

SYMPOSIUM ON THE SYNAPSE

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ALEXANDER FORBES

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SYMPOSIUM ON THE SYNAPSE

Dedicated
with respect and affection
to
CHARLES SCOTT SHERRINGTON, O.M.
who introduced the concept of
The Synapse,
as well as the word itself,
into the literature of neurophysiology

PREFATORY NOTE

THE material contained in this brochure which has been reprinted from the *Journal of Neurophysiology*, formed the subject matter of a symposium on the mechanism of synaptic transmission held at Toronto, April 29, 1939, under the auspices of the American Physiological Society at its annual meeting. The papers of Drs. Bronk and Lorente de N6 were considerably revised and extended prior to publication.

In order to facilitate bibliographical citation, the original pagination of the articles has been carefully preserved.

THE EDITORS OF THE JOURNAL

July 25, 1939.

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H. S. GASSER, Chairman

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AXONS AS SAMPLES OF NERVOUS TISSUE*

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(Received for publication May 27, 1939)

THE FIRST question that would naturally be asked about the synapse is: What is the nature of the material coming in contact at its borders? The answer to the question must come from a direct study of the synaptic region of the neuron, and for that reason it is a difficult one to obtain. As an introduction to the problem, attention has been directed to properties of the axon, because of the expectation that the events which take place in those parts of the neuron entering into the synapse may resemble, qualitatively at least, events taking place in other parts of the neuron. If it could be shown that the expectation has a foundation in fact, to the extent to which it holds, axon physiology could be transferred directly to synapse physiology.

As is well-known, axons are not all alike. This fact in itself is helpful for our present purpose, as samples of different kinds of nervous tissue are presented for review. The common features among the characteristics of these samples may be taken to give an indication of the qualities that are shared generally by nervous structures, and the mode of variation of the characteristics may be taken to give an indication of the directions in which differences are to be anticipated.

I want to mention with the greatest possible brevity the properties of the action in nerve fibers that appear to have application to synaptic conduction. The illustrations which will be cited are typical for the three kinds of nerve fibers, A, B, and C. The designation A refers to the somatic myelinated fibers; B to the autonomic myelinated fibers, that is, the group originally described by Bishop and Heinbecker as B₂; and C to the unmyelinated fibers.

Action in all fibers starts with a spike. The only difference between one type of fiber and another in this regard is in the duration (Fig. 1). The A spike stands at one end of the range with a duration of 0.4 msec. and the C spike at the other end with a duration of a little over 2 msec.

The spike is followed by an after-potential much smaller in size and much greater in duration. After-potentials vary as to form, size, and duration, depending upon the kind of fiber (Fig. 2). The complete sequence is a negative after-potential followed by a positive potential. It is found clearly developed in A and C fibers. In B fibers the negative after-potential is vestigial in single responses, and it appears only after certain forms of activity and after special experimental procedures. When records are prepared at low amplification, as in Fig. 2, so that both the spike and the after-potential are visible in the same tracing, the variation in the size of the positive after-potential

* Symposium on the Synapse, Meeting of The American Physiological Society, Toronto, April 29, 1939.

at once strikes the eye. The positive after-potential is readily visible in the B fibers and somewhat less so in the C fibers, while in the A fibers the configuration that appears so clearly at higher amplification is all but indistinguishable.

Spikes are generally considered to be the message carriers; that is, some agent, physical or chemical, directly under the control of the spike process

