ON THE INTENSITY-TIME RELATIONS FOR STIMULATION BY ELECTRIC CURRENTS. I*

By H. A. BLAIR

(From the Department of Physiology, Western Reserve University Medical School, Cleveland)

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Justification is felt in advancing a new analysis of the time-intensity relations of tissue stimulation by electric currents for these reasons: first, the underlying hypotheses are as simple or simpler mechanically than those of previous formulae; second, the agreement with existing experimental data is as good or better; and third, the derivation of the formulae is very easy for all the common types of electrical stimuli without making any approximations.

The derivation is as follows: let the state of excitation or local excitatory process in the tissue under the influence of the stimulus be represented numerically by p and let the rate of attainment of this state be directly proportional to the exciting current or voltage. Further let there be a tendency of the tissue to remain normal leading to a reaction directly proportional to p so that finally,

$$\frac{dp}{dt} = KV - kp \tag{1}$$

In order that the tissue respond to the stimulus it is supposed that p must attain a liminal value h, so that there obtains for adequate direct current stimuli the relation,

$$\int_0^h \frac{kdp}{KV - kp} = -k \int_0^t dt$$

Integration gives finally,

$$\log \frac{KV}{KV - kh} = kt \tag{2}$$

where t is the time during which the stimulus is required to act.

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If the above hypotheses are correct, equation (2) should give the time-intensity relations for direct current stimulation.

An easy method of testing the equation is derived from noting that as t becomes very great

$$KV - kh \longrightarrow 0;$$

but V is now the rheobase, R, whence comes the close approximation

$$KR = kh$$

giving

$$\log \frac{V}{V - R} = kt \tag{3}$$

If experimental values of $\frac{V}{V-R}$ are plotted on semilogarithmic scale against the appropriate times, linearity tests the validity of equation (3).

In Fig. 1 are plotted three sets of data with $\frac{V}{V-R}$ on logarithmic scale against time on natural scale. These data are from Lapicque's book (1926). The three curves, *a*, *b*, and *c* respectively are of data from *Spirogyra*, sciatic gastrocnemius of the frog, and a nerve-muscle preparation of *Helix*. It will be noted that there is fair linearity except for the long times. In these cases, since V is nearly equal to R, a very small change in either makes a large change in $V/(V-R)$, therefore positions of points corresponding to these times cannot be required to conform closely on account of probable experimental errors. For example in *c* where the value of $V/(V-R)$ diverges most from linearity at long times its value for the last point on the graph is $61/(61-60) = 61$. If the rheobase were in error by $\pm$ 1 the resulting values of $V/(V-R)$ would be 30.5 or ∞ respectively. Small changes in V or in the rheobase do not, however, have much effect upon $V/(V-R)$ when V is large compared to R. Linearity can thus be required at short times if equation (3) is fulfilled but its existence at long times depends on extreme accuracy of measurement. It is evident that the curves do not pass through the origin, so an arbitrary constant will

have to be added to equation (3) giving now as the possible relation,

$$\log \frac{V}{V - R} = kt + C \tag{4}$$

where C is the constant whose meaning is considered later.

Equation (4) may be tested numerically, as follows: consider the rheobase R to be a perfect measurement leaving only k and C to be

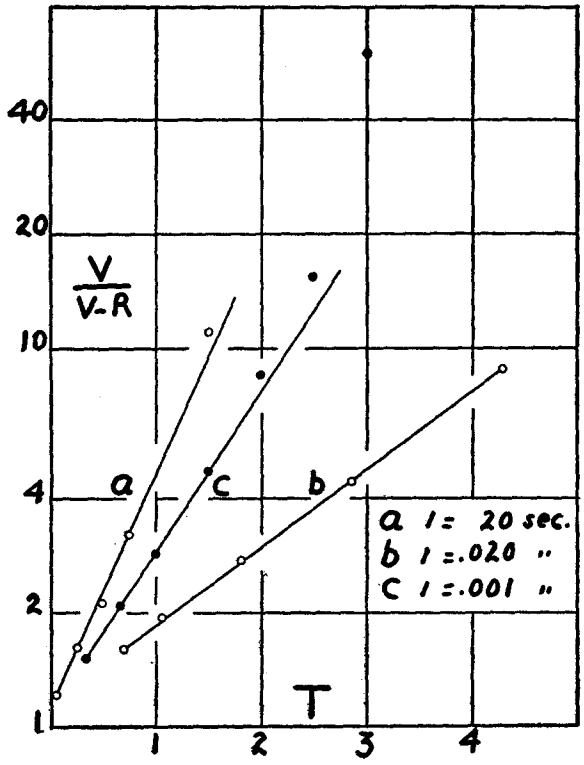

FIG. 1. A convenient scheme for plotting direct current data. *a, Spirogyra; b, Rana; c, Helix.*

determined. Two sets of V's and t's are required for this. It is obvious, of course, that either current data or voltage data may be used equally well without conversion. The sets to be used can best be chosen from a graph like Fig. 1. The data of the first and fourth

