THE ALL-OR-NONE PRINCIPLE IN NERVE.

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In an earlier paper[1] I have brought forward evidence in favour of the view that the size of the propagated disturbance at any point in a nerve fibre depends only on the local condition of the fibre at that point and not on the previous history of the disturbance before it arrived there. If this view is correct, it follows that the size of the propagated disturbance cannot depend upon the strength of the stimulus, provided only that the disturbance is measured at a point where the local conditions are not affected by an alteration in the strength of the stimulus. That is to say, there must be an all-or-none relation between stimulus and propagated disturbance. On the other hand if an increase in the strength of the stimulus causes the slightest variation in the size of the propagated disturbance then it is clear that the size of the disturbance cannot depend upon local conditions only, and the experiments which seem to support this view must be explained in some other way.

As a matter of fact there is a great deal of evidence which favours the all-or-none relation between stimulus and disturbance. This evidence is based on an experiment which has been known for many years. A muscle nerve preparation is set up so that the nerve passes through a narcotising chamber. The central end of the nerve lies outside the chamber and may be stimulated. When the length of nerve in the chamber is narcotised gradually, the stimulus which is just effective before the narcosis, is effective until the moment when the block to conduction is complete. At no stage in the process can a stronger stimulus affect the muscle when the normal threshold stimulus cannot. Originally this fact was considered to show that the "conductivity" of the nerve was unaltered by the narcotic until the moment when it was suspended altogether. This interpretation is justifiable if

[1] This *Journal*, XLV. p. 389. 1912.

"conductivity" means no more than a quantity inversely proportional to the strength of the stimulus needed to affect the muscle. But the conductivity of a nerve is generally taken as proportional to its ability to conduct, and therefore as inversely proportional to the least size of disturbance which can travel down it without extinction. If conductivity has this meaning, it is clear that to measure it in terms of the strength of stimulus necessary to affect the muscle involves the assumption that the size of the propagated disturbance must vary directly with the strength of the stimulus. As a matter of fact the work of Werigo[1], Fröhlich and Boruttau[2], Wedensky[3] and others has shown that the narcotic affects the conductivity of the nerve long before central stimuli became ineffective. The change in conductivity is gradual and does not correspond in any way to the sudden failure of all strengths of stimuli. Evidently a gradual fall of conductivity is quite incompatible with this sudden failure of all stimuli, if the size of the propagated disturbance does depend on the strength of the stimulus. If this were the case there would certainly be a period during which the strength of stimulus would have to be increased above the normal value in order to set up a disturbance large enough to avoid extinction, and so the least strength of an effective central stimulus would rise gradually as the conductivity fell. Thus the fact that the threshold strength does not vary until the moment when all stimuli became ineffective can point to one conclusion only, the conclusion that there is an all-or-none relation between the stimulus and the propagated disturbance. The sudden failure of all strengths of stimuli must be due, not to a sudden drop in the conductivity from its normal value to nil, but to the fact that stimuli of all strengths set up only one size of propagated disturbance. As soon as a disturbance of this size fails to pass the narcotised region, the block to conduction is complete, because an increase in the strength of the stimulus cannot bring about any corresponding increase in the propagated disturbance.

This argument was put forward three years ago by Symes and Veley[4] and later by Veszi[5], Verworn[6] and Lodholtz[7]. It rests on the single assumption that the size of the propagated disturbance is proportional to its ability to pass the narcotised region. This

[1] *Arch. f. d. ges. Physiol.* LXXVI. p. 552. 1899.
[2] *Ztsch. f. allgm. Physiol.* III. p. 148. 1904; *ibid.* IV. p. 153. 1905.
[3] *Arch. f. d. ges. Physiol.* LXXXVII. p. 134. 1900.
[4] *Proc. Roy. Soc.* B. LXXXIII. p. 431. 1910.
[5] *Ztsch. f. allgm. Physiol.* XIII. p. 321. 1912.
[6] *Ibid.* XIV. p. 277. 1913. [7] *Ibid.* XV. p. 269. 1913.

