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"INHIBITION" IN MEDULLATED NERVE.

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Feng and Hill [1933] have recently studied the heat production of frog's nerve during the prolonged application of a stimulus of known frequency. They have shown that with a relatively low frequency (50–100 shocks/sec.), after a certain time a constant rate of production of heat is arrived at; this can be maintained for a very long time but diminishes, rapidly at first and then gradually, when excitation ceases, finally returning to the level corresponding to rest. With a high frequency, however (500–1000 shocks/sec.), a steady production of heat cannot be obtained; the rate at which heat is produced increases rapidly at the beginning of excitation, reaches a maximum, then decreases in spite of the maintenance of the stimulus. If, during this state of apparent fatigue, a stimulus of high frequency is replaced by one of low frequency, an immediate increase is observed in the rate of production of heat: the nerve, which no longer responds to the excitation of high frequency, is nevertheless capable of responding to an excitation of low frequency. This phenomenon, which was further discussed by Hill at the 1933 meeting of the American Association in Chicago [1934], is the subject of the present investigation.

TECHNIQUE.

The apparatus used was similar to that described by Hill [1932] and by Feng and Hill [1933]. The thermostat, however, had been modified as follows. The wooden box, which forms its external cover, instead of being placed directly in the room, was enclosed in a second wooden box covered inside with zinc sheet. The air space, separating the two boxes, was maintained at a constant temperature by an electrical heating arrangement automatically regulated. The temperature of the air space

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could easily be maintained constant within 0·1° C. This made unnecessary the maintenance of a constant temperature in the room as a whole, and increased considerably both the thermal stability and the ease of working.

The deflection of the galvanometer was read directly on a graduated scale without photographic recording. The scale was placed 4·5 metres from the galvanometer and the spot could easily be read to the nearest millimetre. Readings were made every 15 sec. during the first few minutes following the application or removal of a stimulus, and every minute later on, when an approximately steady state had been reached.

As stimuli, condenser discharges were employed at a frequency determined by the speed of rotation of a commutator [Hill, 1932]. Since the frequency had to be varied abruptly, two commutators were used running at different speeds. The reversal of the key allowed an instant transfer from one frequency to the other. One of the commutators was used for low frequencies (50–100 shocks/sec.), the other for higher frequencies (usually 500–1000 shocks/sec.). The condenser discharges themselves were exactly the same whatever the frequency, since they depended only upon the capacity of the condenser, which was the same in every case, and the resistance through which it discharged, which was also the same.

Frogs' sciatics were used, from large Hungarian *R. esculenta,* eight nerves in each experiment.

In general, in order to avoid polarization at the stimulating electrodes, excitation was effected by alternating charge and discharge of the condenser; thus excitation occurred alternately at one electrode and the other. In certain experiments, however, condenser discharges alone were employed, the stimuli being all in one direction, the cathode being at the electrode which was nearer to the thermopile; in certain other experiments there were two pairs of electrodes, each pair being used for one of the two frequencies. A suitable manipulation of the keys allowed an instant transfer from one mode of stimulation to the other (alternating or "one-way") and the use, at will, of one or other pair of electrodes. Actually three electrodes only were necessary, *A*, *B* and *C*, in that order pointing towards the thermopile. The distances were: *A* to *B*, 3 mm.; *B* to *C*, 12–15 mm.; *C* to thermopile, 18 mm. The distance from *B* to *C* was so great that stimulation at *A* or *B* could scarcely have affected the nerve at *C*. For the lower frequencies *A* and *B* might be employed, *B* being the cathode: for the higher frequencies, *B* and *C*, *C* being the cathode. *C* was actually the block of silver ordinarily serving to prevent the passage of heat from the stimulating electrodes to the thermopile [see Hill, 1932,

p. 113, Fig. 3]. The usual electrodes *A* and *B* will be described as the "upper" electrodes.

The capacity of the condenser used for stimulating, the potential to which it was charged, and the resistance short-circuiting the nerve, were chosen according to the principles discussed by Hill [1932]. In view of the high frequency of excitation employed, it was necessary to ensure that the condenser discharges were complete in the short interval of contact on the commutator. Unless this precaution be taken the shocks making up the stimuli will not be independent of the frequency. The capacity required can be determined by calculation, assuming for example that not more than 1 p.c. of the energy of the condenser should be undischarged at the moment when the discharge is cut short.

The following test was made. In the ordinary excitation circuit, namely, nerve in series with 5000 ohms, short-circuited by 1000 ohms, the latter was replaced by a resistance wire (932 ohms) wound non-inductively on a thermopile. The system could be connected to one or other of the commutators. The deflection of a galvanometer connected to the thermopile on which the hot wire was wound allowed one to measure the energy of the current through the wire. With a known frequency of charge and discharge one could determine the maximum capacity which would allow discharge to be complete to any required degree in the time available between separate contacts. Provided that the contacts are clean and not too oily, and the brush in good order, the rules are obeyed.

