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

By H. A. BLAIR

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

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In Part I of the present discussion (Blair, 1932) it was shown that the data for stimulation by direct currents are adequately represented by integrals of the equation,

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

where p and V represent the magnitudes of the local excitatory process and the stimulating voltage respectively and K and k are constants. The threshold value of p was found to depend on the voltage so that the upper limit of integration was given by $p = h_o \pm \alpha V$ where h_o and α are constants. The sign and magnitude of α depended on the method of stimulation. Under some conditions it was zero in which case the threshold was independent of the voltage. In considering now other forms of electrical stimuli in the light of the same hypotheses it is usually assumed for convenience that the threshold is constant.

Condenser Discharges as Stimuli

The potential q/c of a discharging condenser is given by,

$$\frac{q}{c} = \frac{q_o e^{-\frac{t}{cr}}}{c} \tag{2}$$

where q_o and c are respectively the initial charge and capacity of the condenser, r is the resistance of the circuit through which the discharge is taking place, and t the time.

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Substituting in (1) for V from (2) gives,

$$\frac{dp}{dt} = \frac{Kq_o e^{-\frac{t}{cr}}}{c} - kp \tag{3}$$

which is the differential equation for stimulation by condenser discharges. Its solution is,

$$p = e^{-\int k\,dt} \frac{Kq_o}{c} \left\{ \int e^{\int k\,dt} e^{-\frac{t}{cr}} dt + C \right\}$$

$$= e^{-kt} \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{crk-1}{cr}t} + C \right\}$$

When $t = 0$, $p = 0$, therefore $C = -1$
giving,

$$p = \frac{Kq_o r}{crk - 1} \left\{ e^{-\frac{t}{cr}} - e^{-kt} \right\} \tag{4}$$

It is further assumed that the tissue responds to the stimulus when p attains a liminal value h; thus the general equation of stimulation is given by,

$$h = \frac{Kq_o r}{crk - 1} \left\{ e^{-\frac{t}{cr}} - e^{-kt} \right\} \tag{5}$$

It is necessary to discuss the maximum value of p as a response will be obtained only under conditions such that the maximum value of p just equals or tends to be greater than h. p is a maximum when $dp/dt = 0$, *i.e.*, when,

$$\frac{Kq_o r}{crk - 1} \left\{ -\frac{e^{-\frac{t}{cr}}}{cr} + ke^{-kt} \right\} = 0$$

or,

$$t = \frac{cr}{1 - crk} \log \frac{1}{crk} \tag{6}$$

On the basis of the hypotheses this time t should be the time at which a response is elicited if the stimulus is just adequate. In other words, equation (6) should give the "*durée utile*," of the discharge.

In Table I are given all the measurements by the Lapicques of the *durée utile* which could be found (1926, 1907, *b*). The page numbers given with the *Helix* data refer to Lapicque's book. The constant "*k*" was calculated in each case from the data marked with asterisks.

TABLE I

Tissue	Durée utile	R.C. × 10^3	k	Time calc.	C_1
Helix (Lapicque, p. 122)	0.042	*59.0	14.254	0.042	108
	0.026	*39.5	32.85	0.026	142
	0.016	22.5		0.0163	132
	0.012	14.0		0.0122	112
	0.0065	5.6		0.0076	90
Helix (Lapicque, p. 121)	0.038	*50	41.61	0.038	94
	0.013	*25	95.83	0.013	100
	0.009	15		0.0082	106
	0.0043	5		0.0043	92
Sciatic gastrocnemius (*Compt. rend. Soc. biol.*, 1907, **62**, 701)	0.00181	*70	298.4	0.00181	204
	0.00154	*7.0	687.2	0.00154	170
	0.00135	3.5		0.00147	155
	0.00093	1.4		0.00091	142
	0.00063	0.7		0.000602	129

* Values used to determine *k*. Lower value of *k* is to base *e*.

The method of doing this may best be shown by an example: *Helix* (Lapicque, page 122).

$$0.042 = \frac{0.059}{1 - 0.059\,k} \log \frac{1}{0.059\,k}$$

$$0.026 = \frac{0.0395}{1 - 0.0395\,k} \log \frac{1}{0.0395\,k}$$

multiplying by the reciprocal of the factor of the log in each case to leave only the log factors on the right hand side and then subtracting,

$$\frac{(1 - 0.059\,k)\;0.042}{0.059} - \frac{(1 - 0.0395\,k)\;0.026}{0.0395} = \log \frac{0.0395}{0.059}$$

which can easily be solved for "*k*." A better value of "*k*" would perhaps be the mean value from all the data of each set but this was not determined.

It will readily be seen that the *durées utiles* as calculated from equation (6) agree as well as can be expected with the measured values.

The value of "p" at its maximum will be given by substituting the value of t from (6) into (3) when $dp/dt = 0$, *i.e.*,

$$p \text{ max. } k = \frac{Kq_0 e^{-\frac{1}{1-crk}\log\frac{1}{crk}}}{c}$$

which reduces to

$$p \text{ max.} = Krq_0 \, (crk)^{\frac{crk}{1-crk}} \qquad (7)$$

The value of p max. can also be obtained by substituting t from (6) into (4), *i.e.*,

$$\begin{aligned} p \text{ max.} &= \frac{Kq_0 r}{crk - 1}\left\{e^{-\frac{1}{1-crk}\log\frac{1}{crk}} - e^{-\frac{crk}{1-crk}\log\frac{1}{crk}}\right\} \\ &= \frac{Kq_0 r}{crk - 1}\left\{crk^{\frac{1}{1-crk}} - crk^{\frac{crk}{1-crk}}\right\} \qquad (8) \end{aligned}$$

It may easily be shown that (7) and (8) are equivalent expressions. If p max. $= h$ the general equation of stimulation in terms of q, c, and r is given by

$$p \text{ max.} = h = Krq_0 \, (crk)^{\frac{crk}{1-crk}}$$

or for any given tissue the conditions for effective stimulation if q_0, c, or r vary is given by

$$\text{Constant} = rq_0 \, (crk)^{\frac{crk}{1-crk}} \qquad (9)$$

or the equivalent expression derived from (8).

