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THE ELECTRO-SALTATORY TRANSMISSION OF THE NERVE IMPULSE AND THE EFFECT OF NARCOSIS UPON THE NERVE FIBER

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Nervous transmission is generally believed to be effected through excitation of each section of the nerve by the activity of adjacent parts. Most investigators assume that the restimulating agent which excites the resting region may be electrical in nature. This view of electrical transmission has been considerably strengthened by the recent work of Hodgkin (1938).

In the present paper I have attempted, by means of micro-technique, to obtain conclusive experimental evidence for the theory of electrical transmission, and to establish a more complete conception of nervous transmission. The problem of "decrement" in the narcotized region of nerve is also discussed with special reference to the new experimental data.

METHODS. In all experiments, isolated single nerve-fibers (sciatic-gastrocnemius preparation) of the Japanese toad were used. The procedures of isolation and experimentation were essentially similar to those described in previous papers (Tasaki, 1939). For multipolar stimulation, the circuit reported previously was employed, with a slight modification in the position of the current reversers.

For determining the least interval between two stimuli necessary to give a summated muscular contraction, break induction shocks supplied by two inductoria were used; the secondaries were connected in series and the strength of the shock was controlled by precision resistances in the primary circuits. In a single-fiber preparation, a summated contraction is distinctly larger than an ordinary single twitch and can easily be distinguished by visual observation. The least interval for muscular sum-

mation can therefore be much more easily determined in a single-fiber preparation than in the ordinary nerve-muscle preparation.

RESULTS. *1. Transmission over an inexcitable node of Ranvier.* In a previous paper (Tasaki, 1939b), it was shown that, when an isolated single nerve-fiber is excited with tripolar electrodes (fig. 1, inset), the relation between the voltages (V and V') necessary to excite constitutes a "triangle" whose three sides represent excitation at three different nodes of Ranvier. The nerve-fiber is excited by an outwardly directed current through the plasma membrane at the node. Excitation at the middle node (N_0) between the two sets of "ridge-insulators" is represented by the straight line A which can be expressed by the equation $V + V' = constant$.

Experiments on the effect of narcosis immediately indicated that a nervous impulse is able to "jump over" a small number of electrically inexcitable nodes. In a freshly isolated nerve-fiber, narcosis of a single node does not block nervous transmission through the narcotized region even when the narcotic is fairly concentrated. Increase in the concentration of the narcotic apparently did not deepen the narcosis. But when the same narcotic was allowed to act upon a stretch of nerve-fiber including a number of nodes, transmission through the narcotized region always ceased within a few seconds.

Although narcosis of a single node fails to block transmission, it brings about a definite and remarkable change in the excitability of the nerve-fiber, and this change can easily be disclosed by the method of tripolar stimulation. If the narcotic is sufficiently concentrated, *the side of the "triangle" corresponding to excitation at the narcotized node disappears,* while the two remaining sides are almost unaffected.

Figure 1 shows an example. Before narcosis, the usual triangle was obtained; but when a 2.5-per-cent urethane-Ringer solution was applied to the stretch of fiber between the two sets of ridge-insulators, side A of the triangle was extinguished and extensions of sides B and C appeared in the first quadrant.

The outwardly directed current through the plasma membrane at the node N_0 increases with increasing values of $(V+V')$, but there is no sign of excitation at this node. The threshold is ultimately reached by the current flowing outward through the node N_1 or N_2. At these nodes, the excitatory effect of the applied potential-differences is determined by the values $(V' \cot\beta - V)$ and $(V \cot\gamma - V')$ respectively, where β and γ represent the angles which sides B and C make with the horizontal and vertical axes. As shown in a former paper (Tasaki, 1939b), the plasma membrane at the node may be conceived as a semipermeable membrane of relatively high electric resistance, and, since the myelin sheath is a practically complete insulator, the potential-difference V' applied between the node N_2 and N_0 is capable of exciting the node N_1 if it is made sufficiently

great. The value of $\cot\beta$, which represents the effectiveness of the potential-difference V' in exciting the node N_1, depends mainly upon the polarization resistance through the node N_0; we may therefore take it as an *index of polarizability of the plasma membrane* at this node. It should be noted that the polarizability thus measured increases with increasing duration of the stimulating current employed for measurement.

In figure 2, the effect of weak narcosis is also shown. As the threshold at the node N_0 is raised by narcosis, side A of the triangle is shifted. The value $(V + V')$ increases with increasing concentration of the narcotic.

