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THE EXCITABILITY OF A SINGLE FIBRE IN A NERVE TRUNK

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Several factors complicate the measurement of the space distribution of excitability in a nerve trunk. Most trunks get smaller as we pass peripherally, due to loss of fibre content through branching. A current passing down such a trunk will therefore be denser in the distal than in the proximal region. Moreover, any shift of the electrodes will alter the resistance of the circuit in a way not readily predictable, and this may involve difficulties in the measurement of the current.

A fairly satisfactory way to overcome these irregularities is to set the nerve in a uniform rod of agar-Ringer jelly about 1 mm in diameter. If the electrodes are rings through which the jelly rod just slips, a very uniform field may be applied to the outside of the nerve (Rashbass & Rushton, 1949*b*, Fig. 2). And the current may be made nearly independent of the tissue resistance by means of a servo-stimulator (Rushton, 1949*a*).

When the space distribution of the stimulus was made precise by these (or other) means, it was possible to see how accurately the distribution of excitability corresponded to the expectations of the simple cable theory proposed by Hermann, Cremer and others more than 50 years ago. It was found that though undoubtedly the expectations were followed in a general way, there were some clear divergencies in detail. Thus Rushton (1949*b*) showed that the most excitable point might be not at the cathode but some 3 mm distant, and the distribution of excitability in the neighbourhood of the cathode was markedly different from the exponential curves demanded by the simple cable theory (Rashbass & Rushton, 1949*a*, *b*).

These discrepancies received a very simple explanation (Rashbass & Rushton, 1949*c*). The epineurial sheath has substantial electrical resistance, so the current flow through it is distorted. By placing an electric probe beneath the sheath, the field there was mapped out. It was found to be quite different from the field on the outside of the sheath, and precisely of the

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form to account for the observed excitability distribution in terms of the simple cable theory. Moreover, when the epineurium was dissected off, the excitability attenuated with distance from the cathode exactly according to the theoretical exponential curve, from which λ, the space constant of the cable, could be measured.

More recently this type of measurement has been extended to the α, β and γ fibres of the (stripped) frog's sciatic trunk (Lussier & Rushton, 1951), and we have shown that λ for each type of fibre is proportional to conduction velocity, a relation which would be expected upon theoretical grounds (Rushton, 1951).

Now there is one aspect of the application of the simple cable theory which needs further consideration, for this theory is based upon the assumption that current crosses the myelin equally readily at all points, but we know that in fact it crosses chiefly at the nodes of Ranvier.

It must have been apparent from the time of Ranvier himself that these gaps in the insulation were likely to favour the passage of electric currents, and when Kubo, Ono and Tasaki succeeded in dissecting out single medullated fibres (see Kato, 1934) the importance of the nodes in excitation became established. Evidence of different kinds has been advanced by Erlanger & Blair's (1934) segmental blocking, Lillie's (1925) iron wire model made 'medullated' by threading on the wire short lengths of glass tubing, and Huxley & Stämpfli's (1949) beautiful quantitative work. But the very extensive observations of Tasaki and his colleagues constitute perhaps the strongest evidence we have that excitation occurs at the nodes, and that Lillie's 'medullated' model is a fairly accurate representation of nerve excitation.

We need then to reconcile two different relationships. When excitability measurements are made upon the whole (stripped) nerve trunk (using say $\frac{1}{3}$ maximal action potential as index of adequate excitation) the results fit the simple cable theory, but when the same kind of measurements are made on a single isolated nerve fibre, results of quite a different kind are found involving the nodes of Ranvier. Clearly two kinds of explanation are possible. Perhaps the difference is due to the removal of the fibre from the trunk (possibly the effect of damage or change of environment). Or perhaps the difference is not between a fibre removed or intact, but between measurements upon an individual fibre on the one hand, or upon the whole group constituting the $\frac{1}{3}$ maximal response on the other. To investigate these possibilities further is the object of this paper.

METHOD IN PRINCIPLE

If the excitability of one particular nerve fibre in the trunk is to be studied, the first problem is to obtain a reliable index of whether this fibre is active or not. We used a motor nerve fibre and recorded the action potential from the muscle fibres constituting its motor unit. This helped in the problem of isolation and amplification.

Our first hope was that the recording electrodes might be so well localized that no other motor units would confuse the record. This, however, was far from the case, and we saw that it would be impossible to recognize with confidence whether our particular fibre was active or not, in the complex record which often presented itself. However, by a simple device, we were able to overcome this difficulty.

A shock was applied through electrodes S_2, Fig. 1. As the shock strength was increased a point was reached when some small twitches appeared on one or more muscles of the foot. The recording leads were applied to an appropriate place on the muscle surface to give a good action potential. In favourable

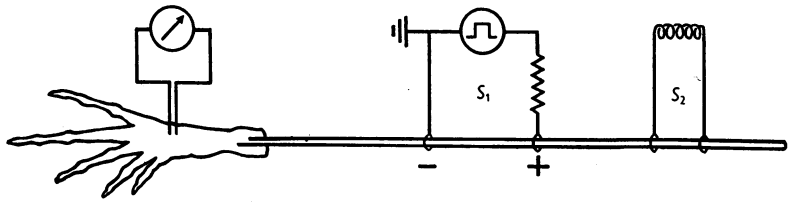

Fig. 1. Arrangement of stimulating electrodes S_1, S_2 on the nerve and fine recording leads on the foot muscles.

cases the action potential was all-or-none over some little range of stimulus strengths. This was interpreted to mean that a single motor unit was involved and that the next within range of the recording leads had a substantially higher threshold. The strength of S_2 was adjusted to the middle of the all-or-none range and the whole system so far described left unchanged throughout the experiment. A record such as Fig. 2(*a*), therefore, could always be obtained.

Now the stimulus to be studied is not S_2 but S_1, which is sent in 1 or 2 msec before S_2. If S_1 does not excite any other fibres affecting the record, it will have no visible effect until it excites the fibre of record (*a*). It will then cause the wave of Fig. 2(*a*) to appear earlier, for S_1 is applied a millisecond or so before S_2, and the conduction distance is also shorter. But the stimulus S_2 cannot now be effective on account of the refractoriness due to S_1, so that Fig. 2(*b*) shows the wave appearing in the earlier position and *disappearing from the later position.*

Now in general, as we gradually increase the strength of S_1, it will excite other nerve fibres affecting the record before reaching the threshold of the particular fibre excited by S_2. So the appearance is as Fig. 3, where (*a*) shows the single motor unit wave due to S_2 alone, and (*b*) shows, in addition, an earlier wave due to S_1 stimulating other nerve fibres. As soon as S_1 is strong enough to excite the particular fibre of S_2, its wave is added to the wave on the left—which may or may not be easy to appreciate. But no one could overlook the fact that the S_2 wave has disappeared from its place on the right, and where there had been a wave there is now none (Fig. 3(*c*)). The procedure,

then, is simply to adjust a pointer to indicate the place on the tube, where the S_2 wave may be expected, and then for every setting of S_1 to note whether there is or is not a wave at this place. The method just described permits the physiological isolation of a single nerve fibre without any anatomical isolation at all. It is therefore suitable for approaching the problem of whether the excitability distribution in an undissected single fibre is described best by a uniform or a segmental cable model.

