

**A NEW MATHEMATICAL TREATMENT OF CHANGES  
OF IONIC CONCENTRATION IN MUSCLE AND  
NERVE UNDER THE ACTION OF ELECTRIC  
CURRENTS, WITH A THEORY AS TO THEIR  
MODE OF EXCITATION. BY A. V. HILL, B.A.,  
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A SHORT time ago Nernst<sup>1</sup> put forward a physical theory of the electric excitation of living tissues, and subjected it to a mathematical treatment. An electric current passing through a tissue containing membranes impermeable to the dissolved ions will set up differences of concentration at and near the membranes. He supposes that these differences of concentration, when sufficiently large, cause an excitation: by solving the diffusion equation  $\frac{\partial y}{\partial t} = k \frac{\partial^2 y}{\partial x^2}$ , he arrives at a formula,  $i \sqrt{t} = \text{const.}$ , connecting  $i$  the least current required to excite with its duration  $t$ : and a formula,  $i/\sqrt{n} = \text{const.}$ , connecting  $i$  the least amplitude of an alternating current with its frequency  $n$ . The theory, however, as Nernst himself recognises, fits the facts only to a limited degree. For

(i)  $i \sqrt{t}$  is constant only for very short durations of current,  $i$  tending to a constant finite value for higher values of  $t$ :

(ii)  $i/\sqrt{n}$  is not absolutely constant, but decreases for increasing values of  $n$ :

(iii) he gives no method of treating the phenomenon long known to physiologists that slowly increasing currents are much less effective than rapidly increasing currents, even though the former be made to reach considerably higher values. In general terms he refers to this fact as an accommodation of the protoplasm to the changes of concentration set up.

<sup>1</sup> Nernst. *Gött. Nachr. Math. Phys. Kl.* p. 104. 1899; and *Arch. f. d. ges. Physiol.* cxxii. p. 275. 1908.

Lapicque<sup>1</sup>, following Nernst, has given some valuable conceptions of the nature of electric excitation. He evolves a theory which, he gives reason to suppose, will explain the existing gaps in Nernst's theory. Unfortunately he was unable to integrate the partial differential equation above for the required boundary conditions, and thus could not compare experimental results with deductions from his theory. By an ingenious idea he used a hydrodynamical model to show *qualitatively* the sort of results his hypothesis would give: these agreed well with experimental observations. Mr Keith Lucas, feeling that the lack of a rigid mathematical treatment was a serious drawback to a purely physical hypothesis, suggested to me that I should attempt a new mathematical consideration of the theory, both to test the validity of Lapicque's views, and to replace the incomplete hypothesis of Nernst. With a slight change in the mathematical method this attempt has been successful, and the formulæ given below for the concentrations produced by various forms of current will, I believe, be of service in the theory, whether the additional hypothesis which I have found it necessary to introduce (in order to explain certain facts of which Nernst's treatment gave no account) is found on later consideration to be sufficient or not. Nernst, in his theory, postulates two membranes impermeable to the dissolved ions. When a current is sent in it is not carried through the space between these membranes, but in the tissues outside it. A certain difference of potential will however exist between the membranes, and hence the positive ions will tend to go in the direction of the current, the negative ions in the opposite direction. Hence changes of ionic concentration will occur at the membrane. Nernst in his treatment of the problem deals with only one of the ions, which he supposes to be the one which is effective as regards excitation, and for simplicity he assumes that the distance between the membranes is so great that for all practical purposes it may be regarded as infinite. This is, *a priori*, unlikely to be a justifiable assumption, as we know that living matter is possessed of a very complicated microscopic structure. The change I have adopted in tracing the consequences of the theory is in making no assumption as to the distance between these membranes. I have supposed (Fig. 1) that in the stimulated tissue there exist two membranes *AB* and *CD* distant *a* from one another: that the ions between *AB* and *CD* cannot pass through the membranes: and that initially, before the passage of a current, *y* the concentration of the ion

<sup>1</sup> Lapicque. *C. R. Soc. de Biol.* LXIII. p. 37. 1907. *Journal de Physiol. et de Path. gén.* ix. p. 565. 1907, *ibid.* p. 620, x. p. 601. 1908, xi. p. 1009. 1909.

which is effective as regards excitation is the same everywhere and has the value  $y = c$ . Then if a current  $i$  be sent through the tissue a difference of potential will be set up between  $AB$  and  $CD$ , and there will arise an increase in the concentration  $y$  of the positive ion near  $AB$ , and a decrease near  $CD$ . Finally, as the current continues to pass, a steady

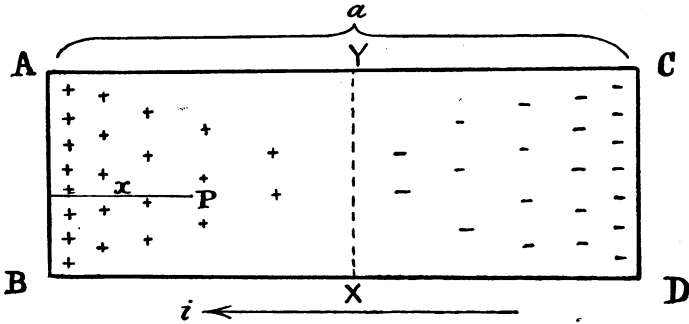


Fig. 1.

state will be set up between  $AB$  and  $CD$  in which the forward transference of the ions by the current will be compensated by their backward diffusion. At  $YX$ , a plane half-way between the two membranes, the concentration  $y$  must (from considerations of symmetry) be unchanged: *i.e.* if  $y$  be the concentration of the ion considered at a point distant  $x$  from  $AB$ , then at  $x = \frac{1}{2}a$ ,  $y = c$ .

The general effect of having the two membranes closer together is as follows. The concentration of the ion is unchanged at a point half-way between the membranes: thus for a given change of concentration at the membrane the gradient of concentration along the line  $BD$  is greater the smaller the distance between the membranes. But the "back diffusion," the tendency of the high concentration to be destroyed by diffusion backwards, is governed by the gradient of concentration, and is therefore greater when the distance between the membranes is less. Thus with closer membranes a greater current is required for a given time to produce the same effect. This is exactly what is required to make Nernst's theory more nearly accord with the facts.

According to Nernst's theory an excitation occurs when the concentration  $y$  at  $AB$  reaches a certain value above normal. If the theory be worked out on these lines by the method given below the theoretical deductions accord exactly with experience both for constant and for alternating currents. Unfortunately it still gives no sort of explanation of the phenomena observed with currents increasing progressively with the time.

Lapicque<sup>1</sup> in his latest hypothesis introduces a function which

<sup>1</sup> Lapicque. *Journal de Physiol.* xi. p. 1009, spec. p. 1011. 1909.

I propose to call  $\phi$ , defined as follows: the concentration at a distance  $b$  from the membrane being called  $y_b$ , and that at the membrane  $y_0$ ,

$$\phi = y_b/y_0.$$

[ $b$  is assumed to be constant for any one tissue.]

Then, according to Lapique,  $\phi$  decreases, as the current goes on passing, from its initial value 1, and when it has reached a certain value  $m$  less than 1 an excitation occurs: expressed in words, when the concentration at  $P$  has fallen to a certain fraction of that at  $AB$  some mechanism is released which constitutes an excitation.

This hypothesis advanced by Lapique can also be made to fit the facts observed for constant and alternating currents: but it can be shown by rigid mathematical analysis that if it does so for constant currents then any progressive current however slowly increasing will finally stimulate the tissue if kept up long enough. This is contrary to observation, and therefore Lapique's as well as Nernst's hypothesis must be either modified or abandoned. I have consequently introduced another hypothesis, which is really that of Nernst slightly elaborated. For currents of short duration it reduces to that of Nernst: for currents of longer duration ("progressive currents," currents increasing "logarithmically") the effect of the time being large is that other terms come in which modify the results obtained from Nernst's theory. This theory agrees with all the results so far obtained, and has the advantage of giving some further insight into the physical nature of the excitation, and of the resulting propagated disturbance. In particular it may be of considerable importance in theories of the transmission of a nervous impulse across a synapse in the central nervous system: and in giving a physical basis for the physiological facts generally known by such terms as Weber's or Müller's Law.

There is another advantage in the mathematical method now introduced, viz. that certain constants can be determined for any tissue of which each has a definite physical meaning. The comparison of these constants for different tissues, and for the same tissue under different conditions, may lead to results of considerable interest both to the zoologist and the physiologist. The simplest of these constants is  $\alpha$  the size of the structure of the tissue in question, which can be determined very easily from a few observations with constant currents. This particular method of analysing a tissue into its fundamental parts is being applied by Keith Lucas in another paper.

MATHEMATICAL CONSIDERATION.

The equation<sup>1</sup> connecting the concentration  $y$  and the time  $t$  with  $x$  the distance from  $AB$  of the point considered is the well known equation,

$$\frac{\partial y}{\partial t} = k \frac{\partial^2 y}{\partial x^2} \dots\dots\dots(A),$$

where  $k$  is the diffusion constant.

At  $AB$  the force tending to concentrate the ions in the immediate neighbourhood of  $AB$  is proportional to  $i, \nu i$  say, where  $\nu$  is a constant which varies inversely as the valency of the effective ion, but does not involve  $k$ . This force has to overcome the tendency of the inequalities of concentration to dissipate themselves by diffusion backwards: this tendency at  $AB$  is measured by  $-k \frac{\partial y}{\partial x}$ . Similarly we may treat of the conditions at  $CD$ . Hence we have the boundary conditions

$$-k \frac{\partial y}{\partial x} = \nu i, \text{ at } x=0 \text{ and } x=a \dots\dots\dots(B).$$

Initially at  $t = 0$

$$y = c \text{ a constant } \dots\dots\dots(C).$$

We have to solve equation (A), with boundary conditions (B), and initial condition (C).

*Constant Currents.*

The first case to be treated is that of a constant current. This is the simplest mathematically, and of the most importance because the majority of the experiments have been done with constant currents.

The conditions we have to satisfy are as follows.

At  $x = 0$  and  $x = a, \frac{\partial y}{\partial x} = -\frac{\nu i}{k}$ , where  $i$  is the constant current: and at  $t = 0 \ y = c$ .

<sup>1</sup> Nernst. *Arch. f. d. ges. Physiol.* cxii. p. 284. 1908. Hoorweg (*Pfűger's Archiv*, cxix. p. 412. 1907) introduces another differential equation for the diffusion. As he does not take into account the distance between the membranes, and as (in order to use this equation) he makes the assumption (for which he gives no sufficient grounds) that although  $AC$  is infinite nevertheless  $AB$  is small, his theory has not been considered here. Moreover he has introduced various supplementary hypotheses of a physiological nature, which would be out of place in a modification of Nernst's theory which is professedly purely physical.

Now

$$y = c - \frac{vi}{k} \left( x - \frac{a}{2} \right) + \sum_1^{\infty} A_r e^{-k \frac{r^2 \pi^2}{a^2} t} \cos \frac{r \pi x}{a},$$

satisfies the differential equation, and  $\frac{\partial y}{\partial x} = -\frac{vi}{k}$  at  $x=0$  and  $x=a$ .

