

Impairment of repetitive impulse conduction in experimentally demyelinated and pressure-injured nerves^{1,2}

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SUMMARY Repetitive impulse conduction was studied in segmentally demyelinated peripheral nerves in guinea-pigs with experimental allergic neuritis (EAN) and in pressure-injured frog sciatic nerves. Normal guinea-pig sciatic-peroneal nerves maintained at 37°C conducted compound action potentials with only minor amplitude decreases at stimulus frequencies up to 200/sec. In contrast, nerves in EAN guinea-pigs maintained at 37°C demonstrated a rapidly progressive decrease in action potential amplitude when stimulated as slowly as 10-25/sec. The decrease is greater the higher the frequency of stimulation. At 100 stimuli/sec all EAN preparations showed more than a 50% reduction in action potential amplitude. These effects are reversible. In pressure-injured frog sciatic nerves similar effects occurred at stimulus frequencies as low as 50/sec. Normal frog nerves conducted up to 200 impulses/sec with little amplitude decrease. The probable mechanism and clinical significance of these results are discussed.

There is a striking similarity in the aberrations of axonal conduction associated with both peripheral and central nervous system demyelination. Marked conduction slowing as well as blockade have been reported in segmentally demyelinated peripheral nerves associated with experimental allergic neuritis (EAN) (Kaeser and Lambert, 1962; Cragg and Thomas, 1964; Hall, 1967), diphtheritic polyneuritis (McDonald, 1963; Morgan-Hughes, 1968; Lehmann, Tackmann, and Lehmann, 1971), tourniquet paralysis (Mayer and Denny-Brown, 1964), and foreign body reaction (Lehmann and Ule, 1964a; Lehmann and Ule, 1964b). Identical defects have been reported in central nervous system demyelination induced by cerebrospinal fluid barbotage (Mayer, 1966) and by the intraneural injection of diphtheria toxin (McDonald and Sears, 1970). Kaeser and Lambert (1962) have suggested that the decreased conduction velocity in segmentally demyelinated nerve might be related to the loss of myelin, which causes a decrease in the density of action current flowing out through the node of Ranvier and thereby

prolongs the time needed to trigger an action potential. Similarly, a block of conduction might be due to a reduction of the action current density below the minimum amount needed just to maintain conduction.

More recently, another conduction defect has been observed in both peripheral and central demyelination. An impairment can occur in the propagation of relatively low frequencies of impulses. In segmental demyelination in peripheral nerves, conduction failure has been observed at stimulation frequencies as low as 60 c/sec (Lehmann, Lehmann, and Tackmann, 1971), while in central nervous system demyelination conduction failure has been observed as low as 290 c/sec (McDonald and Sears, 1970). These findings might also be related to a reduction in action current density. Such a relationship is suggested by Tasaki's classical studies on conduction in myelinated axons (Tasaki, 1953). When an isolated axon conducts two consecutive impulses such that the second falls within the relative refractory period of the first, the action current generated by the second impulse is decreased; the decrease is greater the closer the second impulse lies in relation to the beginning of the relative refractory period. Though this

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phenomenon causes a slowing of conduction in normal fibres there is no danger of a conduction block (except at very high conduction frequencies—that is, around 900–1000 c/sec) since there is normally a five to seven times excess of action current over the minimal amount just needed to maintain conduction. However, if there is a decrease in this action current excess or so-called ‘safety factor’, a failure of conduction would be expected to occur at unusually low frequencies. Tasaki has shown that such a phenomenon does occur in lightly narcotized nerve (Tasaki, 1953). He has also demonstrated that the same explanation can account for the historical Wedensky inhibition phenomenon³ (Tasaki, 1953).

