WEDENSKY INHIBITION IN RELATION TO THE 'ALL-OR-NONE' PRINCIPLE IN NERVE. By E. D. ADRIAN, *Coutts Trotter Student, and Scholar of Trinity College, Cambridge.*

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SOME years ago Gotch[1] put forward the view that the magnitude of the response in a single nerve fibre must be independent of the strength of the stimulus which evoked it. He based this hypothesis on the fact that the electric response of a nerve trunk excited by a submaximal stimulus was indistinguishable from the response produced by a maximal stimulus applied to a smaller number of nerve fibres. This fact by itself is suggestive but hardly conclusive. However Gotch's view has been supported by the results of more than one type of experiment. Thus Symes and Veley[2] called attention to the fact that a disturbance set in motion by a strong stimulus has no greater capacity for passing through an area of imperfect conduction than the disturbance set in motion by a weak stimulus. Recently Veszi[3], Verworn[4] and Ludholtz[5] have put forward the same argument and the present writer has shown that the size of the propagated disturbance in any section of a normal nerve fibre seems to depend only on the local conditions of that section and on nothing else.

Only one serious objection has been brought against the all-or-none principle from an experimental standpoint. This objection is based on the phenomena described as Wedensky inhibition. Wedensky[5] found that at a certain stage in the fatigue or narcosis of a muscle nerve preparation, a series of strong or rapidly recurring stimuli may produce a small initial contraction only (*Anfangszuckung*), whereas a series of

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[1] This *Journal*, xxviii. p. 392. 1902.
[2] *Proc. Roy. Soc.* B, lxxxiii. p. 431. 1910.
[3] *Ztsch. f. allgm. Physiol.* xiii. p. 321. 1912.
[4] *Ibid.* xiv. p. 277. 1912.
[5] *Arch. f. d. ges. Physiol.* xxxvii. p. 69. 1885.

weak or slowly recurring stimuli produce a continued tetanus. At present we are concerned only with the results of an alteration in the strength of the stimuli when their frequency remains unchanged. Since a series of very strong stimuli have an effect on the preparation entirely different to that given by a series of weak stimuli the alteration in the strength of the stimuli must have produced some alteration in the propagated disturbances set up in the nerve. How then can it be maintained that the size of the disturbance is unaffected by the strength of the stimulus? Both Max Cremer[1] and F. Hofmann[2] have used this argument in favour of the view that the size of the propagated disturbance depends on the strength of the stimulus.

On the other hand Keith Lucas[3] has proposed an explanation of the Wedensky effect which is based on the assumption that the size of the propagated disturbance is always independent of the strength of the stimulus. He set out with the observation that a second stimulus following a first very closely might set up a small disturbance which would pass down the nerve but not into the muscle. Such a disturbance would leave a refractory period behind it, although it would be too small to pass the region of imperfect conductivity between nerve and muscle. This refractory period would cut down the size of the disturbance set up by a third stimulus falling very soon after the second and in this way a series of stimuli recurring rapidly enough would set up a train of small disturbances none of which would be large enough to affect the muscle. This accounts for the inhibition produced by increasing the frequency of the stimuli without altering their strength. The inhibition produced by increasing their strength is explained in much the same way. A weak stimulus, falling on tissue which is recovering from the passage of a propagated disturbance, will not have any effect at all unless it falls on nerve which has so far recovered that its excitability is not much less than normal. A disturbance set up at this time will be large enough to pass to the muscle, since it is set up when the recovery of the nerve is nearly complete. Thus a series of weak stimuli will set up a series of large disturbances, each of which is able to affect the muscle. The number of the stimuli per second may be many times greater than the number of disturbances set up, for many of the stimuli will fall on tissue of low excitability and these will have no effect at all. On the other hand, a strong stimulus will be able to set up a disturbance at

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[1] *Nagel's Hdb.* IV. II. III. p. 947.

[2] *Arch. f. d. ges. Physiol.* CIII. p. 328. 1904.

[3] This *Journal*, XLIII. p. 46. 1911.

a much earlier stage of recovery, when the excitability of the tissue is small. Thus a series of strong stimuli will set up a greater number of disturbances than a series of weak stimuli. Consequently an increase in the strength of the stimuli will have exactly the same effect as an increase in the frequency; the disturbances will recur so rapidly that none of them will be large enough to pass to the muscle.

In this explanation of the Wedensky effect it is assumed that the size of the disturbance is quite unaffected by the strength of the stimulus. The fact that an explanation has been based on this assumption shows that the mere existence of the Wedensky effect cannot be used as an argument against the all-or-none theory. However it cannot be said that the foregoing explanation has received a satisfactory proof. In his work on the Wedensky inhibition Lucas was concerned mainly with that type which is produced by increasing the frequency of the stimuli and he made very few experiments on the effect of increased strength. Thus his explanation of the latter type of inhibition rests on the unproved assumption that the all-or-none principle holds good not only for normal nerve but also for nerve which has not completely recovered from the refractory state. As a matter of fact Veszi[1] has recently published some experiments which lead him to the conclusion that the all-or-none principle does not hold good for incompletely recovered nerve. He considers that the size of the disturbance does depend on the strength of the stimulus if the nerve is fatigued, although it does not if the nerve is fresh. He points out that a series of stimuli producing the Wedensky inhibition must recur at such an interval that each stimulus falls on incompletely recovered tissue and in this case he considers that a series of strong stimuli will set up a series of large disturbances and a series of weak stimuli will set up a series of small disturbances. It is not clear why the small disturbances are able to affect the muscle if the large disturbances cannot do so, but there would certainly be some difference in the series of disturbances set up by the weak and the strong stimuli. However the experiments on which Veszi bases his theory are not entirely conclusive. He measured the electric response of a frog's sciatic stimulated by a series of strong or weak stimuli; with the weak stimuli he found that the action current became smaller after the first few responses, but with the strong stimuli this falling off did not take place. It seems possible that some part of this effect might have been due to

[1] *Ztsch. f. allgm. Physiol.* XIII. p. 330. 1912. See also Verworn, *ibid.* XVI. p. 288. 1913.

a local fall of excitability produced by repeated stimulation of the nerve in one place. This might reduce the size of the electric response by reducing the number of nerve fibres thrown into action by the weak stimuli. At the same time there is little reason to doubt that the size of the electric response set up in a nerve trunk by a stimulus falling on partially refractory tissue does depend to some extent on the strength of the stimulus[1]. However we are concerned ultimately not with the response of the whole nerve but with the propagated disturbance in each nerve fibre. A variation in the size of the electric response of the whole nerve trunk may be due to a variation in the response of each fibre but it may be due just as well to a variation in the number of nerve fibres set in action by the stimulus. The nerve trunk of the sciatic contains fibres of many different functions and it is unlikely that all of these would recover at the same rate. Consequently a weak stimulus might give rise to a small electric response, because it would set up disturbances only in those fibres which had recovered their excitability rapidly. A stronger stimulus would be above the threshold value for some of the fibres which recovered more slowly and therefore it would set up propagated disturbances in more fibres and the electric response of the nerve trunk would be greater. For this reason measurements of the size of the electric response in the nerve trunk can give no definite information about the relation between the size of the disturbance set up in an incompletely recovered nerve fibre and the strength of the stimulus which sets it up.

