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EVIDENCE FOR ELECTRICAL TRANSMISSION IN NERVE. PART I

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This paper is concerned with the way in which activity is transmitted in medullated nerve. The most widely accepted theory is that transmission depends upon excitation by the action current. The theory is a plausible one, since the nervous impulse and electrical change travel at the same speed and have many similar properties. Moreover, the amplitude and duration of the action current are not very different from those of an effective electrical stimulus. The theory may be formulated more precisely by saying that each section of nerve is excited by the local electric circuits produced by the activity of adjacent parts. This process is possible, since the direction of the electric change is such that the local circuits set up by an active region would excite a resting one. Many properties of nerve and muscle can be explained on this basis, but it is difficult to accept the theory until more is known about the nature of the local circuits on which transmission is supposed to depend. The fundamental question is to decide whether the local circuits set up by an active region of a nerve fibre are able to excite an adjacent part. The present work was undertaken with the object of answering this question.

The method which has been employed consisted in blocking conduction in one section of nerve and observing any changes which were transmitted through the block. The starting point for the research was provided by an observation which has since been recorded by Blair & Erlanger [1936]. It was found that an impulse which arrived at a blocked region could increase excitability in the nerve beyond the block. Another way of describing the phenomenon is to say that a blocked impulse can sum with a subthreshold electric shock. My own observations were originally made in the following way. A nerve was blocked by the action of local cold. When the block was complete a maximal

shock S_1 applied to A produced no response at C (Fig. 1). A subthreshold shock S_2 was then applied to B; since this was below threshold, it also produced no response. However, if the two shocks were combined so that S_2 followed S_1 by 1 or 2 msec., impulses were set up and could be detected at C. Clearly the volley of blocked impulses increased the excitability beyond the block and enabled S_2 to excite. Subsequent experiments showed that the increase in excitability lasted for a few milliseconds, and that it might involve a decrease of 90 p.c. in the electrical threshold.

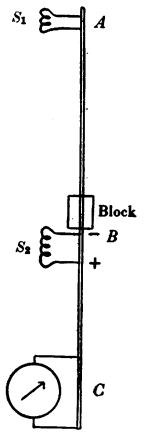

Fig. 1.

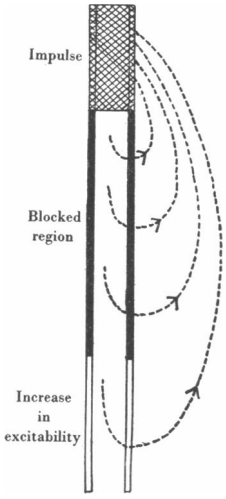

Fig. 2.

This kind of summation can be observed in various ways; thus Blair & Erlanger [1936] found that it occurred in anodally polarized nerves, and I have observed it at pressure as well as at cold blocks. The important point about the observation is that it provides a method of testing theories of nervous transmission. According to an electrical theory the explanation of summation would be that eddy currents spread through the block and increase excitability in the nerve beyond. Fig. 2 shows how the conventional local circuit diagram can be extended to explain the interaction between blocked impulse and subthreshold shock. If the flow of current beyond the block was just below threshold, an impulse would not traverse the block, but it would produce a large increase in excitability. The electrical view of nervous transmission would be considerably strengthened if it could be shown that the increase in excitability was produced in this way. If the local circuits set

up by a blocked impulse caused a 90 p.c. decrease in threshold, there is a strong probability that those associated with a normal impulse would produce a decrease of at least 100 p.c. and could therefore transmit activity electrically. The general aim of this research is to discover how far propagation depends upon excitation by electric currents; its immediate concern is to decide whether the increase in excitability near a block is produced by local circuits.

Apparatus and method

I. *Nerves employed*

Sciatic nerves of Hungarian frogs (*Rana esculenta*) or of English *Rana temporaria* were employed. These were dissected from the spine to the knee, and sometimes the dissection of peroneal and tibial branches was continued to the ankle.

II. *Methods of blocking nerve conduction*

(*a*) *Cold block.* Boyd & Ets [1934] have shown that two kinds of low-temperature block may be distinguished. If supercooling is avoided, conduction is abolished at a temperature of about $-1°$ C. and returns at once when the nerve is rewarmed. If supercooling is allowed, the nerve may be cooled to $-6°$ C. before it freezes, and in this case recovery only occurs after long delay. In the present work the first, reversible, type of block was employed. One end of a silver rod was cooled in ice and salt, the other projected into the moist chamber and made contact with the nerve. The temperature was controlled by adjusting the length of rod in contact with the freezing mixture. The end of the rod was tapered, so that different lengths of nerve (from 3 to 5 mm.) could be cooled. Boyd & Ets, who used an arrangement of this kind, showed that certain precautions must be observed if supercooling is to be avoided. They found that supercooling occurred when the rod was sealed with vaseline into an ebonite chamber, and that reversible blocks could be obtained only if the rod fitted loosely into the chamber wall. Their explanation of this result is that condensed water first freezes near the cold end of the rod, and that the film of ice which subsequently creeps up the rod prevents supercooling of the nerve. A vaseline seal interrupts the spread of the ice film and supercooling occurs beyond it. In my experiments the rod was embedded in a wax chamber, and in order to avoid supercooling a slit was cut in the chamber wall, in such a way as to expose one side of the rod to the air throughout its entire length.

(*b*) *Pressure block.* The nerve was compressed between two blocks of ebonite which were covered with thin rubber pads. Pressure was applied by resting weights on a platform connected to one of the blocks. Two or three millimetres of nerve were compressed and a weight of about 30 g. used. With this arrangement conduction was abolished after about 20 min. This type of block was only partially reversible, so that the time available for experiments was often rather short.

Electrode system. Bright silver was used for stimulating and recording electrodes. The use of metallic electrodes was necessitated by the rather unusual requirements of the research. In order to obtain the curves described on p. 197 it was necessary to measure the distribution of potential over a few millimetres of nerve. Satisfactory results could only be obtained if the whole operation was made within a few minutes, and if the conditions at the block remained constant. For these reasons it was impracticable to use a single movable electrode, and it was necessary to lead off from the nerve with several electrodes. It is difficult to arrange that four or five calomel electrodes make contact within a centimetre of nerve. With the ordinary systems fluid tends to collect round the electrodes, and this is obviously undesirable when the leads are only a millimetre apart. The accumulation of fluid might be avoided if cotton strands soaked in saline or fine capillary tubes were used as leads. These would necessarily have a high resistance and would therefore increase the danger of recording artefacts [see Bishop *et al.* 1926]. For these reasons metallic electrodes were employed, and potentials near the block were recorded by resting the nerve on a grid of fine silver strips, each 0·2 mm. thick and 1–2 mm. apart. The whole system of electrodes and block was sealed into a paraffin wax chamber. This was washed and dried after each experiment, and as an additional precaution against electrical leaks the surface was rewaxed after the chamber had been used for a few weeks.