If Tasaki’s ideas apply to the impaired frequency response observed in demyelinated nerve, then this defect cannot be considered to be specific for demyelination. Instead, the same type of conduction defect would be expected to occur in any nerve fibre in which there is a decreased safety factor. For these reasons, segmentally demyelinated peripheral nerves in guinea-pigs with EAN and pressure-injured frog sciatic nerves, both of which have been postulated to have alterations in action current that would result in a decreased safety factor (Lorente de Nó, 1947; Kaeser and Lambert, 1962), have been tested for their response to repetitive electrical stimulation. In both preparations, a similar impairment of frequency response has been observed.

METHODS

1. *In vitro* FROG NERVE PREPARATION *a. Electrical recording* An excised frog (*Rana pipiens*) sciatic nerve trunk was placed in a stimulating-recording apparatus equipped with paired stainless steel or platinum electrodes. A detailed, illustrated description of the apparatus was presented in a previous publication (Davis and Jacobson, 1971). Electrical stimuli were delivered to the thicker, proximal end of the nerve and compound action potentials were recorded monophasically at the other end by crushing the nerve between the recording electrodes. The preparation was grounded midway between the

stimulating and recording electrodes. Stimuli consisted of 7 sec volleys of 0.1 msec rectangular electrical pulses at frequencies ranging from 10–250/sec. These were delivered from a Grass S-8 stimulator and stimulus isolation unit. A Grass constant current unit (CCU-1A) was placed between the stimulus isolation unit and the preparation to offset any effect due to altered electrode resistance. The stimulus intensity was set at five times the level just needed to produce a maximum compound action potential. In most experiments a single 0.1 msec rectangular pulse was applied 500 msec after the 7 sec volley in order to detect any post-tetanic effects. Compound action potentials were displayed on a Tektronix dual beam 561-A oscilloscope after amplification with a Tektronix FM 122-low level preamplifier and were photographed with a Polaroid camera.

b. Pressure lesions A short segment of nerve located approximately midway between the stimulating and recording electrodes was submerged in a Ringer-filled pool. The temperature of the Ringer solution was monitored with a Yellow-Springs model 44 telethermometer and thermistor probe. Segments of the nerve lying outside the pool were carefully encased in petroleum jelly to prevent drying. Pressure lesions were made in the middle of the segment of nerve submerged in the Ringer-filled pool according to the method of Lorente de Nó (Lorente de Nó, 1947). A lesion, 1 mm long, was made by gently squeezing the nerve with flexible eye forceps; the pressure was gradually increased until the maximum amplitude of the compound A spike was decreased approximately 60 to 80%. Lorente de Nó has shown that, if this type of lesion is not too wide and the continuity of the nerve fibres is not disrupted, some axons continue to conduct because the safety factor enables impulses to ‘jump across’ the lesion (Lorente de Nó, 1947). His observation that these pressure-injured fibres conduct impulses at a decreased velocity has been confirmed in our previous studies (Davis and Jacobson, 1971). It has also been confirmed that if the length of the lesion is extended beyond 4 or 5 mm conduction fails completely or nearly so, supporting the idea that the impulse at the site of the 1 mm lesion ‘jumps’ rather than ‘conducts through’ the injured region.

The Ringer solution was adjusted to pH 7.5 and had the following composition in millimoles per litre: NaCl 115, KCl 2.5, CaCl₂ 1.8, NaHCO₃ 2.4, Tris buffer 1.0.

2. *In vivo* GUINEA-PIG PREPARATION *a. Experimental allergic neuritis (EAN)* EAN was induced in adult male and female guinea-pigs by the method of Waksman and Adams (Waksman and Adams, 1956). Using aseptic techniques, 2 g of sciatic nerve from two freshly killed rabbits were cut into short

³ In 1885 Wedensky reported that a fatigued or narcotized nerve-muscle preparation stimulated through its nerve may respond with only a brief initial contraction rather than a sustained tetanus when the stimulation frequency is increased beyond a certain point (Wedensky, 1885). Though this so-called Wedensky inhibition was due to a failure of neuromuscular transmission, it later became clear that the same phenomenon could also occur with localized changes in the nerve. Thus, in a later paper (Wedensky, 1903) he described the same contraction pattern when the nerve was locally narcotized or injured by exposure to high temperatures or concentrated solutions of electrolytes.

