AN ANALYSIS OF CHANGES AND DIFFERENCES IN THE EXCITATORY PROCESS OF NERVES AND MUSCLES BASED ON THE PHYSICAL THEORY OF EXCITATION. BY KEITH LUCAS, *Fellow and Lecturer of Trinity College, Cambridge.*

THE researches on the summation of stimuli which I published in a recent number of this *Journal*[1] led me to the conclusion that the main differences observed between the excitatory processes of different tissues, and the changes of excitability produced by various conditions, ought to be expressible, in terms of Nernst's theory of electric excitation, by simple physical constants. I withheld the discussion of this point until a modification of Nernst's theory should be available by which the phenomena in question should be capable of quantitative treatment. The mathematical investigation of Nernst's theory carried out by Mr Hill is published in the present number of this *Journal*, and I am accordingly able to return to the question.

In order that the physical constants to which I shall refer may be fully understood, it is necessary that I should first resume briefly the steps which have led to the recent development of the theory of electric excitation.

The word excitation has by somewhat loose usage become applicable to all or any of the successive processes which constitute the connecting links between the application of a stimulus to a nerve or muscle and the appropriate final response. The application of the stimulus is not infrequently spoken of as excitation. The immediate local effect of the stimulus is called by the same name. The disturbance which is conducted away from the seat of application of the stimulus is often called the wave of excitation. A muscle is even said to be excited when it contracts in consequence of a stimulus applied to its motor nerve. It

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[1] Keith Lucas, This *Journal*, xxxix. p. 461. 1910.

seems therefore that we are bound to define precisely at the outset what is meant in this place by a theory of electric excitation.

When an electric current is passed through part of a muscle fibre or nerve fibre there must be produced in the fibre a local physical alteration which is the immediate consequence of the current. This physical alteration provides the necessary condition for starting a disturbance which is then propagated away from the seat of application of the current. A theory of electric excitation means, as here used, a theory of the physical nature of that local alteration within the fibre which constitutes the necessary condition for starting the propagated disturbance. It is not a theory of the nature of the propagated disturbance, though no doubt it may ultimately lead to such a theory. Still less is it a theory of the more remote disturbance which constitutes contraction.

In attempting to trace the steps which have led to the present development of the physical theory of electric excitation I pass over the whole of that important early period during which the pioneer researches of such men as du Bois Reymond, Fick, Hoorweg, Weiss, and Lapicque laid the empirical foundation of the theory. These investigators gave us that knowledge of the precise quantitative relations between such factors of an exciting current as its duration and its liminal strength to which the theory has to look for its confirmation. But the immediate history of the theory must begin with the work of Nernst. In 1899 Nernst[1] put forward an hypothesis of the physical change produced in an excitable cell by the passage of the exciting current. From a mathematical treatment of this hypothesis he subsequently deduced the probable relation between those variable factors of the exciting current which had been the subject of experiment by the earlier workers. In the agreement of his calculated relations with those already observed experimentally he sought for confirmation of his hypothesis.

To render intelligible the subsequent stages of the enquiry it is necessary that I should recall the nature of Nernst's hypothesis, and the considerations by which he was led to put it forward. Nernst's attention had been attracted by the fact that alternating currents of extremely high frequency may be passed through the human body without causing any excitation whatever, as for example in the familiar case of currents from the Tesla coil. The old idea that the absence of stimulation was due to the current flowing only through the surface layer of the body he showed to be untenable. But he saw that an explanation would be afforded if an exciting current could be shown to

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[1] Nernst. *Gött. Nachr. Mathem. physik. Klasse.* p. 104. 1899.

produce its effect by concentrating the ions by which it was carried, at membranes (impermeable to the ions) contained within the excitable cells. For, to put the matter in a general way, if the current used were alternating in direction with extreme frequency the concentration of ions at any membrane would never reach any considerable value, since the change of direction of the current would carry the ions away from the membrane again very soon after they had begun to accumulate there.

Starting from general considerations of this sort Nernst put forward his hypothesis, which may be put in words somewhat as follows. Suppose that the excitable cell is represented by a cylindrical space closed at its two ends by the membranes *A* and *B* (Fig. 1.) and filled with a solution of electrolytes. Now if a current is passed from *B* to *A* this means that the positively charged ions move towards *A*, the negatively charged towards *B*. If the membranes *A* and *B* are impermeable to certain of the ions, such of those ions as are positively charged will accumulate in the neighbourhood of *A*, the negatively charged in the neighbourhood of *B*. But this accumulation of the ions near the membranes will be opposed by the tendency of the ions to equalize their concentration in all parts of the solution by diffusion. Now let it be supposed that the necessary condition for the occurrence of excitation is that in the immediate neighbourhood of one or other of the membranes the concentration of ions shall reach a certain definite value. It then becomes possible to calculate under what conditions of strength, of duration, of rate of alternation, and so forth an electric current will just produce excitation, since the conditions under which the required concentration of ions will just be reached can be calculated.

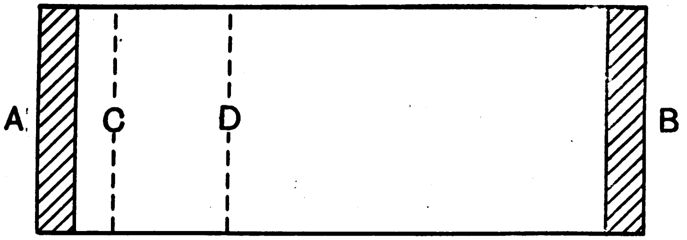

Fig. 1. To illustrate the physical theory of excitation.

At first Nernst confined himself to showing that for the case of alternating currents[1] his reasoning enabled him to predict the observed

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[1] Nernst, *loc. cit.* and Nernst and Barratt, *Zeitschr. f. Electrochem.* xxxv. p. 666. 1904.

relation between the periodicity of alternation and the strength of current which would just cause excitation. In a later paper[1] he extended the mathematical reasoning to the case of excitation by currents persisting at constant values for variable durations. He showed from the published experiments of Weiss and of Lapicque that his theory enabled him to predict with tolerable precision the relation between the duration and strength of currents which would just excite. It should be noted at this point that Nernst in developing the mathematical treatment assumed certain simplifications of conditions which have had a very important bearing on the subsequent history of the theory. In particular he assumed that the two membranes (A and B, Fig. 1) at which the concentration of ions of opposite sign goes on may be regarded as infinitely distant one from the other. The importance of this assumption will appear presently. Also he stated expressly that the formulae which he gave were applicable only within certain limits of current-duration. For currents of longer duration certain disturbing conditions were set up, of which he gave a qualitative discussion, but offered no quantitative treatment in the deduction of his formulae.