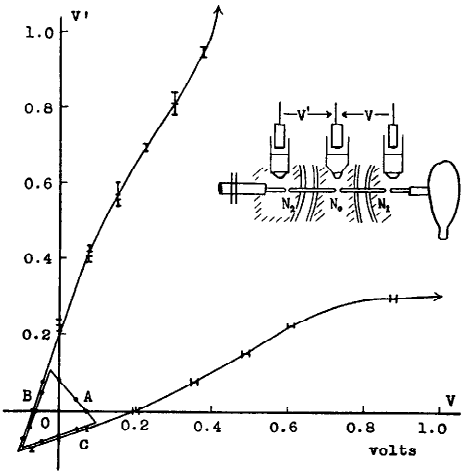

Fig. 1

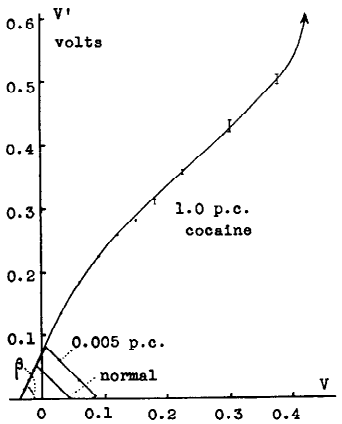

Fig. 2

Fig. 1. Tripolar stimulation of a nerve-fiber during narcosis of a single node of Ranvier. A 2.5 per cent urethane-Ringer solution was used. Duration of stimulating current, 0.5 msec. Temperature, 11.5°C. The small triangle shows the results obtained before narcosis. Side A of the triangle corresponds to excitation at the node N_0, side B to excitation at the node N_1, and side C at N_2.

Fig. 2. A similar experiment done with a cocaine solution. Pulse duration of stimulating currents, 1.0 msec. Temperature, 11.0°C. Conduction through the narcotized region was preserved.

When $(V + V')$ is two or three times the normal (at about 1.7 per cent for urethane and about 0.01 per cent for cocaine), determination of this side of the triangle becomes very uncertain and soon this line disappears completely. It is interesting that, when the excitability of the node N_0 is reduced or completely abolished by narcosis, the polarizability of this node remains unchanged.

As can be seen in the figures, the extension of the straight line corresponding to excitation at the node N_1 or N_2 loses its linearity when the current flowing through the inexcitable node N_0 is increased. For voltages

greater than about one volt, the threshold becomes unstable and rapidly rises, and it is difficult to determine the exact course of the line.

Only rarely does narcotization of a single node bring about reversible suspension of conduction. This seems to occur more often in preparations which have been maltreated. In that case, not only side A of the triangle but also side C disappears. With extremely concentrated narcotics (over 5 per cent in cocaine and over 10 per cent in urethane), conduction through the narcotized region is always suspended. This suspen-

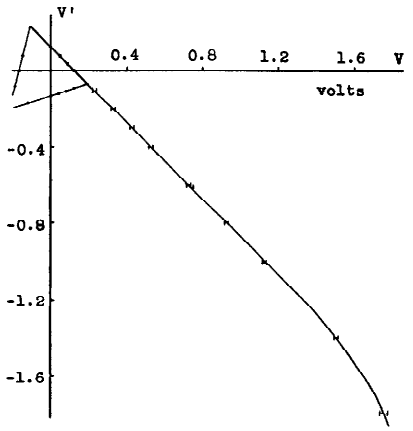

Fig. 3

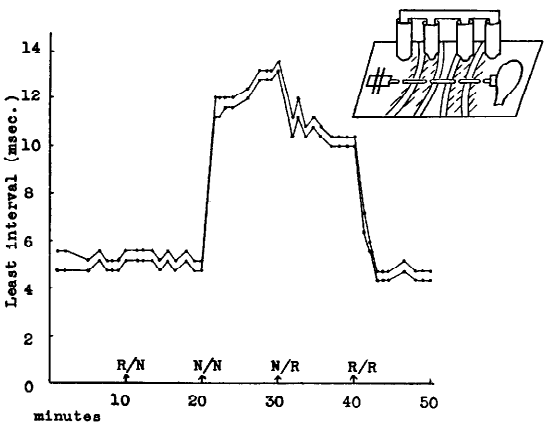

Fig. 4

Fig. 3. A 1.0 per cent cocaine-Ringer solution was introduced into the proximal pool. Conduction through the narcotized region was blocked. Pulse duration, 0.2 msec. Temperature, 9.5°C.

Fig. 4. Changes in the least interval for muscular summation produced by narcosis of nodes of Ranvier. Stimuli were applied about 3 cm. proximal to the isolated region. At the 10th minute from the onset of the experiment, a narcotizing solution (2.5 per cent urethane) was introduced into the distal small pool. At the 20th minute, the narcotic was also introduced into the proximal small pool. At the 30th minute, the narcotic in the distal pool was removed and was replaced with Ringer. At the 40th minute, the narcotic in the proximal pool was also removed. Distances between two sets of points in the figure indicate the accuracy of the measurements. Temperature, 10°C.

sion is usually irreversible and disintegration of the protoplasm seems to set in.

