612.816.1

MULTIPLE RESPONSE TO CONSTANT CURRENT IN FROG'S MEDULLATED NERVE

By BERNHARD KATZ

(*From the Department of Physiology, University College, London*)

(*Received June* 22, 1936)

According to Hill's [1936] theory of electric excitation a constant current applied to an excitable tissue rapidly builds up at the cathode a "local potential" V which is maintained throughout the passage of the current: excitation occurs if and when V becomes greater than U, the "threshold". It would appear that excitation should continue to occur until the threshold U, rising at a rate determined at any moment by the value of V at that moment and by the time constant λ of "accommodation", becomes greater than V once more. During a certain time T, therefore, V will be greater than U (see Fig. 1 and Hill, 1936, Figs. 1 and 3), and throughout this time repetitive response might be expected to occur, at intervals determined by the refractory period. The duration of the repetitive response would clearly be greater the greater, according to theory, the value of λ, i.e. the slower the accommodation process. It will be shown below that $T = \lambda \log_e I/I_0$, where I is the strength of the applied current and I_0 is the rheobase.

The same repetition of response, according to theory, should occur at the anode after breaking a constant current through a nerve [see Hill, 1936, Figs. 2 and 4].

Experiments have been made to ascertain whether the theory can be applied in this way to the phenomena of multiple response in frog's medullated nerves. In crab's nerve [Katz, 1936] repetitive response is very obvious, and—according to the theory—is a natural consequence of the slowness of accommodation.

METHOD

The experiments were made during January and February. Sciatic nerves and gastrocnemius-sciatic preparations of Hungarian *Rana esculenta* previously acclimatized to different temperatures (between 0 and 19° C.) were used; they were soaked in Ringer's solution of various calcium contents. Most experiments were made at room temperature, a few at 2–5° C. A paraffin-wax chamber was used with non-polarizable calomel half cells connected with the nerve by wooden strips saturated with Ringer's solution; strings of wool soaked in Ringer's solution connected the muscle with lead-off electrodes. The electric response of nerve, or muscle, during the passage of continuous current of various intensities through the nerve, was recorded by a three-stage capacity-coupled amplifier and Downing [1936] oscillograph. In the intervals between two stimuli, in order to reverse any after-effects, shocks of equal strength and opposite direction were sent through the nerve. In

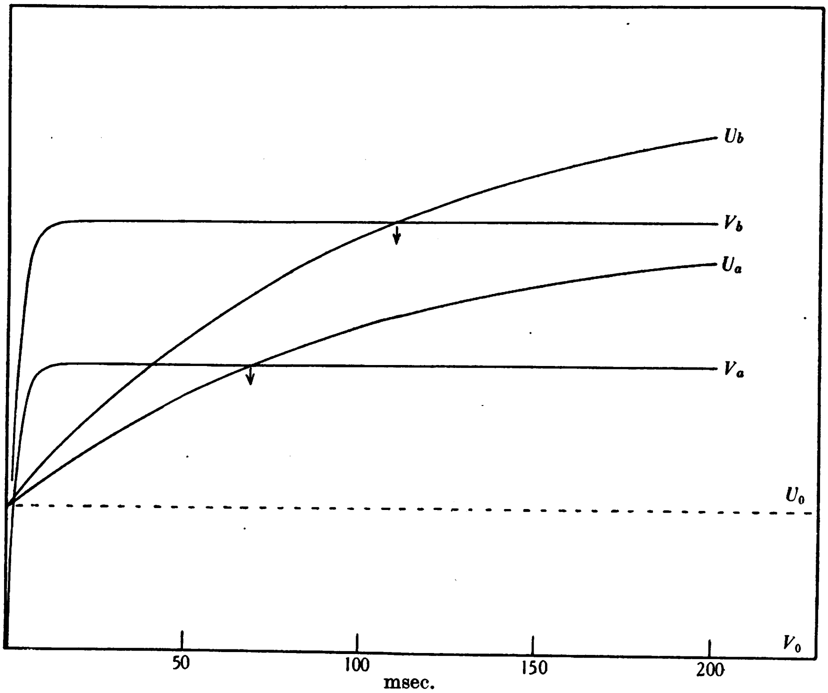

Fig. 1. Diagram illustrating threshold changes after closure of constant current. "Local potential" V and "threshold" U are represented by separate curves [cf. Hill, 1936]. Constant current of (*a*) twice and (*b*) 3 times "rheobasic" strength. Curves calculated, according to Hill, for $k=2\cdot5$ msec., $\lambda=100$ msec. In order to illustrate the rise of threshold and of local potential on the same time scale, a much too large k has been chosen. (A usual value of k would be 0·5 msec.) The end of the interval T of "maintained excitation" is shown by arrows.

some experiments the response of nerve, or muscle, to repetitive nerve stimulation was recorded (condenser discharges of $RC = 0{\cdot}1$ msec. at various frequencies, or constant current pulses of 10 msec. duration at about 30 per sec.). The time factor λ of accommodation was determined with exponentially increasing currents [Solandt, 1936].

