mild partial denervation although clinically normal muscle power was present. In subsequent examinations these were the very muscles that showed gradual onset of weakness. Additional indirect evidence for this finding was that patchy, irregular sensory loss was always present in these cases. This, of course, is not a reliable indicator of the motor condition as, in many cases, the irregular sensory loss was for a long time not accompanied by muscular weakness.

Second, the TIC has been of value in indicating mild partial denervation in unsuspected cases. On the other hand, the TIC was normal initially in two muscles that were weak (Table 2) while in the following examination, the TIC indicated partial denervation. A possible explanation for this discrepancy may be that these two muscles were PL, a large muscle. As already noted, the TIC will only reflect changes occurring between the two electrodes, allowing, therefore, evaluation of only part of a large muscle. In this specific instance it is probable that while part of the muscle was sufficiently damaged to show a decrease of strength, the TIC was performed, by chance, in a part which was still healthy. In the ensuing months, the lesion progressed and the TIC also became abnormal.

Third, in some instances, the TIC showed severe denervation while the muscle was only weak. Without exception, these muscles later became very weak. This finding, together with the abnormal TIC in clinically healthy muscles, which subsequently deteriorated, indicates that the TIC is a good prognostic tool. The TIC may even demonstrate, in certain instances, nerve lesions which are not yet clinically manifest. This is corroborated by two facts. First, in no instances in which the muscle power and the TIC were normal, did muscular weakness subsequently develop. Second, whenever a discrepancy existed between muscle strength and the TIC, with the latter being worse, the clinical condition soon followed the trend indicated by the electric test. These findings would seem to indicate that the TIC has

value both in detecting unsuspected localized nerve lesions, and in providing a reliable indicator of the likely course of the damage. This may prove valuable in the general follow-up of patients with or without motor defects. It is useful in the determination of clinically suspected local lesions during the assessment of specific nerve branch condition if individual muscle corrective surgery is contemplated. It may be useful in the evaluation of drug effects.

Finally, the TIC is a very simple, brief test which does not require elaborate equipment or highly specialized, prolonged training. It may cause some discomfort to the patient, but never to the extent of actual pain (except in the presence of lepra reaction). It would seem that the best technic is to examine at eight preset times, as the curve which can then be plotted may demonstrate even mild partial denervation, and is available for future comparative studies. It is warranted, therefore, that TIC be included in the battery of tests necessary for the evaluation of the peripheral nerve condition in leprosy, especially if this is to be followed for a protracted period of time.

SUMMARY

Fifteen patients suffering from lepromatous leprosy underwent neurologic, histologic, bacteriologic and time-intensity curve examinations, at six month intervals, for a period of six years. Ninety muscles were examined: the opponens pollicis, abductor digiti quinti and peroneus longus, bilaterally in each of the 15 patients. Although the patient's clinical condition was good and the laboratory tests were negative, in a number of instances a gradual muscular weakness developed over a protracted period of time. This was preceded by time-intensity-curve (TIC) evidence of partial denervation. Whenever both the muscular power and the TIC were normal, no deterioration occurred in the ensuing period. The TIC has been proven to be an accurate, simple electric test with a definite value in the investigation of lesions in individual nerve branches, and in determining their prognosis.

RESUMEN

Quince enfermos con lepra lepromatosa fueron sometidos a exámenes neurológicos, histológicos, y bacteriológicos, y al de curva tiempo-intensidad a intervalos de seis meses por un período de seis años. Noventa músculos fueron examinados: el *opponens pollicis*, *abductor digiti quinti* y *peroneus longus*, bilateralmente en cada uno de los 15 enfermos. Aunque la condición clínica del enfermo era buena y los exámenes de laboratorio eran negativos, en un número de casos se desarrolló una debilidad muscular gradual en un período prolongado de tiempo. Esto fue precedido por la curva tiempo-intensidad (TIC) evidencia de una denervación parcial. Siempre que ambos, el poder muscular y el TIC fueron normales, no se producía daño en el período siguiente. El TIC ha demostrado ser una prueba simple y exacta, con un valor definitivo en la investigación de lesiones en ramas nerviosas individuales, y en la determinación de su pronóstico.

RÉSUMÉ

Quinze malades souffrant de lèpre lépromateuse ont été soumis à des examens neurologiques, histologiques et bactériologiques, à des intervalles de 6 mois, et ce pour une période de 6 ans; on a également dressé des courbes de l'intensité en fonction du temps. Un total de 90 muscles a été examiné, à savoir, chez chacun des 15 malades, et des deux côtés, l'opposant du pouce, l'abducteur du cinquième doigt, et le long péronier. Malgré un état clinique satisfaisant chez les malades, et des épreuves de laboratoire négatives, une faiblesse musculaire progressive s'est développée à la longue dans un certain nombre de cas. Cette faiblesse était annoncée par des signes de dénervation partielle, dans les courbes de l'intensité en fonction du temps (TIC). Chaque fois que la force musculaire et le TIC étaient l'un et l'autre normaux, aucune détérioration n'est survenue dans la période qui suivait. Le TIC s'est révélé être une épreuve électrique précise et simple; elle présente un intérêt indubitable pour l'étude des lésions survenant dans les ramifications nerveuses individuelles, ainsi que pour déterminer leur pronostic.

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