QUANTITATIVE RESEARCHES ON THE SUMMATION OF INADEQUATE STIMULI IN MUSCLE AND NERVE, WITH OBSERVATIONS ON THE TIME-FACTOR IN ELECTRIC EXCITATION.

By KEITH LUCAS, *Fellow and Lecturer of Trinity College, Cambridge.*

(*From the Physiological Laboratory, Cambridge.*)

In a number of papers published in this *Journal* during the last few years I have investigated in detail the response of certain excitable tissues to electric currents of varying duration. From these researches it appears that not only different tissues examined under like conditions, but also like tissues examined under different conditions of temperature and of surrounding medium, show well-defined differences in their response to such currents. All tissues examined behave alike in one matter; in every case the weakest current which will excite becomes progressively smaller as the duration of passage is increased up to a certain limit, and beyond that limit the same strength of current is required whatever the duration. It is in the duration of current at which this lowest limit of the exciting current is reached that a clear difference is found to exist between unlike tissues examined under like conditions or between like tissues examined under different conditions.

There is no need to reproduce here the detailed observations on this matter which have already been published[1]. It will be enough to recall the broad facts which have been established. It has been shown that the current-duration at which the lowest limit of the exciting current is first reached is shorter in the motor nerve-fibres to the toad's gastrocnemius than in the sartorius muscle-fibres of the same animal, is shorter in certain tissues of the frog than in the corresponding tissues of the toad, is shorter both in muscle and in nerve when these tissues

[1] References to the original observations made by myself and by Lapicque are given in a later part of this paper (cf. pp. 470, *et seq.*).

are warm than when they are cool, and is shorter in the sartorius muscle of the frog when the concentration of calcium salts in the bathing fluid is high than when it is low.

By another method of investigation I have shown a similar range of differences to exist[1]. For the excitation of any tissue the exciting current must increase from zero with a certain minimum rapidity; and this minimum rapidity or minimum current gradient is steeper for the motor nerve-fibres to the gastrocnemius than for the sartorius muscle-fibres in the toad, is steeper for the nerve-fibres to the gastrocnemius in the frog than in the toad, and is steeper for a muscle surrounded by a solution containing a higher concentration of calcium salts.

The parallel variation of these two phenomena as we pass from tissue to tissue or from one condition to another at once suggests that the existence of a limiting current-duration beyond which the current strength required for excitation no longer falls, and the existence of a limiting steepness of current increase below which no excitation will result, are two expressions of a single property characteristic of each excitable tissue. I have elsewhere[2] called attention to this probability, and have suggested that we may regard the property in question as the need for a completion of the process of excitation with a certain rapidity. Lapicque[3] has noted the same coincidence, and has referred the two phenomena to what he calls the chronological coefficient of excitation[4]. But this amounts in either case to nothing more than a generalized restatement of the experimental facts. It tells us nothing of the conditions within the excitable cell which determine the demand for rapidity, and it gives us no intelligible account of the observed variations in that demand.

In the present paper I wish to describe a series of experiments which show a third property of excitable tissues, namely the summation of inadequate stimuli, to follow a parallel series of modifications as we pass from one tissue to another and from one condition to another in the same tissue. The method used in these experiments has been to determine the greatest time interval at which two stimuli, of a strength less than the threshold strength by a known percentage, may follow one another and just succeed in provoking an excitation.

This interval, which I shall call the "summation interval" for

[1] Keith Lucas. This *Journal*, xxxvi. p. 253. 1907, and xxxvii. p. 459. 1908.
[2] *Ibid.* xxxvii. p. 459. 1908. Spec. p. 476.
[3] Lapicque. *C. R. Soc. de Biol.* lxiv. p. 6. 1908.
[4] *Ibid.* p. 589. 1908.

a given percentage drop below the threshold value of current, is found to be shortened by the same conditions and for the same tissues as have already been shown to present a shorter limiting current-duration and a steeper limiting current gradient. The hypothesis, which may obviously be founded on these experimental facts, that the summation interval is an expression of the same fundamental property which determines the other two phenomena, leads us a considerable step forward towards the understanding of that property. For in determining the time interval at which a second inadequate stimulus following a former will just become adequate we are measuring the rate at which the excitatory disturbance produced by the first stimulus subsides[1].