For  $\sin \frac{r \pi x}{a} = 0$  at  $x=0$  and  $x=a$ . Further  $y = c$  at  $x = \frac{a}{2}$ . We have thus only to make it satisfy the initial condition at  $t = 0$ ,

$$c = c - \frac{vi}{k} \left( x - \frac{a}{2} \right) + \sum_1^{\infty} A_r \cos \frac{r \pi x}{a}.$$

To make it do this, multiply by  $\cos \frac{r \pi x}{a} dx$  and integrate from 0 to  $a$ . This gives

$$\begin{aligned} A_r \frac{a}{2} &= \frac{vi}{k} \int_0^a \left( x - \frac{a}{2} \right) \cos \frac{r \pi x}{a} dx \\ &= \frac{vi}{k} \left[ \frac{a}{r \pi} \left( x - \frac{a}{2} \right) \sin \frac{r \pi x}{a} + \frac{a^2}{r^2 \pi^2} \cos \frac{r \pi x}{a} \right]_0^a \\ &= \frac{vi}{k} \frac{a^2}{r^2 \pi^2} \{ (-1)^r - 1 \}, \end{aligned}$$

- ∴ if  $r$  is even  $A_r = 0$ ,
- if  $r$  is odd  $A_r = -\frac{4vi}{k} \frac{a}{r^2 \pi^2}$ .

Hence the solution of the equation is

$$y = c + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t} \cos \frac{(2n-1) \pi x}{a} \dots\dots (D).$$

Now the series inside the  $\Sigma$  is very convergent: for

- (i) as  $n$  increases  $e^{-k \frac{(2n-1)^2 \pi^2}{a^2}}$  decreases rapidly, the terms being in order the 1st, 9th, 25th, 49th,..... powers of a number less than one.
- (ii) as  $n$  increases  $\frac{1}{(2n-1)^2}$  decreases rapidly.

It will be shown later that experimental results agree very well with a formula which *neglects everything but the first term* of the series inside the  $\Sigma$ . The constants of such calculations give directly  $e^{-k \pi^2 / a^2}$  to a close degree of accuracy. From this can be deduced the order of magnitude of the second term of the series,  $\frac{1}{9} \left\{ e^{-k \pi^2 / a^2} \right\}^9 \cos \frac{3 \pi x}{a}$ . The actual calculation shows that for quantities of the size involved in these experiments the

second and all subsequent terms are absolutely negligible. Hence we may write,

$$y = c + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \frac{4vi}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi x}{a} \dots \dots \dots (E).$$

I shall return to this later in a discussion of the experimental results.

*Alternating Currents.*

Let us suppose that an alternating current of frequency  $n/2\pi$  is sent into the tissue :

$$i = i_0 \sin (nt + \epsilon).$$

The mathematical treatment of this case is somewhat difficult, so it seemed better only to give the *solution*. Its correctness can be tested by substitution in the differential equation, and in the boundary conditions.

The solution is

$$y = c - \frac{a}{\sqrt{2}p} \frac{vi_0}{k} \frac{1}{\{1 + 2e^{-p} \cos p + e^{-2p}\}^{\frac{1}{2}}} \left[ e^{-p \frac{x}{a}} \cos \left\{ nt + \epsilon + \psi + \frac{\pi}{4} - \frac{px}{a} \right\} - e^{-p \frac{a-x}{a}} \cos \left\{ nt + \epsilon + \psi + \frac{\pi}{4} - \frac{p(a-x)}{a} \right\} \right] + \sum_1^\infty A_r e^{-k \frac{r^2 \pi^2}{a^2} t} \cos \frac{r\pi x}{a} \dots (F),$$

where  $p = a \sqrt{\left(\frac{n}{2k}\right)}$ ,  $\psi = \tan^{-1} \frac{e^{-p} \sin p}{1 + e^{-p} \cos p}$ ,

and the  $A$ 's are to be so chosen that at  $t = 0$   $y = c$ . The  $A$ 's may be found by multiplying by  $\cos \frac{r\pi x}{a} dx$  and integrating from 0 to  $a$ . In

this case it can be shown that they all involve a factor  $\frac{1}{p^2}$ , which means that for moderately high frequencies they are small. Furthermore in a very short time all the terms of the Fourier series become zero : hence we may consider only the particular integral and write,

$$y = c - \frac{a}{\sqrt{2}p} \frac{vi_0}{k} \frac{1}{\{1 + 2e^{-p} \cos p + e^{-2p}\}^{\frac{1}{2}}} \left[ e^{-p \frac{x}{a}} \cos \left\{ nt + \epsilon + \psi + \frac{\pi}{4} - \frac{px}{a} \right\} - e^{-p \frac{(a-x)}{a}} \cos \left\{ nt + \epsilon + \psi + \frac{\pi}{4} - \frac{p(a-x)}{a} \right\} \right] \dots (F').$$

*Progressive Currents.*

Let us assume that  $i$  increases proportionally to the time, i.e. we have as one condition, that at  $x=0$  and  $x=a$ ,

$$\frac{\partial y}{\partial x} = -\frac{vi}{k} = -\lambda t, \text{ where } \lambda \text{ is a constant.}$$

The other condition is, as before, at  $t=0$   $y=c$ .

For the particular integral  $y = -\lambda t \left(x - \frac{a}{2}\right) + \phi(x)$ , where

$$\begin{aligned} \phi''(x) &= -\frac{\lambda}{k} \left(x - \frac{a}{2}\right), \\ \phi(x) &= -\frac{\lambda}{6k} \left[ \left(x - \frac{a}{2}\right)^3 + a \left(x - \frac{a}{2}\right) \right], \end{aligned}$$

which vanishes at  $x = \frac{a}{2}$ , as it must do from symmetry.

Further

$$\frac{\partial y}{\partial x} = -\lambda t - \frac{\lambda}{6k} \left[ 3 \left(x - \frac{a}{2}\right)^2 + a \right],$$

and for this to equal  $-\lambda t$  at  $x=0$  and  $x=a$  we must have  $a = 3a^2/4$ .

Hence the solution of the equation is,

$$y = c - \lambda t \left(x - \frac{a}{2}\right) - \frac{\lambda}{6k} \left[ \left(x - \frac{a}{2}\right)^3 - \frac{3}{4}a^2 \left(x - \frac{a}{2}\right) \right] + \sum_1^\infty A_r e^{-k \frac{r^2 \pi^2}{a^2} t} \cos \frac{r \pi x}{a}.$$

Initially this must equal  $c$ , and therefore as before we have,

$$\begin{aligned} 6A_r \cdot \frac{a}{2} &= \frac{\lambda}{k} \int_0^a \cos \frac{r \pi x}{a} \left[ \left(x - \frac{a}{2}\right)^3 - \frac{3}{4}a^2 \left(x - \frac{a}{2}\right) \right] dx \\ &= \left[ \left\{ \left(x - \frac{a}{2}\right)^3 - \frac{3}{4}a^2 \left(x - \frac{a}{2}\right) \right\} \frac{a}{r \pi} \sin \frac{r \pi x}{a} + \left\{ 3 \left(x - \frac{a}{2}\right)^2 - \frac{3}{4}a^2 \right\} \frac{a^2}{r^2 \pi^2} \cos \frac{r \pi x}{a} \right. \\ &\quad \left. - 6 \left(x - \frac{a}{2}\right) \frac{a^3}{r^3 \pi^3} \sin \frac{r \pi x}{a} - \frac{6a^4}{r^4 \pi^4} \cos \frac{r \pi x}{a} \right]_0^a \\ &= \frac{6a^4}{r^4 \pi^4} (1 - (-1)^r), \end{aligned}$$

$\therefore A_r = 0$  if  $r$  is even,

$$A_r = \frac{4a^3}{r^4 \pi^4} \text{ if } r \text{ is odd.}$$

Hence the solution of the equation is,

$$\begin{aligned} y &= c + \lambda t \left(\frac{a}{2} - x\right) - \frac{\lambda}{6k} \left\{ \left(x - \frac{a}{2}\right)^3 - \frac{3}{4}a^2 \left(x - \frac{a}{2}\right) \right\} \\ &\quad + \frac{\lambda}{k} \frac{4a^3}{\pi^4} \sum_1^\infty \frac{1}{(2n-1)^4} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t} \cos \frac{(2n-1) \pi x}{a} \dots (G). \end{aligned}$$



This series is even more convergent than the previous one (for constant currents), so we may safely write,

$$y=c+\lambda t\left(\frac{a}{2}-x\right)-\frac{\lambda}{6k}\left\{\left(x-\frac{a}{2}\right)^3-\frac{3}{4}a^2\left(x-\frac{a}{2}\right)\right\}+\frac{\lambda}{k}\frac{4a^3}{\pi^4}e^{-k\frac{\pi^2}{a^2}t}\cos\frac{\pi x}{a}\dots(\text{H}).$$

In the experiments on progressive currents usually at the end of a certain time the progressive current is made constant at the value it has then reached. Let us suppose that this occurs at time  $t_0$ , so that we have now as our boundary conditions for the integral of the diffusion equation *after* the time  $t_0$ , (i) at  $x=0$  and  $x=a$ ,  $\frac{\partial y}{\partial x}=-\lambda t_0$  and (ii) at  $t=t_0$ ,

$$y=c+\lambda t_0\left(\frac{a}{2}-x\right)-\frac{\lambda}{6k}\left\{\left(x-\frac{a}{2}\right)^3-\frac{3}{4}a^2\left(x-\frac{a}{2}\right)\right\}+\frac{\lambda}{k}\frac{4a^3}{\pi^4}\sum_1^{\infty}\frac{1}{(2n-1)^4}e^{-k\frac{(2n-1)^2\pi^2}{a^2}t_0}\cos\frac{(2n-1)\pi x}{a}\dots(\text{ii}).$$

A solution of the differential equation is,

$$y=c+\lambda t_0\left(\frac{a}{2}-x\right)+\sum_1^{\infty}A_r e^{-k\frac{r^2\pi^2}{a^2}t}\cos\frac{r\pi x}{a},$$

and this satisfies the condition

$$\frac{\partial y}{\partial x}=-\lambda t_0 \text{ at } x=0 \text{ and } x=a.$$

At  $t=t_0$ ,

$$y=c+\lambda t_0\left(\frac{a}{2}-x\right)+\sum_1^{\infty}A_r e^{-k\frac{r^2\pi^2}{a^2}t_0}\cos\frac{r\pi x}{a}\dots\dots\dots(\text{iii}).$$

This relation (iii) must be the same as the relation (ii) above. But from (G) above, at  $t=0$ ,

$$c=c-\frac{\lambda}{6k}\left\{\left(x-\frac{a}{2}\right)^3-\frac{3}{4}a^2\left(x-\frac{a}{2}\right)\right\}+\frac{\lambda}{k}\frac{4a^3}{\pi^4}\sum_1^{\infty}\frac{1}{(2n-1)^4}\cos\frac{(2n-1)\pi x}{a}\dots(\text{iv}).$$

Substitute the value of  $\frac{\lambda}{6k}\left\{\left(x-\frac{a}{2}\right)^3-\frac{3}{4}a^2\left(x-\frac{a}{2}\right)\right\}$ , so obtained, in (ii) above, and we find

$$y=c+\lambda t_0\left(\frac{a}{2}-x\right)-\frac{\lambda}{k}\frac{4a^3}{\pi^4}\sum_1^{\infty}\frac{1}{(2n-1)^4}\cos\frac{(2n-1)\pi x}{a}\left\{1-e^{-k\frac{(2n-1)^2\pi^2}{a^2}t_0}\right\}\dots(\text{v}).$$

From (iii) and (v), equating coefficients of  $\cos\frac{(2n-1)\pi x}{a}$  we find,

$$A_r=0 \text{ if } r \text{ is even,}$$

$$A_r e^{-k\frac{r^2\pi^2}{a^2}t_0}=-\frac{\lambda}{k}\frac{4a^3}{\pi^4}\frac{1}{(2n-1)^4}\left\{1-e^{-k\frac{(2n-1)^2\pi^2}{a^2}t_0}\right\} \text{ if } r \text{ is odd.}$$

So that subsequent to the time when the progressive current has been made constant,

$$y = c + \lambda t_0 \left( \frac{a}{2} - x \right) - \frac{\lambda}{k} \frac{4a^3}{\pi^4} \sum_1^{\infty} \frac{1}{(2n-1)^4} \left\{ 1 - e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_0} \right\} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} (t-t_0)} \cos \frac{(2n-1) \pi x}{a} \dots (K).$$

As before this may be written, because of the rapid convergency for any but very short times,

$$y = c + \lambda t_0 \left( \frac{a}{2} - x \right) - \frac{\lambda}{k} \frac{4a^3}{\pi^4} \left( 1 - e^{-k \frac{\pi^2}{a^2} t_0} \right) e^{-k \frac{\pi^2}{a^2} (t-t_0)} \cos \frac{\pi x}{a} \dots (L).$$

The solution up to time  $t = t_0$  is given by (H): after time  $t = t_0$  by (L).

