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CHANGES IN CONDUCTION VELOCITY AND FIBRE SIZE PROXIMAL TO PERIPHERAL NERVE LESIONS

BY B. G. CRAGG AND P. K. THOMAS

From the Department of Anatomy, University College London, and the Academic Unit, Institute of Neurology, Queen Square, London, W.C. 1

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Our interest in the changes that occur proximal to peripheral nerve lesions was stimulated by the finding that conduction velocity may be reduced proximal to such lesions in man. This has been shown for compression of the deep branch of the ulnar nerve in the hand (Ebeling, Gilliatt & Thomas, 1960), compression of the median nerve at the wrist (Thomas, 1960) and after suture of the median and ulnar nerves at the wrist following traumatic section (Gilliatt, 1961).

Previous investigations in animals have yielded conflicting results. There have been a number of reports that conduction velocity in the central stump is reduced after peripheral nerve section. Acheson, Lee & Morrison (1942) severed the phrenic nerve distally in cats and found that conduction velocity was usually slower in the affected nerve than in the intact nerve after 1–3 weeks. Similarly, Gutmann & Holubář (1951) reported that conduction velocity becomes progressively reduced in the central stump after section of the peroneal nerve in the rabbit. More recently Eccles, Krnjević & Miledi (1959) and Kiraly & Krnjević (1959) showed that in various limb nerves of the cat conduction velocity was slowed proximal to sections performed 6–39 days previously.

On the other hand, Sanders & Whitteridge (1946) found that when the peroneal nerve of the rabbit was crushed, conduction velocity was slightly *increased* proximal to the lesion between 56 and 123 days after operation, and normal at later stages (456 and 486 days). Furthermore, Kiraly & Krnjević (1959) reported that 40 days after the nerve to the lateral head of gastrocnemius of a cat had been crushed conduction velocity was only slightly less than normal.

In an attempt to clarify the issue we have made observations on the peroneal nerve of the rabbit after a variety of lesions and have followed the changes in conduction velocity and nerve-fibre diameter occurring proximal to the lesion between 7 and 446 days after operation. It seemed possible that the disparity between the results of previous investigators might be explained in terms of the different lesions inflicted and the varying

times after operation at which the observations had been made. Apart from the types of lesion made by previous workers, namely crushing and section, we have also examined the effects of section and immediate suture and those produced by applying a persistent constriction to the nerve. Gutmann & Sanders (1943) found that fibres in the central stump above a crush show a reduction in diameter for at least 130 days, but that at later stages (200–300 days) fibre size returns to normal. After severance and suture, although a similar initial diminution occurred, the subsequent increase was not seen, even as late as 346 days after suture. It therefore seemed possible that simple crushing might affect conduction velocity proximal to the lesion differently from severance and suture. Furthermore, different effects might also be produced by a persistent partial constriction applied to the nerve. Weiss & Hiscoe (1948) have shown that under such circumstances axoplasm accumulates in the fibres above the lesion because of interference with its normal proximal-distal flow.

METHODS

The experiments were all performed on adult rabbits which were unselected with respect to sex, weight and breed. At a preliminary operation, carried out under sodium pentobarbitone (Nembutal, Abbott Laboratories, Ltd.) anaesthesia with full aseptic precautions, the lesions were made on the left peroneal nerve in the lower part of the thigh approximately 0·5 cm above the point at which it passes beneath the lateral head of gastrocnemius. The opposite nerve was left untouched and used for control observations.