The hypothesis leads therefore to the conception that the rate of subsidence of the excitatory disturbance is the fundamental property of an excitable tissue which presents itself to us under the three different aspects. The discussion of this hypothesis and of the inferences to which it leads will be continued after the experimental facts have been described.

Method. The fact that two stimuli, of such strength that they fail when applied singly to cause excitation in a tissue, will become effective when following one another at a sufficiently short interval of time has been confirmed by the work of many observers on many different excitable tissues. The experiments of Engelmann[2] on the ureter of the rabbit, of Richet[3] on the muscles of the crab, of Sertoli[4] on the retractor penis of the dog, of Basch[5] and of Engelmann[6] on the cardiac muscle of the frog are typical of the many observations which have been accumulated. Recently Steinach[7] has shown that the same phenomenon is encountered in a great number of tissues ranging widely over the animal and vegetable kingdoms. But these observations afford no ground for a real comparison of the ability of different tissues to sum the effects of successive inadequate stimuli, because they do not give us quantitative data as to both the essential dimensions which we need for such comparison, namely the time interval separating the two

[1] See below, p. 473, for further discussion of this point.

[2] Engelmann. *Arch. f. d. ges. Physiol.* III. p. 282. 1870.

[3] Richet. *Physiol. des muscles et des nerfs.* Paris, 1882.

[4] Sertoli. *Arch. Ital. Biol.* III. p. 88. 1883.

[5] Basch. *Stzber. der k. Akad der Wiss. Wien.* LXXIX. abth. III. p. 37. 1879. *Arch. f.* (*Anat. u.*) *Physiol.* p. 283. 1880.

[6] Engelmann. *Arch. f. d. ges. Physiol.* XXIX. p. 453. 1882.

[7] Steinach. *Arch. f. d. ges. Physiol.* CXXV. p. 239, p. 290 and p. 347. 1908.

successive stimuli, and the percentage by which their strength is below the threshold strength for one stimulus occurring alone. Steinach for example gives precisely the time interval separating his stimuli, but tells us the strength of the stimuli only in terms of the distance between the primary and secondary coils of an induction coil for which no calibration curve is published in his paper.

If we are to arrive at a just comparison of different tissues in this matter there are two courses open to us. We can either fix the time interval separating the two stimuli, and determine by what percentage they may be decreased below the threshold and still cause excitation; or we can fix the percentage by which the stimuli are below the threshold, and then determine the greatest time interval at which they cause excitation. But it is absolutely essential that both the factors should be properly measured. In my experiments I have fixed the percentage by which the stimuli are less than the threshold value for one stimulus occurring alone (usually at 5%) and have determined for each tissue and condition examined the greatest time interval by which such stimuli may be separated if they are just to cause excitation. In this way I obtain for each tissue and condition a characteristic "summation interval."

The technique of obtaining stimuli always less than the threshold value by the same percentage presented more difficulty than I had anticipated. The method finally adopted after several trials was the following:

The exciting currents were obtained from two similar induction coils made without iron cores in the primary. Each coil was first set up with a ballistic galvanometer in its secondary circuit, and the distance between primary and secondary coils was adjusted to give a convenient excursion of the galvanometer at break of the primary circuit. A resistance was then introduced into each primary circuit, of such magnitude as to reduce the galvanometer excursion by 10 % or 5 % as might be required. In the course of subsequent experiments the threshold stimulus for the tissue under examination was first found on each coil by adjustment of the distance between primary and secondary coils with the resistances shunted. When currents of the required percentage below the threshold were wanted the resistances were unplugged. This method is very rapid in working, and ensures that the drop of the exciting current shall be the same in all observations.

The primary circuits of the two induction coils contained the knock-down keys of the pendulum which I have described in a previous

paper[1]. The interval between the two induction shocks could therefore be regulated by the degree of separation of the two keys. In the experiments described below it will be seen that the interval separating two stimuli is given to the nearest ·0001 sec. The actual determinations were made to the nearest tenth of a degree of separation of the primary keys. Since a tenth of a degree is approximately equal to ·00008 sec. within the range of swing of the pendulum used in these experiments, the accuracy obtained is probably represented nearly enough when the results are given to the nearest ·0001 sec.

