A COMPARISON OF THE CHARACTERISTICS OF AXONS THROUGH THEIR INDIVIDUAL ELECTRICAL RESPONSES.1, 2

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Received for publication August 5, 1933

Studies with the cathode ray oscillograph have shown that the fibers composing a peripheral nerve range widely in their reactivities. For instance, a large nerve, such as the sciatic, contains fibers conducting at rates varying as widely as 50 to 1 with an even wider irritability range as determined by induction shocks. But neither in this nor in other nerves is there an even numerical distribution of fibers with respect to these properties. The uneven numerical distribution of fibers with respect to conduction rate is manifested in the consistent elevations which appear on the maximal, conducted action potentials of large nerves.

Attempts have been made to trace to their sources the fibers contributing their potentials to the several elevations and to ascertain the functions the component fibers subserve (Erlanger, Bishop and Gasser, 1926; Erlanger, 1927; Erlanger and Gasser, 1930; Bishop and Heinbecker, 1930). Bishop and Heinbecker recognize four types of fibers, namely A, B1, B2 and C, present in varying combinations according to nerve and species. "The ordinary mixed somatic nerve," they say in one of their latest publications (Heinbecker, Bishop and O’Leary, 1932), "gives rise to all four. The fibers responsible for the A component," they go on to say, "are the large thickly myelinated ones known to include, primarily, somatic motor and sensory elements. The B1 component includes primarily the somewhat smaller and frequently somewhat more thinly myelinated fibers known to be visceral afferents. These two potential components have characteristic physiological properties which permit their differentiation from the B2 and C components possessing properties of a much slower order. The fibers responsible for the B2 potential are the smallest thinly myelinated ones found in the nerve. Unmyelinated fibers give rise to the

1 The experimental data in this paper are taken in part from a dissertation presented by Edgar A. Blair in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Washington University, submitted 1933.

2 This work was made possible in part by assistance from a grant made by the Rockefeller Foundation to Washington University for research in science.
C potential." These four types, they say (Bishop, Heinbecker, and O’Leary, 1932), “can be differentiated by their action potentials.”

Measurements of the reactivities of the component fibers of a nerve have been based upon the superimposed responses of great numbers of fibers contributing to each of the several distinguishable features of the composite potential. Such a method is very apt to overemphasize the properties of the fibers contributing to the features used as guides and consequently to miss any transitional reactivities there may be between them. In order to obviate this danger we have sought to determine the reactivity range by methods that would search out individual fibers of a nerve. The results of this method of investigation have been to show that all of the reactivities of fibers, not conductivity only, but also irritability, however measured (excepting by chronaxies), absolute refractoriness, and time to maximum and amplitude of their action potentials are in continuous range from the most to the least reactive of the fibers, and so also are the summation intervals, excepting in fibers conducting more slowly than 2 m.p.s.

**General Methods.** A recording mechanism for the study of the action potentials of single fibers must a, be able to reproduce with no significant distortion input potentials with an effective frequency of 5000 per second; must b, be sufficiently sensitive to permit the reading of these potentials to 5μv, and c, yield, by a simple technique, records of single events which may be read significantly to 0.01s. The cathode ray oscillograph plant as originally designed (Gasser and Erlanger, 1922) fulfilled the first requirement. The second requirement has been met by the addition of a fifth stage to the original amplifier (see fig. 1) thus increasing the voltage amplification up to 2,200,000. With low input resistance (50,000ω) and maximum amplification, input potentials can be read significantly to 1μv. If speed were sacrificed by inserting parallel capacity, as Rijlant (1932) has done, still higher sensitivity could easily be attained. The third requirement has been met by replacing the Johnson cathode ray oscillograph with that of von Ardenne. With 2000 volts anode potential, the luminosity of the latter is such that photographs can be made of the spot traveling at the required speed. However, the spot can be focussed so sharply that satisfactory contact prints of high speed, single deflections can be made on relatively insensitive (“Process”) film without exercising any particular precautions such as had to be employed previously (Gasser, 1928), and this simpler technique has usually been employed.

The spot is now moved across the X, or time axis, by the logarithmic fall of potential across a condenser, SC, discharging through a variable resistance, SR, the value of the latter determining the rate of the deflection. A brief closure of the series key, S, very rapidly recharges the condenser from a potential source, S, supplied by rectified alternating current. Amplification can be varied through a voltage divider connected with the grid.
Fig. 1. Stimulating, amplifying and Braun tube circuits.