It chanced that in the few years preceding the publication of Nernst's paper a series of investigations carried on independently by Lapicque and myself had brought into particular prominence just those phenomena, observable with exciting currents of comparatively long duration, which the formulae of Nernst left out. We had shown that the current required to excite any tissue becomes smaller, as the duration of its passage becomes longer, only up to a certain limit of duration. For all longer durations the strength of current required for excitation is the same. We had found too that one of the most marked characteristics by which different excitable tissues were distinguished one from another was this value of the duration at which the exciting current reached its constant value[2]. All this lay outside the range of Nernst's formulae, according to which the exciting current would go on decreasing for all increases of duration.

Also Lapicque and I had independently made and published experiments showing another phenomenon of excitation to vary in a characteristic manner from one tissue to another, namely the inability of currents increasing directly as the time to excite if increasing with

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[1] Nernst, *Arch, f. d. ges. Physiol.* CXXII. p. 275. 1908.

[2] Lapicque, *C. R. Acad. Sc.* CXXXVI. p. 1147. 1903. *C. R. Soc. de Biol.* LV. p. 445 and p. 753. 1903. *C. R. Acad. Sc.* CXL. p. 801, 1905. *C. R. Soc. Biol.* LVII. p. 501. 1905. Keith Lucas. This *Journal*, XXXV. p. 310. 1907. *Ibid.* XXXVI. p. 113. 1907.

less than a certain minimum rapidity[1]. This again lay outside the formulae of Nernst, who had, from a consideration of the experiments made by v. Kries[2] upon this subject, suggested a possible explanation of the general fact of the failure of slowly increasing currents to excite, but had not embodied the consequences in his mathematical treatment of the whole problem.

Clearly Nernst's theory did not supply a complete solution of the problem, and the limitations which he had expressly imposed upon his presentation of it rendered it inapplicable to a series of phenomena the interest of which from a physiological standpoint was considerable. But no writer upon the subject appeared to doubt its ultimate validity. Lapicque[3] for example had for some time past been engaged upon the experimental realization of a physical model such as that contemplated by Nernst in this theory. The problem was therefore that of amending or extending the theory of Nernst so that it should take account quantitatively of the phenomena of excitation by constant currents of long duration and by currents increasing slowly. In 1908 I suggested[4] that the amendment which Nernst's theory required could probably be made if to his assumption that the concentration of ions must reach a certain value there were added the further requirement that the said value should be reached within a certain time. But, as I pointed out[5], there was no evidence yet available as to which of the two possible causes determined the need for this rapidity of concentration, namely whether on the one hand the requisite concentration would never be reached if not reached rapidly, or whether on the other hand it might indeed be reached slowly, but would then fail to initiate the propagated disturbance.

Lapicque has since endeavoured in a series of researches to arrive at a modification of Nernst's theory which shall take account quantitatively of the two phenomena to which I have referred above as being left out of account in the incomplete form which Nernst first gave to his calculations. Lapicque's proposals belong to that category which supposes that if the concentration is not brought about with a certain rapidity it will never reach the requisite value. The first suggestion which he made[6] was that it is not a certain absolute value of the con-

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[1] Keith Lucas. This *Journal*, XXXVI. p. 253. 1907. Lapicque, *C. R. Soc. de Biol.* LXIV. p. 6. 1908.

[2] V. Kries, *Arch. f. Physiol.* p. 337. 1884.

[3] Lapicque, *Journal de Physiol.* IX. p. 635. 1907. *C. R. Soc de Biol.* LXIII. p. 37. 1907.

[4] Keith Lucas, This *Journal*, XXXVII. p. 477. 1908.

[5] *Ibid.* p. 478.

[6] Lapicque, *Journal de Physiol.* X. p. 601, spec. p. 612. 1908.

centration in the immediate neighbourhood of the membrane, but a certain difference between the concentrations at two points situated at different distances from the membrane, which is the necessary condition of excitation. For example, in Fig. 1, the requirement might be a certain difference between the concentration of ions at C, and that at D. The supposition enabled him to account for the fact that the strength of current required to excite does not decrease when the duration is increased beyond a certain value, but gave no explanation of the fact that slowly increasing currents do not excite. Accordingly he modified the hypothesis[1], supposing this time that the requirement was a certain ratio instead of a certain difference between the concentrations at two points.

This brings us to the present stage of the enquiry. Lapicque has been unable to obtain a complete mathematical treatment of his new hypothesis, but has with remarkable ingenuity devised a hydrodynamical model[2] by which he is able to realise experimentally and visually (representing the movement of the ions by the flow of water) the conditions which Nernst's equations impose. Both from the use of this model, and from a graphic solution of some of the problems for which the mathematical investigation is incomplete, Lapicque concludes that his hypothesis affords a complete account of all the phenomena, including that of the inability of slowly-increasing currents to excite.

This hypothesis of Lapicque was not satisfactory for the purpose which I had in view (as expressed in my recent paper on the summation of inadequate stimuli)[3] because it had not been worked out mathematically, and so gave no simple means of calculation of the constants concerned.

A more complete mathematical investigation of Nernst's theory has recently been made by Hill, and the results of his work are contained in a paper published in this *Journal*. In order to justify my use in this paper of a certain formula derived from his mathematical treatment I am obliged to trace the main steps which his argument has followed. It will be remembered that Nernst in his original treatment of his theory made the assumption that the two membranes at which ions of opposite sign are accumulated are infinitely distant one from another. Hill has regarded this assumption as inadmissible, and has therefore developed the reasoning afresh, including in his equations a constant (a) which represents the distance between the membranes. The necessity of this step will I think be obvious on a brief consideration. I have referred

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[1] Lapicque, *Journal de Physiol.* XI. p. 1009, spec. p. 1011. 1909.

[2] *Ibid.* p. 1017 and figs. 7 and 8.