The determination of the threshold for each tissue was carried to the nearest 0·5 millimetre coil distance on each coil. Any attempt at closer setting than this leads to longer delay in the making of observations, and does not increase the accuracy of the results. In every case the threshold was determined both before and after the measurement of the summation interval. The following is a typical observation.

Sartorius of frog. In NaCl 0·6 %, $CaCl_2$ 0·1 %. Cathode 3 mm. from pelvic end. Temperature 12·8° C. 1¼ hours after excision.

(i) With resistances in primary plugged.
Threshold for coil A, 201·5 mm.
,, ,, B, 178 ,,

(ii) After currents from A and B have been reduced 5 % below threshold by unplugging resistances.

A followed by B at	·0019 sec.	Contraction.
,, ,,	·0023 ,,	None.
,, ,,	·0021 ,,	None.
,, ,,	·0020 ,,	None.
,, ,,	·0019 ,,	Contraction.

(iii) With resistances in primary plugged.
Threshold for coil A, 201·5 mm.
,, ,, B, 178 ,,

From these observations I take the value of the summation interval to be ·0019 sec. Of course it would happen from time to time that the threshold would alter a little during the determination of the summation time. In cases of this sort I have obtained two values of the summation interval, one of which must be too large, since the tissue became more excitable while the determination was being made, while the other was too small since the excitability became less. For example, in one case the first threshold found for B was 167·5 mm.; a determination of the summation interval gave ·0009 sec.; the threshold for B had

[1] Keith Lucas. This *Journal*, xxxvii. p. 461, Fig. 1, *H* and *J*. 1908.

in the interval risen to 167 mm.; a second determination of the summation interval gave ·0010 sec., and after this the threshold for B had fallen again to 167·5 mm. In this case ·0009 sec. is too small, and ·0010 is too large.

The tissues subjected to experiment were placed, unless the contrary is stated in any case, in my "fluid electrodes," the particular type used being the modification described by Mines[1]. The temperature was read from a thermometer placed inside the electrodes close to the tissue. When necessary for the maintenance or alteration of temperature a water-bath was used, surrounding the whole electrodes.

Determination of summation interval.

1. *The sartorius muscle of the frog.* The values given here are obtained from muscles taken from four different animals. The muscles were in a solution containing 0·6 % NaCl and 0·1 % $CaCl_2$. They had been in this solution for times not less than one hour and not more than two. At such times they would have come very nearly, as some experiments to be described later will show, into equilibrium with the immersing fluid. These experiments will serve for comparison with the motor nerve-fibres to the gastrocnemius and with the ventricle of the frog, in which observations were made under like conditions. The muscles were always excited in the nerve-free pelvic end.

Exp.	Bathing fluid	Time in fluid	Temperature	Percentage below threshold	Summation interval
1	NaCl 0·6 % $CaCl_2$ 0·1	1¾ hrs.	13·0° C.	5	·0011 sec.
2	,,	1¼	12·8	5	·0019
3	,,	1½	13·5	5	·0016
4	,,	1	13·2	10	·0005

There is a fair agreement between the summation intervals found with the stimuli 5 % below the threshold. When this drop is increased to 10 % the summation interval is, as might be expected, very much shortened.

2. *The motor nerve-fibres to the gastrocnemius of the frog.* In these experiments the contraction of the gastrocnemius muscle was used as an index of the excitation of the nerve-fibres in the sciatic nerve. The experiments were made on three nerves taken from different animals.

[1] Mines. This *Journal*, xxxvii. p. 428, Fig. 12. 1908.

Exp.	Bathing fluid	Time in fluid	Temperature	Percentage below threshold	Summation interval
5	NaCl 0·6 % $CaCl_2$ 0·1	1¼ hrs.	12·8° C.	5	·0005 sec.
6	,,	2½	13·7	5	·0004
7	,,	2½	12·3	5	·0005

It appears from these results that the summation interval for the sartorius muscle is about three times as long as that for the nerve-fibres to the gastrocnemius under like conditions.