Four types of lesion were made: simple crushing, section with avulsion of the peripheral stump, section and immediate suture, and ligature. The majority of the observations were made with simple crush lesions (fourteen animals), in which the nerve was crushed with smooth-tipped forceps for 10 sec. With this procedure degeneration of all myelinated fibres distal to the lesion occurs, but since continuity of the endoneurial tubes is preserved regeneration is rapid and complete (Gutmann, Guttmann, Medawar & Young, 1942). In eight animals the nerve was cut with scissors and the peripheral stump avulsed so that regeneration failed to occur and a neuroma formed at the tip of the central stump. In six animals the nerve was cut and the ends united with a fibrin clot (Young & Medawar, 1940); under these circumstances, regeneration is less complete than after crushing, recovery of both fibre number and size in the peripheral stump being defective (Gutmann & Sanders, 1943). Finally, in three animals a steel wire ligature was tied around the nerve so as partially to constrict it and left *in situ*. This produces an initial crush lesion with degeneration of all the larger myelinated fibres distal to the lesion, only a few small myelinated fibres remaining intact. Under these circumstances regeneration occurs, but fibre size distal to the ligature remains small (Weiss & Taylor, 1944; Duncan, 1948).

Conduction velocity was measured *in vivo* under urethane anaesthesia (2·5 g/kg), after survival periods of 7–446 days. The peroneal nerve was carefully exposed and separated from the tibial trunk from the sciatic notch to the knee, and large skin flaps were raised to form the walls of a bath which was filled with liquid paraffin. The temperature of the rabbit was maintained by an electric blanket and warm liquid paraffin was added to the bath as necessary before each measurement of latency to keep the temperature measured beside the nerve trunk within 0·5° C of the initial temperature. The latter was within the range 36–38° C and was made the same for both sides of each animal.

A pair of silver-wire electrodes with a separation of 3 mm was placed on the distal end of the nerve just above the level of the lesion for stimulation. The proximal electrode of the pair delivered negative stimulus pulses of about 0·1 msec duration derived from an isolating transformer, and the amplitude of the pulse was set to elicit a maximal A fibre action potential at the first latency measurement and not altered subsequently during the experiment. The recording electrodes were placed at distances of 10–70 mm proximal to the stimulating electrodes and consisted of another pair of silver wires with a separation of 5 mm, connected through cathode followers to an amplifier with a high rejection ratio against in-phase signals. The clamps supporting the skin round the paraffin bath were earthed.

After each measurement of latency a fine silk thread was tied firmly around the nerve trunk at the level of the more distal recording electrode, and the latter moved distally for the next measurement. At the end of the experiment the position of the stimulating cathode was similarly marked upon the nerve trunk, and the distances from the point of stimulation to each recording point were determined *in situ* with dividers after killing the animal with an overdose of Nembutal.

Each oscilloscope trace contained a 10 kc/sec marker locked both to the time base and to the stimulator. The traces were photographed directly on paper without reduction. The latencies of three points were measured: the first point of inflexion of the A fibre action potential where a tangent drawn down the rising face of the deflexion met the base line, the point half way up the rising face, and the highest point above the base line. Since the stimulus was rigidly locked to the time base of the oscilloscope, the measurements of latency were made from the first time marker, as this was more precisely definable than the onset of the stimulus artifact. The latencies were plotted against conduction distances and a straight line drawn by eye as nearly as possible through the points, not including the origin. The velocity determined from the slope of this line was found to be within 1 % of the velocity calculated by linear regression which was performed whenever the normal and operated nerves showed closely similar velocities.

After measurement of conduction velocity, specimens of the peroneal nerve on both sides were taken for histological examination from the distal, middle and proximal portions of the length of nerve examined. The distal specimen was 1–2 cm above the level of the lesion and the proximal usually 6–7 cm above. Except in the neuroma experiments a specimen was also taken 1 cm below the lesion. The segments of nerve removed were attached to card frames and fixed in Flemming's solution, embedded in paraffin wax and 5 μ transverse sections stained by the modified Weigert method described by Gutmann & Sanders (1943). In one animal the fixation was not adequate for satisfactory measurements to be made.