The arithmetic involved in checking these equations is very cumbersome unless "k" is determined separately from data giving the *durées utiles* or, as will later be seen, from chronaxie. In Table I the numbers C_1 are proportional to the constant of equation (8) for each set of data. The k used was derived from the *durées utiles*. Since one is dealing here with high powers of numbers and since small changes in the exponents make comparatively large changes in the resulting figures, such close agreements are not to be expected here as between the *durées utiles*, calculated and measured. It will be observed, however, that in spite of this the values of C_1 in each set are of the same order of magnitude. The agreement could probably be improved by small adjustments in k, but it may also be necessary to make the threshold a function of the voltage as it was with direct currents in most cases. This does not affect the *durée utile* so it has not been considered. It is to be expected that apart from experimental conditions, the threshold will be less influenced by the voltage of the stimulus with condenser discharges than with direct currents because the voltage is decreasing and is relatively low at the time of the response. It will be seen, however, that if this condition has to be put in equation (9) it can easily be done from (2) and (6).

Chronaxie

Let it be assumed that the rheobase potential is determined by direct current stimuli. From equations (2) and (4) of Part I it follows that the rheobase voltage is given by

$$V = \frac{kh}{K} \tag{10}$$

and twice the rheobase by

$$V = \frac{2kh}{K}$$

From (3) when p is a maximum and equal to h,

$$kh = \frac{Kq_o e^{-\frac{t}{cr}}}{c} \tag{11}$$

Putting

$$\frac{2kh}{K} = V = \frac{q_o}{c}$$

one obtains

$$t = cr \log 2,$$

but this is by definition, the chronaxie for condenser discharges. Let τ_c be this chronaxie so that,

$$\tau_c = cr \log 2 \tag{12}$$

For direct currents it was found that chronaxie,

$$\tau = \frac{1}{k} \log \frac{2}{\beta} \tag{13}$$

It will be of interest to find the ratio of these two chronaxies.

Since (6) is also true for chronaxie one may put

$$t = \tau_c = cr \log 2 = \frac{cr}{1 - crk} \log \frac{1}{crk}$$

giving,

$$(crk - 1) \log 2 = \log crk \tag{14}$$

which is satisfied when $(crk - 1) = 0$ or $cr = \frac{1}{k}$

i.e.,

$$\tau_c = \frac{1}{k} \log 2.$$

This result however is trivial, as may be ascertained by considering its consequences in any of equations (6), (7), and (8).

$crk = 2$ is also a solution of (14) whence

$$\tau_c = \frac{2}{k} \log 2 \tag{15}$$

Dividing (13) by (15),

$$\frac{\tau}{\tau_c} = \frac{\frac{1}{k} \log \frac{2}{\beta}}{\frac{2}{k} \log 2}$$

or,

$$\tau = \frac{\log \frac{2}{\beta}}{2 \log 2} cr \log 2$$

or,

$$\tau = \frac{\log 2 - C}{2} cr \tag{16}$$

which gives the chronaxie as defined originally for direct current in terms of *cr*. Lapicque by experiment has determined this relation to be, on the average,

$$\tau = 0.37\ cr \tag{17}$$

From (16) and (17),

$$\log 2 - C = 0.74$$

$$-C = 0.7400 - 0.6932 = 0.05 \text{ approx.}$$

The values of C determined from Lapicque's direct current data, Table I of Part I, range from 0.084 to -0.016, only one being negative. These have to be multiplied by 2.30, the conversion factor of common to Napierian logarithms, giving 0.18 to -0.037 in order that they may be compared with the value found above. Although the one negative value is close to that calculated from (16) and (17), the positive values would give the τ to *cr* ratio lower than Lapicque's experimental value, the lowest being about 0.26 *cr* while the lowest experimental value was 0.31 *cr* (1926, page 324).

It will be observed that if $C = 0$, equation (16) gives

$$\tau = 0.3466\ cr,$$

a value very near to Lapicque's mean value 0.37 from experiment.

In recapitulation it may be said, that on the bases of the hypotheses used, it has been found that with the stimulus from a condenser discharge the local excitatory process in tissue rises to a maximum and then decreases if the maximum value is not equal to the liminal value h. If the maximum value is at least equal to or tends to be greater than h a response will ensue. If it is just equal to h the ensuing response occurs at the time the maximum is attained. This time is the predicted *durée utile* of the discharge. The close agreement between the predicted and measured values of the *durées utiles* indicates strongly the validity of the hypotheses.

