THE GENESIS OF INHIBITION OF THE CARDIAC GANGLION OF LIMULUS BY STIMULI OF INCREASING FREQUENCY

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FIVE FIGURES

The nature of inhibition, whether peripheral or central, remains obscure despite the many sided experimental approaches to the problems by investigators too numerous to mention, vide Howell ('25). The concepts of central inhibition are the result of studies conducted chiefly on vertebrate reflexes where physiological complexity makes analysis difficult if not impossible. Simpler relationships, both anatomical and physiological, make the ganglionic cord of the heart of Limulus attractive for investigation in this connection. It has been shown that typical inhibition of the autogenous rhythm of the ganglionic impulses results upon faradic stimulation of certain nerve fibers afferent to the ganglion, and also that direct faradization of the ganglion causes inhibition (Carlson, '04, '05). This latter fact was the initial point of interest which led to the present report. We are familiar with the fact that a single stimulus, either electrical or mechanical, results in a ganglionic discharge and an extra-systole of the of the heart (Garrey, '30; Samojloff, '30) and the problem before us is to determine how repetition of stimuli, as in faradization, passes from stimulation over into inhibition—whether we are dealing with two separate and distinct processes or with two phases of a single process.

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PROCEDURE

Kymograph records of the beat of the excised Limulus heart were obtained by the customary methods. Platinum electrodes were hooked under the cardiac ganglion at selected points between the third and ninth segments, these being the segments where ganglionic impulse-forming nerve cells have been demonstrated.

A Campbell ('29) stimulator was found most convenient for delivering stimuli at different rates and with any desired intensity. Constancy of intensity is assured by the fact that the apparatus employs condensor discharges. All the results thus obtained also were demonstrable when induction shocks were employed.

EFFECTS OF RATE OF STIMULATION

When the ganglion was stimulated by electric shocks which were delivered at a frequency which was slow, but slightly faster than the autogenous rate of the heart beat, each stimulus elicited a ganglionic discharge and a full height contraction of the myocardium. Since the time interval between stimuli is less than the normal intersystolic interval there are no autogenous discharges, merely a series of contractions at the rate of stimulation; the behavior is entirely analogous to that of the vertebrate heart when its 'pace maker' is stimulated at rates faster than the normal rhythm. Every heart experimented with responded in this way to stimuli repeated at rates of thirty per minute, which is faster than the normal rate at room temperatures; when heated, however, with the assumption of high rates of impulse formation, some autogenous beats often were interjected into the picture with a resulting irregularity during stimulation. Most hearts follow stimuli repeated once per second.

When short periods of stimulation at this rate are resorted to, at least three types of after-effects may be noted (fig. 1, top line), for example, the autogenous rhythm may be resumed immediately, at the original rate and with full vigor of muscular response; in other cases one may note a definite

delay in the resumption of the autogenous rhythm, or more commonly the height of the muscular contraction is at first considerably below the pre-stimulation level, each of the succeeding contractions being stronger until the normal height is again attained. This is definite evidence that even these slow rates of ganglionic stimulation may leave a residuum of inhibition which lasts for some 10 or 15 seconds. If the