There are two important objections to the use of metallic electrodes. In the first place, polarization may distort the wave form of the potential recorded by the amplifier. Now the input resistance of the amplifier was 0·5 megohm, and the potentials recorded were for the most part about 1 mV. in amplitude and 1–10 msec. in duration. Thus the total charge crossing the electrodes was of the order of 10^{-11} coulomb, and it is unlikely that this could have produced much polarization. The possibility that the electrodes might introduce some wave-form distortion was tested in the following way. A potential difference, 5 mV. in amplitude and 2·5 msec. in duration, was applied to the amplifier through the nerve and electrodes. The quantity of current crossing the electrodes was,

therefore, about the same as that drawn from the nerve in activity. If polarization affected the form of the action potential, it should also have modified the form of the rectangular pulse. The record obtained by calibrating the amplifier through the nerve was compared with one obtained by calibrating through 15,000 ohms. Since these were found to be identical, it was concluded that polarization did not introduce any serious wave form distortion.

The second objection to the use of metallic electrodes is that polarization may affect the form of the stimulating current. This leads to serious errors in some experiments, but the objection does not apply to the present research where the exact form of the stimulus was of no importance.

Stimulating apparatus. Condenser discharges were sometimes used for stimulating, but for the most part break shocks from induction coils were employed. The coils contained iron cores which were removed when brief shocks were required. The strength of the shocks was graded by the insertion of precision resistances in the primary circuits. When iron-cored coils are used, the current in the secondary coil may not be proportional to that in the primary. This possibility was eliminated by a calibration which showed that the primary and secondary currents were directly proportional over the range used experimentally.

The keys controlling the stimuli and the oscillograph time sweep consisted of magneto contact breakers with platinum points. Each was mounted on an adjustable arm and was broken by a cam rotating at a velocity of about 5 m./sec. The time interval between successive stimuli was controlled by moving the arms on which the keys were mounted. Examination with the oscillograph showed that the timing arrangement was satisfactory, and that the break of the contacts was free from chatter. The nerve was stimulated repetitively at rates of 5–10/sec.

Recording system. A resistance capacity coupled amplifier of conventional design was employed; 2 or 4 μF. coupling condensers and 0·5 megohm grid leaks were used. In the earliest experiments the amplifier was connected to a Matthews oscillograph. The arrangement of oscillograph and output stage was similar to the one used by Matthews [1928], and needs no further description. During the greater part of the work a Cossor cathode-ray oscillograph was employed. A linear traverse was obtained by allowing a condenser connected to one pair of deflectors to discharge through a saturated diode. The discharge was started by a contact on the interruptor used for stimulating; thus potentials produced by the nerve could be viewed as a standing wave. The time axis was

calibrated with an oscillatory discharge which was obtained by allowing a condenser to discharge through an inductance. The linearity of the recording system was tested by applying rectangular pulses to the input and photographing the response of the oscillograph. Careful measurement showed that the system was linear over the range employed experimentally. The temporal characteristics of the amplifier were sufficient for the requirements of this research. When a rectangular pulse was applied to the input the deflexion was 95 p.c. complete in 100 μsec.; it subsided to 95 p.c. of its maximum in about 10 msec.

The oscillograph was mounted on a turn-table and could either be viewed directly or swung into the field of a camera. Photographs of single transits were obtained by running film through the camera in a direction opposite to that of the oscillograph traverse. Since the nerve was stimulated repetititively the film had to move on one frame (3 cm.) during each revolution of the interruptor. The time scale of the records obtained was determined by the sum of the velocities of traverse and film. The speed of the traverse was much greater than that of the film, and the records were therefore only slightly influenced by variations in film speed.

Results

(*a*) *Preliminary experiments*

This paper is primarily concerned with the way in which a blocked impulse sums with a subthreshold electric shock. The experiments described in this section do not throw much light upon the mechanism of summation, but they must precede any detailed analysis of the process. In the first place it is necessary to show that summation represents an interaction between blocked impulse and subthreshold shock. All that can be observed is that two shocks, which by themselves are ineffective, may sum to produce an impulse. It is conceivable that this might depend upon a direct electrical interaction between the shocks. The possibility of summation being produced in this way was excluded by the following experiments.

(1) The effect disappeared when the nerve was crushed between *A* (Fig. 1) and the block. If the increase in excitability depended upon the nervous impulse, it would have been abolished by crushing, but if it was caused by an electrical leak there is no reason why it should have been affected.

(2) Summation might be caused by a spread of electrotonus from the stimulating electrodes. The first control does not exclude this possibility, since electrotonus is abolished by crushing. If this explanation were

correct, summation would depend upon the direction of S_1; thus there would be an increase of excitability with a descending current and a decrease with an ascending one. This observation was contradicted by experiment, for summation was obtained with ascending as well as with descending currents.

(3) The view that summation depends upon the nervous impulse is strengthened by the relation between the strength of S_1 and the magnitude of the increase in excitability. It was found that when S_1 was subthreshold there was no increase in excitability: and that increasing S_1 beyond its maximal value led to no further change in the amount of summation. Clearly summation depends upon the nervous impulses set up by S_1 and not upon the shock itself.

(4) The most convincing control depends upon the time relations of the effect. When the two shocks were applied simultaneously, no summation occurred, and the increase in excitability only developed when S_2 followed S_1 by an interval which corresponded to the conduction time. This is illustrated by the results given in Fig. 3. The abscissa indicates the interval between the moments of application of S_1 and S_2. The ordinate represents the increase in excitability produced by an impulse. This was measured by observing the variation in the response to a threshold stimulus. S_2 was adjusted until it just produced an action potential at C. It was then combined with S_1. If the nervous impulses set up by S_1 produced any increase in excitability beyond the block, S_2 would excite more fibres and so S_1+S_2 would give a larger action potential than S_2 alone. The increase in action potential provides a convenient and rapid index of the increase in excitability, and it has been used in this experiment. Fig. 3 shows that there is a brief interval between the moment of application of S_1 and the beginning of the increase in excitability. The obvious explanation of this latency is that it corresponds to the time taken by impulses to travel between A and the block. If this is correct, the latency should be increased by moving the A electrodes away from the block. This deduction was verified; thus curve I was made with an electrode-block distance of 14 mm., and curve II with a distance of 45 mm. In the first case the latency was about 0·4 msec., and in the second it increased to about 1·25 msec. Records of action potentials proximal to the block showed that these latencies corresponded to the actual conduction times. The times at which impulses reached the block are marked by the arrows in Fig. 3; they show the crest and foot of each action potential. This experiment shows that summation starts at about the moment when impulses reach the block,

and that the latency is determined by the conduction time. It is therefore impossible to believe that the increase in excitability depends upon any kind of direct interaction between the two shocks.