With a capacity of 0·105 μF the readings obtained with the commutator and those with a constant current calculated to give the same energy were compared. Between 100 and 1200/sec. the difference was never more than 4 p.c. At a frequency of 1950 the difference had risen to 12·5 p.c. In the experiments reported the stimuli were always as follows: capacity, 0·105 μF, charged to 14·4 volts, 5000 ohms in series with nerve, nerve and resistance short-circuited through 1000 ohms: time of half discharge, 0·06 σ; of 99 p.c. discharge, 0·4 σ. These shocks were well super-maximal. In general the frequency was kept below 1200/sec.

In order to keep permanent control during each experiment on the effectiveness of the stimulus, the following arrangement was finally adopted. The 1000 ohms shunt ordinarily used was replaced by a hot wire wound on a thermopile, the resistance of the hot wire being 932 ohms. At any point during an experiment a reading of a microammeter connected to the thermopile on which the hot wire was wound, is a measure of the energy in the stimulus. During each experiment several readings were made on the microammeter; the readings were always consistent and provided evidence of the efficiency and constancy of the stimuli.

The experiments were all made at a temperature between 21·2 and 22·7° C.

Sensitivity.

The apparatus was calibrated by observing the steady deflection produced by a series of regular condenser discharges applied between the heating electrodes after the nerve had been made inexcitable by prolonged treatment with nitrogen. The sensitivity was practically constant, the following being the mean value: 1 mm. of steady deflection corresponded to $1{\cdot}81 \times 10^{-8}$ cal./sec., or to $12{\cdot}9 \times 10^{-8}$ cal./g./sec.

Heat leak.

By reason of the high frequency of the stimuli used, it was feared that the heat might leak from the stimulating electrodes along the nerve into the thermopile in spite of the usual precaution of a block of silver placed between the two. In a certain number of experiments, therefore, the effect of the various stimuli employed between their usual electrodes was tested on nerves previously killed by long residence in nitrogen. In no case could one detect any important leakage of heat. The maximum effect observed corresponded to 8 p.c. of the heat found in the same experiment with the nerves stimulated alive, and even then only with a very high frequency, namely 2000/sec. In most cases the heat leak was quite negligible.

RESULTS.

In the first experiments the upper electrodes only (*A* and *B*) were used with stimuli alternating in direction in order to avoid polarization. Each individual shock, whether the frequency was low or high, had the same energy and time relations of discharge and was chosen to be approximately optimal for a nerve at rest.

The phenomenon observed is as follows. When, by means of an excitation of long duration and of relatively low frequency (50–100/sec.), a steady state of heat production by the nerve has been established, if the frequency is raised abruptly (*e.g.* to about 1000/sec.) an abrupt diminution is observed in the production of heat, the galvanometer moving rather rapidly in the negative direction. The initial heat production is diminished, or nearly abolished, though of course the recovery heat production from previous stimulation remains and follows its normal course. The nerve appears at first to be "fatigued." If, however, to the nerve apparently fatigued one substitutes in place of the excitation of high frequency the previous excitation of low frequency, one observes at once a production of heat at the previous higher rate and a return to the steady state characteristic of the original low-frequency excitation. The nerve, which seemed to be "fatigued" when tested by a high-frequency stimulus, is not fatigued at all when tested by a low-frequency stimulus. The same series of phenomena can be repeated many times. Some experiments have lasted for more than 3 hours, during which a steady state of heat production has been maintained under excitation of low frequency, interrupted by abrupt falls in the rate of heat production following the application of a stimulus of high frequency (Fig. 1).

It is important, however, to note that the high-frequency stimulus produces a maximal thermal response when applied to a resting nerve. With a stimulus of given short duration to a resting nerve, the heat increases with frequency up to very high values of the latter, as is shown by the usual heat-frequency relation described by A. V. Hill and his collaborators in several previous communications.