RESULTS

(1) *The response of "cold frogs'" nerves to constant current.* The frogs used during these experiments had acclimatized incidentally to a rather low temperature. The isolated sciatic nerves were soaked for 2–6 hours

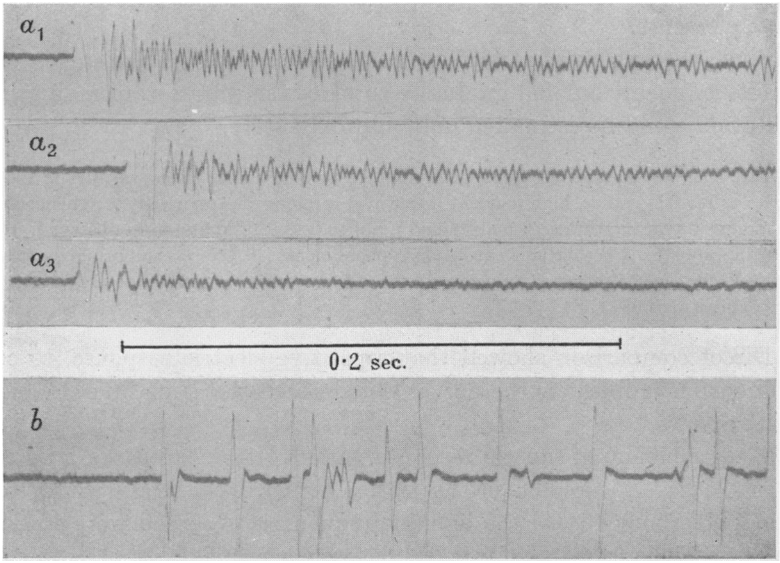

Fig. 2. Response of nerve during passage of constant current. (*a*) "Cool" frog. Nerve at 17° C. after 3 hours' soaking in normal Ringer. Relative intensities (threshold 1): a_1, 5; a_2, 3; a_3, 1·5. (*b*) Nerve after soaking in Ca-free citrate Ringer at 17° C., showing an exceptional phenomenon, viz. slow, rhythmic, synchronized responses to current of 10 μA.

in normal Ringer's solution at room temperature (15–19° C.). These nerves usually gave marked multiple response to constant current, if of slightly more than rheobasic strength (Fig. 2). This was unexpected, since accommodation in frog's motor nerves at 15–19° C. is usually rather rapid: Solandt's [1936] average value was about 30 msec.: and the formula $T = \lambda \log_e I/I_0$, for I only slightly greater than I_0, gives T only a small fraction of λ. Further experiments, however, showed that in these particular nerves the time factor λ was actually very great.

Certain phenomena regularly recorded in these experiments must be described in detail (Figs. 2 and 3). The repetitive nerve impulses diminished rather rapidly in size and frequency and soon became "asynchronous"; this occurred sometimes from the beginning so that the frequency could not then be measured. The interval between (initial) impulses was less with greater current strength, down to a value of about 2·5–3 msec. (frequencies estimated ranged between 80 and 200–400 impulses per sec.). The duration of response was greater with greater current intensity, and at twice the threshold was about 0·1–0·2 sec., varying in different preparations (see Table I below) and in different nerve elements.

Since perceptible electric responses of the nerve did not stop at any definite moment, but fell gradually to zero, the duration of maintained excitation could be estimated only approximately.

While Fig. 2*a* shows the regular behaviour, in rare cases (and these usually in Ca-free nerves and with rather high current intensity) prolonged apparently "synchronous" discharges of slow rhythm and maintained amplitude (see Fig. 2*b*) were observed. (It is doubtful, however, whether this exceptional phenomenon is due to the normal process of electric excitation or rather is associated with a latent state of spontaneous activity [see Biedermann, 1898].)

Direct comparison showed that repetitive electric response, to constant current applied to the nerve, lasted about the same time in muscle as in nerve.

The frequency of muscle response varied with intensity of stimulus. A greater $(V - U)$ would cause excitation earlier in the relative refractory period. At about 15° C., the highest frequencies observed were 150–200 per sec. The lengthening of interval between successive impulses was less distinct in muscle than in nerve response.

The repetitive action of the muscle fibres was, in most cases, "synchronous" for a considerable number of successive impulses (Fig. 3); the size of response decreased gradually (not as rapidly as in nerve, probably because simultaneous activity in different fibres was longer maintained). Eventually, only one or two "motor units" responded, outlasting the rest of the fibres by several impulses and stopping usually at a well-defined point. The duration, therefore, of multiple response in the motor nerve fibres can often be accurately determined.

The frequency of (initial) nerve impulses increased with frequency from 80 up to 200–400/sec., while a variation of muscle response from

80 up to only 150 (rarely 200 per sec.) was observed. This might suggest that, in some cases, during the initial stage of constant current flow, each second nerve impulse is blocked at the myoneural junction. The evidence, however, for this is not conclusive, because (i) the elements of highest frequency are not necessarily identical with the motor fibres and (ii) in estimating the frequency of nerve impulses an error due to asynchronous action of different elements cannot always be excluded.