TABLE I

(*a*) *Spirogyra*, pp. 214–215. $k = 0.03036$; $C = 0.0524$

t sec.	1	5	10	15	30	100
V obs.	*5.8	2.6	1.9	*1.45	1.1	1.0
V cal.	5.8	2.66	1.8	1.45	1.1	1.0

(*b*) *Helix*, nerve-muscle, pp. 214–215. $k = 10.24$; $C = 0.0636$

t sec.	0.014	0.021	0.036	0.057	0.086	∞
V obs.	*8.2	6.4	5.0	*4.0	3.5	3.1
V cal.	8.2	6.5	4.9	4.0	3.5	3.1

(*c*) Sciatic gastrocnemius, pp. 214–215. $k = 422.9$; $C = 0.0422$

t sec.	0.00033	0.00067	0.001	0.0015	0.002	0.0025	0.003	∞
V obs.	*175	115	92	*76	68	64	61	60
V cal.	175	114.1	91.2	76	68.9	65.1	63.1	60

(*d*) Sciatic gastrocnemius, p. 92. $k = 0.07183$; $C = -0.0168$

†*t*	3	4	6	8	12	16	∞
V obs.	*82	63	49	41	*35	32	30
V cal.	82	64.7	49.6	41.5	35	32.4	30

(*e*) Sciatic gastrocnemius, p. 96. $k = 497.0$; $C = 0.0664$

t sec.	0.00033	0.00066	0.001	0.0015	0.002	0.0025	0.003	∞
V obs.	*270	*187	155	126	115	112.5	112	111.5
V cal.	270	187	153.4	131.8	122.1	117.3	114.4	111.5

(*f*) Frog stomach. $k = 0.2299$; $C = 0.0842$

t sec.	0.05	0.10	0.50	1.0	2.0	3.0	10.0	∞
V obs.	41	*30	18	11.8	*9.1	8.3	6.5	6.5
V cal.	33.5	30	17.7	12.6	9.1	7.8	6.5	6.5

(*g*) Frog stomach, p. 86. $k = 0.8843$; $C = 0.0763$

t sec.	0.05	0.10	0.50	5.0	∞
V obs.	*9.5	7.0	*3.3	2.3	2.3
V cal.	9.5	7.3	3.3	2.3	2.3

(*h*) *Vorticella*, p. 99. $k = 88.12$; $C = 0.0461$

t sec.	0.00215	0.00285	0.0036	0.0071	0.0107	0.021	0.050
V obs.	*25	21.5	18.5	14.5	*11.7	10.5	10.5
V cal.	25	21.2	18.5	13.3	11.7	10.6	10.5

TABLE I—*Concluded*

(*i*) *Aplysia*, p. 82. $k = 4.663$; $C = 0.1283$									
t sec.	0.006	0.009	0.018	0.027	0.048	0.078	0.157	0.223	∞
V obs.	7.6	*6.2	5.0	4.3	*3.6	3.1	2.7	2.3	2.0
V cal.	6.7	6.2	5.3	4.5	3.6	2.9	2.3	2.1	2.0

* The numbers marked with asterisks are the values of i or V in each case which were used for determining k and C.

† t arbitrary units.

points of Curve *a* are suitable, for example, as these points both lie on the line going most nearly through all the points. Having determined k and C, and considering the times given to be perfect measurements, it is now easy to calculate what the stimulating voltage should be if equation (4) is a true relation.

This has been done for all the data in Lapicque's book in which a rheobase was given, and with much of his recent data (1931, *a*, *b*). In Table I are shown the values of i or V both experimental and calculated by means of the equation for the data in Lapicque's book. The numbers marked with asterisks are the values of i or V in each case which were used for determining k and C. The calculated values of these have to agree, of course, with the experimental ones.