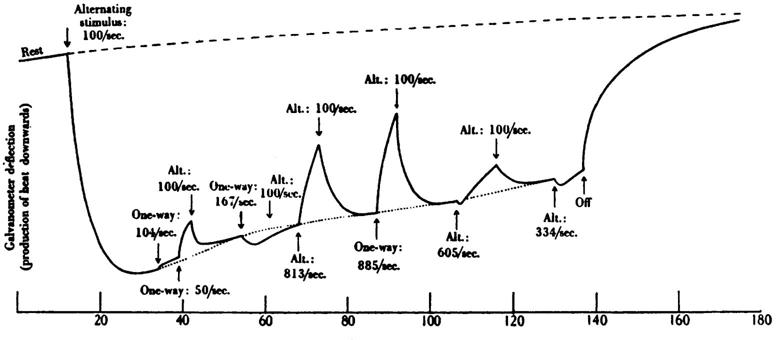

Fig. 1. Heat production of frog's nerve at about 22° C. during continuous excitation at various frequencies for 125 min. Experiment of May 15, 1933. Rate of heat production downwards as galvanometer deflection without analysis. Alternating or one-way stimuli as shown. The broken line interpolated between the beginning and the end of the experiment is a base line corresponding to the rate of heat production of the resting nerve. The dotted line corresponds to the steady and nearly constant rate of heat production during continuous stimulation at 100/sec. For further description see text.

The facts have been verified in fifteen experiments. One may begin by exciting the nerve during a state of rest by a high-frequency stimulus (for example, May 8, 10 and 26 respectively, 1284/sec., 920/sec., 920/sec.). There is an immediate and large positive deflection of the galvanometer corresponding to an intense production of heat by the nerve. At the end of 2 min., in place of the high-frequency stimulus effective on the resting nerve, a low-frequency stimulus is applied; the nerve continues to produce heat, though at first at a lower rate, and in the appropriate time reaches a steady state. The substitution now of the high-frequency for the low-frequency stimulus immediately breaks down the steady state and causes not an increase but an abrupt decrease in the rate of production of heat. A return to the low-frequency stimulus in place of the high causes a gradual re-establishment of the previous steady condition.

The sudden diminution in the rate of heat production caused by substituting a high for a low frequency does not represent a complete cessation of response, at least in all the fibres. If, during the condition of diminished rate of heat production caused by applying a high-frequency stimulus as described, one stops the stimulus altogether, one immediately observes a rather more rapid fall in the rate of production of heat, as shown by an acceleration in the movement of the galvanometer towards its resting position. In one experiment (May 17) deflections in the negative

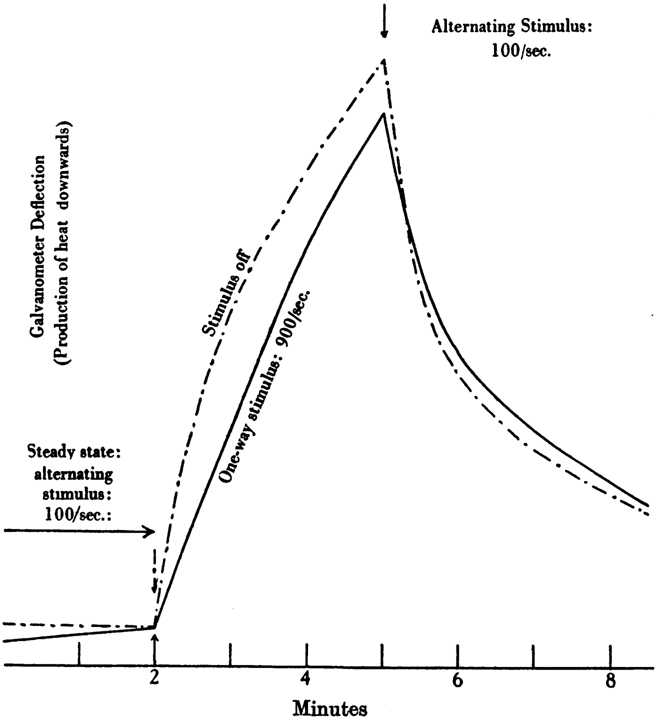

Fig. 2. Experiment of May 17, 1933. Comparison of the effect obtained during a steady state of heat production by a nerve stimulated continuously at a low frequency, 100/sec., (*a*) by stopping the stimulus altogether (broken line) and (*b*) by changing the stimulus to one of high frequency, 900/sec. Rate of heat production downwards as galvanometer deflection without analysis. Note that the high-frequency stimulus does not produce complete cessation of response.

direction were compared during a steady state of stimulation at 100/sec.: (*a*) when excitation was stopped altogether, and (*b*) when a low-frequency stimulus was replaced by one at 900 shocks/sec., the interval in either case being 3 min. For complete cessation the deflection was 74 mm., for high-frequency excitation it was 67 mm. (Fig. 2). A little later in the same experiment, again for 3 min., cessation of excitation gave a negative deflection of 71 mm., a stimulus of 612 shocks/sec., a negative deflection of 55 mm. Similarly, the rise in the heat production on returning to the stimulus of low frequency is greater after an interruption in the stimulus than after an excitation at high frequency. The latter, therefore, does not cause a complete cessation of response, except perhaps at very high frequencies.