*Condenser Discharge.*

If  $V$  be the potential to which a condenser of capacity  $C$  is charged, and if  $R$  be the resistance through which the discharge takes place,

$$i = \frac{V}{R} e^{-\frac{t}{CR}}.$$

Putting  $\frac{1}{CR} = \rho^2$ , the solution of this case is,

$$y = c + \frac{v}{k} \frac{V}{R} \frac{1}{\rho \cos \left( \rho \frac{a}{2} \right)} e^{-\rho^2 t} \sin \rho \left( \frac{a}{2} - x \right) - \frac{4v}{k} \frac{V}{R} \sum_1^{\infty} \frac{1}{(2n-1)^2 \pi^2 - a^2 \rho^2} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t} \cos \frac{(2n-1) \pi x}{a} \dots (M).$$

This series is, as before, very convergent: we may therefore write,

$$y = c + \frac{v}{k} \frac{V}{R} \frac{1}{\rho \cos \left( \rho \frac{a}{2} \right)} e^{-\rho^2 t} \sin \rho \left( \frac{a}{2} - x \right) - \frac{4v}{k} \frac{V}{R} \frac{a}{\pi^2 - a^2 \rho^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi x}{a} \dots (N).$$

*Logarithmic Current.*

For a current increasing logarithmically,

$$i = i_0 (1 - e^{-\beta^2 t}).$$

The solution of this case is,

$$y = c - \frac{v i_0}{k} \left\{ \left( x - \frac{a}{2} \right) - \frac{1}{\beta} e^{-\beta^2 t} \frac{\sin \beta \left( x - \frac{a}{2} \right)}{\cos \beta \frac{a}{2}} - \sum_1^{\infty} \frac{4a^3 \beta^2}{(2n-1)^4 - a^2 \beta^2 (2n-1)^2 \pi^2} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t} \cos \frac{(2n-1) \pi x}{a} \right\} \dots (P),$$

as can be seen by substituting in the differential equation and the required conditions.

Because of the rapid convergency of the series we may write,

$$y = c + \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) - \frac{\nu i_0}{k} \frac{1}{\beta} e^{-\beta^2 t} \frac{\sin \beta \left( \frac{a}{2} - x \right)}{\cos \beta \frac{a}{2}} - \frac{4a^3 \beta^2}{\pi^4 - \pi^2 a^2 \beta^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi x}{a} \dots (Q).$$

#### CONSIDERATION OF THE EXPERIMENTAL RESULTS.

##### *Constant Current.*

According to Nernst's<sup>1</sup> theory of electric excitation, if a current  $i$  acts for a time  $t$  then for excitation to occur  $i\sqrt{t}$  must exceed a certain limit. This is only true for very short times. It fails absolutely to explain why  $i$  never falls below a certain minimum even though  $t$  is increased indefinitely. Lopicque's hypothesis, still involving the conception of one membrane infinitely distant from all others, gives results more in accordance with facts: but the calculation in his case is complicated. By the formulæ given above for the concentration at any point, at any time, one can give a simple mathematical formula whereby to test either of these theories. It will be seen that the conception introduced of two membranes fairly close together makes either theory exactly fit the facts for constant currents.

According to Nernst an excitation occurs when  $(y - c)$ , the excess of the concentration above normal, exceeds a certain limit, at or near the membrane. Let us assume that it must exceed it at a point distant  $b$  from the membrane. Then from (E) above we have,

$$y - c = \frac{\nu i}{k} \left( \frac{a}{2} - b \right) - \frac{4\nu i}{k} \frac{a}{\pi^2} \cos \frac{\pi b}{a} e^{-k \frac{\pi^2}{a^2} t}.$$

This has to reach a value  $m$  (say) before an excitation can occur: hence the liminal current strength is connected with the time by a relation,

$$m = \frac{\nu i}{k} \left( \frac{a}{2} - b \right) - \frac{4\nu i}{k} \frac{a}{\pi^2} \cos \frac{\pi b}{a} e^{-k \frac{\pi^2}{a^2} t},$$

i.e.

$$i = \frac{m}{\frac{\nu}{k} \left( \frac{a}{2} - b \right) - \frac{4\nu}{k} \frac{a}{\pi^2} \cos \frac{\pi b}{a} e^{-k \frac{\pi^2}{a^2} t}},$$

which may be written,

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

<sup>1</sup> Nernst. *Arch. f. d. ges. Physiol.* cxxii. p. 301. 1908.

where  $\lambda, \mu, \theta$ , are constants given by

$$\lambda = \frac{mk}{v \left( \frac{a}{2} - b \right)}, \quad \mu = \frac{4a \cos \frac{\pi b}{a}}{\left( \frac{a}{2} - b \right) \pi^2}, \quad \theta = e^{-k \frac{\pi^2}{a^2} t}.$$

According to Lopicque<sup>1</sup> an excitation occurs when  $\phi = \frac{y_b}{y_0}$  reaches a certain limit,  $m'$  say.

Here we have

$$m' = \frac{c + \frac{vi}{k} \left( \frac{a}{2} - b \right) - \frac{4vi}{k} \frac{a}{\pi^2} \cos \frac{\pi b}{a} e^{-k \frac{\pi^2}{a^2} t}}{c + \frac{vi}{k} \frac{a}{2} - \frac{4vi}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t}}.$$

This reduces, on multiplying up and separating out the terms in  $i$ , to

$$i = \frac{\lambda'}{1 - \mu' \theta^t},$$

where  $\lambda', \mu', \theta$ , are constants given by

$$\lambda' = \frac{c(1 - m')k}{v \left\{ m' \frac{a}{2} - \frac{a}{2} + b \right\}}, \quad \mu' = \frac{4a \left( m' - \cos \frac{\pi b}{a} \right)}{\pi^2 \left( m' \frac{a}{2} - \frac{a}{2} + b \right)}, \quad \theta = e^{-k \frac{\pi^2}{a^2} t}.$$

Later in the paper another hypothesis is introduced to account for the phenomena observed with progressive currents. This, with constant currents, reduces to the hypothesis advocated by Nernst, so that all three hypotheses lead, in the case of constant currents, to an equation

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

connecting the liminal current  $i$  with the time it is allowed to pass.  $\lambda, \mu$ , and  $\theta$  are constants defined above: it is noticeable that  $\theta$  is less than 1, and therefore that  $\theta^t$  decreases as  $t$  increases.

Further these constants  $\lambda, \mu, \theta$ , can be compared for different tissues, and for the same tissues under different conditions. This method provides a very delicate instrument for the analysis of the tissues.

Below are tabulated results calculated from this formula side by side with the experimental results of several observers, and in some cases with numbers calculated by the methods of Nernst and Lopicque. Similar agreement has been obtained between calculation and experiment for a large number of cases which are not given here.

<sup>1</sup> Lopicque. *Journal de Physiol.* xi. p. 1009. 1909.

The improvement resulting from the introduction of the two membranes into the mathematical treatment is obvious on comparing the results: and the most satisfactory agreement between calculation and experiment leaves little doubt of the validity of the physical view of nervous excitation originally suggested by Nernst.

The times in the tables below are given in the units used in the original papers. In the formulæ given for the calculation,  $t$  is in all cases given in seconds: this enables comparisons to be carried out directly between the constants.

I. Nernst. *Arch. f. d. ges. Physiol.* cxxii. p. 302. Table IX. 1908.

$$i = \frac{52.1}{1 - (.933)(.453)^{1000t}}$$

$t$	6	8	10	12	16	20	30	40	$\infty$
$i$ obs.	147	124	110	94	81	73	62	57	—
$i$ calc.	152	122	105	94.4	80.3	71.5	61	56.5	52.1
$i$ calc. by Nernst	136	119	106	97	84	75	61	53	0

II. Nernst. *Ibid.* Table X.

$$i = \frac{69.5}{1 - (.82)(.362)^{1000t}}$$

$t$	4	6	8	10	12	14	20	40	$\infty$
$i$ obs.	185	142	123	112	103	97	86	77	—
$i$ calc.	175	143	120.5	111	102.5	96	84	75.5	69.5
$i$ calc. by Nernst	177	145	126	112	102	95	79	56	0

III. Nernst. *Ibid.* p. 304. Lapique's observations.

$$i = \frac{110}{1 - (.92)(.256)^{1000t}}$$

$t$	0.33	0.60	1	1.5	2	2.5	3	$\infty$
$i$ obs.	270	187	155	126	115	112.5	112	—
$i$ calc.	266	185	144	125	117	113.5	111.8	110
$i$ calc. by Nernst	270	191	155	126	110	98	90	0
$i$ calc. by Lapique	265	189	155	—	116	—	111	—

IV. Keith Lucas. *This Journal*, xxxvi. p. 115 (a). 1907.

$$i = \frac{25}{1 - (.833)(.865)^{1000t}}$$

$t$	.0052	.007	.010	.014	.017	.021	.024	$\infty$
$i$ obs.	41	36	31	28	27.5	26	25.5	—
$i$ calc.	41	35.6	31	28	26.8	26	25.6	25

V. Keith Lucas. *This Journal*, xxxv. p. 320. 1907.

$$i = \frac{.086}{1 - (.730)(.758)^{1000t}}$$

$t$	.00043	.00087	.0017	.0035	.0070	$\infty$
$i$ obs.	.245	.179	.152	.119	.091	.086
$i$ calc.	.244	.201	.158	.119	.096	.086