Thus the precise interpretation of the Wedensky effect remains undecided.

The question is of some importance, for although the existence of the effect does not disprove the all-or-none theory as applied to normal tissue, yet, if Veszi is correct, the all-or-none theory cannot be true for nerve under all conditions, since he holds that in fatigued nerve the size of the propagated disturbance depends on the strength of the stimulus. If Lucas is correct the all-or-none relation holds good for fatigued and fresh nerve alike.

The present investigation deals with some experiments made with the object of defining more exactly the conditions under which the Wedensky effect may be obtained with strong stimuli. These experiments are described in the first two sections and the third discusses their bearing on the all-or-none theory.

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[1] This agrees with Samojloff's experiments on the electric response of the heart. *Arch. f. d. ges. Physiol.* cxLVII. p. 249. 1912.

I. The Recovery-curve of an Excited Nerve.

The curve relating the strength of a second stimulus to the time at which it will produce muscular summation.

In dealing with a question which is bound up intimately with the recovery processes of a muscle nerve preparation, it is necessary at the outset to fix on some standard series of determinations which will give an outline of the course of recovery in a preparation under any given circumstances. For this purpose it is evident that a simple determination of the refractory period is of little value. It is to be noted that the term refractory period applied to a muscle nerve preparation is ambiguous. It might mean (*a*) the period within which a second stimulus fails to set up a second disturbance in the nerve, or else (*b*) the period within which a second stimulus fails to produce a summated contraction in the muscle. To avoid this ambiguity these two intervals will be spoken of in future as (*a*) the refractory period of the nerve and (*b*) the interval for muscular summation. However neither of these intervals can give any information as to the whole course of recovery, and besides this very little can be deduced from them unless they are measured with reference to some definite strength of stimulus.

Now it is well known that as a preparation recovers from the refractory state, the period in which no second contraction can be elicited from the muscle is followed by one in which a strong stimulus gives a summated contraction and a weak stimulus (*i.e.* one not much stronger than the normal maximal stimulus) does not. As the effect of the previous disturbance passes off, the least strength of stimulus necessary to give a summated contraction becomes smaller and smaller, until eventually it coincides with the threshold stimulus for a fresh preparation. It is a simple matter to construct a curve showing the relation between the strength of the second stimulus necessary for a summated contraction and the time which must elapse between the first stimulus and the second. Such curves have been published by Fröhlich[1] and by Lucas and Adrian[2]. It is clear that this gradual increase in the susceptibility of the preparation to a second stimulus expresses some aspect of the recovery from the previous stimulation, although the particular recovery process to which the curve relates has not been decided. In the present case the determination of these

[1] *Ztsch. f. allgm. Physiol.* IX. p. 86. 1909.
[2] This *Journal,* XLIV. p. 114. 1912.

" curves for muscular summation " has proved to be of such importance
that some time must be devoted to a discussion of their form and
significance.

The method of determination was substantially the same as that
used by Lucas and Adrian. Two coreless induction coils were
employed and their primary circuits were opened by a Lucas pendulum.
The strength of the first stimulus was generally four times as great as
that of the threshold stimulus. The second stimulus could be increased
to forty or fifty times that of the threshold stimulus and its value for
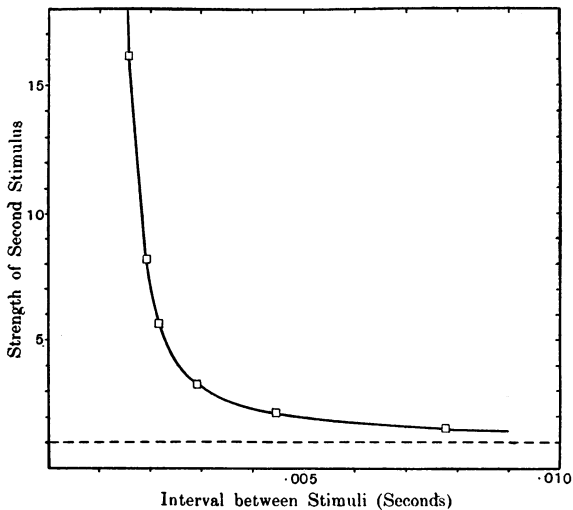each coil distance was determined by means of the calibration curve of
the coil.

Fig. 1.

In each experiment the strength of the normal threshold stimulus is
taken as unity, so that a stimulus ten times as strong as the threshold
stimulus is said to be of ten units strength. The determinations were
made by setting the second coil at some definite position and then
finding the least interval between the first and second stimulus neces-
sary to give a summated contraction. In about half the experiments
an isometric lever was used to record the contractions instead of an
isotonic. The type of lever employed is quite immaterial, for a series
of determinations in which the isometric contractions were recorded
agreed in all respects with the results obtained from the same prepara-
tion by the isotonic method. The approximate error in each determina-
tion is indicated by the size of the rectangle through which the curve

passes.   Fig. 1 and Fig. 2 show typical curves for muscular summation
determined for fresh gastrocnemius-sciatic preparations.   Ordinates
represent the strength of the second stimulus and abscissæ the time
from the first stimulus which must elapse before a summated contraction
is obtained.   The dotted horizontal line shows the strength of the
threshold stimulus.   In Fig. 1 (Exp. 1), the curve shows no discontinuity
and seems to approach a line parallel to the ordinate axis asymptotically.
In this respect it agrees with the curves published by Fröhlich and
by Lucas and Adrian.   In Fig. 2, on the other hand, there is a sharp
break in continuity when the second stimulus is 6·3 times as strong as
the threshold.   An increase in the strength of the second stimulus
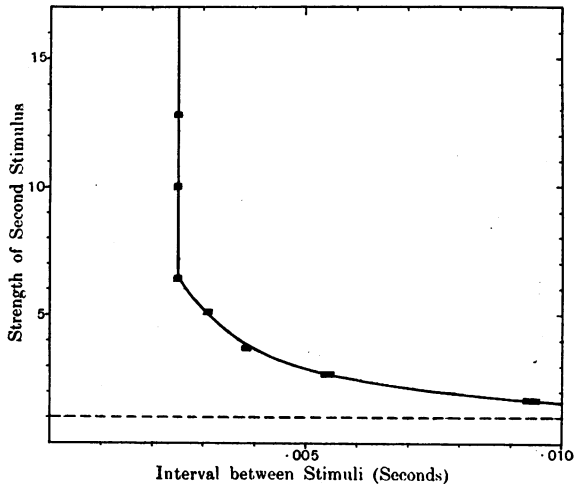beyond this value does not produce any corresponding decrease in the

Fig. 2.

least interval for muscular summation.   Probably this type of curve is
the more usual for fresh preparations.   Which type is given seems to
depend mainly upon the condition of the frogs, for at some periods
every preparation gives a smooth curve and at others the curve is
always discontinuous.   In every case the strength of the first stimulus
has no effect at all on the rate of recovery.

    The form of the curve in Fig. 2 seems to suggest that two distinct
processes are at work, one of which determines the least interval for
summation without reference to the strength of the stimulus, while the
other determines the strength of the second stimulus necessary to have
an effect at different intervals after the first.   As a matter of fact it is

not difficult to show that there are indeed two factors determining the form of the curve for muscular summation, for these factors are affected quite differently by various changes in the condition of the preparation.