lengths and then further sliced with a freezing microtome set at 5 μ advancements. To this tissue mush were added 5 ml. isotonic saline, 10 ml. Freund's adjuvant (Difco) and 150 mg killed, dried *Mycobacterium butyricum* (Difco). The mixture was emulsified in a cold electric blender. The resulting emulsion was nearly solid and did not spread when a small drop was added to water. Fifteen guinea pigs weighing between 300 and 500 g were injected intradermally with 0.1 ml. of the emulsion in each forefoot pad. Nine animals developed a moderate to severe clinical picture of EAN; of these, two died before testing. The remaining seven were studied as described next.

b. Electrical recording Under light sodium pentobarbital anaesthesia administered intraperitoneally and supplemented with ether inhalation, the sciatic and peroneal nerves were exposed in the thigh and tibial regions, respectively. The sciatic nerve was severed proximally at the apex of the thigh wound, and all muscles supplied by the sciatic nerve and its branches were denervated. Care was taken to preserve the nerve's blood supply. Skin flaps were raised to enclose a pool of mineral oil that covered the exposed regions of nerve. Mineral oil temperature was maintained at 37° C by means of a heat lamp and continuously monitored with a Yellow-Springs model 44 tele-thermometer and thermistor probe. The proximal portion of the sciatic nerve was stimulated through paired silver electrodes while compound action potentials were recorded with paired platinum electrodes placed along the peroneal nerve. A ground electrode was inserted under the sciatic nerve approximately midway between the stimulating and recording electrodes. Stimulus parameters and recording techniques were the same as those described previously for the frog except for occasional substitution of diphasic recording for monophasic.

c. Histology Some of the normal and EAN guinea-pig nerves were later fixed for at least one week in 10% formaldehyde-saline, dehydrated, and embedded in paraffin. Sections were stained with the luxol fast blue-cresyl fast violet method for myelin. Haematoxylin and eosin was also used as a general tissue stain.

RESULTS

1. GUINEA-PIG Normal guinea-pig sciatic-peroneal nerves maintained at 37° C conducted compound action potentials with little or no amplitude variation at stimulation frequencies below 200/sec (Fig. 1, Table 1). In contrast, EAN guinea-pig nerves maintained at 37° C demonstrated a decrease in compound action potential

amplitude at stimulation frequencies as low as 10-25/sec; this effect was more marked with increasing frequency of stimulation (Fig. 2 and Table 1). The time course of the decline in action potential amplitude varied in different preparations. Some showed a gradual decline as in Fig. 2, while in others the effect was precipitous with the establishment of a steady-like state within seconds. At 100 stimuli per second all EAN preparations demonstrated more than a 50% decrease in action potential amplitude (Table 1). As seen in Fig. 2, the post-volley

TABLE 1
FREQUENCY RESPONSE IN NORMAL
AND EAN GUINEA-PIG NERVE

Exp.	Temp. (° C)	Percent decrease in compound action potential amplitude at varying stimulus frequencies (sec)							
		10	25	50	75	100	125	150	200
I Control									
1	37	0	0	0	0	2.8	2.8	2.8	2.8
2	37	2.6	2.6	2.5	2.5	2.5	3.7	6.2	6.2
3	37	0	3.8	3.8	4.0	4.0	4.0	8.0	8.0
4	37	2.9	2.9	5.9	5.4	8.1	7.9	13.2	13.2
5	37	0	4.8	6.4	6.4	6.4	7.7	11.3	11.3
II EAN									
1	37	16	26	56	69.2	67.4	69		
2	37	6	24	60	74	80	84	86	
3	37		40.6	50		56			
4	37		16.6	31.3					
5	37.5					80.8			
6	37		23.1	43.3		63.9			
7	37	25	40	62.5	85	90			