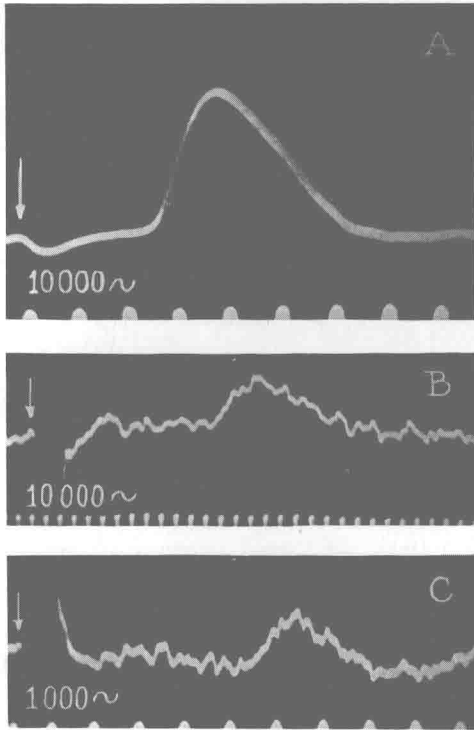


FIG. 1. Spikes of A, B and C fibers; A, potential from a single large fiber of a dorsal spinal root of the cat; B, from the cervical sympathetic nerve of the rabbit, threshold response, possibly not a single fiber (spike $25 \mu\text{v.}$); C, from the splenic nerve of the cat, threshold response (spike $20 \mu\text{v.}$). The fine oscillations are occasioned by the noise level.

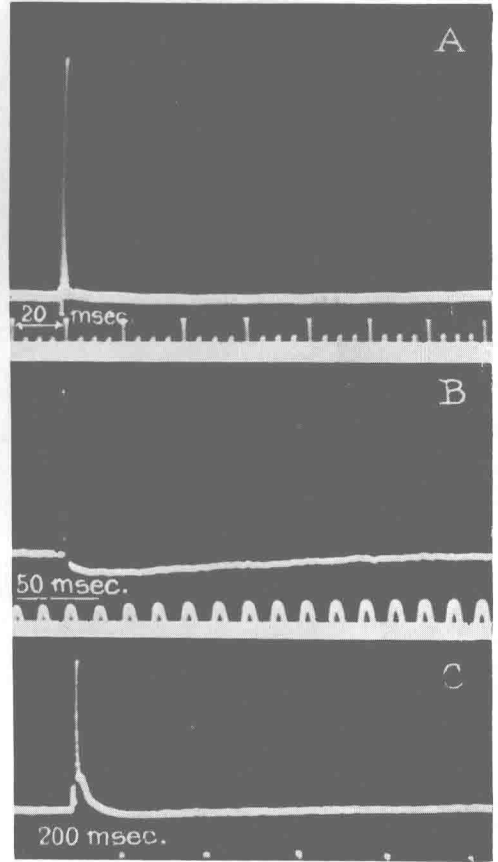


FIG. 2. Action potentials of A, B and C fibers (cat): A, from the phrenic nerve; B and C from hypogastric nerves.

is held responsible for the mediation of transmission. The view that spikes serve this function is well founded, but other views have not thereby been excluded. The contemporary literature contains arguments for impulse initiation by slow potentials as well.¹

One point is certain with respect to the after-potentials; they influence the level of excitability. During the negative after-potential the fibers are supernormal, and during the positive potential they are subnormal (Fig. 3).

Furthermore, when the configuration of the after-potential is altered, as it easily can be in a completely reversible manner by a wide variety of conditions or of states of activity, the excitability curve is altered in parallel with it. The same parallelism that holds between excitability and after-potential form for the various states of a single type of fiber, also obtains for the variation of the after-potential as it appears in the different types. The course