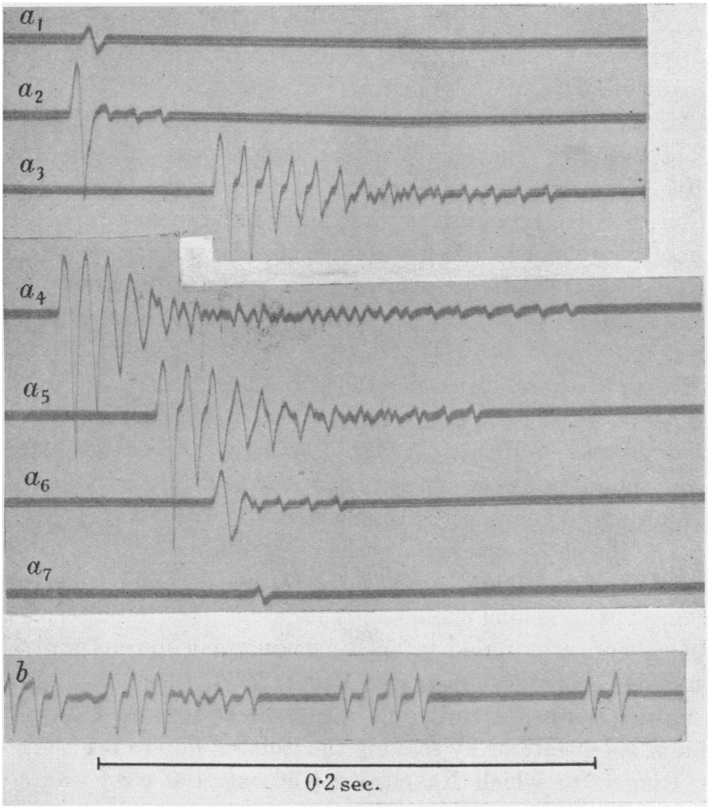

Fig. 3. Electric response of muscle during passage of constant current through nerve. (a) "Cool" frog, preparation at 14° C. after 4½ hours' soaking in normal Ringer. Relative strengths of constant current: a_1, 1·0; a_2, 1·33; a_3, 1·66; a_4, 2·33; a_5, 1·66; a_6, 1·33; a_7, 1·0. (b) Amplification 3·5 times higher than in (a). Record shows "intermittent failure" sometimes observed during decay of repetitive response. Twice threshold strength. Record started about 0·1 sec. after moment of closure.

It was considered whether the duration of the repetitive muscle response might possibly be reduced by a kind of Wedenski-block at the nerve endings, which would prevent the use of the muscle response as index for the duration of maintained nerve excitation. This, however, could not be the case in these experiments: for (i) with greater current intensity (and greater frequency of nerve impulses), the duration of muscle response became considerably greater; and (ii) the muscle response declined finally in obvious steps (Fig. 3*a*); obviously whole motor units were ceasing, and not an increasing number of single muscle fibres (as in the case of a myoneural "fatigue").

The decaying response of the muscle showed sometimes intermittent groups of impulses, spaced by rather long "gaps". These are to be attributed, for the same reasons, to an intermittent failure in nerve excitation: for (i) synchronous intermittent response, apparently of whole motor units, was observed; and (ii) the gaps were either more marked, or occurred after a shorter time, when the intensity was low. Assuming a failure at the neuro-muscular junction, the contrary should be found.

(2) *Calcium nerves.* Injecting Ca into the animals, or soaking the isolated nerve for a few hours in a Ca-rich solution, quickens the accommodation process [Solandt, 1936]. The same procedure is found to reduce considerably, or even to abolish, the multiple response. Nerves soaked for about 6 hours in 8–10 times normal Ca responded to a current of 3 times threshold strength with 1–3 impulses only. The formula $T=\lambda \log_e I/I_0$, for $I/I_0=3$, gives $T=1{\cdot}1\lambda$, which for $\lambda=6$ msec. gives $T=6{\cdot}6$ msec.; this is long enough only for a very few impulses. A similar effect of calcium was found in crab nerves which normally give much more prolonged repetitive response [Katz, 1936].

(3) Ca-*free nerves.* Depriving the nerves of ionized Ca—either by injection of Na citrate or by soaking the isolated nerves for 2–5 hours in Ca-free Ringer, to which Na citrate (150 mg./100 c.c.) was added—increased λ to 10 times the normal average value, sometimes abolishing completely the ability to accommodate [Solandt, 1936]. Nerves which normally gave very little repetitive response (nerves of frogs acclimatized to room temperature, see Table I below) showed persistent repetitive response to constant current of little more than threshold strength. This again applied to the motor fibres as well as to the whole nerve.

After a few hours soaking in "Ca-free citrate Ringer", the nerves started firing off spontaneous discharges, in irregular and asynchronous sequence; they remained in continued "spontaneous" activity for hours, getting gradually into a state of "fatigue" and "refractoriness". It was sufficient to apply Ca-free citrate Ringer locally to an uninjured part of the nerve in order to elicit spontaneous twitching. Removing the citrate Ringer and replacing it, after several times washing, by Ca-free Ringer (without citrate) did not diminish the continued activity. The twitching stopped immediately after cutting away the Ca-free part.

When citrate Ringer was applied to a normal rather rapidly accommodating nerve ("warm" frog), the state of spontaneous discharge was preceded by a remarkable lowering of threshold and a phase in which very prolonged response to constant current occurred. The threshold was lowered, by the removal of Ca-ions, to 1/8–1/10 of its original value (e.g. to 0·2 instead of 1·6 μA.), while soaking for a few hours in 10 times Ca raised the threshold about 3 times. The onset of spontaneous activity thus appears as the limiting result of (i) very slow accommodation and (ii) lowering of threshold, so that casual fluctuations of V make it greater than U_0.

Ca-free nerves, when stimulated in a state of prolonged spontaneous activity, exhibited distinct signs of "fatigue" and rapid lengthening of the refractory period at the point of stimulation [cf. Bugnard & Hill, 1935]. The response to repetitive stimulation at 200/sec. (condenser discharges of $RC = 0{\cdot}1$ msec., submaximal) was irregular: the first impulse being of greatest amplitude, followed by a considerable "refractory gap" and progressive failure in the different elements. In this state, constant current produces usually a few impulses only, rapidly disappearing and followed again by irregular spontaneous discharge.