3. *Ventricular muscle of the frog.* The Stannius ventricle was used. Excitation was by platinum electrodes on the base of the ventricle, since the coreless coils did not give a strong enough current to excite with the fluid electrodes. Owing to the greater difficulty of getting steady results with the heart, and to the relatively great length of the summation interval in this muscle, the determination was made to the nearest 1° of separation of the keys (*i.e.* to the nearest ·0008 sec.), and the times are accordingly given only to the nearest 0·001 sec. This approximation is sufficient where the difference is so large as it is between the summation intervals for skeletal and for cardiac muscle. With the currents 5 % below the threshold the summation interval for the ventricle is five times as long as that for the sartorius. With the currents 10 % below the threshold the corresponding ratio is 6 to 1. The experiments given below were made with different hearts.

Exp.	Bathing fluid	Time in fluid	Temperature	Percentage below threshold	Summation interval
8	NaCl 0·6 % $CaCl_2$ 0·1	1 hr.	13·5° C.	5	·008 sec.
9	,,	1½ hrs.	14·5	10	·003

4. *The effect of calcium salts.* Experiments were made upon this question by two methods. One method was to determine the summation interval in a fluid rich in calcium salts, to substitute a fluid very poor in calcium salts, and after half an hour to make a fresh determination, then to return to the original solution in order to see whether the change observed was really due to the removal of calcium. This was the method used in Exps. 4 and 10 given below. As may be seen from these experiments it was not possible by replacing the fluid rich in calcium to return quite completely to the conditions found before the calcium was removed. But in both experiments the summation times in the fluids rich in calcium are considerably the shorter both before and after the use of the fluid poor in calcium.

Sartorius of frog excited in non-neural region.

Exp.	Percentage below threshold	Temperature	Bathing fluid	Summation interval
10	5	13° C.	NaCl 0·6, $CaCl_2$ 0·1	·0008 sec.
		13·3	NaCl 0·7, $CaCl_2$ 0·01	·0018
		13·3	NaCl 0·6, $CaCl_2$ 0·1	·0010
4	10	13·2	NaCl 0·6, $CaCl_2$ 0·1	·0005
		13·6	NaCl 0·7, $CaCl_2$ 0·01	·0009
		13·6	NaCl 0·6, $CaCl_2$ 0·1	·0006

The other method was to excise the tissue and place it in a fluid rich in calcium salts, and then to observe the progressive change in the summation interval as equilibrium was reached. This was done both for muscles and for nerves. All the experiments show the summation interval becoming shorter after immersion in the fluid containing a high concentration of calcium salts. The change appears from Exps. 1, 3 and 6 to be rapid at first, and then to become slow. Exp. 7 shows that the change may reduce the summation interval to a very small value if the time allowed is very long.

Sartorius muscle of frog excited in non-neural region. Stimuli 5 % below threshold. In NaCl 0·6, $CaCl_2$ 0·1.

Exp.	Temperature	Time of immersion	Summation interval
1	12° C.	20 mins.	·0016 sec.
	13	1¾ hrs.	·0011
	13·2	4 ,,	·0011
	12	6½ ,,	·0010
3	12·8	¼ hr.	·0019
	12·7	½ ,,	·0016
	13·5	1½ hrs.	·0014

Nerve-fibres to gastrocnemius of frog. Stimuli 5 % below threshold. In NaCl 0·6, $CaCl_2$ 0·1.

6	13·0° C.	20 mins.	·0009 sec.
	13·7	2½ hrs.	·0004
	12·6	5½ ,,	·0004
7	12·3	2½ ,,	·0005
	13·1	18 ,,	·0002

Exp. 6 shows that the summation interval for the nerve-fibres examined very soon after removal from the body may be practically as long as that for the sartorius muscle examined after it has been for a

long time in a solution containing a high percentage of calcium. Compare for example the first value given for the nerve in Exp. 6 with the value found for muscle, after 6½ hours' immersion in Exp. 1. It is for this reason that I have been careful, in comparing the summation intervals for muscle and nerve in an earlier part of this paper, to choose values obtained from the two tissues after they have been in the solution over a range of times during which the summation interval is found not to change much, namely between 1 hour and 2½ hours.