In the experiment of figure 3, Ringer's fluid in the proximal pool in which the node N_1 and the intact portion of the nerve were immersed was replaced with a concentrated narcotizing solution. Transmission through the narcotized region was of course suspended. In this case, side C of the triangle corresponding to excitation at the node N_2 was extinguished while the other two sides, A and B, remained unchanged. The extension of

side A of the triangle was perfectly linear for a wide range of voltage. It is clear from this and other experiments that each side of the triangle represents the excitability of a particular node and is not affected by narcosis of the neighboring nodes.

We may now conclude that a nervous impulse can pass beyond an electrically inexcitable node. This naturally leads us to assume a "jump" of the impulse over a short inactive region of nerve fiber. The objection may be raised, however, that the axis-cylinder (or the fibrils) may transmit the impulse even when the plasma membrane at the node is entirely inexcitable to artificial stimuli. The following experiments on the least interval for muscular summation answer this objection.

2. The least interval for muscular summation and the number of nodes of Ranvier exposed to the narcotic. When the least interval for muscular summation was measured, with electrodes on the central nerve-trunk, before and after application of narcotic to a stretch of nerve-fiber including only a single node, it was frequently observed that such a local narcosis brought about no detectable change in the least interval. If some change was produced, the change was not increased by increasing the concentration of the narcotic. It was surprising to find that the least interval remained practically unaltered when the concentration of cocaine was increased step by step from 0.01 per cent up to 1.0 per cent.

Although the least interval for muscular summation is almost independent of the concentration of narcotic, it depends most significantly upon the number of narcotized nodes. Even when narcosis of a single node produces no measurable change, narcosis of a stretch including two neighboring nodes causes a distinct prolongation. This is clearly shown by the experimental results in figures 4 and 5.

Ringer's fluid on a glass plate was divided into four pools with three sets of ridge-insulators (fig. 4 top) and all the pools were connected electrically with one another by means of a "salt-bridge" consisting of glass tubes filled with gelatin-Ringer gel. The narcotic was applied to the nerve-fiber in one of the middle pools or in both of them. In all cases, the least interval was distinctly longer when two nodes were narcotized than when a single node was exposed to the narcotic. In some favorable cases it happened that an impulse set up by a single induction shock could travel beyond one inexcitable node but not beyond two. The recovery of the least interval after the narcotizing solution was replaced by Ringer solution was in general almost complete except when a very concentrated cocaine solution was used.

It should be noted that in these experiments there is always a non-narcotized (desiccated) region in the nerve-fiber between the two small pools. As diffusion is a very slow process, we may assume that this desiccated region of the nerve-fiber (about 1.2 mm. in length) is not affected by

the narcotic. If transmission of the nerve impulse depended upon some continuous process along the axis-cylinder, an impulse which passed beyond the first narcotized stretch would regain its full intensity on emerging into this non-narcotized region, and such an impulse could not be blocked by the second narcotized region. Since blocking actually occurs, we may conclude that the impulse is not transmitted through the axis-cylinder but "jumps" over this medullated region of the nerve-fiber. And, since the electric current is the only possible physico-chemical process which could cause such a jump over the ridges, we are led to conclude further that the restimulating agent which excites the adjacent resting region of the nerve-fiber must be the action current developed at the active region.

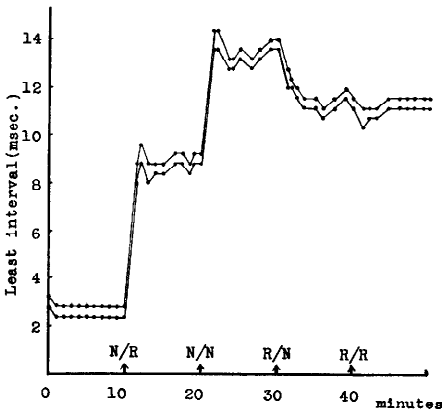

Fig. 5

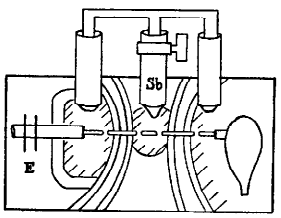

Fig. 6

Fig. 5. A similar experiment done with a 1.0 per cent cocaine solution. The narcotic was introduced first into the proximal pool.

Fig. 6. Arrangement to show the effect of the electrical resistance of the surrounding medium upon nervous transmission. Two nodes in the middle pool were rendered inexcitable with the narcotic, and conduction was thus abolished. Disconnection of the part Sb of the salt-bridge with the middle pool restored the conductivity.