[3] Keith Lucas, This *Journal*, XXXIX. p. 474. 1910.

above to the fact that the concentration of ions due to the passage of current is constantly being dissipated by opposed diffusion. Now the rate of this diffusion depends (ceteris paribus) upon the gradient of concentration along the solution lying between the membranes. For a given concentration at one membrane this gradient will depend on the length of the space within which the concentration has to change from its increased value at one membrane to its reduced value at the other membrane. If the membranes are brought closer together the concentration will have to change by the same amount over a smaller length of solution, and so the gradient of concentration will be steeper. Accordingly the rate of dissipation of the concentration differences will be greater.

The result of the introduction of the distance separating the membranes into the reasoning is, as Hill shows by calculating the results of experiments made by many observers, that the original hypothesis of Nernst (that the requirement of excitation is simply a certain value of the concentration at one membrane) gives a complete quantitative account of the phenomena of excitation by constant currents of variable duration. The fact of the fall of current-strength to a finite value at a certain duration is brought out in the most satisfactory manner.

Hill next examines Lapicque's most recent modification of Nernst's theory, namely that which supposes the requirement for excitation to be a certain ratio between the concentrations at two points differently distant from the membrane. This leads, for excitation by constant currents, to an equation which again satisfies completely the known experimental facts, provided that the distance between the membranes is taken into account. In fact the equations for Nernst's original hypothesis and Lapicque's modification prove to be practically identical.

It appears then that we have reached a formula which gives satisfactory agreement with the experimentally observed relation between the duration and least strength of an exciting current, which moreover neither necessitates nor excludes the more complex assumptions which Lapicque has substituted for that originally made by Nernst. But what of the inefficacy of slowly increasing currents? It is clearly useless to adopt a formula until it is shown to conform with this fundamental fact of excitation.

Hill finds that Nernst's original theory, even when the distance between the membranes is taken into account, affords no explanation of the inefficacy of slowly increasing currents. Moreover Lapicque's modification proves also to fail in this respect.

We are left with a formula which accounts for the phenomena of excitation by constant currents, but does not show even qualitatively the inefficacy of slowly increasing currents. It should be noted that Lapicque's attempts to remove this difficulty have belonged to the category which assumes that excitation fails because with slowly increasing currents the requisite concentration of ions (or ratio of concentrations or whatever the precise requirement may be) is never obtained. Hill now has recourse to the other alternative and supposes that the usual concentration is indeed obtained, but fails owing to its slow increase to set the propagated disturbance in motion. In taking this step he is not content with the mere unfounded supposition that such would be the case; he goes further than this, and shows that it would necessarily follow if the propagated disturbance were initiated by a certain rate of breakdown of a compound contained within the excitable cell. If there is present in the contents of the cell a body which is in combination with the ions in question, this compound will be in equilibrium as long as the amounts of the body and of the ions remain constant, but will break down when the concentration of the ions is changed. The rate of this breakdown will according to the laws of mass action be proportional to the amount of the substance present at any moment and to the excess (or deficiency) of the concentration of the ions over their normal concentration.

The mathematical consideration of this case shows that it leads to the same formula relating the strength and duration of constant currents as that previously reached. In addition it affords a complete account of the inability of slowly increasing currents to excite, and in particular of the phenomena of the "minimal current gradient" which I have described[1]. I do not propose at present to discuss the validity of this addition which Hill makes to Nernst's theory, or to enter upon any detailed account of the way in which it deals with various phenomena of excitation. My reason for mentioning this part of Hill's work is to point out that while explaining the inefficacy of slowly increasing currents it shows the phenomena by which such currents are rendered ineffective to be considerable only at the very long durations which such currents involve, and to be practically negligible in a consideration of the relatively short currents[2] used for determining in the ordinary way the relation of current-strength to current-duration. In fact this addi-

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[1] Keith Lucas. This *Journal*, xxxvi. p. 253. 1907.

[2] It appears from my experiments (This *Journal*, xxxvii. p. 471, Figs. 7 and 8. 1908) that under given conditions a current increasing along the minimal gradient will excite after a time equal to about six times the duration of constant current at which the lowest value of current strength is reached.

tion to the theory makes no important difference in the formula relating the duration of a current to its least strength.

This fact, taken in conjunction with the agreement between the formula and the observed relations of current-strength to current-duration, appears to me to indicate that we are probably on the right track when we look for the explanation of the inefficacy of slowly increasing currents in some phenomenon which interferes very little with the relation of current-strength to current-duration at the shorter times. And I conclude that it is justifiable to accept Hill's formula as giving a sufficiently complete account of the phenomena of excitation by constant currents, even though we may not be satisfied that his hypothesis as to the inefficacy of slowly increasing currents is precisely that which will ultimately be adopted.

Accordingly I shall proceed to the analysis of certain changes and differences of excitability, making use of Hill's formula. The precise form which I shall adopt is that which is deduced from Nernst's original hypothesis. If Lapicque's modification were used there would be an alteration in the meaning of some of the constants, but the form of the equation would remain the same, and the inferences which I shall draw would still hold. I choose Nernst's original hypothesis because it is the simpler. There is no point in accepting the additional complexity of Lapicque's, unless it can be shown to account for any additional phenomena.

THE ANALYSIS OF DIFFERENCES IN THE EXCITATORY PROCESS OBSERVED IN DIFFERENT EXCITABLE TISSUES AND UNDER DIFFERENT CONDITIONS.

Nearly all my comparative experiments on the excitatory process have been carried out by an examination of the relation between the duration of an exciting current and its liminal strength. So I shall turn at once to this relation, and consider in the light of Hill's formula the various factors by which it is conditioned.

The formula found for the relation is in its simplest form

$$i=\frac{\lambda}{1-\mu\theta^t}$$

where

i is the smallest current which will excite,

t is the duration of the current, and

λ, μ and θ are constants of the following significance:—

$$\lambda = \frac{C\frac{k}{\nu}}{\frac{a}{2} - b}$$

$$\mu = \frac{4a \cos . \frac{\pi b}{a}}{\pi^2 \left(\frac{a}{2} - b\right)}$$

$$\theta = e^{-k\frac{\pi^2}{a^2}}.$$

And in these:—

a is the distance between the membranes.

b is the distance (from the membrane at which the ions in question are being concentrated) at which the concentration changes are being considered.

k is the diffusion constant of the ion.

ν is the number of ions by which a given quantity of electricity is carried.