The compound nature of the curve can be shown most clearly by altering the temperature of the nerve first of all at some point between the electrodes and the muscle and then immediately under the electrodes.

The effect of alterations in the nerve between the seat of stimulation and the muscle.

It is well known that the refractory period is lengthened by cooling, and Boycott[1] has shown that the lengthening may be produced by cooling a short length of nerve between the stimulating electrodes and the muscle, a procedure which will not affect the tissue immediately under the electrodes. Fig. 3 (Exp. 3) shows the effect of such cooling on the curve for muscular summation. In this experiment the nerve rested on a glass tube through which cold water could be circulated, the distance between the tube and the electrodes being 18 mm. The dotted curve shows the relation between the time of occurrence of the second stimulus and the strength required for muscular summation when the whole preparation was at 16° C.; the full curve was determined when water at 3° C. was passed through the temperature tube.
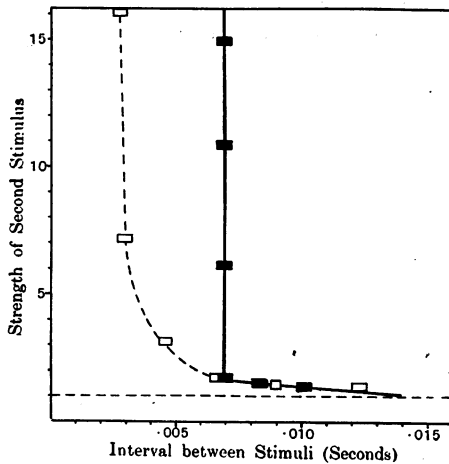

Fig. 3.

The least interval for muscular summation rose from ·0027 to ·0068 sec. However at this interval a stimulus only 1·8 times as strong as the threshold gave a summated contraction just as it did before the cooling, and at any interval greater than ·0068 sec. the least effective strength of the second stimulus coincides exactly with that determined before the cooling. Clearly the only effect of cooling the nerve between the electrodes and the muscle has been to increase the least interval for muscular summation. The strength of stimulus necessary to produce

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[1] This *Journal*, xxiv. p. 144. 1899. See also Adrian and Lucas, *ibid.* xliv. p. 93. 1912.

summation has not been changed. Precisely the same effect is produced by narcotising the nerve between the electrodes and the muscle. The experiment has been repeated four times with cooled and eleven times with narcotised preparations. The correspondence between the lower parts of the recovery curve before and after cooling or narcosis was not always as good as in Fig. 3, although the agreement in Fig. 3 is by no means exceptional. However in the three cases in which there was an appreciable difference between the lower parts of the curves, this difference remained after the nerve had been allowed to return to its original state. Thus there can be little doubt that in these experiments the preparation was not in a steady condition.

The effect on the curve of alterations at the seat of stimulation.

Fig. 4 (Exp. 4) shows the converse of Exp. 3, made on another preparation. In this case the nerve could be cooled in the region of the electrodes while the rest of the preparation remained at the normal
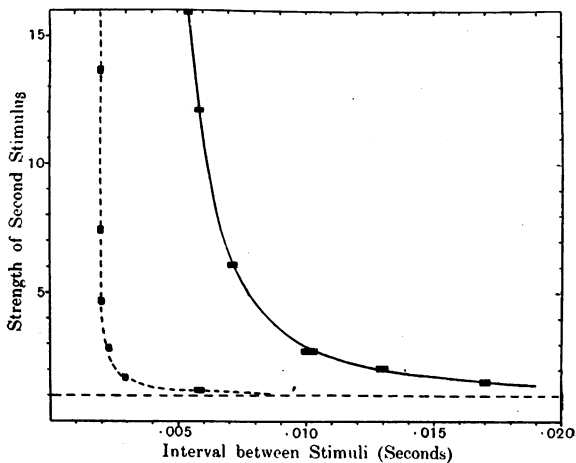

Fig. 4.

temperature. The dotted line shows the curve for muscular summation when the whole preparation was at 16·5° C. and the full curve shows the result of cooling the nerve immediately under the electrodes to 5° C. It will be seen from the figure that the dotted curve becomes vertical like that in Fig. 2, when the interval between the stimuli is ·002 sec. When the nerve is cooled under the electrodes the form of the curve is very much altered and it never becomes quite vertical. Thus Exps. 3 and 4 show that the time and strength relations necessary for muscular

summation are affected by a change in the condition of the nerve under the electrodes but not by a change in some other part of the preparation. The latter affects the least interval for summation but not the strength of stimulus required to produce it.

The same result is shown in Fig. 5. In this experiment (Exp. 5) the curve for muscular summation was determined first of all with the whole preparation at 7° C. (full line) and then with the seat of stimulation warmed to 21·2° C. and the rest of the preparation at 7° C. as before (dotted line).

In this case the least interval for muscular summation is not affected by warming the nerve under the electrodes, but the strength of stimulus necessary for summation is very much reduced and the threshold line is reached very much sooner than before.
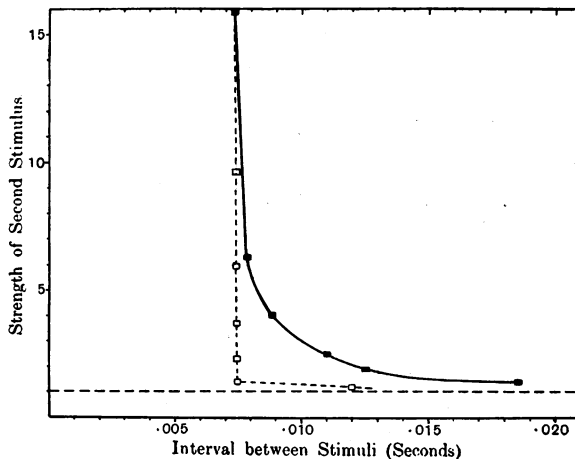

Fig. 5.

It is clear from these experiments that there are two perfectly distinct factors controlling the form of the curve for muscular summation. There is (a) a factor which limits the interval for summation to some fixed value irrespective of the strength of the second stimulus. This accounts for the vertical part of the curve. It depends on the state of the tissue through which the propagated disturbance must pass before reaching the muscle and not on the state of the tissue at the seat of stimulation. The other factor (b) determines the necessary strength of the second stimulus at any interval after the first and accounts for the gradual return of the curve to the threshold value. This depends only on the condition of the tissue at the seat of stimulation and not on the

condition of any other part of the preparation. In some cases (Fig. 1 and Fig. 4 (II)) the limiting value of the interval for muscular summation is never reached and the curve never becomes truly vertical. There is no reason to suppose that in these preparations the interval for summation would decrease continuously as long as the second stimulus increased in strength. Presumably the limiting value determined by the factor (a) is so short that the local recovery process (b) is still predominant even when the second stimulus is 40 times as strong as the threshold value. In other preparations the factor (a) may be predominant so that the curve descends vertically almost to the threshold line before the local recovery factor (b) comes into play. This type of curve may be produced without fail by cooling a portion of the nerve peripheral to the seat of stimulation, but it is also to be obtained in preparations which have been fatigued by repeated indirect stimulation and in preparations in which the nerve has been narcotised between the muscle and the stimulating electrodes.