It will be seen that in most cases the agreement of calculated with experimental values is quite good within the whole ranges. In Case *e* where the general agreement is poorest a better fit could be obtained by assuming an error in the rheobase, *i.e.*, by making the rheobase 110 say, but since there is no justification for doing this it was thought better to use the value given.

In Case *f* the calculated value of V is much too low for the shortest time. This does not occur in *g* which deals with the same kind of tissue, so there is a possibility that the experimental value is too high in *f* due to some variation of conditions or procedure.

On the whole it is felt that taking into consideration the diversity of types of tissues represented, the general good agreement between the calculated and experimental values points fairly definitely to the conclusion that equation (4) gives the time-intensity relation for the stimulation of tissue by direct currents of constant value as closely as can be expected considering the probable errors of measurement.

Relation to Other Direct Current Formulae

Lapicque (1907) applied the conception of the leaky condenser to the problem of tissue stimulation. The leaky condenser is a mechanism whose action conforms to the differential equation (1), as will now be shown.

If a potential V is applied to a condenser of capacity c in series with a resistance R and shunted by a resistance r the equating of electromotive forces gives,

$$V = Ri + \frac{q}{c}$$

where i is the current through R and q is the charge on the condenser. But,

$$i = i_1 + \frac{dq}{dt} = \frac{q}{cr} + \frac{dq}{dt}$$

where i_1 is the current through the shunt. Thus,

$$\frac{dq}{dt} = \frac{V}{R} - q\,\frac{(r + R)}{Rcr}$$

which is of the same form as,

$$\frac{dp}{dt} = KV - kp$$

If the excitation process is like the action of a leaky condenser, an experimental confirmation is possible, in at least one way, through the necessary relations of K and k. For then will,

$$K = \frac{1}{R} \text{ and } k = \frac{r + R}{Rcr}$$

which quantities are not independent. The results of Adrian (1) indicate the independence of K and k, *i.e.*, they are against the condenser hypothesis.

The fundamental hypothesis of Hoorweg (1892) may be written,

$$\frac{dp}{dt} = \alpha\, ie^{-\beta t}$$

where α and β are constants and i is the current, *i.e.*, he supposed the rate of building up of the local excitatory process to be proportional to the current but that the effective current decreased exponentially. A solution for i constant is,

$$\int_0^{\eta} dp = \alpha i \int_0^{t} e^{-\beta t}\, dt, \text{ or, } \log \frac{\alpha i}{\alpha i - \eta\beta} = \beta t$$

where η has the same meaning as the h used here. This solution is the same as equation (3) despite the difference of the hypotheses. It is also equivalent, of course, to Lapicque's equation (1907).

Equation (3) may be written,

$$V/(V - R) = 1 + kt + \frac{k^2t^2}{2} + \ldots \text{ etc.}$$

Neglecting the squared and succeeding terms and multiplying by V–R,

$$V = V - R + Vkt - Rkt,$$

or,

$$V = \frac{R}{kt} + R$$

which is of the form of Weiss's law. Weiss's law is related to equation (3) as a first approximation.

Equation (4) may be put in the form,

$$V = (V - R)\, e^{kt+C} = \frac{Re^{kt+C}}{e^{kt+C} - 1} = \frac{R}{1 - e^{-(kt+C)}}$$

Putting $\theta = e^{-k}$ $\mu = e^{-C}$

$$V = \frac{R}{1 - \mu\theta^t}$$

which is the same as Hill's equation (1910) in its simplified form.

It is generally admitted that Weiss's law, as well as Hoorweg's and Lapicque's equations are inadequate. In regard to Hill's analysis and the present one, since the approximation he used to apply to direct current data is equivalent to the equation derived here, the

direct current data cannot be used to choose between them. The data which fit the one will fit the other. Hill's formulae for other types of stimulation have received very little application. The fact that the present formulae are generally applicable may be due more to their mathematical simplicity than to greater inherent accuracy of representation of the phenomenon. No attempt at a decision in this matter is intended here.

The Constant C

A discussion of the meaning of or the existence of C does not involve the validity of the hypotheses represented by equation (1) for the differential equation of the family of curves.

$$\log \frac{KV}{KV - kp} = kt + C$$

is

$$\frac{dp}{dt} = KV - kp$$

quite independently of the value of C. It is evidently necessary, therefore, to discuss C only in regard to the boundary conditions.