C is a constant expressing what may be called in general terms the ease with which the propagated disturbance is set up. In Hill's treatment of the question this constant is defined precisely, and has reference to the rate at which his compound breaks down. But quite apart from his particular hypothesis it is clear that the current required to excite may be altered by a change in the value of the concentration of ions required for the initiation of the propagated disturbance. There is in fact what might be called an "excitability" factor determined by the ease of production of the propagated disturbance by the local disturbance, as well as the other excitability, with which the present theory is more immediately concerned, namely the ease of production of the local disturbance itself. I have therefore simplified Hill's expression down to this one constant, which expresses the fact in quite noncommittal form.

Lapicque has recently discussed in detail the agreement of various formulae with the observed relation between the duration of a current and the quantity of electricity required for excitation. He has laid particular stress on the fact that when the durations are plotted as abscissae and the quantities as ordinates the observed points do not lie on a straight line as would be required by the formula of Weiss, but present a double sinuosity[1]. For very short times the curve is concave

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[1] *Journal de Physiol.* IX. p. 626. 1907. X. p. 609, Fig. 1. 1908.

towards the abscissa, and for long times it is convex towards the abscissa. Hill has not dealt specifically with this point in his paper, so it may be well to show here that his formula fulfils these conditions.

I take for this purpose the observations made by Lapicque, and stated by him to be made with special precautions for the very purpose of defining the relation of current duration to quantity with the greatest possible accuracy[1]. The figures which he gives as the mean of two experiments made in such order of time as to permit of the legitimate use of the mean are the following, where t is in $\frac{1}{1000}$ths of a second.

t	$\frac{1}{3}$	$\frac{2}{3}$	1	1·5	2	2·5	3	inf.
i	175	115	91	76	68	64	61	60

From these figures the values of the various constants are found in the following manner. The equation is put in the form,

$$i\mu\theta^t = i - \lambda.$$

On substituting in this equation the numerical values $i = 175$, $t = \frac{1}{3}$, $\lambda = 60$, and in a second case $i = 91$, $t = 1$, $\lambda = 60$, we obtain two equations from which μ can be eliminated by the division of one by the other[2]. In this way we obtain the value of $\theta^{2/3}$, from which the value of θ is easily derived. Substituting the known value of θ in either of the equations we find the numerical value of μ.

From these actual times $t = \frac{1}{3}$ and $t = 1$, the values found for the constants are $\lambda = 60$, $\mu = {\cdot}909$, $\theta = {\cdot}375$. If the times chosen are $t = \frac{2}{3}$ and $t = 1{\cdot}5$, the corresponding values are $\lambda = 60$, $\mu = {\cdot}911$, $\theta = {\cdot}377$. The agreement between the two sets of constants is remarkably close, and their mean values may safely be taken for the calculation of the values of i at various values of t. The observed and calculated values of i are tabulated below side by side[3].

i obs.	175	115	91	76	68	64	61	60
i calc.	175·8	115·0	91·2	75·9	68·9	65·1	62·4	60

From the calculated values of i the following values for the quantity of electricity are obtained by multiplying by the corresponding value of t in each case, t is in $\frac{1}{1000}$ths of a second.

t	0·15	0·33	0·66	1·0	1·5	2·0	2·5	3·0	inf.
q	42·0	58·0	75·9	91·2	113·8	137·8	162·7	187·2	inf.

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[1] *Journal de Physiol.* IX. p. 629. 1907.

[2] λ is the value of i at infinite duration. *See* below.

[3] The values of i are a little too high at the longer times. This may perhaps be due to the observed value of λ being slightly disturbed by interference of the factor which renders slow currents ineffective.

It will be observed that I have included in this Table the time 0·00015 sec. which was not used in the experiment. In fig. 2 these quantities are plotted as ordinates, the values of t being abscissae. The points for the medium times lie on a straight line which does not pass through zero; for the shorter times the curve turns below this line and is concave towards the abscissa; for the longer times it rises above the line and is convex towards the abscissa. This is just the point on which Lapicque has insisted as the result of his experiments. Its occurrence in the calculated curve is further evidence in favour of the validity of Hill's formula.

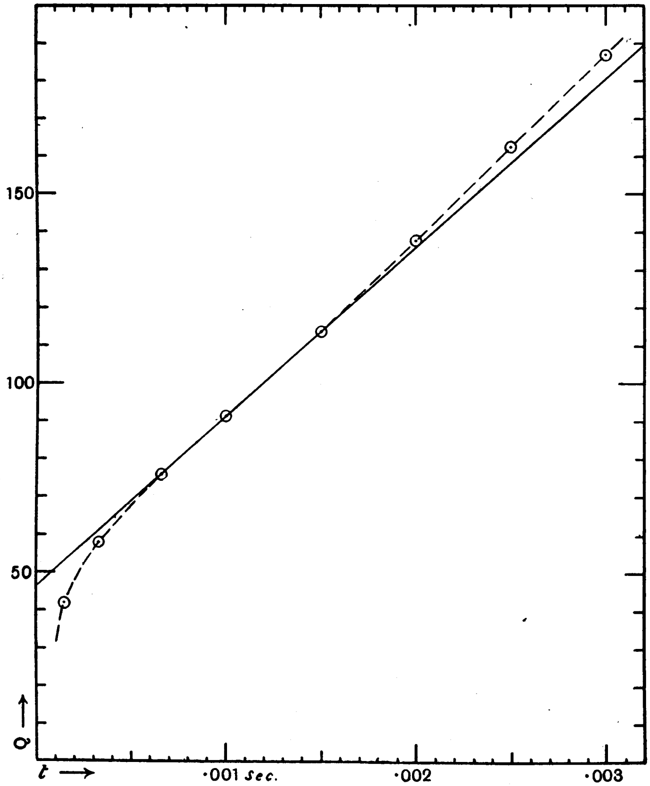

Fig. 2. The relation of current-duration to least quantity as calculated from Hill's formula. The broken line is drawn through the calculated points. The full line represents the formula of Weiss.

I will now consider the three constants λ, μ and θ in detail, and show how any change in their values may affect the relation of current-duration to liminal current-strength.

λ is the smallest current which will excite at all, or in other words the strength of current required to excite when the duration is so long that further increase of duration leads to no further diminution of the current required. With very large values of t in fact $1-\mu\theta^t$ reduces to 1, and $i=\lambda$. It is important to notice that t does not enter into this constant λ, so that any change which alters λ only will affect the value of i in the same ratio for all values of t. Suppose for example that the value of λ is reduced to $\frac{1}{2}$ its former value, then the shape of the curve will not be altered, but the values of i will simply be halved throughout the curve. Now we see from the details of λ, μ and θ given above that C enters only into λ but not into μ or θ. It follows that a change in the ease of production of the propagated disturbance will not alter the shape of the curve relating current-strength to current-duration. This is an important fact to notice, since it enables us to refer any change in the shape of the curve to a change in the factors affecting directly the ease of concentration of the ions or in other words the ease of production of the local excitatory disturbance.