Since conduction velocity was measured for the fastest fibres in the nerve trunk, the anatomical observations were confined to the largest fibres. The mean values for the outside diameter of the myelin sheath (total fibre diameter) and that for the inside diameter of the sheath (axon diameter) for the five largest fibres in each of four sections at each level were obtained by direct measurement at a magnification of $\times 1000$ using an ocular micrometer. Except where specified, the means of the values obtained from the three levels on each side have been utilized, each mean thus being derived from 60 measurements. A more extensive examination was not technically feasible in a nerve of this size, but the changes in fibre diameter are being further studied by a more detailed analysis performed on the nerve to the medial head of gastrocnemius (J. T. Aitken and P. K. Thomas, unpublished). In some nerves longitudinal sections were also taken for examination of the nodes of Ranvier.

The results on the operated nerves, both for conduction velocity and fibre diameter, have been expressed as percentages of those from the unoperated side. A possible objection to the use of the unoperated nerve for control purposes is the report by Greenman (1913) that fibre diameter is reduced in the corresponding nerve of the opposite side after crush lesions of the peroneal nerve of the rat. The validity of this finding, however, has been questioned (Quilliam, 1958).

RESULTS

Changes in conduction velocity

When the three measurements of the latency of each action potential were compared, the latency of the point half way up the rising face of the spike was found to be more accurately proportional to conduction distance than the point of inflexion or the peak, which were less easily defined. Only results based on half-rise latencies will therefore be described,

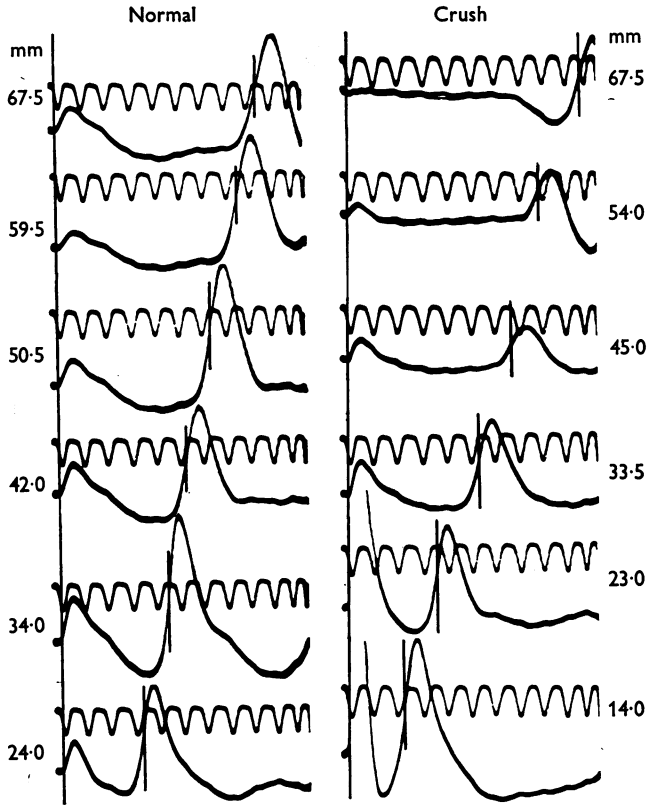

Fig. 1. Action potentials in a normal peroneal nerve and in the contralateral nerve crushed distally 140 days previously. Time marker, 10 kc/sec; conduction distances in mm beside the traces. Five superimposed traces at a repetition rate of 1/sec were recorded in each photograph.

although, whenever the comparison of the velocities of the normal and damaged nerves was critical, it was verified that the other methods of measuring latency gave the same qualitative result. An example of the records obtained is shown in Fig. 1, where each photograph contains 5 superimposed traces due to stimuli delivered at intervals of 1 sec. The

positions of the onset of the stimulus artifact and the half rise point have been indicated, but the latencies plotted in Fig. 2 were measured from an arbitrary zero which was the first peak of the marker on the trace (see Methods). The slope of the lines in Fig. 2 indicates a velocity of 84·9 m/sec for the normal nerve and 70·3 m/sec for the crushed nerve, velocity in the latter being 83 % of normal. The results will be expressed as a proportional reduction in this way since in the thirty-three rabbits investigated, velocities in the normal peroneal nerves ranging from 44 to