As the local factor in the curve depends only on the state of the nerve under the stimulating electrodes and on nothing else, it might be put down to the recovery of the tissue from some local after effect of the first stimulus. However this cannot be the case, for the gradual return of the curve is just as well marked when the first stimulus is sent in 20 mm. or more away from the point at which the second stimulus falls, and with this arrangement the form of the curve depends only on the conditions which obtain at the seat of the second stimulus. Thus the local factor in the curve must be concerned with the recovery of the tissue at the point at which the second stimulus takes effect, and as the first stimulus need not fall at the same point the recovery in question must be a recovery from the first propagated disturbance and not from the local effects of the first stimulus.

The curve relating the strength of an interpolated stimulus to the time at which it will inhibit muscular summation.

The value of these determinations of the curve for muscular summation becomes clearer when we consider the time and strength relations of stimuli which produce the Wedensky effect. It is well known that this effect is due to the fact that a stimulus falling on incompletely recovered nerve may set up a new refractory period in the nerve without affecting the muscle in any way. Clearly it should be possible to plot the relation between the time of occurrence and the strength of these stimuli just as we have plotted the same relation for

stimuli which give a summated contraction. A comparison of the two
curves from the same preparation can scarcely fail to be of interest.

In determining the precise relations of stimuli which set up a
refractory period in the nerve without setting up a summated contrac-
tion, it is necessary to consider several possible sources of error and
uncertainty. The method adopted by Lucas[1] consisted in sending in
three stimuli A, B and C timed so that C following A alone was just
able to give a summated contraction. In this case if B left a refractory
period, the three stimuli A, B and C together could not give a summated
contraction, for the refractory period left by B would render C ineffective.
All three stimuli were sent in through the same pair of electrodes, and
with this arrangement it was found possible to adjust the time and
strength of the three stimuli so that in every case A and C alone gave
a summated contraction and A, B and C together did not. Now it is
clear that the stimulus B might render C ineffective in two distinct
ways; it might set up a propagated disturbance which would leave
a refractory period in the nerve without affecting the muscle, or else it
might set up some local after effect only and this might reduce the
excitability of the nerve locally to such an extent that the third
stimulus C following soon after B would be unable to excite. Gilde-
meister[2] and Levinsohn[3] have shown that a stimulus which is not
strong enough to excite may leave behind it a period of depressed
excitability, so that it seems quite possible that B might reduce the
excitability of the nerve under the electrodes without setting up a
propagated disturbance at all. This complicates matters considerably,
for the inhibition produced by the second stimulus B might be due to
the local after effect if B were weak and to the true refractory period if
B were strong. However there can be no question of any local after
effect of B, if the third stimulus C is sent in through electrodes which
are some distance removed from the electrodes used for A and B. This
arrangement was adopted in the experiments to be described.

The precise strength of the third stimulus C is of some importance,
particularly if the interval between B and C is longer than the absolute
refractory period of the nerve. If C were set so that it would fall
during the absolute refractory period left by the stimulus B its strength
would not matter, for it could not possibly break through the

[1] This *Journal*, XLIII. p. 67. 1911.

[2] *Arch. f. d. ges. Physiol.* CXXIV. 447. 1908 ; and *Btr. z. Physiol. u. Pathol.*, Festschr. f.
L. Hermann, p. 53. 1908.

[3] *Arch. f. d. ges. Physiol.* CXXXIII. p. 267. 1910.

refractory state and excite the nerve. However we can never be certain that C does fall within this interval, for it is quite possible that the length of the refractory period may vary with the state of recovery of the tissue in which the disturbance is set up; moreover the length of the absolute refractory period of the nerve cannot be determined except by the present method of three stimuli[1]. However if C is made just strong enough to give a summated contraction when it follows A alone, there can be no doubt that it would be rendered ineffective by any refractory period set up by B. Whatever may be the length of the absolute refractory period set up by B it cannot fail to retard the course of recovery from the first stimulus to some extent and this would be quite enough to inhibit the action of C. With this arrangement the length of the interval between B and C need not be considered, provided that C falls within the relative refractory period set up by the first stimulus A and provided that it is only just strong enough to give a summated contraction when it follows A alone.

In the following experiments the preparation was set up so that the nerve rested on two pairs of electrodes separated by about 15 mm. The first and second stimuli A and B were sent in by way of the central pair, and the third stimulus C by the peripheral. The stimuli could be sent in at any given interval by breaking the primary circuits of three coils connected to a Lucas pendulum. The first step consisted in determining the recovery curve of the preparation as in Exps. 1–5, both stimuli being sent in by the central electrodes. After this the third stimulus C was so adjusted that C following A alone was just able to set up a summated contraction. B was set at a fixed interval after A slightly shorter than the least interval for muscular summation and its strength was adjusted until it was just able to inhibit the effect of C. The interval between A and B was altered and the strength of B readjusted. In this way it was possible to map out the complete strength and time relations of stimuli which would inhibit and to compare these with the strength and time relations of stimuli which would give a summated contraction.

It has been mentioned that fresh preparations give two distinct types of recovery curve; a smooth curve which never becomes absolutely vertical and a discontinuous curve made up of a vertical portion and

[1] The least interval at which a second electric response may be set up in the nerve does not necessarily give a measure of the refractory period in those fibres which supply the gastrocnemius. The sciatic may contain nerve fibres which recover more rapidly than these.

a portion which descends gradually towards the base line. In every case in which a curve of the former type was obtained, it was found impossible to produce inhibition whatever the time of occurrence and strength of the second stimulus might be. This was never the case when the preparation gave a discontinuous curve for muscular summation. Fig. 6 shows the relation of stimuli which gave inhibition in a fresh preparation of this type (Exp. 6). The full line gives the curve for muscular summation and all stimuli falling to the right of this line gave a summated contraction. The dotted line shows the relation between the time of occurrence and strength of stimuli which inhibited the
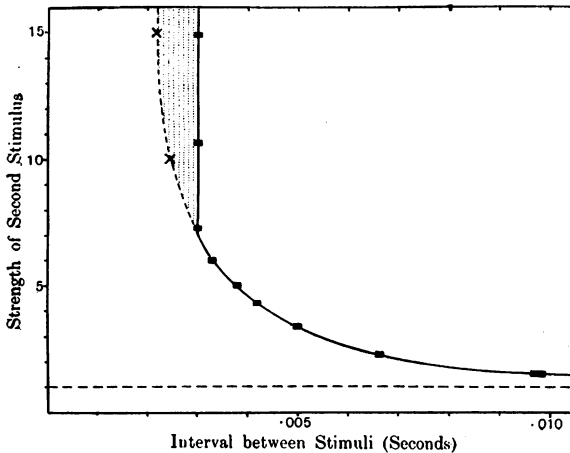

Fig. 6.

effects of a third stimulus without themselves producing any summated contraction. Thus any stimuli falling within the shaded area gave inhibition; a stimulus falling to the left of the dotted curve had no effect at all and a stimulus falling to the right of the vertical line gave a summated contraction.

The continuity of the curve for " inhibition " with the curve
for muscular summation.