Of the constants which condition directly the concentration of the ions ν enters only into λ, so it again cannot alter the shape of the curve. But b, a and k enters also into μ and θ, so that if changed they may alter the shape of the curve.

As may be seen from the equation given above μ has reference only to the position (relative to the membranes) at which the changes of concentration are being considered. If the changes of concentration considered are in the immediate neighbourhood of one of the membranes μ reduces to $8/\pi^2$, which is equal to ·81. It will be observed that in the experiments considered in detail in this paper the values of μ are ·91, ·88, ·80 and ·78. It is probable therefore that this constant may always have a value very close to that required if the concentration is very near the membrane. For the purpose of the present enquiry at any rate this assumption may be made. If the concentration considered took place at a considerable distance from the membrane μ might rise to a value nearly as high as 1·2. This question will no doubt become clearer in the future when special investigations may be directed to its solution.

We are reduced therefore to the conclusion that any considerable alteration in the shape of the curve is produced by a change in θ. The only possible change in θ is a change of k/a^2 since e and π^2 cannot change.

Every considerable change in the shape of the curve will therefore be referable to a change in k/a^2. It is only when we get a change of shape in the curve that the smallest value of t at which i becomes constant, or in other words the current-duration at which the liminal current-strength reaches its smallest value, will be changed. If the whole curve is raised or lowered in the same ratio there will be no such change. The constants k and a are those which determine the rate of dissipation of the concentration by diffusion, for k is the diffusion constant and a is the distance between the membranes, which determines (as explained above) the concentration gradient and so the rate of diffusion. We reach therefore from a consideration of this formula the fact which I have previously put forward as an hypothesis on purely experimental grounds, that an alteration of the current-duration at which the liminal current-strength reaches its smallest value means an alteration in the "rate of subsidence of the excitatory disturbance," that is, in the rate at which the concentration of the ions is dissipated by opposed diffusion.

We are now in a position to go beyond this general statement, and to consider in each particular case how the rate of diffusion has been changed, whether for example by change of k or by change of a, and how the other constants have been simultaneously affected. I take some typical examples from my published experiments, and subject them as far as possible to this analysis. The values obtained for the several constants will be seen to show a fair agreement in different experiments where conditions are alike, so they are probably reliable enough for the preliminary reconnaissance. But it can hardly be doubted that we shall be able to define them with greater precision in the future, seeing that the experimental requirements for their determination are now more clearly understood.

(1) *The effect on a given excitable tissue of change of conditions.*

(*a*) *Change of Temperature.* I take this case first because it proves to be the most straightforward at present known. It is well known that Gotch and Macdonald[1] first showed the paradoxical effect that a nerve becomes when cooled more excitable to currents of long duration, and less excitable to currents of short duration. They suggested that these opposed effects might be due to the occurrence of two different kinds of excitation, one provoked by long currents the

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[1] Gotch and Macdonald. This *Journal*, xx. p. 247. 1896.

other by short. Mines and I[1] opposed this suggestion on the ground that at each temperature the curve relating current-duration to liminal current-strength showed no discontinuity. The view that the phenomenon observed by Gotch and Macdonald is not due to two different kinds of excitation is now strengthened by the fact that Hill's formula shows the phenomenon with a single set of constants at each temperature. For example in the first experiment published by Mines and myself the figures calculated from Hill's formula are the following:

At 19·4° C. $i = \dfrac{3{\cdot}5}{1 - {\cdot}91\,({\cdot}215)^{1000t}}$

t	·00044	·00087	·0017	·0035	·0052
i calc.	6·5	4·6	3·76	3·52	3·5

At 12° C. $i = \dfrac{3{\cdot}0}{1 - {\cdot}88\,({\cdot}372)^{1000t}}$

t	·00044	·00087	·0017	·0035	·0052
i calc.	7·0	4·8	3·6	3·1	3·0

The values of i calculated from the formula exhibit the phenomenon observed by Gotch and Macdonald. With the duration ·0052 sec. the current required to excite the cooler nerve is the smaller, with the duration ·00044 the current required to excite the warmer nerve is the smaller. We have then to enquire whether the equation throws any light on the cause of this phenomenon, which may be referred to in general terms as the crossing of the curves relating current-strength to current-duration at the two temperatures. An examination of the equations for the two temperatures will show that the explanation is a simple one. Consider first the constant θ. The values of θ are at 19·4° C. ·215, and at 12° C. ·372. Let us enquire what would be the effect on the curve if the fall of temperature from 19·4° C. to 12° C. effected nothing but this change in the value of θ. We have seen above that $\theta = e^{-k\pi^2/a^2}$. The change of temperature can change nothing in this expression except k the diffusion constant; so that k must be changed in the same ratio as $\log\theta$ namely 67 : 43. The only other way in which k enters into the whole equation is in the determination of

$$\lambda = \frac{C\dfrac{k}{v}}{a/2 - b},$$

from which it is clear the λ varies directly as k, so that λ will be reduced in the ratio 67 : 43. It is simple then to calculate the exact effect at

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[1] Keith Lucas and Mines. This *Journal*, xxxvi. p. 334. 1907.

different current-durations of the observed change in *k*, supposing *k* to be the only constant changed. In column 1 of the accompanying Table there are given values of *t* which range over the same values as those used in the experiment. In column 2 there are the corresponding values of *i* calculated from the numerical values of the constants found experimentally at 19·4° C. In the third column there are the values of *i* calculated on the assumption that *k* alone is changed, its change being in the same ratio as the change of $\log\theta$ observed experimentally on the fall of temperature to 12° C. This change does not make the curves cross, 2·2 is less than 3·5, and 8·7 is less than 10·6. But it is important to notice that the value of *i* is decreased in smaller ratio for the short currents than for the long.

$$2{\cdot}2/3{\cdot}5 = {\cdot}63, \qquad 8{\cdot}7/10{\cdot}6 = {\cdot}82.$$

The change of *k* produced by fall of temperature reduces *i* less for short currents than for long.

