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Some observations on the responses of single nerve fibers

Nobel Lecture, December 12, 1947

Dr. Gasser, in his Nobel Lecture delivered here in 1945, restricted his discussion to a review of the classification of mammalian nerve fibers. His reason for confining himself to that phase of the development of the researches that have occupied us since 1921, was the fact that after the termination of our association in St. Louis most of the recent work in his laboratory "has", to quote him, "been turned in that directions". Similarly, my review will be restricted largely to a consideration of some of the results that have been derived through observations on the responses of *single nerve fibers*, since that is the main method that has been employed in the continuation of the studies in my laboratory since 1931. Much of this recent work was conducted in collaboration with E. A. Blair.

Before considering any of these results a brief statement is in order regarding the technique which made possible the work on nerve that was begun in St. Louis by Dr. Gasser and myself. The action potential of nerve, that is, the electrical manifestation of the nerve impulse, is exceedingly brief; it is so brief that there were reasons for believing, in 1921, that the details of its configuration had never been accurately recorded - that, of the physical instruments then available, the cathode-ray oscillograph alone would be fast enough to give true pictures of nerve action potentials. Undoubtedly, many physiologists had realized the advantages that would accrue to electrophysiology through the use of this practically inertialess electrical recording instrument, but although this oscillograph was available as early as 1890, the only statement regarding its possibilities in physiology that had appeared in print prior to 1921 is to be found in Bernstein's *Electrobiologie*, published in 1912. It reads as follows: "Von Bernstein ist der Vorschlag gemacht worden, den Kathodenstrahl als Indikator für die Oszillationen der bioelektrischen Ströme zu benutzen, da dieser mit absoluter Genauigkeit den Stromschwankungen folgen würde. Es ist aber bis jetzt nicht gelungen, Versuch in dieser Richtung mit Erfolg auszuführen."

It becomes evident from this statement that Bernstein failed to realize that

the Braun tube did not possess the sensitivity that is requisite for the direct recording of nerve action potentials, the smallest of which may be of the order of a few microvolts.

At a meeting of the American Physical Society held in Chicago in 1920, J. B. Johnson of the Western Electric Company described a cathode-ray oscillograph possessing a greatly increased sensitivity; it was such as to suggest the possibility that, with the aid of amplification, the Braun tube might become available as the perfect instrument for the recording of brief electrical phenomena of physiological origin. At that time the physiological laboratory of Washington University was in the possession of an amplifier which had been built by Gasser and Newcomer for the recording, with the string galvanometer, of action potentials carried by the phrenic nerve during respiration. However, another amplifier was built in order to embody some improvements suggested by the experience of those investigators.

Records of the responses of single axons had previously been made by Adrian and collaborators. To secure them they interrupted, through teasing, the continuity of all save one of the fibers of a nerve at some point between stimulator and lead, and the responses of that fiber were recorded, at first, with the capillary-electrometer, and later, with the Matthews oscillograph. Our method of securing responses of single fiber has consisted of recording from a nerve that contains relatively few fibers, the frog's phalangeal nerve or a spinal root, for example. These nerves are apt to contain a fiber of outstanding excitability, such that a just threshold stimulus will excite that fiber only. An advantage of this method is the assurance it gives that the characteristics of the responding fiber have not been altered by rough handling in preparation. Since of the total electrical response of a fiber, that of the spike is relatively stable, it has been unnecessary in this series of experiments to supply the nerve with exactly the environment (gaseous and thermal) that prevails in the normal animal organism. Environmental conditions were, however, kept constant where constancy was a requirement. The temperature was usually that of the room, about 27°C

The observations on the responses of single nerve fibers first became feasible when, in 1932, the amplification available in the laboratory was increased from the previous maximum of about 100,000 times, at which a spike of about 27 microvolts produced a deflection of 1 mm on the screen of the oscilloscope, to a maximum of about 2,000,000 times, an increase of about 20 in sensitivity. The noise level then, was of the order of 5 microvolts.

The first phenomenon to be revealed by this higher amplification and

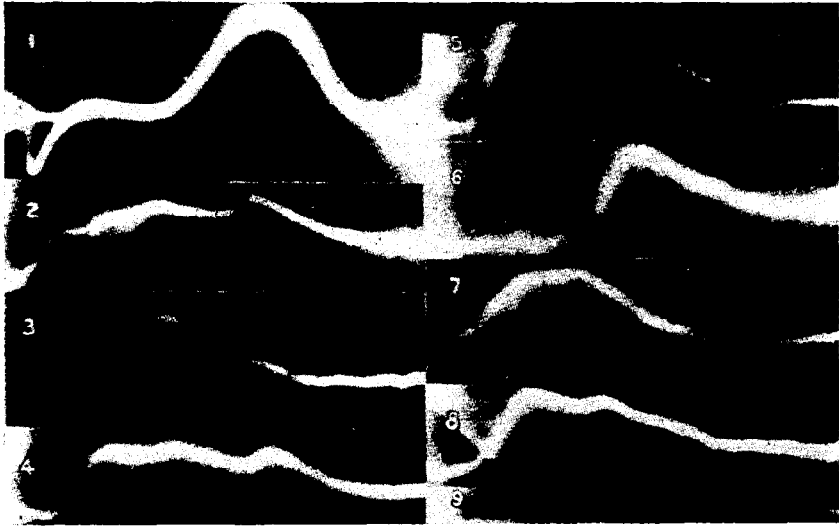


Fig. 1. (1) Contact print of 40 successive half-maximal α spikes of the sciatic nerve, to show the superimposability of successive multifibered-conducted action potentials. The sweep is slower than in records 2 to 9, and the amplification less.

(2-8) Successive contact prints all obtained under exactly comparable conditions to show the spontaneous variations in the response of the sciatic to shocks, uniform as above, but just threshold; the records are mounted so that the time from the stimulus is the same for all.

(9) A sweep without stimulation, showing the noise level for 2-8.

(These records were made before better techniques became available.)

thinner preparations was an instability of a fiber's reactivity. With low amplification but the maximum originally available, the conducted multifibered action potential elicited from a large mixed nerve by half maximal stimulation has a constant, smooth configuration, as may be seen in 1 of Fig.1. This is a record made by 40 successive superimposed sweeps during each of which the nerve was stimulated with a single shock. These 40 half-maximal alpha spikes match perfectly and give a smooth curve, record 1. In contrast to the smoothness of this record of superimposed spikes are records 2 to 8, inclusive. These seven action potentials were secured under the same conditions as those that obtained while making the superimposed half-maximal records of 1, except that the amplification was maximal and the stimulation strength threshold. Each of the records, 2 to 8 is that of a single sweep. The striking feature of these records is their variety. No two are alike. Of this variability only a very small part is referable to amplifier noise, as may be

seen in the faint record 9, which was made by a sweep during which the nerve was not stimulated. Here the irregularities are insignificant in comparison with those seen in records 2 to 8.