stimulus (occurring 0.5 sec after cessation of the 7 sec volley) frequently elicited an action potential with a reduced amplitude. This depression is more marked the higher the frequency of the preceding volley (Fig. 2). It is probably related to the post-tetanic depression in EAN reported by Cragg and Thomas (1964). After a 2 min tetanus at 368 c/sec they found a depression lasting up to five minutes. Although the time course of this effect was not systematically examined in the present study, it reversed within seconds; in the experiment shown in Fig. 2 the time elapsed between the last two volleys was approximately 45 sec. Significant post-tetanic effects were not observed in normal guinea-pig nerves.

Limited histological examinations of some EAN nerves were performed as described in the

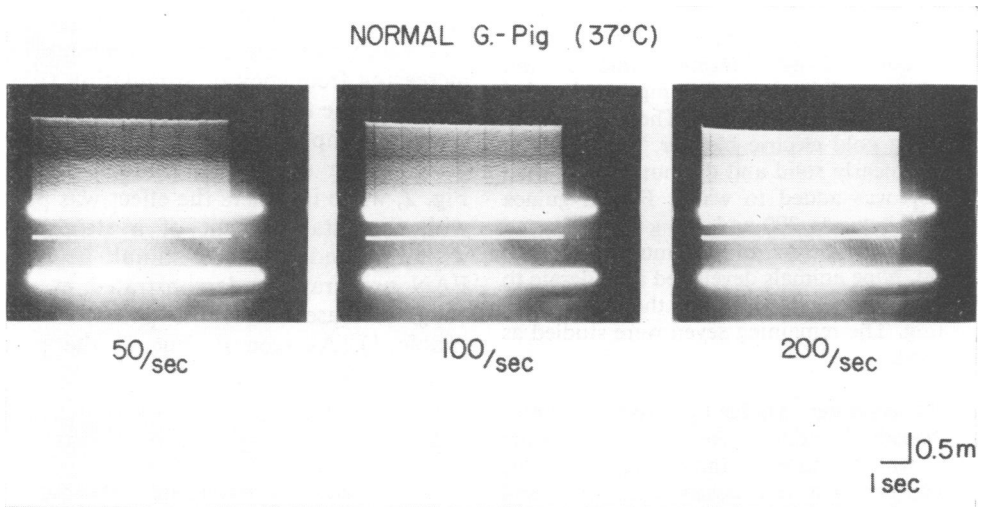


FIG. 1. Successive responses of a normal guinea-pig nerve to 7 sec stimulus volleys at 50 (left), 100 (middle), and 200 (right) c/sec. Stimulus intensity was five times supramaximal. Upper trace: monophasic, compound action potentials. Lower trace: stimulus monitor. Only a relatively small, progressive decline in action potential amplitude occurs even at the highest frequency.