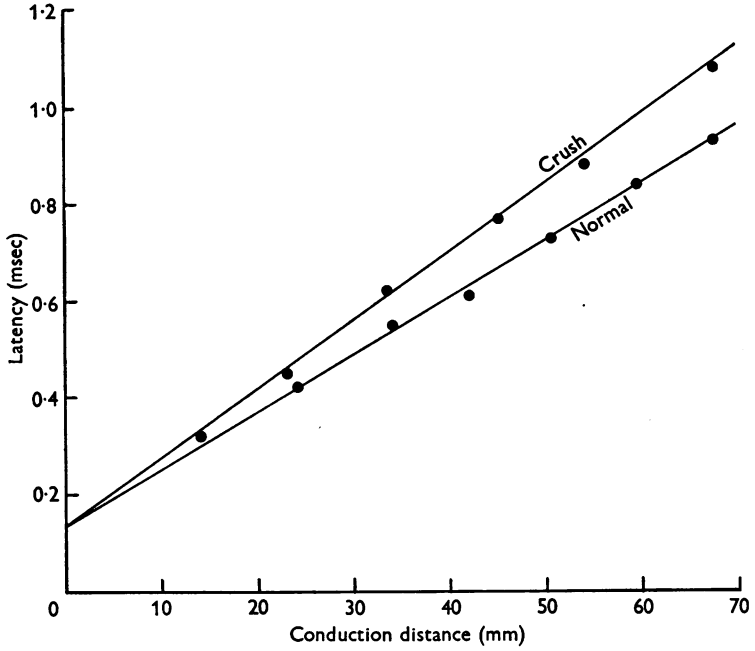

Fig. 2. The latencies of the records shown in Fig. 1 plotted against conduction distance. The normal nerve had a conduction velocity of 84·9 m/sec, the crushed nerve 70·3 m/sec.

108 m/sec were encountered. In order to obtain some assessment of the natural variation between the two sides in a single animal and also the accuracy of the measuring procedure, the conduction velocities of the peroneal nerves were measured on both sides in two normal rabbits and found to be 92·9 and 95·8 m/sec, differing by 3·1 % in one rabbit, and 81·4 and 83·7 m/sec, differing by 2·8 % in the other.

Measurements of conduction velocity in the peroneal nerves of thirty-one rabbits with distal nerve injuries are plotted in Fig. 3. After crush, constriction, or section and suture injuries the conduction velocity above the lesion falls to less than 90 % of normal within 25–30 days. A further

reduction to about 80% of normal is reached after 50–100 days and maintained until nearly 150 days after injury. By 200 days most nerves recover normal velocities, and there is no further change in the subsequent 240 days. Only two operated nerves showing a higher velocity than the control nerves have been encountered, one being 109% of normal 273 days after a crush, and the other 108% of normal 347 days after suture. The changes in these last two animals are perhaps rather larger than should be