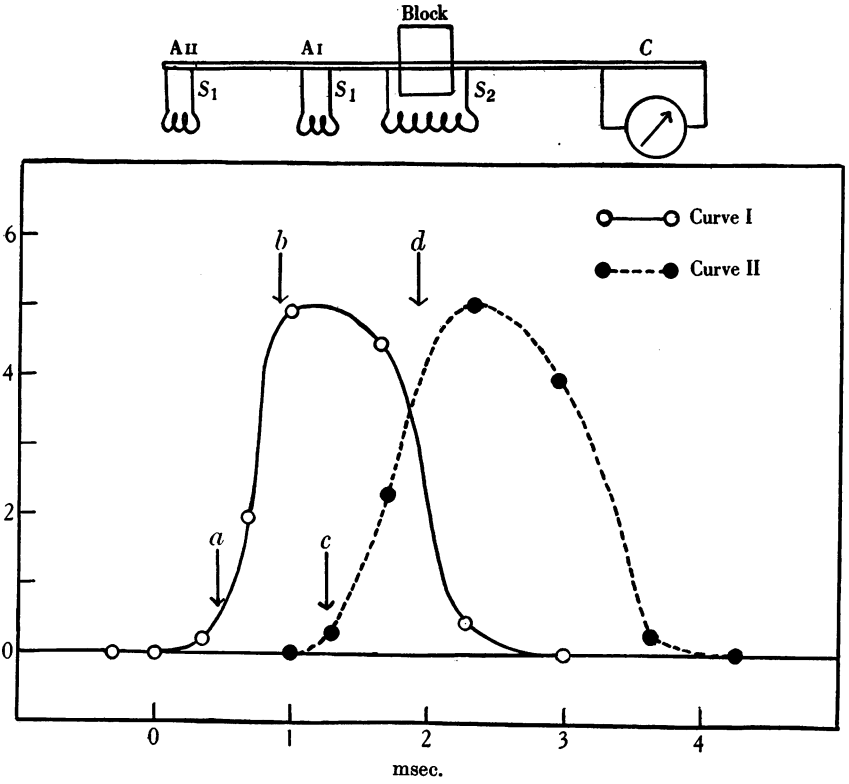

Fig. 3. 4 mm. pressure block. Abscissa: interval by which S_2 follows S_1. Ordinate: increase in action potential at C produced by combining S_1 with S_2. Curve I: S_1 applied 14 mm. proximal to block. Curve II: S_1 applied 45 mm. proximal to block. The ordinate scale for I is 1 unit = 0·18 mV and for II, 1 unit = 0·37 mV. The difference is due to the fact that the effect diminished between making curve II and curve I. Arrows: show time of arrival of impulses at a point 3 mm. proximal to block. a = beginning, b = crest of action potential starting at A I. c, d = beginning and crest of potential starting at A II. The beginning is defined as the moment when the potential rises to one-twentieth of its maximum.

Conditions necessary for obtaining summation.

It was important to use blocks whose intensity could be delicately graded. If the intensity of the block was increased beyond the point at which conduction failed, the increase in excitability was reduced and

might be abolished. No increase could be detected if the nerve was crushed at the block, or if conduction was abolished by tying a ligature round the nerve. It will be shown later that the increase in excitability declines fairly rapidly along the nerve distal to the block. Consequently we should not expect to obtain summation with blocks of more than a certain width. Summation was observed with 5 mm. cold blocks, but no experiments have been tried with blocks wider than this.

The position of the anode.

The electrodes at the block may be arranged in various ways. In Fig. 1 the anode was connected with a point distal to the block; an alternative, and in some ways a more convenient arrangement, was with the anode proximal to the block. There did not appear to be any great difference between the magnitudes of the change in threshold obtained with the two electrode arrangements. The change usually seemed to be larger when the anode was proximal to the block, but the difference was not significant in the two experiments where the percentage change in threshold was carefully measured.

The magnitude of the increase in excitability.

The largest changes in threshold were observed when the block had abolished conduction in the majority of fibres, but when a few impulses were still transmitted through it. The measurement of summation in partially blocked nerve was complicated by the fact that S_1 alone produced a response at C. The threshold for S_2 in presence of a blocked impulse was determined by observing whether the addition of S_2 to S_1 led to a response which was larger than that produced by S_1 alone. A 90 p.c. decrease in threshold implies that, in presence of an impulse, S_2 only had to be $\frac{1}{10}$ threshold intensity to excite. Actually this means that the response produced by S_1+S_2 was significantly larger than that due to S_1 alone as long as the intensity of S_2 was more than a tenth of its normal threshold.

The decrease in threshold usually amounted to between 50 and 70 p.c. and greater changes were sometimes observed. The following figures show the largest values obtained.

Pressure block:	9. xii. 1936	...	84 p.c.
	10. xii. 1936	...	95 p.c.
Cold block:	12. xi. 1936	...	78 p.c.
	14. xii. 1936	...	76 p.c.

(b) *The electrical changes near a blocked region*

The experiments described in the preceding section show that summation depends upon an interaction between blocked impulse and subthreshold shock, but they do not throw any light upon the way in which

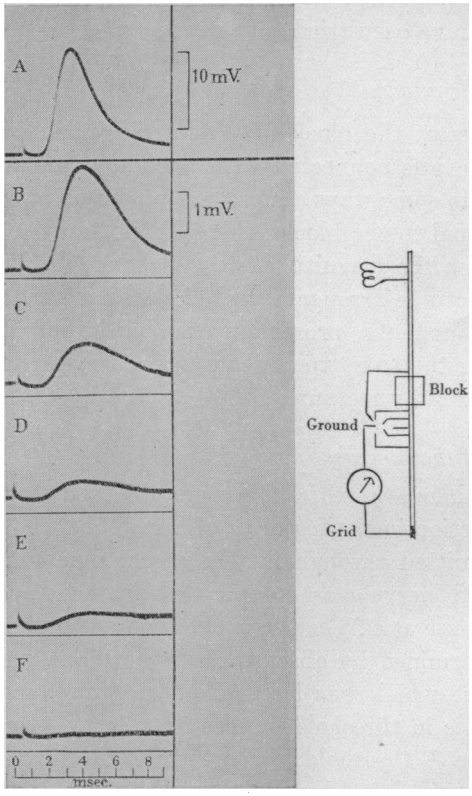

Fig. 4. Potentials proximal and distal to block. 3 mm. cold block. A, action potential 2 mm. proximal to block. B–F, extrinsic potentials distal to block; all at same amplification which was about five times greater than in A. B, 1·4 mm. distal to block; C, 2·5 mm. distal to block; D, 4·1 mm. distal to block; E, 5·5 mm. distal to block; F, 8·3 mm. distal to block. The time scale applies to all the records.

it is produced. The most plausible theory is that the increase in excitability is caused by local electric circuits spreading through the blocked region. Now current spread of this kind would be associated with a potential change which could be observed experimentally. This suggests that an investigation of the electrical changes near the block might throw light

upon the mechanism of summation. If the experimental results showed that the increase in excitability was invariably accompanied by an electrical disturbance, the view that it depended upon local circuits would be strengthened. On the other hand, if the increase could be dissociated from any potential change, we could no longer maintain that it was electrical in origin. The electrical changes near the block were investigated and are described in this section. The experiments were made in the following way. A nerve was blocked with cold or pressure, and potentials were led off from various points beyond the block. Under these conditions a response could be recorded from just beyond the

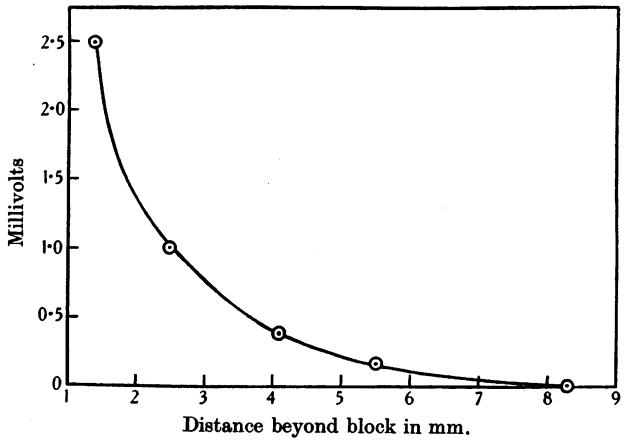

Fig. 5. Potential spread beyond block. Measurements were made from the records illustrated in Fig. 4.