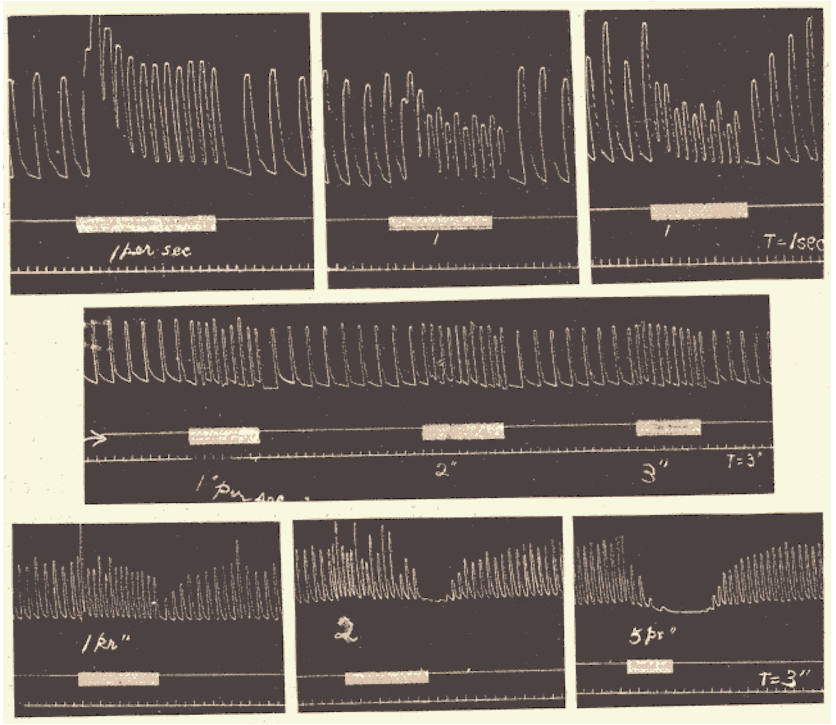

Fig. 1 Three sets of records illustrating the effects of low rates of ganglionic stimulation. The upper series shows pure excitation at the rate of stimulation (1 per second) at the left, weakening of contractions during stimulation in the middle tracing and distinct after-inhibitory effects in the right-hand record. The middle series show excitation of the ganglion, a response due to each stimulus in the left-hand example. Increasing the rate of stimulation to 2 per second and 3 per second in the middle and right-hand records did not increase the rate of response—the ganglion was refractory to some of the stimuli. In the lower tracing is illustrated the progressive increase of inhibitory effects as the stimulation rate is increased from 1 to 5 stimuli per second; inhibition was produced at unusually low rates of stimulation in these instances. The signals mark only the duration of stimulation, not the rate, which is designated by figures.

ganglionic stimulation at the slow rates of 1 or 2 stimuli per second be maintained for many minutes, the contraction of the muscle falls to a small fraction of its original height, usually there is a marked irregularity both of rate and height of the feeble responses and often the responses fail altogether. One might gain the impression that the ganglion becomes fatigued and that the fatigue involves the entire extent of the ganglionic cord, since there is a failure in the vigorous responses of the entire myocardium, but the error of this conclusion is demonstrated by the fact that the recovery of vigorous contractions is immediate upon cessation of stimulation. This prompt recovery has been found to take place even after the ganglion has been subjected to continuous stimulation for periods of 40 minutes or more. The weak contractions are attributable to the establishment of an inhibitory state which becomes more pronounced as stimulation is prolonged and the very weak responses may well be due to a complete suspension of activity of a large proportion of the ganglion cells. This inhibitory state is evidenced by the depression in the output of carbon dioxide (Garrey, '20) and reduction in the consumption of oxygen (Dann and Gardner, '30). Quite surprising recoveries have been noted after long periods of complete or nearly complete inhibition produced by the more rapid rates of stimulation of the ganglion, as will be described subsequently. Inhibitory suspension of activity evidently causes no obvious injury to the ganglion, an immunity which is probably associated with the depression in respiratory metabolism and is similar to that described for the inhibited vertebrate heart by Garrey and Boykin ('34).

When the rate of stimulation of the ganglion is increased to 2 or 3 stimuli per second, there is usually no commensurate increase in the rate at which the ganglion responds. Evidently many of the stimuli fail to stimulate and the increase in rate of stimulation merely increases the number of ineffective stimuli. Sometimes, however, there is acceleration of the contractile responses in the case of a highly excitable ganglion and at high temperatures. On the other hand, there fre-