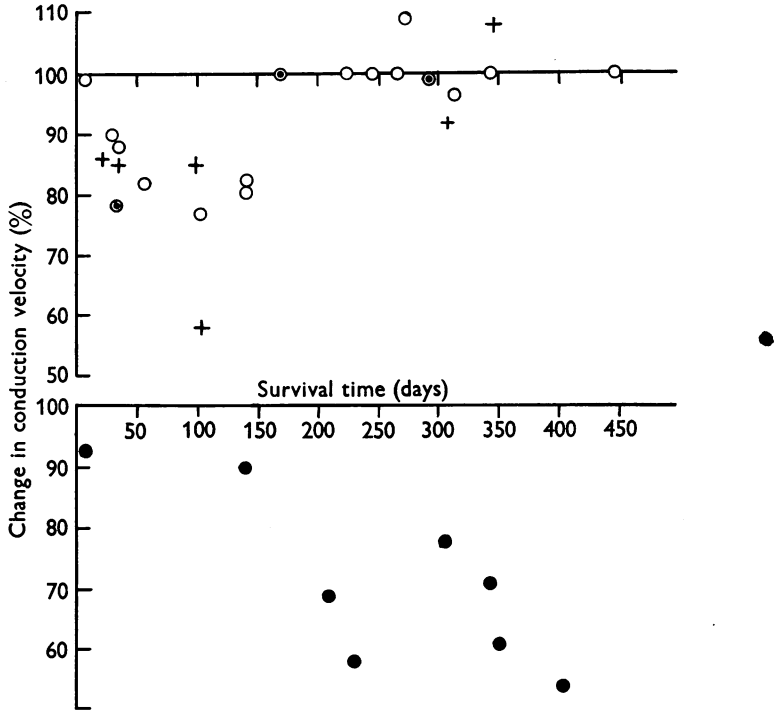

Fig. 3. The conduction velocity of the injured nerve expressed as a percentage of that of the control nerve plotted against survival times after the following injuries: crush ○, constriction ⊙, section and suture +, neuroma ●. The neuromas are plotted separately and, unlike the other injuries, show no recovery.

expected to occur through natural variation and errors of measurement, but are not correlated with especially large axon or fibre diameter (see below), so that their significance is uncertain.

It will be seen from Fig. 3 that the nerves that formed neuromas showed a greater reduction of conduction velocity than nerves subjected to other injuries. The velocities were only 60–70% of normal 200–400 days after the injury, and the trend does not suggest that recovery would ever occur.

Changes in fibre diameter

The changes in total fibre diameter (D) and axon diameter (d) for the different survival times are shown in Fig. 4. Each point is the mean of 60 measurements. As an index of the alterations in the thickness of the myelin sheath relative to axon diameter, the changes in the ratio D/d have also been plotted. This is the reciprocal of the ratio g introduced by Schmitt & Bear (1937).

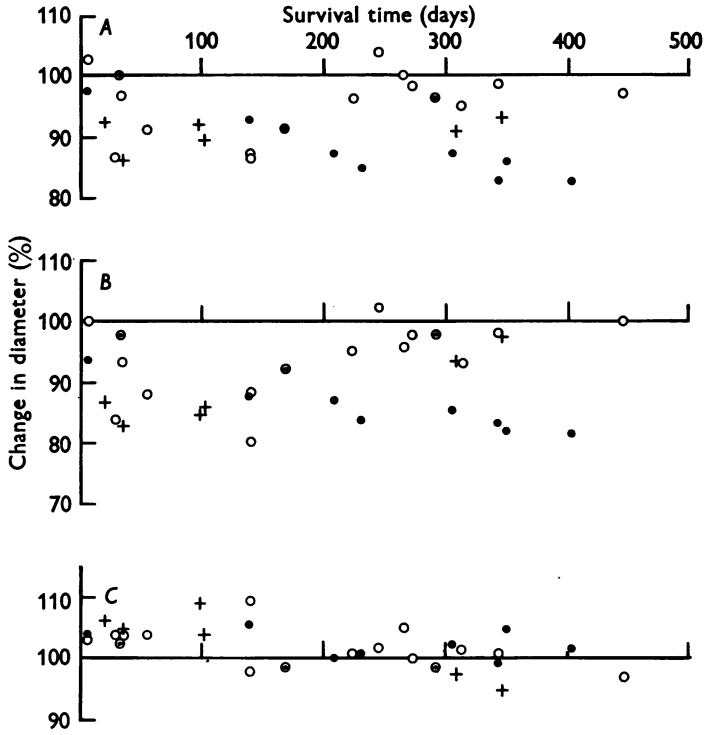

Fig. 4. *A* The total fibre diameter (D), *B* the axon diameter (d), and *C* the ratio (D/d) of the injured nerves expressed as percentages of the corresponding dimensions of the control nerves plotted against survival times. Symbols as in Fig. 3.