(4) *Opening response.* The intensities required for break excitation were usually much higher than the threshold for a single closing response. More than two or three repetitive impulses, after break of constant current, were not observed in normal preparations (even at 7–10 times closing threshold strength). This is probably due to the well-known electrotonic changes of excitability at cathode and anode. The state of "normal accommodation" [Hill, 1936], in which the final steady value of $U - V$, during a continuously flowing polarizing current, is equal to $U_0 - V_0$, independent of the sign of the local potential produced, is usually not present. The steady value of $(U - V)$ is generally increased at the anode, lowered at the cathode. (Hill [1935, Fig. 1]: the line OAA_1 meets the "accommodation curve" only at rather high intensities.)

Reversing the normal electrotonic effects would facilitate the occurrence of multiple opening impulses at relatively low intensities. Such states are well-known (e.g. Werigo's cathodal depression; see Cremer [1909], Biedermann [1898]; they result, for example, from application (*a*) of strong long-lasting current, (*b*) of low temperature [Eichler, 1933], (*c*) of K-rich solution [Chweitzer, 1935; Bouman, 1936]; and (*d*) from fatigue and deterioration.

Isolated sciatics were kept at 4° C. and used at 2–5° C. After 7 hours no change of the normal state was observed, after 20 hours, however, the normal response to closing and opening of constant current was completely reversed. Repetitive opening response occurred at relatively low intensities (above about 2μA.), while the threshold for make response was much higher. (In this anomalous state, even at 10–20μA., only a small number of fibres responded to make of constant current.)

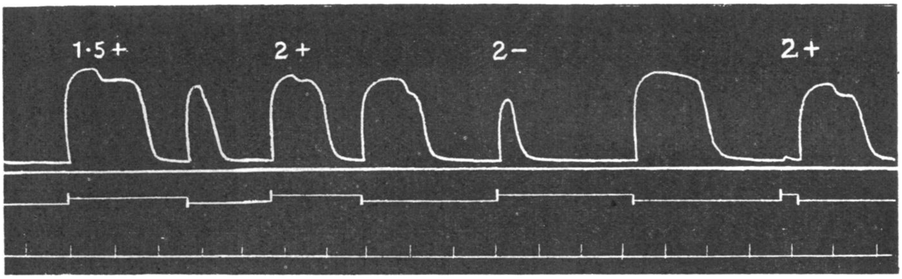

Fig. 4. Response of crab muscle during the passage of continuous current through the limb nerve. Time marks: 3 sec. Stimulus marks: rise shows "make", fall "break" of constant current. Intensities (volts) see record. + means "descending", − means "ascending" current. Note that with successive stimulations, the closing response fails, while the opening tetanus becomes enhanced.

The dependence of repetitive opening excitation on the electrotonic condition of the nerve appeared most clearly in the dissected crab nerve. Stimulation of limb nerves of *Carcinus maenas* with constant current produced at first prolonged closing tetani, while break of constant current was usually ineffective. With successive stimulations, however, the closing tetani became shorter and finally disappeared, while opening tetani appeared, which sometimes lasted considerably longer than the duration of previous current closure (see Fig. 4). The failure of make response could partly be reversed by introducing current pulses of opposite direction. These phenomena are much the same as Werigo's cathodal depression, viz. a reversal of the normal electrotonic excitability changes [see Cremer, 1909].

(5) *The relation between λ and T. Accommodation in "warm" and "cool" frogs.* The regular prolonged repetitive response in "cold frogs'" nerves, which had been soaked for many hours at room temperature, was surprising, although v. Frey [1883] had stated that the tetanic response

to constant current found in the isolated nerve-muscle preparations of cooled frogs may still be produced after a few hours at 15° C. There was an apparent discrepancy between Solandt's average value of λ (about 30 msec. at room temperature) and the duration of maintained response (about 0·2 sec. at 3 times threshold strength).

Determinations of λ in these preparations, however, settled this apparent disagreement. Nerves of "cool" frogs, used shortly after dissection, showed in some cases practically no accommodation at all. They gave persistent tetanic response even to threshold stimuli, the current intensity being independent of the time constant of current rise. During the first hour after dissection, λ was of the order of 300 msec., even after 6 hours at about 16° C., it was usually well above 100 msec. This agrees well with the observed duration of repetitive response to constant current.

Prolonged "injury discharges", after tying off the central end of the nerve, were often observed; the immediate twitch-like response during the ligature was followed, after a delay of a few seconds, by repetitive discharges continuing for a minute or more (in one case, it stopped only after 4 minutes, which approaches the similar phenomenon observed in crab motor nerve after amputation of the limb [Barnes, 1930]).

The time factor k of excitation [Hill, 1936] was determined in one experiment with single condenser discharge and a small muscle twitch as index: one hour after dissection, at 15° C., a k of 0·6 msec. was found (λ/k being about 500).

A clear relation between λ and T was found which will be discussed below. The greater λ, the longer was the duration of multiple response; this was the case when comparing different preparations as well as under different conditions in the same nerve. Nerves of cooled frogs soaked for a few hours in Ca-rich solution (8–10 times normal) showed a reduction of λ to less than 1/10 of its previous value, and at the same time abolition of repetitive response (Table I). Nerves of rapidly accommodating warm frogs soaked in Ca-free citrate Ringer showed a progressive lengthening of λ (increasing 10-fold in 4 hours) and a corresponding increase in T, until finally spontaneous activity prevailed. During prolonged experiments, λ and repetitive response were reduced both to the same degree. Further, nerves of any "cool" frogs which did not show marked multiple response, correspondingly had a small λ.