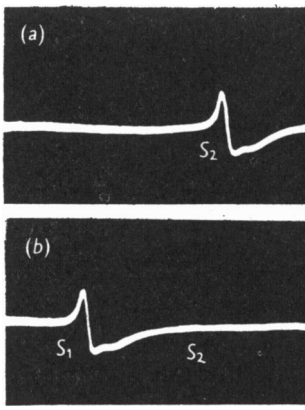

Fig. 2.

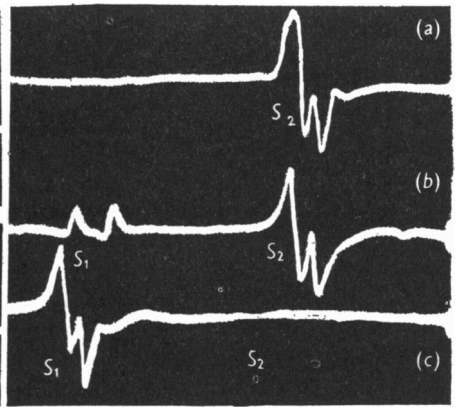

Fig. 3.

Fig. 2. Records from single motor unit. (*a*) excited by S_2 only; (*b*) by S_2 anticipated by S_1 and hence falling in refractory phase.

Fig. 3. (*a*) record from single unit excited by S_2 only; (*b*) as in (*a*) but S_1 also applied at a strength subthreshold for the fibre of S_2; (*c*) strength of S_1 increased to excite that fibre so S_2 falls in refractory phase. (Records retouched.)

When the singleness of an excitable system is inferred from the all-or-none nature of the response, one has to guard against the possibility that two fibres happen to have exactly the same threshold. The present method is exceptionally free from error of this kind. For not only would the two fibres need to have the same threshold for S_2, but also these two excitabilities would have to be identical for every point occupied by S_1, otherwise when S_1 gradually increased in strength only half of the S_2 wave would disappear—a phenomenon never observed.

A slight change in wave form of the single unit was often seen as in Fig. 3 (*a*) and (*b*). This was no doubt due to small movements of the contracting muscle relative to the microelectrode. In long experiments, also, some fibres of the unit dropped out intermittently due to fatigue. As appears from Fig. 3 such variations did little to dim the sharpness of the presence-or-absence criterion upon which the measurements of this paper rest.

EXPERIMENTAL PROCEDURE

Sciatic nerves of English frogs (*Rana temporaria*) were used. The nerve was dissected out with the foot attached, stripped of epineurium and set in a jelly rod by the method of Lussier & Rushton (1951). It was then set up in a suitable Perspex moist chamber, threaded through the ring electrodes of S_1, S_2 which made a good fit, and fixed in position by threads. The recording electrodes were two 50 μ insulated silver wires separated by about 100 μ and sealed into a hypodermic needle

cut off 'square'. The needle was earthed, but insulated by varnish outside so that the preparation was not connected to it since the distal lead of S_1 was earthed. The needle could be rotated on its axis to get the best orientation for recording. A suitable nerve fibre was chosen as follows. The stimulus S_2 was increased until some muscle groups could be seen to respond in the foot. The needle end was then applied to the surface over one of these groups and adjusted to give a good record. If this showed an all-or-none relation over a fair range of stimulus strengths, S_2 was left fixed in the middle of the range with reasonable expectation that this strength would elicit the response of just this unit throughout the course of the experiment. If, on the other hand, the recording site was not satisfactory, the needle was moved, or the position of the S_2 electrodes shifted.

The stimulus S_2 was a brief shock delivered through a small transformer from a thyratron discharge. S_1 was a square pulse of 0·5 msec duration throughout. The distal electrode was earthed and the proximal connected to the stimulator (either positive or negative pulse) through a resistance of 60 kΩ. The fairly high amplification required with the present system of recording made it important that the nearest stimulating electrode should be earthed, otherwise large artifacts appeared. This requirement precluded the use of the servo-stimulator (Rushton, 1949*a*), employed in former investigations. The 60 kΩ series resistance is not sufficient entirely to swamp the resistance of the jelly rod at great interpolar lengths, but the experiments were so arranged that errors due to this did not affect any conclusions to be drawn from the results.

RESULTS

Experiment I

This was designed to throw light upon the question: 'Is a nerve fibre when still *in situ* in the trunk excitable at all points, or only at the nodes?'

The electrodes S_1 (Fig. 4(*a*)) in this case were three rings of rather fine silver wire lying close together but insulated from each other by a layer of varnish. They formed together a little tunnel of about 1 mm length and 1 mm bore. The three wires each made good contact with the jelly rod within. The middle wire was cathode and the other two both earthed anodes, and the whole system could be gently slid over the nerve by a rack-and-pinion movement easily read to 0·1 mm.

Now the significance of this tripolar electrode system is that except for the 1 mm occupied by the electrodes, the whole nerve surface is at earth potential. So if the nodes alone are excitable the nerve will only be capable of response when the electrodes lie over a node. The experiment thus was simply performed. The stimulus S_1 was made as strong as the equipment permitted. The electrode system was then pushed very slowly along the nerve and for every position it was noted whether the excitation was effective or not. The effect was (as described earlier) the abolition of the all-or-none wave due to S_2 which falls upon a refractory fibre when S_1 has excited it.

The results of six experiments are summarized in Fig. 4(*b*). The black parts show the regions where excitation occurred, the white parts where it did not. It is apparent that excitation only occurred in certain regions of the fibre, and the spacing was about right for the distances from one node to the next. The width of the black regions in the figure is due partly to current spread about

the electrodes and so the excitable area of the fibre itself must be somewhat narrower.

In the isolated fibre Tasaki (1939) has observed that the nodes alone are excitable. Our observations are in complete accord with this, and we believe that the black regions of Fig. 4(*b*) represent the positions of successive nodes.

Upon this interpretation, the lowest nerve of the figure appears to have one internode about twice the normal length. This might possibly be an experimental error since it was not discovered until the results were plotted later, and so could not be re-checked. But Vizoso & Young (1948) have observed (rabbits) that an occasional dropping out of a node is not uncommon.