block, although no impulses were transmitted through it. This was distinguished from an ordinary action potential by the fact that it was not propagated, but declined exponentially along the nerve. The records of Fig. 4 illustrate the phenomenon. The response beyond the block has roughly the same form as an action potential from the proximal side of the block, but it is smaller in amplitude. The prolonged duration of the wave was due to the low temperature of the nerve near the block; for the potential was actively produced by cold nerve, although it may have been led off at some distance beyond the block. The form of the potential gradient is shown in Fig. 5, where the amplitude of the potential wave is plotted against the distance from the block. The electrical change illustrated by these records has been observed in more than eighty nerves. It is not caused by the activity of nerve under the lead and it

seems to be produced by a spread of current along the nerve fibres themselves. In order to distinguish the change from a propagated action potential, it will be called the extrinsic potential. This term has been employed because Erlanger *et al.* [1926] used extrinsic phase to describe the part of the action wave which is due to current flowing in front of the active region.

A small action potential, due to unblocked impulses was usually superimposed upon the extrinsic potential. This is illustrated by the records in Fig. 6, where a response due to blocked and to unblocked impulses may be distinguished. The distinction has been emphasized by marking the probable time course of the extrinsic potential. Although unblocked impulses did not obscure the extrinsic potential, they often made accurate measurement impossible. Their presence was a continual source of difficulty, and numerous methods of eliminating them have been tried. Repeated freezing and thawing of the nerve often produced a condition which left the extrinsic potential, but eliminated unblocked impulses. Increasing the stimulation rate from 5 to 10/sec. sometimes reduced the number of unblocked fibres. This observation is interesting, because it suggests that recovery from activity may be extremely slow in a region which has been impaired by cold.

With pressure blocks the difficulty of eliminating unblocked fibres has been much greater, and satisfactory results have only been obtained on a few occasions. Gasser & Erlanger [1929] showed that pressure affected large before small fibres; in the present work the small fibres were eliminated by using shocks at intensities which were maximal for the α group, but below the threshold of smaller fibres.

The extrinsic potential may be observed in a different way. It has been known for a long time that cooling a section of nerve increases the interval for muscular summation, and that this effect is due to failure of the second impulse in the cold nerve. The cold region behaves as though it had a prolonged absolute refractory period, and acts as a block to the second but not to the first of two impulses. This property of cold nerve provides the basis for a method of abolishing transmission; for the intensity of the block can be adjusted so that one nearly maximal action potential is transmitted but a second is almost completely extinguished. Under these conditions the second impulse produces an extrinsic potential which is similar to that produced by a single blocked impulse. Fig. 7 illustrates this. The records show the descending phase of the first action potential and, following this, a smaller wave which dies out along the nerve. This experiment is interesting for two reasons. In

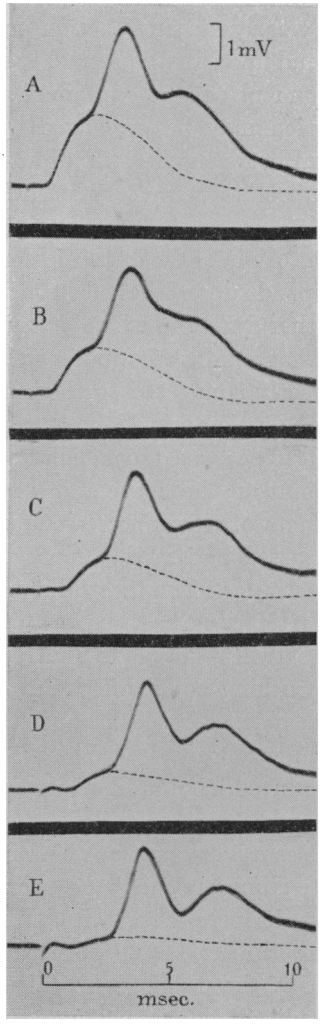

Fig. 6.

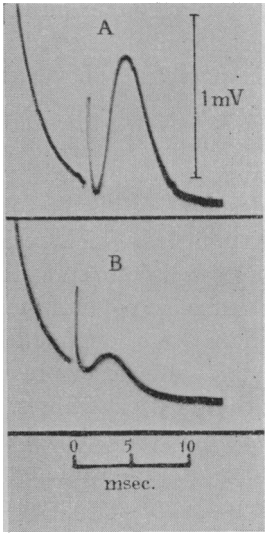

Fig. 7.

Fig. 6. Extrinsic potential and propagated action potentials. 3·5 mm. cold block. A, 1·2 mm. distal to block; B, 2·4 mm. distal to block; C, 3·7 mm. distal to block; D, 5·4 mm. distal to block; E, 7·3 mm. distal to block. Amplification and time scale same throughout.

Fig. 7. 3 mm. cold block. Temperature adjusted so that the first but not the second of two impulses was transmitted. Descending phase of first impulse shown; followed by extrinsic potential. The nicks in the upper record are due to interference. A, 1·4 mm. distal to block; B, 4·2 mm. distal to block.

the first place, the fact that the extrinsic potential can be produced in nerve which is capable of conducting a nearly maximal action potential suggests that the potential does not depend upon any abnormal or specific property of blocked nerve. In the second place, the experiment shows how much the absolute refractory period may be prolonged by local cooling. In this experiment the interval between the two impulses was about 15 msec., and blocks with an absolute refractory period of as much as 50 msec. have been observed.

So far nothing has been said about the origin of the extrinsic potential. The most attractive theory is that it depends upon local electric circuits, but it is necessary to consider any other ways in which it might be produced. Bishop *et al.* [1926] found that small action potentials could often be recorded from regions not directly connected to the amplifier. Such artefacts usually occurred when the resistance of the ground lead to the nerve was high, and they appeared to be caused by a high resistance or capacitative connexion between a point on the nerve and ground. I have occasionally observed small artefacts of this kind, but unlike the extrinsic potential, they were always associated with a poor contact between the nerve and recording electrodes. The possibility of the extrinsic potential being any kind of artefact is best excluded by the fact that it was abolished by crushing between the block and recording electrodes. It is difficult to see how crushing could affect an artefact depending upon a high resistance or capacitative leak, but it would prevent local circuits spreading along a nerve fibre.

The extrinsic potential might be produced in the following way. The sciatic nerve gives off small branches, and if these were less susceptible to the action of cold or pressure, impulses might traverse the block and stop at the cut ends of fibres. In order to eliminate such a possibility, the nerve was always arranged so that an unbranching stretch lay distal to the block. At the beginning of each experiment, action potentials from this stretch were measured on the face of the oscillograph tube. These showed only a slight decrease in amplitude along the nerve (about 2–5 p.c./mm.), which was probably due to the temporal spreading introduced by differences in conduction rate. The possibility that the decrement might depend upon impulses stopping at cut branches was excluded in a different way. The nerve was stimulated peripherally, and potentials were recorded from the central end. In this case a potential gradient which depended upon cut branches would be impossible, since any fibres stimulated must have run the whole length of the nerve. The experimental result showed that peripheral stimulation produced a

potential gradient which was very like that obtained in the ordinary way.