It would appear from Fig. 6 (and Exp. 6 is typical of four other experiments) that the curve for inhibition is simply a continuation backwards of the lower half of the curve for muscular summation. This suggests that both parts of the combined curve are an expression of the same process. The gradual descent of the curve for muscular summation has been connected with some local recovery factor which is

not influenced by changes occurring in other parts of the preparation.
Consequently the same process may determine the time and strength
conditions necessary for a second stimulus to produce inhibition.   In
this case the condition of the tissue at the seat of stimulation would
determine whether a second stimulus should have any effect on the
preparation or not and the nature of this effect (inhibition or a summated
contraction) would depend on what has been called the factor (*a*) which
limits the interval for muscular summation and accounts for the
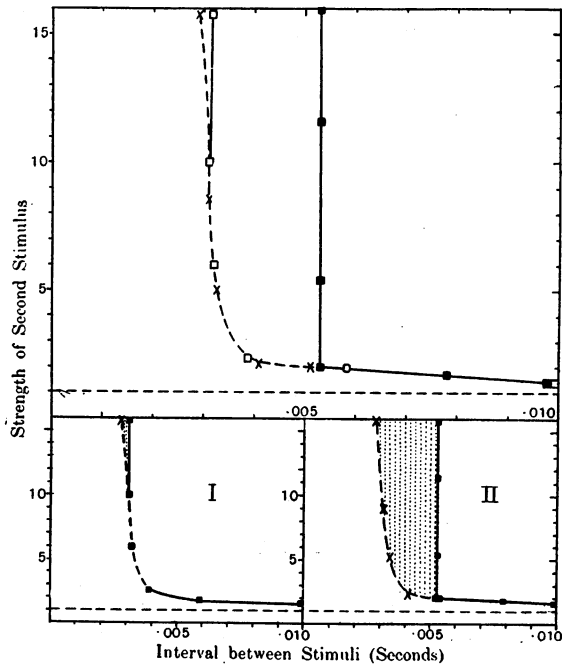

Fig. 7.

vertical portion of the summation curve; if the effective stimulus fell
to the right of this vertical line it would produce a summated contrac-
tion and if to the left it would set up a new refractory state and inhibit
a third stimulus.   This would account for the fact that it is impossible
to produce inhibition in a preparation which gives a continuous curve
for muscular summation.   In such a preparation the limiting value of
the interval for muscular summation is never reached and therefore any
second stimulus which is effective must give rise to a summated
contraction.   The truth of this hypothesis may be tested by taking
advantage of the fact that it is possible to increase the limiting value of

the interval for muscular summation by cooling or narcotising the nerve peripherally, without affecting the local recovery process in any way. Fig. 7 is constructed from an experiment in which this was done (Exp. 7). The inset marked I shows the curve for muscular summation when the whole of the nerve was in Ringer's fluid at 16·3° C. and the dotted curve shows the relations of stimuli which would inhibit (cf. Fig. 6). The shaded area is extremely narrow as only very strong stimuli would give inhibition. The inset II shows the result of treating a short length of nerve between the electrodes and the muscle with 5 % alcohol in Ringer's fluid for 29 minutes. The interval for summation is increased from ·0031 sec. to ·0053 sec., but the shaded area is very much larger and stimuli which were formerly just strong enough to give a summated contraction are now just strong enough to inhibit a third stimulus. The large figure gives the actual determinations; the white rectangles mark the time and strength relations of stimuli which produced a summated contraction before the treatment with alcohol, and the black rectangles show the altered relations of these stimuli after treatment. The crosses refer to the stimuli which were just able to inhibit a third stimulus when the nerve had been narcotised peripherally. It will be seen that the curve drawn through these crosses coincides almost exactly with the curve drawn through the white rectangles (the original curve for muscular summation). The same result was given by four more experiments in which the nerve was cooled, and by five in which it was narcotised between the electrodes and the muscle by nitrogen or by alcohol. In two of the cooling and one of the narcotic experiments the agreement between the two curves was not so good, but it was evident that the tissue under the electrodes had been altered by the repeated stimulation for the lower portion of the curve for muscular summation, determined before cooling or narcosis did not coincide with that determined during the treatment or after the nerve had been allowed to regain its original state. In every case the curve showing the time and strength relations of inhibiting stimuli was perfectly continuous with that showing the relations for muscular summation no matter what might be the limiting value of the interval for muscular summation.

If these two curves are really continuous with one another and expressions of one and the same recovery process, it must follow that a stimulus which occurs later than the least interval for muscular summation cannot possibly give inhibition. If it is strong enough to fall above the curve for muscular summation it must give a second

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contraction, and if it is not strong enough it can have no effect at all.
This point may be tested by setting the second stimulus so that it
is just strong enough to give a summated contraction and then reducing
its strength slightly and determining its effect on a third stimulus.
The experiment was made on 18 preparations and in every case
a stimulus which was just too weak to give a summated contraction did
not prolong the refractory state of the nerve in the slightest degree.
This result holds good under all conditions, for fresh and fatigued
preparations as well as for those in which the nerve has been cooled or
narcotised. Fig. 8 shows this graphically in the case of a preparation
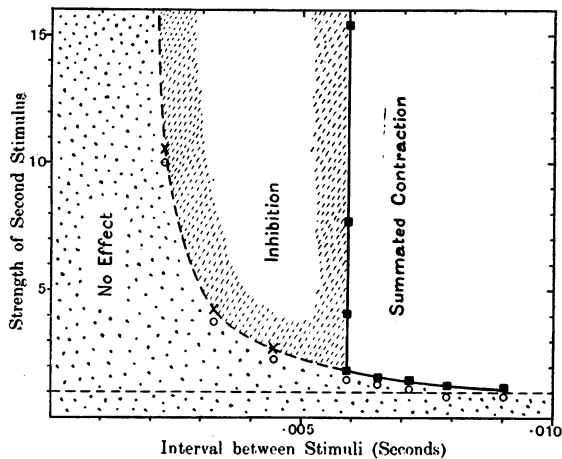treated with nitrogen. The least interval for muscular summation was

Fig. 8.

originally ·0025 sec. After 17 mm. of nerve between the electrodes
and the muscle had been in pure nitrogen for 3 hrs. 37 min., the curve
for muscular summation was determined. It is shown by the line
passing through the black rectangles. The dotted curve shows the
conditions necessary for the second stimulus to give inhibition. Stimuli
falling at the points marked by the small circles had no effect at all.
Thus it is possible to divide the diagram into three areas. A stimulus
falling within the shaded area gives inhibition, a stimulus in the blank
area to the right of this gives a summated contraction, and a stimulus
in the dotted area below these has no effect.

It is clear then that the curve which gives the limiting conditions
for inhibition is perfectly continuous with that which gives the limiting
conditions for muscular summation. Thus the combined curve must be

an expression of the local recovery process which has been called the factor (b) and it will be spoken of, for the present at any rate, as the local recovery curve. It shows the time and strength relations necessary for a second stimulus to produce inhibition or a second contraction. If the effective stimulus falls earlier than the least interval for muscular summation it will set up a new refractory period in the nerve without affecting the muscle, if it falls later it will give a summated contraction.