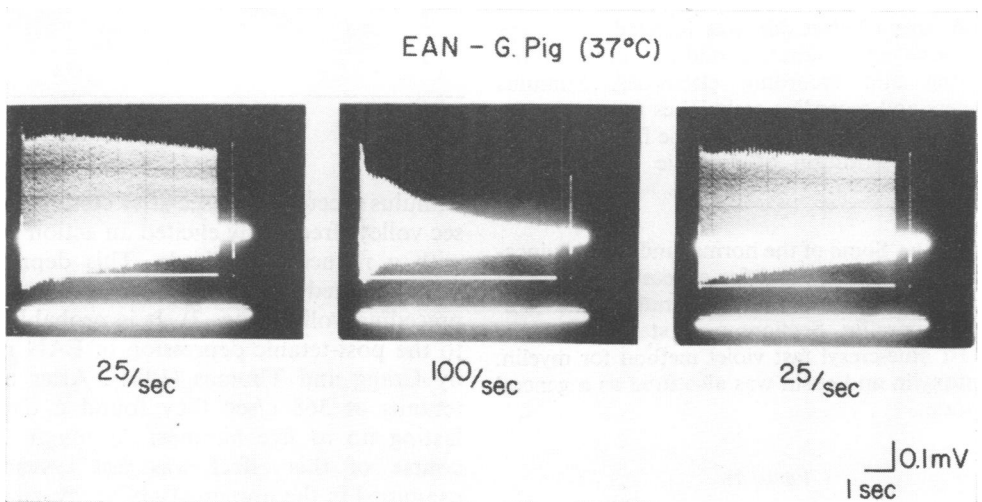


FIG. 2. Successive responses of an EAN guinea-pig nerve to 7 sec stimulus volleys at 25 (left), 100 (middle), and 25 (right) c/sec. Stimulus intensity was five times supramaximal. Upper trace: diphasic compound action potentials. Lower trace: stimulus monitor. A moderate and severe, progressive decline in action potential amplitude occurs at 25 and 100 c/sec, respectively. Note that the single test stimulus occurring 0.5 sec after the termination of the 100 c/sec volley evokes a submaximal amplitude action potential; approximately 45 sec later the response to 25 c/sec stimulation indicates that recovery has occurred (compare left and right).

Methods section. Segments of nerve lying approximately midway between the stimulating and recording electrodes were studied; these showed segmental demyelinating changes identical to those described and illustrated in an earlier study from this laboratory (Davis and Jacobson, 1971).

2. FROG Three separate experimental procedures were employed on each frog sciatic nerve studied. Before making a pressure lesion the nerve was stimulated at varying frequencies using two different stimulus intensities. First the nerve was tested at the usual intensity, which (as described in the Methods section) was five times the minimum amount needed to produce a maximal compound action potential. Nerves stimulated in this manner at frequencies below 200/sec conducted compound action potentials with little or no amplitude variation (Fig. 3, left; and Table 2, control, A).

Next the stimulus intensity was decreased to a level that produced a submaximal compound action potential; this submaximal stimulus was carefully adjusted so that a slight further decrement in its intensity produced a marked decrease in the action potential amplitude. In

TABLE 2
FREQUENCY RESPONSE IN NORMAL AND PRESSURE-INJURED FROG NERVE

Exp.	Temp. (° C)	Percent decrease in compound action potential amplitude at varying stimulus frequencies (c/sec)			
		50	100	150	200
I Control					
A. Supramaximal stimulus					
1	23	0	0	4.5	14.3
2	23	2.4	2.4	7.5	13.1
3	26.2	0	0	2.4	2.6
4	28	0.9	2.8	4.6	6.5
5	26	0	2.0	2.1	8.3
B. Submaximal stimulus					
1	23	28.1	56.3	71	74.2
2	23	28.6	50	61.5	82.6
3	26.2	30.4	40	52.5	60
4	28	28.1	45.2	59.5	68.7
5	26	26.7	41.4	50	63.6
II Pressure lesion					
A. Supramaximal stimulus					
1	23	17.1	34.5	56.5	70.8
2	23	16.1	28.5	53.6	65.5
3	26.2	5.7	25.7	43.4	53.8
4	28	6.2	16.6	29.6	36
5	26	25.7	48.2	58.4	70