Another possibility is that the potential gradient might be produced by impulses which emerged from the region where cold or pressure was applied and failed in the distal stretch of nerve. This argument would be tenable if the decrement occupied only a millimetre, but a consideration of dimensions makes it unlikely. It is difficult to see how an impulse could pass a region where the cold was most severe, run 6 or 7 mm. in more normal nerve and then fail. A process of this kind is even less likely to occur at a compression block, where the effect of the pressure is sharply localized. Moreover, this hypothesis provides no satisfactory explanation of records like those shown in Fig. 6. Here there is a component which is caused by propagated impulses, but it shows no sign of decrement. Consequently it is difficult to suppose that the extrinsic potential itself could be made up of propagated impulses.

The nature of the extrinsic potential may now be considered more closely. The shape of the decrement suggests that it might be fitted by a formula of the type

$$p = p_0 e^{-x/L}, \qquad \text{.....(1)}$$

where p is the potential at a distance x from a point ($x=0$), where $p=p_0$. L is a constant with the dimensions of a length; the potential falls to $1/e$ of its value in a distance L.

In order to illustrate the exponential nature of the decrement several experiments are plotted in semi-logarithmic co-ordinates in Fig. 8. If the decrement obeys an exponential formula the results should fall on a straight line. This is approximately true. There are deviations, but they are mostly of a random kind and may be due to experimental errors. The principal sources of error were of two kinds. First, the determination of potentials at distances greater than 4 mm. was often made rather uncertain by the presence of unblocked impulses. The second and more serious type of error was introduced in the measurement of the abscissa. The position of the electrodes was fixed and could be accurately measured, but a slightly asymmetrical collection of fluid might alter their effective point of contact with the nerve and errors of at least half a millimetre may have arisen in this way.

The principal interest of these results lies not in the exponential nature of the curves, but in the value of L, the space constant involved. Fig. 8 shows that there is a considerable amount of variation in the slope of the lines and hence in the value of L. Table I indicates the value of L obtained in the most accurate experiments. In each case the results

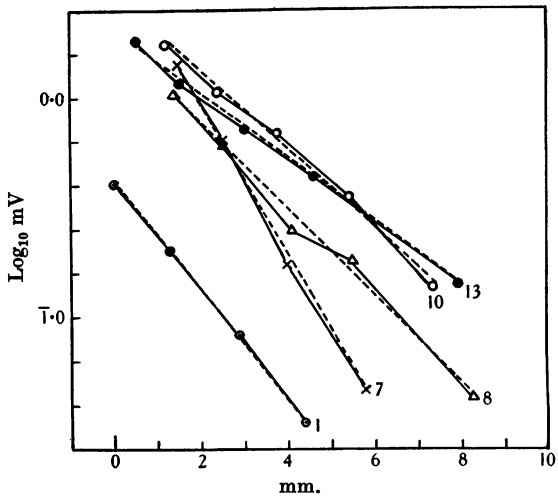

Fig. 8. Abscissa: distance in mm. from block. Ordinate: extrinsic potential, $\log_{10}$ mV. The numbers on the curves refer to the experiments in Table I below, where details of the type of block used are given.

TABLE I. The extent of spread of the extrinsic potential

Several sets of determinations have often been made during the course of one experiment; since these were fairly consistent, one set of values has been chosen to represent the whole experiment. With the exception of No. 2, the potentials were measured from photographic records. In three cases (6, 10 and 11) the potential was measured at a constant interval after the stimulus artefact; in the remainder the maximum of the wave was measured. In the experiments marked with an asterisk, the nerves were subjected to prolonged action of the block.

Experimental details, type of block	Range of measurement: Distance from block mm.	Range of measurement: Amplitude of potential mV.	L (mm.)
(1) 10. iii. 36: 4 mm. pressure	0–4·4	0·42–0·037	1·9
(2) 20. iii. 36: 2 mm. pressure	0–4·6	1·4–0·07	1·8
(3) 25. v. 36: 3 mm. cold	1·4–6·0	0·87–0·058	1·7
(4) 29. v. 36: 3 mm. cold	1·4–6·0	0·51–0·057	2·1
(5) 8. vi. 36: 3 mm. cold	1·4–6·0	0·88–0·074	2·0
(6)* 11. vi. 36: 3 mm. cold	1·4–6·0	1·35–0·078	1·6
(7)* 16. vi. 36: 3 mm. cold	1·5–5·8	1·41–0·046	1·25
(8) 10. vii. 36: 3 mm. cold	1·4–8·3	1·07–0·043	2·15
(9)* 11. vii. 36: 3 mm. cold	1·4–5·5	2·5–0·11	1·55
(10) 25. x. 36: 4 mm. cold	1·2–7·3	1·74–0·14	2·4
(11) 6. xi. 36: 4 mm. cold	1·2–5·4	0·86–0·11	2·0
(12) 18. xi. 36: 4 mm. cold	1·2–5·4	2·1–0·34	2·2
(13) 4. xii. 36: 3 mm. pressure	0·5–7·9	1·8–0·16	2·9

Average value for $L = 2·0$ mm.

were plotted in semilogarithmic co-ordinates, and L obtained from the slope of a straight line drawn through the points. When Briggsian logarithms are used L is of course given by the distance in which the potential falls by 0·434 ($\log_{10} e$).

The electrotonic nature of the extrinsic potential.

The properties of the extrinsic potential suggest that it may be similar to an electrotonic potential. This is probable on theoretical

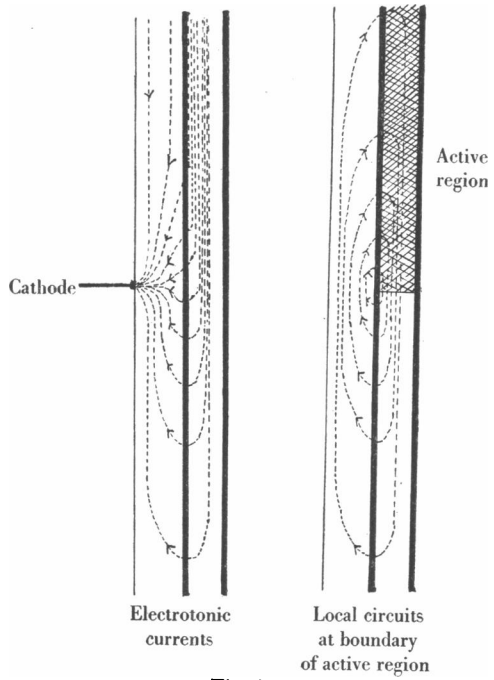

Fig. 9.

grounds, for the type of current flow described by the conventional local circuit diagram is essentially similar to the current flow which is supposed to be responsible for electrotonus. Both involve local circuits, in which current in the core is associated with an equal and opposite component in the interstitial fluid. A high-resistance sheath has the effect of spreading out electrotonic currents, and this should operate equally for the currents produced in activity. Fig. 9 illustrates this argument.