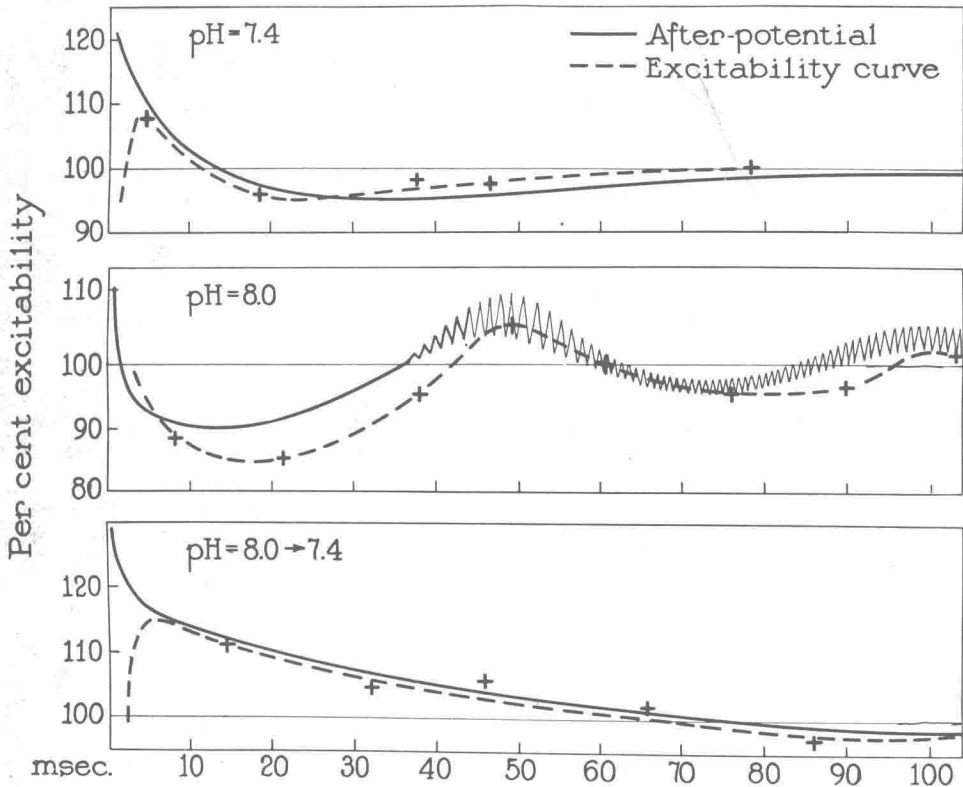


FIG. 3. Relation between the excitability curves and the after-potentials in A fibers (phrenic nerve of the cat) Lehmann⁸ (1937). The three parts show from above downward the normal condition, alkalinity resulting from removal of CO_2 from the atmosphere, and an early stage following restoration of CO_2 before the normal steady state is reached. The ordinates give the reciprocal of the threshold for excitation in percentage of the resting threshold.

of the excitability curves following a single response is plotted for the three types of fibers in Fig. 4. The curve for the C fibers⁶ resembles that for the A fibers but for the fact that it is much more drawn out in time. As would be expected, the B fiber curve differs from both of them. In keeping with the absence of negative after-potential, there is no early supernormal period.

When a nerve is tetanized, the positive after-potential following the last spike in the train is larger than one following an isolated spike. The manner in which the growth takes place in A fibers is shown in Fig. 5, and an analo-

gous process occurs in the other types. If the tetanization is severe enough, the positive after-potential at the end of the tetanus, which corresponds to the one seen after a single response, is followed by a second positive potential. Unlike the first, the second potential increases in duration as well as size as the length of the tetanus and particularly the frequency of the tetanus are increased. The end result is the same in all fibers (Fig. 6)—an after-potential yielding records characterized by an initial sharp notch followed by a long