A. Amplifier employing 5 Western Electric 102-D tubes. HP. High potential amplifier plate batteries. First stage heavy duty "B" batteries. Other stages Edison cells. LP. Low potential acid filament batteries. V. Braun tube plates deflecting the spot vertically, recording input potentials (Y axis). H. Braun tube plates deflecting the spot horizontally, recording time (X axis). VF. Vertical electromagnetic field controlling resting position of spot on X axis. HF. Horizontal electrostatic field from voltage divider in parallel with the amplifier output, controlling resting position of spot on Y axis. S. Sweep circuit supplying potential for deflection of spot along X axis. SC. Precision condenser in timing circuit. SR. Precision resistance in timing circuit. Key S. Key initiating the sweep of the spot along X axis. P. A.C. operated power supply for Braun tube. C. Calibrated variable condenser for the condenser-constant current stimulating circuit. CP. Point switch controlling stimulating potential. CD. Voltage doubling switch for determination of chronaxies. Key C1. Series make key initiating stimulus from condenser-constant current circuit. Key C2. Series break key for breaking constant current circuit. Key C3. Condenser discharging key, closing while C1 is open. C1. Selector switch; in up position circuit delivers condenser charges, in down position, constant currents whose durations are determined by the separation of C1 and C3. I. Porter inductorium. IR. Precision resistance controlling primary current. Key I. Break key in primary current. R1R2. Balancing circuits to reduce shock artifacts. N. Nerve. E. Low resistance nonpolarizable calomel stimulating electrodes. L. Lead electrodes.
of the third tube and was determined by calibrations carried out under the conditions of the experiment.

With maximum amplification it is possible to obtain a record of the action potential of a single axon by leading from a nerve as large even as the green frog peroneal, provided it contains an axon of outstanding irritability. The invariable, all-or-none nature of the response characterizes it as an axon potential. For the purposes of this research, however, it was essential to be able to identify in a single preparation the responses of each of a series of axons with reactivities illustrative of the entire range.

In the main, two preparations have been employed for this purpose. Use has been made chiefly of the entire length of the sciatic nerve of the green frog (Rana pipiens) from the spinal column to the tip of the third digit. This we designate the plantaris preparation. It was stimulated near its central end (with cathode proximal to lead) through calomel half-cells of a type differing slightly (see fig. 1) from those of Bishop, and the responses were led from its distal end through silver electrodes into the amplifier. The grid (distal) electrode is a minute spring clip designed to hold the end of the nerve (fig. 1). From frogs of medium size conduction distances up to 135 mm. are obtainable. The end from which the lead is taken measures only 20 to 50 μ in diameter and contains 20 to 100 fibers with diameters ranging from some 12 μ down to that of the smallest unmyelinated fibers. Presumably they are representative of all functional types contained in the sciatic, excepting possibly voluntary motor. The distal end of the nerve between the leads is probably not wholly free of branches, but the small branches produce no significant distortion of the action potential except that the potentials of fibers leaving the nerve here are consistently diphasic and cannot be made monophasic by killing the stretch distal to the point of egress.

Rarely have we been able to obtain more than twenty axon potentials from such a preparation. The discrepancy between the number of axons present and the number responding is attributed to peripheral anastomoses and to damage of some fibers in preparation. But whatever the cause of the discrepancy between the number of fibers present and the number responding to distant stimulation, it was fortunate that the number of active fibers was small for only then is it possible to identify the axon potential of each of the active fibers through irritability, conduction rate and configuration of axon potentials and then only when the latter happen to be sufficiently and advantageously spaced. The longer the preparation the more satisfactory is the spacing. Care was exercised to avoid injuring mechanically, and drying of the slender peripheral end of the nerve during its preparation. However we are not sanguine enough to believe that all of the fibers of a preparation were undamaged.

It is an easy matter to find in frogs skin nerves that contain fewer fibers
even than plantaris. But in the former all of the fibers at the lead respond
to stimulation centrally and, since the distance of conduction is short,
identification and measurement of the responses of the individual axons
are much more difficult than with plantaris. The skin nerves, however,
have the advantage that they lie free in the lymph sacs and, therefore,
can be prepared without any other damage than that involved in cutting
the two ends. They have been used mainly for the purpose of controlling
in a minimally injured nerve the conclusions derived from the intensive
study of plantaris.

Extra precautions must be taken after mounting these very slender
nerves to prevent drying and also to prevent condensation of water on
them. To this end the attenuated parts are mounted vertically in the
moist chamber and drops of Ringer's solution, brought to the temperature
of the nerve by means of a coil within the chamber, are permitted to flow
over it, rapidly while the chamber is open and infrequently during observa-
tions. The nerve chamber is kept at a constant temperature. In many
experiments in order to increase the accuracy of time measurements it
has been held, by means of built-in refrigerating coils, to a temperature
considerably below that of the room.

The keys operated by the metal segment wheels of the rotator consist of
a single, nonconducting, short, stiff spring which carries one contact point.
When properly adjusted with a clearance of about 0.1 mm. between con-
tact points there is no demonstrable time variation in the case of the break;

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Fig. 2. 1. A contact print of 40 successive half maximal a spikes from the un-
branched sciatic, showing the superimposability of the shock escape and of the con-
ducted potential wave. The time is slower than in records 2 to 9 and the amplifica-
tion less.