Values of *t* in sec.	Values of *i* calculated		
	With $\lambda = 3{\cdot}5$ $\mu = {\cdot}91$ $\theta = {\cdot}215$	With $\lambda = 2{\cdot}2$ $\mu = {\cdot}91$ $\theta = {\cdot}372$	With $\lambda = 3{\cdot}0$ $\mu = {\cdot}91$ $\theta = {\cdot}372$
·005	3·5	2·2	3·0
·002	3·6	2·5	3·5
·001	4·3	3·3	4·5
·0005	6·0	4·9	6·7
·0002	10·6	8·7	11·9

But it is clear that the change of *k* cannot be the only effect brought about by the fall of temperature, for the observed change of *k* if acting alone reduces λ from 3·5 to 2·2, whereas the actual experiment at 12° C. shows λ to be reduced only to 3·0. Some other factor determining λ has been changed. The constants *a*, *b* and *ν* cannot have been altered, so the change of λ must have been effected by a change of *C* in the ratio 30/22. If now we calculate again assuming that *k* has changed as before in the ratio 43/67, and *C* in the ratio 30/22 we get the values given in the fourth column of the Table, which are of course those in the third column all increased in the ratio 30/22. The curves now cross. 3·0 is less than 3·5, and 11·9 is greater than 10·6. In this way the crossing of the curves receives a simple explanation. The fall of temperature reduces the value of *k*. The effect of this is to reduce all the values of *i*, but to reduce those for small values of *t* in smaller ratio than those for large values of *t*. The fall of temperature increases the value of *C*. This raises the value of *i* for all values of *t* in the same ratio. For about $t = \cdot 0015$ sec. the reduction of i due to change of k is equal to the increase of i due to change of C, so that i is unchanged. For smaller values of t the net result of the two changes is (since the decrease due to k is in a smaller ratio, and the increase due to C is in the same ratio) an increase of i. For larger values of t the net result is on the same grounds a decrease of i.

The results of this analysis may be expressed in physiological terms as follows. Fall of temperature produces a slower rate of subsidence of the excitatory disturbance. The effect of this acting alone would be to render the tissue more excitable to currents of all durations but in a smaller ratio for currents of shorter duration than for currents of longer duration. Fall of temperature renders the propagated disturbance less easily started by the local excitatory disturbance. This effect alone would make the tissue less excitable in a ratio constant for currents of all durations. At a certain duration of current these opposed changes of excitability are equal, so that the excitability is apparently unchanged. At durations less than this the net result of the fall of temperature is a decrease of excitability, at longer durations the net result is an increase of excitability. The opposing factors are, then, not two different sorts of excitation differently affected by temperature-change, but opposite effects of temperature-change on the local excitatory disturbance and on the ease with which the excitatory disturbance sets up the propagated disturbance.

Similar results to these can be deduced from the experiments made by Mines and myself on the sartorius muscle of the Toad. For example in the experiment figured on p. 344 of the paper quoted above, at 17·6° C. $\log \theta = -\cdot 08$ and $\lambda = 40$, at 9° C. $\log \theta = -\cdot 03$ and $\lambda = 22$. If k alone had been changed λ would have become 15 instead of 22, so the change of temperature must have increased C as well as reducing k. Of course it will be obvious that the occurrence of actual crossing of the curves within the range of an experiment depends on the chance that within that range there is a value of t at which the decrease of i due to change of k is equal to the increase of i due to change of C. If either change were a little greater or smaller the curves might never cross. In fact the important point is not the actual crossing of the curves, but the more rapid rise of i with decrease of t when the tissue is cooler. Mines and I called attention to this point in our paper[1], and maintained that the frequent failure of the curves to show an actual crossing in the case of the excitation of muscle is not to be regarded as establishing

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[1] *loc. cit.* pp. 340, 341.

any essential difference between the phenomena in muscle and nerve. The present analysis supports this view.

(*b*) *Change of the ions in the bathing fluid.* The case which I wish to consider is the removal or reduction of the calcium in the bathing fluid, as when NaCl 0·71 per cent. is substituted for NaCl 0·6 per cent. $CaCl_2$ 0·1 per cent. This is by no means so simple a case as that of change of temperature, since there is the additional possibility of a change in the value of ν to be taken into account. But the inferences which can be drawn from the experimental data are so suggestive with reference to the conditions which lead to spontaneous excitation, that I feel bound to carry the analysis as far as the available data allow.

On examination of Mines' observations[1] on the relation of current-strength to current-duration in the presence and absence of calcium we obtain the following equations.

Exp. 9 B, in which the frog's sartorius is in NaCl 0·6 per cent. $CaCl_2$ 0·1 per cent. gives

$$i = \frac{21}{1 - \cdot 803\,(\cdot 933)^{1000t}}\,.$$

Exp. 9 C from the same muscle one hour later in NaCl 0·71 per cent. gives

$$i = \frac{8}{1 - \cdot 781\,(\cdot 992)^{1000t}}\,.$$

These values of the constants give good enough agreement between the observed and calculated values of i, as shown in the Table below.

Sartorius of frog excited in pelvic end.

t		·0076	·0155	·032	·050	·069	·092	·121	inf.
NaCl 0·6 $CaCl_2$ 0·1	i obs.	40	29	24	21		21		21
	i calc.	40	29	23	21		21		21
NaCl 0·71	i obs.	32	26	20	17	16	14	12	8
	i calc.	30·2	26	20·4	17	14·7	12·9	11·5	8

The important constants are then, in the presence of Ca $\lambda = 21$, $\log \theta = -\cdot 03$, and when the Ca has been removed $\lambda = 8$, $\log \theta = -\cdot 003$. The possible sources of change in λ are C, k and ν, and λ varies as $C.k/\nu$. The change in k must be in the same ratio as that of $\log \theta$. The value of ν may have been unchanged or may have been doubled by the substitution of the monovalent Na for the divalent Ca. On removal of calcium then these two factors acting alone would reduce the value of λ either in the ratio $\frac{\cdot 003}{\cdot 03}$ or in the ratio $\frac{\cdot 003}{\cdot 03} \times \frac{1}{2}$, *i.e.* would reduce λ

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[1] Keith Lucas. This *Journal*, xxxvii. p. 472. 1908.

to $\frac{1}{10}$ or $\frac{1}{20}$ of its former value, making it 2·1 or 1·05. From the values given above it may be seen that λ (which was determined directly in each case) has fallen only to 8. This must be due to an increase of the only other constant which can have altered λ, namely C.