One naturally asks whether the fact that the shocks alternated in direction might not explain their inadequacy at high frequency. To test this possibility, in spite of the danger of polarization, in a certain number of experiments stimuli were employed consisting of shocks in one direction only, the electrode nearer the thermopile being made the cathode. The effect was compared with that of alternating shocks of the same frequency. First of all it was verified that with excitations of low frequency (50–167/sec.) it is a matter of indifference whether alternating or one-way stimuli are used. The steady state of heat production is not modified at all, or at most to an insignificant extent, when alternating shocks at 100/sec. are replaced by one-way shocks at the same frequency. In order, therefore, to avoid polarization alternating shocks were used at the low frequency as conditioning stimuli to obtain the steady state.

In one experiment (May 11) there were applied successively, during a steady state with an alternating stimulus at 100/sec., and replacing that stimulus, (*a*) an alternating stimulus of 807/sec., (*b*) a one-way stimulus at 884/sec., and (*c*) an alternating stimulus at 807/sec. The alternating stimulus gave at first in both cases a slight extra production of heat followed by a very rapid diminution. The one-way stimulus gave immediately a rapid diminution. In all three cases a return to excitation at 100/sec. gave an immediate positive deflection and a return to the steady state.

In another experiment (May 15) an alternating stimulus of 813/sec. and a one-way stimulus of 885/sec., when substituted for a steady stimulus of 100/sec., were immediately followed by a large negative deflection more rapid in the case of the one-way stimulus. A return to the stimulus at 100/sec. brought an immediate positive deflection and a return to the steady state. The same result was obtained in another experiment

(May 17). It seems therefore that high-frequency shocks in one direction produce the same phenomenon as alternating shocks of the same frequency, and that it is not the alternation in direction of the latter that is the cause of their inadequacy. Indeed, the diminution of heat is slightly greater when the shocks are in one direction only. This may be due to an effect of polarization adding on to the effect of the high frequency, but it is at least possible that with alternating shocks at electrodes *A* and *B*, when the frequency is high, the impulses set up at *A* are unable to pass electrode *B* and so to reach the thermopile. Thus, alternating shocks at 1000/sec. at *A* and *B* may effectively be no more than one-way shocks at 500/sec. at *B*. If so, the high-frequency effect would be more obvious with one-way shocks at 1000/sec. at *B*.

In one experiment (May 26) the following result was observed. During the state of diminished heat production caused by substituting a one-way stimulus of 1000/sec. for an alternating stimulus of 100/sec. during a steady state caused by the latter, an alternating stimulus of 1090/sec. was applied. The immediate effect was a very slight positive deflection followed by a negative deflection similar to that preceding it. It seems, therefore, that one-way stimuli are at least as effective in producing the type of "inhibition" referred to as alternating stimuli.

Another possible explanation of the phenomenon was a local modification of the nerve set up at, or between, the electrodes by the low-frequency stimulus. This local experimental modification of the condition of the nerve might affect it in its response to the high-frequency stimulus between the same electrodes. To test this possibility, in a certain number of experiments two pairs of electrodes were utilized as described above, *A* and *B* or *B* and *C*. First of all it was verified that the two pairs of electrodes were identical for the establishment of a steady state of heat production with an excitation of low frequency. In one experiment (May 18), during a steady state of activity set up by an alternating stimulus at the upper electrodes *A* and *B* (frequencies 100/sec.), the nerve was excited at the lower electrodes *B* and *C* at frequencies of 611/sec. and 912/sec. In both cases an abrupt negative deflection was produced followed by a positive deflection and a return to the steady state when the low-frequency stimulus at the upper electrodes *A* and *B* was substituted for the high-frequency stimulus at *B* and *C*. In the same experiment a stimulus of 912/sec. at the upper electrodes *A* and *B*, substituted for 100/sec. at the same electrodes, produced the same phenomenon, the negative deflection being more rapid than when *B* and *C* were employed. Some local effect, therefore, may occur, but it is not the cause of the phenomenon.

In the experiment of May 22, during a steady state with a stimulus of 48/sec. at the upper electrodes *A* and *B*, successive stimuli were applied as follows, all at 605/sec.: (1) at *A* and *B*, (2) at *B* and *C*, (3) at *A* and *B*. In all three cases, owing to the rather lower frequency, a very short positive deflection was observed followed by a large negative deflection. The same results were obtained in the experiments of May 24 and May 26. The phenomenon, therefore, cannot be explained by a local modification of the nerve at or between the electrodes of the conditioning stimulus. The distance from *B* to *C* was 12–15 mm., so it is very unlikely that shocks of low frequency at *B* could directly affect the nerve at *C* sufficiently to block it to subsequent high-frequency stimulation. The effect found in high-frequency stimulation at *C* must have been conditioned by low-frequency impulses previously reaching *C* from above, and not by the direct effect of the shocks.