assumption has been discussed elsewhere[1] and it has been pointed out that it is little more than a question of definition, since the ability of the disturbance to propagate itself is its most fundamental property. However the chief difficulty lies not so much in the foregoing argument, as in the experimental evidence on which it is based. The experiment consists in measuring the strength of effective stimuli during the narcosis of a length of nerve between the stimulating electrodes and the muscle. Measurements of the kind have been made by Piotrowski[2] Werigo (Rajmist[3]), Fröhlich[4], Ishikawa[5] and others, and in many cases it is quite true that the threshold for central stimuli does not rise

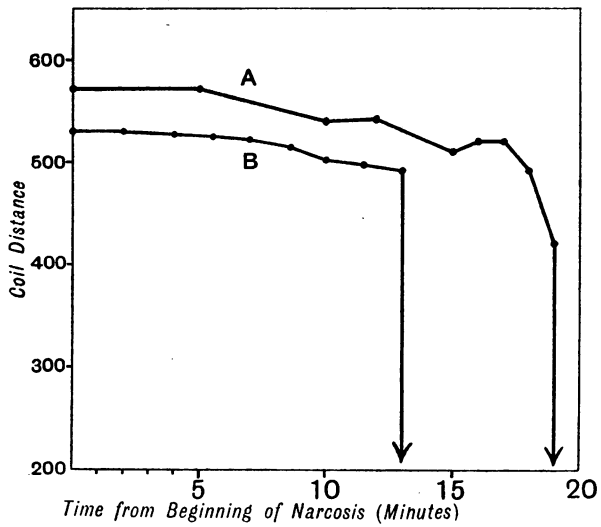

Fig. 1.

until conduction fails. However in an appreciable number of these experiments the threshold does rise; stimuli which are just effective before the narcosis become ineffective at a time when stronger stimuli still reach the muscle. The threshold strength may rise gradually throughout the narcosis or it may rise suddenly, a very short time before conduction fails altogether. Fig. 1 shows two out of the large number of published experiments which give this result. The upper curve *A* is from an experiment of Fröhlich's[6] and the lower *B* from

[1] This *Journal*, XLVI. p. 406. 1913.
[2] *Arch. f. Anat. u. Physiol.* p. 205. 1893.
[3] *Arch. f. d. ges. Physiol.* LXXVI. p. 552. 1899.
[4] *Ztsch. f. allgm. Physiol.* III. pp. 75, 131, 148. 1904.
[5] *Ibid.* XIII. p. 227. 1912.
[6] *Ibid.* III. p. 167, Tab. VIII. 4. 1904.

one of Werigo's (Rajmist[1]). Abscissæ represent minutes after the application of the narcotic (Fröhlich used ether and Rajmist alcohol vapour) and ordinates give the coil distance at which a stimulus central to the narcotic area is just able to affect the muscle. In both cases the curve falls suddenly when the block to conduction is complete, but the coil distance has to be reduced to some extent before the sudden fall occurs. Are we to conclude that in these cases the all-or-none relation between stimulus and disturbance does not obtain, although it does in the majority of muscle nerve preparations?

This conclusion is certainly not inevitable. In the first place the gradual rise in the strength of the threshold stimulus might be due to an alteration in the local excitability of the nerve. Lucas[2] has shown that a stimulus acting on nervous or muscular tissue sets up the propagated disturbance not directly, but by the mediation of a local disturbance different in kind from that which is propagated. The propagated disturbance is not started until the local excitatory disturbance has reached a certain intensity, and so the condition of the tissue immediately under the electrodes may determine what strength of stimulus will give rise to a local excitatory disturbance large enough to set a propagated disturbance in motion. Thus an increase in the threshold stimulus might be due to an increased local resistance to the setting up of a propagated disturbance and not to the necessity for setting up a propagated disturbance of greater size. It is true that, in the experiment described, the excitability of the nerve under the electrodes must remain approximately constant, for it is not likely to be affected by the narcosis of another part of the nerve. However it is a difficult matter to avoid small alterations of excitability, and the gradual changes in the strength of the threshold stimulus are certainly no greater than the changes which may be found in a nerve not acted upon by any narcotic.