I see no escape from this conclusion that the value of C has been increased by the removal of calcium. The only possible supposition by which the high value of λ in the absence of calcium could be explained apart from the alteration of C is that the observed value of λ is wrong. It might be supposed that, since the λ in the absence of calcium is obtained at a much longer current-duration than in the case when calcium is present, there has been in the former case some interference of the disturbing factor which causes the inefficiency of slowly increasing currents. Such interference might indeed make the observed value of λ too high. But it can easily be shown that this supposition cannot explain the increase of λ from 2, its value calculated on the assumption that the change of k is the only change, to 8 its observed value. For if we assume $\lambda = 2$ and take the observed value $\log \theta = {\cdot}0034$ then the calculated values of i for the short times ·0076 sec. to ·050 sec. are hopelessly at variance with the observed values. For example if we take

$$i = \frac{2}{1 - {\cdot}995\ ({\cdot}992)^{1000t}}$$

which gives the correct value of i for ·0076 sec., we obtain for ·032 sec. $i = 8{\cdot}8$, and for ·050 sec. $i = 6{\cdot}1$, the observed values of i for these times being 20 and 17 respectively. If 2 were the real value of λ, then at the short times the values of i calculated on $\lambda = 2$ ought to be correct, since the interference postulated to explain the observed value of λ could come in only at very long times such as that actually used in the experimental determination of λ.

The same effect can be observed in the other experiment of the same sort published by Mines[1]. In the first set of observations in NaCl 0·6 per cent. $CaCl_2$ 0·1 per cent. $\lambda = 19$, $\log \theta = {\cdot}016$. When NaCl 0·7 per cent. without calcium is used $\lambda = 8$ and $\log \theta = {\cdot}004$. If the change of k had been the only change effected, λ should have fallen to 4·8 instead of 8. If ν were also doubled λ should have fallen to 2·4. So again C must have been increased.

The increase of C on removal of calcium is of some significance. It is well known that the removal of calcium leads a muscle-fibre to exhibit

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[1] *Ibid.* p. 439.

spontaneous excitation. Mines[1] has given experimental evidence that such spontaneous excitation occurs in the muscle-fibres themselves. The fact that the change of conditions which leads to spontaneous excitation actually renders the propagated disturbance less easy of initiation by the altered concentration of ions which constitutes the local excitatory disturbance suggests that we may attribute the spontaneity to the one factor which is observed to be changed in the direction of greater ease of excitation, namely to the reduction of λ by the decrease of k and the possible increase of ν. Of the constants k and ν by far the greater effect must be attributed to k, the effect of whose change on the value of λ is at least five times as great as that of the possible change in ν.

In this way we arrive at the conclusion that spontaneous excitation may be largely conditioned by the fact that the rate of dissipation of the concentration differences by diffusion is very much reduced, so that any small differences which may arise are not at once abolished, but add up to the requisite value for initiating the propagated disturbance. It is of interest in this connexion that, as I shall show in the next section, the rate of diffusion is much less in the cardiac than in the skeletal muscle of the frog.

II. THE COMPARISON OF DIFFERENT EXCITABLE TISSUES UNDER LIKE CONDITIONS.

I have pointed out above that k/a^2 gives a measure of the rate of diffusion of the ions concerned in excitation. Since $\theta = e^{-k\pi^2/a^2}$ we shall obtain values proportional to k/a^2 if we take log θ. I shall therefore use log θ in all the comparisons which I have to make. I have tabulated below the values of log θ for a number of different tissues on which I have previously made observations.

It will be observed from the values given for the different tissues of the toad that the nerve fibres, whether the fibres in the sciatic which lead to the gastrocnemius, or the intramuscular fibres of the sartorius, give values which range about ·3 with not very wide divergence. For the muscle fibres of the sartorius the mean value is about ·07, and for the "substance β" of the myoneural junction it is about 2. The values for the different tissues do not overlap, though the extreme cases of nerve and muscle fibres come very close one to another.

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[1] Mines. This *Journal*, XXXVII. p. 408. 1908.

Animal	Tissue	log θ	Reference to exp.
Toad	Motor nerve to gastrocnemius	−·12	*J. P.* xxxv. p. 320, Exp. 3
	,, ,,	−·34	,, p. 321, Exp. 4
	Intramuscular nerve of sartorius	−·28	*J. P.* xxxvi. p. 132, Exp. 4
	,, ,,	−·37	,, p. 133, Exp. 5
	,, ,,	−·54	,, p. 133, Exp. 6
	Muscle fibre of sartorius	−·113	,, p. 132, Exp. 1
	,, ,,	−·074	,, p. 132, Exp. 2
	,, ,,	−·058	,, p. 132, Exp. 3
	,, ,,	−·061	,, p. 133, Exp. 6
	,, ,,	−·027	,, p. 133, Exp. 7
	,, ,,	−·071	,, p. 134, Exp. 12
	,, (after curare ·03 $^0/_0$)	−·059	,, p. 135, Exp. 15
	Substance β of sartorius	−1·3	,, p. 133, Exp. 10
	,, ,,	−2·4	,, p. 134, Exp. 11
	,, ,,	−2·3	,, p. 134, Exp. 12
Frog	Intramuscular nerve of sartorius	−·33	,, p. 135, Exp. 17
	Muscle fibre of sartorius	−·063	,, p. 115, Exp. *a*
		−·091	,, p. 135, Exp. 16
	Substance β of sartorius	−1·8	,, p. 135, Exp. 18
	Ventricular muscle fibre	−·00030	*J. P.* xxxix. p. 471, Exp. 14
	,, ,,	−·00065	,, p. 471, Exp. 15

For the frog the number of observations is far smaller, but the values are obviously of the same order in each case. If we compare with these the ventricular muscle of the frog we encounter values which are much smaller than those of the other tissues. We may then, bearing in mind that the values of log θ are proportional to k/a^2, arrange these tissues in order of rapidity of diffusion of ions as follows:

Substance β of sartorius	2
Nerve fibre to sartorius or gastrocnemius	0·3
Muscle fibre of sartorius...	0·07
Ventricular muscle	0·0005

The values are clearly to be regarded only as a first approximation indicative of the order. It is evident however that the order is that found from the current-durations at which the current-strength reaches its smallest value, where the approximate figures are for the frog under like conditions:

Substance β of sartorius	0·0009 sec.
Nerve fibre to gastrocnemius or sartorius	0·003 sec.
Muscle fibre of sartorius	0·02 sec.
Ventricular muscle	2 sec.