Equation (4) may be written,

$$\log \frac{KV}{KV - kp} = k\ (t \pm t_o) \qquad (4, a)$$

which expressions may be obtained from the integrals of equation (1),

$$\Big[\log KV - kp\Big]_0^k = -k \int_0^{t \pm t_o} dt$$

The first of these conditions giving C a positive value may be interpreted as a continuation of the process for a time t_o after the current is off. The second giving C a negative value denotes a delay t_o, after the stimulus is applied, before the process starts. That the first conditions should be fulfilled is extremely unlikely. The second would represent approximately the case of a delayed rise of the stimulus due to induction. Equation (4, a) would also represent a case in which the calibration of the circuit breaker was in constant error $\pm t_o$. None

of these considerations appear to be useful with the present data, particularly as C may be interpreted in quite a different way.

Equation (4) may also be written,

$$\log \frac{C' V}{V - R} = kt \qquad (4, b)$$

where $\log C' = C$. This expression may be obtained by considering the integrals,

$$\left[\log KV - kp\right]_o^{h \pm \alpha V} = -kt$$

where α is a constant.

This gives

$$\log \frac{KV}{KV - k(h \pm \alpha V)} = kt$$

But when t is large

$$(K \mp k\alpha)V = kh = (K \mp k\alpha)\, R,$$

where R is again the rheobase voltage. Substituting above for kh,

$$\log \frac{KV}{(K \mp \alpha k)V - (K \mp k\alpha)R} = kt$$

or,

$$\log \frac{C' V}{V - R} = kt$$

where $C' = K / (K \mp k\alpha)$.

These probably represent the proper boundary conditions. These considerations, which are based on the assumption that the threshold value of the local excitatory process may be influenced by the magnitude of the stimulating current, are perhaps the same that should be applied to the problem of the difference in stimulating powers of "ascending" and "descending" currents. The results of this point of view may be considered.

Since C' of equation $(4, b)$ equals $K/(K \mp k\alpha)$, C which equals log

C' and is transposed will be positive when $C' > 1$ and negative when $C' < 1$. C is positive when $C' = K/(K + k\alpha)$, but this occurs when the limit of integration is $p = h - \alpha V$, *i.e.*, with a low threshold. But, since low thresholds occur with "descending" currents, C should be positive for "descending" currents and negative for "ascending" currents, providing, however, that h is the same for currents in both directions. If h is different no generalization can be made at present.

It will be seen that the recent data of Lapicque, now to be considered, show that C may disappear with certain electrodes, indicating that the electrodes as well as the direction of the current are a factor. But when C is present it usually changes sign with reversal of direction of the current, as may be expected from present considerations. No conclusions can be drawn in this matter, however, without the investigation of a large number of cases. This presents another problem in the experimental investigation of the effect of electrodes recently reopened by Rushton (1931). Consideration of the data of Table II will illustrate this point.

The data of Table II which consist of a large part of Lapicque's recent work (1931, *a*, *b*) have been handled in the same way as the older data in Table I. Some of his new data whose plots do not give smooth time-intensity curves obviously are combinations of the so-called α and γ types of response. The selection considered here was made, perhaps not always successfully, with a view to avoiding these mixed curves. A point to be noted, which affects the agreement of the calculated and observed voltages at the longer times, is that the rheobases, as Lapicque states, were difficult to determine. A rheobase either too small or too great produces a systematic divergence of observed and calculated voltage for the long times.

Sets *j* and *l* were obtained with one fluid electrode and one stigmatic on normal muscle. The sets differ in that the current is reversed. C exists, is about the same size in each set, but changes sign with change of the direction of the current.

Sets *m* and *n* are on the same muscle as *j* and *l* but with the fluid electrode at the opposite end. C is greater, changes sign with change in direction of the current, but is now positive when the fluid electrode is positive whereas in *l* it was negative when the fluid electrode was positive. It thus appears possible that the sign of C depends on the

TABLE II

(*j*) (1931, *a*) p. 200. Frog sartorious, fluid electrode, distal −, $k = 3.24$; $C = 0.0038$

t sec.	0.014	0.025	0.041	0.100	∞
V obs.	*17.0	10.0	*7.0	2.1	1.9
V cal.	17.0	10.7	7.0	3.5	1.9

(*l*) as *j* but fluid electrode + $k = 90.1$; $C = -0.0077$

t sec.	0.0012	0.0023	0.0045	0.009	0.014	0.025	0.041	0.100	∞
V obs.	*12.5	8	*5	3.8	3.6	3.3	3.0	3.0	2.7
V cal.	12.5	8.2	5.0	3.6	3.2	3.1	3.1	3.0	3.0