Two factors that account for this variability of the successive pictures are spontaneous variations in the excitability of the responding fibers and of the latencies of their responses. That variation in excitability is one of the factors is clearly demonstrable when a phalangeal nerve preparation happens to contain, say, two fibers of approximately the same outstanding excitabilities and approximately the same conduction velocities, but spike potentials which, through fortuitous circumstances, differ appreciably in appearance, so that the spikes of each of the fibers can be identified. Under such circumstances threshold shocks, all of the same strength, elicit responses that shift to and fro on the screen of the oscilloscope, and come and go, in a wholly unpredictable manner. Thus, both of the fibers may respond to one of the shocks, only one of them to the next, the other only to a third, or neither axon may respond, and the responses shift their positions irregularly on the screen. It is obvious that such behavior cannot be ascribed to fortuitous variations in stimulus strength, for then the two fibers would behave alike. Rather, as has been said, the uncertainty of a response to a threshold stimulus must be referable to spontaneous, independent variations in the excitabilities of the two fibers.

A measure of the range of these fluctuations in the excitability can be gained by determining the change in the ratio of the number of responses to the number of stimuli as the strength of the shocks is increased in small steps while stimulating at a regular rate - say, 30 shocks per minute. As the shock strength is gradually increased from subthreshold level, a strength will be reached at which the fiber at first responds only rarely, say, once in 20 stimulations. (Twenty stimulations is the number commonly employed in such determinations.) To increase this low probability of response to a high probability, where, for example, the shock strength is such that it fails to attain the fiber's threshold in the same ratio, that is, 1 in 20, it may be necessary to increase the strength of the shock through about 2 to 4% of the threshold. On account of these spontaneous fluctuations in the threshold of a fiber it has been necessary to adopt as threshold the strength of current that stimulates half of the times it is applied.

The temporal shift of the successive responses might be due to fluctuation of conduction velocity and to latency of the response to the threshold stimuli. Since, however, the shifts are equally prominent with both uncondacted and

conducted spikes, fluctuations in the latency of the responses alone would be sufficient to account for them. An example of the shift in latency of un-conducted spikes is seen in Fig.2. Here A, B, and C are responses of a fiber to successive "just threshold" brief induction shocks of identical strength. Conduction has been eliminated by using the proximal electrode as both the lead into the amplifier and the cathode of the stimulating shock. The shock artifact therefore badly distorts the records; its form is given, however, by S - C, a response that resulted when one of the equally strong shocks failed to elicit a spike. The latencies of the two responses can be ascertained by subtracting this shock artifact from the two records, A and B; they are 0.21 and 0.34 msec; the shift, therefore, is 0.13 msec. This, however, was not the widest shift exhibited by this particular axon. The longest shock-spike range we have encountered has been 0.4 msec. But with stimulation by long rectangular constant currents at rheobasic strength the latency under constant conditions has ranged between 1.61 and 3.05 msec, a shift 1.4 msec or about 10 times that observed when the stimulus is a brief shock such as was employed in the experiment illustrated by Fig. 2. Since latencies are shortened by increasing the strength of the stimulus it seems probable that their spontaneous variations are related to the spontaneous variations in the fiber's excitability.

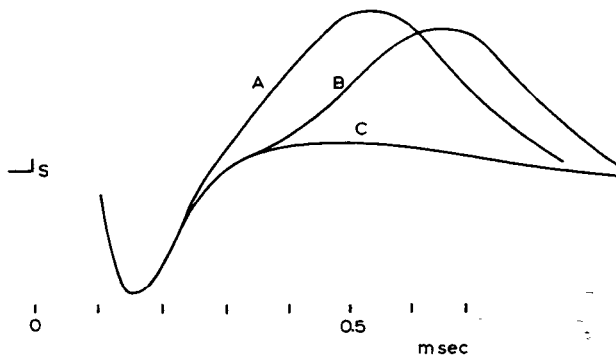


Fig. 2. Superimposed tracings of serial records obtained from the stimulated locus (stimulus just threshold) to show fluctuations in response latency. Time in 0.1 msec.

In an attempt to gain information relative to the basis of the variations in excitability, determinations were made of the effect on the range of the variations of exposing the fibers to some of the conditions that are known to influence their reactivity. Anode polarization and cathode polarization, which respectively decrease and increase excitability, and quite markedly,

presumably by varying the stability of the surface membrane, were found to be without any consistent directional effect on the variations - sometimes increasing them, sometimes decreasing them, but usually within the limit of the experimental error. Sodium citrate, which is known to increase excitability, may actually cause fibers to discharge spontaneously, presumably through the de-ionization of calcium, which increases, though not markedly, the range of the excitability fluctuations. Decreasing calcium action would result in an increase in the activity of potassium, and potassium acts in many respects like cathode polarization. For example, it, like cathode polarization, diminishes the height of the axon spike and eventually blocks the nerve impulse. Since cathode polarization may increase or decrease the range of the excitability variations whereas sodium citrate increases it, though slightly, the possibility suggests itself that this phase of the action of the citrate is referable to some process that is not mediated by the membrane. Cold, we among others have shown, lowers excitability, but it has definitely increased the range of the excitability variations, commonly by as much as 50%. Cold, in our experience, increases the height of the axon spike. It probably modifies all of the processes concerned with nerve action.

But of all of the agents tested in this connection, strychnine has had the greatest effect. In a concentration of 1:100,000 it may quadruple the range of the excitability fluctuations. It does this despite the fact that it raises somewhat the threshold of the fiber to electrical stimulation. In concentrations that produce these effects it does not alter the action potential appreciably. It may be inferred from all of these tests that the surface membrane is not the seat of the excitability oscillations, but, further than this, the experiments have failed to throw any light on the nature of the mechanism producing them.

It may be of interest to note here that the characteristic action of strychnine on central nervous mechanisms is the initiation of "spontaneous" repetitive discharges. Thus Bremer has shown that strychnine convulsions are characterized by a regular succession, in all parts of the anterior gray substance of the spinal cord, of action potentials at a frequency of 10 to 30 per second. And Dusser de Barenne and McCulloch find that the local application of a strychnine solution to the cerebral cortex results in a typical change in its electrical activity, the usual brain waves being replaced by large rapid voltage fluctuations. It seems not unlikely that this central action of strychnine, leading to a discharge of impulses, is related in some way to the enhancement of the spontaneous variations of excitability that results from the

treatment of nerve fibers with strychnine. It may also be of interest to note in this connection that cold, which, like strychnine, increases the range of the excitability variations of nerve fibers, also increases reflex responses of the spinal cord.