Again, the objection may be raised that the medullated region of the axis-cylinder may transmit impulses of varying intensity. However, if conduction is assumed to be continuous and if the nodes are assumed to behave in an all-or-none manner, it would be impossible to explain the experimental fact that a nerve impulse cannot travel beyond three inexcitable nodes even when it can pass beyond two. And, since transmission is blocked only when regions including nodes are narcotized, we must assume either that the impulse jumps or that it undergoes a discontinuous steplike "decrement" as it passes beyond each narcotized node. This latter type of continuous transmission would resemble very closely

the discontinuous jumping, because the electric current flowing along the axis-cylinder would show an attenuation of exactly the same type in each case. At first it seemed impossible to distinguish these two possibilities experimentally, but more direct evidence for electrical transmission was obtained in a subsequent experiment.

3. The effect of the electrical resistance of the medium upon nervous transmission. If the nerve impulse jumps from one node to another by its action current, it should be theoretically possible to block or facilitate nervous transmission by changing the electrical resistance of the surrounding medium. And, conversely, if the effect of electrical resistance of the medium is proved to exist, we may now definitely conclude that the transmission of the impulse is electrical. This experiment was accomplished by using ridge-insulators. With a set of newly prepared ridge-insulators, it is easy to make the external resistance between two neighboring nodes enormous,—over 100 megohms. Since the internal resistance between two nodes is considered to be of the order of 50 megohms, ridge-insulators may be expected to influence the electrical transmission from node to node.

The method consisted in changing the leakage of current through inexcitable nodes. Figure 6 illustrates the experimental arrangements. Two sets of ridge-insulators were carefully coated with fresh paraffin before every experiment. Around each insulator, a salt bridge (consisting of three glass tubes filled with gelatin-Ringer gel and connected together with cotton wool moistened with Ringer) was placed. Two nodes of Ranvier were placed in the middle pool, and the fluid in this pool was replaced with a small amount of 4.0 per cent urethane Ringer solution. This often led to suspension of transmission. In case the transmission through the narcotized region was not suspended, a dilute (0.5 per cent) urethane solution was applied to the nerve in the other pools. When the transmission was completely blocked by narcosis, the middle glass tube (*Sb* in fig. 6) was elevated and thus the middle pool was electrically insulated from the other pools. It was found that transmission through the narcotized region was always restored by this procedure. When the end of the middle tube was again dipped into the fluid, transmission was immediately blocked. The experiment was simple and was consistently repeatable for hours.

This experiment is very easy to perform, probably the easiest of all the experiments described in this paper. As I shall show elsewhere, an irregular distribution of nodes as shown in figure 6 is very common among the toad's motor fibers. Further, it is easier to introduce into the middle pool two neighboring nodes (situated a short distance apart) than a single node. In narcosis of a single node, it is seldom that the transmission is blocked; but in this case, when the least interval for muscular summation is prolonged by narcosis, it can easily be observed that the least interval is

unmistakably shortened by removal of the middle tube. Removal of the whole bridge makes the excitability of the nerve-fiber extremely unstable and the muscle frequently shows powerful tetanic contractions, probably excited by atmospheric electricity.

This experiment is apparently comparable to that done by Osterhout and Hill (1929) on the large plant cell and can be regarded as conclusive evidence for electrical transmission in the nerve. Insulation of the inexcitable nodes reduces the leakage of the action current through these nodes and makes them behave as if they were covered with myelin sheath.

4. Summation and inhibition of the outflow of action current with subthreshold induction shocks. A nerve impulse passes beyond an inexcitable

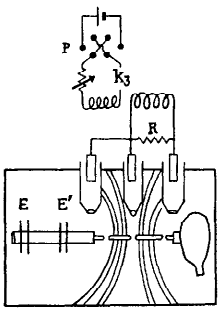

Fig. 7

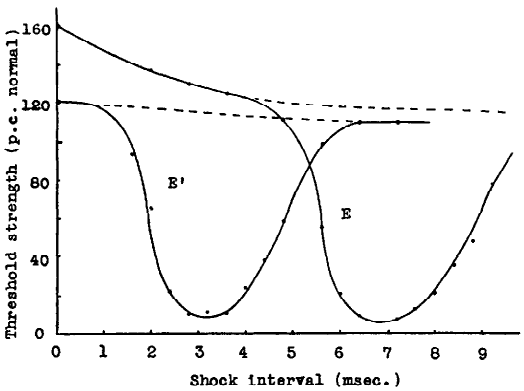

Fig. 8

Fig. 7. Arrangement for the experiments of figures 8 and 9. *P:* Pohl's reverser, k_3: contact of a Helmholtz pendulum, *R:* 6,000 ohms. Inductorium was coreless.

Fig. 8. Depression of the threshold by a blocked impulse. *E*: conditioning shocks were applied at about 4.2 cm. proximal to the operated region. *E'*: conditioning shocks at about 2 cm. proximal. The least interval was about 24 msec. and the intervals between shocks applied at the proximal electrodes were shorter than the least interval at that moment by 0.6 msec. Temperature, 5.5°C.

node when its accompanying action current is sufficiently strong to excite the irritable node beyond, and it fails to do so when the strength of the current is below the threshold. An impulse which is barely blocked by narcosis should therefore reduce the threshold of the node beyond the narcotized region. Hodgkin (1938) has studied this type of reduction of threshold with cold and compression blocks and has shown that the change in excitability occurs parallel to the change in the action current. I have also investigated this effect with the structure of the myelinated nerve-fiber in mind.