quently is no change in the rate of response with the gradual increase in these slow rates of stimulation up to 3 or 4 stimuli per second, as is illustrated in figure 1 (middle tracing). This behavior suggests that impulse formation establishes a refractory state, complete or partial, during which no stimulus is effective. After the lapse of this state the next stimulus becomes effective and the ganglion again responds with impulse generation; thus there is a fixed maximum rate at which the entire ganglion can respond to localized ganglionic stimuli. By this criterion our experimental data suggest a refractory condition which may last one-third to one-half a second. This is in conformity with the duration of the ganglionic discharge as determined by measurement of action currents in the muscle, motor nerve and ganglion as made by Garrey ('32) and Rijlant ('32). A stimulus which impinges on the ganglion during the course of any given discharge can only stimulate a portion of the cells of the ganglion and thus simply prolong a given discharge or produce a new and weak contraction to alternate with a strong contraction. Examples of such responses are quite customary, and may be found among the tracings reproduced in this report. The phenomenon will be referred to in subsequent discussions.

Increasing the rate of ganglionic stimulation ultimately slows the frequency of contractions and one naturally inquires whether this is a consequence of a progressive prolongation of the refractory period by the succession of stimuli, and, if so, whether this stage of partial inhibition—for it is the initial phase of ganglionic inhibition—is not, after all, due to prolonged refractoriness, as Verworn ('13) maintained. Many experimental results favoring this viewpoint were obtained, for example, the change from 1 stimulus per second to 2 or 3 per second is often accompanied by abrupt transitions to slower rates of response which correspond to one-half, one-third or some other fraction of the stimuli. Such a result is usually pronounced at the rate of 5 stimuli per second. While at such slow rates the contractions may reach their full height, more frequently they are reduced in height, thus indicating a

decrease in the number of ganglion cells discharging impulses along their motor fibers; some of the ganglion cells are therefore inhibited or at least fail to function.

The cardiac responses to very slow rates of stimulation of the ganglion are occasionally followed by a surprising degree of inhibition; thus in the three tracings of the lower line of figure 1, the response to one stimulus per second is only to every second stimulus, while after the stimulation ceased the autogenous contractions were weak and recovered normal height only with the eighth contraction, i.e., after 20 seconds had elapsed. With 2 stimuli per second, the rate of response of the ganglion was accelerated, although only every third or fourth stimulus was effective and during the period of stimulation the contractions became progressively weaker. After stimulation had ceased the autogenous contractions were hardly perceptible and the recovery to their normal vigor was definitely retarded. In this heart as is seen in the right-hand tracing in the lower line (fig. 1) the extremely slow rate of 5 per second caused immediate inhibitory effects and complete after-inhibition with slow recovery over a period of more than half a minute after the stimulation was interrupted.

The progressive increase in the inhibitory effects with increase in the rate of stimulation is well illustrated in the series of tracings just considered, although usually more rapid stimuli were found necessary to induce the inhibitory effect. The change from stimulation to definite evidence of predominant inhibitory effects usually was found to take place at a rather critical rate of stimulation which did not vary much from 5 stimuli per second; above that rate inhibition was definite, both slowing and weakening of the contractions being in evidence. Complete inhibition was obtained in some hearts as an immediate effect of stimulating at rates as slow as 10 per second, other preparations required, under similar conditions, rates of 20 or even 50 per second. Three illustrations of the progressive onset of inhibition with increasing rates of ganglionic stimulation are reproduced in figure 2, which should be consulted for the details of the phenomenon of progressive onset of inhibition with increase in the rate of stimu-

lation. Figure 3 is presented to show that a sudden increase in rate of stimulation developed complete inhibition when a slower rate only partially inhibited; this is the invariable rule.

