THE CONTROL OF EXCITATION IN THE NERVOUS SYSTEM

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Ten years ago Professor Erlanger addressed the Harvey Society on the subject of the action potential of nerve. In that lecture he described the technique of recording the action potential with the cathode ray oscillograph and presented the developments which had taken place through its use in the laboratories of Washington University. One of the principal points which he made in the lecture was that a peripheral nerve is made up of fibers which conduct impulses at various velocities. If a nerve be stimulated with an induction shock, all the impulses start out together; but they soon become spatially separated, as the faster outrun the slower impulses. Thus, if a lead be taken at some distance from the stimulated point, the near electrode records first the fastest impulses and then in turn the slower impulses as they arrive. As all velocities are not equally represented, the composite action potential appears as a series of elevations, the exact configuration of which is dependent upon the fiber content of the particular nerve that is being tested.

In 1927 the potentials of all the fibers had not yet been recognized; consequently an appropriate point at which to start the presentation of this evening is the picture as it was completed two years later through the finding by Professor Erlanger and myself[10] in somatic nerves, and by Bishop and Heinbecker[4] in visceral nerves, of a system of fibers in which the velocity of conduction was much slower than the velocities previously known. These fibers were called C fibers. In mammalian nerves the largest fibers, which are the fibers of fastest conduction, carry impulses at 100 meters per second, and the slowest at less than one meter per second. An idea of the distribution of the velocities may be gained from the electrical map of the saphe-

nous nerve (Fig. 1). The fast group, made up of velocities between ninety and fifteen meters per second, appears with two major and several secondary elevations. Although the second elevation represents about as many fibers as the first, it is much smaller, since it is produced by smaller fibers and individual fibers contribute potential to the aggregate in proportion to their cross-sectional area. The third or C elevation, made up of velocities below 1.7 meters per second, represents many more fibers than the other two elevations combined,[32] but the component potentials are so small that in order to reveal the presence of the fibers it is necessary to use an amplification higher than is needed for the elevations produced by the large fibers. It must also be recorded on a much slower time scale.

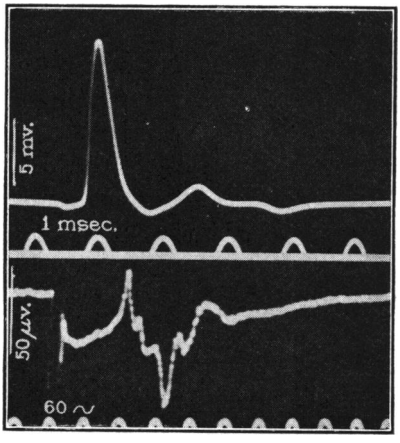

Figure 1

Nerves going to muscles differ from the saphenous nerve, which is purely sensory, in that the first elevation is relatively somewhat higher, owing to a large content of fibers of the highest velocities,[9] some of which are higher than the maximum velocities found in the saphenous nerve. These fibers are in part motor and in part sensory, the sensory fibers going to proprioceptor endings in the muscles.

What may be the significance of this wide range of velocities is a question which we have often asked ourselves.

The velocities of motor fibers are distributed about a single mode, the velocities of sensory fibers about a number of modes. This fact suggested the possibility of a relationship between the elevations in the action potential and the modalities of sensation, but the experimental evidence has turned out for the most part to be incompatible with this notion. The fastest fibers carry touch impulses but not pain, and the C fibers carry pain without touch or pressure.[5] However, pain is also found in the second elevation,[22] and overlaps warmth and probably pressure.[13] In fact it is not clear that some fibers may not mediate both pain and pressure (Goldscheider,[18] Adrian[1]). There surely must be, therefore, some reason other than the modalities of sensation for the numerous velocities. A suggestion as to what may be their function will be made later, but before discussing the matter further it will be necessary to consider some other qualities of the action potential and their relation to the physiology of the central nervous system.

The aspects of the functioning of the nervous system which we examine in the laboratory are so far removed from the manifestations of activity which we experience in everyday life that it may be worth while to say a word at the outset concerning the relation of laboratory studies to the larger problem. Admittedly the nervous system can be understood only as it is operating as a whole, but it is equally true that an insight into its working can be gained only by a detailed analysis of its parts. If the isolation of a part results in the sacrifice of some of its qualities, the loss is compensated for by the acquisition of a degree of simplicity making the part more amenable to investigation. The organization of the nervous system is such that an understanding of the mode of activity of any part of the ganglionic apparatus would mean a long step forward, for all parts of the nervous system are fundamentally alike. We can, therefore, proceed, confident in the belief that when the parts are understood, they can be added together into larger units; and that, as the addition takes place, the lost

qualities will again emerge and be recognized. Bit by bit it should be possible in the end to build back to the elaborate patterns of activity which are characteristic of the intact organism.