The arrangement shown in figure 7 was used. A narcotizing solution (2.5 per cent urethane Ringer) was introduced into the middle pool.

When the least interval for muscular summation was not sufficiently prolonged by this procedure, a dilute narcotic (below 1 per cent in urethane) was applied to the nodes in the proximal pool. Two stimuli were delivered to the nerve-fiber through the central electrodes (E or E' in fig. 7) at an interval just shorter than the least interval for muscular summation; and, at varying intervals after the second shock, the strength of a third (subthreshold) stimulus necessary to excite the node N_1 beyond the narcotized region (producing a summated muscular contraction) was determined with the exciting circuit shown in figure 7. By this method, I could demonstrate a distinct change in the threshold produced by the impulse which just failed to pass the block.

Figure 8 shows an example of the results. In this figure the threshold strength (as per cent of the normal) necessary to excite the node N_1 is plotted against the interval from the second induction shock applied at E or E'. The broken lines in the figure indicate the threshold level when the second shock was not applied; these lines deviate from 100 per cent due to the refractoriness produced by the first impulse. It is evident that, for a certain period after the arrival of the second impulse at the block, there is a marked depression in electrical threshold. The depression in threshold can be made as much as 98 per cent or more by controlling the interval between the shocks given at the central electrodes and by adjusting it to be just shorter than the least interval for muscular summation at that moment.

If the interval between the shocks applied at the central electrodes is made slightly longer than the least interval, the impulse set up by the second shock will just excite the node N_1. This excitation was found to be easily inhibited by superimposing a weak ascending current at an appropriate interval. The strength of the superimposed current necessary to inhibit increased, as was expected, with the increasing interval between the two impulses set up in the nerve fiber.

In the experiment shown in figure 9, a single stimulus was sent into the fiber at E or E' and the response was inhibited with ascending current pulses applied across the ridge. In this experiment the middle node was made inexcitable with a 2.5 per cent urethane solution as before, but the other nodes were all normal. When the interval between the two shocks was adequate, ascending currents of 3 to 4 times the threshold were sufficient to block the impulse.

Now, since we have clearly seen that nervous transmission depends upon excitation by the action current, it is important to know at what part of the nerve fiber the action current is developed. A nerve impulse set up at a node is transmitted, as is well known, in both directions, centrifugally and centripetally. In order that an electromotive force developed at a node may produce outwardly directed potential-drops at the neighboring

nodes on both sides, an electric double layer with inwardly directed moment must appear on the surface of the axis-cylinder at the node. Thus, it is clear that *the plasma membrane at the node of Ranvier is the place where the action potential is developed.* This is exactly what is expected from the membrane theory.

5. The electric circuit in the nerve fiber and quadripolar stimulation. In a previous paper (Tasaki, 1939b) it has been shown that, if a potential difference is applied between two neighboring nodes, potential-drops are produced at the nodes all along the fiber due to the insulating property of the myelin sheath and the relatively high resistance through the plasma membrane at the node. The resistance through the axis-cylinder (R in

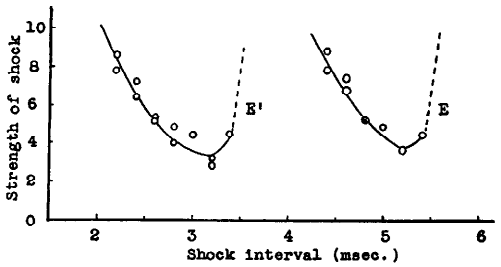

Fig. 9

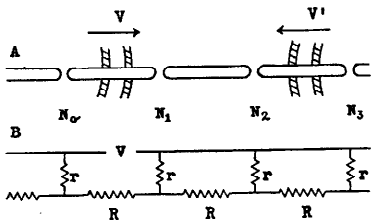

Fig. 10

Fig. 9. Inhibition of nervous transmission beyond an inexcitable node with an ascending induction shock. Ordinate: strength of ascending current necessary to block transmission (threshold for descending current as the unit). Abscissa: interval between the first and second shocks. *E:* the first shock applied at 59 mm. proximal to the isolated region. *E'*. the first shock at 21 mm. proximal. Temperature, 5.5°C.