Some manifestations of segmentation in myelinated axons - All nerve fibers of vertebrates, excepting certain of the very slender ones, are surrounded by a sheath of myelin that gives to them the appearance of electrically insulated conductors. The myelin of the peripheral fibers is segmented; in the case of the larger fibers, such as we have dealt with, the segments range, probably rather widely, about a length of 1.25 mm. The nodes between the segments are generally believed to be free or relatively free, of myelin and they have a width that is about equal to the diameter of the fiber, probably about 15μ in the case of the larger fibers.

Evidence indicating that applied crystalloids in solution act upon the nerve fiber primarily via the nodes of Ranvier has been gained through observations of responses of single nerve fibers. The solutions were so applied to the nerve that they acted over a length that did not exceed 1 mm. By moving the applicator, filled with a salt-free isotonic solution of glucose, along the

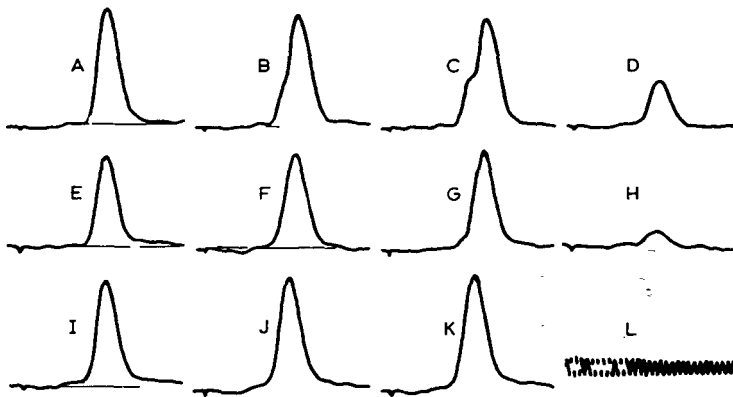


Fig. 3. Stages in the blocking of transmission in a fiber induced by a 1 mm application of glucose solution successively at two adjacent loci of highest susceptibility, one located 1.2 to 1.5 mm central to the lead, at 0,2,3, and 4 seconds after contact (records A, B, C, and D); the other, 3.0 mm central to the lead, 0,3,5 and 7 seconds after contact (records E, F, G, and H). I, J, K, made 0, 10 and 16 minutes after contact, respectively, show that application at an intermediate position does not block within that time. (L, the time, 10,000 cycles, applies to all records.)

nerve in close proximity to the point from which the record is taken, a locus can be found from which, within a few seconds of application, a succession of pictures can be obtained such as are shown in the topmost row of spikes of Fig. 3. Here A is a typical monophasic axon spike before the application of the glucose solution to the locus thus found. The time is indicated in 10,000 cycles per second. During the period of only 4 seconds of application, the picture changed through B and C to D. Then the original picture, that of A, was restored by washing the treated locus with Ringer's solution, and then, with the applicator refilled with the glucose solution, search was made for the locus next removed centralwards from the recording electrode at which a similarly quick transformation of the picture developed. This series of changes, which transpired in 7 seconds, gave the middle row of records. The two loci of quick action thus found were situated about 1.2 and 3.0 mm centralwards of the lead. Then recovery was again effected by washing with Ringer's solution, and the applicator, filled again with glucose solution, was

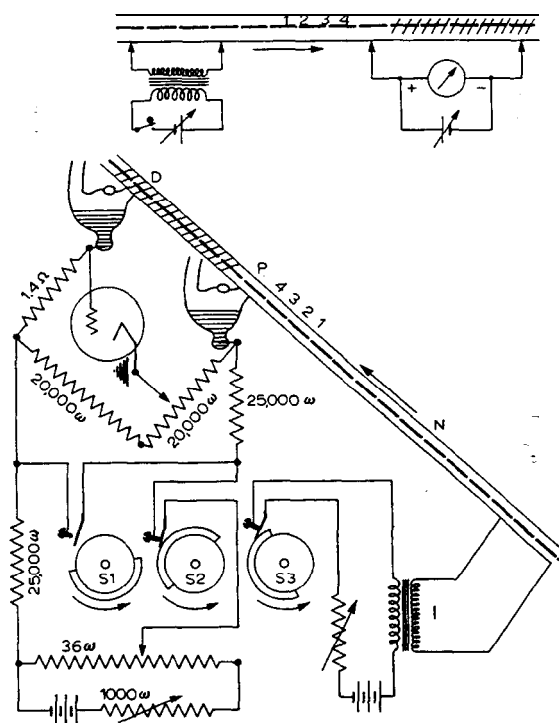


Fig. 4. Diagrams of apparatus. (Upper one: simplified.) N is the nerve, one myelinated axon of which is indicated by the broken line. The records obtained (see Fig. 5) indicate that the part shaded was killed.

placed midway between the two loci from which the upper and middle rows of records had been obtained. Spikes I, J and K of the third row were then recorded with intervening lapses of 0, 10 and 16 *minutes* (not seconds), respectively. Thus there are located points at which the salt-free solution rapidly blocks the propagation of the nerve impulses; the spacing of these loci suggests the inference that they are successive nodes of Ranvier.

Action of applied currents - Similar pictures are obtained when electric currents are passed through the fibers, indicating that currents, likewise, act upon the axis cylinder of medullated nerve fibers primarily via nodes of Ranvier. The upper diagram of Fig. 4 shows a simplified network for the conduct of a typical experiment. The segmented line represents the one nerve fiber in the phalangeal preparation whose action potential reaches the recording leads under the conditions of the experiment. The nerve rests upon two pairs of electrodes; the pair to the left supplies the shock that initiates the nerve impulse, which then travels along the fiber in the direction of the arrow; the pair to the right leads the polarizing current into the nerve, and also the potential difference determined by the travelling nerve impulse into the recording mechanism, the cathode-ray oscillograph, through the amplifier. The lower diagram presents the actual arrangement.