Like all other parts of the body, the nervous system is made up of cells. This statement contains the essence of the neurone doctrine which for half a century has dominated all thinking about the subject. The most obviously distinctive feature of neurones, as compared with cells in general, is the profuseness of their branching. Neurones are fashioned in a way so as to make possible numerous discrete contacts of one with the other. The anatomy of the nervous system puts before us myriads of possible pathways over which messages may pass from any part of the body to any other. The physiology of the nervous system reminds us that the utilization of these pathways is restricted. Excitation initiated in any part of the peripheral field does not spread in all directions in the centers, but proceeds along lines which are prepared for it, although not fixed in nature. A given afferent stream of impulses over a peripheral nerve may follow one pathway in the centers at one time and another pathway at another time. The direction of the switching is conditioned by the situation obtaining at the moment, and is always consonant with a coordinated reaction of the whole organism. Every junction point of the transmission lines at the synapses between cells is guarded. Anatomical peculiarities of the form and arrangement of endings differentiate the ease of transmission spatially, and the nature of the previous activity differentiates it temporally. Ultimately excitation in a pool of neurones is dependent upon everything which is taking place in the nervous system anywhere, because of the direct or indirect representation of this activity in the population of endings in the pool. It is for this reason that a part of the system in isolation has lost some of the plasticity of behavior which it possesses in its normal relations.

The laws describing the mode of transmission of excitation across a synapse thus must be the basic laws of the

nervous system. What happens at the synapse must be determined by the qualities of the tissues which meet at that point, by the qualities of the terminals of the axon on the one hand, and by the qualities of the cell bodies and dendrites on the other. Of these two, only our knowledge of axons is at all extensive,—this because of studies made on peripheral nerve.

Two decades ago Keith Lucas[29] proposed the hypothesis that the phenomena taking place in the central nervous system could be explained without the assumption of any properties which could not be experimentally identified in peripheral nerve. On account of the untimely death of its author, this bold hypothesis was left to his successors without adequate support. Lucas' adherents defended it for a time, but in recent years the opinion of many observers has turned away from it.

The reason for the failure of the hypothesis is not far to seek. It does not lie in Lucas' employment of the now discredited notion of conduction with a decrement, but rather in the fact that the knowledge of peripheral nerve was so meagre that it supplied but little material with which to work. The known facts had to be used in the interpretation of the hypothesis in so fanciful a manner that the result could not be accepted. When one pauses to think that the reactions of the central nervous system are very labile and continue for considerable periods of time, it is easy to realize how difficult it would be to explain them in terms of events obeying the law of all-or-nothing and lasting less than one-thousandth of a second.

If the reactions in the central nervous system are to be explained on the basis of occurrences in peripheral nerves —if nervous tissue as it appears in peripheral nerve is to be made representative of nervous tissue in general—it is evident that the starting point of all discussions must be a thorough-going understanding of the physiology of nerve fibers.

As many as have been the studies made of peripheral nerve, much still remains to be done. Previously unsus-

pected qualities are continually being brought to light, but already enough information about nerve has accumulated to permit the beginning of a composite picture of nervous tissue.

Ten years ago the term "action potential" referred to only one process, that which is represented by what is now called the spike potential. At the present time we must recognize that activity is not characterized by the spike alone, but that it means the setting in train of a series of processes each of which reveals itself by a potential change. The latter are called after-potentials, and they, as well as the spikes, vary in the composite picture.

Velocity of conduction has already been mentioned as a variable. Where fibers are otherwise homogeneous, as in the first elevation of the action potential, the difference is based simply on the size of the fibers, the velocity varying linearly with the diameter of the fiber.[14] But between the first and the last elevation some other variable enters, probably the duration of the spike, as spikes last 0.4 msec. in the fastest fibers and about 2.5 msec. or even longer in the slowest.

Spikes may be characterized as the message carriers of the nervous system, both in the tracts of the brain and in peripheral nerves. As shown so clearly by Adrian and Bronk, the messages are carried by a succession of signals or spikes in the individual fibers. The signals are all alike, but differently spaced, and the interpretation of the message at the receiving end depends upon the pattern of fibers occupied and the frequency of the signals in the individual fibers. We shall see that the frequency of arrival of impulses has an important bearing on whether or not they can pass a synapse.

Following the sequence of spikes which carries the message—and even during its continuation under appropriate conditions—, the after-potentials may be seen. They occur in their simplest form in a single response, appearing to rise out of the tail of the spike rather than being continuous with it. The potential generally is made up of

two parts, an initial, negative portion and a later, positive portion. In the fibers of fast conduction, under normal conditions, the negative portion is first seen at its maximal value. In its subsequent course (Fig. 2) it subsides along a decremental curve for a period of about fifteen msec., and then gives way to the positive portion lasting about eighty msec.[17] A representative value for the degree of positivity at its maximum would be twenty-five μv, which would be equivalent to about 0.2 per cent of the potential of the spike crest. In C fibers (Fig. 3) the positive after-potential is much larger in proportion to the size of the spike[3] and lasts up to one-half second or more. It is preceded by a negative after-potential, but no statement can be made as yet concerning the dimensions of the latter under physiological conditions. The negative after-potential in appropriate records is visibly made up of a period of development followed by a period of decline, a property which can be demonstrated in the fast fibers only under special conditions.