(*m*) as *j* same muscle pelvic electrode, fluid, −, $k = 8.33$; $C = -0.0468$

t sec.	0.014	0.025	0.041	0.100	∞
V obs.	*14	*8	4	2.5	2.5
V cal.	14.0	8.0	5.1	3.0	2.5

(*n*) as *m* fluid electrode + and pelvic $k = 79.1$; $C = 0.0448$

t sec.	0.0012	0.0023	0.009	0.014	0.025	0.100	∞
V obs.	*12	7	*4.0	3.5	3.4	3.2	3.3
V cal.	12.0	8.1	4.0	3.5	3.3	3.3	3.3

(*o*) (1931, *a*) p. 206. Fluid electrode, pelvic, +, $k = 292.3$; $C = 0$

t sec.	0.001	0.002	0.003	0.005	0.010	0.020
V obs.	*4.5	3.2	2.45	2.3	2.2	2.2
V cal.	4.5	3.0	2.5	2.3	2.2	2.2

(*p*) As *o* but position of stigmatic electrode different $k = 359.1$; $C = -0.4752$

t sec.	0.002	0.003	0.005	0.010	0.100
V obs.	*7.0	*4.0	3.2	3.2	3.0
V cal.	7.0	4.0	3.2	3.0	3.0

(*q*) As *o*, stigmatic electrode in new position $k = 289.8$, $C = -0.0939$

t sec.	0.001	0.002	0.003	0.005	0.050
V obs.	*16	*9.0	6.5	5.8	5.8
V cal.	16.0	9.0	6.9	6.1	5.8

(*r*) As *q* but stigmatic electrode + $k = 12.74$; $C = 0.0187$

t sec.	0.003	0.005	0.010	0.020	0.050	0.100
V obs.	*18.5	13.0	*8.0	4.5	2.6	2.3
V cal.	18.5	13.3	8.0	4.9	2.9	2.3

TABLE II—*Continued*

(*s*) (1931, *a*) p. 209 two fluids electrodes $k = 53.8$; $C = 0.0$

t sec	0.0023	0.0045	0.009	0.014	0.025	∞
V obs.	*20	13.0	7.0	5.9	5.1	5.0
V cal.	20	11.7	7.4	6.1	5.2	5.0

(*t*) As *s* current reversed $k = 46.6$; $C = 0.0$

t sec	0.0023	0.0045	0.009	0.014	0.025	∞
V obs.	*19	11	7.2	5.8	5.0	4.2
V cal.	19.0	11.0	6.8	5.4	4.5	4.2

(*u*) As *s* but current at 30° to muscle $k = 14.48$; $C = 0.0$

t sec	0.0045	0.009	0.014	0.025	0.100	∞
V obs.	11.0	*5.8	3.9	2.9	1.5	1.5
V cal.	10.8	5.8	4.0	2.7	1.6	1.5

(*v* 1) Sciatic fluid electrode (1931, *b*) p. 237. $k = 227.5$; $C = 0.0677$

t sec	0.0006	0.0015	0.0025	0.0045	0.010	0.040	0.100
V obs.	*2.8	1.7	*1.3	1.2	1.0	1.0	1.0
V cal.	2.8	1.64	1.3	1.2	1.05	1	1

(*v* 2) $k = 229.1$; $C = 0.0556$

t sec	0.0006	0.0015	0.0025	0.0045	0.010	0.040	0.100
V obs.	*3.6	1.9	*1.7	1.4	1.3		
V cal.	3.6	2.2	1.7	1.4	1.3		

(*v* 3) Mean k of $v_1 v_2 = k = 228$; $C = 0.1642$

t sec	0.0006	0.0015	0.0045	0.010	0.040	0.100
V obs.	*2.7	1.8	1.4	1.4	1.4	1.3
V cal.	2.7	1.84	1.39	1.3	1.3	1.3

(*w* 1) Descending current (1931, *b*) p. 237. $k = 587$; $C = -0.0257$

t sec	0.0006	0.0015	0.0025	0.0045	0.010	0.100
V obs.	*7	*4.3	3.8	3.7	3.7	3.7
V cal.	7.0	4.3	3.8	3.71	3.7	3.7