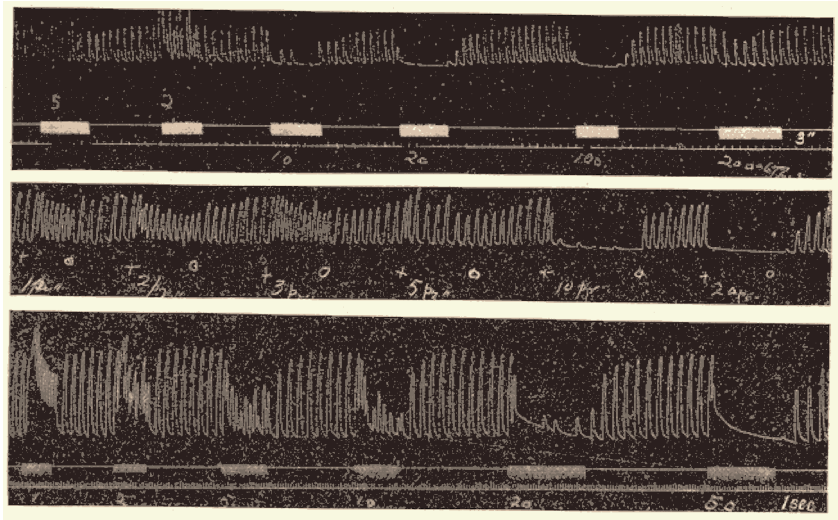

Fig. 2 Three examples of the genesis of inhibition in three different hearts. The figures represent the rate of stimuli per second, the signals the durations of application which in the middle series is noted by + at the beginning and ○ at the end of the stimulation. Time record gives 3-second intervals in the upper tracing, with the same kymographion rate in the middle tracing.

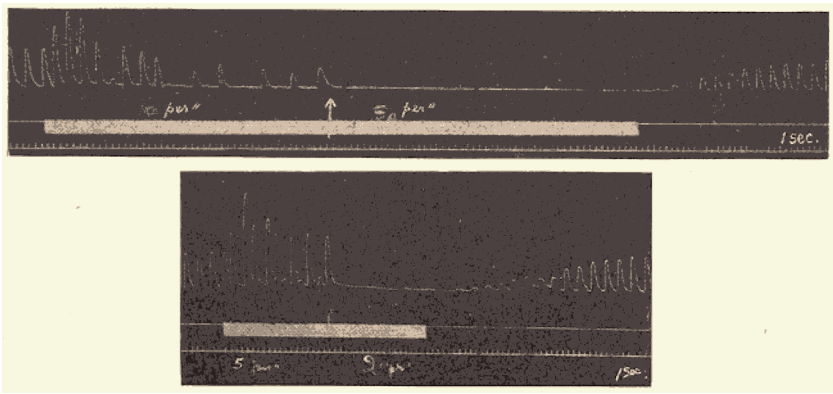

Fig. 3 Two examples of the effects of sudden increase in the rate of stimulation of the ganglion thus changing partial inhibition to complete inhibition. In the upper tracing the rate was changed from 10 per second to 50 per second; in the lower tracing the change was from 5 per second to 20 per second.

One further point requires passing mention; we have frequently found, when rates of 20 to 50 per second induced complete inhibition, that stimulation of the ganglion at much higher rate, 200 or 300 per second, failed to either stimulate or inhibit. The use of these high rates, however, introduced an intensity factor which we were unable to evaluate satisfactorily with the means at our disposal and hence will not be considered further. An illustration in the upper tracing in figure 2 shows only a mild inhibitory effect resulting from 200 stimuli per second, although slower rates had produced complete inhibition; other tests indicated that this particular heart exhibited no detectable alteration in rate, rhythm, or force when the ganglion was stimulated at a rate of 300 per second.

The study of a large number of tracings dealing with the genesis of inhibition brings out the fact that even when a slow rate of stimulation, say, 1 per second, is gradually increased to 2 or 3 or more stimuli per second, many stimuli are ineffective so that muscular contractions drop out of the picture leaving a definitely slowed rate of rhythmic response, furthermore, many of the contractions are markedly weakened. Weak contractions can result only by the elimination of some of the ganglion cells from participation in impulse formation; in other words, some cells are inhibited, even at very low rates of stimulation, and others drop out as the frequency of stimuli is increased. The phenomenon just considered recalls the effects of rate of stimulation of cardiac tissue, reported by Erlanger ('10), who showed that as the frequency of stimulation was increased there was a progressive decrease in the rate of contraction until the heart failed to respond. The increase in the degree of functional heart-block with increasing frequency of contraction until block becomes complete is a familiar picture; similar results of artificial block produced in motor nerves produced by pressure have been described by Meek ('11) and the nerves of the heart of Limulus have been found by Garrey ('12) to behave similarly. The Wedensky inhibition may be in the same cate-

gory and thus also related to the ganglionic inhibition under consideration, although it is not a sufficient explanation of it, as will be pointed out subsequently.