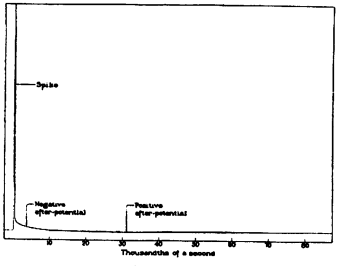

Figure 2

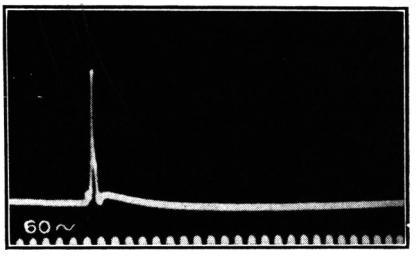

Figure 3

After-potentials stand in contrast to the spike with respect to their lability. The form of the spike is rigidly maintained through a wide variety of conditions, while the after-potentials change their form with every event that happens. Small changes in the concentration of hydrogen ions, or of the salt balance, are readily detectable and the potentials are differentially susceptible to asphyxia.[2, 15, 20, 27, 34] Tetani modify them greatly, an observation of no small importance in view of the fact that nerve messages are carried by a sequence of spikes. The principal effect

of a mild tetanus is to curtail the negative after-potential and to increase the depth of the positive potential (Fig. 4). After a more severe tetanus the positive after-potential is further increased in depth, without showing an increase in duration, until a maximum is reached; and it is succeeded by a second positive component which increases in duration in proportion to the severity of the tetanus (Fig. 5). Durations of five minutes have been observed in isolated nerves (fast fibers) and of one minute in nerves receiving their natural perfusion of blood in the body.[17] Thus it is no longer permissible to say that events of long duration are confined to the centers.

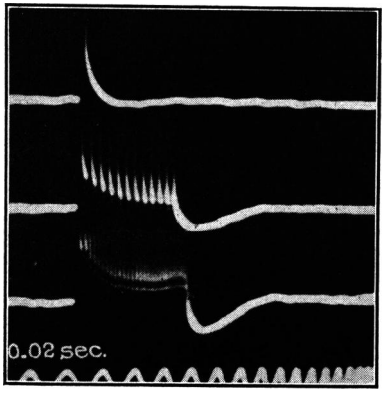

Figure 4

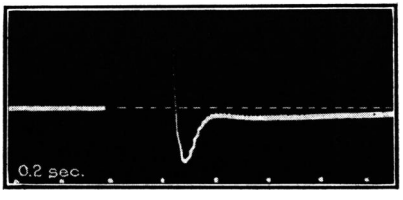

Figure 5

Undoubtedly one of the most significant facts that has come out of recent studies on nerve, from the standpoint of the application of peripheral nerve physiology to the centers, is the form of the recovery curve after excitation. It has been found that the refractory period of classical nerve physiology is succeeded by a period of deviation from normal excitability lasting as long as the after-potentials. The recovery of the fibers of fastest conduction, as measured in the body after a single response (Fig. 6), is characterized first by the refractory period (in which the fiber is at first wholly inexcitable, and later excitable only with stimuli of greater than normal intensity), then by a

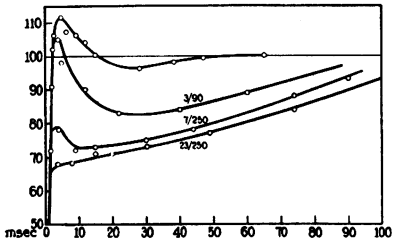

Figure 6

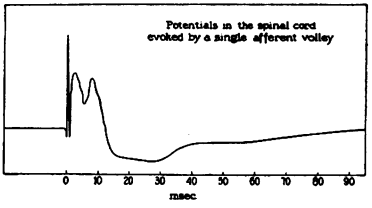

Figure 7

period of supernormal excitability lasting fifteen msec., and a period of subnormal excitability lasting eighty msec.[17] These periods in turn are related to the spike, the negative after-potential, and the positive after-potential. In other conditions the form of the excitability curve differs widely from that which has just been described, but in every instance the changes parallel the course of the after-potentials. For example, if the potential oscillates between negative and positive, as it does in tetany, the excitability oscillates with it; or if the positive potential is increased and prolonged, as after a tetanus, the subnormality likewise is increased and prolonged. If the spikes may be called the message carriers of the nervous system, the after-potentials in contrast may be called the indicators of the readiness with which messages will be accepted.

After this brief summary of the qualities of axons we are in a position to consider the extent to which these qualities represent the qualities of the parts of the neurone which enter into the formation of the synapse. Synapses are formed by contact of axon branches with the cell body or its dendrites. The axon branches may be expected to partake of the properties of the parent stem; but a question may be raised with respect to the cell bodies and dendrites, inasmuch as in their cytoplasm are found structures which are not present in axons. However, if the descriptions of these structures be reviewed, it is found that there are present only those structures which are generally found in cells; in other words, the structures which must be present if the normal vegetative functions of the neurone are to

go forward. Thus the histological picture does not provide a compelling reason for concluding that cells and axons are different in nature.