If, during a steady state of heat production, due to prolonged excitation at low frequency, more rapid stimuli of various frequencies are applied, a graduated effect is obtained in the modification of the heat production. In one experiment (May 8), during a steady state produced by a stimulus of 112/sec., a stimulus of 705/sec. replacing it, caused a positive deflection followed by a large negative deflection. A stimulus of 1008/sec. produced a slight positive deflection followed by a negative deflection more rapid than the preceding. A stimulus of 1570/sec. produced a negative deflection immediate and abrupt. In another experiment (May 15) analogous results were obtained at frequencies of 305/sec., 605/sec., 813/sec. The same was found in eight experiments in which, not only the frequency was varied, but also the electrodes and the mode (one-way or alternating) of excitation. All the effects intermediate between a production of heat and its almost complete suppression can be obtained when a prolonged excitation at low frequency is changed to an excitation of high frequency. In every case the return to the excitation of low frequency causes a re-establishment of the previous state.

The duration of the preceding excitation of low frequency also has an influence on the thermal response of the nerve to a stimulus of high frequency. In one experiment (May 22) after 30 min. stimulation at 48/sec., the steady state of heat production not having been quite reached, an excitation of 605/sec. was applied. A small positive deflection was observed which lasted for 3 min. and was succeeded by a negative deflection. A return to the 48/sec. then caused a restoration of the previous state of steady heat production. After a total of 80 min. of low-frequency excitation the stimulus of 605/sec. was again applied, this time with an immediate fall in the production of heat. In another experiment (May 23) a stimulus of 906/sec. maintained for 2 min., after 12 min. of stimulation at 103/sec. which had not yet led to the establishment of a steady state, produced an immediate negative deflection of 60 mm. After a total of 30 min. of stimulation at 103/sec., a steady state of heat production being

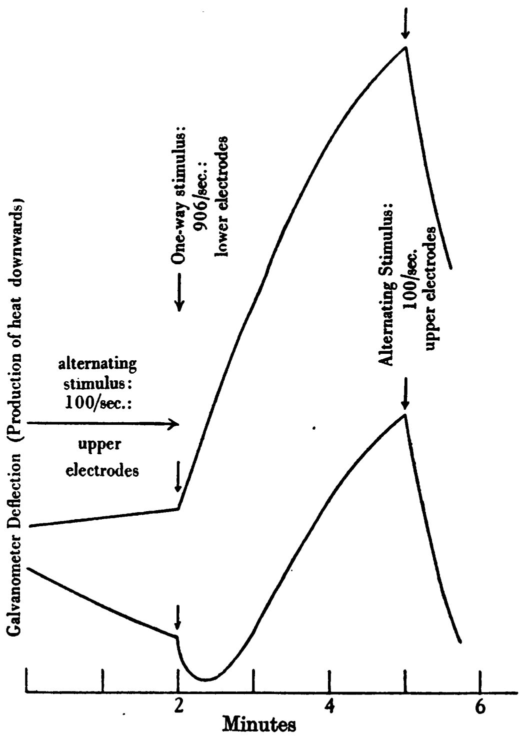

Fig. 3. Influence of the duration of the conditioning low-frequency stimulus (100/sec.) on the heat production of nerve when the frequency is suddenly raised to 906/sec. Experiment of May 24, 1933. The lower curve shows the application of the high-frequency stimulus to a nerve previously stimulated for 12 min. only at 100/sec., the steady state of heat production corresponding to this low frequency not yet having been attained. An immediate extra production of heat occurs, followed after 30 sec. by a diminution. The heat production rises again on returning to the lower frequency. The upper curve corresponds to the high frequency applied to the same nerve previously stimulated for 31 min. at the lower frequency, the steady state of heat production corresponding to the low frequency having already been reached. The diminution in heat production is immediate but the curve rises again when the frequency is again lowered. The low and the high-frequency stimuli were applied at two different pairs of electrodes, as described in the text, the conditioning low-frequency shocks being at electrodes more distant from the region of the nerve in which the heat production was measured. Heat production downwards as galvanometer deflection without analysis.

now established, the same high-frequency excitation now gave an immediate negative deflection of 82 mm. Analogous results were obtained in the experiments of May 24 and 26 (Fig. 3). The production of heat by the nerve, therefore, is more rapidly and intensely diminished as the result of an excitation of high frequency, when the duration of the low-frequency excitation which it replaces has been greater.