INTENSITY

While the inhibitory effect of ganglionic stimulation at any given intensity of the stimuli is a function of the rate at which the stimuli are delivered, the intensity factor also is significant. In general, it may be stated that the weaker the stimuli the more rapid will be the rate required to produce inhibition and similarly with strong stimuli, inhibition is produced by slower rates of stimulation. In figure 4 some illustrations are given in which intensity is expressed in percentage of the maximum voltage at which the condensor was charged when set for a definite rate of stimulation. The figure shows the effects of intensity changes when rates of 20, 30 and 50 per second were used. It will be noted that at the slowest rate, 20 per second, complete inhibition was produced only with the full voltage of the condensor discharge (marked 100 per cent), while at the fastest rate of 50 per second complete inhibition resulted from a discharge of only 60 per cent of the condenser capacity. In general, it may be stated that with any appropriate rate of stimulation the inhibitory effect increases with the increase in rate of stimulation and that with an appropriate rate of stimulation the inhibitory effect increases with the intensity. These are practically the words with which Forbes ('22) describes similar phenomena in spinal reflexes of mammals. It is also true that stronger stimuli produce inhibitory effects which persist longer than those due to weaker stimuli. This behavior differs from the reaction to rate changes. The stimulating effects of slow rates cease abruptly with the cessation of stimulation, the inhibitory effects persist, but there is no clear-cut evidence that the inhibitory effects of rapid rates of stimulation last longer than those due to slower rates. Instances of such a relationship were found, but it was not a universal finding and the factor of differences in intensity of stimuli could not be excluded.