Grey matter and white matter are differentiated by their metabolic needs. Greater vascularity, greater oxygen consumption, and greater susceptibility to asphyxia are characteristic of the centers as opposed to the fibers. But here again the difference is not traceable to cells. Gomez and Pike[19] found that the dorsal root ganglia are not sensitive to anemia; Holmes [24] found that the metabolism is not high, and Dunning and Wolff[6] found that the vascularity is not great compared with peripheral nerve. Dorsal root ganglia are without synapses. In line with the suggestions of these authors, the high metabolism and high vascularity of the grey matter of the nervous system must be connected with the structure of the synaptic system. The strands of protoplasm which enter into the synapses are numerous and fine. According to current notions about the intimate structure of irritable tissues, conduction takes place along a delicately poised surface film which is maintained in repair only at the cost of a continuous expenditure of energy derived from oxidation. Removal of oxygen soon brings about loss of conduction even in peripheral nerve. It is to be expected, therefore,—in view of the fact that the area of the surface of a given volume of cytoplasm increases inversely to the diameter of the strands of which it is made up—that the metabolism in the fine strands of the neuropil would be higher than in the cell bodies or axons. In order to keep up the surface, a small strand must oxidize faster than a large one. Thereby it is made more dependent upon available oxygen and thus is caused to be the first to disintegrate when oxygen is removed. Support for this argument may be derived from the fact that the small nerve fibers, which are responsible for the second elevation of the action potential, are blocked by asphyxia before those in the first elevation.

In the end the question of whether cells and dendrites are different from axons must be settled by direct observa-

tion. One method of examining them is to measure properties of the former and to compare the result with measurements of the same properties in the latter. There are available two sets of measurements which are particularly useful for this purpose; both have been made by Lorente de Nó[28] on the oculomotor nucleus.

The first measurement is of the period of latent addition. When a subthreshold impulse current of short duration is applied to a nerve fiber, for a brief period thereafter an effect is produced which permits a second impulse current, by itself ineffective, to bring excitation to threshold. The time during which this summation of effects takes place is known as the period of latent addition. In motor fibers it lasts about 0.2 msec. To test this phenomenon at the synapse requires the bombardment of the nucleus with two volleys of impulses in two portions of the tract fibers. When the two volleys arrive simultaneously, summation is at its best. If they are separated by more than 0.2 msec., summation falls off rapidly, and it disappears almost entirely at separations of 0.4 msec. Considering the difference in the testing mechanism of axon and neurone, the correspondence in the periods of latent addition of the two is very close indeed, much closer in fact than the periods of latent addition in different kinds of axons.

The second measurement is of the absolutely refractory period, that is, of the interval during which a second response cannot be evoked by a stimulus of any kind, no matter how intense. In motor fibers the period lasts from 0.4 to 0.5 msec. Measurements previously made of the absolutely refractory period of neurones have been unsatisfactory, because a supermaximal stimulus is required for the testing, and excitation of neurones by way of their synapses is limited by the possible density of active terminals. In the oculomotor-nucleus preparation, however, the necessary density of endings was found and the refractory period turned out to be 0.6 msec.—a value so close to that holding for axons as to leave no doubt that the two are identical.

Another aid to the comparison of neurones and axons is found in the potentials of internuncial neurones and

their behavior under various experimental conditions. Surprising as it may appear at first sight, electrical studies of the grey matter of the spinal cord are capable of yielding valuable information about its activity, despite the unfavorable situation presented by the intertwining in all directions of the numerous fine strands of the neuropil. The same characteristic, basic potential picture is obtained with great regularity;[16, 25] and the variations found are only those which are to be anticipated from the extent of the connections with other parts of the brain stem permitted by the conditions of the experiment, and from the state of the preparation. The differences may be accounted for largely on the basis of the extent of spread which is possible into the delay paths of Forbes[11] or the reverberatory arcs considered by Kubie[26] and by Ranson and Hinsey.[33]

When a single afferent volley enters the spinal cord (Fig. 7), if gross leads from the surface of the cord are employed the first visible event is the spike potential in the continuation of the fibers in the dorsal columns. Following this potential and separated from it by the time consumed at the synapses, the potential in the internuncial neurones appears. The potential in the motor neurones is also detectable, but it makes a very small contribution to the potential recorded with the leads which are being described.

In its basic form the internuncial potential consists of two parts, an initial negative portion lasting about ten to twenty msec., and a later positive portion lasting 100 msec.; but in its variations the potential differs widely from this form, there being a succession of other events lasting a second or longer. When the picture was first seen[16] it was difficult to interpret, as the necessary facts about mammalian nervous tissue were not known, and it became evident that the interpretation could not go forward until the missing information was supplied. Accordingly, the cord studies were suspended and a flank attack was substituted for a frontal advance. After the compo-

site picture of the time course of the potentials in mammalian fibers began to take form it became increasingly clear that the internuncial potentials follow a similar course.

The best interpretation that has been found is that the initial negative portion is made up of spikes temporally dispersed, and the ensuing positive portion of positive after-potential. The disproportion between the magnitudes of the two parts as compared with those in nerve fibers of rapid conduction can be accounted for by the much greater reducing effect of temporal dispersion upon the very short spikes than on the long after-potentials. It is also possible that the positive potential is large in the individual internuncial neurones, as it is in fibers of slow conduction.