2–8. Serial contact prints obtained under exactly comparable conditions showing
the variations in the response of the sciatic to a shock, uniform as above, but just
threshold; records mounted so that the time from the shock is the same for all.

9. Deflection without stimulation, showing the noise level.

Fig. 3. Three cleanly separated spikes of axons of slow conduction; from plantaris.
All subsequent records are from this nerve unless otherwise specified. In this and in
subsequent figures numerals in front of waves give conduction rates in m.p.s.; under
the waves, crest times in \( \sigma \); over the waves, amplitudes in \( \mu \nu \); and on the base line,
time in \( \sigma \). Where zero time is not noted in the figure it is at the left edge of the rec-
ords. The slower the propagation the lower the amplitude. The lower record
shows the change resulting from the entrance of a fourth axon spike (diphasic) be-
tween the first and second, as a result of a spontaneous increase in its irritability.

Fig. 4. Three successive responses of an axon stimulated at the lead by three suc-
cessive identical threshold constant currents each lasting through the period of the
response it produces, to show spontaneous variations in utilization period (and
latency ?).
and the variation in the time of closure on the make is not over 0.01σ. Throughout observations, unless otherwise stated, the nerves have been stimulated steadily 58 times a minute.

RESULTS. Momentary variations in axon state. When we first began to use amplification high enough to render visible the responses of single axons (Blair and Erlanger, 1932; Blair and Erlanger, 1933a) we were struck by the kaleidoscopic appearance of threshold responses obtained from large nerves under absolutely constant conditions (see fig. 2). The variability of this picture, which apparently has been seen also by Monnier (1932), we now know is referable to spontaneous and independent variations of the reactivities of the responding axons, and before comparing axons with one another it will be necessary to consider those phases of variability that qualify comparison.

Variations in irritability. When a preparation containing a fiber of outstanding irritability is stimulated with shocks increased in strength by small steps from below the fiber's threshold, there are at first only rare responses. To elicit a spike with every shock it usually is necessary to increase the strength further by about 2 per cent. This increase in strength necessary to stabilize the response is far in excess of uncontrolled variations in shock intensity. Directly observed upon the screen of the Braun tube the shocks with any given setting do not vary perceptibly in height, and a variation of 1 per cent would be appreciable. Neither is there any appreciable variation in the configuration of the shocks. However, a variation of, say, 5 per cent in the duration of a shock lasting 0.03σ would scarcely be demonstrable, yet might alter considerably its stimulation value. That the shock is steady is proved by the fact that in large nerves a submaximal alpha spike, whose height changes demonstrably with a change in primary current of 0.25 per cent, shows no appreciable change with any given setting of the same stimulating circuit (fig. 2, t).

That this shifting irritability of the axon is spontaneous is readily demonstrable. One not infrequently obtains preparations containing two fibers equally irritable but with different conduction rates. When these two fibers are stimulated with threshold shocks all possible response variations are seen,—both fibers may respond to one shock, one only to the next, the other only to a third, or neither may respond. Variation in shock strength could produce no such variations as these; they must be due to spontaneous and independent fluctuations in the irritabilities of the two fibers.

Latency and its variations. The time intervening between successive threshold shocks and the resulting conducted axon spikes, or the shock-spike time, under exactly comparable conditions is not constant. The range of fluctuation in the case of the more irritable fibers may be as great as 0.5σ, but usually is about 0.2 to 0.3σ; in the case of the less irritable fibers
it may be more than $2.4\sigma$ (conduction rate 5.28, 24°C.). The extreme ranges for the different fibers could be determined by statistical methods only and this has not been done systematically. That these fluctuations are independent of variations in shock strength and are, indeed, spontaneous on the part of the fibers, can readily be demonstrated in preparations in which there happen to be two fibers with identical irritabilities and conduction rates but whose spikes are identifiable through differences in amplitude or configuration (see fig. 14). When such a preparation is stimulated with threshold shocks not only will the resulting picture exhibit the play referable to fluctuations in irritability, but, in addition, the shock-spike intervals will vary independently, first one spike appearing earlier, then the other, etc.

The extent of the play in position is not affected by varying the distance of conduction; indeed, it is seen, apparently undiminished in extent, when the axon potential is led directly from the stimulated locus. The play, therefore, develops at the stimulated point. This conclusion is confirmed by the fact that the shock-spike time can be stabilized by increasing the strength of stimulation. As the shock strength increases the play at first diminishes rapidly in extent and shifts forward; eventually it disappears but the shock-spike time continues to diminish indefinitely, though very slowly. Some of the forward shift, particularly when the shock becomes strong, is to be attributed to spread of stimulation, but how much it is impossible to say.