II. THE BEARING OF THE "RECOVERY CURVE" ON THE UNDERSTANDING OF WEDENSKY'S INHIBITION.

We may now consider how it comes about that a series of weak stimuli may give a continued contraction when a series of strong stimuli produce inhibition. This is shown in Fig. 9 which is the recovery curve of a preparation which had been kept in Ringer's fluid for eight hours.
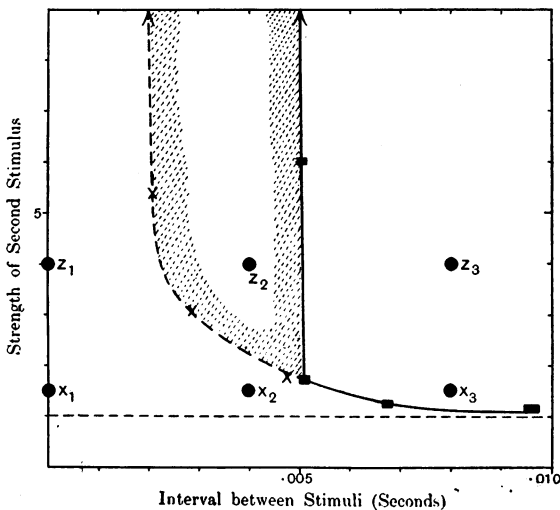

Fig. 9.

The diagram is of the type shown in Figs. 7 and 8 and no stimulus falling outside the shaded area can give inhibition. The points marked x_1, x_2 and x_3 represent three stimuli of strength 1·5 recurring every ·004 of a second. Of these three only x_1 and x_3 can be effective, for x_2 falls at a time when it is too weak to produce inhibition. The interval between x_1 and x_3 is greater than the least interval for muscular summation and therefore x_3 will give a summated contraction. In the same way a series of stimuli of the same strength and frequency would

give a continued tetanus, every other stimulus being too weak to have any effect on the tissue. The stimuli z_1, z_2 and z_3 recur at the same interval but they are four times as strong as the threshold. Consequently z_2 is able to affect the nerve, and as it falls too early to give a summated contraction it will prolong the refractory period and inhibit z_3. Thus the three stimuli will give a single twitch due to z_1 only and a series of strong stimuli will give a continued inhibition. Fig. 10 shows the record of the contractions given by these two groups of three stimuli. The first two and the last two contractions are single twitches due to one stimulus. The groups of four summated contractions were given by the stimuli x_1, x_2 and x_3, and the groups of small contractions were obtained by increasing the strength of the three stimuli to four times the threshold strength. None of these contractions produced by the three strong stimuli are higher than the single maximal twitch.

It is evident that this explanation of the inhibiting effect of a series of strong stimuli corresponds entirely with that given by Lucas. The strong stimuli can prolong the refractory period of the nerve at an early
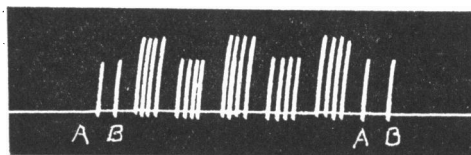

Fig. 10.

stage of recovery before a summated contraction can be produced. The weak stimuli are not effective until a more advanced stage has been reached and then it is too late for them to give inhibition.

The fact that the local recovery curve is not affected by changes which take place in other parts of the nerve explains the ease with which the Wedensky effect may be produced when the nerve has been cooled or narcotised between the electrodes and the muscle. This prolongs the least interval for muscular summation without affecting the local recovery curve, with the result that a much wider range of stimuli will satisfy the conditions necessary for inhibition. Thus in Fig. 7 I, when the preparation is fresh, the shaded area is very small and it would be a very difficult matter to adjust the strength and time relations of a series of stimuli so as to set up a train of disturbances

each of which would leave a refractory period in the nerve without affecting the muscle. In Fig. 7 II and in Fig. 8 the shaded area is very much larger and the stimuli may vary within comparatively wide limits as regards frequency and strength without interfering with the condition that each effective stimulus shall fall at a time when it will give inhibition and not contraction.

A discussion of the theoretical deductions to be drawn from these experiments must be left to the next section.

In the foregoing experiments the third stimulus, used to test the inhibiting effect of the second, was sent into the nerve at a point where it would not be influenced by any purely local after effects of the second stimulus. In the majority of cases in which the Wedensky inhibition has been recorded, all the stimuli have been sent in by the same pair of electrodes and therefore some part of the inhibition might have been due to a local fall of excitability confined to the region of the stimulating electrodes. Woolley[1] made some experiments to test this point and found that the inhibition was certainly not accounted for completely by the polarising effect of the current. However it would be surprising if a strong second stimulus had no effect at all on the excitability of the tissue on which it fell, and as a matter of fact a small local effect is to be observed in most preparations. This is shown by a comparison of the strength and time relations necessary for a second stimulus to inhibit a third sent in (a) by the same pair of electrodes and (b) by another pair some distance away.

As a rule a weaker second stimulus is needed to produce inhibition in case (a) than in case (b); the interval between the first and second stimulus need not be so great, and a second stimulus may produce some inhibition although it falls so late that it would give a summated contraction if it were stronger. In other words a second stimulus which falls below and to the left of the local recovery curve may give some inhibition. The effect is not always easy to demonstrate unless the second stimulus is strong and the third stimulus weak. The inhibition is never complete however short the interval between the second and third stimulus may be. After a second stimulus which gives local inhibition only the third stimulus may need to be increased by some 10 or 20 % if it is to remain effective, but a strong third stimulus always gives a summated contraction. The actual increase necessary depends on the strength of the second stimulus. This is never the case with that type of inhibition which affects a third

[1] This *Journal*, xxxvi. p. 182. 1907.

stimulus sent in at some other point on the nerve. This transmitted inhibition is always complete if the interval between the second and third stimuli is short enough, and if the interval is longer the amount by which the third stimulus must be increased to give summation is quite independent of the strength of the second stimulus.

There is little reason to doubt that this local inhibiting effect of an inadequate second stimulus falling on refractory tissue is due to precisely the same causes as the local inhibiting effect of a subminimal stimulus on normal tissue (Gildemeister's phenomenon). The effect is more intense and lasts longer when the stimulus falls on tissue which has not completely recovered, but this is only to be expected in view of the fact that the stimulus is many times stronger than a normal subminimal stimulus. In other respects the two phenomena agree completely.

It is probable that the local effect does not play a large part in the Wedensky inhibition produced by a series of stimuli of equal strength at one point on the nerve, for as a rule it is only to be detected when the inhibiting stimulus is several times as strong as the inhibited. It may account for the fact that every fresh preparation can be used to show the Wedensky effect when all three stimuli are sent in by the same pair of electrodes, whereas a certain number of fresh preparations give a continuous recovery curve with which the transmitted inhibition is impossible.

From the point of view of the present investigation the transmitted effect is much more important. The foregoing analysis of the conditions under which it takes place has a direct bearing on the nature of the propagated disturbance in nerve and in particular on the validity of the all-or-none principle. This point will be discussed in the following section.

III. THEORETICAL.

In the preceding section some importance was attached to the "local recovery curve" of a preparation after the passage of a propagated disturbance. This curve shows the relation between the time of occurrence and the least strength necessary for a second stimulus to produce either a summated contraction in the muscle or a second refractory period in the nerve. The same curve applies to stimuli giving inhibition and to stimuli giving muscular summation, the nature of the effect (inhibition or a second contraction) depending only on the time of occurrence of the second stimulus in relation to the least

interval for muscular summation. It has been shown that the curve is the expression of some purely local recovery process, since its form depends only on the state of the nerve at the point where the second stimulus falls. In view of this the simplest explanation would be to suppose that the curve represents the gradual return of excitability in the nerve at the seat of the second stimulus.