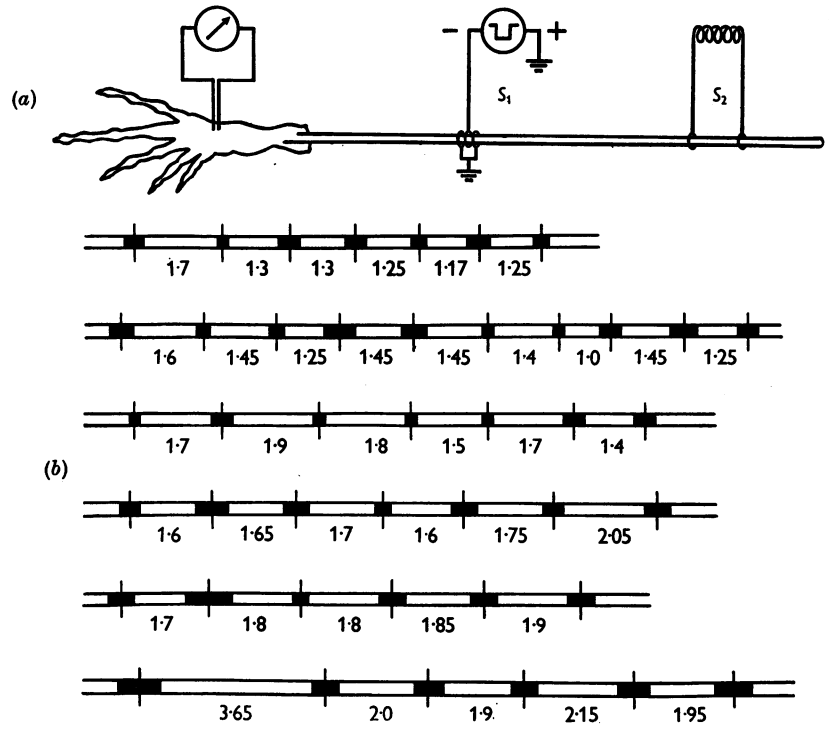

Fig. 4. (*a*) arrangement of electrodes; (*b*) results on six nerve fibres showing the regions (black) where excitation could be obtained and (white) where it could not be obtained using the tripolar system S_1 (Fig. 4(*a*)), with the strongest shocks available. Numbers give distance (mm) between mid-points of black regions.

Experiment II

In this the nerve was stimulated through the usual bipolar electrodes (Fig. 1) to find how the threshold depended upon the distance between the cathode and the nearest node. In our investigations on the space constant of the α, β and γ fibres (Lussier & Rushton, 1951) we had seen that fibres of

each group, though pretty uniform with regard to λ and to conduction velocity, had thresholds which showed a large scatter: indeed the most excitable β fibres had a considerably lower threshold than the least excitable α fibres. One possible cause of threshold variation was the variation in position of the nearest node in relation to the fixed cathode. The effect of this could be calculated and gave the result that thresholds should vary by about 30% from this cause. At the time, this working seemed rather too hypothetical to be accepted with any confidence. The present experiment, however, shows that the theory is quantitatively correct, but that the position of the nodes is not the only factor upon which threshold variation depends.

The simplest form of the experiment is when the distance between the two electrodes of S_1 (Fig. 1), is large. The distal electrode was the cathode and was earthed. It was moved in steps of 0·25 mm and the anode was kept 10 mm distant from it. For each position of the electrodes the threshold was found, and in Fig. 5(*a*) the reciprocal (=excitability) is plotted in arbitrary units against the cathode position. The theoretical expectation, assuming each node to have the same excitability and the myelin to be a perfect insulator, is worked out in Appendix A, and the results of this calculation are shown by the straight lines of Fig. 5(*a*). The excitability should be greatest at the nodes and decline symmetrically on either side. As we travel away from the node the excitability should fall linearly until at the mid-internodal point the line cuts that from the next node. From here this second node becomes more excitable and the observed excitability of the whole fibre should be given by the (undotted) upper portions of the intersecting lines. Only the slope of the lines is arbitrary.

The excitability values actually observed (circles, Fig. 5(*a*)) follow closely the theoretical lines. The first three peaks are given an arbitrary excitability of 1. The slope of the lines is such as to bring the excitability down to 0·4 when the cathode is a whole internode distant. This value of 0·4 is quite an important measure. For the nerves of a given type of animal it should be independent of fibre size according to the theory recently advanced by Rushton (1951). And we have found that though there is some little variation from nerve to nerve this does not seem correlated with fibre size. From the value of 0·4 we shall deduce at the end of this paper that when the space constant is obtained by excitability measurements on the whole nerve trunk (cf. Lussier & Rushton, 1951) the value of λ for each fibre group is 1·2 times the internodal lengths of the fibres involved.

Now Tasaki (1939) has a measure which is almost exactly comparable. By means of his ridge-insulator technique he placed a single fibre so that electrodes could be applied to three consecutive nodes 1, 2 and 3. He plotted the current entering through node 3 against the current leaving through node 1 when the latter was just excited. The relation was a straight line making an angle β with

the horizontal (his fig. 2). Now cot β is precisely the fraction of the excitation at node 2 which spreads to node 1 and adds to the excitability there measured. It should thus be the same as our average value of 0·4 which represents the same thing under only slightly different conditions of excitation. Tasaki gives values of 0·35–0·45 for cot β when the stimulus duration was 5 msec.

Our stimulus was only 0·5 msec, but Tasaki's curves show that very little change occurs in cot β for durations between 0·4 and 5 msec and we had chosen 0·5 msec because our previous observations (Lussier & Rushton, 1951) showed that longer durations produced no change in λ.

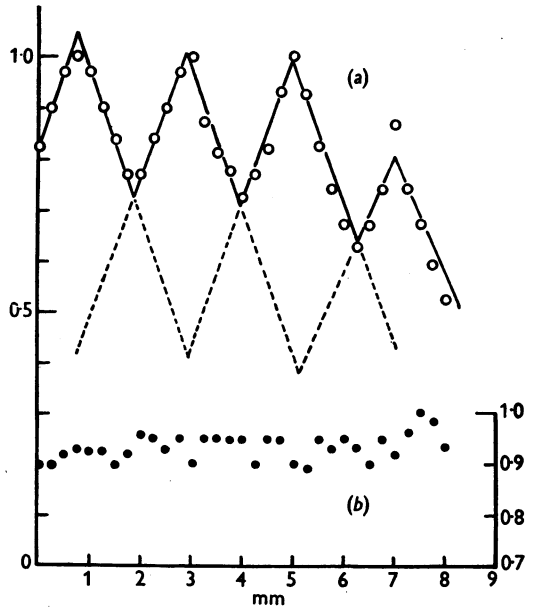

Fig. 5.

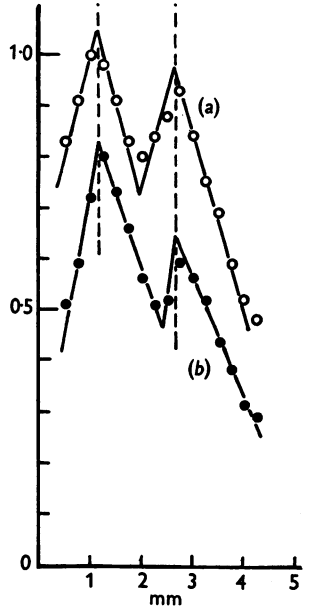

Fig. 6.

Fig. 5. Nerve excited by dipolar electrodes 10 mm apart. Position of cathode relative to some fixed point on the nerve shown by horizontal axis, excitability plotted as ordinate. (*a*) epineurium stripped, axis on left; (*b*) epineurium intact, axis on right. The lines in (*a*) show the theoretical excitability relation to be expected if excitation occurs only at the nodes.