A better conception of what is happening under these circumstances is gained by recording the axon spike at the stimulated point. With the very high amplification necessary, the escape of the shock covers the start of the action potential. The axon potential crest, however, is clear and shock-crest time can be accurately determined. When the induction shocks are at threshold the crest position plays through more than $0.25\sigma$ (29.1°C.). With shock strengths that eliminate the play and, probably the greater part of the forward shift the shock-crest time is $0.45\sigma$. By a method to be described later one can ascertain at the stimulated locus the crest time of the axon potential. In the present instance it measured $0.25\sigma$. There is no assurance that in this experiment the maximum forward shift with increasing strength was attained. Furthermore, though the stimulating cathode and ground lead are one, the point stimulated and the point led from presumably are not the same. The former must be on the anodal side, the latter on the grid side of the electrode, a separation of 1 mm. certainly, possibly 2 mm. Assuming that the conduction rate was 20 m.p.s. 0.05 to 0.1$\sigma$ would, therefore, have to be allowed for conduction time. It thus appears that with shocks considerably above threshold strength the shock-spike time probably is as long as $0.1\sigma$ and exceeds considerably the measurable duration of the shock (in this case 0.03 to 0.04$\sigma$).
Since a utilization period cannot by definition exceed the duration of the applied potential it follows that in this case the response to the strongest shock used was preceded by a latent period of the order of 0.06σ and the response to the weakest shock by a latent period of the order of 0.3σ. The play in shock-spike time in a nerve stimulated at threshold is due almost entirely to variation in latency indicative of a local play in reactivity.

Previous determinations of shock-spike time at the site of stimulation, 0.06σ by Erlanger and Gasser (1924) and 0.06 to 0.1σ by Bishop (1927), led to the conclusion that this period is little if any longer than the "effective duration" of the shock. Comparable values, it has just been seen, are obtained from single axons when the shocks used are as much above threshold as were those probably used to produce submaximal potentials in the earlier work. The direct demonstration of a latency of the response to a shock confirms the indirect demonstration made some years ago (Erlanger and Blair, 1931b).

Variations in utilization period. With constant current stimulation the fluctuations in the reactivity of the axons becomes more striking even than with induction shock stimulation. At the threshold the make-spike time play is much wider than that of the shock-spike time. This is the case not only when conduction is involved but also where the cathode of the constant current and the lead into the oscillograph are one (fig. 4). In an experiment of the latter character in which the shock-spike play at threshold was at least 0.25σ, the maximum recorded make-spike play at threshold was at least 0.5σ. In neither case was the recorded shift the maximum seen on the screen.

The remote possibility that the fluctuation in the shock-spike and make-spike times is due to shifting of the point stimulated along the nerve is rendered untenable by the fact that the fluctuation may be greater than the calculated time for conduction along the distance subtended by anode and cathode. Furthermore, the extent of the play is independent of the interelectrode distance in the range studied (0.2 to 2.0 cm.).

The fact that the shock-spike time in an axon, in observations involving conduction, becomes fairly constant when the shock strength is well above threshold does not definitely eliminate the possibility of spontaneous fluctuations in conduction rate. It does signify, however, that if such fluctuations do occur they are local, and that the conduction time as measured remains constant because such local differences balance.

There are many reasons for believing that this play in the state of the fibers is normal and may be independent of the treatment to which the nerve is subjected. Among others may be mentioned: a. The play is seen in all parts of the plantaris preparation including the thick unbranched portion. Here size of nerve and thickness of sheath rule out the possibility of accidental damage in preparation. b. The easily prepared unbranched,
dorsal skin nerve yields a similarly variable picture; e, and so do refrigerated preparations 24 to 36 hours old in which the demarcation potential must be insignificant.

The base line,—conduction rate. In this paper a number of activities of individual axons, distinguished by their action potentials, are to be compared. Since these activities cannot, in the present stage of our knowledge, be assigned to the anatomical units which they characterize, it becomes necessary to correlate the activities by measuring them in terms of some one activity. Conduction rate is the one that has been selected to serve as the common denominator.

Conduction alone of all of the activities that have been studied is at one and the same time a physiological response to a physiological stimulus (except at the locus of stimulation), occurs in regions removed almost entirely from the influence of abnormal contacts, and is not, so far as is known, affected by anatomical relations outside the axon itself. It is, furthermore, the most constant from moment to moment, and from point to point on the nerve, of the activities we have investigated. This constancy presumably is referable to the fact that, whereas all other activities are measured at a point, conduction time is the sum of the conduction times in the parts of the fiber, and even if conduction rate varied at random from part to part the total time over a considerable stretch might still remain constant from trial to trial.