This suggestion must be examined a little more closely. It is generally understood that the excitation of a tissue implies the starting of a propagated disturbance, and therefore the statement that the local recovery curve is the curve of returning excitability implies that a stimulus which is too weak or too early to fall on this curve does not set up any propagated disturbance in the nerve. In order to prove this we must have some means of detecting the presence or absence of a propagated disturbance. The presence of an effect in the end-organ, in this case the contraction of the gastrocnemius, is certainly an indication that a disturbance has passed down the nerve, but the absence of a contraction cannot be taken as a proof that the nerve has not been excited. It is generally assumed that the electric response in the nerve is the invariable accompaniment of a propagated disturbance, but in the present case we are concerned only with those fibres which supply the gastrocnemius and it would be impossible to discover whether a small electric response in the nerve trunk was due to those fibres or to some others which recovered at a different rate. The only other measurable change associated with the propagated disturbance is the development of the refractory state in the nerve. It has been shown that a second stimulus which falls below the local recovery curve does not set up a refractory period in those fibres which supply the gastrocnemius, and therefore it seems reasonable to conclude that such a stimulus has failed to excite. It is of course conceivable that under certain circumstances a propagated disturbance might be un-accompanied by a refractory period, and it is as impossible to disprove this universally as it is impossible to prove that a disturbance is invariably accompanied by an electric response. However in every case investigated the refractory period seems to be an invariable consequence of the passage of a disturbance[1], whatever the size of the disturbance and the state of the tissue through which it passes. The present experiments are no exception to this, for it has been shown that the same curve applies to stimuli setting up a second refractory period

[1] Bramwell and Lucas. This *Journal*, XLII. p. 495. 1911. Lucas, *ibid.* XLIII. pp. 70 *et seq.* 1911.

and to stimuli producing a second contraction, and that therefore
a stimulus which is too weak to set up a refractory period cannot
be strong enough to affect the muscle and *vice versa*. Again the form
of this curve depends on local conditions only. If it gave the time and
strength relations necessary for a second stimulus to set up a disturbance
large enough to affect the nerve ending or the muscle, its form could
scarcely remain unaffected by a change of conditions which would alter
the size of the disturbance on its way down the nerve. Thus we may
conclude that a second stimulus which is just strong enough to fall on
the local recovery curve is the weakest stimulus which will set up
a propagated disturbance in those nerve fibres which supply the
gastrocnemius.

Having defined the conditions under which a second stimulus is
able to set up a second disturbance we may proceed to enquire whether
the size of the disturbance does or does not vary with the strength
of the stimulus. Veszi[1] measured the size of the electric response
in incompletely recovered nerve and found that it did vary with
the strength of the stimulus. However it has been pointed out in the
introduction that such a method really gives no indication as to the
size of the disturbance in each nerve fibre, because the electric response
may vary with the number of fibres in action. A method which avoids
this difficulty is that which assumes that the size of the disturbance is
proportional to its capacity for passing a region of decrement without
extinction. The application of this method has been discussed else-
where[2] but it may be as well to point out that the assumption on which
it is based is really taken for granted whenever it is said that the
disturbance becomes smaller and smaller as it passes through a region
of decrement; actually its capacity for transmission becomes less and
less. The same assumption is made by Symes and Veley and by
Veszi and Verworn[3] when they argue in favour of the all-or-none
principle in fresh nerve from the fact that the disturbance set up by
a strong stimulus cannot pass through a region of narcosis which
extinguishes the disturbance set up by a weak stimulus. As the
meaning of the phrase size or intensity of the disturbance is not self-
evident, there is no reason why it should not be defined as proportional
to the capacity of the disturbance for passing through a region of
imperfect conduction. This definition avoids the assumption mentioned
above and it will be made use of in the following discussion.

[1] *Loc. cit.*   [2] This *Journal*, XLV. p. 393. 1912.
[3] *Loc. cit.*

Now Lucas and Adrian[1] have shown that, if the strength of the second stimulus is constant, the size of the second disturbance (defined as above) varies with the interval between the two stimuli. If the all-or-none principle does not apply to disturbances set up in incompletely recovered tissue we should expect to find that the size of the second disturbance would depend also on the strength of the second stimulus. When a strip of nerve is narcotised between the stimulating electrodes and the muscle, the least interval for muscular summation is increased because all disturbances set up at an early stage of recovery are too small to pass the region of decrement without extinction. Consequently with this arrangement all disturbances which are below a certain size will be extinguished before they reach the muscle and therefore it will be possible to detect any difference in the size of the disturbance set up by weak or strong stimuli.

In Exp. 8 (Fig. 8), 17 mm. of the nerve between the electrodes and the muscle was treated with nitrogen for 3 hrs. 37 minutes. This caused the interval for muscular summation to rise from ·0025 sec. to ·0058 sec. Thus any disturbance set up sooner than ·0058 sec. after the first must have been too small to pass the region of decrement without extinction. When the interval between the stimuli was ·0058 sec., the weakest stimulus which would excite the nerve set up a disturbance large enough to reach the muscle. If the size of the disturbance depends on the strength of the stimulus as well as on the state of recovery, it should be possible to set up as large a disturbance by means of a stronger stimulus occurring slightly earlier than ·0058 sec. In other words an increase in the strength of the second stimulus over and above the value required to excite should lead to a reduction in the interval for muscular summation. Evidently this is not the case. A stimulus 40 times as strong as the threshold stimulus will not affect the muscle if it falls earlier than ·0058 sec. and at this interval the weakest stimulus which will excite the nerve sets up a disturbance large enough to pass the region of decrement and produce a summated contraction. Consequently the size of the second disturbance must depend only on the interval between it and the first and not at all in the strength of the second stimulus.

The same result was given in sixteen experiments with nitrogen, alcohol vapour and alcohol in solution as narcotic. In none of these was there the slightest indication that the disturbance set up by a strong second stimulus was able to pass a region of decrement which

[1] This *Journal*, XLIV. p. 100. 1912.

extinguished the disturbance set up at the same stage of recovery by a weak second stimulus. This result is true for all stages of narcosis. This point is important for it shows that the second disturbance is unaffected by the strength of the second stimulus whatever may be the state of recovery of the tissue in which it is set up. When the narcotic has nearly brought about the complete failure of conduction the second disturbance will be extinguished unless it is set up so late that it is nearly as large as the first disturbance. The fact that under these circumstances its size is not affected by the strength of the second stimulus rules out the possibility that there might be a lower limit to the size of the second disturbance and that above this limit there might be some variation.