This point has been proved conclusively by the experiments of Lodholtz[3]. He has taken great precautions to prevent any change in the condition of the nerve central to the narcotising chamber, and under these circumstances he finds that the threshold stimulus never rises gradually during the narcosis. Thus the gradual change never appears when the local excitability of the nerve under the electrodes is kept constant, although it may appear when the local excitability is not so well controlled. There can be no doubt, therefore, that the effect is

[1] *Arch. f. d. ges. Physiol.* LXXVI. p. 567, No. 5. 1899.
[2] *Proc. Roy. Soc.* B. LXXXV. p. 501. 1912.
[3] *Loc. cit.*

due simply to uncontrolled variations in the local excitability of the nerve.

This explanation accounts well enough for the gradual changes of threshold which sometimes appear during the narcosis, but it does not account for the sudden increase in the threshold often observed just before the failure of conduction (cf. Fig. 1, *A*). It is extremely improbable that this sudden change, occurring always at the same stage in the experiment, could be due to nothing more than a change in the local excitability. That it cannot possibly be due to this is shown by Lodholtz's experiments, for the effect in question was quite unaffected by the careful control of the excitability. Evidently some other

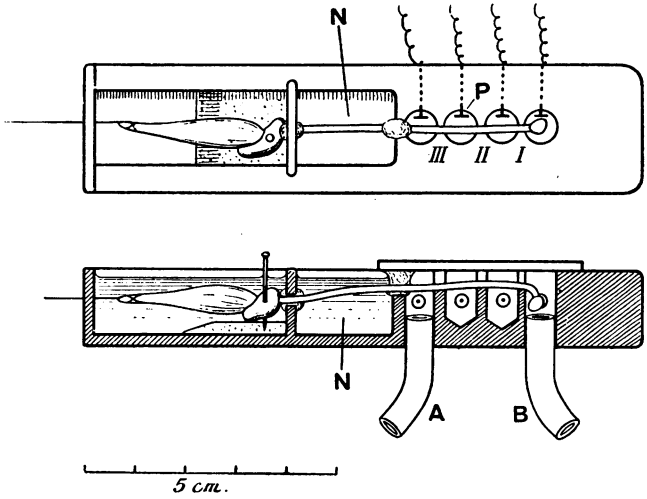

Fig. 2.

explanation must be found if we are to avoid the conclusion that some nerves do not obey the all-or-none principle.

A probable explanation has been suggested by Lodholtz. He points out that the threshold stimulus excites only the most excitable fibres of the nerve and does not affect the rest. If it should happen that conduction failed sooner in these than in the fibres which were less excitable, it would follow that a stimulus strong enough to affect the less excitable fibres would still produce a contraction in the muscle, although the original threshold stimulus would be unable to do so. Thus the increase in the threshold would be due simply to the premature failure of conduction in the most excitable fibres and not to a change of excitability in any one fibre.

This explanation is not only probable, but as it turns out it is also true. However Lodholtz contents himself with pointing out that the sudden increase in the strength of effective stimuli just before the conduction fails is of the same order of magnitude as the increase necessary to convert a minimal stimulus (which excites a few fibres only) into a maximal (which excites all the fibres). Apart from this he makes no mention of any attempt to test his suggestion. Yet the point is of no little importance, for if his explanation is correct then we may say definitely that the nerve fibre obeys the all-or-none principle. If it is not correct, then the relation between stimulus and disturbance is still a matter of some doubt. The fact that the explanation seems highly probable does not make it any the less worthy of proof, and on the whole it must be admitted that Lodholtz's paper leaves the question still unsettled.

The experiments described in the following pages were arranged to test the validity of this explanation. Five of them were carried out a year and a half ago, and the remainder after Lodholtz had published his paper.

Experimental.