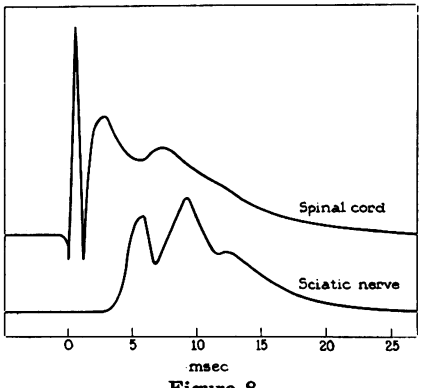

Figure 8

Additional evidence that the initial negative period is made up of spikes is found in its relation to the discharge of impulses by the motor neurones. The period of the discharge and the duration of the negative potential parallel each other (Fig. 8). As the local excitatory effect in the motor neurones does not last longer than 0.5 msec.,[28] the only way in which the succession of motor impulses could be kept up would be through excitation of the neurones in succession. This would mean that the motor neurone pool is being bombarded by spikes from the internuncial neurones throughout the time during which the potential of the latter is negative.

In the summary of the properties of axons it was mentioned that the excitability of the axon correlates with its potential. Correlation of potential and excitability must, therefore, be demonstrated in internuncial neurones if the hypothesis of similarity of the axon and the synaptic portions of the neurone is to hold. When the neurones are subjected to the test they pass it perfectly. They do not reach a state of responsiveness to a second afferent volley, equivalent to that obtaining in the equilibrated steady state, until all trace of positive potential residual from the first response has disappeared. The refractory period is followed by a subnormal interval (Figs. 9, 10) without intervention of measurable supernormality, as would be expected from the absence of demonstrable negative after-potential, and in keeping with the recovery curves of peripheral nerve conditioned by a short train of spikes (lowest curve, figure 6) instead of by a single one. (Occasionally supernormality is absent in peripheral nerve after a single conditioning action.)

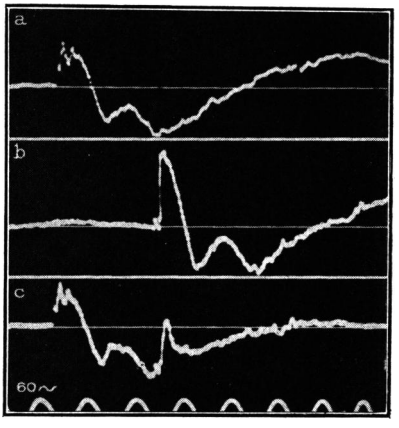

Figure 9

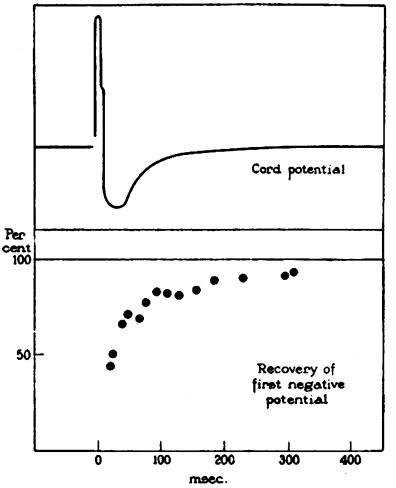

Figure 10

The correlation which occurs between the excitability of internuncial neurones and their potential throws new light on an old problem. We have seen that discharge of

the motor neurones is brought about by their bombardment with internuncial volleys during the period in which the internuncial potental is negative. From this observation it should follow that during the subnormal excitability of the internuncial neurones obtaining in the course of the positive potential, the failure of a calibrated afferent volley to evoke the full quota of negative potential (excited internuncial neurones) should result also in failure to bring about a normal reflex response. This is exactly what happens.

The relationships are brought out most vividly in experiments on the flexor reflex, in which a conditioning volley too weak to produce a motor response is followed by a testing volley sufficiently strong in isolation to produce a good contraction of the muscles.[8,25] If the second volley falls during the period of negative internuncial potential of the first volley, it may be reinforced by the latter with a resultant facilitation of the reflex. On the other hand, if the separation is such that the second volley can no longer be facilitated, the size of the reflex will depend almost entirely on the amount of internuncial potential evoked by the second volley. Presumably because subnormality of the neurones excited by the first volley would prevent contribution of part of the excitation that would be necessary to bring into activity the larger pool of neurones which the larger testing volley would normally excite, the internuncial activity produced by the second volley may be very small and the reflex greatly reduced. In the language of the physiology of the central nervous system, the reflex would be inhibited.

Inhibition is a term of convenience used without exact definition in connection with a group of phenomena having certain qualities in common. The essential condition is the stoppage or prevention of action through the temporary operation of a process which does not harm the tissue. It is usually also implied that the process results from nervous activity, or imitates the results of nervous activity.

In the absence of an exact definition, current usage is the only guide to the employment of the term. Stoppage of the heart through the vagus is one of the most commonly cited instances of inhibition. But it is equally correct to say that the flexor reflex is inhibited by previous activity. Clearly, the term "inhibition" must apply to very different mechanisms. Inhibition of the heart is attributable to the intervention of a humoral substance, acetylcholine. The cardiac tissue is altered. Inhibition of the flexor reflex is caused by the high threshold of the internuncial neurones. The so-called "inhibited" motor neurone is unaltered; it simply has failed to be excited. It is improper, therefore, to speak in terms implying that there is a general explanation of inhibition. One can only describe mechanisms which would be included in that category.