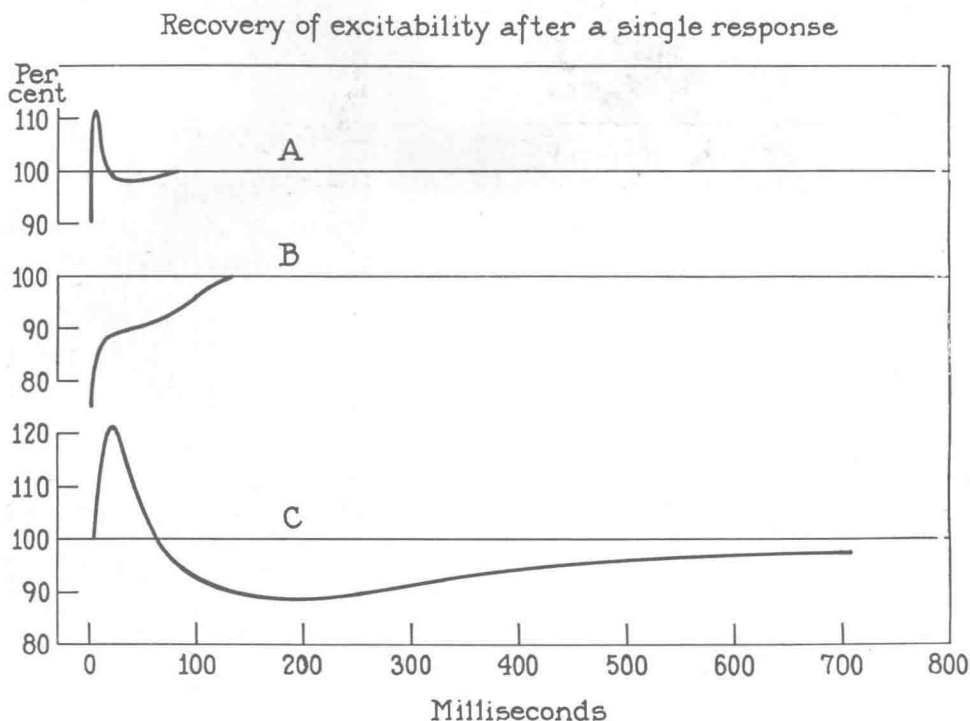


FIG. 4. Excitability curves of A, B and C fibers shown for comparison on the same time scale.

shallow trough. But for the time scale and the size of the potential in comparison with the height of the spike, the after-potential following a tetanus of C fibers resembles greatly that recorded after a tetanus of A fibers.

The excitability of a nerve following a tetanus is exactly as would be predicted from the after-potentials: the longer the duration and the higher the frequency of the tetanus, the greater and more prolonged the ensuing subnormality. Some of the early stages in the development of this subnormality are shown in Fig. 7. Among other things, the curves show that the supernormal period is a phenomenon restricted to very mild activity and that supernormality following the cessation of the tetani responsible for message transmission could hardly occur.

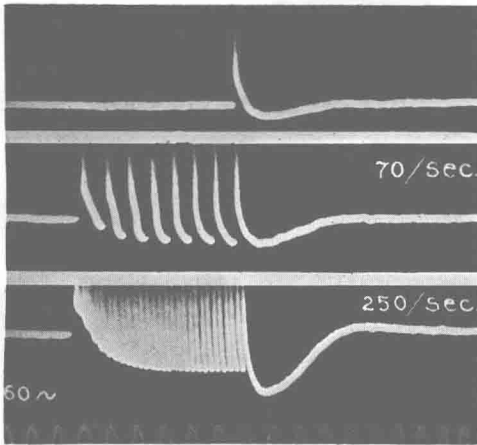


FIG. 5. Increase in the positive after-potential produced by a short tetanus (A fibers, phrenic nerve of the cat, 37°C., 5 per cent CO₂ in O₂). The records start with the negative after-potential. The spikes would extend far above the tops of the records. Changes in the negative after-potential are also to be noted.

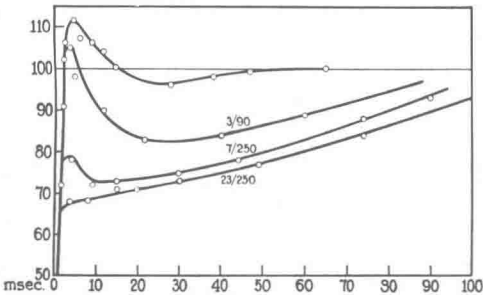


FIG. 7. Recovery of the saphenous nerve *in situ*, decerebrated cat. The ordinates give the reciprocal of the threshold strength of stimulation in percentage of the resting threshold; the abscissae, the time after the end of the conditioning excitation. In the course of the experiment conditioning was changed from a single action to a tetanus. 3/90 means conditioning by 3 shocks at 90 per sec. (Gasser and Grundfest 1936).