If Lodholtz's suggestion is correct it follows that the threshold strength can never rise to a greater value than that required to excite the least excitable fibres of the nerve. Assuming that the condition of the nerve at the electrodes has not changed during the narcosis, the strength will be the least which was required to give a maximal twitch in the normal preparation. Such a stimulus excites every fibre in connection with the muscle and therefore it excites the least as well as the most excitable. Consequently the explanation may be tested by comparing the rise of threshold strength at the end of the narcosis with the strength of stimulus necessary to elicit a maximal contraction.

Nineteen experiments of this type have been carried out. The sciatic-gastrocnemius preparation was placed in an ebonite trough, the nerve passing through a narcotising chamber 20 mm. in length (*N*, Fig. 2). The stimulating electrodes on the central side of the narcotising chamber were of the fluid type recently devised by Keith Lucas[1]. The nerve passes through four holes $\frac{1}{4}$ inch in diameter, connected by narrow slots. The holes are closed above by a glass plate and Ringer's fluid can be perfused through the system by means of the tubes *A* and *B*. A small ring of platinum wire, *P*, is fastened against the side of each hole and

[1] This *Journal*, XLVI. p. 480. 1913.

connected to a copper wire which passes to the exterior. If two adjacent rings are connected with an induction coil, the current will be able to pass from one to the other through the Ringer's fluid by way of the slot. The current density will increase suddenly in the neighbourhood of the slot, and the nerve will be stimulated at the point where the current leaves the slot and spreads into the surrounding fluid. The advantage of this type of electrode for the present experiment is that the nerve is completely surrounded by Ringer's fluid and therefore the local excitability is not likely to vary from such causes as drying or the formation of drops of liquid on the nerve. The four holes are not absolutely necessary, but it is convenient to have some means of testing the excitability of the nerve at more than one point, and in the chamber described the nerve can be stimulated at three points (marked I, II, and III in the figure).

The contractions of the muscle were recorded by an isometric lever, and the stimuli were break induction shocks from a coreless coil, the primary circuit being broken by means of a Lucas pendulum. The nerve was narcotised by 5–6 % alcohol dissolved in Ringer's fluid. The exact strength used depended on the temperature, but it was adjusted so as to suspend conduction in from 25 to 35 minutes. Leakage of the alcohol into the adjacent chambers was prevented by vaseline plugs filling the slots through which the nerve entered and left the narcotising chamber.

In the earlier experiments records were made of (*a*) the least strength of stimulus required to give a minimal contraction, (*b*) the least strength required to give a maximal contraction, and (*c*) the height of the maximal contraction recorded on a stationary drum. Stimuli were sent in at intervals of 20 seconds from five or ten minutes before the beginning of the narcosis until after the complete failure of conduction. The threshold strength never varied by more than 8 % until three or four minutes before the failure of conduction. As a rule the variation was less than this. Typical records are shown in Figs. 3 and 4. Ordinates represent current strength expressed as percentages of the value required for a minimal contraction at the beginning of the narcosis. The upper continuous line marked "maximal" shows the strength necessary for a maximal contraction and the lower dotted line marked "minimal" shows the strength necessary for the smallest contraction which could be observed. The vertical arrow at the ends of these curves records the complete failure of conduction; a stimulus ten or twenty seconds later failed to produce any contraction in the muscle

although it was fifteen times as strong as the threshold stimulus. The lines rising vertically from the time axis give the heights of the maximal contractions at different stages of narcosis.