Fig. 1 is a graphical representation of the discharge of the condenser along with the curve of the growth of the local excitatory process p according to equation (4) for the data of the first line of Table I. The dotted continuation of the p curve represents the value it would have had, had not the maximum been adequate. It will be noticed that the top of the p curve is fairly flat. This lack of sharpness indicates that a substantial error may easily be made in the measurement of the *durée utile.* Had the maximum value of p been inadequate it will be observed that even at 0.15 seconds after the beginning of the discharge the comparatively slow decay of p still leaves about one-third of the maximum left. This is of interest as regards the summation of in-

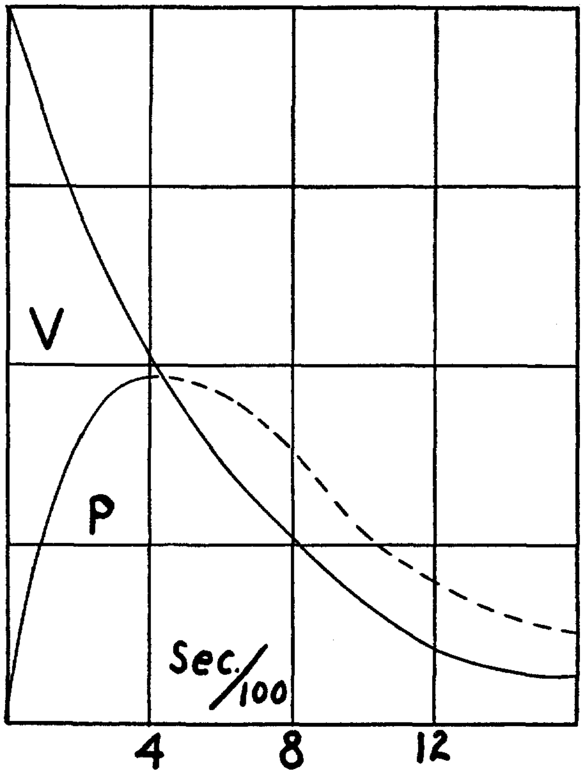

FIG. 1. Graphic representation of the stimulus and response for the first line of Table 1.

adequate stimuli. The rate of decay of p is, of course, slower in this case than after a direct current stimulus, as here the current is still acting after p commences to decrease.

The Summation of Condenser Discharge Stimuli

For condenser discharge stimuli there was obtained

$$p = e^{-kt} \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{crk-1}{cr} t} + C \right\}$$

which gives, if $p = 0$ initially, equation (4), *i.e.*,

$$p = \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{-t_1}{cr}} - e^{-kt} \right\}.$$

If this p is inadequate at its maximum its value at a time t_1 will be given by

$$p = \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{-t_1}{cr}} - e^{-kt_1} \right\}$$

Let a similar stimulus be given now at time t_1 which will give

$$p = e^{-kt} \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{crk-1}{cr}} + C \right\},$$

where now

$$p = \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{-t_1}{cr}} - e^{-kt_1} \right\}$$

when $t = 0$;

i.e.,

$$C = e^{\frac{-t_1}{cr}} - e^{-kt_1}$$

or,

$$p = \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{-t_1}{cr}} + e^{\frac{-t_1}{cr}} - e^{-kt_1 - kt} \right\}$$

If this is again inadequate after time t_1, again,

$$p = \frac{Kq_o r}{crk - 1} \left\{ e^{\frac{-t_1}{cr}} + e^{\frac{-t_1}{cr} - kt_1} - e^{-2kt_1} \right\}$$

Similarly for the third stimulus,

$$p = \frac{Kq_o r}{crk - 1}\left\{e^{\frac{-t}{cr}} + e^{\frac{-t_1}{cr} - kt_1} + e^{\frac{-t_1}{cr} - kt_1 - kt} - e^{-2kt_1 - kt}\right\}$$

If again this is inadequate p is given after another interval t_1 by

$$p = \frac{Kq_o r}{crk - 1}\left\{e^{\frac{-t_1}{cr}} + e^{\frac{-t_1}{cr} - kt_1} + e^{\frac{-t_1}{cr} - 2kt_1} - e^{-3kt_1}\right\}$$

Similarly in a time t_1 after the n'th stimulus

$$p = \frac{Kq_o re^{\frac{-t_1}{cr}}}{crk - 1}\left\{1 + e^{-kt_1} + e^{-2kt_1} + e^{-3kt_1} + \ldots\ldots + e^{-(n-1)kt_1} - \frac{e^{-nkt_1}}{e^{\frac{-t_1}{cr}}}\right\}$$

If n is large the two final terms will be small and may be considered equal giving

$$p = \frac{Kq_o re^{\frac{-t_1}{cr}}}{crk - 1}\left\{1 + e^{-kt_1} + e^{-2kt_1} + e^{-3kt_1} + \ldots + e^{-(n-2)kt_1}\right\}$$

Let $e^{kt_1} = \theta$, then,

$$p = Kq_o re^{\frac{-t_1}{cr}}\left\{1 + \frac{1}{\theta} + \frac{1}{\theta^2} + \frac{1}{\theta^3} + \ldots\ldots + \frac{1}{\theta^{n-2}}\right\}$$

Lapicque (Evans, 1930) by considering that the local excitatory process dropped to $\frac{1}{q}$ of its maximum value between stimuli, arrived at the conclusion that for n stimuli,

$$p = M\left\{1 + \frac{1}{q} + \frac{1}{q^2} + \ldots\ldots + \frac{1}{q^{n-1}}\right\}$$

where M is the maximum value of p due to the first stimulus. This expression agreed (Evans, 1930) with the experimental values of the Chauchards. Evidently the expression derived here is equivalent except that the interpretation of $\frac{1}{\theta}$ is not quite the same as Lapicque's $\frac{1}{q}$.