Fig. 10. A. Quadripolar stimulation of a single nerve-fiber. B. The electrical circuit in the nerve fiber. *R:* resistance through the internodal axis cylinder. *r:* total resistance of a node to the radial current. Resistance through the surrounding medium and the electric double layer at the plasma membrane are omitted in the diagram.

fig. 10) is considered to be purely ohmic and that through the plasma membrane (r) is at least partly reactive. If, for simplicity, all the R's are assumed to be the same and all the r's to be the same and all purely ohmic, it is predicted from the electrical network theory that the law of attenuation of the current flowing along the fiber is exponential, the potential drop through the nth node in figure 10B being given by

$$V_n = VB^n/(1 + B),$$

where V is the potential difference applied between the nodes N_0 and N_1, and B is the smaller root of the characteristic equation

$$B_2 - (2 + R/r)\, B + 1 = 0$$

(cf. Jeans, 1933, p. 319). This theory can be tested experimentally

by the method of multipolar stimulation, as these potential-drops produce excitatory effects.

Suppose that, in the quadripolar arrangements shown in figure 10A, potential differences V and V' are adjusted to constitute threshold stimuli and that excitation is to occur at the node N_2. In this case the resultant potential-drop through the plasma membrane at the node N_2 must always be constant, as we have assumed the plasma membrane to be non-reactive; hence we have

$$VB^2/(1 + B) + V'B/(1 + B) = \text{constant}.$$

As B is constant in a given nerve-fiber, this equation represents a straight line of which the slope is given by the value of B. In an entirely analogous manner, if excitation is assumed to occur at the node N_3, we have

$$VB^3/(1 + B) - V'B/(1 + B) = \text{constant}.$$

This also represents a straight line of which the slope is given by B^2. Thus the quadripolar stimulation of a nerve fiber is expected to yield a "tetragon" of which two sides in the first quadrant intersect the axes at arctan B and the remaining two sides at arctan B^2. It will easily be noticed that this "B" is nothing but what we have proposed to take as an index of polarizability from the experiments on tripolar stimulation.

Figure 11 is an example of the results of quadripolar stimulation. It is obvious that the results lie on straight lines which constitute a "tetragon". The values of $\cot\beta'$ and $\cot\beta''$, when measured with constant current pulses of a duration of 0.5 msec., were generally 0.30 to 0.55; and the values of $\cot\gamma$ and $\cot\gamma''$ were between 0.07 and 0.20 and were a little smaller than the square of $\cot\beta'$. This discrepancy from the simple electrical network theory is considered to be due mainly to our ignoring the capacity of the plasma membrane. Moreover, the extreme irregularity in the internodal distance seems to complicate further such a mathematical treatment of the problem.

There is little doubt that the above-stated rough estimation of the spread of stimulating currents along the fiber holds for the spread of the action current. If an electromotive force V is developed at the plasma membrane at the node N_0 in figure 10B, it will easily be found that the potential-drop produced at the nth node is given by the formula

$$V_n = VB^n.$$

It is interesting that the action potential developed at the node N_0 is just $(1 + B)$ times as effective as the external electromotive force of the same magnitude and duration applied between the nodes N_0 and N_1.

It would probably be possible to establish a more complete physical theory as to the electrical network in the nerve-fiber. But, as we know nothing definite about the physical nature of the excitatory state, it would be difficult to make it available for the theory of nervous transmission. That some process besides polarization plays a part in electric excitation

would be evident from the experimental fact that narcosis changes the chronaxie but not the polarizability.

6. The general theory of nervous transmission and the interpretation of various phenomena. Lillie in 1925 first suggested the possibility of "electro-saltatory" transmission of the nerve impulse in the myelinated nerve fiber. Lillie observed that, when a passive iron wire is covered with a glass tube broken at regular intervals, the activation does not spread over the whole wire but jumps from one break to another; and from this observation he assumed a similar jump of the nerve impulse from one node of Ranvier to another. Several papers that have been published since assume and discuss electrical transmission of this type (Gerard, 1931; Rashevsky, 1933 and 1934; Zottermann, 1937). Now the hypothesis is

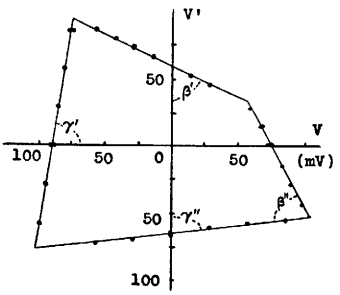

Fig. 11

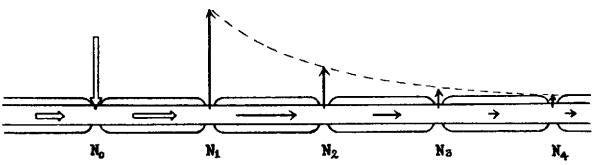

Fig. 12

Fig. 11. A "tetragon" obtained by the quadripolar stimulation of a nerve-fiber. The duration of the rectangular current pulses employed for stimulation was 0.5 msec. Temperature, 8°C.