(*w* 2) Ascending current. $k = 392.6$; $C = 0.1893$

t sec	0.0006	0.0015	0.0025	0.0045	0.010	0.100
V obs.	*7.2	*5.4	4.7	4.5	4.5	4.5
V cal.	7.2	5.4	4.8	4.55	4.5	4.5

TABLE II—*Concluded*

(w 3) Ascending. $k = 384.7$; $C = 0.0813$						
t sec	0.0006	0.0015	0.0025	0.0045	0.010	0.100
V obs	*4.2	*2.8	2.5	2.3	2.3	2.2
V cal	4.2	2.8	2.4	2.25	2.2	2.2
(w 4) Descending. $k = 377.0$; $C = 0.1612$						
t sec	0.0006	0.0015	0.0025	0.0045	0.010	0.100
V obs	*2.2	*1.6	1.4	1.3	1.3	1.3
V cal	2.2	1.6	1.41	1.3	1.3	1.3

* The numbers marked with asterisks are the values of i or V in each case which were used for determining k and C.

direction of the current through the muscle, not on which type of electrode is cathode. This seems to be contradicted in q, r, however.

Sets o, p, q, and r are on the same muscle, the stigmatic electrode being cathode in the first three but placed, in o, on the outside of the ventral part of the muscle, in p, on the middle of the same side, and in q, on the middle of the opposite (back) side. It will be observed that $C = 0$ for o but is quite large for p, smaller and negative for q. This indicates that the existence of C may depend on electrodes insofar as different types of electrodes will cause the current to flow through the tissue in different directions relative to its structure. In regard to time constants it will be observed that the k of o is equal, approximately, to that of q.

The sets, s, t, and u using fluid for both electrodes have $C = 0$ in all cases. Changing the direction of the line joining the electrodes to 30° from the axis of the muscle, lowered the time constant k but made no change in C.

The sets v_1, v_2, and v_3 are on the same sciatic nerve (frog) with fluid electrodes. C is not zero as with fluid electrodes on muscle. The constant k of v_3 was, on account of the incompleteness of the data, taken from the mean of those of v_1 and v_2. The value so obtained is apparently suitable. w_1, w_2, w_3, and w_4 are on still the same nerve after an interval, the electrodes being the same. It will be seen that the k's of w_2, w_3, and w_4 are approximately the same although the C's are quite different. The same thing is true of v_1, v_2, and v_3. This indi-

cates that the C's and k's are not simply related. It may be pointed out that although the time constants k of v_1, v_2, and v_3 are approximately equal, the chronaxie will differ on account of differences of the C's. The same consideration is applicable to w_2, w_3, and w_4.

No attempt can be made from these data to determine the relations of C and k to the type of electrodes used. The data suffice to show, however, that the magnitudes of both these factors have to be taken into account in choosing a method of stimulation, and it is hoped that the electrode problem will be simplified greatly by the fact that it can be examined in terms of the two quantities C and k. The fact that C can be made zero is extremely important as the results of experiments satisfying this condition are much more easily related mathematically. It is also important in that it indicates that C represents something apart from the essential mechanism, because it is not to be expected that the nature of the response process can be altered by a suitable choice of electrodes.

The significance of the data and considerations up to this point may be summed up as follows: integrals of equation (1), which represents the fundamental hypotheses used here regarding the growth of the local excitatory process, represent quite adequately the time-intensity relations for direct current stimulation. The upper limit of integration, *i.e.*, the liminal value of p necessary for the stimulus to be adequate is not in general constant, but is a function of the voltage. The form of this function imposed by the data is *threshold* $= h \pm \alpha V$. There is some indication that the sign of αV depends on the direction of the current, but the matter is further complicated by the fact that α becomes zero with certain electrodes, showing that its value may depend on electrodes as well. The quantity αV may be a measure of the condition known as electrotonus. It represents at least a similar phenomenon, *i.e.*, a raising or lowering of the threshold by the current flowing through the tissue, in this case by the stimulating current itself.

Stimulation by Breaking Constant Currents

The fact that the threshold is dependent on the voltage suggests that break stimuli may be explained on this basis. There may be a certain threshold, h_o say, at which the local excitatory process is

adequate when there is no current flowing through the tissue. When there is a current flowing the threshold is $h \pm \alpha V$. Let $h \pm \alpha V$ be greater than h_o and let the current have raised p to a value between h_o and $h \pm \alpha V$. Excitation will now be accomplished when the current is stopped if the threshold drops more quickly than the local excitatory process decays, or rather if the threshold drops quickly enough to overtake p before it decays beyond h_o. This suggestion has little value until the threshold problem has been further investigated but it has some qualitative experimental basis other than the dependence shown here of the threshold on the current, and it is worthy of consideration in that it offers a possibility of explaining break stimuli without invoking additional phenomena.