It will be observed that the magnitude of successive terms depends on k as well as the interval t_1. Since k is large for excitable tissue and small for relatively inexcitable, very short intervals will have to be used for excitable tissue to get the additive effects obtainable for fairly long intervals on inexcitable tissue.

For any given tissue short intervals, *i.e.*, small values of t_1, increase both the factor $e^{\frac{-t_1}{c r}}$ as well as the factors in $\frac{1}{\theta}$. It follows that the voltage threshold will be low with rapid repetition of stimuli and will increase as the interval becomes longer approaching finally the threshold for a single stimulus.

Currents of Linear Rise

There are two cases of currents increasing linearly which may be considered: the first being that in which the circuit is broken while it is still rising and the second that in which the current is caused to rise to a certain value and then allowed to flow steadily at that value for a given time.

The differential equation of the first case is evidently given by

$$\frac{dp}{dt} = KV_o\, t - kp \tag{19}$$

where V_o is the gain of voltage per second. The solution is,

$$p = KV_o e^{-kt} \left\{ \int e^{kt}\, t\, dt + C \right\}$$

which finally reduces to,

$$p = \frac{KV_o}{k} \left\{ t - \frac{1}{k} \left(1 - e^{-kt} \right) \right\} \tag{20}$$

Again assuming that for the stimulus to be effective p must attain a liminal value h, the general equation for effective stimulation is given by,

$$kh/K = \text{Constant} = V_o \left\{ t - \frac{1}{k} \left(1 - e^{-kt} \right) \right\} \tag{21}$$

As $t \rightarrow \infty$ evidently $V_o t$, which is the liminal voltage, tends to become equal to kh/K, *i.e.*, to the rheobase for constant direct current, as reference to equation (10) will show. For shorter times the liminal voltage will be greater than kh/K. The conclusion to be drawn is that any rate of rise no matter how small will eventually stimulate.

In the second case after the current has reached its maximum value it can be treated as a constant direct current. Therefore,

$$\frac{dp}{dt} = KV_o t_1 - kp$$

where t_1 is the time taken in reaching the maximum. Integrating

$$\Big[\log (KV_o t_1 - kp)\Big]^{p}_{\frac{KV_o}{k}\left\{t_1 - \frac{1}{k}(1 - e^{-kt_1})\right\}} = -kt$$

where the lower limit of p is derived from equation (20). This expression on simplification gives

$$p = \frac{KV_o}{k}\left\{t_1 - \frac{1}{k}(e^{-kt} - e^{-k(t+t_1)})\right\}$$

and for effective stimuli,

$$\text{constant} = kh = KV_o\left\{t_1 - \frac{1}{k}(1 - e^{-kt_1})\,e^{-kt}\right\} \tag{28}$$

where t is measured from the top of the rise of the current, *i.e.*, t is the duration of the constant current which is added to the initial varying current.

This equation indicates that if t_1 is small compared to t and t is large there exists the approximation,

$$KV_o t_1 = kh = \text{constant},$$

or since $V_o t_1$ is the liminal voltage one may say that the liminal voltage is nearly constant independently of the rate of rise under these conditions. Since kh/K is the rheobase potential this is equivalent to saying that in measuring the rheobase the mode of initial rise does not change the result providing the time of rise is a small part of the total time. Lapicque (1926), page 133 says in this regard, "But it can be said that up to a certain limit, variable with each excitability, the duration of the period of establishment is practically irrelevant." Lapicque (1926) also mentions the finding of Fick on *Anodonta*, that the liminal voltage did not have to be raised until the time of rise of the current exceeded 10 seconds.

The extensive data of Keith Lucas (1907) on this subject were obtained with linearly rising currents of the second kind, *i.e.*, they would be represented, if at all, by equation (22). He plotted his results as in Fig. 2, with the liminal voltages as ordinates and the time of rise as abscissae ($V_0 t_1$ in terms of equation (22) against t_1). He found usually, in these graphs, that $V_0 t_1$ remained constant or increased but slightly until the current gradient reached a certain minimum. With gradients less than this minimum no excitation at all could be evoked even though the current was raised greatly above the rheobase. Referring to Fig. 2 the rheobase is represented by RX. Currents which rose to the value R were effective provided they attained the value R within the interval of time RA. If they did not reach the value R within this time they did not excite at all.

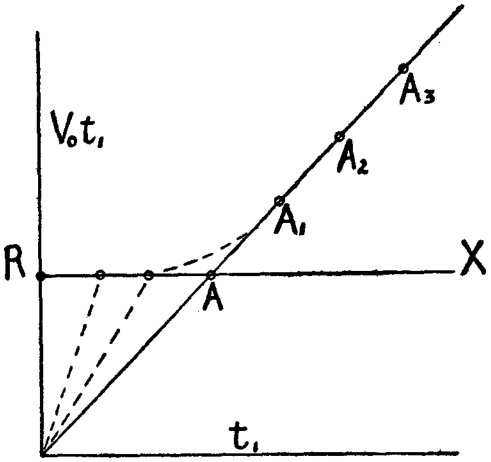

FIG. 2. The results of Keith Lucas with linearly rising currents

It should be remarked that the points A_1, A_2, A_3 do not indicate, as they appear to at first sight, that the liminal voltage has to be increased as the time of application of the liminal gradient is increased. Obviously if the currents for A_1, A_2, and A_3 had stopped rising at A they would still have been adequate. The only use of these points is to determine the liminal gradient. What they really indicate is that when the minimal gradient is being used to excite, continuing the rise beyond the rheobase is equivalent to stopping at the rheobase.