Fig. 6. (*a*) as Fig. 5(*a*); (*b*) the same except that exciting electrodes are 2 mm apart instead of 10 mm. Note the peaks corresponding to the position of the nodes are in the same places for (*a*) and (*b*); the troughs should not be.

The fourth node of Fig. 5(*a*) appears less excitable than the others. Irregularities of this kind were common, and usually more pronounced than in Fig. 5. We did not discover the cause.

Though the curve of Fig. 5(*a*) is symmetrical, we give quite a different interpretation for the peaks and the troughs. Each peak represents the maximum of excitability which occurs at the node and is therefore fixed in the structure of the tissue. Each trough represents the place where the line declining from one node crosses the line declining from the next node. It

indicates, therefore, the transition from excitation at one node to the next, and the transition place is not fixed by any feature of tissue structure.

Lest it seem rather arbitrary to interpret so differently features of the curve which appear so similar, we modified the foregoing experiment to substantiate the interpretation and to demonstrate a further application of the theory. The modification was simply to repeat the experiment, keeping the two electrodes of S_1 a distance 2 mm apart instead of 10 mm. Fig. 6 shows the curve in this case (dots) as well as with 10 mm interpolar distance (circles). A change-over switch allowed us to obtain for each position of the cathode an excitability measurement with the two different interpolar lengths. With short interpolar lengths the excited node is affected by movement not only of the cathode but also of the anode. As the cathode approaches the node from the left, the anode on the right recedes and the excitability rises from both these causes. When the cathode has passed the node the excitability declines, but this is partly offset by the simultaneous recession of the anode. Thus comparing the circles and the dots of Fig. 6 we should expect that as we go from left to right the dots would rise more steeply and fall more gently than the circles. Not only is this seen to be the case, but a comparison of the positions of the peaks and the troughs reveals a feature which substantiates the difference in our interpretation. For the peaks are in the same position in curves (*a*) and (*b*)—as they must be if both represent the positions of the nodes of Ranvier. But the troughs are in different places and so they cannot be linked with any fixed feature of nerve structure. The shift is, however, exactly to be expected upon the interpretation given.

The dots in Fig. 5(*b*) show the results of performing the experiment upon a nerve with epineurium intact but otherwise identical with the experiment of Fig. 5(*a*). With intact epineurium the variation of excitability from point to point is practically abolished. Rashbass & Rushton (1949*c*) found that the epineurium was a powerful potential barrier and that sharp potential changes outside were spread smoothly over several millimetres within. The sharp localization of the cathode in relation to the nodes could thus hardly be expected to appear if the epineurium were not first removed, and the uniform level of the dots of Fig. 5(*b*) entirely confirms this expectation. This very featureless uniformity provides a neat answer to the question raised earlier as to how much of the scatter in threshold among the α fibres is due to the random position of the nearest node relative to the cathode. For in an unstripped nerve the position of the node is practically without effect, as Fig. 5(*b*) shows. So the threshold scatter observed in the unstripped nerve must all be due to other causes.

Experiment III

We are now in a position to describe and interpret the experiment mentioned at the outset of this paper, namely to find the relation between excitability and interpolar distance for a single fibre in the (stripped) nerve trunk.

First of all, measurements were made like those in Fig. 5(*a*), where the points of maximal excitability give the positions of the nodes. One electrode was then placed at one of these nodes and kept there for the rest of the experiment. The other electrode was shifted in steps of 0·25 mm, and for each position two threshold measurements were taken, one with the fixed electrode cathode, and one with it anode. The excitability (=reciprocal threshold) in each case is plotted in Fig. 7.

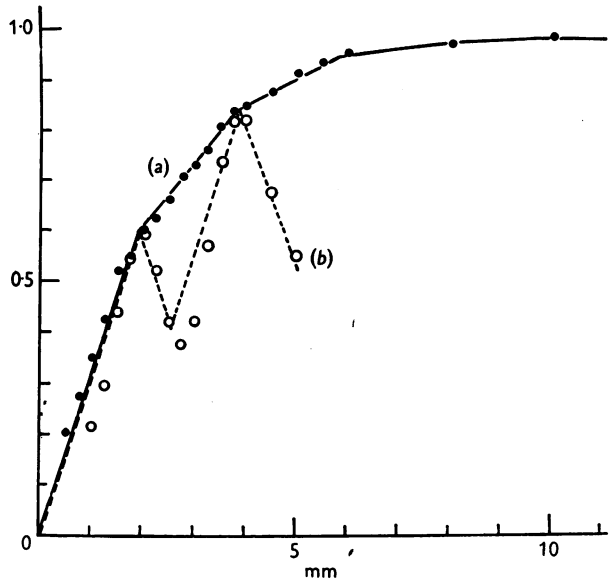

Fig. 7. Excitability-length curve. Abscissa, interpolar distance (mm); ordinate, excitability. (*a*) the cathode is kept fixed on a node (dots show experimental measurements, lines give theoretical relation); (*b*) the anode is kept fixed on a node (circles show experimental measurements, dotted lines give theoretical relation).

Now the theoretical relation when the cathode is fixed on a node is shown by the continuous line of Fig. 11 in Appendix A (p. 104). It differs but slightly from the exponential excitability-length relation deduced from the simple cable theory. In fact, if we consider only the values where the anode also lies on a node, the points so considered fall exactly upon the exponential. The full curve is obtained by joining these nodal points by straight lines.

The dots of Fig. 7(*a*) fall well enough upon such a set of chords to the exponential, but our precision is by no means sufficient to insist either upon chord rather than arc, or upon these chords rather than any others that might be selected. The thresholds with reversed current afford a powerful substantiation for the particular chords selected.

Fig. 11 gives the theoretical curve (dotted) to be expected when the anode is fixed on a node. The peaks show the points where the cathode is also at a node. At such points (from symmetry) the excitability must be the same

whichever the direction of the current, and hence at these points all three curves of Fig. 11 meet. It can be shown, moreover, that all the dotted lines have absolutely the same slope, namely 0·6 per internodal length. Thus the curves of Fig. 11 should account quantitatively for the experimental findings when scaled in units of internodal length, with no arbitrary constants at all.

Now in Fig. 7 (*b*) the experimental points are seen to conform fairly well to these theoretical expectations shown by the broken lines, and so the results may be used to justify the interpretation placed upon curve (*a*). For if the dots correspond to simple cable conditions, they should lie on a smooth exponential, and the circles should also lie on the same exponential, which latter is far from the case. If, on the other hand, current can only cross the sheath at the nodes and hence excitation is always nodal, then the circles should lie on the toothed curve shown and the dots should lie on chords to the exponential. The particular chords are those which meet the exponential at points indicated by the up-pointing teeth. Obviously this is a better interpretation.