These two figures show quite clearly that the final increase of the effective current strength is due to nothing more than the early failure of the most excitable fibres. In both cases the minimal current strength must be increased just before the failure of conduction; in Fig. 3 it must be increased by 12%, and in Fig. 4 by 56%. In neither case however is there any increase in the strength of current required for a maximal contraction. In Fig. 3 the maximal strength falls by

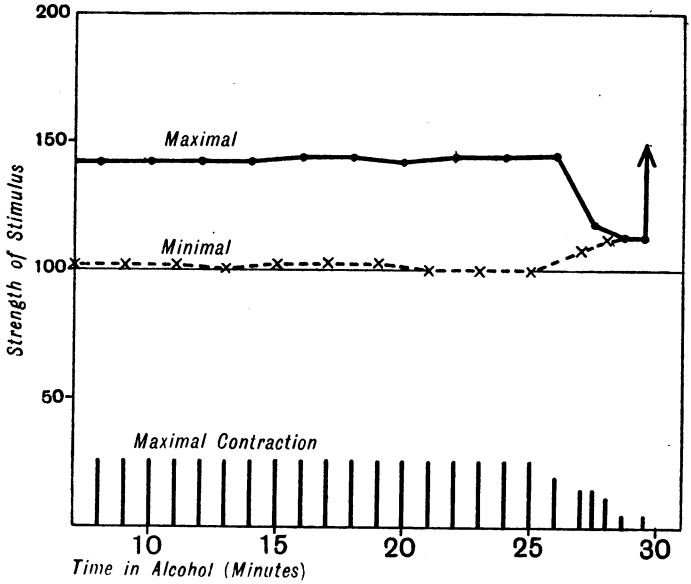

Fig. 3.

34% and eventually coincides with the minimal strength (as the contractions are by this time so small that it is impossible to distinguish a minimal from a maximal contraction). In Fig. 4 the maximal strength remains constant until the conduction has failed completely. These results are exactly what one might expect on the assumption that each fibre obeys the all-or-none principle and that fibres of different excitabilities may cease to conduct at slightly different times. If this were the case the final value of the current strength required to affect the muscle should never lie outside the values required for maximal and minimal contractions before the narcosis. The final value might

lie anywhere between these limits and its exact position will depend simply on the excitability of the fibre which happens to resist the narcotic for the longest time. This result has been found in all the 19 experiments. In three cases the final current strength was equal to the original maximal value (as in Fig. 4) and in four it was equal to the minimal. In the remainder it occupied an intermediate position as in Fig. 3.

If a change in the maximal or minimal current strength corresponds to a reduction in the number of nerve fibres in action, we should expect it to be accompanied by a reduction in the height of the maximal contraction. This effect is shown in Figs. 3 and 4 and in all the other

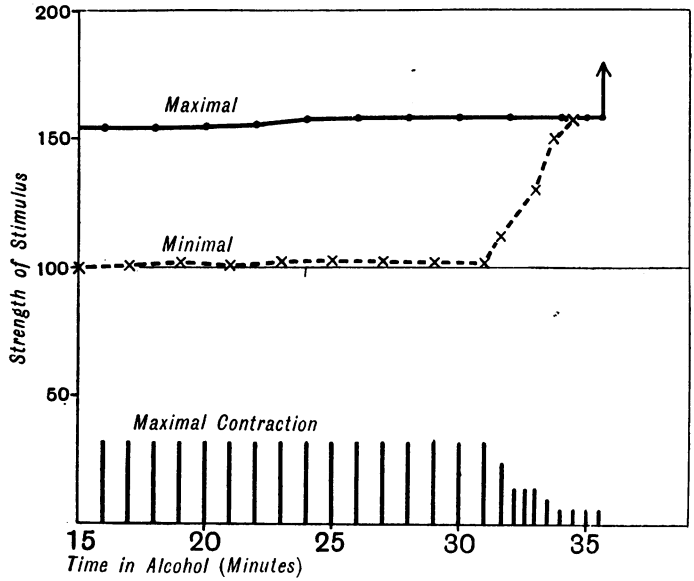

Fig. 4.

experiments. It is to be noted that the contraction does not still remain at its normal height at a time when the current strength has begun to change. As long as the contraction is still unreduced none of the nerve fibres can have ceased to conduct, and therefore if an alteration in the threshold were observed at this time it could not have been due to the failure of some of the fibres. Such an alteration was never found in any experiment.