Of other possible gauges, the relative irritabilities of the fibers of a nerve to some extent must be influenced by local anatomical relations of the responding fibers and, in different nerves, not only by that but also by differences in nerve diameter. Summation intervals are not readily measurable and have as yet an uncertain significance. As to refractory periods, those of the more irritable fibers can be measured easily and sharply, not, however, as will be seen, those of fibers of low irritability. The amplitude of the axon potentials in different nerves is affected by the amount of inactive shunting tissue; and time to maximum, for reasons to be given later, is apt to be a difficult measure to apply.

We compare with conduction rate certain manifestations of activity, such as irritability, refractory period and summation interval, measured at the proximal end of the nerve, and certain manifestations, such as amplitude and time to maximum of the axon potential, at the distal end. If such a comparison is to be valid, either all parts of the stretch must have the same mean reactivity, or, if they have not, the departure from the mean must follow some rule. Thus if conduction rate falls off toward the periphery, as Gerard and Marshall believe (1933), and if such slowing developed regularly and uniformly comparisons still would be valid. There are reasons for believing, however, that there may occasionally be discontinuous alterations in reactivity along an axon. There is, for example,
indubitable evidence of occasional axon branching in the sciatic-plantaris preparation, and this may be used to illustrate one of the possible sources of error when conduction rate is used as the common denominator. Figure 20, A shows three axon spikes initiated, it can be shown, by stimulation of a single axon which branches a considerable distance from the lead. That the three spikes come from a common trunk is proved by the unchangingness of the picture under conditions which unquestionably would alter it were the potentials from fibers discrete throughout their length. Thus in the play that occurs at threshold stimulation either the entire triple deflection appears, or none at all; and the spacing between the spikes always is the same whether stimulation be by induction shock or by constant current. The spikes are not repetitive discharges in one axon. For 1, we have never seen repetition in an axon from stimulation with a threshold induction shock; 2, the picture is not that of repetition, the potentials of repeating spikes never falling to so low a relative height as does the third of these three; and 3, in a fiber repeating under the influence of a constant current the axon spikes would be spaced by at least 3σ whereas here the spacing is roughly 1σ.

The complications that branching might give rise to in a comparison of axon activities are many. Only one need be instanced. If, say, the two most rapidly conducting of these three daughter axons had left the preparations proximally to the lead, conduction time (consumed mainly in the branch, the smallest one) would have been unaccountably long in comparison with irritability (measured in the parent trunk). In view of such possibilities the wide discrepancies occasionally encountered in the usual relation of irritability to conduction rate cannot be regarded as significant.

As in previous publications from this laboratory conduction time is taken to be the shock-spike interval. This interval may be quickly determined by making the shock artifact coincide with the initiation of the sweep along the time line and adjusting the charging resistance of the condenser in the sweep circuit so that the spike appears when the sweep has been 63.2 per cent completed. This point, which is marked by a dot on the face of the tube, has been chosen because, with a 1μf condenser, the transit time of the spot to the dot is 1σ for each 1000ω in the charging circuit. The charging resistance may be read to 20ω or to 0.02ω. Since the total conduction time for the quickest fiber in a full length plantaris preparation is of the order of 7σ this represents a minimum accuracy of 0.3 per cent in the measurement of this time.

In order to minimize in these measurements the disturbing influence of latency, shock strength is always increased to the point where the play due to latency variations ceases. In the case of the fastest fibers the interval between shock start and initiation of the impulse locally may be taken as 0.1σ. As no allowance is made for this in our determinations the conduc-
tion rates for the fastest fiber in long plantaris preparations are too slow by something over 1 per cent. The slower the fiber the longer is this initiation time; it is presumed, though, that the percentage error due to it will be approximately the same for all fibers.

Not infrequently, in order to get a complete series, it is necessary to include the conduction rates of fibers whose potentials overlap somewhat at the lead. In such cases the beginning of the spike cannot be located with the customary accuracy. The error from this source cannot be over half the time to maximum of the spike, or, in the case of the fastest fibers, 0.2σ, about 3 per cent of the total conduction time. The extreme error in conduction time determinations in long nerves probably is never higher than 5 per cent; and determinations usually can be duplicated within 2 per cent. Conduction rates determined from two loci of stimulation not widely separated agree within 4 per cent. With wide separation between loci of stimulation the agreement is not quite so good and often wide discrepancies are seen. These are always in the direction of slower conduction in the more peripheral parts of the axon and may be referable to branching.

Conduction distances less than 20 mm. have not been used in determining conduction rates. In nerves as short as this electrode width and the difficulty in estimating the tension required to bring the nerve to its normal length introduce additional errors. The error for 20 mm. of conduction is probably not over 10 per cent, but relative conduction rates in such preparations probably are valid to 3 per cent.