Anode polarization - When the proximal recording electrode is also the anode of the polarizing current, as was the case in this experiment, and the current strength is gradually increased, the propagated axon-action potential as it approaches the lead passes through a series of changes in configuration, the critical stages of which are seen in the retraced records of Fig. 5. These, like those of Fig. 3, are monophasic records; the nerve on the distal lead has been killed in order to stop the nerve impulse there. As the strength of the polarizing current is increased, the normal action potential, A, increases in height and also in duration; it grows to the height seen in B. (The time is in milliseconds.) As it grows, a notch appears on the ascending limb; it deepens, until at a critical polarization strength, the part of the action potential above the notch abruptly disappears leaving a considerably lower action potential, shown as the underlying curve of B. With continuing increase in current strength this process repeats itself, as in C, and again as in D. Each of these pictures, A, B, C, and D, was obtained with conditions momentarily constant, including the strength of the polarizing current. The two action potentials, upper and lower, in B, C, and D, each resulted because

of spontaneous variations in the excitability of the fiber at a time when the polarization strengths were at the critical stages. That the first of these deflections, the one pictured in B, results from the blocking of the nerve impulse is proved by pictures that are obtained from preparations in which the nerve impulse is permitted to travel to the distal lead. The normal action potential then records diphasically; it becomes monophasic with the first of the sudden deflections (like that in B) and remains so with further increase in polarization. The upper diagram of Fig. 4 supplies a clue to what may be taking place in this experiment. The diagram is constructed on the assumption that the cross-hatched portion of the fiber is coextensive with the part that was killed in order to obtain monophasic recording, and that, under the condi-

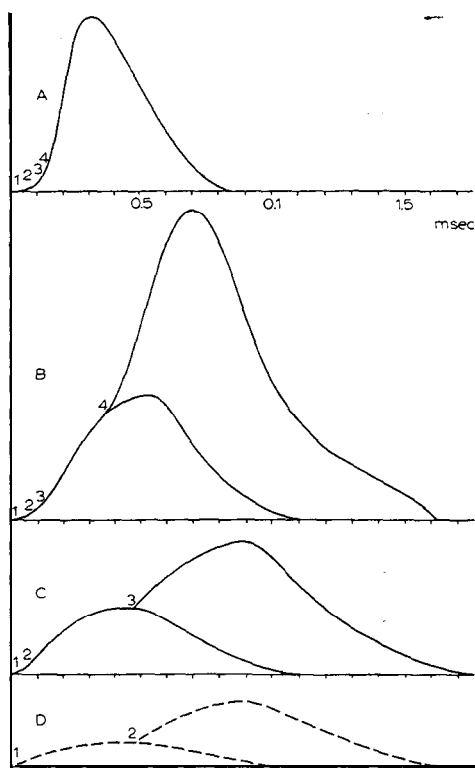


Fig. 5. Deflections obtained from the nerve diagrammed in Fig. 4.

A, B, and C, traced from records; D, seen but not recorded. A, normal axon potential in unpolarized nerve. B, C, and D, three critical stages of increasing anode polarization.

The lower curve in each case is what remains of the action potential after deflection of the part above the notches, 4, 3, and 2, in B, C and D, respectively. Time in msec.

tions of the experiment, the potential, extending electrotonically ahead of the active locus, records perceptibly through a distance about equal to that subtended by three internodes - a distance of perhaps 4 mm. It is assumed in other words that when, under normal conditions, internode 1 becomes active there would result a scarcely perceptible difference in potential between the two leads into the oscillograph - that it records as the lower deflection in D of Fig. 5, that this difference in potential increases logarithmically with the decrease in the distance from the proximal lead as the successive internodes 2, 3 and 4 become active. In the same sense it is assumed (these assumptions were made in 1934) that the effect of anode polarization on spike height falls off logarithmically along the fiber from the position of the anode. With zero polarization, i.e. under normal conditions, the recorded potential differences contributed by the numbered segments might have the magnitudes that are indicated roughly by the corresponding numbers on

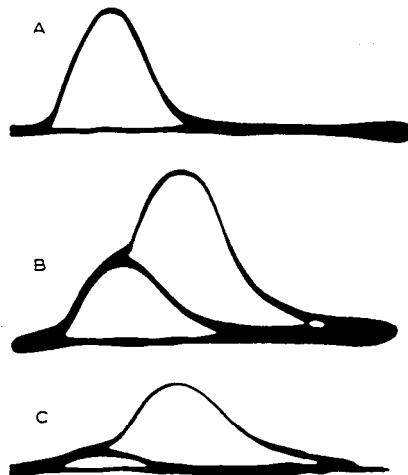


Fig. 6. Typical changes in the configuration of a monophasic axon spike produced by anode polarization at the proximal recording lead.

(A) The normal spike.

(B) The spike under anode polarization just strong enough to block at the most accessible node. Spontaneous variations in the fiber's excitability cause the block to fluctuate between one that is just not complete (the notched spike) and one that is just complete (the unnotched lower spike).

(C) Further increase in the polarizing current to the next critical strength converts the unnotched spike of B into the notched spike of C, and when the latter blocks again, it records as the unnotched, lower spike of C. The *time* is linear and may be estimated from the time to maximum of A, which is 0.37 msec.

record A of Fig. 5, segment 1 contributing practically nothing to the height of the normal spike, 2 a trace, 3 a bit more, and segment 4 all of the rest. At the degree of anode polarization obtaining when block is apt to appear at the node between segments 3 and 4, all of the contributions will have increased in height, but mainly those from 3 and, particularly, from 4. With the blocking out of the contribution from 4, all above 4 in record B would drop out leaving the action potential beneath 4. Next, the contribution from segment 3 would be the one mainly affected; its contribution would grow in height and then disappear, and so on. The process probably continues as the anode polarization is further increased but the spike at this stage becomes imperceptibly low. In Fig. 6 are reproduced actual records made at the critical stages in another similar preparation, again, with monophasic recording.

The fact that under the conditions of these experiments it is regularly possible to record three successive blocks as the strength of the polarizing current is increased, and the fact that three internodes subtend the length of nerve through which an electrotonic extension of the potential of a spike would produce a visible deflection, exclude any fortuitous factors, such as cut branches or lack of linearity of the fiber, as the basis of the successive anode blocks. These experiments, then, indicate that applied currents gain access to the reactive part of the nerve fiber primarily via nodes of Ranvier, just as has been shown in the previous section to be the case with applied solutions. Our result, it should be added, is consistent with the observation of Kubo and Ono that the threshold to electrical stimulation of a fiber is lowest at nodes of Ranvier.

Cathode polarization - It has long been known that cathode polarization reduces the height of the compound action potential and finally blocks transmission. Fig. 7 shows the transformation of the conducted spike of a single fiber action potential as cathode polarization is increased*. In addition to the gradual reduction in the height of the negative, the upward directed, phase of the action potential it can be seen (in record C) that a notch appears, first at, or slightly beyond, the peak of the spike. This notch and the peak following it (they correspond with the part above 4 in B of Fig. 5) may then move slightly downward along the descending limb of the spike and at a critical applied voltage they abruptly disappear (in record D) and the impulse ceases to be conducted beyond the proximal lead (and cathode), as evidenced by the conversion of the diphasic into a monophasic record.