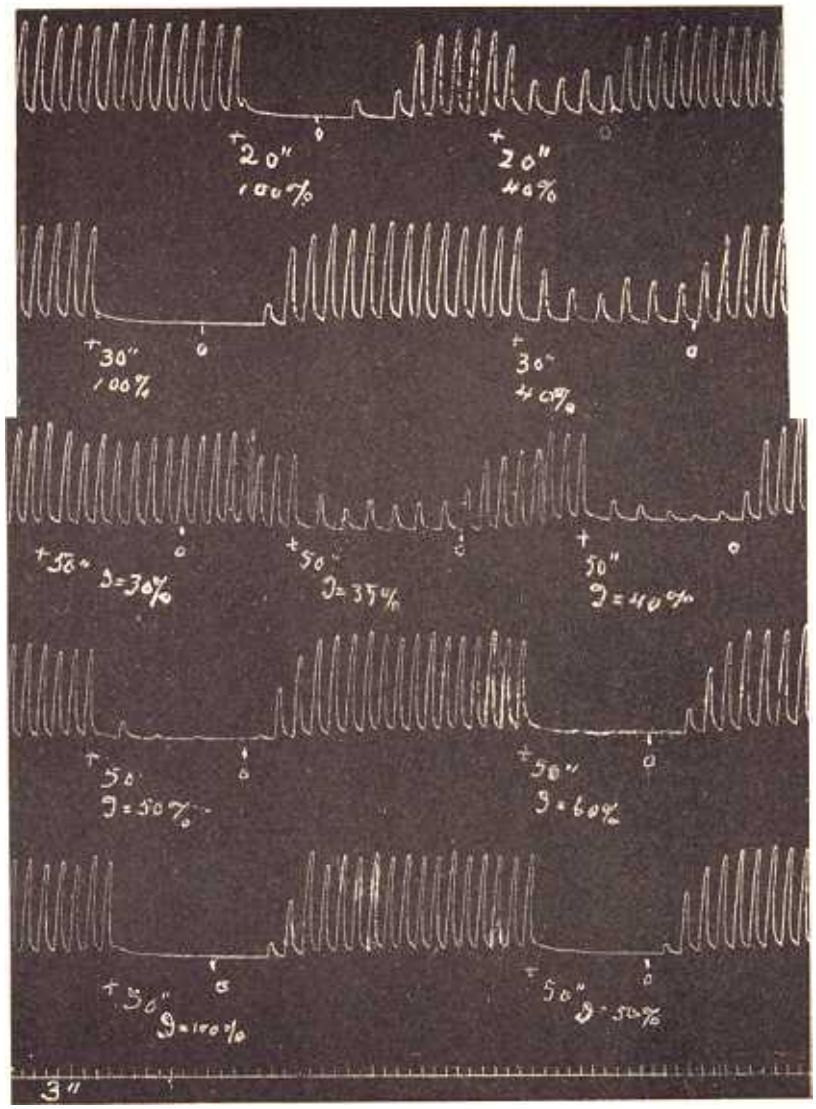

Fig. 4 Illustration of the fact that at fixed inhibitory rates of stimulation greater intensities of current produce greater inhibitory effects. The rate in the upper line was 20 per second, in the second line from the top it was 30 per second and in the three lower lines it was 50 per second. Intensities (I) are indicated as percentages of the maximum voltage of the condensor charge. The beginning and end of stimulation are marked by + and ○, respectively. Signal at the bottom marks 3-second intervals for all tracings.

At this point attention should be directed to the fact that, independently of the rate or type of stimuli which cause complete inhibition, this state involves the entire length of the ganglionic cord and is not confined to the restricted locus of stimulation. This was tested by simple resort to direct stimulation of the ganglion at various points along its course by single induction shocks which normally cause extra-systoles (Garrey, '30; Samojloff, '30). It was found that in the state of complete inhibition extra-systoles cannot be produced in this way and if partial inhibition obtains the extrasystolic contractions are weak. Carlson ('05) has published tracings showing similar results when the ganglion was inhibited by stimulating afferent nerves; furthermore, the inhibition is confined to the ganglionic cord, the motor nerves and myocardium remain normally excitable and will respond to artificial stimulation during inhibition of the ganglion. When intraganglionic motor fibers are incidentally stimulated by the inhibiting stimuli, tetanus of the muscle occurs pari passu with inhibition (fig. 5), as has been described previously by the authors (Garrey and Knowlton, '34).

TEMPERATURE EFFECTS

We have called attention to individual differences between individual Limulus heart preparations which are expressed in differences in the minimal rate of stimulation which will cause complete inhibition of the ganglion. Similar differences can be established by subjecting a given heart preparation (ganglion) to differences in temperature. Elevated temperatures increase the rhythmogenic activity of the ganglion (Garrey, '20 a) and cause a general quickening of all phases of impulse formation in the ganglion; so, in conformity with expectations it was found that the ganglion gave individual responses to more rapid rates of stimulation at higher temperatures and that more rapid rates of stimulation were required to produce inhibition. This was brought out forcibly in experiments in which hearts were inhibited at low temperatures by relatively slow rates of ganglionic stimulation which

at room temperature produced only moderate, if any definite evidence of inhibition. More striking were experiments in which the minimal rate of stimulation necessary to produce inhibition was used and with this stimulation in progress, the ganglion was suddenly heated to around 32°C. with the result