The relation to multi-fibre response

The experiments just described show clearly enough that excitation occurs at the nodes of Ranvier in fibres left intact in the nerve trunk, just as it does in the isolated fibres of Tasaki and others. With this established we may now return to the fact with which this paper opened—that when (say) $\frac{1}{3}$ maximal action potential is taken as the index of excitation of a nerve trunk, the results fit rather accurately the expectations of the simple cable theory. Clearly this does *not* mean that the current crosses the sheath equally readily at all points, for most of the current probably passes at the nodes. It must mean that in the population of nerve fibres whose summed response is observed, the average results turn out to fit the simple cable expectations pretty closely. In Fig. 8 we shall show how to construct the theoretical excitability length curve when a fraction θ of the maximum action potential is used as index of excitability. It is assumed that the nerve fibres excited are from a homogeneous population with the position of their nodes randomly distributed, and that the myelin is a perfect insulator. The justification for the construction is given in Appendix B: here we simply state how to get the required curve, which is easy.

(i) Mark off on the x axis, starting from 0, distances corresponding to 1, 2, 3, . . ., internodal lengths.

(ii) The upper curve *OPAD* is the theoretical curve of Fig. 7 (*a*). Draw it as follows. At node 1 the curve is 0·4 below the horizontal line through 1. At node 2 it is $(0{\cdot}4)^2$ below it. At node n it is $(0{\cdot}4)^n$ below it. These points are now joined up by straight lines.

(iii) The dotted lines *DCAB*..., constitute the theoretical curve of Fig. 7 (*b*).

Draw them as follows. At every nodal point on the curve *OPAD* draw two lines, one parallel to *PO* and the other its reflexion in the vertical.

(iv) Let these lines meet in *B*, *C*,.... Join *O*, *B*, *C*. Then, as we have seen in Fig. 7 (*a*), the curve *OPAD* is the curve for a single fibre, so θ, the fraction of the maximal action potential obtaining, is practically zero. It is shown in Appendix B that the curve *OBC* corresponds to the condition when every fibre is excited, thus $\theta = 1$.

(v) To obtain some intermediate value of θ (say $\frac{1}{3}$), mark off on *DC* a point θ of the way down from *D* to *C*. Similarly on *AC*, *AB*,.... In each case the point is the fraction θ of the way along the line. Then by joining up these successive points we obtain the theoretical excitability curve.

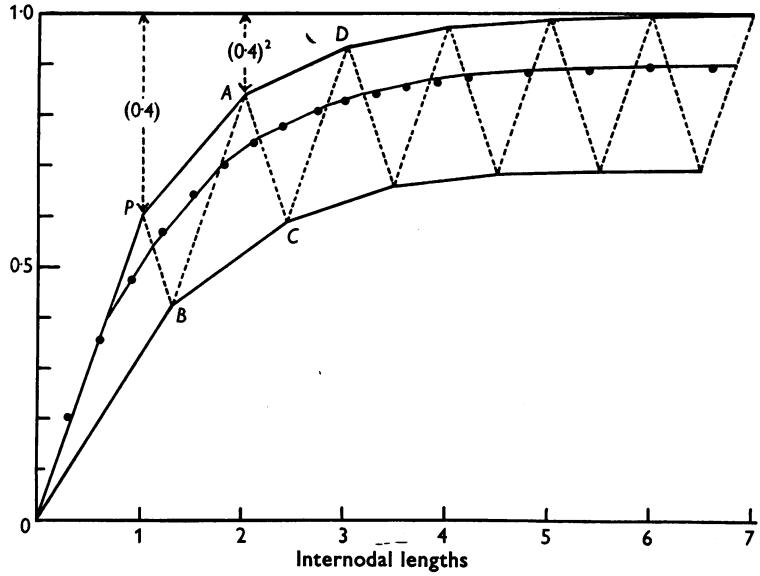

Fig. 8. Diagram to show how an excitability-length curve may be constructed for a homogeneous multi-fibred population (see text).

This curve of course is not an exponential, but the true exponential which is represented by the series of dots could not be distinguished from it in our excitability measurements. This exponential has λ of about 1·2 internodal lengths. So if we take the α fibres to have internodal lengths of 1·7 to 2 mm (see Fig. 4 (*b*)), they should have a λ of 2·05 to 2·4 mm. The values we found (1951) for λ in the α group varied between 2·1 and 2·4 mm. Since λ appears to be proportional to velocity, fibre diameter and internodal length (Rushton, 1951), the fit seen above for α fibres will no doubt apply also to β and γ.

It is thus demonstrated not only that our exponential curve is to be expected from a homogeneous population of nerve fibres, but that the exact values of λ can be derived from measurements on the single fibres.

In our earlier paper (1951) we performed the experiment of finding the excitability-length curve for the α fibres using as index of excitation $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$ and $\frac{3}{4}$ maximal action potential. The results were given in Fig. 4 of that paper, whence it appeared that the four sets of measurements when scaled to unity for great interpolar lengths coincided within a random scatter of 5 % or less. The construction of Fig. 8 now permits us to calculate the relation to be expected.

Instead of θ being $\frac{1}{2}$ it is made in turn $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, and the four curves so obtained are scaled vertically to reach unity for great interpolar lengths. The results show that the curve $\theta = \frac{1}{8}$ lies about 5 % above $\theta = \frac{3}{4}$ in the region 1–2 internodes (=2–4 mm) of electrode separation. The other curves are intermediate and the divergence is less at greater and less distances. This is not a bad correspondence between theory and observation, but a systematic divergence of 5 % in excitability should have been observed. A possible explanation lies in the known fact that there are some nerve fibres intermediate between the main α and β groups. When changing from $\frac{1}{8}$ to $\frac{3}{4}$ maximum α response, the increase of stimulus strength will bring in some of these smaller and higher threshold fibres as well as normal α fibres with remoter nodes. Thus the slight increase of λ which we should expect from the construction of Fig. 8 may well be offset by the slight decrease introduced by these smaller fibres.

DISCUSSION

The results of the experiments quoted are pretty well consistent with the theory that current can only cross the nerve sheath at the nodes of Ranvier, and that the depolarization of some node must reach a critical level for excitation to occur. The simple and unifying nature of these results, however, must not be allowed to obscure two important qualifying considerations. In the first place, not all the nerve fibres studied behaved as those here described; in the second, the fact that perfect myelin insulation is consistent with these results does not prove that myelin is a perfect insulator. It is not.

Though Expt. I could always be satisfactorily performed, it very frequently happened in Expt. II that there was great variation of excitability as electrodes were moved along the nerve. There is no difficulty in explaining away these variations as due to irregularities natural or introduced, but we were unable to decide which, if any, of such explanations were true, nor by practice to rectify matters. We incline to the belief that all fibres exhibit the essential excitability of the node (Expt. I), but that a proportion of the fibres do not show the space distribution of excitability expected from the uniform electric field applied, because they are somewhat screened from that field by the wisps of perineurium which remain after the epineurium has been dissected away.