Some of Keith Lucas's data indicate a gradual approach to the minimal gradient as represented by the dotted line in Fig. 2. Unfortunately the interval *RA* was not well investigated, not at all with nerve, as his fastest gradient was very near the minimal. With muscle the minimal gradient was slow enough to allow his apparatus to give more than one point in the region *RA*. In this case (1907, page 268) the graphs show the liminal voltage very nearly constant up to the minimal gradient.

It appears that the conclusion to be drawn from Keith Lucas's experiments is that the rheobase is adequate or very nearly adequate no matter how it is linearly attained as long as it is attained within a certain time. If it is not attained within this time raising the voltage still further is of no avail. In other words, the least adequate stimulus is the rheobase whether it is attained abruptly or along a gradient. When the gradient is too low for the rheobase to be effective no voltage is effective. At the liminal gradient the rheobase is just as effective as any higher voltages.

Referring again to equation (22) it will be remembered that its prediction is a constant threshold equal to the rheobase for any rate of rise providing the steady current attained is continued indefinitely. If the steady current is not sufficiently prolonged the liminal voltage will increase somewhat above the rheobase. Evidently equation (22) represents the results of Keith Lucas for all adequate stimuli. It does not explain why gradients less than the minimal are ineffective. A complete theory will have to do this, but as far as is known at present it may be some phenomenon quite apart from the local excitatory process but which is also evoked by the passage of the stimulating current which causes this sudden lack of response.

It will be seen that experiments of the type represented by equation (22) are strictly speaking not investigations of the effect of current gradients, except insofar as they determine the minimal gradients. Evidently this information will have to be obtained by using currents which are cut off while still rising, or from rising and falling currents such as those used by Lapicque (1926). No data on this question appears to have been obtained using rising currents alone, so equation (21) cannot be tested at present. Like (22) it will not explain a liminal gradient, if such a gradient appears, and it probably will. If equation (21) can be tested experimentally it probably will be necessary usually in doing so to make the threshold depend on the voltage. This is easily done. With equation (22) no different conclusions can be drawn by inserting this condition.

Currents of Exponential Rise

Since an exponentially rising potential can be represented by

$$V = V_o\,(1 - e^{-\gamma t}),$$

where V_o is the terminal potential, the differential equation for p is

$$\frac{dp}{dt} = KV_o\,(1 - e^{-\gamma t}) - kp \tag{23}$$

and its solution,

$$hk = KV_o \left\{1 - \frac{ke^{-t}}{k - \gamma} + \frac{\gamma\, e^{-kt}}{k - \gamma}\right\} \tag{24}$$

where h is the liminal value of p for response.

The determination of k from these equations alone is also extremely difficult. Data used for easily testing them will have to give means of determining k from direct current or condenser discharge measurements. None of the existing data appear to be suitable.

As with currents of linear rise, equation (24) indicates that when t is very great V_o becomes equal to the rheobase voltage. This conclusion is probably untrue as it is with linear currents.

It seems that no very definite conclusions can be reached at present in regard to the validity of the equations for currents increasing with time. Fortunately, however, although existing data are unsuitable the required measurements for checking the equations can be obtained by usual procedures.

Alternating Currents

Let the applied potential be of the form $V = V_o \sin \omega t$ where ω is 2π times the frequency and V_o the maximum voltage.

The differential equation of the local excitatory process is then given by,

$$\frac{dp}{dt} = KV_o \sin \omega t - kp \tag{25}$$

and,

$$p = e^{-\int k\,dt} KV_o \left\{ \int e^{\int k\,dt} \sin \omega t \, dt + C \right\} \tag{26}$$

This may be simplified by the method of integration by parts, giving finally

$$p = \frac{KV_o}{k^2 + \omega^2} \left\{ k \sin \omega t - \omega \cos \omega t + \omega e^{-kt} \right\} \tag{27}$$

Two sets of maxima of p may be considered, the one including the transient term ωe^{-kt} and the other after the transient term has become negligible. In the first case,

$$\frac{dp}{dt} = 0 = \omega k \cos \omega t + \omega^2 \sin \omega t - k \omega e^{-kt}$$

These maxima may account for the short tetanus observed when a high frequency circuit is applied to tissue even though the threshold for prolonged tetanus has not been reached.

In the second case,

$$\frac{dp}{dt} = 0 = k \omega \cos \omega t + \omega^2 \sin \omega$$

whence,

$$\tan \omega t = -\frac{k}{\omega}$$

or,

$$t = \frac{1}{\omega} \tan^{-1} - \frac{k}{\omega}$$

Substituting in (27) and ignoring the transient term,

$$p = \frac{KV_o}{k^2 + \omega^2} \left\{ \frac{k^2}{\sqrt{k^2 + \omega^2}} + \frac{\omega^2}{\sqrt{k^2 + \omega^2}} \right\} = \frac{KV_o}{\sqrt{k^2 + \omega^2}}$$

If p at its maximum is adequate, *i.e.*, equal to h,

$$h = \frac{KV_o}{\sqrt{k^2 + \omega^2}} \tag{28}$$

which is the general equation for tetanizing stimulation by alternating currents. When ω is large compared to k there will exist the approximation $V_o = \frac{h}{K}\omega$, or the applied voltage at its maximum is proportional to the frequency. This is a conclusion which has also been reached from experiment by Asher (1923) for high frequencies.