VI. Keith Lucas. *This Journal*, xxxvi. p. 132. 1907.

$$i = \frac{36}{1 - (.761)(.525)^{1000t}}$$

<i>t</i>	.000175	.00035	.000525	.000875	.0017	.0035	.0052	.0070	.01	.017
<i>i</i> obs.	1.29	.92	.75	.58	.48	.41	.39	.38	.37	.37
<i>i</i> calc.	1.12	.92	.79	.64	.48	.39	.37	.36	.36	.36

VII. Lapique. *Journal de Physiol.* ix. p. 629. 1907.

$$i = \frac{35}{1 - .903(.440)^{1000t}}$$

<i>t</i>	1	2	3	4.5	6	7.5	9
<i>i</i> obs.	175	115	91	76	66	62	58
<i>i</i> calc.	175.1	115.4	91.4	75.8	66.8	62.6	59.6
<i>i</i> √ <i>t</i>	175	162.5	164.2	161	161.2	169.7	174

VIII. Lapique. *Journal de Physiol.* ix. p. 631. 1907.

$$i = \frac{103}{1 - .860(.373)^{1000t}}$$

<i>t</i>	1	2	3	4.5	6	7.5	9
<i>i</i> obs.	270	185	154	125	115	112	111
<i>i</i> calc.	270	185	152	128.4	117	111.3	108
<i>i</i> √ <i>t</i>	270	261	266	265	282	306	333

### Progressive Currents.

The stumbling block of all physical theories of the nature of electric excitation has been that they give no explanation of the phenomena observed with currents increasing slowly to their full value. The fundamental fact observed is that currents increasing at less than a certain rate never cause an excitation however long they are continued: even though they finally reach a very considerable value. Nernst's hypothesis that it is merely the concentration near the membrane which determines an excitation takes no account of this: for according to formula (H) above,

$$y - c = \lambda t \left( \frac{\alpha}{2} - x \right) + \text{other terms.}$$

Thus (*y* - *c*) increases indefinitely as the current goes on increasing, and thus according to Nernst an excitation should occur. Nernst<sup>1</sup> indeed considers this difficulty and refers it in very general terms to an "accommodation" which takes place in the protoplasm to the slowly produced changes of concentration set up by progressive currents. The word accommodation was unfortunate as it gave the impression that he

<sup>1</sup> Nernst. *Arch. f. d. ges. Physiol.* cxvii. p. 280. 1908.

was referring back to some physiological factor the gaps in a theory which was purely physical. The rate of accommodation he says is proportional to  $(y - c)$ : what he probably intended therefore is just such a hypothesis as I have given below, though he never made it definite nor introduced it quantitatively into his equations. By the accommodation he refers to he probably means a change of equilibrium of the reversible chemical or physical combination between the salts and the protoplasm, under the action of the increased concentration of the salt ions: this would go on, among other things, at a rate proportional to  $(y - c)$ . The hypothesis I arrived at independently to explain the phenomena of progressive currents can be stated in a very general way almost in the same terms as Nernst uses.

Lapicque<sup>1</sup> in his latest theory shews, (by his hydrodynamical model) that his function  $\phi = y_b/y_0$  has a definite minimum as the time increases, and that this minimum is lower the greater the value of  $\lambda$ , *i.e.* the faster the current increases. He goes on to say that if this minimum is *not so low* as the value which has to be reached for stimulation to occur, then the current corresponding to that rate of increase  $\lambda$  will never stimulate, however long continued: while if the minimum is *lower* than this value then that progressive current will cause an excitation. I have been able mathematically to confirm his statement that his function  $\phi$  has a minimum as the time increases. Above, (H), is given the value of  $y$  for a progressive current: hence

$$\phi = \frac{y_b}{y_0} = \frac{c + \lambda t \left( \frac{a}{2} - b \right) + \frac{\lambda}{2k} \left\{ b^2 \left( \frac{a}{2} - \frac{b}{3} \right) - \frac{a^3}{12} \right\} + \frac{\lambda}{k} \frac{4a^3}{\pi^4} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi b}{a}}{c + \lambda t \frac{a}{2} - \frac{\lambda}{2k} \frac{a^3}{12} + \frac{\lambda}{k} \frac{4a^3}{\pi^4} e^{-k \frac{\pi^2}{a^2} t}}$$

This quantity I have calculated at different times for certain arbitrary values of the constants

$$a=1, \quad k=1, \quad b=\frac{a}{6}=\cdot1666, \quad c=\cdot001.$$

The calculation is not given for times so small that there is an error greater than 3% resulting from the neglect of all but the first term of the Fourier series. At and after  $t = \cdot03$  the error is less than 1%.

The following values of  $\phi$  are plotted in Fig. 2. It is easily seen that  $\phi$  falls to a minimum (which is lower the greater the value of  $\lambda$ ), and then rises again to the common asymptote of all the curves.

<sup>1</sup> Lapicque. *Journal de Physiol.* xi, p. 1009 etc. 1909.

TABLE. Value of  $\phi$  for

Time	$\lambda=1$	$\lambda=2$	$\lambda=.333$	$\lambda=.5$	$\lambda=.666$	$\lambda=.8$	$\lambda=1.0$	$\lambda=2$	$\lambda=3$
0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
.02	.862	.763	.672	.592	.536	.502	.462	.3575	.314
.03	.790	.672	.577	.505	.459	.433	.404	.3365	.310
.04	.737	.617	.533	.474	.439	.420	.399	.3535	.336
.05	.700	.588	.516	.469	.443	.428	.413	.380	.368
.06	.673	.572	.510	.473	.452	.441	.430	.404	.396
.07	.654	.564	.511	—	—	—	.447	—	—
.08	.643	.561	.517	.491	.477	.470	.463	—	.442
.09	.633	.560	.522	—	—	—	.478	—	—
.1	.627	.562	.528	.509	.501	.496	.490	.480	.477
.15	.619	.579	—	—	—	—	.540	—	—
.2	.620	—	—	—	—	—	.569	—	—
.25	.628	—	—	—	—	—	.591	—	—
.3	.633	.618	.612	.607	.606	.605	.603	.602	.601
.4	.641	—	—	—	—	—	.621	—	—
.5	.646	—	—	—	—	—	.633	—	—
.6	.649	—	—	—	—	—	.639	—	—
.7	—	—	—	—	—	—	.643	—	—

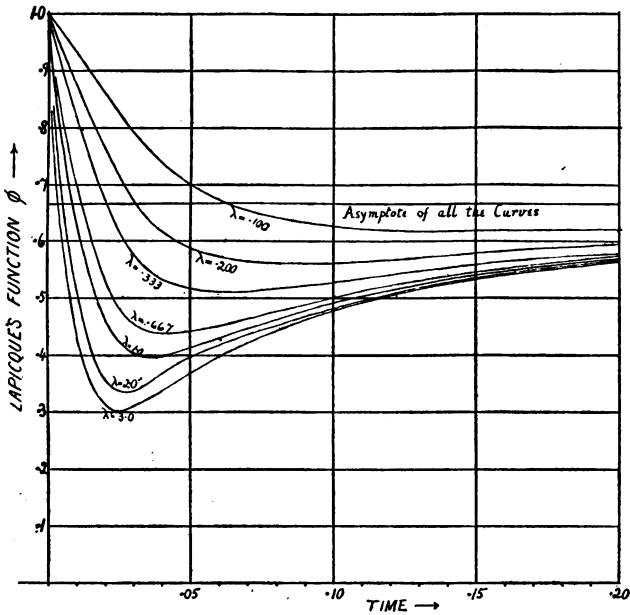


Fig. 2.



This asymptote, the value of  $\phi$  when the current is continued for a relatively very long time, is at a height in my calculations of .6667. More generally it is the

$$\text{Limit}_{t=\infty} \phi, \text{ i.e. } \frac{\frac{\alpha}{2} - b}{\frac{\alpha}{2}} = 1 - \frac{2b}{\alpha}.$$

Lapicque's theory, to take a particular numerical case, is that  $\phi$  has to reach the value .51 and then the stimulation occurs. It is thus seen from the figure that all currents whose rate of increase is greater than .333 reach this value of  $\phi$ : while all currents whose rate of increase is less than .333 never reach this value of  $\phi$  however long they are continued.

Thus far therefore Lapicque's theory holds. Unfortunately the considerations given below show that his simple and attractive hypothesis must be abandoned.

For a constant current the least current that will stimulate if allowed to pass for a time  $t$  is, according to Lapicque's theory,

$$i = \frac{\frac{k}{\nu} c(1-m)}{b - \frac{\alpha}{2}(1-m) - \frac{4a}{\pi^2} \left( m - \cos \frac{\pi b}{\alpha} \right) e^{-k \frac{\pi^2}{a^2} t}}.$$

This equation is shown above to accord very well with experimental facts, if  $b - \frac{\alpha}{2}(1-m)$  and  $\left( m - \cos \frac{\pi b}{\alpha} \right)$  are assumed to be positive. Hence if Lapicque's theory holds these quantities are undoubtedly positive, for otherwise the equation would be, not  $i = \frac{\lambda}{1 - \mu\theta^t}$ , but

$i = \frac{\lambda}{\mu\theta^t - 1}$ . This latter is not in accordance with facts.

Now for progressive currents, at an infinite time, the asymptotic value of  $\phi$  is  $1 - \frac{2b}{\alpha}$ . But from above

$$b - \frac{\alpha}{2}(1-m) > 0, \text{ i.e. } m > 1 - \frac{2b}{\alpha}:$$

therefore the value of  $\phi$  which must be reached for stimulation to occur lies above the value which  $\phi$  reaches at some time or other for every current however slowly increasing. Put graphically, the horizontal line which each curve has to meet for stimulation to occur, is *above* the asymptote of the curves, and therefore every curve reaches it. Hence

on Lopicque's theory every progressive current however slowly increasing will finally stimulate; since this is not the case we must either modify or abandon the theory.

Again in (L) above is given the formula connecting the concentration with the time in the case of a current which has reached a value  $\frac{k}{\nu} \lambda t_0$  by increasing slowly,  $(i = \frac{k}{\nu} \lambda t)$  and has then remained constant at that value. After a certain time  $e^{-k \frac{\pi^2}{a^2} (t - t_0)}$  has become zero, so we may put

$$y = c + \lambda t_0 \left( \frac{a}{2} - x \right).$$

Thus Lopicque's hypothesis that  $\phi = \frac{yb}{y_0}$  never reaches a certain minimum  $m$  means that

$$\frac{c + \lambda t_0 \left( \frac{a}{2} - b \right)}{c + \lambda t_0 \frac{a}{2}} \text{ is } > m,$$

*i.e.*  $c + \lambda t_0 \left( \frac{a}{2} - b \right) > mc + m \lambda t_0 \frac{a}{2},$

*i.e.*  $c(1 - m) > \lambda t_0 \left\{ m \frac{a}{2} - \frac{a}{2} + b \right\}.$

But this means

$$\lambda t_0 < \frac{c(1 - m)}{m \frac{a}{2} - \frac{a}{2} + b},$$

*i.e.*  $\frac{k}{\nu} \lambda t_0 = i < \frac{c(1 - m) \frac{k}{\nu}}{m \frac{a}{2} - \frac{a}{2} + b},$

which is the value of the least constant current that will excite.