Irritability by induction shocks. For stimulation with induced currents, break shocks from a Porter induction coil have been used (fig. 1). Under the conditions of the experiments, with the core in, the shock has a measurable duration of 0.06σ; with the core out 0.03σ. Except when otherwise stated shocks from the cored coil have been employed. Shocks resulting from interruption of the primary circuit in the manner described above, are sufficiently reproducible to allow an accuracy of 0.25 per cent in the expression of threshold induced voltages.

As a routine the secondary coil has been home and the induced voltage varied by a precision resistance, IR, in series with a five volt Edison primary battery. With a given primary potential the induced voltage varies practically directly as the primary current or inversely as the primary resistance. From readings of the precision resistance, relative thresholds may be expressed as calculated primary current, or the resistance readings may be taken directly as an expression of irritability. Under routine conditions, with the core in and secondary home, the most irritable fiber is stimulated by a primary current of about 0.5 ma. The make and break shocks are widely spaced temporally, and as the make shock is usually below the threshold of the fiber under observation its effect may be disregarded.
When necessary to balance out the shock artifact a 1000 ohm "noninductive" resistance is placed in series with the electrode proximal to the lead, and a 20,000 ohm "noninductive" potential divider connected across the coil terminals in parallel with the circuit formed by calomel cells, nerve and the 1000 ohm resistance. By grounding and adjusting the slider of the potential divider (see fig. 1) a partial balance in the circuit, B2, may be established according to the principles outlined by Bishop (1927), and the shock escape reduced to a negligible value. This modification of Bishop's balancing circuit has the advantage that changes in the balance produce only slight variations in strength of stimulation and in the physical constants of the circuit.

Owing to the spontaneous variability of fibers described above, thresholds cannot be measured precisely, and must be defined as the strength of shock that stimulates as often as it fails to stimulate. In the case of the most irritable fibers this point can be found with an accuracy of about 0.5 per cent; for the least irritable fibers the limit of accuracy is of the order of 10 per cent. Under certain circumstances an unusually marked treppe may reduce still further the accuracy of the readings by this criterion. In addition to this difficulty it is found that the relative irritabilities of axons may vary widely along the length of the nerve. To cite an extreme case, at one point on a fresh nerve the irritabilities of two fibers were to each other as 1:3, at another as 1:9. Such great differences probably are not entirely attributable to differences in the accessibility of the fibers to the applied current.

As a matter of routine determinations were made of the irritability $I_1$ of the most irritable fiber extending, in the plantaris preparation, from the stimulated point to about the point (the level of the knee) from which leads usually are taken in sciatic preparations, and $I_2$ of the most irritable fiber extending to the plantar nerve. In one preparation the most irritable fiber in the peroneal reached the plantar nerve. In other preparations the most irritable plantar fiber was the less irritable by from 2 to 62 per cent. Judged, therefore, by the irritability criterion and by conduction rate, the axons of plantaris are representative of the entire range found in the peroneal nerve.

If the axon threshold expressed as primary voltage be plotted against conduction rate the points derived from a nerve determine a curve of the hyperbolic type, concave upwards (fig. 5). In most cases the points fall quite regularly about the indicated curves, in others (curve D) rather irregularly. The scattering of the points is particularly noticeable with fibers conducting more slowly than 2 m.p.s. In part this probably is an expression of the damage done by the very high voltages required to bring the short shocks up to the threshold of these low irritability fibers, and, in part, possibly of greater frequency of branching. When composite
curves are made of the data derived from many different preparations; these individual variations are seen to be random. Conduction rate plotted against threshold voltage, therefore, gives a curve without demonstrable discontinuities in any part of the range.

Irritability measurements by constant currents. Chronaxie. For the determination of the relation of current duration to strength and of chronaxie in axons a circuit (fig. 1) was devised by which constant currents of any desired duration, or condenser charges of any desired duration, and of known voltage could be applied to the nerve. The potential for this cir-

![Fig. 5. The relation of the thresholds of axons to their conduction rates. Induction shocks. Data from six preparations. The D curve has not been drawn. Ordinates, relative volts.](image)

The circuit is supplied by heavy duty radio batteries, CP, through an 8 point switch with 4.5 volt steps. Intermediate ranges are obtained through a low resistance potential divider with a 5 volt range which may be read accurately to 0.2 per cent. For rapid determinations of chronaxie the voltage is doubled (switch CD) by leading from a similar point switch in gang, with 9 volt steps and by imposing 10 volts across the potential divider. When the switch, CS, is in the proper position a constant current is initiated by the closure of one key, C1, and broken by the opening of a second series key, C2. These keys may be moved independently and their temporal separation determined by direct observation of their electrical
artifacts on the face of the Braun tube. A selector switch, C', removes the second series key, C₂, from the circuit and the same make key, C₁, initiates the charging of a calibrated variable condenser through the same resistances and to the same potential as with the constant current. A third key, C₃, serves to discharge the condenser, C, a half second later. The circuit is so designed that only 18 per cent of the total potential is required for stimulation of the nerve and the resistances are, therefore, of such an order that the physical constants of the system are almost wholly independent of the nerve circuit. From the capacity of the condenser and the resistance in the charging circuit, the RC product may be calculated. According to Lapicque (1926) and Monnier (1928), the RC product multiplied by the factor 0.37 gives the equivalent duration of a constant current of the same voltage. With the system employed the calculated values obtained by the condenser method approximated the observed constant current durations. As the capacity of the variable condenser may be more quickly read than the duration of the constant current subsequent determinations of chronaxies and of voltage-duration relations were determined by the former method.