As the data on alternating current are not very extensive measurements were made to determine the validity of equation (18).

Apparatus and Method

The source of current used was the low frequency oscillator of the General Radio Company, a vacuum tube oscillator giving very pure sine waves of frequencies from 25 to 70,000. The preparation sciatic gastrocnemius of the frog, was mounted in a moist chamber. The electrodes consisted of two test-tubes each of 1 cm. diameter placed 1 cm. apart and vertically. The tubes were filled with Ringer's solution and the nerve laid across the open end so that the part traversing each tube was completely immersed. Silver chloride electrodes connected the liquid electrodes to the oscillator. The use of non-polarizable electrodes is probably quite unnecessary, but it is unlikely that they will do any harm. A non-inductive resistance of about 2,000,000 ohms in series with the nerve was used in all experiments. The applied voltage was measured on a cathode ray oscillograph. The scale is arbitrary but the numbers given are almost exactly equal to twice the actual voltage. The accuracy of the voltage measurements was in general to about 0.2 or 0.3 of the unit. The method used to determine the threshold was to raise the voltage gradually, stimulating at intervals for short times until the least voltage for a steady contraction was attained. The condition of steady contraction was determined visually without the use of a lever.

In all the experiments but *d* the measurements were made starting at the high frequencies and going to low frequencies. *d* was taken after about forty readings had been made at different frequencies lower than 400. The method of determining constancy of excitability was to make a measurement at frequency 1000 occasionally. If the reading at 1000 changed appreciably the experiment was stopped. This is not an entirely adequate test as shown by the Experiments *e* and *f*. These were done on the same preparation in the order, *e*, *f*. It will be observed that the threshold for high frequencies has become much lower during the interval of about 1 hour separating the two sets. This effect is encountered in nearly every case but the increase of excitability is usually much less and so slow that a single complete set of readings can be taken without changes greater than the usual variations in successive readings for the same frequency. In *b* for instance the range from 25,000 to 8000 was repeated after going through the complete set. In spite of both twitch and tetanus readings having been taken previously, two of these frequencies gave identical readings the second time and the remainder were sometimes greater and sometimes smaller than the original.

Experimental Results

It will be observed that on putting the constant h/K in equation (28) equal to A and squaring,

$$V_o^2 = A^2k^2 + A^2\omega^2 \qquad (29)$$

i.e., V_o^2 is a linear function of ω^2. This provided a convenient means of checking the experimental results. It was surprising to find when this was done that although equation (29) represented the voltage frequency relation extremely well, particular constants A and k applied to limited regions of frequency only, *i.e.*, the graphs of the relation of equation (29) turned out to be straight lines having abrupt changes of slope at various points on the frequency scale.

In Table II are given the data obtained using several preparations for frequencies above 300 or 400. Lower frequencies than this are not considered here as they are in the region in which the voltage-frequency relation may be very variable due to the existence of optimal frequencies (see for example: Renquist and Koch, 1930). The columns containing A and k respectively give the values of these constants for each frequency range. These constants were determined in each case from those observed voltages which are marked with asterisks. Those particular voltages were chosen from the $V_o^2 - \omega^2$ graphs, being values which fell on the straight lines going most nearly through all the points plotted for each range. The column headed *voltage calculated* was obtained by solving equations (29) for V_o using the A's and k's previously determined. This method was adopted to show the fit of equation (29) as the range of ω^2 is too large to plot on one scale.

It will be observed that in each range the theory and experiment agree extremely well, which indicates that the threshold voltage throughout the whole range of the frequencies used is that function of the square of the frequency predicted by equation (29). The theory does not, however, predict changes in the constants. Such a situation was quite unexpected and no reasonable explanation of the effect can be offered. It was expected that if equation (28) applied at all, it

TABLE II

Exp........	(a)			(b)				(c)		
Frequency		Voltage		Twitch voltage		Voltage			Voltage	
		Obs.	Calc.			Obs.	Calc.		Obs.	Calc.
40,000	*A*	63.0	68.6		*A*			*A*		
30,000	0.0002501	55.0	54.6		0.0003816			0.0005304		
25,000	*k*	*48.0	48.0	52.0	*k*	*71.0	71.0	*k*		
20,000	110,200	42.5	41.8	53.0	100,100	62.0	61.3	76,470	74.3	
18,000		*39.5	39.5	45.0		56.0	57.6		70.0	
16,000		37.0	38.0	45.0		54.0	54.1		*67.0	67.0
14,000		35.0	35.3	44.0		51.0	50.8		62.4	61.8
12,000		33.0	33.4	42.0		48.0	47.8		56.0	57.0
10,000	*A*	*31.7	31.7	40.0		45.0	45.1		*52.5	52.5
9,000	0.0004365	28.00	29.4	38.0		43.5	43.9		50.3	50.5
8,000	*k*	27.5	27.1	37.0		42.0	42.7		48.0	48.5
7,000	36,430	25.3	24.9	37.0		42.0	41.7	*A*	36.5	39.9
6,000		23.0	22.9	37.0		41.0	40.8	0.000745	35.0	36.0
5,000		*21.0	21.0	37.0		*40.0	40.0	*k*	33.7	32.4
4,000	*A*	19.7	20.5	35.0		39.0	39.4	39,380	30.7	29.1
3,500	0.0005249			32.0		36.0	38.4		27.3	27.7
3,000		*18.5	18.5	30.0	*A*	*34.0	34.0		*26.0	26.0
2,500	*k*	18.1	17.7	27.0	0.001567	29.7	29.9		24.8	25.1
2,000	29,790	18.0	17.0	24.5	*k*	27.5	25.9		*23.8	23.8
1,800		17.3	16.7	24.3	10,740	25.0	24.4	*A*	22.0	23.1
1,600		*16.5	16.5	21.0		23.5	23.1	0.001841	*21.0	21.0
1,400	*A*	15.5	16.0	20.5		22.0	21.8	*k*	19.2	19.0
1,200	0.00160	14.0	14.3	18.5		20.3	20.6	5,384	17.2	17.1
1,000		*12.6	12.6			*19.5	19.5		16.2	15.2
900	*k*	11.8	11.8		*A*				15.0	14.4
800	4,747	11.2	11.1	14.5	0.00316	*17.0	17.0		13.5	13.6
700		10.5	10.4	14.0	*k*	15.0	15.2		*12.8	12.8
600		*9.7	9.7	13.0	1,922	14.0	13.4		12.4	12.1
500		9.1	9.1	11.0		11.0	11.6		11.2	11.5
400		8.3	8.6	9.5		*10.0	10.0		10.5	10.9
300										