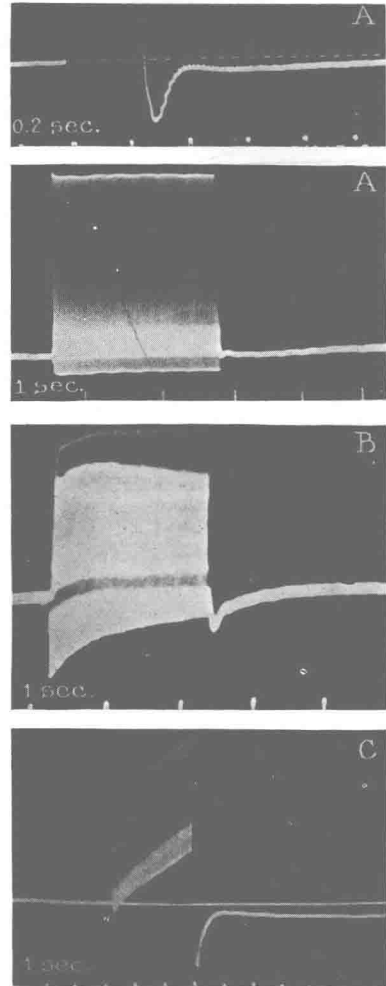


FIG. 6. Tetani of A, B and C fibers: A (lower), from the phrenic nerve of the cat; B and C, from the hypogastric nerve of the cat. The tops of the A and C spikes are at the tops of the records, the tops of the B spikes at the tops of the heavy white lines. The form of the A after-potential can best be seen in the upper record taken with higher amplification and with a faster sweep than in the record below it.

So much for the axon. Now, do any analogous phenomena occur at the dendritic end of the neuron? Numerous bits of information indicate that they do, but it would be impossible to summarize them within the compass

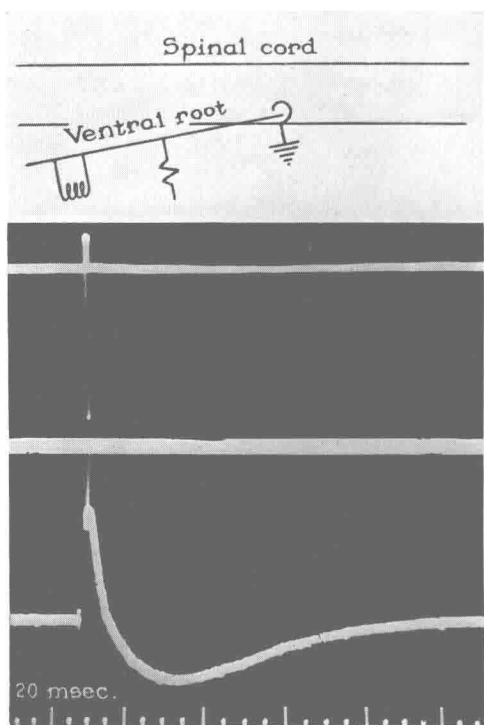


FIG. 8. Records obtained with the leads shown in the diagram when a single volley was backfired into the spinal cord of a cat through a motor root. (Dial narcosis). The lower record is at approximately 100 times the amplification of the upper. Control observations showed that the potential contributed by the spinal cord was not caused by a spread of the stimulating current to central structures but, as held by Eccles and Pritchard, was evoked by the antidromic volley itself.

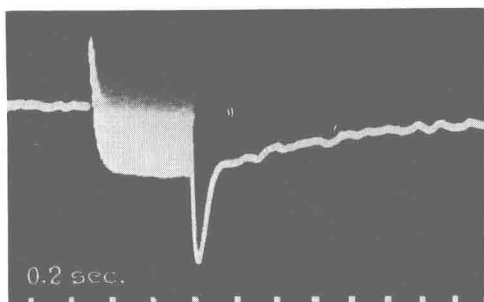


FIG. 9. Leads as in Fig. 8. The record shows the potential evoked by an antidromic tetanus. (Dial narcosis.)

ing the cord through the dorsal root of the same segment. The remaining records show the conditioning effect of the antidromic volley upon the size of the reflex. The record was occasioned chiefly by the motor reflex discharge. The remaining records show the conditioning effect of the antidromic volley upon the size of the reflex. Arrows indicate the moment of stimulation of the dorsal root.