Sakamoto (1933) by using a capillary pore electrode has succeeded in obtaining from the frog’s sciatic the data needed for plotting eight smooth strength-duration curves of individual motor fibers, each one, presumably, from a different preparation. Other characteristics of the fibers were unknown. In a number of plantaris preparations, we have obtained the same information in each case from a number of fibers of known and widely differing conduction rates (Blair and Erlanger, 1933a).

In the first experiments chronaxie alone was determined, using essentially the method of Lapicque (1926) except for the use of calomel half-cells instead of Ag-AgCl stimulating electrodes and of the charge of a condenser instead of the discharge. It became necessary, owing to the inadequacy of the condenser method, particularly in the case of fibers of low irritability, to determine rheobase with the constant current. Typically (fig. 6) the fastest fibers (conducting at 25 m.p.s. at 25°C.) have an average chronaxie of 0.3σ. As conduction rate diminishes chronaxie diminishes regularly to reach about 0.2σ at about 10 m.p.s., and returns to its original value when the conduction rate has fallen to about 5 m.p.s.; it then lengthens very rapidly as conduction rate continues to fall, reaching a maximum of about 7σ in the case of the slowest fibers. The validity of these direct determinations of chronaxie was controlled by chronaxies read from complete strength-duration curves of axons (see below and figs. 7 and 8). The relation between conduction rate and chronaxie was the same by both methods.

These observations, therefore, fail to support the contention of the Lapicque school (Monnier and Dubuisson, 1931) that there is an inverse
relationship between the conduction rates and the chronaxies of nerve fibers. Indeed, the peculiarity of the relationship to conduction, differing as it does so radically from the relationship between conduction rate and every other index to nerve activity we have investigated, casts serious doubt on the value of chronaxie as a measure of irritability.

Three factors, among others, have been shown to qualify chronaxie deter-
minations: the electrode (Davis, 1923), the external resistance (Eichler, 1931), and the length of the interelectrode span (Lapicque, 1926). Although in the present studies the physical electrodes are identical for all of the fibers of a nerve the effective physiological circuits (to and through the individual fibers) are not; each fiber has its own electrode, resistance and relative interelectrode distance. That these may be among the factors modifying chronaxie values at a point is indicated by the fact that determinations on the same fiber tend to be slightly longer with a decrease

![Fig. 7. Strength-duration curves of individual fibers of a nerve. 2/16/33. 22°C. Conduction rates indicated by numbers on the curves. The inset is the first unit of the coordinate system plotted on a larger scale to show the positions of the chronaxies (τ). The lines sloping toward zero in the added coordinate system are the Weiss law curves for the fastest and for the slowest of the fibers.](image)

in the cross section of the shunting tissue. Furthermore, Grundfest (1932) shows that the chronaxie of a single fiber varies along its length. In how far these variable conditions, inherent in nerve structure, are responsible for the behavior of the chronaxie values in the present experiments, it is impossible to say.

**Strength-duration curves of axons.** Strength-duration curves derived from different tissues approximate in general the form of rectangular hyperbolae. On the basis of this resemblance, various investigators, notably Weiss (1901) and Lapicque (1926), have endeavored to derive
formulae expressing the relation of strength to duration which will be applicable in all cases. It has been difficult to compare strength-duration curves of different origins with each other and with calculated values because of the inability to obtain the necessary data under comparable conditions. For instance, data cannot be secured from motor nerve and from smooth muscle without modification of both the physical electrodes and the characteristics of the stimulating circuit. Neither can one be certain when dealing with different structures that they have been treated alike in other respects. But fibers in one and the same nerve have a reactivity range, as indicated, for example, by their conduction rate range, of
1 to 100; they are observed under identical experimental conditions involving no change of stimulating circuit, physical electrodes or question as to relative rheobasic values. The data thus secured are accurate within 2 per cent and, since nerves do not fatigue at the rate of stimulation used, remain constant for hours.

The strength-duration curves derived from the various fibers (figs. 7 and 8) are similar in configuration, but not identical. The dissimilarity is indicated by the fact that while rheobasic voltage has an inverse relation.