Thus if Lopicque's hypothesis holds for constant currents  $i$  the current finally reached is not so great as the smallest current which will stimulate. We know however that a current may be increased slowly and then kept constant at a value many times greater than the liminal value, without an excitation occurring. According to Lopicque's hypothesis the only currents which will not stimulate when their full value is arrived at slowly are those currents which would not stimulate anyhow. This we know to be untrue, so we must turn elsewhere for a theory.

It seemed inevitable that no reasonably simple function of the concentration alone can be made to condition the stimulation in a way

which will accord with the facts known about progressive currents. What is needed is some opposing time factor<sup>1</sup> which has little effect during times of short duration (as in stimulation by a constant current), but very considerable effects during the longer times involved in the action of progressive currents. Two such hypotheses I have considered. The first which I have had to abandon owing to mathematical difficulties was that the membranes are to a certain extent permeable by the salts, and therefore that the ions in the neighbourhood of the membrane were being lost by going through the membrane. For short times this effect would be inconsiderable, for longer times it might modify *in toto* the effects observed. The hypothesis involves the boundary condition

$$i = \sigma(y - c) - \frac{k}{\nu} \frac{\partial y}{\partial x}, \text{ at } x=0 \text{ and } x=a,$$

instead of the simple condition

$$i = -\frac{k}{\nu} \frac{\partial y}{\partial x}.$$

As I could not obtain a solution with this condition, and as Professor Forsyth (who was kind enough to give me his advice) was unable to give me much hope of doing so, the hypothesis has not been further considered. A strong objection to it is given below (p. 223). The second theory I have considered accords with all the facts hitherto observed, and has the advantage of giving a further insight into the actual processes which determine an excitation.

It may be profitable to take an analogy before proceeding to describe the present theory in detail. Let us suppose a long cylinder filled with a mixture of  $O_2$  and  $H_2$  gas. At any one point the temperature of the cylinder is raised. We know that the action  $O_2 + 2H_2 \rightarrow 2H_2O$  (vapour) goes on very slowly at ordinary temperatures. When the temperature is raised it goes on more quickly and at a certain temperature the mixture combines explosively: an explosion occurs when the heat produced by combination is no longer conducted away as fast as it is produced. When once the explosive stage is reached, *i.e.* when once the rate of combination exceeds a certain limit the explosion takes place and travels as a wave down the tube. At any given temperature the rate of combination is proportional to (tension of  $O_2$ ) (tension of  $H_2$ )<sup>2</sup>. If now we raise the temperature very slowly to the explosive temperature, just before the latter is reached the combination  $O_2 + 2H_2 \rightarrow 2H_2O$  goes on at an appreciable rate. Thus considerable quantities of  $O_2$  and  $H_2$  may be transformed into water vapour, and the tension of each may correspondingly fall. Now when finally the temperature which was originally that of an explosion is reached the rate of combination which is proportional to  $[O_2][H_2]^2$  may be nowhere near what it would have been if that temperature had been reached quickly: for there will be very little  $O_2$  and  $H_2$  left to combine. Thus if we reach the explosive temperature too slowly the explosion will never occur at all. This I believe to be an exact analogy to the effects of slowly increasing currents.

<sup>1</sup> Cf. Keith Lucas. *This Journal*, xxxvii. p. 477. 1908.

Suppose a nervous impulse to be started by the rate of breakdown of *some substance*<sup>1</sup> in the tissue exceeding a certain limit, *M* say. The amount of substance at any time *t* being *S<sub>t</sub>* we shall have two relations:

(1) the rate of breakdown,  $-\frac{dS_t}{dt}$ , is proportional to the amount still present at that moment:

$$-\frac{dS_t}{dt} \propto S_t.$$

(2) the rate of breakdown is conditioned by the degree of concentration set up by the current, and is proportional either ( $\alpha$ ) to the excess of the concentration of some ion over the normal concentration,  $-\frac{dS_t}{dt} \propto (y - c)$  or ( $\beta$ ) to the difference in concentration between two given points,

$$-\frac{dS_t}{dt} \propto (y_0 - y_b).$$

[These possibilities ( $\alpha$ ) and ( $\beta$ ) lead to exactly the same type of results: in fact ( $\alpha$ ) is a particular case of ( $\beta$ ), when  $b = \frac{a}{2}$ . For simplicity I have used ( $\alpha$ ).]

Hence we shall have

$$-\frac{dS_t}{dt} = \gamma S(y - c),$$

where  $\gamma$  is some constant:

*i.e.* 
$$-\frac{d}{dt} \log S_t = \gamma (y - c) \dots\dots\dots(1).$$

Let us consider the consequences of this theory applied to constant currents. Here the concentration at any time is given by

$$y - c = i \frac{\nu}{k} \left( \frac{a}{2} - b \right) - i \frac{4\nu}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi b}{a}.$$

Hence integrating the equation (1) above we find,

$$\frac{1}{\gamma} \log \frac{S_t}{S_0} = -i \frac{\nu}{k} \left( \frac{a}{2} - b \right) t - i \frac{4\nu}{k^2} \frac{a^3}{\pi^4} \cos \frac{\pi b}{a} \left( 1 - e^{-k \frac{\pi^2}{a^2} t} \right),$$

<sup>1</sup> [Compare the "receptive substances" of Prof. Langley. The compound whose breakdown is measured by  $-\frac{dS}{dt}$  may be of any nature, physical or chemical. It is not necessary, or possible to make specific assumptions as to its nature, except that the fact that its stability is affected by changes (+ or -) in the concentration of the ions suggests that it actually combines with the ions in question. The action of paralysing poisons might possibly be by rendering the breakdown complete (hence the initial stimulating effect of some of these) by replacing the ions which normally complete the compound, and then preventing the possibility of further breakdown by the stability of their own combination with the substance.]

$$i.e. \quad -\frac{dS_t}{dt} = S_0\gamma \left[ i \frac{\nu}{k} \left( \frac{a}{2} - b \right) - i \frac{4\nu}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi b}{a} \right] \\ \times e^{-i\gamma \frac{\nu}{k} \left( \frac{a}{2} - b \right) t - i\gamma \frac{4\nu}{k^2} \frac{a^3}{\pi^4} \cos \pi \frac{b}{a} \left( 1 - e^{-k \frac{\pi^2}{a^2} t} \right)}$$

Now for constant currents,  $t$  the time required to reach an excitation is small. Then if  $\gamma$  is not large we have the second term  $e^{-\theta}$ , which is 1, so that

$$-\frac{dS_t}{dt} = S_0\gamma \left[ i \frac{\nu}{k} \left( \frac{a}{2} - b \right) - i \frac{4\nu}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi b}{a} \right].$$

Now by hypothesis  $-\frac{dS_t}{dt}$  has to exceed a certain limit  $M$  before stimulation occurs: hence the liminal current is given by

$$\frac{M}{S_0\gamma} = i \frac{\nu}{k} \left( \frac{a}{2} - b \right) - i \frac{4\nu}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi b}{a}, \\ i.e. \quad i = \frac{\lambda}{1 - \mu\theta^t} \quad \text{where } \lambda = \frac{M k}{S_0\gamma \nu}, \quad \mu = \frac{4a \cos \frac{\pi b}{a}}{\pi^2 \left( \frac{a}{2} - b \right)}, \quad \theta = e^{-k \frac{\pi^2}{a^2}}.$$

This equation has been shown above to hold with considerable accuracy.

*Application of the new theory to progressive currents.* For progressive currents the concentration (see (H) above) is,

$$y - c = \lambda t \left( \frac{a}{2} - x \right) - \frac{\lambda}{6k} \left\{ \left( x - \frac{a}{2} \right)^3 - \frac{3}{4} a^2 \left( x - \frac{a}{2} \right) \right\} + \frac{\lambda}{k} \frac{4a^3}{\pi^4} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi x}{a}.$$

Integrating as before,

$$\log \frac{S}{S_0} = \gamma \left[ -\frac{\lambda t^2}{2} \left( \frac{a}{2} - x \right) + \frac{\lambda t}{6k} \left\{ \left( x - \frac{a}{2} \right)^3 - \frac{3}{4} a^2 \left( x - \frac{a}{2} \right) \right\} + \frac{\lambda}{k^2} \frac{4a^6}{\pi^6} \cos \frac{\pi x}{a} \left( 1 - e^{-k \frac{\pi^2}{a^2} t} \right) \right], \\ \therefore -\frac{dS}{dt} = S_0\gamma \left[ \lambda t \left( \frac{a}{2} - x \right) - \frac{\lambda}{6k} \left\{ \left( x - \frac{a}{2} \right)^3 - \frac{3}{4} a^2 \left( x - \frac{a}{2} \right) \right\} + \frac{\lambda}{k} \frac{4a^3}{\pi^4} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi x}{a} \right] \\ \times e^{-\gamma \left[ \frac{\lambda t^2}{2} \left( \frac{a}{2} - x \right) - \frac{\lambda t}{6k} \left\{ \left( x - \frac{a}{2} \right)^3 - \frac{3}{4} a^2 \left( x - \frac{a}{2} \right) \right\} - \frac{\lambda}{k^2} \frac{4a^6}{\pi^6} \cos \frac{\pi x}{a} \left( 1 - e^{-k \frac{\pi^2}{a^2} t} \right) \right]}$$

Now in the case of progressive currents  $\lambda$  is small and  $t$  is large (compared with the quantities used in the experiments on constant currents), while  $\lambda t$  is finite.

Hence in  $-\frac{dS}{dt}$  we may neglect, in the first term, all except  $\lambda t \left( \frac{1}{2}a - x \right)$ , and in the second all but  $-\frac{1}{2}\gamma \lambda t^2 \left( \frac{1}{2}a - x \right)$ , and nevertheless obtain results which are almost exactly correct. This is not the case

when we consider currents increasing very rapidly, for then  $\lambda$  is no longer small: the only cases however at present of interest are when  $\lambda$  is small ("progressive currents"), and when  $\lambda$  is very large ("constant currents" whose values are arrived at almost instantaneously). With the condition that  $\lambda$  is small we have

$$-\frac{dS}{dt} = S_0 \gamma \lambda t \left(\frac{a}{2} - x\right) e^{-\gamma \frac{\lambda t^2}{2} \left(\frac{a}{2} - x\right)}.$$

Excitation will occur when this quantity exceeds a certain limit  $M$ . In the figure (Fig. 3) are given some curves for the value of  $-\frac{dS}{dt}$ , the

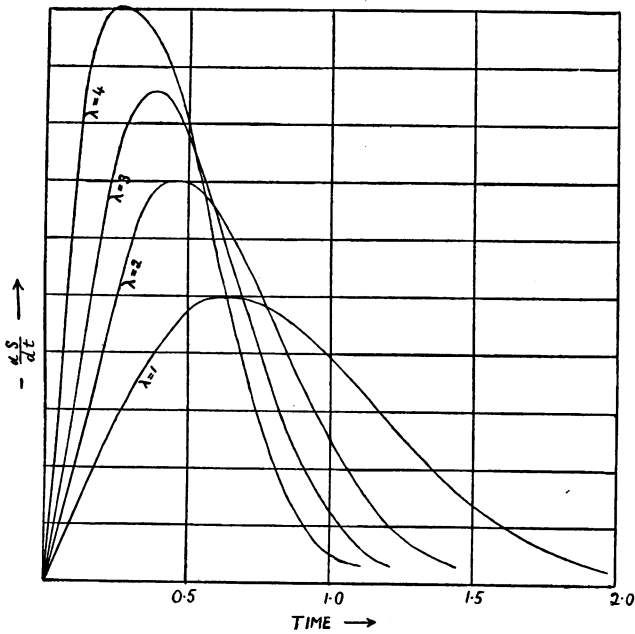


Fig. 3.

quantity which has to exceed a certain limit for excitation to occur, for different values of  $\lambda$ , the rate of increase of the exciting current. It will be seen that each of these curves shows a definite maximum, and that the maximum is higher the faster the current increases (*i.e.* the greater the value of  $\lambda$ ). The hypothesis I have advanced is that (to take a numerical case) the value of  $-\frac{dS}{dt}$  has to reach a value greater than 140 if excitation is to occur. The vertical height of the figure

is represented by 200. It is then seen that all progressive currents whose rate of increase is *less* than 2 never cause excitation: that the current whose rate of increase is 2 exactly causes it: and that all currents whose rate of increase is *greater* than 2 cause it.