The discussion of the last paragraph was concerned with break stimuli in general. The problem of determining the least effective break stimuli for given durations has been considered experimentally by Laugier (1921). His data are not available here except for two cases taken from a paper by de Almeida (1931) nor has his paper been seen. These two sets were selected by de Almeida as being those which best fitted his formula. They may, however, be typical.

In Table III the results of applying equation (4) to these cases are given. The calculated voltages marked with asterisk are the same as the observed from which the constants were calculated.

It will be seen that the agreements, particularly in the first set, are not as good as those in Table I, although they are good up until fairly long times. It appears that the voltage tends then to become too low for the relation. This point is illustrated by using the voltage 2.00 at 0.086 seconds as rheobase for an additional set of calculated values. It will be seen that this makes the agreement better. There is no reason to believe, however, that the measured rheobase is not correctly given. The only conclusion to be drawn assuming equation (4) to be true is that in Case 1 the excitability of the nerve became greater with the longer stimulating times.

The values of k are much smaller than those obtained with excitation at the cathode. The C's are large and positive. These correspond to integrals of equation (1) of the type,

$$\left[\log (KV - kp)\right]_o^{h - \alpha V} = -kt$$

TABLE III

(1) Sciatic gastrocnemius, excitation at the anode. $k_1 = -50.4$; $k_2 = 53.69$; $C_1 = 0.0765$; $C_2 = 0.0811$

t sec.	0.0005	0.001	0.002	0.0036	0.0050	0.0072	0.0086	0.0122	0.0179	0.0287	0.050	0.086	∞
V obs.	9.95	7.50	5.50	4.20	3.55	3.05	2.75	2.45	2.30	2.15	2.10	2.00	1.90
V calc.	9.10	*7.50	5.67	4.24	3.58	2.99	*2.75	2.38	2.12	1.96	1.90	1.90	1.90
V calc.	9.09	*7.50	5.68	4.27	3.62	3.03	2.80	*2.45	2.20	2.05	2.03	2.00	2.00

(2) Sciatic gastrocnemius, excitation at the anode. $k = 40.1$; $C = 0.1066$

t sec.	0.0036	0.0072	0.018	0.0286	∞
V obs.	49.0	35.00	25.25	23.75	21.50
V calc.	*49.0	35.97	*25.25	22.77	21.50

* The calculated voltages marked with asterisk are the same as the observed from which the constants were calculated.

i.e., the threshold in each case is a constant quantity less a quantity varying as the voltage. This may not be significant but the smallness of k probably is.

It is unsafe to draw many conclusions from these two cases but they indicate the probability that equation (1) represents the growth of the excitatory process at the anode as well as at the cathode.

The Chronaxie

Using Lapicque's definition of chronaxie one obtains by putting $V = 2R$ in (4),

$$\log \frac{2R}{2R - R} = kt + C,$$

which can be written

$$\log 2 - \log \beta = kt \text{ where } \log \beta = C;$$

thus

$$t = \tau = \text{chronaxie} = \frac{1}{k} \log \frac{2}{\beta} \tag{5}$$

or chronaxie is inversely proportional to k. It is interesting that the definition of chronaxie should make it proportional to the reciprocal of the rate of return to normal of the tissue per unit state of excitation.

In order to make chronaxie the type of measure of excitability intended by those who employ it, it will be seen that C must be the same for all the chronaxies to be compared. Conditions giving $C = 0$ are much to be preferred.

The Summation of Inadequate Stimuli

Let the stimulus be sufficient to raise p to θh only, where $\theta < 1$. From equation (1) the local excitation will not return to zero immediately but will decay according to the equation,

$$\frac{dp}{dt} = - kp$$

$$\Big[\log p\Big]_{\theta h}^{p} = - kT$$

or,

$$p = \theta h e^{-kT}$$

i.e., p will decay exponentially, and if a second stimulus is applied soon enough an appreciable part of θh will still remain and addition will occur.