It remains to be seen if these results can be explained adequately on the assumption that the nerve fibre does not obey the all-or-none relation, and that an increase in the stimulus does produce an increase

in the size of the propagated disturbance. If this were the case one would expect to find a stage in which in any single fibre a strong stimulus would set up a disturbance large enough to reach the muscle, although the stimulus which was originally just strong enough would set up a disturbance too small to pass the region of decrement. Thus for each fibre there would be a stage in which the least effective stimulus would have to be increased in strength in order to set up a disturbance capable of reaching the muscle. This would apply to the least as well as to the most excitable fibres of the nerve, and therefore there should be an increase in the strength of stimulus required for a maximal as well as for a minimal contraction. But as we have seen, the strength required for a maximal contraction never rises until the moment when conduction fails altogether. There is one possibility which might account for this result. It is just conceivable that in these particular experiments the conductivity fell so rapidly that it had been reduced from its normal value to zero during the twenty seconds which intervened between two successive stimuli. In some cases the interval was smaller than this and the change of conductivity must have taken place in less than ten seconds. This is extremely unlikely, for as a rule alcohol affects the conductivity of a nerve quite gradually. However it is a simple matter to find out if the conductivity of the nerve has or has not altered before the last few seconds. Lucas[1] has shown that alcohol has no effect on the rate of recovery of a nerve from a previous disturbance; consequently any lengthening of the interval for muscular summation must be due to impaired conduction. As the decrement becomes greater, disturbances set up in the early stages of recovery are too small to pass the narcotised region without extinction, and so the interval between two stimuli must be increased if both are to affect the muscle. So in the present case if it is found that the interval for muscular summation has risen considerably before the failure of conduction, it is clear that the nerve must be conducting with a decrement at this time, and therefore the changes of conductivity cannot all take place within the last few seconds.

In five of the nineteen experiments the interval for muscular summation was measured at intervals of about five minutes throughout the narcosis. The stimuli used for measuring the interval were sent in by electrode I (Fig. 2) and those used for measuring the threshold were sent in by II or III in order to avoid the possible effects of strong stimuli on the excitability. In every case it was found that the interval for

[1] This *Journal*, XLVI. p. 470. 1913.

muscular summation started to rise after the first eight or nine minutes and continued rising steadily until the conductivity failed. Figs. 5 and 6 show records in which this measurement is combined with that of the

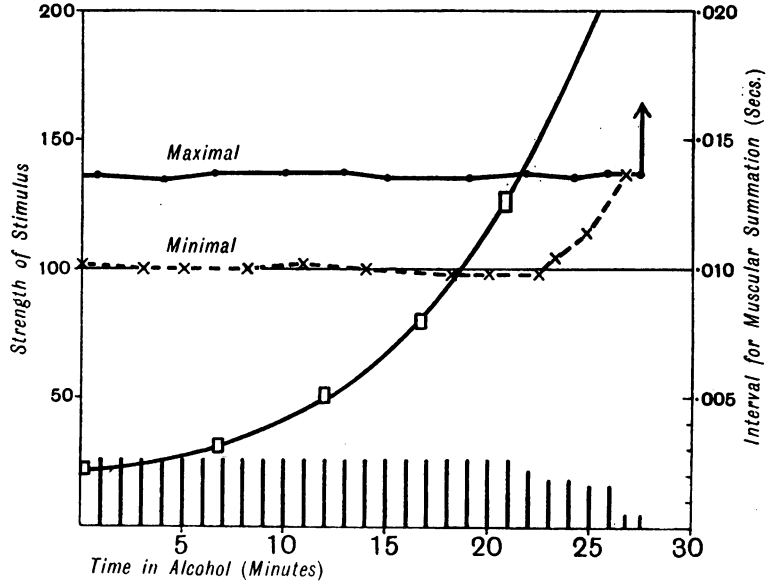

Fig. 5.