Hence we have a perfectly rigid explanation of the fact that there is a certain rate of increase of a progressive current, below which no excitation can occur.

Much work has been done by Lucas<sup>1</sup> and others in tracing a connexion between the rate of increase of a current and the least value which must be reached if an excitation is to occur. Unfortunately none of the observers have taken the precaution to cut off the current *immediately* it has reached its full value: the current has been made constant and then been allowed to pass for some arbitrary (and presumably inconstant) time before it has been cut off. For rapidly increasing currents this fact is of the utmost importance for it means that for cases where  $\lambda$  is large what they have observed is almost entirely the least *constant* current which will cause excitation. This current has been allowed to pass for a relatively long time, and therefore has itself caused the excitation which they have observed. For more slowly increasing currents this fact is of much less importance, and we may assume in order to test the experimental results that the current has been cut off immediately at the end of its increase. In this case we have the relation

$$M = S_0 \gamma \left( \frac{a}{2} - x \right) \lambda t e^{-\gamma \frac{\lambda t^2}{2} \left( \frac{a}{2} - x \right)},$$

connecting the time and the rate of increase of the current which just causes excitation. But  $\frac{k}{v} \lambda t$  is the current  $i$  which is reached in time  $t$ : hence we may write

$$B = i e^{-\alpha i t},$$

where  $B$  and  $\alpha$  are two constants. I have calculated below the values of  $i$  for values of  $t$ , with certain arbitrary values of  $B$  and  $\alpha$ .

$t$	0	8	19	29	38	56	71	85	98	109	119
$i$	125.75	127.5	130	132.5	135	140	145	150	155	160	165
$t$	128	137	144	151	158	163	166	168	170.5	172	175
$i$	170	175	180	185	190	195	197.5	200	202.5	205	207.5

The numbers are plotted in the figure: the dotted line represents the minimum gradient necessary to excite. The figure is obviously like

<sup>1</sup> Keith Lucas. *This Journal*, xxxvi. p. 253. 1907.

those given by Lucas<sup>1</sup>, except near  $t=0$ , the vertical axis, where according to his observations the curve becomes horizontal. For this there are two reasons, both explained above: (1) the method of calculation involves the assumption that  $\lambda$  is not large: for observations near  $t=0$   $\lambda$  is large and therefore the method of calculation is no longer quite rigid: (ii) his observations were taken without the precaution of shutting off the current *directly* the full value of the current was reached. Until the results of experiments with this precaution taken

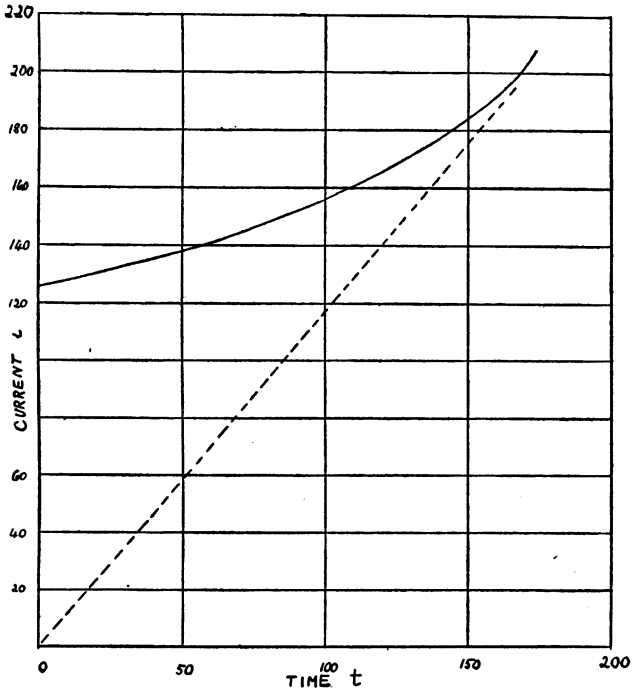


Fig. 4.

are available it is of no use calculating results and comparing them with the experimental facts. The general results of such experiments can be seen at present, and qualitatively these fit the formula given above well. The concordance observed between the experimental results is probably due to the fact that about equal intervals of time have always elapsed between the reaching of the full value, and the breaking of the current.

<sup>1</sup> This *Journal*, xxxvi. p. 260 etc. 1907.



*Alternating Current.*

For an alternating current  $i = i_0 \sin (nt + \epsilon)$  it was shown above (F) that

$$y - c = -\frac{a}{\sqrt{2p}} \frac{\nu i_0}{k} \frac{1}{\sqrt{1 + 2e^{-p} \cos p + e^{-2p}}} \left[ e^{-p \frac{x}{a}} \cos \left( nt + \epsilon + \psi + \frac{\pi}{4} - \frac{px}{a} \right) - e^{-p \frac{a-x}{a}} \cos \left( nt + \epsilon + \psi + \frac{\pi}{4} - p \frac{a-x}{a} \right) \right],$$

where  $\psi$  is an auxiliary angle which does not in the least concern the argument and  $p = a \sqrt{\frac{n}{2k}} : \frac{n}{2\pi}$  is the frequency. As the absolute value of the frequency does not come in, we may for simplicity take  $n$  as the frequency.

Now if we consider the changes of concentration so near to the membrane that  $x$  may be put small compared with  $a$ , and if we suppose  $n$  the frequency is rather large, then we may neglect  $e^{-p \frac{a-x}{a}}$  as being too small to have any effect and write,

$$y - c = -\frac{a}{\sqrt{2p}} \frac{\nu i_0}{k} \frac{1}{\sqrt{1 + 2e^{-p} \cos p + e^{-2p}}} e^{-p \frac{x}{a}} \cos \left( nt + \epsilon + \psi + \frac{\pi}{4} - \frac{px}{a} \right).$$

Now  $(y - c)$  is on the whole as often + as -, for

$$\cos \left( nt + \epsilon + \psi + \frac{\pi}{4} - \frac{px}{a} \right)$$

is as often + as -. Hence over any finite time (say several times the period of the current) the average value of  $(y - c)$  is zero, and therefore  $-\frac{dS}{dt}$  which is proportional to  $(y - c)$  has an average value of zero, and therefore  $S$  is relatively unaltered.

Hence since, for excitation,  $-\frac{dS}{dt} = \gamma S (y - c)$  has to be greater than a certain limit,  $(y - c)$  has to be greater than a certain limit. But the maximum value of  $(y - c)$  is when the time is such that the cosine = -1. Hence

$$\frac{\nu i_0}{k} \frac{a}{\sqrt{2p}} e^{-p \frac{x}{a}} \frac{1}{\sqrt{1 + 2e^{-p} \cos p + e^{-2p}}}$$

must be > a certain limit,  $h$  say. Putting in the value of  $p$  we find the liminal current  $i_0$  to be connected with the frequency by the relation,

$$\frac{\nu i_0}{\sqrt{kn}} \frac{1}{\sqrt{1 + 2e^{-a \sqrt{\frac{n}{2k}} \cos a} \sqrt{\left(\frac{n}{2k}\right) + e^{-2a \sqrt{\frac{n}{2k}}}}} = h,$$

i.e. 
$$\frac{i_0}{\sqrt{n}} = \frac{h\sqrt{k}}{v} \sqrt{1 + 2e^{-a\sqrt{\frac{n}{2k}}}\cos a} \sqrt{\left(\frac{n}{2k}\right) + e^{-2a\sqrt{\frac{n}{2k}}}.$$

Now Nernst<sup>1</sup>, by his method of calculation, finds that  $i_0/\sqrt{n}$  should be constant. As a first approximation this is true experimentally, and his formula can be derived from the one above by putting  $a = \infty$ . It is noticeable however on looking at the figures which he quotes that  $i_0/\sqrt{n}$

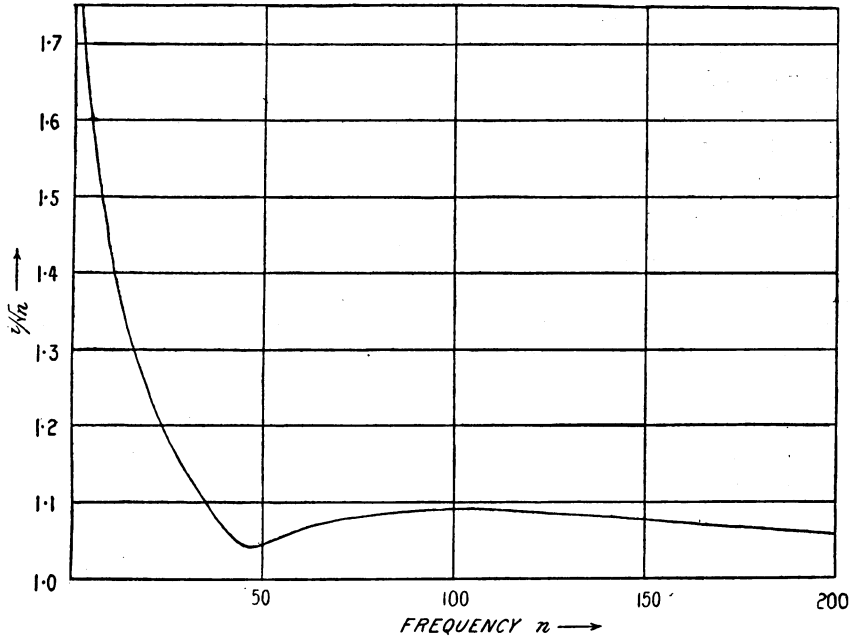


Fig. 5.

is not constant but exhibits regular divergencies from a constant value:  $i_0/\sqrt{n}$  always decreases as  $n$  increases, and then after awhile with higher values of  $n$  begins slightly to increase again. To test whether this was the case with the formula deduced above I have calculated the value of

$$\sqrt{1 + 2e^{-a\sqrt{\frac{n}{2k}}}\cos a} \sqrt{\left(\frac{n}{2k}\right) + e^{-2a\sqrt{\frac{n}{2k}}}$$

for a particular arbitrary value of  $\frac{a}{\sqrt{2k}} = .2305$ . The numbers for different values of  $n$  are given below.

<sup>1</sup> Nernst. *Arch. f. d. ges. Physiol.* cxxii. p. 285. 1908.