* These records were made recently (1947); similar records were published in 1934.

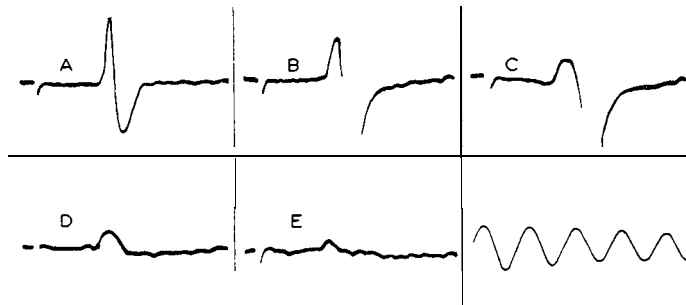


Fig. 7. Action of cathode polarization on the conducted diphasic spike of a fiber. The records are from the polarized locus.

(A) normal; (B-E) polarization increasing, block occurring in D. Time approximately in msec.

With further increase in current strength the height of this blocked spike continues to decrease (record E). If, with continuing increase in polarization strength, this blocking process repeats itself at the node next removed from the polarizing (and recording) electrode, this cannot be ascertained, owing to the approximation of the spike height to the noise level of the amplifier.

It has been assumed up to this point that the *steplike* changes in the height of the spike that are observed during local polarization of a fiber are the result of blocks developing at successive nodes of Ranvier. There is, however, another hypothesis that seems to fit the facts. It may be that progression of the impulse along fibers that are covered with segmented myelin is saltatory in character (to use a term introduced by Lillie) that the fiber segments, acting as units, respond in succession to stimulation by eddy currents issuing from the adjacent active segment. All of our observations seem to fit into this hypothesis also, as do also the more recent observation of Tasaki and of Pfaffmann.

Experiments bearing on the mechanism of transmission of the nerve impulse - In 1872 Hermann expressed the view that at each locus of a nerve fiber the action potential of the excitation wave acts in turn as the stimulus to the adjacent locus, so that the propagation of excitation can be regarded as of the nature of an electrical restimulation. This view is now known as the local circuit theory of impulse propagation. An alternative theory, proposed by Bernstein attributing conduction to some propagated chemical reaction has never, however, been completely abandoned. Recently a combination of the

two views has been suggested according to which stimulation releases a substance, acetylcholine, which then, by breaking down the membrane resistance, permits a local current to flow which in turn releases acetylcholine at adjacent loci. The consensus of opinion, however, seems to be that this view is based on premises that are in need of substantiation.

Some of our observations on single fibers have shed light on the role played by the action potential in the propagation of the nerve impulse. Take, for example, the experiment from which Fig. 8 was derived*. The figure

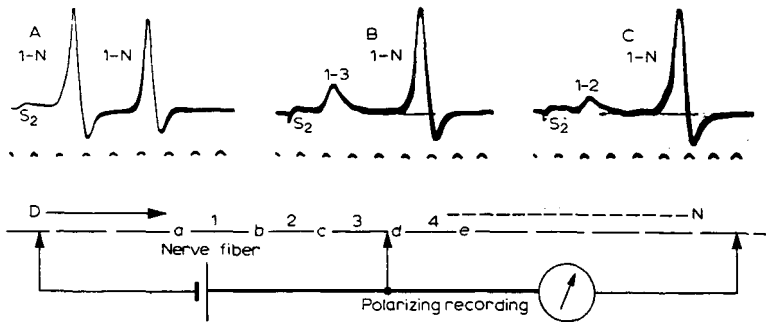


Fig. 8. Diagram showing the probable relation of the polarizing and recording electrodes to the nodes of a single fiber that is conducting impulses in the direction of the arrow. For each of the records, A, B and C, the nerve is stimulated twice, the interval in each case being 3 msec.

(A) normal response; (B) the first impulse, 1-3, is blocked, probably at node d, by anode polarization, but the 2nd impulse, 1-N, is not; (C) the first impulse, 1-2, is blocked now at node c as well as d by stronger polarization, but again the 2nd impulse, 1-N, is not. The time is in msec.

shows diagrammatically the spikes of the reacting nerve fiber and the relative positions of the electrodes (the vertical arrows), the middle one serving as the anode of the polarizing circuit and as the proximal lead into the recording mechanism. The nerve impulses were made to travel from the left in the direction of the arrow, D. On the basis of what has gone before it may be assumed that the normal impulse (1-N) is made up of potentials contributed by segments 1 to N +; that segment 4 contributes the largest part and segments 3, 2 and 1 parts that are smaller in the order mentioned. The seg-

* This figure is from a later paper but is identical in import with a figure published in 1936.

ments between 4 and N and beyond N also make their contributions in rotation, those close to N determining the downward directed portion of the diphasic action potential.

Record A shows two impulses arriving at the lead in quick succession, the interval between them being about 3 msec. (The time is indicated in msec.) Both of these spikes are diphasic, signifying that both impulses are travelling past the two recording leads. The second of these two spikes is slightly lower than the first because it is travelling in the latter part of the relatively refractory period of the first. Record B shows the result of the first critical stage of anode polarization at the proximal lead. The first spike of the pair is reduced in height and is monophasic. This, as has been explained, is the result of block at the anode. Here the block presumably is at a node occupying the relative position of *d*, since at *d* the polarizing current lines would be densest. This assumption implies that segments 1 to 3, inclusive alone enter into the make-up of this spike. The second spike, however, records diphasically and is as high as the first spike in A: the second spike obviously is not blocked, and this despite the continuance of the blocking current. In explanation of this lifting of the block it may be assumed that the local current, the electrotonic current, determined by the first action potential flows across the block through the fiber beyond - that is, from *prefiber* to *postfiber* - and acts as a subthreshold stimulus to the segment (segment 4) beyond the block; that then, while the excitability thus increased there has not yet subsided, the current eddying ahead of the second of the two impulses can, through temporal summation, attain the threshold of the postfiber and so initiates in segment 4 an action potential which then travels on through the preparation. The result pictured in C was obtained after a further increase in the strength of the polarizing current. The first spike, 1-2, of the pair of action potentials here has undergone another of the steplike reductions in amplitude indicating that the first impulse of the pair now is blocked at the next node anteriorly, namely, *c*. Nevertheless, the second spike again regains the characteristics of the first spike of A. Here, presumably, we are dealing with the temporal summation of two subthreshold stimuli: the current eddying ahead of the blocked, the first, action potential is raising to such a level the excitability of the fiber a distance of two internodes ahead of the block, that a second similar spread of current from an action potential arriving at the block 3 msec later can attain the threshold of the fiber beyond the block and so initiates an impulse there. By correlating many observations on single fibers in different preparations subjected to varying degrees of polarization in-

formation has been obtained indicating that the summing effects of the two action potentials across the block attain a maximum when the interval between them is 2 to 4 msec, and that the summing effects then decline slowly through 80 to 100 msec.