The great variation in respect of repetitive response [v. Frey, 1883; Fessard, 1935] which is found in different animals, presumably corresponds to the great variation of λ found by Solandt [1936]. Solandt's experiments suggest that these differences may be due to a variation in the ionized serum Ca. The effect of acclimatizing frogs to different temperatures might possibly be due also to a change in the blood Ca-content and connected with the fact [de Boer, 1918; for further references see Morgenstern, 1933] that summer frogs have twice the blood Ca of winter frogs.

DISCUSSION

It appears from these experiments that, in a general way, the theory of accommodation can be applied to the phenomena of multiple response. It remains to be seen how far the agreement is quantitative.

For the case of "normal" accommodation, i.e. neglecting electrotonic alterations of excitability, the change of $(U-V)$ following the "make" of a constant current through a nerve is given [Hill, 1936, equation (16)] by

$$U-V=(U_0-V_0)\left[1-\frac{I/I_0}{1-k/\lambda}\left(e^{-t/\lambda}-e^{-t/k}\right)\right].$$

If I is greater than the rheobase I_0, $(U-V)$ starts by being positive, then becomes negative, and finally becomes positive again. During the interval in which $(U-V)$ is negative repetitive excitation should occur. The end, therefore, of repetitive excitation is at time T given by putting $(U-V)=0$; hence

$$\left[1-\frac{I/I_0}{1-k/\lambda}\left(e^{-T/\lambda}-e^{-T/k}\right)\right]=0.$$

Unless accommodation is impossibly rapid T is great compared with k, so that $e^{-T/k}$ is effectively zero and we may write

$$e^{T/\lambda}=\frac{I/I_0}{1-k/\lambda}.$$

Since, in nerves which show repetitive response, k/λ is small, we may for simplicity neglect it, and finally obtain

$$T=\lambda\log_e I/I_0.$$

Thus for a current e times the rheobase (e being the base of Napierian logarithms) the interval T of repetitive response should be equal to λ, the time constant of accommodation. In Table I the interval T calculated from the above formula is compared with that actually observed in experiments on frog's nerve. Fig. 5 shows that the duration of repetitive response to a certain relative current strength agrees approximately with the calculated values (four preparations with different λ's). The agreement is better than was expected and probably gives an undue impression of accuracy. Actually, the figures of Table I and of Fig. 5 are affected by several possible errors: (i) average values were taken from several oscillograph records, which showed often a large "scatter" of T; (ii) the determination of "rheobase" from the oscillograph records was not very exact; and (iii), in cases of very slow accommodation, λ could not be very

TABLE I. Accommodation and repetitive response. (Muscle response as index.)

λ sec.	I/I_0	Multiple response Duration observed sec.	Multiple response Duration calculated sec.	
0·135	3·0	0·2	0·15	4½ hours at 14° C. "Cool" frog
0·17	3·75	0·2	0·22*	6 hours at 14° C. "Cool" frog
0·18	3·0	0·22	0·2	5 hours at 14° C. "Cool" frog
0·3	2·0	0·2	0·21	1 hour at 15° C. "Cool" frog
0·02	4·0	0·0	0·028	After soaking in 9 times Ca
0·016	3·0	0·018	0·018†	"Warm" frog
0·013	3·5	0·012	0·016‡	"Warm" frog
0·03	3·5	0·036	0·038§	"Warm" frog
0·015	4·0	0·0	0·02	"Warm" frog
0·15	3·5	0·25	0·19‖	After soaking in Ca-free citrate Ringer

* At twice threshold: 0·107 sec. calculated, 0·04 sec. observed; at 10 times threshold: 0·39 sec. calculated, 0·4 sec. observed.

† Up to 2·3 times threshold, no "extra impulses".

‡ Up to 2·7 times threshold, no "extra impulses".

§ Up to 2·5 times threshold, no "extra impulses".

‖ Occasional spontaneous twitching was already manifest. Duration of repetitive response, therefore, could be estimated only roughly.

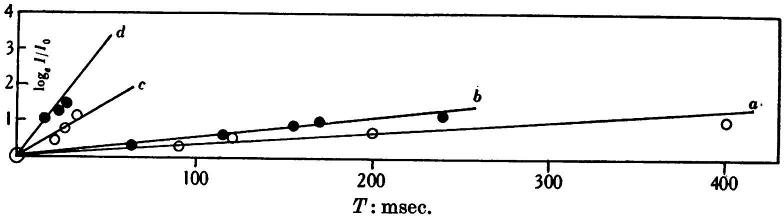

Fig. 5. Relation between multiple response and speed of accommodation. 4 preparations with different λ's. (a, $\lambda = 300$ msec.; b, $\lambda = 180$ msec.; c ("cool" frog, nerve with little repetitive response), $\lambda = 35$ msec.; d, $\lambda = 16$ msec. (up to 2·3 times threshold, no "extra impulse": not represented in the figure)). The plotted points show the observed duration T of repetitive response, in msec., against $\log_e I/I_0$. These values were obtained from oscillograph records (muscle response as index; average taken from two or three series of observations made before and after determination of λ). The lines give the slope $1/\lambda$.

accurately determined because the slope of the line relating threshold to rate of current rise was then very small. The exactness of the agreement, in some cases, may have well been due to favourable chance. In other cases, more distinct deviations were found (cf. Table I). T seemed often to be smaller than expected, if λ was small, it was sometimes even greater than expected if λ was great. The "scatter" of the observed values was sometimes large, particularly in cases of small λ. In general, however, the agreement is satisfactory, considering the various disturbing factors involved.