TABLE II—*Concluded*

Exp.	(*d*)			(*e*)			(*f*)		
Frequency		Voltage			Voltage			Voltage	
		Obs.	Calc.		Obs.	Calc.		Obs.	Calc.
30,000							*A*	76.0	79.0
25,000							0.0004021	*67.0	67.0
20,000							*k*	55.0	55.3
18,000									
16,000				*A*	88.0	89.2	55,630	*46.2	46.2
14,000				0.0007909	*80.5	80.5			
12,000				*k*	72.0	72.1			
10,000				51,180	64.0	64.1	*A*	38.0	34.4
9,000					62.3	60.3	0.0003292	*33.2	33.2
8,000					56.3	56.7	*k*	31.5	32.1
7,000					53.3	53.4	83,480	30.5	31.1
6,000					50.5	50.3		30.0	30.2
5,000					*47.5	47.5		29.3	29.4
4,000					43.0	45.1		*28.7	28.7
3,500					43.0	42.6		28.0	28.4
3,000				*A*	*40.0	40.0	*A*	*27.3	27.3
2,500	*A*	36.5	37.6	0.001284	38.5	37.7	0.0006173	26.0	26.5
2,000	0.002191	*31.5	31.5	*k*	35.5	35.7	*k*	26.0	26.0
1,800	*k*	29.3	29.0	24,800	*35.0	35.0	40,020		
1,600	6,969	27.5	26.8		33.4	34.4			
1,400		24.5	24.6	*A*	30.2	32.3			
1,200		*22.5	22.5	0.003363	*28.5	28.5			
1,000		20.6	20.6	*k*	25.5	24.8		*25.0	25.0
900		18.5	19.7	3,863	24.0	23.0	*A*	24.0	24.8
800		17.8	18.8		22.0	21.3	0.003555	22.5	23.0
700	0.003251	*17.0	17.0		19.5	19.7	*k*	*21.3	21.3
600	*k*	15.7	15.3		18.2	18.2		20.5	19.7
500	2,828	13.3	13.8		17.0	16.8	4,068	18.0	18.3
400		*12.3	12.3		*15.5	15.5		*17.0	17.0
300		10.5	10.6						

* Values used to determine *A* and *k*.

would do so fairly well for a limited range of frequencies, but would perhaps diverge gradually at higher frequencies due to the electrical skin effect or to other purely electrical effects arising from the complex structure of the nerve trunk. The equation, however, appears to represent the data just as well at high as at low frequencies. There appears to be no question that each range is distinct and linear in $V_o^2 - \omega^2$. It is possible, of course, to represent smooth curves approximately by series of straight lines, but if this were being done here systematic differences should appear between the voltages observed and calculated and it is unlikely that the constants A whose squares give the slopes of the line segments would change so greatly in magnitude in going from one segment to the other.

It was pointed out previously that Experiments e and f were on the same preparation. It will be seen that in these experiments the A's and k's both change, although those for the lowest frequency range are about the same in both cases. The procedure of these two experiments was adopted to show that the changes in constants encountered on going through a large frequency range were not due to the properties of the electrical circuit used, as, if they were, the change should always occur at the same frequencies.

The conclusion to be drawn from the values of k observed in these experiments is that the tissue used may become much more excitable, as measured by the time constant, to high frequency currents. The values of k for the highest frequencies are of the order of 100 times those for direct currents. No explanation of this can be offered.

It may be improper to neglect in these experiments the dependence of the threshold on the voltage. This condition may be put in as follows: the maximum of p occurs when $t = \frac{1}{\omega} \tan^{-1} \frac{k}{\omega}$. Since $V = V_o \sin \omega t$, V will be equal to $\frac{\pm V_o k}{\omega\sqrt{k^2 + \omega^2}}$ at this time. Putting the threshold $= h \pm \alpha V$,

$$h \pm \frac{V_o \, \alpha \, k}{\omega \sqrt{k^2 + \omega^2}} = \frac{KV_o}{k^2 + \omega^2}$$

or,

$$h = \frac{K\omega \pm \alpha k}{\omega} \times \frac{V_o}{\sqrt{k^2 + \omega^2}}$$

If K is large compared to $\alpha k/\omega$, as it will probably be for high frequencies, this expression is approximately equal to equation (28).