For survival periods of 7–150 days the changes are similar for all types of lesion, although the observations were predominantly obtained from crush and from section and suture experiments. During the period 7–50 days axon diameter declines sharply (Fig. 4*B*), total fibre diameter becoming diminished to a lesser extent (Fig. 4*A*). The mean reduction in axon diameter over this period, as compared with the control nerves, is 8·9 % and that for total fibre diameter is 5·3 %. The myelin sheath becomes thicker, showing a mean absolute increase, as compared with the control

nerves, of 5·9 %. Thus, with respect to the changes in total fibre diameter, the increase in myelin-sheath thickness partially compensates for the reduction in axon diameter. The increase in myelin thickness relative to axon diameter is evident in Fig. 4*C*. Between 50 and 150 days there is a mean reduction in axon diameter of 14·1 % and in total fibre diameter of 10·2 %, compared to the control side. The mean value for the absolute thickness of the myelin sheath is 3·5 % greater in the operated nerves over this period.

For survival periods exceeding 150 days the results for the neuroma experiments differ from those for the other types of lesion. For the neuroma experiments, with survival times of 208–403 days, there is a mean reduction in axon diameter of 16·1 % and in total fibre diameter of 15·0 %. The relative thickness of the myelin sheath (Fig. 4*C*) is approximately normal or perhaps a little increased.

For the other lesions axon diameter and total fibre diameter increase, so that after 225 days there is little difference between the operated and unoperated nerves, although the fibres on the operated side remain, in general, slightly smaller. There is little difference between the crush, suture and ligature experiments except that fibre diameter for the two late survival suture experiments (308 and 346 days) is somewhat lower than that for the other two types of lesion. It is of interest that the constricted nerves showed the same reduction in diameter and subsequent recovery as after crush lesions. Evidently the increase in diameter of fibres immediately above the lesion observed by Weiss & Hiscoe (1948) does not prevent the reduction in diameter that occurs higher in the nerve during this period after injury.

The results were examined to determine whether there was any gradient of anatomical change in the operated nerve above the lesion. This was done by comparing the values from the proximal, intermediate and distal levels above the lesion for all experiments in which there was a diminution in total fibre diameter or axon diameter of 10 % or more on the operated side as compared with the control nerve. There was no systematic change along the nerve between the three levels, and when the values were compared statistically none of the differences between levels was found to be significant at the 5 % level of probability.

The relationship between conduction velocity and fibre size

Providing that it is legitimate to compound the results obtained from all four types of lesion, certain conclusions as to the relationships between conduction velocity and the histological dimensions can be derived. A clear relationship between conduction velocity and axon diameter emerges. Thus, during the period between 7 and 150 days after injury both conduction velocity and axon diameter become reduced, whereas myelin

thickness is increased. Subsequently, except in the neuroma experiments, velocity, axon diameter and myelin thickness return to normal. In the later neuroma experiments velocity is further reduced and is associated with a reduction both of axon diameter and myelin thickness.