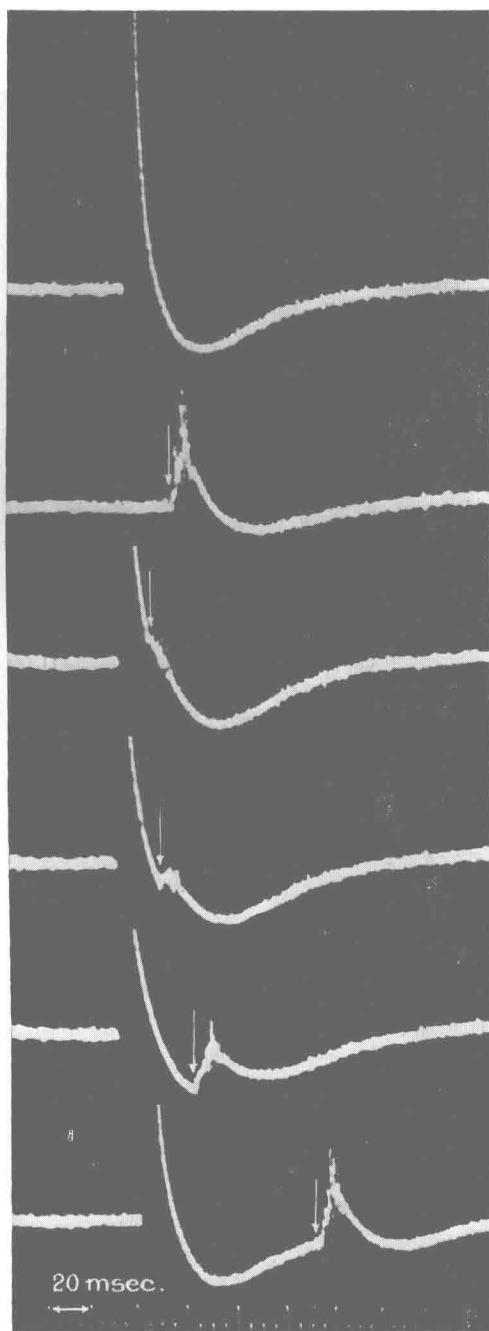


FIG. 10. Leads as in Fig. 8, except that both electrodes were on the root, the central electrode about 2 mm. from the cord. (Dial narcosis.) The upper record was produced by a single antidromic volley. The second record was produced by a single volley entered

of the same segment. The potential was occasioned chiefly by the motor reflex discharge. The remaining records show the conditioning effect of the antidromic volley upon the size of the reflex. Arrows indicate the moment of stimulation of the dorsal root.

of the present discussion. Only one point will be brought forward, that is, subnormality in motor neurons. That motor neurons have a subnormal period similar to that of the axon first became apparent in considerations involving the interpretation of the silent period following a reflex discharge (Gasser,³ p. 199). The arguments adduced in support of the association of the two events can now be passed over, however, because new and more direct evidence has become available from the experiments of Eccles and Pritchard,² in which a study was made of the effects of backfiring an antidromic volley of impulses into the spinal cord by way of a motor root.

Figure 8 was prepared in the course of repetition of one of Eccles and Pritchard's experiments. The first sacral motor root at its exit from the spinal cord was severed and stimulating electrodes were placed near the cut end. A single volley was backfired into the cord and the action potential led off from the side of the root and from the cord adjacent to the point of emergence of the root. The diphasic spike obtained at low amplification helps in the clarification of the potential picture obtained at high amplification. The latter has the appearance of a monophasic action potential of an A fiber (spike upward) as observed at high amplification (Fig. 5). Evidently, as concluded by Eccles and Pritchard, the form of the action potential of the intramedullary portion of the neuron is being revealed. If the cord is asphyxiated, the potential rapidly disappears and there is left only the after-potential of the root fibers. Under the conditions of the experiment, the centrally contributed portion of the potential so dominates the contribution from the root that in the algebraic summation of the two in the records, the configuration of the centrally produced potential is not obscured.