5. *The effect of temperature change.* Rise of temperature decreases the summation interval. The change is not a large one, not more, it appears, than about 30 % for a change of temperature from 8° to 18° C. The following experimental results were obtained from the sartorius muscle excited in the non-neural region.

In Exps. 12 and 13 the muscles were excited in Ringer's fluid of the composition NaCl 0·63 %, $CaCl_2$ 0·045 %, NaCl 0·025 %, and the temperature change was effected by drawing fluid of the required temperature through the electrodes. In Exp. 11 the fluid was NaCl 0·6 %, $CaCl_2$ 0·1 %; and the temperature change was made by means of a water-bath surrounding the electrodes. The three experiments are from muscles taken from different animals.

Sartorius muscle of frog, excited in non-neural region.

Exp.	Temperature	Summation interval with stimuli 5 % below threshold		Sum. int. at $t°$ / Sum. int. at $t°+10$
11	8·4° C.	·0010 sec.	...	1·25
	18·2	·0008		
12	8·7	·0012		
	18·3	·0009	...	1·33
	8·8	·0012		
13	9·2	·0017		
	18·9	·0013	...	1·31
	8·5	·0017	...	1·36
	18·7	·0012	...	1·33
	9·0	·0015		

It is noteworthy that these observations show a temperature quotient which is much smaller than that which I have found from the measurement in various ways of the velocities concerned in the conducted disturbance in muscles and nerves. In such cases I have found values ranging from 1·5 to 1·9, the most usual being about 1·7.

THE PARALLEL VARIATION OF THE SUMMATION INTERVAL WITH THE CURRENT-DURATION AT WHICH THE LIMINAL CURRENT STRENGTH REACHES ITS MINIMUM.

The experiments described in the last section show that whenever we encounter a shorter limiting current-duration, whether on passing from one tissue to another under like conditions, or from one condition to another in the same tissue, we find also a shorter summation interval. It is known that the limiting current-duration is shorter for the motor nerve-fibres to the gastrocnemius muscle than for the muscle-fibres of the sartorius in the same animal. This fact was shown directly for the case of the toad by my own experiments[1]. For the case of the frog it rests on the following evidence. Lapicque[2] has found the limiting duration to be shorter for the motor nerve-fibres to the gastrocnemius in the frog than in the toad; and I have shown[3] that the limiting duration is longer for the sartorius muscle-fibre of the frog than for the motor nerve-fibres to the gastrocnemius of the toad. It appears from these observations that under like conditions the durations are in the frog about 0·003 sec. for the nerve-fibre to the gastrocnemius, and 0·02 sec. for the muscle-fibre of the sartorius. We have seen above that under like conditions, and with stimuli in each case 5 % below the threshold, the motor nerve-fibres to the gastrocnemius give the summation interval of 0·0005 sec., the muscle-fibres of the sartorius 0·0015 sec.

We find a similar agreement when we compare the sartorius muscle-fibre with the ventricular muscle of the frog in the same respects. I have not previously published any experiments on the relation of current-duration to liminal current-strength in the ventricular muscle, so I give here the results of two experiments which are typical of seven made under similar conditions of temperature and bathing fluid. The Stannius heart was used, excitation being by the usual fluid electrodes containing a Ringer's fluid of the same composition as that used in my experiments on the sartorius of the frog. The method used for obtaining currents of variable duration was identical with that described in my former paper, with the exception that the pendulum[4] described there

[1] Keith Lucas. This *Journal*, xxxvi. p. 114. 1907.

[2] Lapicque. *C. R. Acad. des Sciences*, cxl. p. 801. 1905. *C. R. Soc. de Biol.* lxiv. p. 6. 1908.

[3] *Loc. cit.* and This *Journal*, xxxvii. p. 470. 1908.

[4] Cf. This *Journal*, xxxvii. p. 461, Fig. 1. 1908.

was replaced, in order that longer durations might be available, by an arm driven round on a vertical axis by means of the governed clockwork drive of a gramophone. The arm made a complete revolution in ten seconds, and the interval between the opening of the two keys was adjustable by means of a circle divided to 1000 parts, so that the duration of the current could be adjusted to the nearest 0·01 sec. The observations were always made in duplicate, first with successively increasing, then with decreasing durations, and a mean was taken. I give one set of observations in full.