The simplest case to consider is that in which the stimuli are all equal and the intervals between the stimuli equal in duration to the stimuli. Let the stimulating voltages be V and the durations t_1. For the first stimulus,

$$\log \frac{KV}{KV - kp} = kt_1$$

whence,

$$p = \frac{KV}{k}(1 - e^{-kt_1})$$

But p decays in the interval according to the equation,

$$\frac{dp}{dt} = -kp$$

$$\left[\log p\right]_{\frac{KV}{k}(1-e^{-kt_1})}^{p} = -kt_1$$

and p at the end of the first interval is given by,

$$p = \frac{KV}{k}(1 - e^{-kt_1})\, e^{-kt_1} = \frac{KV}{k}(e^{-kt_1} - e^{-2kt_1})$$

For the second stimulus,

$$\left[\log (KV - kp)\right]_{\frac{KV}{k}(e^{-kt_1} - e^{-2kt_1})}^{p} = -kt_1$$

or,

$$KV - kp = \left\{KV - KV\,(e^{-kt_1} - e^{-2kt_1})\right\} e^{-kt_1}$$

or,

$$p = \frac{KV}{k}\left\{1 - e^{-kt_1} + e^{-2kt_1} - e^{-3kt_1}\right\}$$

For the decay after the second stimulus,

$$\left[\log p\right]_{\frac{KV}{k}\{1-e^{-kt_1}+e^{-2kt_1}-e^{-3kt_1}\}}^{p} = -kt_1$$

or,

$$p = \frac{KV}{k}\left\{e^{-kt_1} - e^{-2kt_1} + e^{-3kt_1} - e^{-4kt_1}\right\}$$

For the third stimulus,

$$p = \frac{KV}{k}\left\{1 - e^{-kt_1} + e^{-2kt_1} - e^{-3kt_1} + e^{-4kt_1} - e^{-5kt_1}\right\}$$

Similarly after n stimuli,

$$kp = KV\left\{1 - e^{-kt_1} + e^{-2kt_1} - \ldots\ldots - e^{-(2n-1)kt_1}\right\} \tag{6}$$

The bracket is a geometric series whose common ratio is $-e^{-kt_1}$. The sum of a large number of terms will be given by,

$$\frac{1}{1+e^{-kt_1}}$$

For one adequate stimulus,

$$kh = KV_1\,(1 - e^{-kt_1}),\ C \text{ being neglected.}$$

For n stimuli to be adequate where n is large,

$$kh = KV_2 \times \frac{1}{1+e^{-kt_1}}$$

where V_1 and V_2 are the liminal voltages for a single stimulus and multiple stimuli, respectively. Equating these expressions,

$$\frac{V_1}{V_2} = \frac{1}{1+e^{-kt_1}} \times \frac{1}{1-e^{-kt_1}} = \frac{1}{1-e^{-2kt_1}} \tag{7}$$

which gives the ratio of the threshold voltages for a single direct current shock to that for many repeated shocks, each of the same duration as the single shock. As far as is known there have been no experiments to test these results. The similar problem arising with

repeated condenser discharge stimuli, however, has been investigated. It will be considered later.

Supernormal Excitability

It was shown by Adrian (1920) that the time-intensity curve for the supernormal phase of excitability as compared to that for resting excitability is merely displaced along the current axis. It is evident from equation (3) that this involves only a change in K as multiplying V and R by a constant does not change the right hand side of the equation. This is of interest here as it shows that one of the postulated processes can be altered without a change of the other, *i.e.*, the direct action of the current is facilitated without altering the rate of the counter action toward normal and without altering the liminal value h of p. As was previously pointed out, these results are against the leaky condenser hypothesis.

SUMMARY

Formulae are derived for the time-intensity relations for stimulation by direct currents using the following hypotheses: first, the current produces an excitatory effect whose rate of growth is proportional to the voltage; and second, the tissue reacts toward the normal state at a rate proportional to the amount of excitation. If p represents the local excitatory process numerically, the hypotheses are represented by the differential equation

$$\frac{dp}{dt} = KV - kp$$

where K and k are constants and V the applied voltage. For the stimulus to be adequate it is assumed that p must be built up to a certain liminal value. It appears as a deduction from the data that this liminal value is a function of the voltage of the form $h \pm \alpha V$ where h and α are constants. α is zero or negligible for certain electrodes. αV is a measure of electrotonus or a similar phenomenon. Experimental data are discussed and are shown to agree satisfactorily with the derived formulae for stimulation both at the anode and cathode.

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