The refractory period. The recovery of excitability following excitation, together with the value of $(V-U)$, presumably determines the frequency of repetitive response. The recovery of excitability is not necessarily the same as that following a single shock, since the refractory period is known [Bugnard & Hill, 1935] to be lengthened during "high-frequency", particularly one-way, stimulation. This lengthening of refractory period presumably occurs also in the repetitive response of nerve to constant current, which is clearly a limiting form of "high-frequency one-way" stimulation. A state of maintained local refractoriness might reduce, or even prevent, multiple response, even with slow

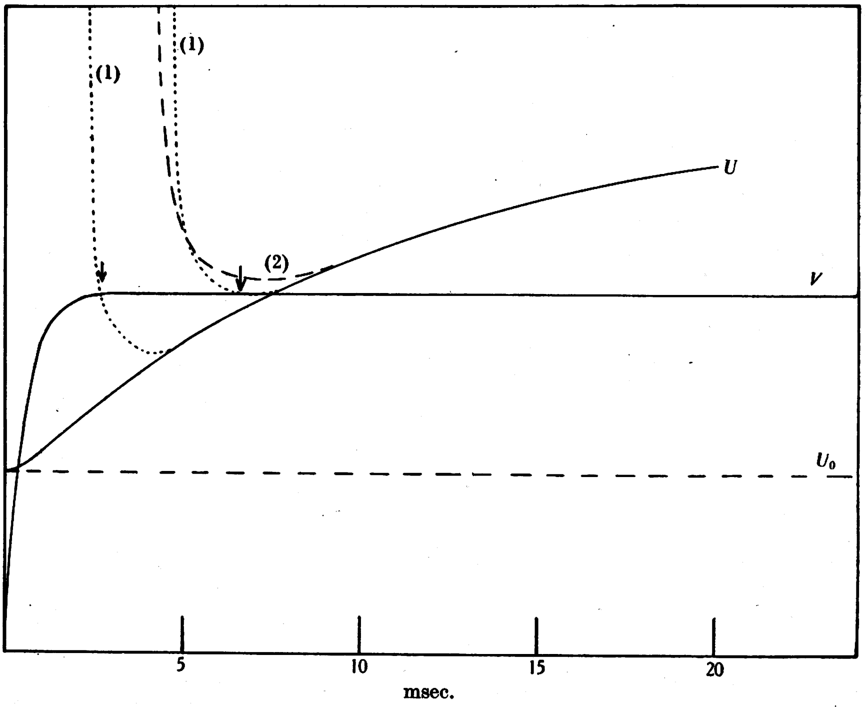

Fig. 6. Diagram illustrating influence of refractory period on multiple response. $k=0{\cdot}5$ msec., $\lambda=10$ msec. (1) absolute refractory period 2 msec., relative refractory period 5 msec. (2) absolute refractory period 4 msec., relative refractory period 9 msec. $I/I_0=2$. In case (1) two extra impulses (see arrows), in case (2) no extra impulse would occur during T. (T would be found experimentally as zero in case (2).)

accommodation: this is probably the case in Ca-free nerves, after continued spontaneous activity.

When accommodation is quick, a variation in the length of the refractory period would produce a considerable change of the apparent value of T. If λ is short, e.g. 10 msec., and the relative refractory phase rather long, one may get, even at 3 times threshold intensity, no repetitive impulse at all, simply because the recovery period outlasts or is equal to T. This is illustrated in Fig. 6. In this figure the refractory period is shown as a variation in threshold after effective excitation. This is arbitrary, because what is actually known is only that, during the "recovery phase", stronger currents are required to make V equal to U. Whether this is due to a rise in "threshold" or a temporary drop in "local potential" is unknown.

If, however, λ is large (e.g. 100 msec.) there is time for many impulses to occur, and the observed value of T would not be considerably reduced by the failure of one or two final impulses.

Electrotonic changes of excitability. The extent to which the duration of repetitive response might be altered by a strong, enhancing, or depressing, effect of catelectronus, is illustrated in Fig. 7. Fig. 7 (1) shows the theoretical state: $(U-V)$ becomes finally equal to (U_0-V_0). Fig. 7 (2) illustrates the lengthening of T by a catelectrotonic rise of excitability: $(U-V)$ becomes finally 0·5 (U_0-V_0). Fig. 7 (3) shows the shortening of T by a "cathodal depression": $(U-V)$ becomes finally 1·66 (U_0-V_0). In this figure the arbitrary assumption is made that the shape of the curve, and the time factor λ, are not affected by electrotonic changes.

The comparison of λ and T would not seriously be affected by electrotonus, because both were determined under similar electrotonic conditions. A variation, however, of refractory period and electrotonic changes during successive stimulation might conceivably account for the sometimes considerable "scatter" of the observed values.

Repetitive response to a single strong shock. A peculiar deduction may be drawn from the theory, namely that a strong shock, even of very short duration, may produce an extra response. With a strong enough shock V is raised a long way above U and then falls: if it has not fallen below U by the end of the refractory period a second excitation must occur. This is illustrated in Fig. 8 for the case of a crab's nerve with $k=2$ msec., a recovery period lasting 4 msec., and an instantaneous shock of 8 times threshold. A condenser discharge of duration $RC=0{\cdot}5$ msec. and of three times threshold should be sufficient to produce two impulses. The longer the duration of the discharge the less the strength of the current need be for a second impulse.