That the threshold of the segments beyond the block is lowered by the blocked impulse was demonstrated directly through the employment of a rather complicated procedure that need not be described in detail here. Suffice it to say that for these experiments the responses of several fibers, not of a single fiber, were employed as a measure of the excitation. The blocking current was set at a strength that blocked all save 3 of the fibers. The degree of excitation at the blocked region was then determined by applying testing shocks at various time intervals after the arrival there of impulses conducted into the blocked region from afar. The intervals between the two shocks were gradually *reduced* and it was found that when they became about 20 msec the number of the fibers responding to the testing shocks began to increase, and the increase continued as the interval between the stimuli was further reduced. It will be noted that the duration of the increased excitability as determined by the present method, namely, 20 msec, is considerably shorter than the duration of the temporal summation as determined by the single fiber method, namely, 80 to 100 msec. The single fiber method, however, is regarded as the more reliable one. A further difference in the results given by the two methods is that with the multifibered preparation maximum excitability was attained at the minimum separation of the two stimulations, whereas with the single fiber method maximum excitation was attained, as has been said, when the interval between the arrival of the two impulses was 2 to 4 msec. With the former method, however, it was necessary to make a correction based on the assumed conduction time, and it is quite possible that the values chosen were in error in such a direction as to account for this discrepancy. It should be mentioned here that Wedensky in 1903 observed that a succession of impulses impinging on a local complete block may lower the threshold to artificial stimulation of the nerve beyond the block; he did not, however, describe reactivation.

It was possible on the basis of two items of information made available in 1934, to form a rough estimate of the rate of decline of the potential with the distance beyond the block. (1) Data on record indicated that the average segment length of the fibers with which we were dealing is of the order of 1.25 mm. (2) In our experiments the action potential on the average fell to approximately one-half its height with each of the successive blockings. In

other words, the potential determined by the blocked spike fell to half value with each 1.25 mm of distance.

If the changes in excitability inaugurated in a fiber beyond a blocked nerve impulse are determined by currents eddying ahead of the block, one would expect the sequence of the excitability changes there to be the same as those initiated by any subthreshold current of comparable duration. The excitability changes inaugurated by subthreshold currents of brief duration have frequently been investigated. They were studied by us in 1931 in multifibered preparations. The stimulating shocks for the most part were very brief in duration, perhaps not longer than 0.1 msec. The usual result obtained from the sciatic of the frog by methods employed at that time is seen in Fig. 9. The first effect of the subthreshold shock was to raise the excitability above the normal, the 100%, level for a brief period - the so-called summation interval. The excitability then fell below the 100% level into what has been termed the period of post-cathodal depression, and finally returned to normal during the course of 2 to 4 msec. With increasing strength of stimulation this post-cathodal depression approached the curve of relative refractoriness as a limit (squares). However, the magnitude of the post-cathodal depression was found to vary greatly from nerve to nerve under conditions that seemed

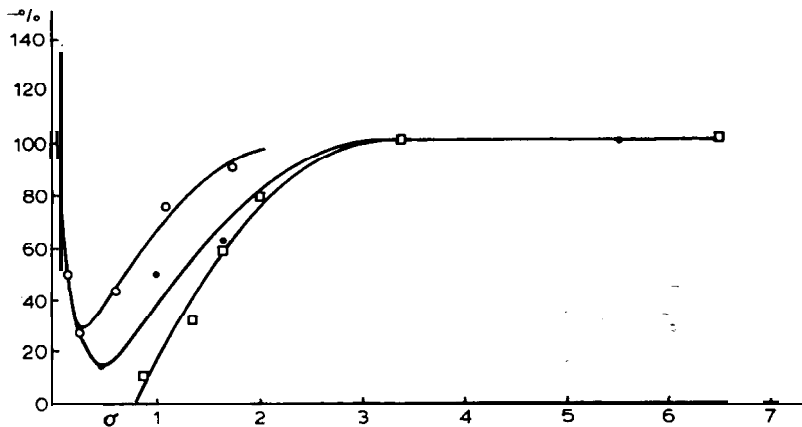


Fig. 9. Excitability of sciatic nerve as altered by brief induction shocks.

Ordinate - strength of testing shocks in % of normal (= 100).

Abcissa - intervals between sensitizing and testing shocks in msec.

(Circles): sensitizing shock subthreshold and relatively weak.

(Dots): sensitizing shock subthreshold and relatively strong.

(Squares): curve of relative refractoriness.

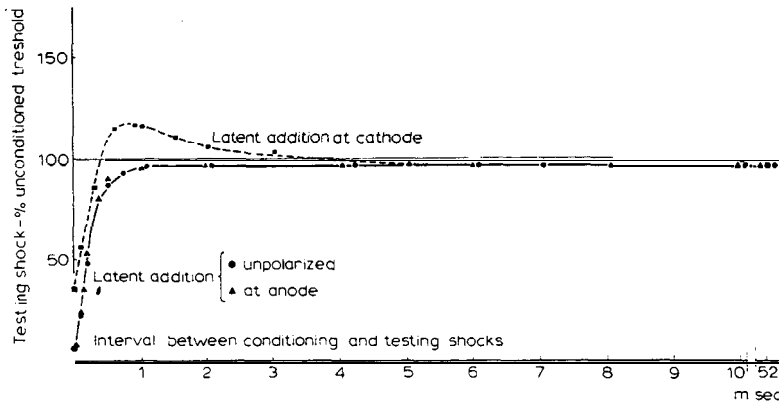


Fig.10. Sequence of threshold changes in a single fiber subsequent to the delivery of a subthreshold conditioning shock.

Ordinate - strength of testing shock in % of threshold.

Abscissa - interval between conditioning and testing shocks.

(*Dotted curve*): stimulated locus cathodally polarized.

(*Continuous curve*): nerve unpolarized (*circles*), and anodally polarized (*triangles*). (Blair).

to be quite comparable. "Occasionally", so we then wrote, "it is so poorly developed that it can be scarcely detected."