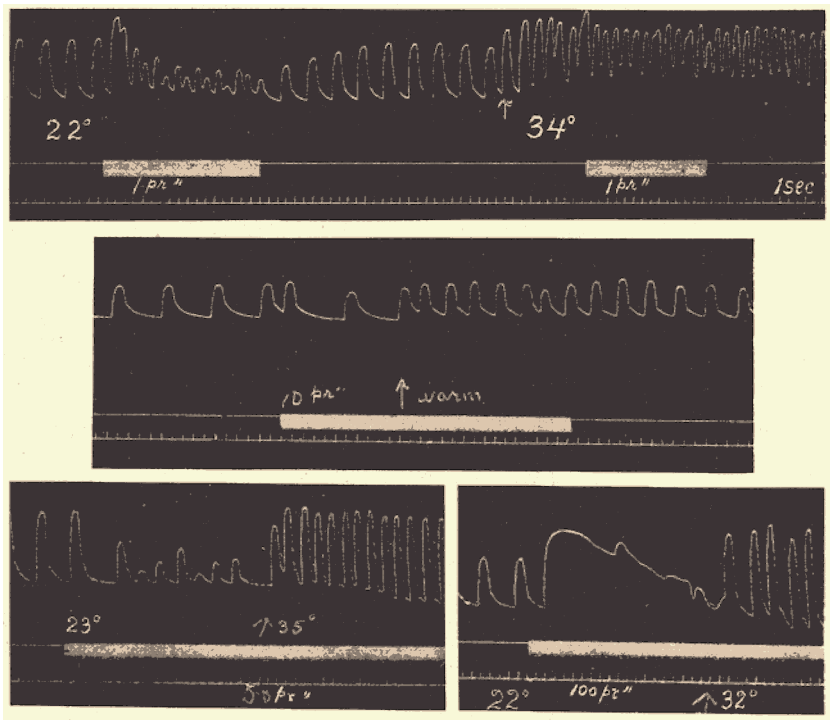

Fig. 5 Temperature effects, indicating the prompt release from inhibition when the ganglion is warmed. The rate of stimulation in the upper line was 1 per second, 10 per second in the middle tracing, while the rates in the two lower tracings were 50 and 100 per second. Appropriate intensities were selected in each instance. The tetanic effect in the right-hand tracing of the lowest series is due to faradic stimulation of intraganglionic motor nerves.

shown in figure 5 viz., an instantaneous escape from inhibition and a restitution of a rapid automatic rhythm. At the higher temperatures, above 35°C., inhibition, even with high rates of stimulation, was usually only partial and difficult to sustain.

DISCUSSION

The ease with which the heart of Limulus can be isolated and its ganglion directly stimulated, the fact that the ganglion generates rhythmic impulses which are registered in the contractions of the myocardium, the hardiness of the preparation and the simple procedures by which experimental conditions may be altered make this preparation most favorable for the study of nerve cell physiology. The records of our study have shown many similarities and some deviations from the results reported in studies dealing with mammalian reflexes. The most striking development in the experiments herewith reported is the gradual and progressive translation of excitation at slow rates of stimulation into partial, then complete inhibition of the autogenous rhythm as the rates of stimulation are increased. This is highly suggestive of the possibility that the exhibition whether of excitation or inhibition is merely an expression of different phases of a single process. Wedensky inhibition is the outstanding example of this type of physiological responsiveness; Lucas invoked it as an explanation of central inhibition, but the view is not generally accepted. Wedensky effects are ascribed to the extinction of excitatory processes at a region of decrement, to the establishment of a physiological state which blocks the excitatory effect, possibly at a synapse beyond which cells are in a passive state of inaction. We might be attracted to the application of the Wedensky concept were it not for the fact that the inhibition exhibited in the Limulus heart ganglion is most certainly something more than simple synaptic block, more than immunity to excitation, more than a passive state of rest. Inhibition as we have found it is definitely an active process in which the automatic rhythmogenic functions are suppressed, in which a reduction in the respiratory metabolism takes place and in which the cells fail to respond to stimulation. There is in these respects a complete parallel to the peripheral inhibition in heart tissue innervated by the vagus nerves.

Sherrington and Sowton ('11), in their stimulation of reflex afferents, found that slow alternating currents caused central excitation, while rapid stimulation (faradization) caused inhibition, thus electrical reversal can take place in mammalian reflexes, but Forbes ('22, '30) has demonstrated inhibitory effects resulting from a single stimulus causing only a single action current, although he suggests mechanisms by which repetitive stimuli may be the provoking agency in such instances.