In frog's nerve, k is so short compared with the refractory period that excitation by very short shocks could not in practice lead to more than one response: with longer shocks, however, particularly in slowly accommodating nerve, repetitive response should be easy to obtain.

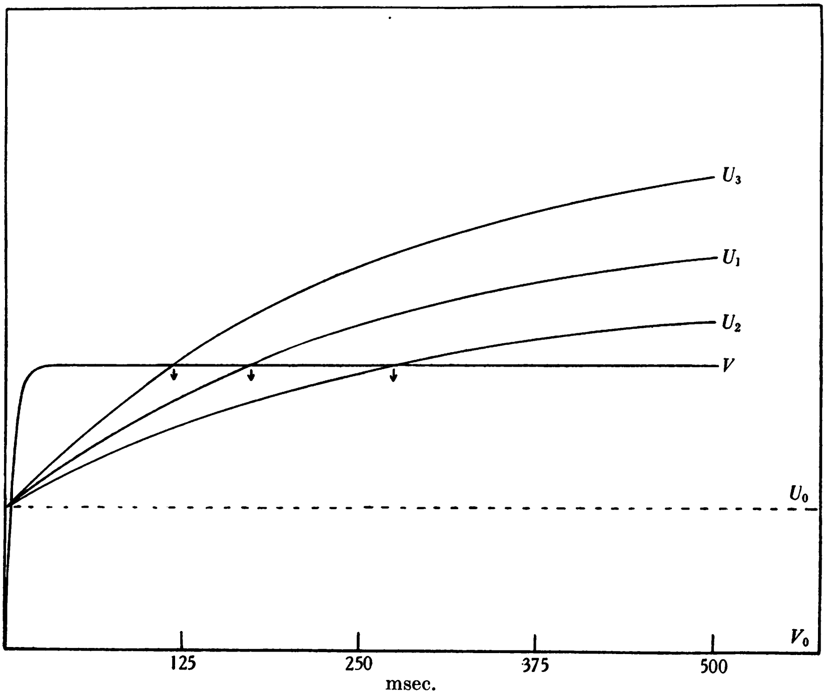

Fig. 7. Diagram illustrating threshold changes during passage of constant current. $k=5$ msec., $\lambda=250$ msec. (In order to make the rise of V visible, a k has been chosen, about 10 times greater than the actual value.) The curves illustrate the possible influence of electrotonic excitability changes. (1) theoretical state; (2) rise of excitability by catelectrotonus (Pflüger effect); (3) lowering of excitability by catelectrotonus (Werigo phenomenon).

The response to linearly progressive currents. Hoffmann [1910] has shown that the response of frog's nerves to linearly increasing current (muscle action potential as index) always consists of a train of impulses lasting as long as the current rises. This is in agreement with Hill's scheme [1936, p. 312, Fig. 5]: with this particular form of stimulus, only two possibilities exist: (i) the rate of current increase in smaller than the "minimal gradient", V then never reaches U and excitation does not

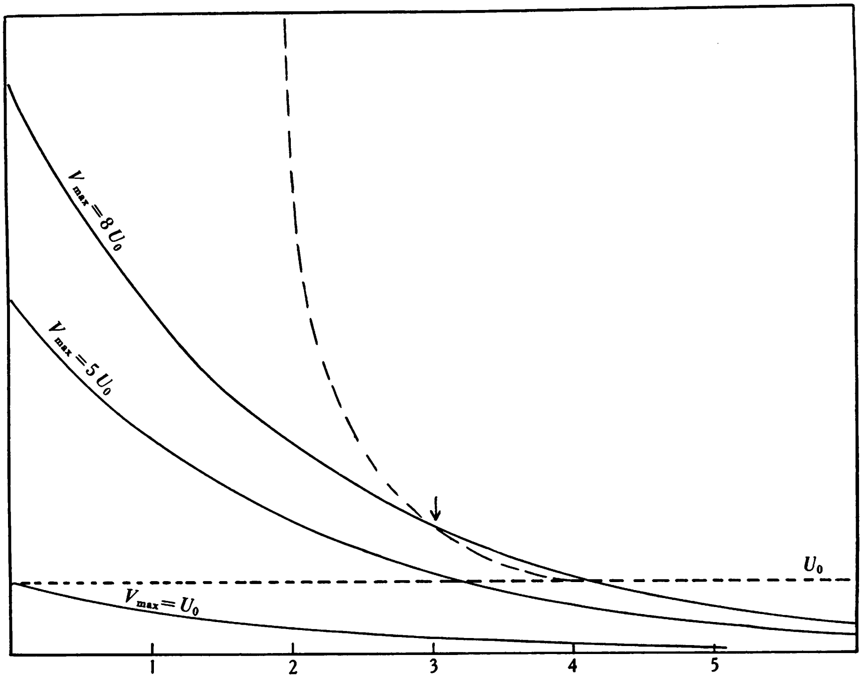

Fig. 8*a*.