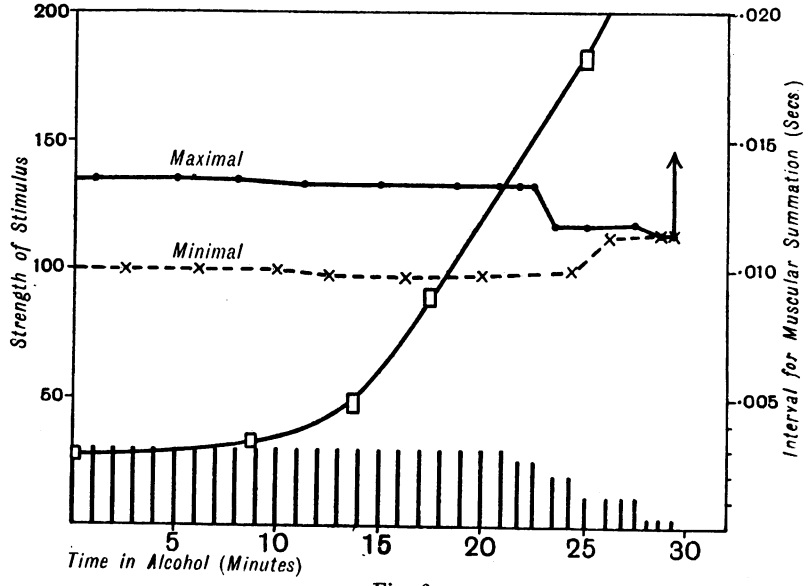

Fig. 6.

current strengths for maximal and minimal contractions. It will be seen that the interval for muscular summation starts rising long before conduction fails in any of the fibres of the nerve. Evidently the conductivity of the nerve falls gradually, and not suddenly during the last twenty or ten seconds.

This is shown even more clearly in three additional experiments in which the conduction was suspended by treating 20 mm. of the nerve with distilled water instead of alcohol solution. The process took about an hour at 16·5° C. The interval for muscular summation began to rise after the first 15 minutes but there was no sign of any increase in the strength of stimulus required to produce a maximal contraction until the conduction had failed altogether. In these experiments the changes are more gradual than they are in the alcohol experiments and therefore an alteration in the effective current strength would be less likely to escape notice.

Clearly these results are quite incompatible with the view that the propagated disturbance varies in size with the strength of the stimulus, and we must conclude that the size of the disturbance is independent of the strength of the stimulus, *i.e.* that in each nerve fibre the all-or-none relation holds good.

Summary.

When a nerve is narcotised locally and stimulated at a point central to the narcotised area, the strength of stimulus necessary to affect the muscle does not rise gradually, but remains approximately constant until conduction fails. This indicates, as Symes and Veley, Verworn and others have pointed out, that the ability of the propagated disturbance to pass a region of decrement does not depend upon the strength of the stimulus which sets it up. In other words there would seem to be an all-or-none relation between the strength of the stimulus and the size of the disturbance in each nerve fibre. However the experiment is not always satisfactory. Sometimes there may be a small rise in the strength of the threshold stimulus occurring suddenly just before the failure of conduction, and sometimes there may be a small gradual rise throughout the narcosis. Lodholtz has shown that the latter is due to a local fall of excitability in the nerve under the electrodes, and he has suggested that the sudden rise may be due to the premature failure of the most excitable fibres of the nerve. Experiments prove that this is the true explanation, for the strength of stimulus required to give a maximal contraction never rises, although

the strength for minimal contractions may do so. It follows that the effective strength of stimulus for any one nerve fibre remains absolutely unchanged until the moment when conduction in that fibre is completely suspended. This result is independent of the total duration of the narcosis and it can be shown that the nerve is conducting imperfectly long before the moment of complete failure.

We must conclude that in any nerve fibre under normal conditions there is an all-or-none relation between the strength of the stimulus and the size of the propagated disturbance which follows it. This agrees with the fact that the size of the disturbance at any point in a normal fibre depends only upon the local condition of that point and not upon the previous history of the disturbance.

ADDENDUM.

A suggested explanation of the all-or-none relation between the stimulus and the propagated disturbance.