With regard to the insulation due to the myelin, however perfect this may be to direct current, there must certainly be the capacity currents inherent in the geometry of the nerve. These have been observed by electrical records (Huxley & Stämpfli, 1949) and by excitability measurements (Tasaki, 1950). It is likely that in the present paper, where relatively long stimuli were used (0·5 msec), the capacity currents were small, for Tasaki (1939) found small variation in his tan β between stimulus durations of 0·4 msec and infinity, and Lussier & Rushton (1951) found no change in λ for durations greater than 0·5 msec. But even if the myelin leak was everywhere as great as at the nodes

themselves, it would only alter the theoretical straight lines of all our figures by the change seen in Fig. 11 (*a*) when chords become arcs. Since then, whatever the myelin leak, the results of our experiments would be practically the same, we have chosen for this paper to assume the insulation perfect, since this concept is simple and in our experiments probably not far from true. We have, however, worked out the case of steady current distribution when current leaks across the myelin as well as through the nodes, and we give at the end of Appendix A two formulae which will permit anyone interested to obtain the result for any given spatial conditions of stimulation.

We were concerned to work out this more general case in order to satisfy ourselves that no gross errors were introduced by making the simplifying assumptions of this paper. That the error is appreciable but not great appears from the experiment of Fig. 7. According to the simplified theory, curve 7 (*a*) coincides with 7 (*b*) for the first internode. Actually it was invariably found that (*a*) was more excitable than (*b*). This is easily understood if the myelin is leaky, for with cathode on the node and anode half an internode away, the myelin leak will permit more current to enter the nerve and leave by the cathode, so curve (*a*) should lie above the theoretical line. On the other hand, suppose the anode is on the node and excitation is due to the current leaving the nerve through the adjacent node and then passing back to the cathode situated in the mid-internode position. In this case the myelin leak will shunt the node to be excited and so curve (*b*) should lie below the theoretical line.

It is probable that the systematic difference seen in Fig. 7 between circles and dots in the mid-internode is due to this cause and if so it will represent twice the size of the maximum error to be expected from using the simplified theory in the experiments of this paper.

One can then deduce that for a 0·5 msec pulse a single node has the same resistance as a whole internode of myelin to radial currents, and this is equal to the resistance of two internodal lengths of axon to longitudinal currents.

APPENDIX A

DISTRIBUTION OF CURRENT IN A MEDULLATED NERVE FIBRE IN THE STEADY STATE

Assumptions

(i) The resistance of fluid on the outside of the fibre is small compared with that of the axis cylinder.

(ii) The conductivity of the myelin sheath is negligible.

(iii) Fibre diameter, internodal lengths, specific resistance, etc., are uniform along any one fibre.

(iv) We may consider the current flow from the stimulus as determined passively by the application of Ohm's law to the various parts of the circuit.

(v) For a given duration of stimulus, the necessary and sufficient condition for excitation is that the current leaving through some node should attain a critical value.

Definitions

l = internodal length in mm.
x = distance along the nerve.
R = resistance at the node.
r = resistance per mm of axis cylinder.
ρ = resistance per mm of external fluid.
U_x = potential outside nerve at x.
V_x = potential of axis cylinder at x.
ψ_n = current flowing out through nth node,
$\propto$ excitability of the nth node.

The fundamental equation

The current flowing out through the nth node

$$\psi_n = \frac{(V_n - U_n)}{R} = \frac{(V_{n-1} - 2V_n + V_{n+1})}{lr}. \tag{1}$$

This is the finite difference equation analogous to the well-known second-order differential equation for the simple cable.

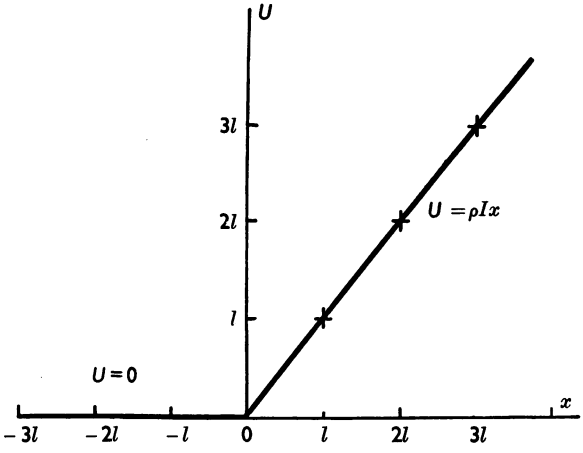

Fig. 9.

We require to solve for the case of a uniform field between two electrodes on the nerve and zero field beyond them. Consider first the case shown in Fig. 9, where U is zero to the left of $x=0$, and increases at the rate of ρI per internodal length to the right. This is the case where the cathode is at 0, the anode far to the right and a current I passed between them.

$$x<0, \quad U=0;$$
$$x>0, \quad U=\rho Ix.$$

We wish to find ψ_n, the current exciting the nth node, and we proceed to show that

$$\left.\begin{aligned}\psi_n &= A\alpha^n \quad \text{for } n \leqslant 0,\\ \psi_n &= A\alpha^{-n} \quad \text{for } n \geqslant 0,\end{aligned}\right\} \tag{2}$$

will satisfy all the conditions for a particular value of A and of α which must be independent of n.

We note that ψ is zero at $\pm\infty$ and that $\psi_0 = A$ in both ranges.

Applying now eqn. (1) in the range $n > 0$,

$$U_n = \rho n l I,$$

therefore

$$V_n = \rho n l I + RA\alpha^{-n},$$

therefore

$$A\alpha^{-n} = \frac{\rho I}{r}(n-1-2n+n+1) + \frac{RA}{rl}(\alpha^{-n+1} - 2\alpha^{-n} + \alpha^{-n-1}),$$

therefore

$$\frac{rl}{R} = \left(\alpha - 2 + \frac{1}{\alpha}\right). \tag{3}$$

The result for the range $n < 0$ is obtained by substituting in the foregoing $I = 0$ and $\alpha = 1/\alpha$, and so we again obtain relation (3). If therefore α satisfies (3) it will also satisfy (1) for all values of n except $n = 0$.

In that case (1) becomes

$$rl\psi_0 = rlA = RA(\alpha^{-1} - 2 + \alpha^{-1}) + \rho l I;$$

therefore

$$A[rl + 2R(1 - 1/\alpha)] = \rho l I, \tag{4}$$

which determines the value of A.

We conclude that the excitability of each node in the present case is given by eqn. (2), where the values of α and A are given by eqns. (3) and (4) respectively.

Two poles

In order to generalize the foregoing results to any case of dipolar stimulation we may first observe that the values of U only at the nodes contribute to our analysis. Since the myelin is assumed a perfect insulator, internodal values of U cannot affect the current distribution in the nerve. In the second place we may note that the superposition theorem applies to all these conditions of current flow.

Consider the case of four electrodes applied to the nodes as shown dotted in Fig. 10. The two cathodes are at nodes number 0 and 1 carrying currents $(1-a)I$ and aI respectively, and the two anodes are at nodes number n and $n+1$ carrying currents $(1-b)I$ and bI respectively (where a, b are fractions lying between 0 and 1). It may readily be seen that the potential of every node in this system is the same as in the case of the lower dipolar electrodes, each of which carries a curent I, the cathode situated a fraction a of an internode to the right of node 0, the anode a fraction b to the right of n.