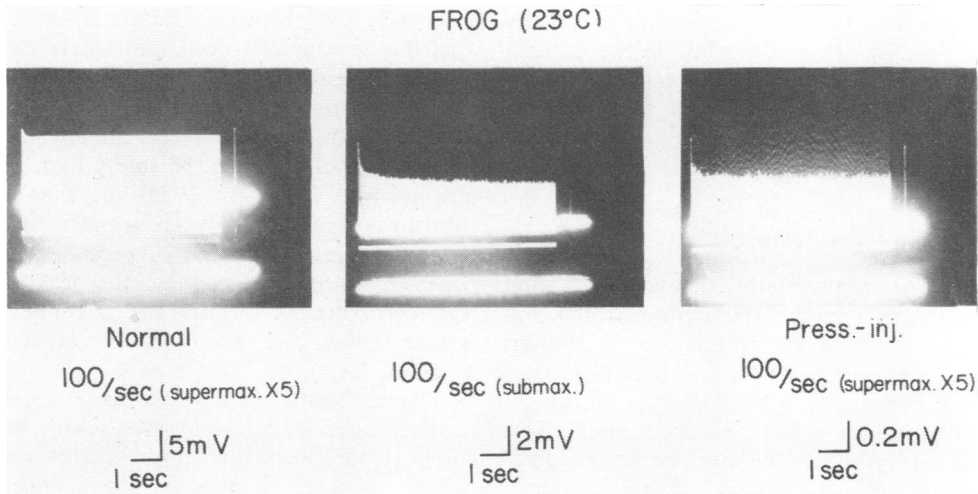


FIG. 3. Responses of a frog nerve to 7 sec stimulus volleys at 100 c/sec before (left, middle) and after (right) making a pressure-injury. Upper trace: monophasic, compound action potentials. Lower trace: stimulus monitor. Left and middle, response of normal nerve to five times supramaximal and submaximal stimulus intensities, respectively. The submaximal stimulus results in an abrupt and progressive decline in action potential amplitude. Right, after the production of a pressure-injury there is an abrupt and progressive decline in action potential amplitude even with a five times supramaximal stimulus. See Results section for explanation.

this situation the stimulus can be considered to be just threshold for many fibres. This threshold electrical stimulus is analogous to the amount of action current available for impulse propagation in a nerve fibre whose safety factor is drastically reduced to a value of 1. As seen in Table 2 (control, B) and Fig. 3 (centre) the same nerves now show a marked decrease in action potential amplitude, which becomes more marked with increasing frequency of stimulation. In Fig. 3 (centre) the initial response decreases precipitously and within several seconds approaches a steady state.

Pressure lesions were then made in the same nerves and the response to five times supra-maximal stimulation observed. As seen in Table 2 (pressure lesion) and Fig. 3 (right), the responses are similar to submaximally stimulated normal nerve, with impaired conduction occurring at frequencies as low as 50/sec. In the case of submaximally stimulated nerve the effect is no doubt due to the failure of the threshold stimulus to stimulate during the relative refractory period of the preceding impulse. In the pressure-injured nerve stimulated with a five times supra-maximal stimulus the effect is presumed to be related to a decrease in the density of action current available for maintenance of propagation at the site of the lesion. In both instances the offered explanations are analogous, the main difference being that in the former the 'weak link' is the externally applied electrical stimulus, while in the latter it is the intrinsic, natural stimulus (action current).

Unlike the findings with EAN, the pressure-injured frog nerves did not demonstrate a post-tetanic depression.

DISCUSSION

In both the segmentally demyelinated and pressure-injured nerves the demonstrated impairment to repetitive stimulation is similar. There is an abrupt decrease in the amplitude of the compound action potential often approaching a steady-like state within seconds. This decrease can be caused by any one or combination of the following factors. These include a block of conduction in some fibres, a decreased conduction velocity causing increased temporal dispersion or a decrease in the action potential amplitude of individual axons. It is likely that all three factors contribute to the decline in the compound action potential. As mentioned in the introduction, both a slowing of conduction and

a decrease in action current (and also action potential) occur when an impulse is initiated during the relative refractory period of a preceding impulse. The most severe conduction defect related to the latter change would be a complete block when the action current falls below the minimum amount needed to maintain conduction. The very marked decreases in compound action potential amplitude observed in this study are compatible with a conduction block in some fibres. A definitive answer would, of course, require a similar study on single axons.