$n$	0	1	4	9	16	25		
$\sqrt{1 + 2e^{-a\sqrt{\frac{n}{2k}} \cos \sqrt{\left(\frac{n}{2k}\right) a + e^{-2a\sqrt{\frac{n}{2k}}}}$	2	1.812	1.617	1.448	1.302	1.184		
36	46.6	49	64	81	100	121	169	196
1.092	1.040	1.046	1.07	1.0835	1.090	1.084	1.0685	1.059

In the figure (Fig. 5) are plotted these values. It is seen that  $i/\sqrt{n}$  falls at first rapidly as  $n$  increases: then rises again slowly to a maximum, after which it remains almost constant with a slight tendency to decrease. This is exactly what is observed experimentally. This is really one of the strongest pieces of evidence in favour of the validity of the whole method of calculation above, and of the physical theory first suggested by Nernst.

[For the variations of  $i/\sqrt{n}$  the following figures for  $i/\sqrt{n}$  may be quoted from Nernst's paper. I have not been able to give parallel columns of calculated figures because of the complexity of the equation involved, but the general effect is obvious. If the arbitrary value of  $a/\sqrt{k}$  taken for the figure had been taken smaller the changes of  $i/\sqrt{n}$  would be much less noticeable for increasing  $n$ ,

$n$	100	200	600	1000	100	300	600	1000	571	830	1200	1846	3660
$i/\sqrt{n}$	3.8	3.2	3.1	3.2	2.7	2.1	2.3	2.2	1.81	1.83	1.75	1.69	1.56
$n$	105	136	785	960	2230	920	1030	1120	1285	1350	1400	1430	
$i/\sqrt{n}$	78	75	77	77	81	1.87	1.74	1.77	1.70	1.69	1.67	1.66	
$n$	857	1600	3430	3950	4280	5740	460	760	940	1120	1410	2040	
$i/\sqrt{n}$	172	169.2	159	153	150	150	1.31	1.09	1.04	1.16	1.14	1.24	
$n$	2700	3570											
$i/\sqrt{n}$	1.21	1.22]											

### Logarithmic Currents.

Lapicque<sup>1</sup> finds that the liminal current necessary to secure stimulation is less when the current increases linearly than when it increases "logarithmically," *i.e.* when  $i = i_0 \{1 - e^{-\beta^2 t}\}$ . Of course this must depend on the rate at which the "logarithmic" current reaches its value, for if  $\beta^2$  is very large  $i = i_0$  from the beginning and we have the case of a constant current: which we know to be *more* effective than a progressive one in causing excitation. For the case of a "logarithmic" current not instantaneously established we have from (P) above,

$$y - c = + \frac{v i_0}{k} \left( \frac{\alpha}{2} - x \right) - \frac{v i_0}{k} \frac{1}{\beta} e^{-\beta^2 t} \frac{\sin \beta \left( \frac{\alpha}{2} - x \right)}{\cos \beta \frac{\alpha}{2}},$$

for after a very short time the terms inside the  $\Sigma$  are all zero.

<sup>1</sup> *Journ. de Physiol.* xi. p. 1044, 1909.

Hence integrating the equation  $-\frac{d}{dt} \log S = \gamma (y - c) S$ ;

$$\log \frac{S}{S_0} = -\gamma \left\{ \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) t - \frac{\nu i_0}{k \beta^3} \left( 1 - e^{-\beta^2 t} \right) \frac{\sin \beta \left( \frac{a}{2} - x \right)}{\cos \beta \frac{a}{2}} \right\},$$

giving 
$$-\frac{dS}{dt} = S_0 \gamma \left\{ \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) - \frac{\nu i_0}{k \beta} e^{-\beta^2 t} \frac{\sin \beta \left( \frac{a}{2} - x \right)}{\cos \beta \frac{a}{2}} \right\}$$

$$\times e^{-\gamma \left\{ \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) t - \frac{\nu i_0}{k \beta^3} \left( 1 - e^{-\beta^2 t} \right) \frac{\sin \beta \left( \frac{a}{2} - x \right)}{\cos \beta \frac{a}{2}} \right\}}.$$

Comparing these with the values of  $\log \frac{S}{S_0}$  and  $-\frac{dS}{dt}$  found for progressive currents on p. 210 we see that if at time  $t$  the "progressive" current be made constant, and the "logarithmic" current be then practically at its full value we have for the progressive current which has reached a value  $i_0$

$$-\frac{dS}{dt} = S_0 \gamma \left[ \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) + \text{negligible terms} \right] e^{-\gamma \frac{\nu i_0}{2k} \left( \frac{a}{2} - x \right) + \text{negligible terms}},$$

while for the logarithmic current

$$-\frac{dS}{dt} = S_0 \gamma \left[ \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) + \text{negligible terms} \right] e^{-\gamma \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right) + \text{negligible terms}}.$$

The only difference between these is that the exponential in the first case is  $e^{-\gamma \frac{\nu i_0}{2k} \left( \frac{a}{2} - x \right)}$  and in the second case  $e^{-\gamma \frac{\nu i_0}{k} \left( \frac{a}{2} - x \right)}$ .

The first is greater than the second, for they are both less than 1, and the second is the square of the first. Hence at the time  $t$  when both currents are practically fully established the value of  $-\frac{dS}{dt}$  is greater for the "progressive" than for the "logarithmic." This agrees with Lopicque's experimental observation that the "logarithmic" current needs a higher threshold value to obtain excitation than the "progressive" current.

*The connection between the least slope of a progressive current and the liminal strength of a constant current.*

From (E) above (putting for simplicity  $x = 0$ , i.e. considering the concentrations at the membrane) the liminal strength of a constant current is found to be, by putting  $t = \infty$ , proportional to  $\frac{k}{\nu a}$ . For

excitation by progressive currents we have on p. 211 the condition that

$$\lambda \frac{a}{2} t e^{-\gamma \lambda \frac{a}{2} \cdot \frac{t^2}{2}}$$

must exceed a certain limit.  $\lambda t = \frac{\nu i}{k}$ , where  $i$  is the current finally reached. Hence

$$a \frac{\nu i}{k} e^{-\frac{\gamma}{4} a \frac{\nu i}{k} \cdot t}$$

must exceed a certain limit,  $m$  say. Now the liminal slope is the tangent from the origin to the curve whose equation is obtained by equating this quantity to  $m$  (see Fig. 4), and is therefore given by  $\frac{di}{dt} = \frac{i}{t}$ . We have

$$m = \left(a \frac{\nu}{k}\right) i e^{-\frac{\gamma}{4} a \frac{\nu}{k} i t} \dots\dots\dots(i).$$

Taking logarithms and differentiating we find

$$\frac{1}{i} \frac{di}{dt} - \frac{\gamma}{4} a \frac{\nu}{k} \left(t \frac{di}{dt} + i\right) = 0,$$

*i.e.*  $\frac{di}{dt} \left\{ \frac{1}{i} - t \frac{\gamma}{4} \left(a \frac{\nu}{k}\right) \right\} = \frac{\gamma}{4} \left(a \frac{\nu}{k}\right) i,$

into which putting  $\frac{di}{dt} = \frac{i}{t}$  we have,

$$1 - i t \frac{\gamma}{4} \left(a \frac{\nu}{k}\right) = \frac{\gamma}{4} \left(a \frac{\nu}{k}\right) i t,$$

*i.e.*  $i t = \frac{2}{\gamma} \left(\frac{k}{a \nu}\right).$

Putting this into (i) above, after squaring we find,

$$i^2 = m^2 e \left(\frac{k}{a \nu}\right)^2.$$

Hence

$$\frac{i}{t} = m^2 e \frac{\gamma}{2} \left(\frac{k}{a \nu}\right).$$

Thus the least slope is directly proportional to  $\frac{k}{a \nu}$ , which constants are affected by temperature changes, or by passing to other tissues. Thus an increase of  $k$  as by a rise of temperature, or a decrease of  $a$  as by passing from one tissue to another, or possibly a decrease (to 1/2) of  $\nu$  by placing the tissue in a solution of a divalent salt, all tend to increase the least slope of a progressive current. They will have exactly the same effect on the liminal constant current, which is also proportional

to  $\frac{k}{av}$ . The divergencies from an exact relation between these two quantities may be due to the fact that the other quantities (*e.g.*  $m^2$  and  $\gamma$ ) change also. This explains however why the least slope of a progressive current always runs parallel at any rate to the liminal strength of a constant current<sup>1</sup>.

*Summation of Stimuli.*

The case of induction shocks is simpler to carry out experimentally, that of short constant currents is simpler mathematically. The object of the inquiry below is to trace the factor to which "summation of stimuli" can be credited qualitatively and quantitatively: so for simplicity I have taken the case of short constant currents, as this factor will be the same in either case. The fundamental observation<sup>2</sup> is that two induction shocks, each (say) 5% below the liminal strength necessary for excitation, will cause excitation if sent in consecutively at less than a certain interval  $t_2$  apart: and it is suggested that this time  $t_2$ , the "summation time," is a measure of the rate at which the excitatory process dies away. Below the variations of  $t_2$ , for different tissues, and for the same tissue under different conditions, are shown to be connected directly with  $k$  the diffusion constant and  $a$  the size of the structure of the tissue in question:  $t_2$  has to increase if  $\frac{k}{a^2}$  decreases, and vice versa, so that increase of the diffusion constant (as by raising the temperature), or decrease of the distance apart of the membranes of the tissue (as by passing to a different tissue) will decrease the summation time of two stimuli. Thus the summation time for two stimuli, each  $n\%$  below the liminal current strength, is a very simple function of the physical constants of any tissue, and may be used as a means of comparing different tissues, and the same tissue under different conditions.

Suppose a constant current  $i$  is sent into a tissue for a time  $t_1$ : and that  $i$  is less than the least current necessary to stimulate in time  $t_1$  in the ratio  $p:1$ . The concentration at any point is, at the end of the time  $t_1$ , (See (D) above),

$$y = c + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_1} \cos \frac{(2n-1) \pi x}{a} \dots\dots(i).$$

<sup>1</sup> Keith Lucas. *This Journal*, xxxvii. p. 471. 1908.

<sup>2</sup> Keith Lucas. *This Journal*, xxxix. p. 461. 1910.

Then the current is broken, and the ions begin to return to their normal position and concentration. A solution of the diffusion equation for the time subsequent to the break is

$$y = B + \sum_1^{\infty} A_r e^{-k \frac{r^2 \pi^2}{a^2} t} \cos \frac{r \pi x}{a} \dots\dots\dots(ii).$$

Also at  $x=0$  and  $x=a$ ,  $\frac{\partial y}{\partial x} = 0$  (the condition that no current is passing): and at  $t=0$   $y$  must equal the quantity above, (i).