The excitability at node 0 due to this lower pair of electrodes may thus be written down at once by applying formula (2) to the equivalent four upper electrodes, making use of the superposition theorem to add the cathodal effects and subtract from this the anodal effects.

$$\psi_0 = (1-a) + a/\alpha - (1-b)\alpha^{-n} - b\alpha^{-n-1}, \tag{5·0}$$

A is made 1 so that ψ is scaled to 1 when $n=\infty$, $a=0$. Also at node 1

$$\psi_1 = (1-a)/\alpha + a - (1-b)\alpha^{1-n} - b\alpha^{-n}. \tag{5·1}$$

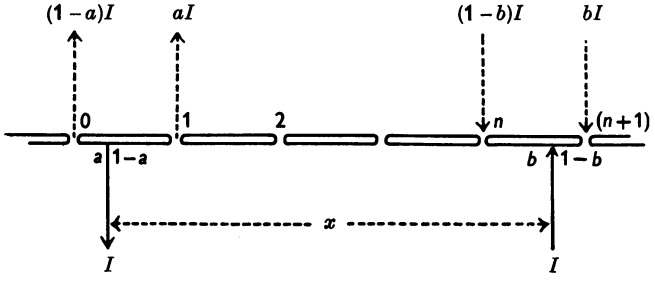

Fig. 10.

Excitation will occur at node 0 or 1 whichever has the greater excitability. A relation of interest is when the cathode is fixed at node 0 and the anode moved at various distances (Expt. III). The excitability at the cathode is given by eqn. (5·0) with a put zero.

$$\psi_0 = 1 - \alpha^{-n}(1 - b + b/\alpha). \tag{6}$$

When the anode is on the rth node, ψ has the value obtained from (6) by putting $n=r$, $b=0$ or $n=r-1$, $b=1$. They both give $\psi = 1-\alpha^{-r}$. Thus points 0, 1, 2, 3,..., n lie on an exponential curve (Fig. 11 (a)). When the anode lies to the right of the nth node a fraction $b \leqslant 1$, there is a linear relation between ψ and b as appears from eqn. (6). Thus the undotted curve (a) in Fig. 11 consists of points 0, 1, 2, 3, ..., lying on an exponential, and the chords joining successive points.

If, on the other hand, the anode is fixed on the node and the cathode is moved, quite a different relation appears, the dotted line (b) in Fig. 11. In this case b is zero and (5·0) and (5·1) become

$$\psi_0 = 1 - \alpha^{-n} - a(1 - 1/\alpha), \tag{7·0}$$

$$\psi_1 = 1/\alpha - \alpha^{1-n} + a(1 - 1/\alpha). \tag{7·1}$$

When the cathode lies on a node so that a is 0 or 1 we naturally obtain points 0, 1, 2, 3,..., again. Now

$$\frac{\partial\psi_0}{\partial a} = -\left(1 - \frac{1}{\alpha}\right), \quad \frac{\partial\psi_1}{\partial a} = +\left(1 - \frac{1}{\alpha}\right); \tag{8}$$

hence as the cathode moves from any node in either direction the excitability

falls off along a straight line of gradient $\pm(1-1/\alpha)$. Since the threshold is always given by the most excitable node in each circumstance the excitability curve (*b*), Fig. 11, involves only the upper portions of the intersecting lines.

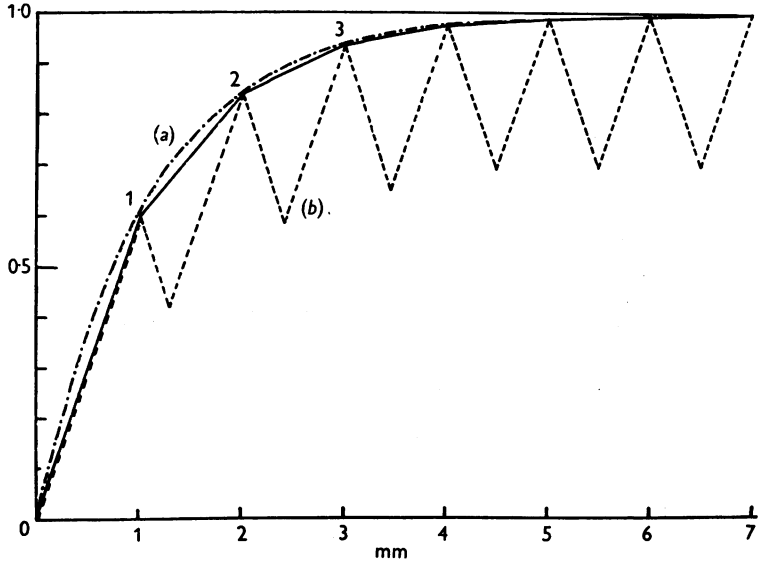

Fig. 11. The theoretical curves of Fig. 7, the excitability-length relation.

Leaky myelin

If the myelin is supposed not to be a perfect insulator then the regions between one node and the next will obey the simple cable relations, where the space constant has some value μ.

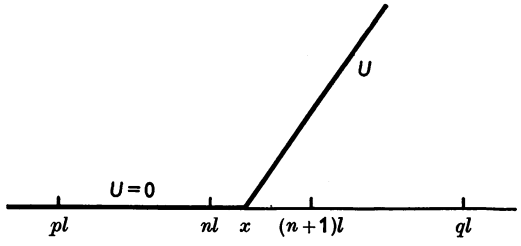

Fig. 12.

The mathematical treatment in this case is very much harder than the foregoing, and we simply state the solution of a particular and useful example. This is shown in Fig. 12, where one electrode is placed at x which lies between nodes n and $n+1$ and the other electrode is far away. The excitability of node p

$$\psi_p=\beta^{p-n}\left[\sinh\frac{(n+1)\,l-x}{\mu}+\frac{\sinh}{\beta}\left(\frac{x-nl}{\mu}\right)\right]\Big/\sinh l/\mu. \qquad (9{\cdot}1)$$

Similarly,

$$\psi_q = \beta^{n+1-q}\left[\sinh\frac{x-nl}{\mu}+\frac{\sinh}{\beta}\left(\frac{(n+1)\,l-x}{\mu}\right)\right]\Big/\sinh l/\mu, \tag{9·2}$$

where

$$\beta+1/\beta=2\cosh l/\mu+r\mu R^{-1}\sinh l/\mu. \tag{9·3}$$

As an example of how this formula may be used, let us consider the excitability-length curve where the cathode is placed on node zero, and the anode at some point x.

We find the excitability at node zero first due to the cathode there, by putting in (9·1) $0=p=n=x$. From this we subtract the effect of the anode at x, by simply putting $p=0$ in (9·1).