The large number and the diversity of the theories about the nature of inhibition in the nervous system may be taken as a measure of the obscurity which has surrounded the subject. Some of the theories are hardly more than restatements in other terms of the fact that the neurones are inhibited. Others are fabricated in analogy with conditions making for unresponsiveness in other situations. A humoral agent is often postulated, but no such agent has been found; nor is there any evidence for two kinds of fibers, excitatory and inhibitory, nor for two types of endings of one type of fiber. The Wedensky mechanism and anodal polarization are also not infrequently mentioned. In every instance the suggestions can neither be accepted nor rejected.

The subnormal period of responsiveness but recently discovered in nerve by H. T. Graham,[21] thus stands in contrast with the other possible explanations of inhibition which have been suggested, in that it has been found to be experimentally applicable to the cases of inhibition in which it has been tried. Descriptions of the phenomena connected with inhibition elsewhere also indicate that there are many other situations in which it will fit. We have seen how the flexor reflex is inhibited when the internuncial neurones fail to respond as the result of an induced high

threshold. We shall now see that failure to respond can also occur because of a raised threshold of the motor neurone itself. Following a tendon jerk, such as the knee-jerk, the background excitation of the muscle stops for a time equivalent to the subnormal period of a motor fiber. This interval is known as the silent period.[23] The same phenomenon can be produced by exciting the motor neurone antidromically through its axon.[7] The latter experiment shows that antidromic excitation passes back over the neurone as far as the synapses; that the synaptic region of the neurone has the same period of subnormality as the fiber; and that while the raised threshold is in progress, the neurone cannot be excited by the impinging volleys from the internuncial neurones. It shows furthermore that the subnormality of the motor neurone, after its occupation by the reflex, is all that is necessary to explain the silent period. Very probably, however, the reflex is also followed by a decreased bombardment of the motor neurones during this period, because of the subnormality which would be produced at the same time in the internuncial neurones, owing to the spread of excitation over them from the stretch afferent fibers.

The general properties of inhibition are well known from the classic experiments of the Oxford school, carried out under the leadership of Sir Charles Sherrington. Inhibition appears at various intensities; it accumulates by summation of the effects of a succession of afferent volleys; it lasts 0.1 sec. or longer, and its subsidence follows a typical curve of decay. In these respects its behavior follows exactly that of the subnormal period of peripheral nerve, for in the latter the intensity and duration also depend upon the number of impulses which produces it, beginning with about 0.1 sec. for a single response. Accumulation of subnormality in nerve is attended by augmentation and prolongation of the positive after-potential. In this connection some fragmentary observations on the internuncial neurones of the cord are of interest; in these a tetanus was succeeded by a prolonged positive potential and diminished responsiveness.

Inhibition is usually described as being pitted against excitation, the description being based on the fact that an inhibited activity may be reinstated by intensifying the exciting afferent volleys. This again is what would be expected from the properties of the subnormal period. Subnormality is a matter of thresholds only; if excitation is brought to the limen, a full-sized response is obtained. Thus a neurone with raised threshold would be induced to respond if more active endings were brought to play upon it, or if successive volleys could be made to arrive during the period of latent addition. Then, with the neurone restored to the performance of its proper function in the chain, the reaction in which it takes part would be reinstated.

No mechanism for bringing about inhibition can have very wide application, however, unless it will account for reciprocal innervation: the fact that when one muscle contracts, its antagonist relaxes. This case is the most difficult of all to explain. Its consideration demands taking into account both the nature of the neurone linkages and the effect of the timing of impulses.

The *timing* of impulses is an aspect of nervous activity which has received little attention, although it is in all probability of great importance. It may indeed be the occasion for the numerous velocities of conduction in nerve trunks which were mentioned previously and for which no satisfactory explanation has as yet been found. Their purpose may be to insure the arrival of impulses at the secondary neurones in the proper time relations. Let us consider some peripheral event, like an injury to the foot. The first report would come to the spinal cord in about thirteen msec.; two msec. later impulses would be on their way out over the motor nerves, and only ten msec. later (on the basis of data obtained in animal experiments) would the first impulses arrive at the brain at the level of the medulla. In the meantime, impulses would be approaching the cord over some of the more slowly conducting lines. The first of the impulses capable of arousing a sen-

sation of pain would require forty msec. to reach the cord, and the sensation itself would be felt only after half a second (Piéron).[31] Even at that time, however, the first impulses over the slowest fibers would not yet have reached the cord. The fastest impulses in the slow pain system would require three-quarters of a second, and the slowest about a second and a half.

These figures give some idea of how impulses starting simultaneously from a common point become separated. Electrical records from the cord show that the first impulses to arrive produce a large amount of activity,[30] and this activity has a marked effect on the subsequent course of the excitability of the cord neurones. It is quite possible that the function of the impulses which run on ahead of the others is to adjust the excitability of the synapses in preparation for the arrival of the later impulses. By carrying the idea of timing one step further it is possible to account for reciprocal innervation in terms of the known properties of nervous tissue.