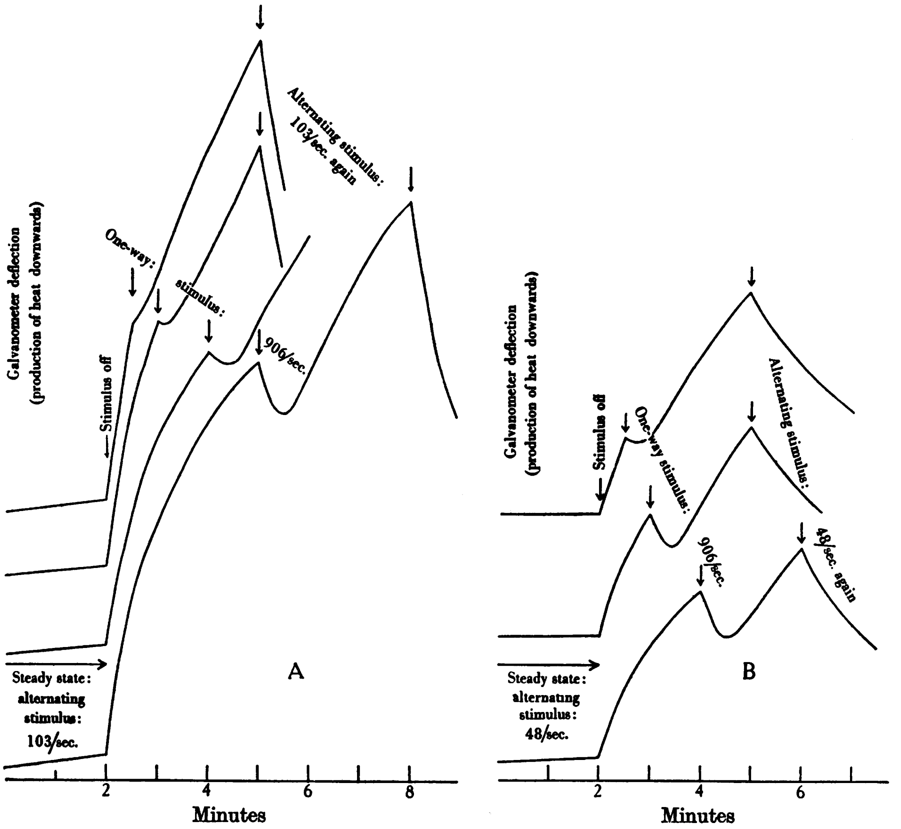

Fig. 4. Effect of an excitation of high frequency (906/sec.) on the heat production of nerve rested for various intervals after a previous prolonged stimulation leading to a steady state at low frequency. A, conditioning frequency 103/sec.; B, conditioning frequency 48/sec. Intervals of rest: A, ½, 1, 2 and 3 min.; B, ½, 1 and 2 min. Note that in B the response to the high-frequency stimulus is greater after a conditioning stimulus of low frequency than after one of a rather higher frequency. Heat production downwards as galvanometer deflection without analysis. Experiment of May 23, 1933. For discussion see text.

The frequency of the initial slow stimulus plays a similar part in the response to a high-frequency stimulus following it. In the experiment of May 23 an excitation of 906/sec., lasting for 2 min., followed first an excitation of 100/sec. lasting for 12 min., then an excitation of 48/sec. lasting for 12 min. In the first case the negative deflection was 60 mm., in the second case it was 40 mm. Similar results were obtained in the experiment of May 22. For equal durations of prolonged excitation at low frequency the negative response to the same excitation of high frequency replacing it is greater the greater the frequency of the slow preceding stimulus.

In a last series of experiments the response was studied to an excitation of high frequency at various intervals after the suppression of a stimulus of low frequency. For example, in the experiment of May 23, after a stimulus of 103/sec. which had lasted for 45 min. and led to a steady state of heat production, the stimulus was suppressed altogether for 30 sec. A very rapid negative deflection was observed. A stimulus of 906/sec. was then applied and the negative deflection continued but less rapidly. The low-frequency stimulus was reapplied and the steady state was re-established. Excitation was suppressed for a minute with an immediate negative deflection. The high-frequency stimulus of 906/sec. was then applied again for 2 min.: the negative deflection stopped and then continued at a diminished speed. Later, following a steady state at low frequency, the nerve was rested for 2 min. and then an excitation of 906/sec. produced at first a small positive deflection and then a negative one. A rest of 3 min. caused an accentuation of the same phenomenon (Fig. 4). It seems, therefore, that the modification produced in the nerve, in respect of which it fails more or less to respond to a stimulus of high frequency, lasts for a certain time after the suppression of the prolonged stimulus of low frequency which caused it. The complete return of the power of the nerve to respond to a high-frequency stimulus probably does not occur before the nerve has completely recovered from its preceding steady excitation.