Fig. 12. Distribution of the outwardly directed action-current flow at the boundary of the active region of a nerve fiber.

provided with a series of rigid experimental proofs and is further extended to explain various phenomena in nervous transmission.

Figure 12 illustrates the flow of the action current at the boundary of the active region. The resting nodes are excited with the sum of "action-current outflows" caused by all the nodes in action. Even when several nodes, say N_1 and N_2 in the figure, are rendered inexcitable, the current flowing outward through the irritable node N_3 is, in most cases, strong enough to excite it. As Hodgkin (1938) states, there is a wide margin of safety in the electrical transmission of impulses.

Let us introduce, modifying Hodgkin's idea, a new quantity, the *"safety factor" in nervous transmission*, as indicating the ratio of the total action-current outflow through a node to the current (of the same shape) required for excitation. When this factor is larger than a unity, the node is excited before the total current is used up and transmission occurs. When it is larger than about 2.5, the impulse has the ability to jump over one in-

excitable node, for the current decreases to from 0.3 to 0.5 (index of polarizability) times the original value when it spreads beyond a node. In freshly excised nerve-fibers, impulses jump over at least two completely inexcitable nodes. Therefore, the safety factor in the normal nerve-fiber is greater than about 8; it is probably about 10 and seems to decrease gradually with the time after isolation of the nerve-fiber.

The main causes which change the safety factor are probably as follows:

1. The magnitude and duration of the action potential developed at the plasma membrane.
2. The irritability of the node.
3. The polarizability of the plasma membrane.
4. The true latency of response.

A decrease in these quantities which characterize the nerve-fiber will decrease the safety factor in transmission. It seems at present impossible to formulate theoretically the accurate relation between these quantities and the safety factor, due to lack of our knowledge of the excitatory state and the latency. But, if we adopt the simple network theory stated above and if we assume the transmission to be sufficiently rapid, the safety factor (s.f.) will roughly be given by

$$\text{s.f.} = \frac{VB}{1 - B} \div \frac{EB}{1 + B},$$

where V is the action potential developed at the membrane, E is the threshold voltage measured with a current pulse of the same temporal configuration as V, and B is the polarizability measured with the same current pulse. The first term $VB/(1 - B)$ expresses the total action-current outflow through a node to be excited, and the other term $EB/(1 + B)$ represents the current necessary to excite a node. Since E and B are about 30 millivolts and 0.5 respectively, the magnitude of the action potential in the normal nerve-fiber should be of the order of 100 millivolts. This estimate must of course be regarded with great caution.

A practical method of measuring the safety factor is supplied by the experiment shown in figure 9. If an induction shock of the strength of n times the threshold is required for inhibition of transmission, the safety factor in the jump of impulse beyond a single inexcitable node should be equal to $(n + 1)$, as it was shown in a few preliminary experiments that the law of superposition holds good in such cases. Further, the safety factor in the normal nerve-fiber can be obtained by measuring the polarizability of the inexcitable membrane.

The first problem which I want to explain in terms of the elementary properties of the nerve-fiber revealed by the present investigation is that of the "decrement" of the impulse in the narcotized region. Adrian (1912) and many others have shown that in order to extinguish conduction by

local anesthesia of a nerve-trunk, the narcotic had to be applied for a longer time, the shorter the length of nerve upon which the narcotic acted. Further, Kato (1924) found that this effect of the length of the narcotized stretch is limited to about 6 mm. and consequently that a long stretch can resist narcosis for the same length of time as a short one provided the latter is longer than this "limit length." All these experimental facts can clearly be interpreted in terms of the "jump" of impulse beyond a short narcotized stretch. As we have already seen, a normal impulse is capable of jumping over about two inexcitable nodes; and, since the internodal distance can be 2 to 3 mm., most of Kato's limit length must be attributed to the length of nerve beyond which a normal impulse can jump by its action current.

Davis and his co-workers (1926) expressed the view that the transmission of the impulses along a (weakly) narcotized nerve could be "transitionally" decremental. As long as we define, as these authors do, a nerve impulse as a propagated tendency to excite the adjacent inactive region of nerve (which we found to be an electrical current), the intensity of impulse should show a transitional change at the boundary of the normal and weakly narcotized regions. Not only the intensity of impulse but also the conduction rate is considered to show transitional decrement and increment at the boundary. As regards the problem of decrement, we must agree in general with Davis *et al.*, except for their assumption that transmission is continuous in each fiber.

The next problem we are interested in is that of local non-conducted response. If the safety factor in the transmission is decreased to a low value (below one, but not equal to zero), a local response may occur at the seat of stimulation. This seems to be actually the case during the absolutely refractory period. In the experiments shown in figures 4 and 5, it can be seen that the least interval for muscular summation is not determined by the refractoriness of the narcotized node; in this case all the nodes which take part in the transmission are normal, and it is obvious that the least interval is determined by the interdependence of the excitability and the power of restimulation at the two regions on both sides of the narcotized region, namely, by the recovery of the safety factor. The least interval in normal and in uniformly narcotized nerve represents the length of the absolutely refractory period, and this also appears to be determined by the recovery of the safety factor in the transmission and not by the recovery of the local response.