Exp. 14. Ventricle of frog in Stannius standstill. 1½ hours after placing in Ringer's fluid. Temp. = 13° C.

	Duration of current Seconds	Liminal current-strength Arbitrary units
	0·3	77·5
	0·6	45
	1·2	27·5
	2·4	17
	3·6	15
	5·0	15
	3·6	15
	2·4	17
	1·2	25
	0·6	42·5
	0·3	77·5
Mean values:		
	0·3	77·5
	0·6	43·7
	1·2	26·2
	2·4	17
	3·6	15
	5·0	15

This experiment shows the limiting current-duration to be about 3 sec. Exp. 15 shows the corresponding time as about 2 sec.

Exp. 15. Ventricle of frog in Stannius standstill. ¾ hour after placing in Ringer's fluid. Temp. = 12·5° C.

Mean values.

Duration of current Seconds	Liminal current-strength Arbitrary units
0·3	52·5
0·6	45
1·2	38·2
2·4	36
3·6	36

These times are very much longer than those found for the sartorius muscle-fibres of the frog. And accordingly on referring back to the

experiments on summation interval we see that under like conditions the summation interval for the sartorius muscle-fibre is 0·0015 sec., that for the ventricle 0·008.

The shortening of the limiting current-duration as the effect of calcium in the bathing fluid has been described by Mines. For example, one of his experiments[1] gives the limiting duration in the frog's sartorius as about 0·05 sec. in NaCl 0·6 and $CaCl_2$ 0·1%, while in NaCl 0·7 % it is greater than 0·12 sec. In accordance with this we find (in Exps. 4 and 10 described above) the summation interval for the sartorius muscle of the frog made practically twice as long when a solution containing only 0·01 % $CaCl_2$ is substituted for one containing the high percentage 0·1 % $CaCl_2$.

I have shown that when a frog's sartorius is excised and placed in a solution containing a high percentage of calcium the limiting current-duration becomes progressively shorter as equilibrium is reached, the change being more rapid at short times after immersion[2]. Exps. 1 and 3 show that a corresponding shortening of the summation interval goes on in the same tissue under like conditions.

Finally it may be seen from experiments made by Mines and myself that at high temperatures the limiting current-duration is shorter than at low. Compare for example the figure given for the relation of current-strength to current-duration at 17·6° C. and 9·0° C. in the sartorius muscle[3]. The current-strength has practically become steady at 0·02 sec. with the temperature 17·6° C., whereas at 9·0° C. there is still a well-marked fall going on. The same fact has been noted by Lapicque[4]. Again we find a parallel change in the summation interval. From Exps. 11, 12 and 13 given above it appears that the interval is prolonged in the ratio 1 to 1·3 by a fall of temperature from 18° C. to 8° C.

All these changes then which we know to produce an alteration in the limiting current-duration alter the summation interval in the same direction. I would lay particular stress upon the case of the high concentration of calcium salts and on the progressive changes observed after immersion in Ringer's fluid, since other time relations, such for example as the length of the refractory period, do not undergo a parallel change.

[1] Mines. This *Journal*, xxxvii. p. 439. 1908. See also an experiment by Mines in a paper of mine. This *Journal*, xxxvii. p. 472. 1908.

[2] Keith Lucas. This *Journal*, xxxvii. p. 470, Exp. 8 and Fig. 8. 1908.

[3] Keith Lucas and Mines. *Ibid.* xxxvi. p. 344, Fig. 4. 1907.

[4] Lapicque. *Journal de Physiol.* p. 631, July 1907, and *C. R. Soc. de Biol.* lxiv. p. 6. 1908.

Conclusion.

Having described the experimental facts which lead to the hypothesis that the summation interval is an expression of the same fundamental property which determines the limiting current-duration, I will examine this hypothesis in greater detail.