Now in (D) if we put  $t=0$  we have the relation,

$$c = c + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} \cos \frac{(2n-1) \pi x}{a},$$

*i.e.* 
$$\frac{vi}{k} \left( \frac{a}{2} - x \right) = \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} \cos \frac{(2n-1) \pi x}{a}.$$

Inserting this in (i) and equating (i) to (ii) we find on equating coefficients of  $\cos \frac{(2n-1) \pi x}{a}$  that (ii) becomes

$$y = c + \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \left( 1 - e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_1} \right) e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t} \cos \frac{(2n-1) \pi x}{a} \dots(iii),$$

which on putting  $t=t_2$  gives the concentration at the end of a pause in the current of length  $t_2$ . Now at the end of the pause the current  $i$  is sent in again for a time  $t_1$ : we have for the time beginning now,

$$y = B' + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \sum_1^{\infty} A'_r e^{-k \frac{r^2 \pi^2}{a^2} t} \cos \frac{r \pi x}{a} \dots\dots\dots(iv).$$

For this satisfies the diffusion equation, at  $x=0$  and  $x=a$   $\frac{\partial y}{\partial x} = -\frac{vi}{k}$ , and at  $t=0$  it has to be equal to the concentration in (iii) at the end of time  $t_2$ ;

$$y = c + \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \left( 1 - e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_1} \right) e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_2} \cos \frac{(2n-1) \pi x}{a} \dots\dots(v).$$

Putting in

$$\frac{vi}{k} \left( \frac{a}{2} - x \right) = \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} \cos \frac{(2n-1) \pi x}{a},$$

and equating coefficients of  $\cos \frac{(2n-1) \pi x}{a}$  in (iv) and (v), we find that the concentration at the end of the time  $t_1$ , *i.e.* at the end of the passage of the constant current, is

$$y = c + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} \times \left\{ 1 - e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_2} + e^{-k \frac{(2n-1)^2 \pi^2}{a^2} (t_2+t_1)} \right\} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t_1} \cos \frac{(2n-1) \pi x}{a},$$

which, owing to the rapid convergency of this series, we may write

$$y = c + \frac{vi}{k} \left( \frac{a}{2} - x \right) - \frac{4vi}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1} \left( 1 - e^{-k \frac{\pi^2}{a^2} t_2} + e^{-k \frac{\pi^2}{a^2} (t_2 + t_1)} \right) \cos \frac{\pi x}{a} \dots \text{(vi)}$$

Now  $t_2$  is by hypothesis the "summation time," *i.e.*  $y - c$  has risen to a value just sufficient to stimulate: while  $i$  is only  $pi_0$ , where  $p$  is a fraction and  $i_0$  is the least current that will stimulate in time  $t_1$  if sent in only once. If  $(y - c)$  has to reach a value  $m$  for stimulation to occur we know that

$$i_0 = \frac{m \frac{k}{v}}{\frac{a}{2} - 4 \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1}},$$

if we consider the concentration at the membrane, *i.e.* put  $x = 0$ .

Hence

$$i = \frac{pm \frac{k}{v}}{\frac{a}{2} - 4 \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1}}.$$

But  $i$  just stimulates when sent in a second time: *i.e.*  $(y - c)$  in (vi) reaches the value  $m$ : hence

$$i = \frac{m \frac{k}{v}}{\frac{a}{2} - 4 \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1} \left( 1 - e^{-k \frac{\pi^2}{a^2} t_2} + e^{-k \frac{\pi^2}{a^2} (t_2 + t_1)} \right)}.$$

Equating these last two values of  $i$  we have,

$$\frac{a}{2} - 4 \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1} = p \left\{ \frac{a}{2} - 4 \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1} \left( 1 - e^{-k \frac{\pi^2}{a^2} t_2} + e^{-k \frac{\pi^2}{a^2} (t_2 + t_1)} \right) \right\},$$

*i.e.* 
$$(1 - p) = \frac{8}{\pi^2} e^{-k \frac{\pi^2}{a^2} t_1} \left\{ 1 - p + pe^{-k \frac{\pi^2}{a^2} t_2} - pe^{-k \frac{\pi^2}{a^2} (t_2 + t_1)} \right\}.$$

Now  $e^{-k \frac{\pi^2}{a^2} t_2}$  is considerably greater than  $e^{-k \frac{\pi^2}{a^2} (t_2 + t_1)}$ . Hence if we increase  $\frac{k}{a^2}$  we decrease  $e^{-k \frac{\pi^2}{a^2} t_1}$ , and decrease the second term, for the decrease of  $pe^{-k \frac{\pi^2}{a^2} t_2}$  is much greater than the increase of  $-pe^{-k \frac{\pi^2}{a^2} (t_2 + t_1)}$ . Hence in order to keep the right-hand side constant we must decrease  $t_2$  considerably. Hence the summation time is decreased either ( $\alpha$ ) by increasing the diffusion constant, or ( $\beta$ ) by decreasing the distance between the membranes of the tissue.

Thus we have a reason for the conclusion which Lucas<sup>1</sup> reached experimentally that (i) the summation interval, (ii) the time it is

<sup>1</sup> *loc. cit.*

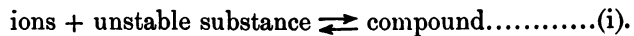


necessary to pass the least exciting constant current and (iii) the least rate of increase of a progressive current, are all seen to run parallel, and are intimately connected with one physical factor,  $\frac{k}{a^2}$ : which is really a measure of the rate at which diffusion tends to equalise concentration differences at the membranes.

*Excitation at Break of Constant Current.*

According to the theory advanced above as to the nature of electric excitation one can explain how the break of, or a pause in, a constant current causes an excitation. Further one can predict the form of the curve relating the liminal strength of a constant current to the duration of a short pause which causes an excitation. Any theory which pretends to explain the excitation physically should be able to account equally for its occurrence at break and make, as these are both equally obvious and important. Nernst<sup>1</sup> supposes that the protoplasm which has become "accommodated" to the presence of an excess of ions in its neighbourhood is excited when the break of the current causes a *diminution* in the concentration of the ions. This is in effect an additional hypothesis, viz. a lowering of the concentration of the ions is supposed to be as efficacious for causing excitation as an increase in the concentration. The hypothesis I have described above, on the other hand, will apply directly to this case, so we obtain a solution of this important fact without any multiplication of hypotheses.

In Fig. 1 the current  $i$  is supposed to be passing from  $CD$  to  $AB$ . If now it continue passing for some considerable time the unstable substance at the end  $CD$  where the current *enters* will take up a new equilibrium with the ions in its immediate neighbourhood, according to the scheme



Since the concentration of the ions at this end is largely diminished the equilibrium will have gone  $\leftarrow$ . Now the current is broken and the ions return to their normal position, *i.e.* the ions referred to in (i) have their concentration largely increased, (not instantaneously of course, but gradually,) and hence the action goes  $\rightarrow$ . This is exactly what the theory supposes to happen when a current is *sent into* the tissue, and if the rate at which the action goes  $\rightarrow$  is greater than a certain limit then excitation occurs. *This also explains why excitation at make occurs at*

<sup>1</sup> Nernst. *Arch. f. d. ges. Physiol.* cxxii. p. 281. 1908.

the cathode, and at break occurs at the anode: for the action takes place at the ends *AB* and *CD* respectively (Fig. 1).

At the moment when the current was broken we have for the concentration at any point, (putting  $t = \infty$  in (E) above),

$$y = c + vi/k(\frac{1}{2}a - x).$$

A solution of the equation  $\frac{\partial y}{\partial t} = k \frac{\partial^2 y}{\partial x^2}$ , which satisfies this initial condition, and the further one that no current is passing is, (cf. p. 220),

$$y = c + \frac{4vi}{k} \frac{a}{\pi^2} \sum_1^{\infty} \frac{1}{(2n-1)^2} e^{-k \frac{(2n-1)^2 \pi^2}{a^2} t} \cos \frac{2(n-1)\pi x}{a}.$$

Now for excitation the change of  $y$  must in a given time  $t$  exceed a certain limit, for then as before  $-\frac{dS}{dt}$  will exceed the limit required for excitation, (cf. p. 209). Hence

$$y - [c + vi/k(\frac{1}{2}a - x)]$$

must exceed a certain limit, and therefore (neglecting all but the first term of the series),

$$-\frac{vi}{k} \left(\frac{a}{2} - x\right) + \frac{4vi}{k} \frac{a}{\pi^2} e^{-k \frac{\pi^2}{a^2} t} \cos \frac{\pi x}{a}$$

must exceed a value, say  $m$ , at or near  $x = a$ .

This gives,

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

where  $\lambda$ ,  $\mu$ , and  $\theta$  have exactly the same values as those given on page 201 if we measure  $b$  from the other end of the box (Fig. 1).

This explains why Lucas<sup>1</sup> obtained exactly similar relations in the case of either a short passage or a short pause of a constant current.

The suggestion above (p. 208) that the effects observed with progressive currents are due to the gradual diffusion of the ions considered *through* the membranes seems to be negatived by the ready explanation which the other theory gives of the effects of short pauses in a constant current, in fact of the excitation at break. This explanation would not be possible if the diffusion of the ions through the membranes were of much account: for at break there would be no possibility of a large return to normal of the concentration, because the concentration has been kept down by a steady diffusion across the membrane.

My heartiest thanks are due to Mr Keith Lucas for the ever ready information and suggestions which he has given me as to the papers and experimental observations of himself and others: and to Mr C. G. Darwin for his kindness in looking through and criticising the mathematical treatment of the problem.

<sup>1</sup> Lucas. This *Journal*, xxxv. p. 313. 1907.

*Mechanical and Chemical Stimulation.*

The theory provides an explanation of these methods of excitation. A mechanical stress, or an increase of the osmotic pressure outside the space  $ABCD$  by the presence of some chemical body, may lead to a concentration of the fluid inside  $ABCD$ . The ion which effects an excitation will not be separated electrically from its complementary ion, but its increase of concentration will cause a change in the equilibrium between itself and the unstable substance  $S$ . This might lead to an excitation. The theory given above seems to me therefore to give, or at any rate to suggest, an explanation of all the phenomena in excitation of which I am at present aware. Mr W. B. Hardy has suggested to me that in case of any phenomena being observed which do not accord with the theory, various other physical effects may be introduced to account for them. For example,  $AB$  and  $CD$  may not be membranes, but portions of colloidal matter in combination with one of the dissolved ions. These ions would tend to diffuse outwards, and so there might be formed an electric double layer held together by electrical attraction, tending to separate by diffusion of the ions forming the outer layer. When the current is passed the concentration of these ions at  $AB$  is increased; and consequently the tendency to diffuse out is not so strong. The result would be a higher degree of combination between ions and colloid, following the above mathematical treatment. Now colloidal matter in living organisms is in what may be called a "critical state": it is in that position where very small changes in the external conditions may have almost infinite effects on the internal equilibrium and state of the tissue. Hence the extreme sensibility of living matter to very small changes of condition ("stimuli"), especially in higher animals where the temperature of the body is constant at that of the "critical state" of the tissue colloids. This conception of a double electric layer gives an interesting explanation of mechanical excitation. A very slight mechanical stress will change the *curvature* of the surfaces of the colloidal body  $AB$ : this will change the difference of potential between the two layers, and may cause at certain points a very large alteration in the equilibrium of ion and colloid, leading to excitation.

Another factor which may possibly be of importance has been entirely omitted from the theory: no mention has been made of *endosmotic effects*. An electric current passing down the nerve will transport water across the membrane by electric endosmose. The direction in which it is transported depends on the sign of the charge on the water in the double electric layer between water and colloid. Thus electric endosmose may, on making the current, tend to lower or raise the concentration of the salts in the neighbourhood of a membrane, by passing water in one direction or the other. Whether these and other physical effects are of importance remains for future work to decide, but they should be borne in mind when phenomena are observed which do not accord with the theory in its simpler form.