DISCUSSION.

The experiments reported show that prolonged excitation of a nerve by shocks of low frequency renders it incapable, to a greater or less degree, of responding to a stimulus of high frequency. This is not a question, however, in any ordinary sense of "fatigue." The nerve, which is no longer excitable by, or gives only a small response to, a stimulus of high frequency, responds to a stimulus of low frequency by a production of heat which is constant and may be continued for a very long time, or almost indefinitely. It seems rather that the nerve during the course of prolonged excitation at low frequency is put into a state in which it is "inhibited" or partly inhibited, by a stimulus of high frequency. The state in which inhibition, instead of excitation, occurs when a rapid stimulus is applied, is reached only gradually, after a time of stimulation at low frequency of the order of 10, 20 or 30 min. The duration required depends upon the frequency of the slow excitation employed. The inhibitory effect is shown in all degrees as one increases progressively the frequency of the conditioning stimulus, its duration, and the frequency of the rapid stimulus tested.

Experiments of Hill [1932] and of Feng and Hill [1933] have shown that there is no simple relation between the frequency of excitation and the heat produced by the impulses set up. Another variable is involved, namely, the duration of the stimulus employed, and it now seems that the state of the nerve as affected by previous stimulation also must be taken into account. The heat per impulse is a function, not only of the frequency of excitation, but of the duration of previous stimulation and of the previous history and the state of recovery of the nerve.

One naturally asks whether the effect observed may not be due to a modification in the duration of the refractory period. Forbes and his collaborators [1923], Gasser and Erlanger [1925], and numerous other authors, have shown that if impulses follow one another in a nerve, at intervals short enough to make it necessary for them to travel in fibres incompletely recovered, the velocity of propagation and the size of the action current are modified: the refractory period is increased, the speed of propagation reduced, the size of the electric changes diminished. Such experiments have been concerned with the propagation of two impulses only, or of a series of impulses far shorter than we have considered in the present experiments.

The lengthening, however, of the refractory period, after a long interval of excitation at low frequency, is not sufficient alone to explain the "inhibition" to stimuli of high frequency. While admitting that a greater proportion of the shocks in the high-frequency stimulus would fall, in consequence of the lengthening of the absolute refractory period, within an interval of inexcitability of the nerve, it is difficult to understand why the response to an excitation of high frequency should not be (as it is in a nerve at rest) at least as great as to the excitation of low frequency. It seems, as Hill [1934] remarks, and as Verworn [1914] supposed for a series of shocks leading to Wedensky inhibition, that a stimulus *B* falling in the absolute refractory period of an impulse *A* must extend the refractory period, *i.e.* must render the nerve inexcitable by a following stimulus *C*, although *C* following *A* alone would have produced a response.

Fröhlich also (referred to by Lucas [1911]) supposed that "recovery" may be hindered by stimuli falling within the absolute refractory period: though Lucas himself could find no trace of such a relation with three stimuli applied to a previously resting nerve. The state in which the relation seems actually to occur is acquired by a nerve during slow steady stimulation at a rate to which it can respond indefinitely, and which does not therefore in any ordinary sense fatigue it. In a resting nerve, with a stimulus of short duration, the higher the frequency the greater the response.

This "inhibition" recalls in certain respects the phenomenon described under the name of Wedensky inhibition. When a muscle-nerve preparation has been modified by fatigue, or by a narcotic, stimuli of high frequency to the nerve no longer produce muscular response. The explanation generally given of this phenomenon involves the modification of the state of the neuro-muscular junction. Wedensky [see Lucas, 1911, p. 84] showed, moreover, that similar inhibition may occur in nerve alone, with local impairment of conduction. Tsai [1931] also has shown that a narcotized portion of nerve will allow impulses derived from a muscular sense organ to pass at a limited frequency but will arrest impulses of a higher frequency. In the present case the conditioning cause can scarcely be a local block since previous slow excitation at a point 12–15 mm. above the point tested renders the nerve liable to "inhibition" on high-frequency stimulation. H. and P. Davis [1932] have shown that the tension exerted by a muscle is a maximum for stimuli of low frequency and is diminished when the frequency is raised. These phenomena are probably all of the same nature.

It seems then, that when a nerve is subjected to prolonged steady non-fatiguing stimulation of moderate frequency, a condition is gradually set up in which a stimulus of high frequency produces a state of inhibition. During, and for some time after, this state of steady and constant excitation (which is presumably at least as representative of the normal physiological state as one of complete rest) the process of "recovery" from the refractory condition following a shock is different from that observed in the case of an isolated impulse, or during stimulation of short duration of whatever frequency applied to an otherwise resting fibre.