We thus obtain

$$\psi_0=1-\beta^{-n}\left[\sinh\frac{(n+1)\,l-x}{\mu}+\frac{\sinh}{\beta}\left(\frac{x-nl}{\mu}\right)\right]\Big/\sinh l/\mu, \tag{9·4}$$

which is the required solution. If the nodes are completely non-leaky this should reduce to the simple cable exponential. Putting $R=\infty$ in (9·3) gives

$$\beta=e^{l/\mu}.$$

Introducing this into (9·4) results in the expected

$$\psi_0=1-e^{-ln/\mu}\,e^{(ln-x)/\mu}=1-e^{-x/\mu}.$$

If, on the other hand, the myelin is completely non-leaky, eqn. (9·4) should reduce to eqn. (6) obtained above on this assumption. Putting $\mu=\infty$ in (9·3) and noting that in this case

$$\mu\sinh x/\mu=x,$$

we obtain from (9·3) and (3) that $\beta=\alpha$. Noting also from Fig. 10 with a put zero that $x=(n+b)\,l$, we may substitute in (9·4) and obtain

$$\psi_0=1-\alpha^{-n}[1-b+b/\alpha] \tag{6}$$

as expected.

APPENDIX B

EXCITABILITY-LENGTH RELATION USING A FRACTION θ OF THE MAXIMAL ACTION POTENTIAL AS INDEX

Assumptions

There is a homogeneous population of nerve fibres whose nodes are randomly distributed in position so that their population density may be assumed the same everywhere.

Proof

The electrodes which are situated a distance x apart (Fig. 10) will excite some fibres at node 0 (in the extrapolar stretch) and some at node 1 (in the interpolar stretch).

Let the given stimulus $1/\psi$ be just threshold at node 0 for a fibre where $a=a_0$. Then from (5·0), rearranging the terms, we have

$$\psi=1-\alpha^{-n}+(1-1/\alpha)[-a_0+\alpha^{-n}b_0], \tag{10·0}$$

where

$$x=(n+b_0-a_0)\,l. \tag{11·0}$$

Similarly, for the fibre which is just excited at node 1 by this same stimulus we have, from (5·1),

$$\psi=1/\alpha-\alpha^{1-n}+(1-1/\alpha)[a_1+\alpha^{1-n}b_1], \tag{10·1}$$

where

$$x=(n+b_1-a_1)\,l. \tag{11·1}$$

From (10·0) and (11·0) it follows when x is kept constant that $\partial\psi/\partial a_0$ is always negative, unless n is zero. In that case ψ_x is the same for all values of a, and a_0 may be defined as the greatest a admissible ($=1-x$). Hence, whatever n, the stimulus $1/\psi$ will excite all fibres with $a<a_0$ and (at node 0) none with $a>a_0$. Similarly, $\partial\psi/\partial a_1$ is always positive and so all fibres with $a>a_1$ will be excited at node 1. It thus appears that if $a_0\leqslant a_1$ the fraction of nerve fibres excited by the stimulus $1/\psi$ is

$$\theta=1-a_1+a_0. \tag{12}$$

In particular, when $a_0=a_1$ as at the lowest points of the curve Fig. 11 (b), all the fibres are excited and

$$\theta=1. \tag{13}$$

Now to find the curve relating ψ and x for any value of θ it is convenient to perform the whole analysis, not in terms of the variables ψ, a_0, a_1, b_0, b_1, θ, x, but in terms of their partial derivatives with respect to x, which may be written

$$\bar{\psi},\ \bar{a}_0,\ \bar{a}_1,\ \bar{b}_0,\ \bar{b}_1,\ \bar{\theta},\ 1.$$

The equations (10·0), (10·1), (11·0), (11·1), (12) respectively become

$$\bar{\psi}=(1-1/\alpha)\,[-\bar{a}_0+\alpha^{-n}\bar{b}_0], \tag{14·0}$$

$$=(1-1/\alpha)\,[\bar{a}_1+\alpha^{1-n}\bar{b}_1], \tag{14·1}$$

$$1/l=\bar{b}_0-\bar{a}_0=\bar{b}_1-\bar{a}_1, \tag{14·2}$$

$$\bar{\theta}=\bar{a}_0-\bar{a}_1. \tag{14·3}$$

These five equations are linear in 6 variables with constant coefficients. If we introduce one more such equation we can solve for any variable in terms of the constants. For instance suppose $b_0=0$, then $\bar{b}_0=0$ is such an equation. The condition is when the anode is upon a node and excitation occurs at the extrapolar node 0. We have seen that the relation (x, ψ) is given by the lines in curve (b), Fig. 11, which have a positive gradient, such as AB, Fig. 8. That AB is a straight line is confirmed from (14) since we obtain $\bar{\psi}=$constant. More important is the result $\bar{\theta}=$constant. This means that θ changes at a uniform rate along the line AB. θ is zero at A where only a single fibre is excited, and

it is unity at B as we saw above, eqn. (13). Thus if $\theta=\frac{1}{3}$ it will lie on AB, $\frac{1}{3}$ of the way from A to B.

If instead of $b_0=0$ we have $b_1=1$ (therefore $\bar{b}_1=0$), we obtain exactly the same relation along the other set of dotted lines such as AC, Fig. 8. Thus for any given value of $\theta=\theta_0$ the position (x, ψ) is given on all the dotted lines AB, AC, etc., by points θ_0 of the way from A to B and A to C. In the region BAC the relation (x, ψ) is linear. For we may add to (14) the relation $\theta=\theta_0$, therefore $\bar{\theta}=0$ and obtain $\bar{\psi}=$constant.

Now since the line AC was defined by the relation $b_1=1$, we cannot cross it and enter into the region ACD without modification of (14) otherwise $b_1>1$. But the only change required is to write $-n$ for $1-n$ in (14·1). In conjunction with $\bar{\theta}=0$ we again derive $\bar{\psi}=$constant for the region ACD.

So the excitability-length curve is completed simply by joining with straight lines the points previously found upon the dotted curve $BACD$....

SUMMARY

1. A simple method is described for studying the excitability of a single nerve fibre in an undissected nerve trunk.

2. This method is used to answer the question: 'Is a nerve fibre *in situ* excitable only at the nodes? If so, why does the space distribution of excitability fit so well the expectations derived from a simple (unsegmented) cable?

3. When a nerve is stripped of epineurium and stimulated through a cathode with an earthed anode very close on each side, it is found that excitation occurs only at certain points on the fibre (Fig. 4), apparently when the cathode lies over a node.

4. The curve between excitability (=1/threshold) and the position of the two electrodes in relation to the nodes has been investigated for a number of conditions. In Figs. 5–7 are shown experimental points, and the theoretical lines calculated on the assumptions that current can enter or leave the axis cylinder only at the nodes. The fit is adequate.

5. Appendix A derives the theoretical expectations. Results (but no working) are also given for the far harder case where the myelin is assumed leaky.

6. When a multi-fibre response (e.g. $\frac{1}{3}$ maximal action potential) is used as index of excitation, the fibres involved have nodes at various distances from the cathode. In Appendix B it is shown that the excitability-length relation of the group is almost identical with the result derived from the simple cable theory.

7. It is concluded that medullated nerve fibres *in situ* are only excitable at the nodes. The space relations of excitability can be predicted closely from the assumption that the current only enters and leaves through the nodes. Multi-fibre responses statistically obey the simple cable excitability relations.

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