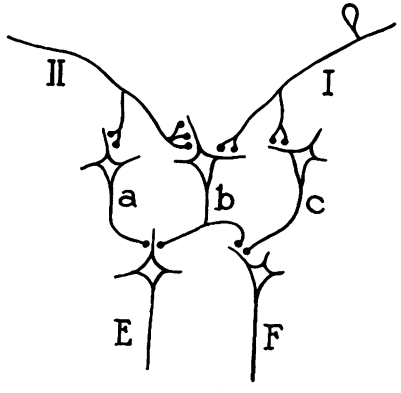

Figure 11

In the accompanying schema (Fig. 11) the linkages are hypothetical, but drawn in accord with the known facts. Excitation at the synapses is widely held to be proportional to the number of active endings, and this view is followed in the interpretation of the schema. For the sake of the

argument, the minimal number of endings which must be active for excitation to occur is arbitrarily taken to be two. Use is then made of the fact that the period of latent addition is not over 0.5 msec., and that subnormality increases with the number of responses.

If a neurone *b* common to two pathways be switched out of one pathway when it is taken up by another, the necessary condition for reciprocal innervation would be fulfilled. Let us suppose that rhythmic stimulation of fiber *I* is maintaining a flexor reflex. Neurones *b* and *c* are excited, and their discharges arriving synchronously at *F* cause it to respond. Then let us suppose that in the course of this response an extensor reflex is set up through stimulation of fiber *II*. The latter can excite *b* in the intervals between the responses to *I*, because of the stronger excitation which it is able to deliver through its three endings. No discharges can result therefrom in *F*, as the impulses in *b* are out of time with those in *c*; and *I* is no longer able to excite *b* and *c* in unison, because of the raised threshold of the former. Neurone *b* is dominated by fiber *II*. Its discharges are caused to be synchronous with those in *a* instead of with those in *c*, and activity begins in *E*. Thus, when innervation of the extensor muscles starts it must be withdrawn from the flexor muscles.

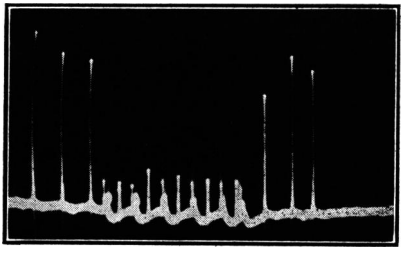

Figure 12

The taking over of a neurone by intercurrent stimulation may be imitated on peripheral nerve. Figure 12 shows the responses of the phrenic nerve to weak shocks at twenty per second. Intercurrent stimulation of the nerve with

stronger shocks at the same frequency causes most of the fibers which had been responding to the original series to fail to do so.

Notwithstanding the fact that inhibition may include other processes as well as that described, and that the explanation of reciprocal innervation must be taken only as illustrative of how subnormality may be applied to the problem, the value of utilizing the properties of axons in the interpretation of the physiology of the centers is, I think, apparent. The applications of other properties await development. In order to indicate that there are

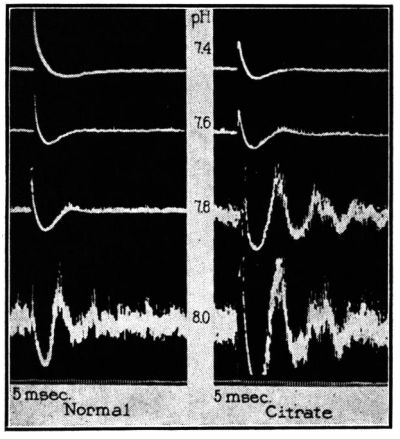

Figure 13

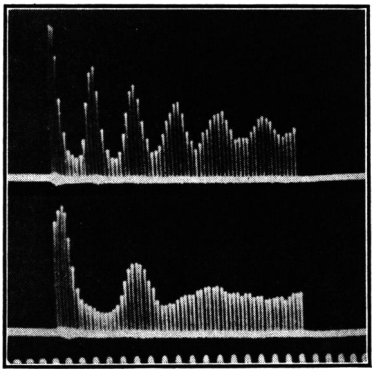

Figure 14

other possibilities, I shall mention in conclusion the representation in peripheral nerve of a property which is often considered as though it were exclusively central—namely rhythmicity.

There are at least two rhythms in nerve, but the most obvious rhythm is the oscillation in the after-potentials. Following a single response of a mammalian fiber at the normal reaction of the body, oscillation of the after-potential is not readily made out, and it becomes rapidly attenuated; but if the nerve be made alkaline, or if it be deprived of calcium (Fig. 13), or asphyxiated, the oscilla-

tion becomes obvious, its period shortens, and it passes through a number of cycles before it is lost to view.[27]

Nerves so treated are in tetany and subject to spontaneous firing of their constituent fibers, but the intensity of the firing varies with the changes in excitability. During the subnormal periods at the troughs of the waves the firing is decreased, or one may say inhibited. And during the supernormal periods at the crests of the waves the firing is augmented or facilitated. It was records like these which prompted my suggestion two years ago that there is an analogy between the first sub-normal period and the silent period of motor neurones following a knee-jerk, and a possible relationship between the second supernormal period and the rebound discharge that follows the silent period.[12]