On the basis of these earlier results one would hardly expect any temporal summation that is induced by action potentials across a block to last much longer than 1 to 2 msec. It has just been stated, however, that summation resulting from blocked spikes may be demonstrable through a period lasting as long as 100 msec. This discrepancy led Blair to reinvestigate the subject of temporal summation. This time he used the single fiber technique, which provides a far more sensitive test of excitability than does the multifiber technique previously employed. This is so because with the former method the responses are all-or-nothing, whereas with the latter method they are graded. The sequence of the changes in threshold following the delivery of a subthreshold conditioning shock as ascertained by the single fiber technique is seen in Fig. 10. The two curves present the changes in threshold under three different experimental conditions, namely, with stimulated locus (1) normal circles), or polarized either (2) cathodally (*dotted curve*) or (3) anodally (*triangles*). They show that only the cathodally polarized fiber exhibits a period of post-cathodal depression. This depression period, however, is temporary; after about 4 msec the threshold again falls - the excitability of the fiber again becomes greater than normal - and it remains so through, again,

50 or even 100 msec. Indeed, after the depression period seen in the cathodally polarized fiber the curve of excitability comes to coincide with the curves derived from the normal and from the anodally polarized fiber, which, during recovery, do not pass through a period of post-cathodal depression. The essential observation here, then, is that though the excitability after the lapse of a few msec is only slightly greater than normal, roughly about 4%, it remains so through 50 to 100 msec under all three of the conditions, just as does the excitability of the postfiber which has been raised by an impinging blocked nerve impulse.

In what has gone before, consideration has been given to temporal summation across a block as effected by a single impinging nerve impulse. It should be added that it is possible to produce by anode polarization blocks of such a degree that an action potential is elicited in the postfiber only after the pre-fiber has conducted two or more impulses to the block. Fig. 11 pictures an

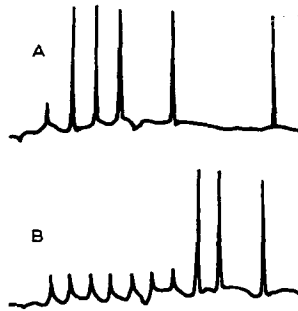


Fig. 11. (A) A degree of anode polarization such that one blocked impulse suffices to overcome the block. (B) Polarization increased; the block now is overcome by the eighth impulse. Time intervals, 5 msec.

instance, obtained in 1936, in which the temporal summation of seven nerve impulses was required to initiate an impulse in the postfiber. It may be mentioned again that this result goes beyond the facilitation described by Wedensky in that here there is actually *restimulation* beyond the block.

Presumably the type of temporal summation that obtains in the fiber beyond a block is essentially identical with the phenomenon known as recruitment. This phenomenon was being studied by Gasser while we, independently, were occupied with the investigation of the present subject. Gasser found that a succession of initially subthreshold electrical stimuli applied to a nerve trunk could eventually attain the thresholds of constantly increasing

numbers of the constituent fibers through as many as several hundred stimulations delivered at an adequate rate. He, too, noted that the phenomenon was elicitable even when the stimulation intervals were longer than the then known summation interval, and he likewise reinvestigated the summation produced by subthreshold shocks. He found that "the recruitment depends upon the fact that the excitability curve following a subthreshold shock is continued after the initial period of latent addition and the subsequent period of postcathodal depression by a second summation period..." The curve obtained by Gasser agrees in configuration with the one derived by Blair from a fiber when cathodally polarized (see Fig. 10).

At the time we were studying temporal summation of impulses blocked by anode polarization Hodgkin began independently the investigation of the same subject. His method, however, differed from ours in two respects: (1) he used cold and pressure as the blocking agents instead of anode polarization, and (2) the summation of impulses beyond the block was measured exclusively by direct electrical stimulation there, whereas such electrical stimulation was employed by us merely for the purpose of confirming the inference that the excitability beyond the block actually is increased by the blocked impulse.

The results of both of these researches, where they dealt with related topics are essentially alike. (1) Thus the general configuration of the curves of the changes in excitability induced beyond the block are qualitatively alike; there are, however, some quantitative differences in that in our experiments excitability attains its maximum more rapidly and is more protracted, in these respects conforming more nearly with the excitability changes that are consequent to a brief electrical stimulus as plotted by Blair and by Gasser. (2) Another quantitative difference concerns the gradient of the drop of potential of the blocked impulse extending beyond the block. Hodgkin obtained his data by direct measurement - and we, as has been stated, (*a*) mainly through measurement of the heights of the potentials contributed to the records by the 2 or 3 segments anterior to the block, upon the assumption that the segments averaged 1.25 mm in length, but (*b*) to some extent also by actual measurement of the excitability. From our data Hodgkin has calculated that 1.8 is the space constant of the gradient of the decline in potential and adds that this is close to his "average value for the potential spread near a block". (3) As a third quantitative difference, Hodgkin found in his experiments that a blocked impulse lowered the threshold by as much as 50 to 90%. In our experiments the postfiber almost invariably was actually reexcited by

the second impulse to arrive at the block. These differences probably are referable to differences in the width of the blocks in the two sets of experiments. Thus the cold applicators used by Hodgkin were 3.5 mm in diameter and, where he employed pressure, it was applied to lengths of 2 to 3 mm, whereas in our experiments the blocks probably rarely exceeded the length of a segment or two, that is, 1.25 to 2.5 mm. However, Hodgkin observed, to quote, "that in fresh nerves block does not occur until ice has formed over the whole of the cooled section and that it often has to spread for $\frac{1}{2}$ mm beyond". "It is reasonable to suppose", he goes on to say, "that the whole of the frozen region is inexcitable..." This would signify that the action potential can stimulate across a nonresponding stretch measuring somewhat less than 4.5 mm in length.

And, finally, Hodgkin states as "the main conclusion... that it is possible for nervous impulses to be transmitted by the electrotonic currents produced in activity". "The experiments", he goes on to say, "do not prove that this is the only process involved in propagation, but the assumption of an additional mechanism would be unnecessary if all of the properties of the nervous impulse could be explained in terms of an electrotonic theory". His "general conclusion is that it is possible for nervous impulses to be transmitted by electronic currents". And we say, "Our observations, therefore, signify that propagation in nerve is accomplished by a mechanism that is in part, at least, electrical. It does not seem possible to attribute the summation to a mechanism involving the liberation of neurohumors."