The expectation that the extrinsic potential would be of an electrotonic nature is strengthened by considering the equations which determine the distribution of current in cable-like systems. In order to treat electrotonus mathematically it is usual to consider the current flow in core and interstitial fluid as strictly parallel. An alternative statement of the same assumption is that in any transverse section the potential is uniform throughout the core and throughout the interstitial fluid. When this assumption is made, it can be shown that the distribution of electrotonic potential in the extrapolar region is governed by the equation

$$p = p_0 e^{-x/\sqrt{\frac{R}{r+\sigma}}}, \qquad \text{.....(2)}$$

where r = resistance of interstitial fluid per unit length to axial currents; σ = resistance of core per unit length to axial currents; $1/R$ = conductivity of sheath per unit length to radial currents. The other symbols are the same as in equation (1). For a derivation of this equation see Appendix.

For our purpose, the important point about this equation is that it applies equally to electrotonus or to a potential depending upon currents produced in activity. In this mathematically simplified system, the local circuits produced by the application of an external potential difference are precisely similar to those depending upon an internal change. It is uncertain how far the assumption of parallel current flow is legitimate, and there may in fact be some difference between electrotonic and activity local circuits. But there seems to be good ground for supposing that the two would be at least approximately similar.

The exponential distribution of the extrinsic potential agrees with the observed properties of electrotonus as well as with the theoretical requirements of equation (2). For it has long been known that the spatial distribution of an electrotonic potential conforms to an exponential law. The important problem, however, is to decide whether the space constant of electrotonus is similar to that of the extrinsic potential. The fact that both potential gradients could be fitted by an exponential formula would be of no significance if the logarithmic slope of the gradients were completely different. At first it appears that the decline of the extrinsic potential is too rapid for an electrotonic potential. The average value for L was 2·0 mm., and extremes of 1·2 and 2·9 mm. were obtained. Now the general opinion is that the exponential space constant of electrotonus is about 3 mm. Curves published by Hecht [1931*a*] and by Bishop *et al.* [1926] indicate that the potential falls to $1/e$ of its value in 2·6 and in 2·8 mm. Schultz [1924] obtained values ranging from 2·1 to 5·6 mm., and Bogue & Rosenberg [1934] give values of 3·6 mm. at

20° C. and 2·4 mm. at 2·5° C.[1] With the exception of the last, all these measurements were made with constant currents lasting many seconds, and the results may have been complicated by slow after-variations. These seem to be small in the case of catelectrotonus [e.g. Hecht, 1931*b*], and a space constant of about 3 mm. probably applies to potentials lasting only a few milliseconds. This indicates that the decline of electrotonus is more gradual than that of the extrinsic potential. However, the difference is not very great, and it might conceivably be due to abnormal conditions near the block.

The question of the electrotonic nature of the extrinsic potential can only be settled by comparing the distribution of the two potentials under similar experimental conditions. The work of Bogue & Rosenberg [1934] and of Harris *et al.* [1936] indicates that the distribution of an electrotonic potential depends upon its wave form. Consequently it is desirable to compare the extrinsic potential with an electrotonic potential of similar form. A current pulse of suitable shape was obtained from a circuit involving two condensers, and was applied to the nerve through electrodes x and y (Fig. 10). In this way electrotonus could be measured at the same time and in the same stretch of nerve as the extrinsic potential. The leading-in electrodes consisted of cotton wicks soaked in gelatine Ringer and joined to chlorinated silver wires. When pressure blocks were used the current was applied through a moist cotton thread which lay in a groove cut in one of the pieces of ebonite. A gap of at least 2 mm. was left between the cathode y and the recording electrodes. In experiments with brief pulses of current, it is easy to record potentials which have nothing to do with electrotonus, but are similar to some of the artefacts responsible for stimulus escape. These were reduced by careful screening and by passing the double condenser discharge through a transformer. The circuit employed is shown in Fig. 10, and with this

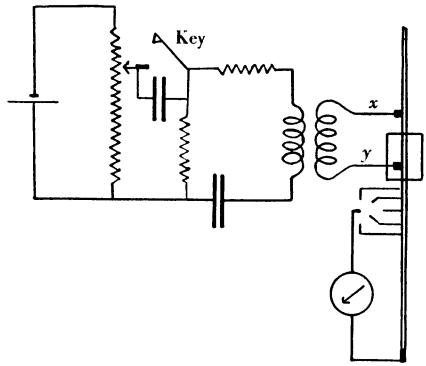

Fig. 10. Circuit diagram for applied electrotonic potential measurements. On break of the key this gives a current pulse of the form illustrated by Fig. 11.

[1] Schultz and Bogue & Rosenberg calculate a constant α which is defined by the equation $p = p_0 e^{-\alpha x}$ (other symbols are the same as in equation (1)). α is the reciprocal of the space constant which is used here.

arrangement artefacts did not appear as long as the electrodes made good contact with the nerve. The electrotonic nature of the potentials recorded was established by the fact that when increased in intensity they reached threshold and produced action potentials, and by the fact

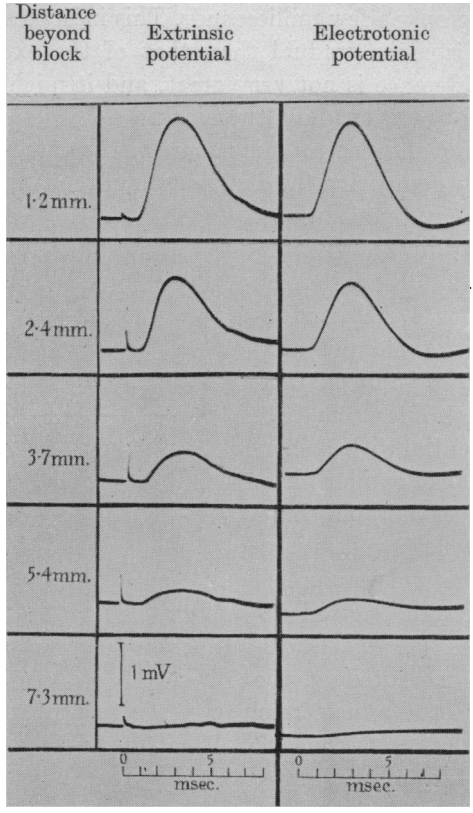

Fig. 11. Extrinsic potential and applied electrotonic potential at corresponding distances beyond block. 3·5 mm. cold block. Amplification and time scale same throughout.

that they were abolished by crushing between the block and recording leads. The actual course of an experiment was as follows. The intensity of the block was increased until the extrinsic potential was freed from propagated impulses. The applied potential, led in through x and y, was adjusted so that electrotonus had the same amplitude as the extrinsic potential. The potentials from different points along the nerve were then recorded photographically. At the end of an experiment the nerve was

usually crushed between block and electrodes. The records reproduced in Fig. 11 were obtained in an experiment of this kind; they show that the distribution of the extrinsic potential was almost identical with that of the electrotonic potential.

The records in Fig. 11 call for comment in two respects. At 7·3 mm. from the block, the extrinsic potential has practically vanished, but there is still a small and irregular disturbance of the base line. This component was due to unblocked impulses (cf. Fig. 6), and it can be traced through all the records.