SUMMARY.

When a nerve is subjected to prolonged stimulation of low frequency (up to 100 shocks/sec.) it finally reaches a steady state in which the rate of heat production is constant. In this state, although in no ordinary sense fatigued, it is largely incapable of responding to an excitation of high

frequency of the order of 1000 shocks/sec. It remains, however, capable of responding by the same steady heat production on returning to the stimulus of low frequency. If, during a state of rest, the nerve is subjected to the same high-frequency excitation, it now gives an immediate maximal response. The phenomenon seems to be of the same nature as Wedensky inhibition, but it occurs in the nerve trunk.

The effect is not due to any local modification of the nerve at the exciting electrodes. It appears at a considerable distance from the point at which the conditioning stimulus of low frequency is applied, as is shown by the fact that the same failure to respond to a high frequency may occur at a distant electrode. The effect is the same whether the stimuli alternate in direction or are all "one-way."

All degrees can be observed between complete inhibition and a steady production of heat when the frequency of the secondary stimulus (the rapid one) is varied.

The fall in the response on the application of the higher frequency is greater and more rapid the higher the frequency of the basic conditioning stimulus and the longer the time of its application. When the low-frequency conditioning stimulus is stopped and an interval of recovery allowed, the response to the high-frequency stimulus is greater the greater the interval of intervening rest.

It is difficult to give an explanation of the phenomenon on the basis of what is known about the passage of a single impulse, or of a few isolated impulses, in an otherwise resting nerve. As the result of prolonged steady activity, not so intense, however, as to lead to fatigue, the processes of "recovery" from the refractory state following a shock are modified, so that a continuously refractory condition may be set up by shocks succeeding one another at sufficiently short intervals.

My warmest thanks are due to Prof. A. V. Hill for suggesting the subject of this work and for providing the material and the counsel necessary for its realization. My thanks are due also to Mr J. L. Parkinson for his help and advice.

APPENDIX.

By A. V. HILL.

The state of "inhibition" described in the preceding paper is not propagated away from the stimulating electrodes, as is shown by the following experiment. A thermopile was prepared with four electrodes, A, B, C and D, the distances being as follows: $AB = 2{\cdot}2$ mm., $BC = 16$ mm., *CD* = 3·4 mm., *D* to nearer end of thermopile = 18 mm. A high frequency stimulus (1000/sec.) initially producing a maximal response was applied at *A* and *B* until the response was largely reduced; without stopping the stimulus at *A* and *B* a low frequency stimulus (100/sec.) was then applied at *C* and *D* and a good response was obtained.

Another experiment was made as follows. A short (16 sec.) high-frequency stimulus at *A* and *B* initially caused a much greater response than a similar low-frequency stimulus at *C* and *D*. When the latter had been continued for some time, the former applied for 16 sec. during the continuance of the latter always gave a slight positive effect, showing (*a*) that there was not complete failure at *A* and *B*, and (*b*) that nothing like "inhibition" was being propagated from *AB* to *CD*. If, however, the low frequency at *CD* was turned off while the high frequency at *AB* was turned on, there was a negative response, showing that the high frequency was now producing a smaller effect than the low frequency, therefore a much smaller effect than it did initially.

It seems, therefore, that the "inhibition" referred to by Bugnard is connected with the process of excitation, each element of the high-frequency stimulus causing, or maintaining, a higher threshold or a prolonged refractory period. The condition in which this "inhibition" may be observed on high-frequency stimulation can be produced by a steady stream of impulses propagated from a distant point. The "inhibition" itself, however, is local. One cannot "inhibit" low-frequency impulses starting at *CD* by high-frequency stimulation at *AB*; though one can block (at *CD*) low-frequency impulses starting from *AB* by high-frequency stimulation at *CD*.

REFERENCES.

Davis, H. and Davis, P. A. (1932). *Amer. J. Physiol.* **101**, 339.
Feng, T. P. and Hill, A. V. (1933). *Proc. Roy. Soc.* B, **113**, 356, 366.
Forbes, A., Ray, L. H. and Griffith, F. R. (1923). *Amer. J. Physiol.* **66**, 553.
Gasser, H. S. and Erlanger, J. (1925). *Ibid.* **81**, 473.
Hill, A. V. (1932). *Proc. Roy. Soc.* B. **111**, 106.
Hill, A. V. (1934). *Science* (in the Press).
Lucas, K. (1911). *J. Physiol.* **43**, 46.
Tsai, C. (1931). *Ibid.* **73**, 382.
Verworn, M. (1914). *Erregung und Lähmung*, p. 205. Jena: Fischer.