It would seem then that the size of the second disturbance must depend only on the state of recovery of the nerve and not*at all on the strength of the second stimulus. However before this conclusion can be accepted there is one possible source of error to be excluded. It has been assumed that when the interval for muscular summation has been increased by the action of a narcotic, the capacity of the second disturbance to reach the muscle depends upon its size and upon nothing else. It is quite conceivable that the increase in the interval for summation is due not so much to the imperfect conduction of the disturbance through the area of decrement as to a slowing of the recovery process in this area. Such an effect might account for the extinction of all disturbances set up earlier than a certain interval after the first, without reference to their size. If this were the case the ability of the second disturbance to reach the muscle would depend only on its time of arrival in the affected area and not at all on its size, and the experiments described would tell us nothing about the size of the disturbance in relation to the strength of the stimulus. It is unlikely that this slowing of the recovery process by the narcotic plays an important part in the lengthening of the least interval for muscular summation, for previous experiments with various narcotics[1] have shown that the lengthening is due almost entirely to the decrement suffered by the disturbance in passing the narcotised area. Fortunately it is a simple matter to decide the point for every preparation upon which the above experiment is made. An increase in the interval for muscular summation due to the slowing of the recovery process will depend only on the duration of the narcosis and not on the length of narcotised tissue through which the disturbance must pass. An increase due to

[1] This *Journal*, XLV. p. 403. 1912.

the decrement suffered by the second disturbance will depend also on the length of the narcotised region, for the extent of the decrement depends upon this. When the two disturbances started from the central pair of electrodes outside the narcotising chamber they had to pass 17 mm. of affected nerve. Another pair of electrodes were in contact with the nerve inside the chamber and the disturbances starting from these had to pass only 6 mm. of narcotised tissue. In Exp. 8, the interval for muscular summation was originally ·0025 sec. at both pairs of electrodes. After the nerve had been in nitrogen for 3 hrs. 37 mins. the interval for muscular summation rose to ·0058 sec. when measured by the central pair of electrodes, but it was not more than ·0032 sec. when the electrodes inside the chamber were used. Thus the slowing of the recovery process will not account for a rise in the interval for muscular summation to more than ·0032 sec. and the rest of the increase must be due to the decrement suffered by the disturbances in their passage down the nerve. So when the interval between the first and second disturbance is greater than ·0032 sec. the ability of the second disturbance to produce a summated contraction must depend entirely on its size. The same test was made in all but three of the sixteen experiments. In those three a 5 % solution of alcohol in Ringer's fluid was used as a narcotic and with this it was impossible to stimulate satisfactorily inside the narcotising chamber. In all the other experiments the increase in the interval for muscular summation measured by stimuli inside the chamber was never more than ·4 times the rise measured by the central electrodes. Thus in every case the capacity of the second disturbance to affect the muscle must have depended on its size and not on its time of arrival and therefore in every case the size of the second disturbance was unaffected by the strength of the stimulus which set it up. In other words the all-or-none principle does hold good for disturbances set up in incompletely recovered tissue just as it holds for normal tissue.

This conclusion is perhaps not unexpected, but up to the present it has been difficult to accept it unreservedly on account of the fact that within limits the length of the interval for muscular summation is certainly reduced by increasing the strength of the second stimulus. This might well have been due to an increase in the size of the second disturbance. As a matter of fact the analysis of the recovery curve in the first section of this paper shows that the reduction in the interval for muscular summation depends on the fact that a strong second stimulus can excite the nerve at an earlier stage of recovery than

a weak second stimulus, that is to say that relation between the strength of the second stimulus and the length of the interval for summation depends simply on the gradual return of excitability after the first disturbance. If once the second stimulus is strong enough to set up a propagated disturbance, no increase in its strength will alter the size of that disturbance.

It should be pointed out that the foregoing argument deals only with the relation between the size of the disturbance and the strength of the stimulus which sets it up. The fact that this is an all-or-none relation does not show that the size of the disturbance in any section of a nerve fibre depends solely on the state of recovery of that section and that the conduction of a disturbance down the nerve is necessarily an all-or-none process. The setting up of a disturbance by an external stimulus may involve entirely different processes to those concerned in the propagation of the disturbance from one section of the nerve fibre to the next. As a matter of fact evidence has been brought forward in an earlier paper[1] in favour of the view that the size of the disturbance in any section of normal fibre is quite independent of the previous history of the disturbance. This follows from the observation that a disturbance regains its full size on emerging into normal fibre after it has undergone a decrement in a region of local narcosis. Thus in normal fibre at any rate the propagation of the disturbance from one section of the fibre to another may be considered an all-or-none process. This has still to be proved for incompletely recovered nerve although there is a certain amount of evidence (as yet unpublished) in favour of it. In the present paper it has been shown that the size of the disturbance in incompletely recovered nerve does not depend on the strength of the stimulus. This observation certainly does not prove that the size of the disturbance depends only on the state of recovery of that section of the fibre in which it is measured. However it does remove a very serious objection to this view, namely the objection based on the statement that in incompletely recovered nerve the size of the disturbance depends on the strength of the stimulus.

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

CONCLUSIONS.

1. When a stimulus falls on a nerve of a sciatic-gastrocnemius preparation which has not recovered completely from the effect of a previous disturbance, the effect which the stimulus will produce depends upon two factors. In the first place the nerve recovers its excitability slowly and the stimulus will have no effect at all unless it is strong enough to set up a propagated disturbance. The curve showing the relation between the time of occurrence of the stimulus and the strength required to excite the nerve depends only on the condition of the tissue immediately under the stimulating electrodes. If the stimulus is strong enough to set up a disturbance, the nature of the effect produced depends upon another factor which limits the interval at which a second contraction may be set up in the muscle. If an effective second stimulus occurs too early to give a summated contraction, it will set up a new refractory period in the nerve. If it falls later than the least interval for muscular summation it will give a second contraction and no alteration in its strength will cause it to set up a new refractory period in the nerve without affecting the muscle. The factor which limits the interval for muscular summation depends upon the condition of the tissue through which the propagated disturbance must pass. It is increased by cooling or narcotising the nerve between the electrodes and the muscle and by fatiguing the preparation by repeated stimulation, etc.

2. The refractory period set up by a strong second stimulus which falls too early to give a summated contraction may inhibit a third stimulus following soon after the second. Wedensky's observation that a series of strong stimuli may produce inhibition whilst a series of weak stimuli of the same frequency produces a continued tetanus is to be explained by the fact that strong stimulus can excite the nerve at an early stage of recovery before a summated contraction can be produced. The disturbance set up in the nerve will be followed by a refractory period which will cut down the size of a succeeding disturbance. Thus a series of strong stimuli will set up a series of small disturbances none of which will reach the muscle. A weak stimulus has no effect on the nerve until a more advanced stage of recovery has been reached and then the stimulus cannot avoid affecting the muscle as well as the nerve. Thus a series of weak stimuli cannot produce inhibition.

This agrees in all respects with the explanation advanced by Lucas.

3.   An entirely different phenomenon may account for the inhibiting effect of a second stimulus on a third stimulus which is sent in by the same pair of electrodes.   A second stimulus which is not strong enough to excite the nerve may lower the excitability of the tissue immediately under the electrodes and this may render a weak third stimulus ineffective.   The effect does not depend on the setting up of a true refractory period and it is not transmitted down the nerve.   Probably it has little to do with the normal type of Wedensky inhibition.

4.   The size of the propagated disturbance set up in incompletely recovered tissue does not depend on the strength of the stimulus but only on the state of recovery of the tissue in which it is set up.   Thus the all-or-none relation between disturbance and stimulus holds good for refractory as well as for normal tissue.