The diphasic shape of the electrotonic potential was due to the fact that the double condenser discharge was passed through a transformer. The records show that the positive phase falls off much more rapidly along the nerve than the negative phase which precedes it. This may be explained by the fact that electrotonus rises and falls more slowly the greater the distance from the polarizing electrodes. At a distance from the block the smaller positive phase is swamped by catelectrotonic potential which lasts longer than the negative phase of the applied potential. This point will be further discussed on p. 205.

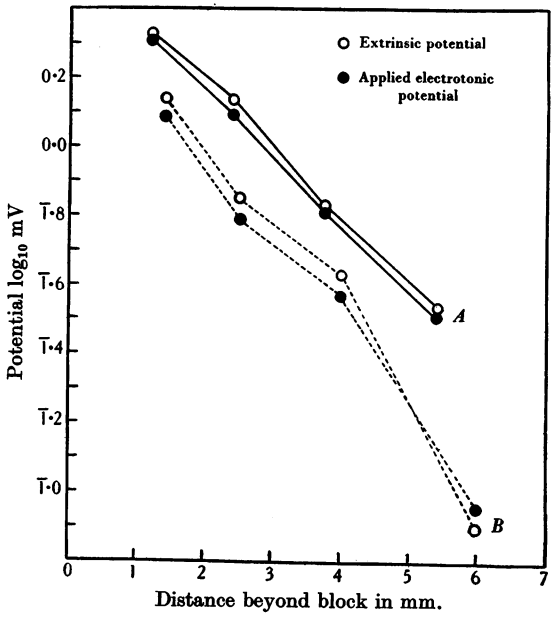

Fig. 12. Distribution of extrinsic and applied electrotonic potentials. *A*, 3·5 mm. cold block, 18 November 1936; *B*, 3 mm. cold block, 11 June 1936.

The results of two experiments of this kind are plotted in Fig. 12. Not only is the general slope of the two curves similar, but the same irregularities are reproduced in both cases. This is easy to understand if we suppose that the experimental error lies mainly in the measurement of the abscissa. If, for example, accumulation of fluid altered the

effective point of contact of an electrode with the nerve, the error introduced would have affected both determinations equally. Or the irregularities may have depended upon local variations in the resistance of the interstitial fluid, and this again would have produced deviations of the same kind in both determinations. The agreement shown in Fig. 12 could only be obtained if the two determinations were made in rapid succession. Any experimental manipulation, such as that involved in blotting off moisture which condensed on the nerve near the block, destroyed the precise agreement of the curves, although they still had the same general slope. The parallelism in spatial distribution seems to hold for pressure as well as for cold blocks. Owing to the difficulty of eliminating unblocked fibres, only one experiment was performed with a compression block, but in this case the agreement between the two potentials was as good as in any of the cold block experiments. In all, eleven sets of determinations have been made on nine different nerves. Eight of these show the close agreement illustrated in Fig. 12. In the remaining experiments, which were among the earliest to be performed, the curves were less strictly parallel although their general slope was similar.

A point which requires further discussion is the difference between the spread of electrotonus in normal and in blocked nerve. Observations on unblocked nerve showed that the electrotonic space constant was about 3 mm., but in blocked nerve the constant was similar to that of the extrinsic potential and had a value of about 2 mm. Indeed, on one occasion the constant of both potentials was reduced to 1·2 mm. The low values for the spread always occurred in nerves which had been subjected to prolonged blocking (cf. Table I), and in freshly blocked nerve the electrotonic constant was closer to the accepted value of 3 mm. The reason for the reduced spread in blocked nerve is not clear, but it is interesting to note that Schultz [1924] showed that any slight injury reduced the spread of electrotonus. The close parallelism between the two potentials in blocked nerve suggests that if we could observe the extrinsic potential in normal nerve it would still be similar to electrotonus and would have a space constant of about 3 mm.

The time relation of the potential at different distances from the block.

If a rectangular pulse of current is applied to nerve, electrotonus does not reach its maximum instantaneously, but lags behind the applied potential by an amount which depends upon the distance from the cathode [Bogue & Rosenberg, 1934]. In view of the similarity

between electrotonic and extrinsic potentials we should expect the form of both to change as the distance from the block was increased. The potential curves at a distance should rise and fall more slowly and should have a later maximum than those recorded close to the block. A small effect of this kind can be observed in the records of Figs. 4 and 11, but before discussing it we must consider some of the difficulties introduced by such a comparison. In the first place the change in form with distance is not likely to be large; for at a cold block the rate of change of the potential is small in comparison with the electrotonic response to a rectangular pulse. At a pressure block the potential changes are more rapid and a greater modification in form is to be expected. Unfortunately it was impossible to eliminate the unblocked impulses completely, and since these were propagated they affected the form of the potential to an extent which depended upon the electrode block distance. This can be allowed for, but the correction is unsatisfactory since the unblocked fibre component is rather variable. In nerves blocked with cold it was occasionally possible to obtain a response which was quite free from unblocked impulses. An example of this is provided by the records in Fig. 4. Here the potential wave has approximately the same form at different points, but small differences can be brought out by a careful examination. The waves at 1·4 and 2·5 mm. were traced and replotted so that they had the same amplitude. This showed that the maximum at 2·5 mm. occurred $\frac{1}{2}$ msec. later than at 1·4 mm. However, the principal difference was that the potential wave at the longer distance had a slower falling phase. The same kind of modification may be seen in the records of the electrotonic potential (Fig. 11). Close to the block the second positive wave is quite distinct, but at the longer distance the falling phase of the negative wave is prolonged and neutralizes the positive phase. Another difference was that both potentials started to rise slightly later at the longer distances than close to the block. This effect was small, but it was usually quite definite. In view of the difficulty of obtaining accurate records of the extrinsic potential, I do not wish to lay much stress on an exact comparison of its wave form at different points. However, it is clear that the wave form is approximately constant, and that the differences which do occur are consistent with the electrotonic nature of the potential.

Discussion

The investigation of the electrical changes near a block was undertaken as a step in the analysis of the increase in excitability produced by an impulse. The results show that an action potential causes a spread of electrotonic potential in the nerve beyond a block. Since the potential was observed with the same type of block and under the same conditions as the increase in excitability, the experiments suggest that the spread of potential may be responsible for the increase in excitability. Although the results are consistent with an electrical theory, they do not afford any kind of proof that the excitability and potential change are causally related. For the electrotonic potential might be no more than an incidental accompaniment of activity, and its association with the increase in excitability a matter of chance. The importance of the results is that they provide a basis for further experimental analysis. If the increase in excitability was produced electrically, it should have the same temporal and spatial properties as the electrotonic potential. Hence both electrical and excitability change should last for the same time, and both should spread for the same distance beyond the block. The temporal and spatial characteristics of the increase in excitability have been investigated and compared with those of the electrotonic potential. An account of these experiments will be given in a subsequent paper, and further discussion of the origin of the increase in excitability must be reserved until they have been described.