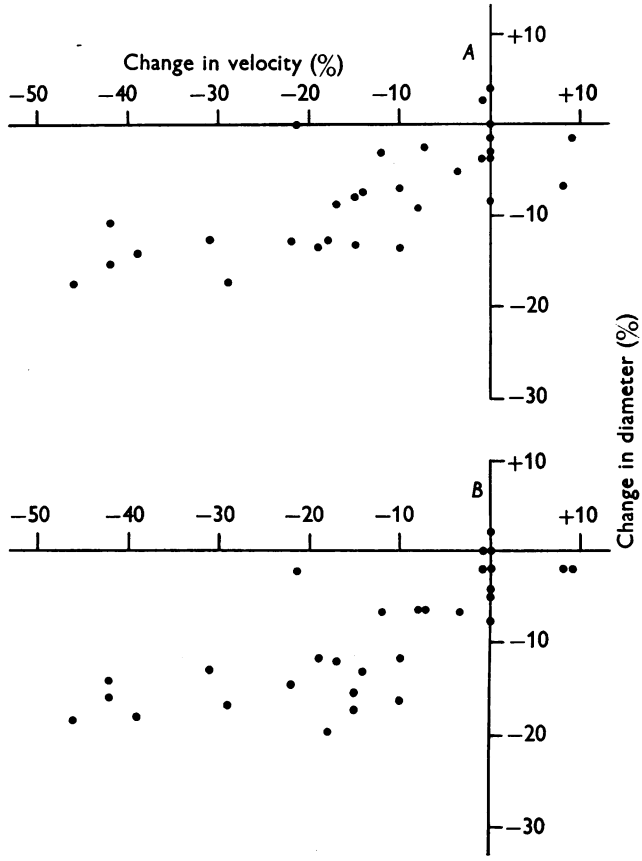

Fig. 5. The percentage difference in conduction velocity between the injured nerve and the control nerve plotted against the percentage difference (*A*) in total fibre diameter and (*B*) in axon diameter.

There is an indication that conduction velocity may also show some correlation with myelin thickness. When the results for the neuroma experiments with long survival times (200–400 days) are compared with those for all types of lesion with shorter survival periods (50–150 days), it will be seen (Fig. 4) that axon diameter is only slightly less, whereas total fibre diameter is reduced to a greater extent because of the difference in myelin-sheath thickness. Yet conduction velocity is substantially less in the former (Fig. 3). The suggestion that conduction velocity may be related

to the thickness of the myelin sheath as well as to axon diameter is supported by Fig. 5, where the percentage change in conduction velocity has been plotted against the percentage change in total fibre diameter (Fig. 5*A*) and axon diameter (Fig. 5*B*). The relationship with total fibre diameter is more nearly linear than that with axon diameter.

The nodes of Ranvier

The nodes of Ranvier were examined in longitudinal sections stained by the Weigert method in eight nerves, all of which showed a reduction in total fibre diameter of between 8 and 18% as compared with the unoperated side. They comprised crush experiments 29, 56 and 102 days after injury, suture experiments 35 and 102 days after injury and neuroma experiments with survival times of 231, 350 and 403 days. The nerves were examined at all three levels proximal to the lesion. No abnormal appearances were noticed. In particular, the nodal gap between adjacent myelin segments did not appear to be increased, as observed by Sanders (1948) in regenerating nerves below the lesion and by Causey & Palmer (1952) during the early stages of degeneration.

DISCUSSION

The present results confirm the previous reports, notably those of Gutmann & Holubář (1951) and Kiraly & Krnjević (1959), that conduction velocity becomes progressively reduced in the central stump after peripheral nerve section if contact with the periphery is not re-established. Gutmann & Holubář noted that the reduction was at first rapid and later more gradual. For lesions following which contact with the periphery is achieved, the situation is clearly different. An initial diminution in conduction velocity is followed by a return to normal. We have been unable to confirm the finding of Sanders & Whitteridge (1946) that velocity is slightly increased between 56 and 123 days after such a lesion.

Numerous observers have noted that fibre diameter in the central stump becomes reduced during regeneration (Greenman, 1913; Gutmann & Sanders, 1943; Weiss, Edds & Cavanaugh, 1945; Sanders & Young, 1946; Sanders, 1948; Gutmann & Holubář, 1951; Eccles & McIntyre, 1953). These investigators confined their examination to distances not greater than 2 cm above the lesion, or did not specify the level of examination. The present observations demonstrate that the changes extend for at least 7–8 cm above the lesion, while in man (see introduction) they may extend for 40–50 cm, since conduction velocity is reduced even as high as this above a lesion. It is evident that widespread changes are produced along a nerve fibre by an injury to its peripheral part.

The alterations in axon diameter and the thickness of the myelin sheath above crush lesions have been studied by Sanders (1948), who also examined the peroneal nerve of the rabbit. Sanders found that there was at first no change in fibre diameter although axon diameter became diminished, the reduction being compensated by a thickening of the myelin sheath. Between 60 and 100 days after operation axon diameter continued to decline and this was also associated with a reduction in total fibre diameter. After 100 days axon diameter increased, myelin sheath thickness remaining unchanged until 200 days and then diminishing. Even at 300 days, however, by which time total fibre diameter was restored, the sheaths were still somewhat thicker than normal. The changes above crush and above section and suture lesions observed in the present study closely parallel those observed by Sanders, except that total fibre diameter tended to decline rather earlier than was suggested by Sanders.