The duration and form of the central positive potential evoked by an antidromic volley are the same as the duration and form of the positive after-potential in a single action of A fibers. After a tetanus the similarity between the two potentials still holds. When a tetanus is backfired into the cord, the central positivity is increased and prolonged and the potential develops a two-part contour (Fig. 9) in keeping with the general pattern that holds for the after-potentials following tetani in all nerve fibers. The distinguishing feature in positive after-potentials is the first positive notch. In the motor neuron potential the notch corresponds to the one which is characteristic of A fibers.

That the locus of production of the central positive potential includes that part of the neuron in which the motor impulses are set up follows from the fact shown by Eccles and Pritchard that a motor reflex discharge is conditioned throughout the period during which the positive potential following a backfired volley persists. Records from a repetition of the backfiring conditioning experiment are shown in Fig. 10. They make it clearly evident that throughout the positive potential the excitability of the motor neurons is subnormal. A full-sized reflex is obtained only when the positive period is cleared.

The positive potential in the motor neurons not only has the duration of the positive after-potential in motor axons, but it is attended by the expected subnormality. There is indeed no reason for not calling it the positive after-potential of the neurons. The interpretation of the negative part of the central potential, on the other hand, is not so clear. In the experiment pictured in Fig. 10 there was nothing resembling supernormality; nor have we seen supernormality in other experiments. Recovery takes place along a continuously rising curve, just as it does in the internuncial neurons,⁷ without separation of the refractory period and the subnormal period by a transient period of low thresholds. One may question whether there is any negative after-potential included in the recorded negativity. If there is, there must be an additional factor controlling excitability which has not yet been resolved. Quite possibly also under other conditions the finding may be different, as Eccles and Pritchard have described low thresholds during the negative period.

The peripheral endings of afferent fibers, which in a morphological sense are dendritic, provide another place where the conditioning effect of an antidromic volley can be tested. Here, too, there is a subnormal period. The number of impulses set up by a controlled tap on the skin is reduced as

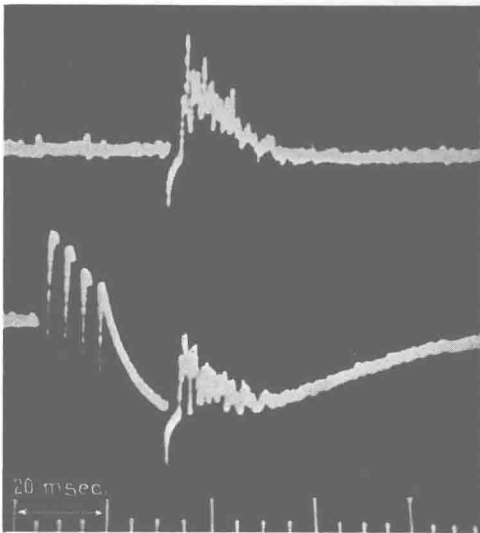


FIG. 11. Monophasic lead from the central end of a branch of the saphenous nerve of the cat. A gentle tap was applied to the skin of the leg with a device prepared by Toennies from a loud-speaker cone, and the discharge of impulses set up by the sensory endings recorded from the nerve (upper record). The discharges were reproducible as to size. In the lower record the size of the discharge has been conditioned by four volleys backfired into the periphery from a stimulating electrode on the nerve distal to the leads. The record shows four negative after potentials and the ensuing positive after-potential upon which is written the action potential of the conditioned discharge from the endings.