In an earlier part of this paper I stated that the summation interval may be regarded as a measure of the rate at which the excitatory disturbance subsides. This statement needs both explanation and justification. By excitatory disturbance I mean that local change which is directly produced by the passage of the exciting current, the change which modern theories of excitation tend to recognise as the concentration of ions at suitable surfaces within the excitable cell. The statement amounts therefore to saying that the phenomena of summation of stimuli are due to the fact that the said disturbance does not subside instantaneously when a current ceases to pass, and, if partially persisting, facilitates excitation by a second current. That something persists and makes matters easier for the second current is of course the experimental fact. The assumption which my statement contains is that the disturbance which persists and favours the second current is that identical disturbance immediately produced by the first current, the excitatory disturbance. The justification which I offer for such an assumption is that this is the simplest account which can be given of the phenomenon. There is no conducted disturbance or other recognisable change set up by an "inadequate" stimulus, so that it would be superfluous to postulate the persistence of any change other than that local change which we recognise as the immediate effect of the current. But it must be borne in mind that this assumption is made.

If we admit that a longer summation interval means a slower subsidence of the excitatory change, then on our hypothesis a tissue in which the lowest limit of the exciting current is reached at a longer current-duration is also one in which the excitatory change subsides more slowly. And the slow subsidence of the excitatory disturbance is the condition which determines the longer limiting current-duration.

This conclusion suggests at once many possible inferences with regard to the properties of different excitable tissues and the effects of various changes of conditions. In particular I am tempted to discuss the difference between those tissues which normally undergo spontaneous

excitation and those which are quiescent until roused by a definite stimulus reaching them from outside, or to attempt an analysis of the changes of excitability brought about by such conditions as temperature. But I hesitate to carry the discussion any further at present for the following reasons.

In terms of recent theories of electric excitation the excitatory disturbance which is the subject of discussion in this paper means a change of concentration of ions at suitable surfaces within the excitable cell. And the "rate of subsidence" of the excitatory disturbance will be the rate of diffusion of the ions, by which the concentration changes effected by the exciting current are opposed. It would seem therefore that we have two reasons for postponing discussion. In the first place the hypothesis put forward in this paper on experimental grounds ought to be examined in the light of that theory. And in the second place, if the two should prove conformable, then we ought to be able to replace the vague physiological expression "the rate of subsidence of the excitatory disturbance" by a physical constant; so that the comparison of different tissues and the analysis of the effects of temperature change should become quantitative instead of qualitative, a question of physics instead of physiology.

The cogency of these reasons has recently become even greater. For since the experiments described in this paper were completed, Mr A. V. Hill of Trinity College has taken up the mathematical investigation of the theory of electric excitation with a view to obtaining a modification of Nernst's theory which shall give a more complete conformity with the experimental facts than was obtained by the theory in the original form which Nernst put forward. This investigation, which will shortly be published in this *Journal*, realises the hopes expressed in the last paragraph. I shall accordingly return to this discussion in connexion with the mathematical investigation of the theory of excitation.

Summary.

In several papers published within the last four years I have shown by experiments made with exciting currents of variable duration and of variable rate of increase that there is for each excitable tissue a characteristic time-factor involved in excitation. This time-factor determines the duration at which an exciting current reaches its smallest value, and the smallest rate of increase at which a current will

excite. The time-factor is for example smaller in the motor nerve-fibres to the gastrocnemius than in the muscle fibres of the sartorius of the toad.

This characteristic time-factor has been shown by my experiments to be variable by change of such conditions as temperature and the inorganic salts contained in the fluid which bathes a tissue.

Experiments described in this paper afford a measure in various tissues and under various conditions of the maximum time interval at which two stimuli 5 % below the threshold strength will sum their effects and cause excitation. This summation interval is found to vary, as we pass from tissue to tissue and from one condition to another, always in the same direction as the time-factor mentioned above.

On these experimental facts is based the hypothesis that the time-factor of excitation and the summation interval are determined by a common function, namely the rate at which the excitatory disturbance subsides. In terms of recent theories of the excitatory disturbance this would mean the rate at which the concentration of ions brought about by the exciting current is dissipated by opposed diffusion.

The expenses of this Research were defrayed in part by a grant assigned to me by the Government Grant Committee of the Royal Society.