We have then in these numbers proportional to k/a^2 a method of characterising the excitatory process of different excitable tissues which is obviously better than any previously used, since it not only gives a sharp distinction, but also is expressed in terms of what we are led to recognise as the basis of the time factor in excitation, namely the rate of diffusion of the ions.

I hesitate to give in this paper values of log θ from the experiments of other observers, since I do not know the conditions of immersing fluid under which the observations were made. But it may just be noted that Lapicque's observations on the motor nerve-fibres to the gastrocnemius of Rana esculenta (*Journ. de Physiol.* IX. p. 629. 1907) give log $\theta = -\cdot 42$, which is fairly close to my results obtained from Rana temporaria; while as an example of a slow tissue, the mantle of aplysia (Lapicque, *Journ. de Physiol.* X. p. 615. 1908) gives log $\theta = -\cdot 0003$, which is of the same order as my results from the ventricular muscle of the frog.

It should be observed, for the guidance of future observers, that if λ is determined experimentally two values (fairly wide apart) of i with different values of t give all the requisites for determining log θ, whereas if λ is not determined even a very large number of values of i at different values of t will give log θ only after a laborious series of trials.

The constants which determine the rate of diffusion.

The determinations of the value of log θ given in previous parts of this paper lead to certain inferences with regard to the constants on which that value depends. It was pointed out above that of the constants involved in log θ only k and a can change. And we saw that log θ varies as k/a^2.

Between the substance β of the frog's sartorius and the ventricular muscle-fibre of the same animal k/a^2 changes in the ratio 4000 : 1. If the ions concerned in the excitatory process were simple ions such as H, Ca, Na, Cl and so forth it is clear that the possible variations of k would not come near to accounting for this wide variation of k/a^2. The velocities of such ions differ in the ratio 10 : 1 at the most. If then such simple ions were concerned it would be necessary to suppose that there were considerable changes in the value of a between one tissue and another.

On turning to the experiments on temperature change, in which it is obvious that a cannot have been altered during an experiment, we find that for a rise of temperature of 8° C. k/a^2, and consequently k, has changed in the ratio 43 : 67, or in other words has increased about 50 %. Over a similar range of temperature I have found in other experiments increases as large as 120 % and 150 %. In fact the actual example worked out in this paper gives an increase which is smaller than that usually encountered. But even this is much greater than that which would result from the change of velocity of a simple ion by the same change of temperature. The velocity of an ion is increased about 2·5 per cent. for a rise of 1° C., so that we should expect for a rise of 8° C. an increase of 20 per cent. Similar remarks apply to the case of substitution of NaCl for $CaCl_2$. The observed change in k in this case is of the order of 1 : 10. The velocities of Na and Ca are approximately 44 : 53.

It is clear from this brief examination that k does change much more widely than would be expected on the supposition that simple ions are being concentrated by the exciting current. There is an obvious need for future work on this point. There can be no use in discussing the matter any further until more experimental evidence is available.

SUMMARY.

Hill has given to Nernst's physical theory of excitation a less limited form by the rejection of the assumption that the membranes at which ions of opposite sign are concentrated may be regarded as infinitely distant one from the other. Under these conditions the mathematical reasoning leads to a new equation relating the duration of an exciting current to its least strength.

This equation satisfies the experimental observations of the relation between current-strength and current-duration either on Nernst's original hypothesis, that excitation occurs when a certain definite concentration of ions is reached at one membrane, or on either of the modifications of this hypothesis recently put forward by Lapicque. It seems therefore to be applicable to the analysis of experimental results.

In the present paper this equation is applied to the analysis of the observed differences between the excitatory processes of different excitable tissues and to the analysis of the changes of excitability effected by various alterations of conditions.

It is shown that according to this equation the characteristic time-factor in excitation is determined, as I had previously suggested on experimental grounds, by the rate of diffusion of the ions concerned.

The factors which condition this rate are the diffusion constant of the ion concerned, and the distance between the membranes.

Application of this method of analysis to the case of fall of temperature affords an explanation of the paradoxical effects first observed by Gotch and Macdonald. The increase of excitability towards currents of long duration and the simultaneous decrease towards currents of short duration are conditioned by two opposed changes in the tissue. On the one hand the fall of temperature causes a greater ease of production of the concentration of ions owing to the slower rate of diffusion; at the same time the initiation of the propagated disturbance by this concentration is rendered more difficult. The former of these effects reduces the current required for excitation in a ratio which is greater the greater the duration of the current. The latter increases the current required in the same ratio for all durations. If then the change of temperature used is such that the two opposed effects are exactly balanced at a certain medium duration of current, it follows that for longer currents the net result will be to reduce the current required for excitation, for shorter currents the net result will be to increase the current required. In this way the current required to excite becomes less at long durations and greater at short durations when the tissue is cooled.

Similar analysis of the changes of excitability effected by the removal of calcium from the fluid bathing a muscle shows that the spontaneous excitation associated with the removal of calcium is accompanied by a great increase in the ease of production of the concentration of ions and a simultaneous decrease in the ease of production of the propagated disturbance. The former effect is brought about mainly by a slowing in the rate of diffusion of the ions. In so far then as automatic excitation is due to an increased excitability it must be attributed to a slowing of the rate at which any concentration differences which may arise are abolished by opposed diffusion. In this connexion it should be observed that the diffusion rate is found to be very greatly slower in cardiac muscle than in skeletal muscle.

A comparison of different excitable tissues by the same method shows that the diffusion rates found for the different tissues range over values far more widely divergent than would be expected on the assumption that the only factor which changes this rate between tissue and tissue is the occurrence of different ions having different diffusion constants. Two alternative explanations of this fact present themselves. Either the diffusion rate is made to vary also by a variation of the distance between the membranes in the different tissues, or else the charged bodies which are concentrated by the exciting current are such as may present diffusion constants ranging over vastly wider variations than those encountered among the simple ions. In favour of the latter alternative is the observed fact that in the case of change of temperature, where the question of change of distance between the membranes cannot come in, the change of rate of diffusion is much greater than that which can be accounted for by the known change in the rate of diffusion of ions brought about by the same change of temperature.