Although rhythm is not obvious in the after-potential at normal reaction, it becomes very clear when the nerve is excited with a train of shocks from a thyratron adjusted to stimulate only a group of the most irritable fibers (Fig. 14). The initial responses condition the fibers involved, and during the ensuing subnormal period the fibers drop out in relation to the narrowness of the margin between their resting thresholds and the shock strength employed. In the rebound they appear again and help to keep up the cycle, but eventually secondary events equilibrate all fibers to a common excitability. If the responses were sufficiently asynchronous, they would not be seen individually, and all that would be visible would be the envelope of the crests of the waves. The latter would then appear like the waves which are recorded from the spontaneously active nervous system. Different as are the conditions in the two cases, the nerve analogy serves to show how neurones which are subject to reexcitation in closed circuits would fall into a rhythm of response dependent upon their own natural period of excitability.

Nerve fibers have been studied for years, while the mechanics of the nervous system is almost an untried field. If I have given too little time to recounting the accumu-

lated facts about the physiology of fibers and spent too much time in looking over the fence into the new field, it is because this lecture has been motivated by the idea that for the understanding of the nervous system it is better, before turning to postulates, to look to peripheral nerve for what it has to offer of suggestions and explanations.

FIGURES

Fig. 1. Action potential of the saphenous nerve. The nerve is mounted in serum equilibrated with 5 per cent of O_2 in CO_2. 37° C. Conduction distance 41 mm. The upper record shows the elevations produced by the faster fibers. The lower record shows the C fibers. They appear on the positive after-potentials of the fast fibers, the spikes of which are bunched near the break in the line. Although the distal lead is from killed nerve, the C elevation is recorded from both leads and hence is repeated in an inverted position.

Fig. 2. Diagram of the potentials in a mammalian nerve fiber in their normal relationship in a single response.

Fig. 3. Potentials in C fibers, splenic nerve of the cat. The spike elevation, which has a secondary group in its falling phase, is succeeded by a negative after-potential (from which it is separated by a notch known as the diphasic artifact) and a long positive after-potential. Isolated nerve at 37° C.

Fig. 4. Alterations produced in the after-potentials in a phrenic nerve by short tetani. a) single response, b) tetanus at 180 per second, c) tetanus at 350 per second. 37° C. Time, 20 msec.

Fig. 5. After-potentials in a phrenic nerve after a longer tetanus. The tetanus starts at the break in the line; the spikes go far beyond the record. The potential is first visible as the negative after-potential and is continued by the positive after-potential in two parts. (Gasser and Grundfest).

Fig. 6. Excitability curves of the saphenous nerve of the cat *in situ*. Ordinates. Excitability in terms of resting thresholds (reciprocals of shock strength). Abscissae: Separation of conditioning and testing shocks. The upper curve is conditioned by a single shock; the other curves are conditioned by tetani as indicated, e.g. 3/90 means three shocks at ninety per sec. (Gasser and Grundfest).

Fig. 7. Potentials in the spinal cord evoked by a single afferent volley.

Fig. 8. Relation of the reflex discharge into the sciatic nerve to the internuncial potential in the lumbar cord of the cat. (Spinal preparation). (Drawn from Hughes and Gasser).

Fig. 9. The effect of previous activity on the responsiveness of internuncial neurones in the spinal cord of the cat. a) Response to a submaximal volley from the tibial nerve. b) Response to a volley from the saphenous nerve. c) The two volleys in succession. Note the decreased response to the volley from the saphenous nerve and the effect of the latter on the late part of the response to the tibial volley. Spinal preparation. Concentric needle electrodes in unexposed cord.

Fig. 10. Size of response of internuncial neurones in relation to the potential evoked by a conditioning volley. Conditioning and testing shocks of the same size and applied to a sensory root. (Drawn from Hughes and Gasser.)

Fig. 11. Schema illustrating reciprocal innervation.

Fig. 12. Effect of a dominating train of stimuli on the rhythm of response of a phrenic nerve. Stimuli of near-threshold strength are applied at a frequency of twenty per second through one pair of electrodes, and midway between the responses another train of the same frequency is started with stronger shocks at electrodes further removed from the leads. The larger responses to the latter are seen as faint lines followed by positive after-potentials. During the intercurrent tetanus most of the fibers accessible to the first train are taken over into the rhythm of the intercurrent train.

Fig. 13. Accentuation of the rhythm of the after-potentials in the phrenic nerve by increased alkalinity and by deionization of calcium. The first column shows the effect of altering the hydrogen ion concentration alone, the second column the behavior at the same pH values 80 minutes after exposing the nerve to the same saline with citrate added. The spikes occur at the first breaks in the lines and are not visible. When the alkalinity is high, spontaneous firing of the fibers occurs. 37° C. Conduction distance, 4.5 cm. (Lehmann).

Fig. 14. Rhythmic response of the phrenic nerve of the cat to a train of shocks of constant strength selected to include the low threshold fibers only. The upper curve differs from the lower in that the nerve is more alkaline. The two rhythms are rapidly interchangeable. Time, sixty cycles. Frequency of stimulation, 220 per sec. 37° C.

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