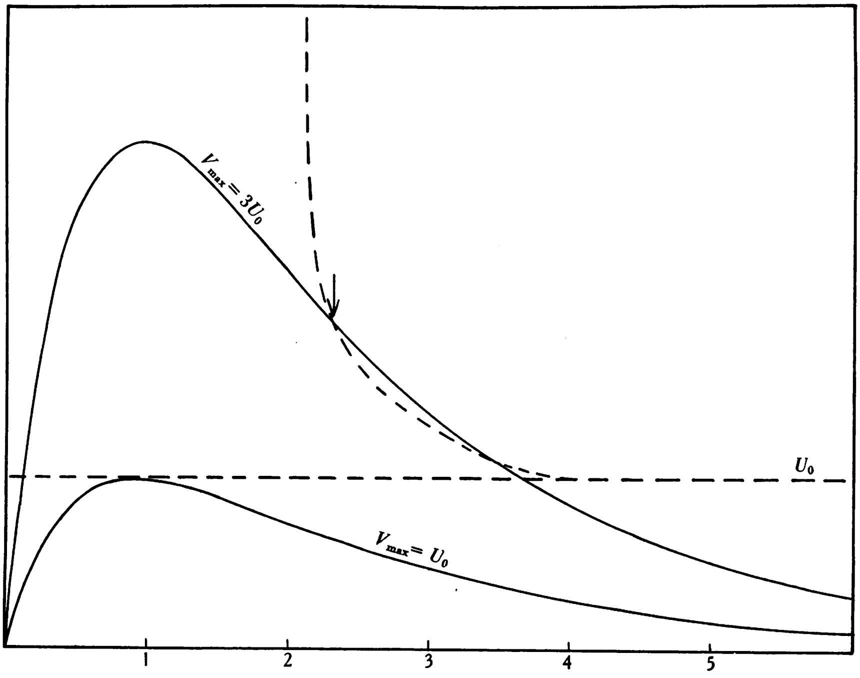

Fig. 8*b*.

Fig. 8. Diagram illustrating after-effect of short condenser discharges. (*a*) "instantaneous" discharge, $RC = 1$ μsec. $k = 2$ msec. λ about 1 sec. Absolute refractory period 2 msec., relative refractory period 4 msec. At 8 times threshold strength one extra response charge may occur (arrow). (*b*) condenser discharge, $RC = 0{\cdot}5$ msec. k, λ, and refractory period as in (*a*). At 3 times threshold strength, one extra response may occur (arrow). Absicissa: msec.

occur at all. (ii) The rate of current rise becomes greater than the "minimal gradient", V then soon crosses U and remains above it until cessation of stimulus. The response, therefore, to linearly progressive current must be repetitive, as soon as the "threshold gradient" is passed.

SUMMARY

1. According to theory, repetitive response to constant current should occur in nerve so long as the "local potential" V remains above the threshold U. The duration T of repetitive response is greater with slower accommodation and with stronger current, according to the formula $T=\lambda \log_e I/I_0$, where λ is the time constant of accommodation, I is the current employed and I_0 is the rheobase. The frequency of repetitive response at any moment depends upon the refractory period and upon $(V-U)$.

2. Nerves of cooled frogs, even after 4–6 hours soaking at room temperature, often show repetitive response to constant current of slightly more than rheobasic strength. This is due to very slow accommodation: λ at first was about 300 msec., even after 4–6 hours' soaking at room temperature above 100 msec.

3. Soaking the nerves of cooled frogs in Ca-rich solution, or keeping the animals a few days at room temperature, reduced λ to about 20 msec., and reduced or abolished the repetitive response to constant current.

4. Prolonged repetitive response to constant current (and eventually spontaneous activity) is produced in the nerves of warm animals by removing the Ca-ions from the surrounding fluid, corresponding to a great increase in λ and a considerable lowering of threshold.

5. The observed duration of repetitive response to constant current, under various conditions, agrees approximately with that calculated from the theory.

6. While λ is the only factor which systematically controls the duration of repetitive excitation of nerve during the passage of constant current, other factors which affect it are discussed. Recovery of excitability ("refractory period") and electrotonus are such factors.

My sincere thanks are due to Prof. A. V. Hill for much helpful advice and criticism. This paper resulted from the opportunity of using the suggestive ideas of his theory of excitation, and from enjoying the invaluable technical help of Mr A. C. Downing and Mr J. L. Parkinson.

REFERENCES

Barnes, T. C. (1930). *J. Physiol.* **70**, 24 *P*.
Biedermann, W. (1898). *Electrophysiology.* London.
de Boer, S. (1918). *Arch. néerl. Physiol.* **2**, 352.
Bouman, H. D. (1936). In preparation.
Bugnard, L. & Hill, A. V. (1935). *J. Physiol.* **83**, 394.
Chweitzer, A. (1935). *C. R. Soc. Biol.*, Paris, **120**, 626.
Cremer, M. (1909). *Nagel's Hand. Physiol.* IV, **2**, 955.
Downing, A. C. (1936). In preparation.
Eichler, W. (1933). *Z. Biol.* **93**, 527.
Fessard, A. (1935). *C. R. Soc. Biol.*, Paris, **119**, 1355.
v. Frey, M. (1883). *Arch. Anat. Physiol.*, Lpz., p. 43.
Hill, A. V. (1935). *Advances in Modern Biol.*, Moscow, **4**, 131.
Hill, A. V. (1936). *Proc. Roy. Soc.* B, **119**, 305.
Hoffmann, P. (1910). *Arch. Anat. Physiol.*, Lpz., p. 247.
Katz, B. (1936). *J. Physiol.* **86**, 285.
Morgenstern, V. (1933). *Pflügers Arch.* **232**, 174.
Solandt, D. Y. (1936). *Proc. Roy. Soc.* B, **119**, 355.