Evidently in this case as with others it is desirable to make the threshold independent of the voltage if possible in order to attain the greatest simplicity. What conditions existed with the present experiments are not known.

It may be quite improper also to consider that p may take on negative values as has been tacitly assumed in the analysis. In assuming this it must be supposed that the value of p at a given point due to a current in one direction appears to be negative when the current is reversed and p commences to be built up by the current in the new direction. The legitimacy of this assumption cannot safely be decided by the fit of equation (28) with the data. A knowledge of what p actually represents may be necessary, but lacking this a good deal of information may be obtainable experimentally, by finding the relation a stimulus applied immediately after an inadequate stimulus in the opposite direction has to the normal.

Equation (28) does not account for the existence of optimal frequencies, nor for the fact that in going from frequencies about 20 to 200 per second the threshold decreases gradually, then increases. No explanation of these phenomena can be offered on the basis of the present hypothesis. It is not improbable, however, that these effects are primarily due to something quite apart from the postulated mechanism. The electrotonus, for example, will be with alternating current a periodic phenomena as will any other secondary effects depending on the current alone. The existence of periodic phenomena which are known to be mutually related suggests a possibility of an optimal frequency.

On the whole the agreement of the data with equation (28) must be regarded with some distrust as regards its significance. The probability that it is fortuitous is small, but the situation is undoubtedly much more complex than with the unidirectional stimuli, and more should be known about the meaning of k before it can be assumed that it can take on a group of values whose members apply to different frequency ranges. On the other hand, however, if equation (28) is found to be valid quite generally it may be suggestive in determining the nature of the physical mechanism.

The Transient Term

In Experiment *b* of Table II are given the voltages required for the short tetani which always appear with high frequency currents before the threshold for steady tetanus is reached. It will be observed that these values diverge more and more from the steady tetanus values as the frequency increases. This is to be expected from the nature of the transient term of equation (27). No attempt has been made to get a numerical check of this transient phenomenon because of algebraic difficulties. The prediction of equation (27) that the twitch threshold will be farther and farther below the tetanus threshold, is qualitatively fulfilled by the data.

General Considerations

The methods employed here may be considered to be highly artificial, but quite the contrary is true. In attacking the problem there are but three possibilities presented in regard to the action of the current. Its action depends on its magnitude or on its energy or on both. This allows of three possible initial hypotheses:

$$\frac{dp}{dt} = KV, \quad \text{or} \quad \frac{dp}{dt} = KV^2, \quad \text{or} \quad \frac{dp}{dt} = f\,(V,\ V^2)$$

The third would be tried only in event of the failure of the other two, as such a relation would be unusual. The second has been used; *e.g.*, by Lapicque, and by Lassalle (Evans, 1930) and de Almeida (1931). The nature of the problem indicates, however, the use of the first, since the movement of ions is a function of the current or voltage rather than of the energy. A serious objection, also, to using the energy is that the excitation process depends on the direction of the current. This fact cannot safely be ignored.

The nature of the second hypothesis is imposed by observation. It is a fact that the local excitatory process decays spontaneously. The view may be taken that it decays only when it is not being built up (*i.e.*, after the current has been stopped), or only after it has reached a certain magnitude. The former view is definitely at variance with the facts, because the local excitatory process is not directly cumulative during stimulation. The latter view is of the nature of a very special hypothesis. *A priori*, if the local excitatory process decays at all and decays to completion, there is no reason why it should not decay whenever it exists and no reason why it should not decay according to the same law at all times. This being admitted there remains only to discover the law of decay. The one chosen, $dp/dt = -kp$, which appears to be entirely adequate, is the simplest one of the class of relations $-dp/dt =$ function of p. Had this not been adequate the procedure would have been to try more complicated functions of p.

The third hypothesis, that the local excitatory process must attain a certain liminal value, in order that the stimulus be adequate, is the only one suggested by the phenomenon. It can be avoided only by postulating that the response process to any given stimulus is different from those for all other stimuli.

It has already been pointed out that the direct current formula used here is closely related to those of Lapicque (1907) and Hoorweg, and to Weiss's law, and is exactly equivalent to Hill's equation (1910). The relating of formulae which fit or nearly fit the same data depends only on mathematical dexterity in reducing them to equivalent forms. It follows, however, that much of the present analysis must be closely related to older work, particularly that based on the leaky condenser idea which is just a particular case of the present hypotheses. No attempt has been made to discover or to point out all the possible parallelisms. The only novelty that is claimed for the present analysis is, that it is more complete than any other which in any of its aspects is mathematically equivalent, and that it is based on a more simple and more general point of view. It is thought that the hypotheses used here are the simplest that have any promise of being adequate. That they appear to be entirely adequate in so many cases indicates strongly that they embrace the main features of the excitatory process. It is unlikely that any particular case will involve anything more for its elucidation than minor additions to the general hypotheses.

SUMMARY

Hypotheses previously used (Blair, 1932) in deriving formulae for stimulation by direct currents are applied to other forms of electrical stimuli. This consists in considering solutions of the equation

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

where p is assumed to represent the local excitatory process, V is the voltage of the stimulus and K and k are constants. The solutions are discussed in regard to condenser discharges, linearly rising currents, exponentially rising currents, and alternating currents. New experimental work with alternating currents of frequencies above 400 per second on the sciatic gastrocnemius of the frog is related to the formulae.

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