The abrupt decrease in action potential amplitude seen at the beginning of a stimulus volley is probably an example of Wedensky inhibition. Fibres with severely decreased safety factors might be able to conduct a limited number of closely spaced impulses but with repetition there would be a gradual whittling down of the action current (if impulses are separated by intervals less than the relative refractory period) and an abrupt block would eventually occur. The time course of this Wedensky-like inhibition would largely depend upon the number and severity of diseased or injured axons. If the conduction safety factor ratio was only slightly greater than 1 in a very large number of fibres, a very large and abrupt decrease in action potential amplitude would be expected. On the other hand, a more widely distributed range of decreased safety factors in the same number of fibres should cause a more gradual decrease in amplitude of the compound action potential. These effects are not prominent in normal nerves since the safety factor ratio is around 5 to 7 (Tasaki, 1953), allowing conduction to continue even when impulses fall in the relative refractory period of preceding activity. In fact, in normal nerves, the least interval between successive impulses is only slightly greater than the absolute refractory period (Tasaki, 1953).

The similarity of the responses in segmentally demyelinated nerve and pressure-injured nerve support the idea that any adverse condition which tends to depress the conduction safety factor will result in an impaired response to repetitive stimulation. As mentioned in the introduction both segmentally demyelinated and pressure-injured nerves have been postulated to have a decreased safety factor. It is important to stress, however, that the decreased safety factors are brought about by different means in these

two preparations. In EAN the action current density is believed to be decreased by the widened nodal gap as well as by shunting of current through demyelinated internodes (Kaeser and Lambert, 1962). In pressure-injured nerve where the impulse is believed to 'jump over' the blocked segment, current must flow through a longer segment and therefore through a greater internal longitudinal resistance. In addition, the current presumably still flowing out of the nodes in the blocked segment is unavailable for propagation. It is not known whether or not alterations in excitability also contribute to safety factor changes in these preparations. A discussion of conduction parameters that can affect the safety factor has been presented elsewhere (Davis, 1970).

Phenomenologically, the similarity of conduction defects in segmental demyelination and pressure-injured nerve includes more than the frequency response changes. Both preparations exhibit slowing of conduction (Lorente de Nó, 1947; Kaeser and Lambert, 1962), conduction block (Lorente de Nó, 1947; Cragg and Thomas, 1964) and an increased sensitivity to temperature (Davis and Jacobson, 1971). The usefulness of the pressure-injured preparation in studying possible conduction defects in demyelinating diseases such as multiple sclerosis has been described in a previous communication (Davis and Jacobson, 1971). It has been shown that conduction in pressure-injured nerves is improved by lowering the concentration of calcium ions around the site of the lesion. This effect is believed to be due to a decrease in threshold caused by the calcium depletion which, in turn, increases the conduction safety factor. This idea was tested clinically in multiple sclerosis patients by observing the effects of hypocalcaemic inducing agents on visual and oculomotor function. Transient improvement in scotomas, nystagmus, and oculomotor paresis occurred with intravenous infusions of sodium bicarbonate or disodium edetate (Na_2EDTA) (Davis, Becker, Michael, and Sorensen, 1970).

The demonstration that conduction failure can occur at very low frequencies in segmentally demyelinated nerve raises the possibility that the phenomenon may have clinical significance in the segmental demyelinating neuropathies as well as in central nervous system demyelinating disorders. McDonald and Sears (1970) have suggested that the failure of demyelinated axons faithfully to conduct repetitive activity could

help explain such symptoms as the rapid increase of muscle weakness during exercise. The Wedensky-like inhibition could also explain certain sensory phenomena. For example, multiple sclerosis patients who have optic nerve lesions can experience a 'fading out' of vision while looking at an object continuously for several seconds (Bender, 1963). This adaptation phenomenon is short-lived and can usually be reversed simply by closing the eyes for several seconds.

It would appear that studies on conduction defects in experimental demyelinated models and even pressure-injured nerve can contribute to our understanding of the pathophysiology of clinical demyelinating conditions. This appears to be particularly true when phenomena are viewed in terms of general concepts of axonal physiology; with closer probing of specific conduction parameters such as resting potential, threshold, action current, spike amplitude-duration, etc., it is likely that important dissimilarities will emerge.

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