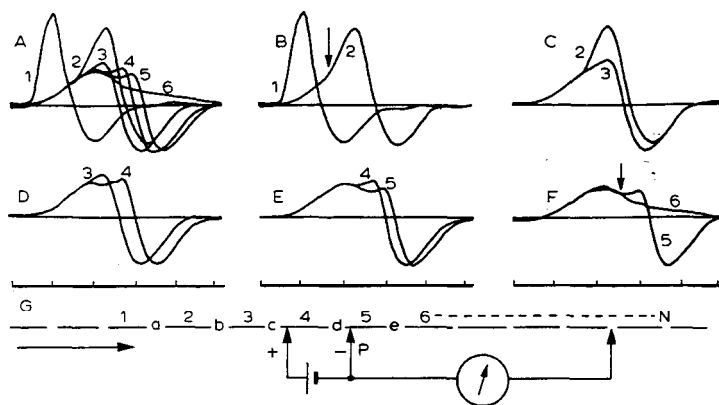


Fig. 12. Records indicating that the impulse has succeeded in traversing the nerve fiber despite the failure of at least one internodal segment to respond. The time is in msec. Further details in text.

Further evidence has been obtained indicating that the nerve impulse can jump across a nonresponding internodal segment, possibly two of them, employing for this purpose a procedure involving simultaneous anode and cathode polarization. In this case the relation of the polarizing electrodes to the leads was as shown in Fig. 12. The anode and cathode, separated by a millimeter or two, were moved along the nerve until they presumably came to occupy some such relation to two adjacent nodes of a fiber as is indicated in diagram G. A strength of polarizing current can then be found at which successive conducted spikes of the axon alter their configurations without any apparent rule; yet, from the many configurations can be selected a series which permits one to infer the nature of process probably transpiring. Six spikes from such a series, all with starts superimposed, are collected in A of Fig. 12; and in B to F pairs from the series are superimposed which, we believe, show the successive stages of the phenomenon. The records of B are characteristic of developing anode block at a node. Among the multitude of other records not included in the figure every transition between the configurations of 1 and 2 can be found. But between 2 and 3 in C there are no intermediate stages, and it is necessary to conclude that at the time 3 was recording there was complete anode block, presumably at node c and that the spike remains diphasic because the fiber has been restimulated beyond the block. The remaining pictures are characteristic of developing cathode block (cf. Fig. 7), which becomes complete in F, as witnessed by the change to monophasicity there (5 to 6). Presumably the cathode block develops at node d, the node most accessible to the cathode current. In other words, the action potential, though blocked at node c by the anode current, nevertheless restimulates the fiber at node d and so the impulse continues on its way until the cathode current blocks it at d. Here, clearly, conduction is maintained the length of the fiber although a segment has failed to respond. In the premises the nerve impulse here could not have been propagated chemically.

In concluding this topic reference should be made to some experiments reported by Br. Werigo in 1899. In those experiments different lengths of the nerve of a nerve-muscle preparation were treated with chloroform or alcohol vapor. When the treated length became less than 5 mm the time required for block to develop began to increase very rapidly. Werigo, consequently, concluded that the nerve impulse is capable of jumping a non-responding stretch that does not exceed 5 mm in length and that such jumping could be effected by electric currents, only. Werigo's interpretation of his data seems never to have been accepted, or else it has been overlooked; it

is abundantly substantiated by the results described above - ours, and those of Hodgkin - and, in addition, by those of Tasaki.

From among results that have been derived through experiments on single nerve fibers brief reference may be made to just a few additional sets of observations. Fig. 13 shows the relation that obtains between the conduction

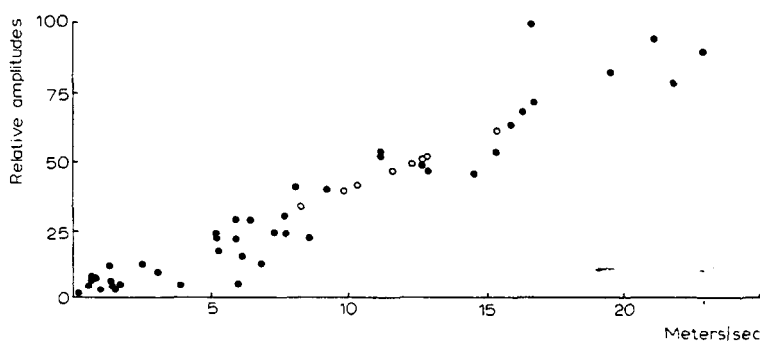


Fig. 13. Relation of amplitude of axon spikes to conduction velocity. The points fall about a straight line.

velocity in a fiber and the height of its action potential. Obviously the velocity is directly proportional to the height of the spike. There is in this relation indirect evidence in support of the local circuit hypothesis of impulse propagation.

When a fiber is made to respond rhythmically, as it occasionally will under the influence of a superrheobasic constant current, the regular series of responses not infrequently is interrupted by gaps. The durations of these pauses are even multiples of the unit intervals, as if the fiber were the seat of a continuous series of rhythmical variations in excitability, some of which failed to attain the fiber's threshold. Moreover, a series of subthreshold decrementing oscillations of excitability has been seen to follow the recovery of a fiber from stimulation by the make of a constant current.

The frequency of these oscillations, namely, 200 per second, is the same as that of the rhythmical discharges observed during the passage of a constant current.

By means of records of action potentials of single fibers it has been possible to show that the chronaxies of fibers do not vary inversely as their diameters, or, if you will, as the speeds with which they conduct, as had previously been believed. Instead; there seems to be no simple rule in this respect. In general,

though, the chronaxies diminish slightly through the range of fibers that conduct, under the conditions of our experiments, at rates ranging between 26 and about 8 to 10 m.p.s. The chronaxies then increase quite rapidly in the fibers that conduct still more slowly.

Absolutely refractory period - It has been held that the durations of the absolutely refractory period and of the spike of the action potential are alike. In the frog the refractory period increases as the conduction velocity in the different fibers decreases, and observation indicates that the spike duration increases also. This has been confirmed by Tasaki. However, when the duration of the spike is increased by cooling the nerve the refractory period increases in duration faster than that of the spike, indicating that there is no necessary relation between these two values. Of the same significance is the finding by Gasser and Grundfest that whereas in mammals the spike durations of A fibers are all alike, the absolutely refractory periods are longer in the more slowly conducting of the fibers.

In this review I have outlined briefly some of the results that have been obtained through the study of the responses of single nerve fibres. The work is being continued because it is felt, as has been said so frequently by others, that in the investigation of this comparatively simple structure, the nerve fiber, lies the hope of finding clues to an understanding of the much more complicated mechanisms that determine the activities of peripheral and central nervous mechanisms.