Although the main interest of the electrical changes at a block lies in their possible relation to the increase in excitability, they are, in themselves, worth some attention. In the first place, it is necessary to consider how far the results are consistent with previous work. Davis *et al.* [1926] examined the way in which an action potential was extinguished at a narcotized region. They showed that if any potential gradient was produced by an impulse it did not extend for more than 7 mm. into a narcotized region. This can be reconciled with my results, since the potential change at 7 mm. would be small and might not have been detected by their string galvanometer. Erlanger & Blair's [1934] work on axon segmentation provides an entirely different method of observing how potential spreads along the inactive parts of a nerve fibre. They found that, under the influence of anodal polarization, the action potential in a single fibre loses its normal continuous shape and acquires a characteristic notched configuration. The notches involve a sharp inflexion and are spaced at intervals of about 0·5 msec. The only satis-

factory way of explaining these action potentials is to assume, first, that several internodes of each axon contribute to the potential which is recorded at any point, and secondly, that in polarized nerve activity is transmitted across each node of Ranvier with a significant delay. Since the response is determined by the activity of several internodes, the delay at each node leads to a notch, and each inflexion is caused by the activity of a new segment. A detailed account of the evidence for this hypothesis would be out of place; for our purpose the important point is the conclusion that the response is determined by the activity of several segments. It follows from this that an active segment produces a potential gradient in the inactive part of an axon. Erlanger & Blair estimated the extent of the gradient from the contributions of segments at different distances from the recording lead. They found that the potential fell to approximately half its value in one internode, which, assuming an exponential decline and 1·25 mm. for the segment distance, gave a value of 1·8 mm. for the space constant of the gradient. This is close to my average value for the potential spread near a block. Erlanger & Blair do not discuss how the potential spread occurs, although they compare it with electrotonus. It seems very likely that it depends upon the same electrotonic mechanism as the extrinsic potential which can be observed near a cold or compression block.

At first the properties of the extrinsic potential seem to be in conflict with what is known about the rising phase of the action potential. Since electrotonic currents spread in front of the action potential at a block, we should expect the rising phase to have an electrotonic component. The initial rise should be exponential, and its rate should be determined by the conduction velocity and the electrotonic space constant. The initial rise of the axon action wave seems to be exponential, but it is considerably steeper than would be expected from the assumption of full electrotonic spread. Erlanger & Blair's [1934] record of an axon wave shows that the exponential time constant of the initial rise is about 40 μsec. Assuming a conduction velocity of 25 m./sec. this implies that in the front of the wave the potential falls to $1/e$ of its value in 1 mm. The reduced spread of potential may be explained in two ways. In the first place, my estimate of 3 mm. for the potential spread was for a large nerve trunk, and it is possible that the value for the electrotonic constant might be much smaller in the thin bundles studied by Erlanger & Blair. In the second place, it is important to consider the temporal as well as the spatial properties of electrotonus. Bogue & Rosenberg [1934] have shown that electrotonus rises more slowly the greater the

distance from the polarizing electrode, and this implies that electrotonus takes an appreciable time to spread to its full extent. Consequently we should not expect that the potential could spread far in front of an active region which was advancing with a velocity comparable to that of the electrotonus itself. The difference between the electrotonic spread at a block and in front of the action wave is due to the difference in the velocity of the active region. When the impulse is propagated, there is no time for full electrotonic spread, but when it is checked at a block electrotonus can spread for some distance beyond the active region.

Summary

1. When an impulse arrives at a cold or compression block, it can decrease the electrical threshold beyond the block by as much as 80 to 90 p.c.

2. An action potential on one side of a block produces a transient potential gradient in the stretch of nerve beyond the block. The gradient is exponential in shape and the potential falls to $1/e$ of its value in about 2 mm.

3. The spatial distribution of the potential is almost identical with that of an electrotonic potential of similar form.

4. It is concluded that an impulse produces a spread of electrotonic potential in the nerve beyond a block.

5. It is suggested that the local circuits which produce the electrotonic potential are the cause of the increase in excitability.

APPENDIX

A mathematical basis for the spread of electrotonus was first provided by Hermann [1905]. He derived equations for a core conductor model, where one of the conductors—core or interstitial fluid—was supposed to have zero resistance. The object of this appendix is to give a more general treatment, which takes into account the resistance of both core and interstitial fluid. The method is essentially the same as that of Rushton [1934], and indeed the problem is only an example of the general case which he considered.

Assumptions

A nerve fibre is assumed to have a cable-like structure with a conducting core and a resistant sheath. Any capacity across the sheath may be ignored, since a case of steady current distribution is considered. The system is assumed to obey Ohm's Law. It is assumed that in any transverse section the potential is uniform throughout the core and throughout the interstitial fluid. This cannot be strictly true, but calculations based on this assumption will be valid as long as the potential difference across core and interstitial fluid is small in comparison with that across the sheath.

Let x = distance along nerve, p = potential of interstitial fluid, v = potential of core, i = current in interstitial fluid, r = resistance of interstitial fluid per unit length to axial currents, σ = resistance of core per unit length to axial currents, $1/R$ = conductivity of sheath per unit length to radial currents. Since the nerve does not form part of an external circuit, the current in the interstitial fluid must be equal and opposite to that in the core.

Hence
$$i = -\frac{1}{r}\frac{dp}{dx} = \frac{1}{\sigma}\frac{dv}{dx}. \qquad \text{.....(1)}$$

Now the current leaving the interstitial fluid at any point must be proportional to the potential difference across the sheath at that point:

$$-\frac{di}{dx} = \frac{p-v}{R}. \qquad \text{.....(2)}$$

Differentiating
$$-\frac{d^2i}{dx^2} = \frac{1}{R}\left(\frac{dp}{dx} - \frac{dv}{dx}\right). \qquad \text{.....(3)}$$

On combining with (1) this becomes
$$\frac{d^2i}{dx^2} - i\Big/\frac{R}{r+\sigma} = 0. \qquad \text{.....(4)}$$

Now the general solution of this equation is

$$i = Ae^{x\Big/\sqrt{\frac{R}{r+\sigma}}} + Be^{-x\Big/\sqrt{\frac{R}{r+\sigma}}}. \qquad \text{.....(5)}$$

The source of potential will be considered to be in the direction of $-\infty$; at $x = +\infty$ the current flow will therefore be zero. Hence A must be zero and

$$i = Be^{-x\Big/\sqrt{\frac{R}{r+\sigma}}}. \qquad \text{.....(6)}$$

Combining (6) with (1) and integrating between x and ∞

$$p - p_\infty = Ce^{-x\Big/\sqrt{\frac{R}{r+\sigma}}}, \qquad \text{.....(7)}$$

where C is another constant.

Potentials are measured with reference to a remote point on the nerve, which is considered to have zero potential; thus p_∞ is zero. C must be equal to p_0, the value of p at $x = 0$. Hence

$$p = p_0 e^{-x\Big/\sqrt{\frac{R}{r+\sigma}}}. \qquad \text{.....(8)}$$

This result has been reached without referring to the nature of the source of current, and thus it applies equally to the steady distribution of an electrotonic potential or to that of an extrinsic potential produced by an action current.

The application of this equation is not affected by the fact that resting nerve probably has a potential difference in series with the sheath. The resting potential can be allowed for by adding an extra term to equation (2); but this term does not vary with distance, so that it disappears when (2) is differentiated to give (3).

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