We have made an insufficient number of observations on neuroma experiments during the earlier period after operation (7–150 days) to decide whether the changes in axon diameter and myelin thickness differ from those found after crush lesions. In the later neuroma experiments (200–400 days), axon diameter and myelin sheath thickness appear to be reduced to an approximately equal extent. This is in conflict with Gutmann & Holubář (1951), who reported a relatively greater reduction in the thickness of the myelin sheath than in axon diameter after section of the peroneal nerve of the rabbit with survival times of this duration. This question is being further investigated (J. T. Aitken and P. K. Thomas, unpublished).

The present observations have shown that in this series of nerves conduction velocity is clearly correlated with axon diameter, and have suggested that it may also be influenced by myelin thickness. The question of the correlation between conduction velocity and the anatomical dimensions of myelinated nerve fibres has been discussed in a previous paper (Cragg & Thomas, 1957). The theory of saltatory conduction leads to the expectation that conduction velocity will be equal to the internodal length divided by the transmission time, that is, the delay between the times at which adjacent nodes reach action potential threshold (see Tasaki, 1953). However, it was shown that it is not possible to express conduction velocity directly in terms of the anatomical variables. Empirically, conduction velocity has been found to be most closely correlated with fibre diameter (see Rushton, 1951; Cragg & Thomas, 1957), although Sanders & Whitteridge (1946) reported that in regenerating fibres velocity was more closely correlated with myelin thickness.

In the present experiments, although internodal length was not examined it is presumed to be unaffected; changes in internodal length are confined

to a distance of a few millimetres above a localized lesion (Weiss & Hiscoe, 1948; Lubinska, 1959). As far as can be ascertained from light-microscopy examination, the nodes of Ranvier show no alteration. However, differential changes in axon diameter and the thickness of the myelin sheath occur. Since the latency of activation of a nerve fibre increases as the strength of an applied electrical stimulus is decreased, a reduction in axon diameter is likely to reduce conduction velocity by increasing the potential gradient from an active node to the following inactive node, as a result of an increase in the distributed resistance of the axon. On the other hand, an increase in myelin sheath thickness may produce an effect in the opposite direction by diminishing current leak across the sheath.

The situation may well be more complex than this in that the changes in axon diameter and myelin-sheath thickness may be accompanied by changes in their electrical properties. Thus Kiraly & Krnjević (1959) have suggested that the absolute increase in the thickness of the myelin sheath above the lesion during the early stages of regeneration described by Sanders (1948) may be due to the uptake of water rather than simply to the formation of additional myelin. This would be likely to reduce its capacitance.

SUMMARY

1. Conduction velocity, axon diameter and total fibre diameter have been measured in the peroneal nerves of rabbits proximal to lesions produced by crushing, constricting, cutting and suturing or cutting and avulsing the distal end of the nerve, 7–446 days previously.

2. After the first three types of injury conduction velocity falls to 90% of normal within 25–30 days, and is further reduced to 80% of normal within 50–100 days. This reduction is maintained until 150 days, but most nerves recover normal velocities by 200 days and remain normal thereafter.

3. When the distal end of the nerve is avulsed, conduction velocity above the consequent neuroma falls to 60–70% of the normal 200–400 days after injury and shows no sign of recovery.

4. After all four types of injury a reduction of axon diameter in the largest fibres above the injury to an average of 85·9% of normal tends to precede an overlapping reduction of total fibre diameter to an average of 89·8% of normal in the period 50–150 days after injury.

5. For the first three types of injury axon and total fibre diameter increase after 150 days and return to near normal by 225 days after injury.

6. After avulsion of the distal end of the nerve, from 200 to 400 days after injury the largest proximal fibres show a further reduction in diameter, total fibre diameter and axon diameter being reduced approximately equally.

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