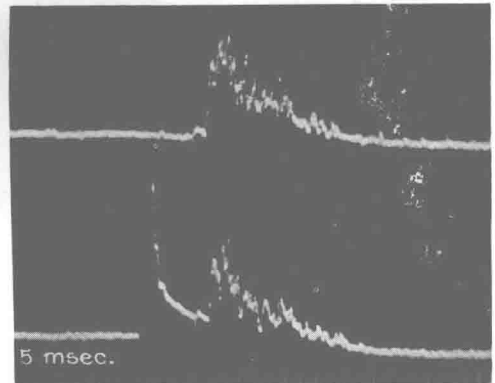


FIG. 12. Arrangement of experiment as for Fig. 11. Afferent discharge conditioned by a single volley backfired into the periphery. A discharge set up from the endings at the time when the nerve would be supernormal contains fewer than the number of impulses in the normal control.

long after the arrival of a backfired volley as the positive after-potential lasts in the nerve (Fig. 11). The probability, therefore, is strong that a positive after-potential is present in the endings. Supernormality, however, is absent, as it was seen to be in the motor neurons (Fig. 12).

Subnormal excitability following single spikes and trains of spikes is characteristic of all kinds of axons and all parts of the neuron. It is also found in all parts of the central nervous system, only it is there called inhibition. The significance of subnormality in the interpretation of inhibition makes the subnormal period, first described in nerve fibers by Graham,⁵ one of the most important features of nervous activity which the axon has to present to the understanding of the synapse. The axon can also contribute to the understanding of facilitation, but the mechanism involved belongs in the group of phenomena which take place below the threshold of excitation, and facilitation, therefore, falls within the province of the next speaker.

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THE INITIATION OF IMPULSES IN AXONS

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IT IS QUITE generally believed that, to quote from a current textbook (Bard, 1938, p. 6), "where there are synapses conduction of excitation takes on certain characteristics that are not found elsewhere, e.g., in nerve trunks composed of axons"; and that "there is some reason for attributing the peculiarities of central conduction to the synapse."

These assertions, of course, hark back to Sherrington. How fundamental are the differences between nerve fiber and synapse conduction? I propose to devote my time to a consideration of that question, rather than limit my remarks exactly to the title as announced. I shall single out for consideration a few of the asserted differences with which my laboratory has had some experience, namely, latency, one-way transmission, repetition, temporal summation or facilitation and transmission of the action potential across a nonconducting gap.

To take up latency first, the action potential ceases to pass an anode block in a nerve fiber when the impulse is delayed there for an interval that is slightly longer than the time to maximum of the action potential. In the case reproduced as Fig. 1, for example, the block develops when the action potential lag amounts to about 0.6 msec. It seems safe to infer on the basis of observations on the relation of the duration of the action potential to conduction rate (Blair and Erlanger, 1933), that the time to maximum of the spikes in fibers of the sizes that ultimately reach the frog's neuromuscular synapse ranges between 0.3

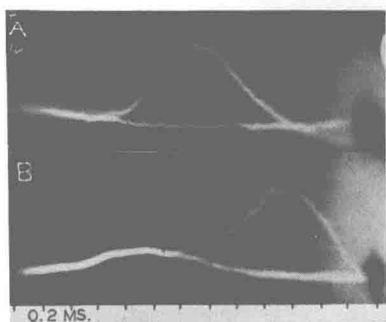


FIG. 1. Configuration changes in an axon spike at the locus of anode polarization.

A. The normal (unpolarized) diphasic axon spike on its bent base line.

B. *The higher spike* is the same axon spike, polarized anodally to the limit still permitting of conduction. The notches on the ascending limb (in this case somewhat atypical in spacings) are determined by loci of greatest susceptibility (nodes of Ranvier) of the fiber to anode polarization. *The lower spike* is the same spike after block at the first notch. The starts of the two spikes (blocked and unblocked) are superimposed. Block is indicated by the change from diphasicity to monophasicity of response. The lag at the node, due to the developing block, is of the order of 0.6 msec. Time is indicated in 0.2 msec. intervals.

and 3.0 msec. These figures about encompass the range of neuromuscular delays one finds in the literature. Granting block delay as the main factor determining latency, it follows that about the whole of the spike potential is needed for transmission at the neuromuscular synapse.

To pass to the next "peculiarity" of the synapse, namely, one-way trans-