The statement that a nerve fibre obeys the all-or-none principle is open to more than one interpretation. It might mean that the size of the propagated disturbance at any point was (*a*) independent of the strength of the stimulus which set it up, or (*b*) that it was invariable, or at least dependent on the local conditions only, and not on the past history of the disturbance in its course down the nerve. If (*b*) is true, then (*a*) must be true also. Previous experiments[1] showed that (*b*) was probably true, and therefore it was necessary to investigate (*a*). Thus the relation between stimulus and disturbance was a point to be decided, and it is satisfactory to find that it is an all-or-none relation.

The experiments in this paper serve to confirm the view that the size of the disturbance is invariable, because they show that at any rate it does not vary with the strength of the stimulus. But there are many other conditions under which it might vary. The setting up of a propagated disturbance by an external stimulus may involve entirely different processes to those concerned in the propagation of the disturbance from one section to another; thus it is quite conceivable that a fibre might be able to conduct disturbances of different sizes provided that the differences were brought about in the course of conduction (*e.g.* by passage through a region of decrement), although the process of excitation would not admit of the setting up of more than one size of disturbance by an external stimulus.

[1] This *Journal*, XLV. p. 389. 1912.

For this reason it may be doubted whether the existence of an all-or-none relation between stimulus and disturbance, taken by itself, is as important as Verworn and Lodholtz seem to suggest. Whatever its explanation may be, it tells us nothing about the nature of the propagated disturbance, the mechanism of conduction, etc. As a matter of fact, the relation might be explained very simply and without the introduction of any new hypothesis by considering two well-known facts, namely that a propagated disturbance is preceded by a local excitatory disturbance, and that it is accompanied by a refractory period. The argument may be stated as follows. To start a propagated disturbance, *i.e.* to excite, the stimulus must bring about a certain local change of conditions, and this change must exceed a certain value[1]. Whatever the rate of the process, there will always be a time at which the extent of the change is just great enough to start a propagated disturbance. We have only to suppose that a disturbance is set in motion as soon as this change has reached its critical value, and it is clear that the all-or-none relation must follow. A strong stimulus may cause the local change to exceed the value required for excitation, but the disturbance will have been set up at the moment when the critical value was reached, and the refractory state accompanying the disturbance will prevent any subsequent change in the local conditions from affecting its size in any way. This may appear more obvious if we consider the effects of sending in two stimuli separated by a very short time interval. If the interval is short enough, the second stimulus falls on refractory tissue and has no effect. We may imagine the interval to be reduced further and further until eventually the two stimuli coincide. The two will then be equivalent to one stimulus of double strength, but the addition of the second is not likely to have any more effect on the size of the disturbance when there is no interval than it had when there was an appreciable interval between the two stimuli.

Another factor may come into play when the conditions necessary for excitation are attained in a very short time, as is the case with the break stimulus from an induction coil. It is well known that a stimulus many times stronger than the threshold affects the nerve over a considerable area round the point at which it is applied. Thus for every stimulus strong enough to excite there will be a region at the edge of the affected area where the conditions will be changed just enough to set the propagated disturbance in motion. Unless the change proceeds very slowly at this point, the disturbance set up here

[1] Lucas. *Proc. Roy. Soc.* B. LXXXV. p. 501. 1912.

will forestall any other disturbance which might have travelled from the centre of the affected area where the stimulus was more intense. Thus however strong the stimulus may be, the propagated disturbance which passes down the nerve will have been set up in a region where the change of conditions has been only just great enough to excite.

We may conclude that there is an all-or-none relation between the stimulus and the propagated disturbance because the disturbance will always be set up as soon as the local excitatory change has reached a certain critical intensity at any point on the nerve; any further increase in the local change will have no effect on the propagated disturbance on account of the refractory state which is developed as soon as the disturbance is set in motion.

If this explanation is correct, it is clear that the existence of an all-or-none relation between stimulus and disturbance does not even tell us anything new about the local excitatory process. In any case the result of these experiments must be looked upon as confirmatory evidence and nothing more; taken apart from other evidence, it can give no information as to the all-or-none character of the nervous impulse.