Currently accepted views tend to the belief that excitation and inhibition in the central nervous system are the outcome of two independent processes which establish two states which are quite unrelated. Without dogmatically excluding this concept of a dual mechanism in the explanation of our experimental finding, there are deterrents to its acceptance and difficulties arise whether one assumes two different types of fibers which cause opposite types of effect on membrane permeability or which secrete an excitatory (E) and an inhibitory (I) hormone, respectively (Sherrington, '25). In our experiments the ganglion was directly stimulated, although intraganglionic premotor fibers most certainly mediate the cellular inhibition. We are not confronted, however, with the complicating exhibitions about which the dual mechanism has been built, for example, we have not observed algebraic summation, alternation of excitation and inhibition, or conflict between the two processes (Forbes, Davis and Lambert, '30) and there has never been a post-inhibitory rebound. It is our experience that excitation of the Limulus ganglion progressively passes over into inhibition with increasing frequency of stimulation so that we incline to the view that the two states are but phases of a single process and that when inhibition is complete, excitation is an impossibility.

The persistence of the inhibitory state and the gradual recovery from it may be taken as evidence of the development and gradual removal of an inhibitory humoral substance. We recognize this possibility and the desirablity of a further study from this angle, but the evidence thus far obtained is

not convincingly in favor of this explanation and certain observations are difficult or impossible to explain on this basis, for example, complete inhibition may be produced by an appropriate rate of stimulation at room temperature, if now the inhibiting stimulation be continued and the ganglion suddenly subjected to a higher temperature there is an immediate escape from inhibition (fig. 5); this could hardly take place in the presence of an inhibiting humor, it is a response which suggests rather that the inhibition is due to some reversible physical state induced by the antecedent excitatory process. The gradual recovery of the height of the contraction of the myocardium after inhibition is suggestive of the recovery of contractility following inhibition of the vertebrate heart, but one is not justified in drawing onclusions from any such superficial similarities. In the vertebrate heart the muscle itself is inhibited, while in the Limulus heart it is not; the gradual recovery of the myocardial contractions can be due only to a progressive increase in the number of ganglion cells which recover their functional integrity after inhibition and thereby increase the motor innervation of the myocardium. The differences in cardiac motivation between the vertebrates and the Limulus heart make any conclusions based on analogy quite valueless in any appraisal of the underlying mechanism of inhibition.

In view of the fact that sharply localized stimulation will induce inhibition throughout the entire ganglion even at points some centimeters distant, a concluding reference may be made to the question of spread of the inhibitory state. Although Pavlov ('27) has maintained that the inhibitory state can be propagated within the cerebrum of mammals, it will be recalled that Verworn ('00) contended that inhibition is a localized state and that the excitatory process alone could be propagated. So far as concerns the conclusions from our work, this problem seems to present no difficulties, since the inhibitory state may very well be the after-effect of repetitive excitation and therefore would spread pari passu with the spread of excitation.

SUMMARY

Each of a goup of slowly repeated electrical stimuli applied to the cardiac ganglion and sharply localized, will cause excitation and impulse formation involving the entire ganglion. When the rate of repetitive stimuli is increased many of the stimuli fail to excite and at a certain rate, varying with the individual preparation, partial inhibition and at still faster rates complete inhibition is induced. The entire ganglion is inhibited and unresponsive to stimuli applied anywhere along its course. With an appropriate strength of stimuli increasing rates therefore progressively increase the inhibition up to limiting rates which fail to excite (Wedensky effect); similarly with appropriate inhibitory rates of stimulation increasing strength increases the inhibitory effect. An existing inhibitory state may be promptly dissolved by a rise of temperature and inhibition at high temperatures is difficult to induce. The inhibitory process is not the result of a simple Wedensky effect or synaptic block; it is an active process consequent upon repetitive excitation. Other aspects of the mechanism of inhibition are briefly discussed and tentative conclusions based on the experimental data are presented.

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