When the least interval of a node was measured with a tripolar arrangement (fig. 1, inset), it was found that the interval was lengthened not only by a weak narcosis of that particular node (N_0 in fig. 1) but also by narcotization of the adjacent node (N_1); and, as the least interval is always longer when both of these nodes are narcotized than when the same narcotic is applied to either one of them, it is clear that the impulse set up

at an early stage in the refractory period fails to be transmitted when the adjacent node is also narcotized. In the normal nerve, it is well known that the least interval changes with the direction of the currents employed for measurement, and this effect of the direction of the stimulating current is more marked in the narcotized nerve-fiber. From these data we may conclude that the recovery curve first introduced by Adrian and Lucas (1912) consists of two different parts, one, the absolutely refractory phase, representing the recovery of the safety factor in transmission and the other, the relatively refractory phase, representing the recovery of local excitability.

Recent work by Katz (1937) appears to suggest that a local response may also exist in a fresh normal nerve, but my own observation indicates that it is improbable. I have shown that the threshold of a node of Ranvier is independent of the irritability of the adjacent nodes. This seems to be convincing evidence that the nerve impulse is released by a trigger mechanism. A local response in a fresh normal nerve, if it exists at all, has practically no power restimulation.

Lastly, let us turn our attention to the effect of repetitive stimulation of a locally narcotized nerve-fiber. We have already seen that, when two impulses are sent along a nerve-fiber to face a stretch including a small number of inexcitable nodes, the second impulse may fail to be transmitted beyond the narcotized region unless it follows the first at an interval longer than a certain critical value (i.e., the least interval). This indicates that the safety factor in the jump of the second impulse is smaller than that of the first. Refractoriness of the node just beyond the narcotized region and reduction of the action potential and polarizability during the refractory period seem to be the only possible causes for this reduction of the safety factor. If the second impulse fails to be transmitted, the excitability of the node beyond the narcotized region should recover to normal, but the action-current outflow which stimulates this node may still be subnormal. Thus, when the safety factor in the jump of the first impulse is slightly greater than unity, all the successive impulses except the first may fail to pass beyond the narcotized region. We may therefore conclude that the apparent inhibition of successive impulses (Wedensky's inhibition) is due to decrease in the ability of the proximal (normal or weakly narcotized) region of nerve to excite a node beyond the region of impaired conductivity. A few additional experiments revealed that reduction of polarizability during the refractory period is only slight in the normal nerve fiber, but the action potential is known to suffer a considerable reduction (Gasser and Erlanger, 1925). Undoubtedly the safety factor in the normal nerve fiber is decreased by repetitive stimulation.

Discussion. The idea that the nerve impulse may jump beyond a stretch of impaired conductivity is by no means new. Werigo (1899) long

ago believed that a wave of excitation was capable of setting up a similar disturbance in a normal region beyond the impaired stretch. Then this idea was abandoned and for many years was replaced by the theory of continuous decrement. Quite recently, this old idea of jump was revived by Osterhout and Hill (1929) in their beautiful work on the plant cell. Now, the presence of jump in the myelinated nerve fiber is, I believe, firmly proved by a number of rigid experiments. The only reasonable objection against this conclusion seems to be my own observation that cooling the medullated region of a nerve-fiber blocks conduction (cf. Kato, 1936), but this objection may be eliminated by assuming demarcation surfaces of very high electric resistance at the boundaries of the frozen protoplasm.

SUMMARY

1. A nerve impulse can pass beyond a few completely inexcitable nodes of Ranvier.

2. The least interval for muscular summation increases as the number of inexcitable nodes over which impulses must jump increases.

3. It is possible to block or facilitate nervous transmission by changing the electrical resistance of the surrounding medium. It is concluded that nervous transmission depends upon stimulation of the resting region of the nerve-fiber by the action current developed at the active nodes, and that the impulse jumps, as Lillie suggests, from one node of Ranvier to another.

4. Hodgkin's experiment showing a depression of threshold by a blocked impulse was reexamined on the isolated single nerve-fiber with positive results. Furthermore, transmission beyond an inexcitable node can be blocked by a weak ascending induction shock.

5. The electric circuit in the nerve-fiber has been investigated by the method of quadripolar stimulation.

6. Nervous transmission through a narcotized region of nerve is discussed and various phenomena are interpreted in terms of the "safety factor" in nervous transmission.

7. The nerve impulse undergoes transitional decrement and increment as it passes through a narcotized region.

8. The importance of the plasma membrane at the node of Ranvier in excitation and transmission is stressed.

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