Fig. 9. Relation of thresholds to conduction rates of axons in a relatively large nerve. Stimuli, condenser charges. For the curve marked by triangles the condenser capacity was ten times that for the curves indicated by dots.

ship to conduction rate, chronaxie initially varies in the same direction as the rate (down to 10 m.p.s.) and then oppositely. Since the configurations of the curves are not identical, no formula based on the value of a single point (chronaxie) can express the relation of strength to duration.

Additional curves expressing the relation between conduction rate and threshold voltage can be derived by plotting against the conduction rate of the fibers whose strength-duration curves have been drawn the voltages of the constant currents of any given duration required to stimulate. In the insert, figure 8, are the curves drawn on the basis of constant current.
durations of 0.02, 0.04, and 1.0 and "infinite." The result is a family of smooth curves concave upwards and of the hyperbolic type. Naturally, the range of threshold voltage is narrowest with currents of "infinite" duration and increases progressively with decrease in the duration of the stimulating current. The chronaxies of the same fibers, derived also from the strength-duration curves, are plotted on the same graph in such a way as to bring out clearly the differences between the results of these two general methods of measuring irritability.

Two curves illustrating effectively the same result as the one depicted in figure 8 (inset), but from a nerve assuredly undamaged, and supplying a sufficiently large number of fibers to control random variations, are shown in figure 9. They are based on determinations of the conduction rates and threshold voltages in a considerable number of the axons of a relatively large nerve with shocks derived in one case (dots) from a short condenser charge, in the other (triangles) from one ten times as long. All the curves expressing the relation between threshold and conduction rate of axons are free of discontinuities.

**Summation intervals.** The summation intervals of axons have been determined in a number of preparations by essentially the method previously described (Erlanger and Blair, 1931a). The sensitizing shock, 80 per cent of threshold, was from an air-cored coil excepting where, as occasionally...
happened, it became necessary to insert the iron core in order to obtain shocks sufficiently strong to stimulate fibers of very low irritability. The results from ten of these experiments done, for the most part, at room temperature, are shown in figure 10. It is seen that as the conduction rate diminishes the interval shortens from about 0.4 to 0.5 sec at 20 m.p.s. to about 0.3 sec somewhere between 2 and 3 m.p.s. In all excepting one case it then lengthens, rapidly attaining durations as long, sometimes, as 70 sec, in fibers conducting at rates slower than 1 m.p.s. Determination of the longer summation intervals is markedly interfered with by treppe but the results of this can be controlled. However, there are frequent fluctuations in the values for a fiber, far too wide to be assigned to experimental error. Since the chart includes all of the data of the experiments selected this fluctuation appears there. The number of determinations included is amply sufficient to take for this difficulty and to indicate the general trend of the mean. The duration of the summation interval at no time is less than five times that of the sensitizing shock; in the case of the fastest fibers it usually is about twelve times as long and of the slowest fibers hundreds of times.

There is no apparent simple relation between the summation interval and other manifestations of fiber activity. This result is of interest in view of the belief (Keith Lucas, 1910) "that the summation interval may be regarded as a measure of the rate at which the excitatory disturbance subsides." This view is based upon the observation, among others, that in the case of different tissues such, for example, as motor nerve, voluntary muscle and heart muscle, the summation interval increases in the order given which is also the order of the duration of their responses. In a comparison of different tissues, however, one has to consider not only speed of response and voltage threshold, but also the influence of both gross tissue differences and contact differences on polarizability. In the case of nerve one deals with fibers ranging in speed of response as widely in many respects as do nerve and muscle, but all exposed to the same conditions, and yet, excluding now fibers conducting under 2 m.p.s., summation intervals actually shorten as the reactivity of the fibers diminishes. The summation interval, therefore, does not vary with speed of response per se and in the case of axons, at least, there is no simple relation between them.

One might at first be inclined to account for the configuration of the summation interval curve on the basis of the presence in nerve of two types of fibers. There is not the slightest evidence of more than two. One type would include fibers conducting at rates over 2 m.p.s. and would be characterized by summation intervals that shorten slightly as conduction rate decreases. The slower fibers would make up the other type and would be characterized by summation intervals that increase, and very rapidly, in duration as conduction rate slows. This interpretation is
rendered improbable by the position of the discontinuity. According to Bishop and Heinbecker the most sudden alteration in the continuity of fiber properties lies between their B₁ and B₂ types. On that basis the break should, therefore, occur at about 4 m.p.s. Though evidence is lacking, we are much more inclined to attribute the result to some secondary action of the current on the irritable mechanism of the fibers; it must be this, or else the recovery speed of the excitable mechanism has no relation to its speed of action. It might be supposed, in explanation of our result, that just as constant currents, when increased in strength, at first enhance irritability and then depress it, so these subthreshold shocks, as their strength is increased, might very well at first facilitate a readjustment of some secondary polarization which they produce and later retard it, with the result that the nerve recovers its normal irritability more and more quickly at first and then, with still greater strength of shock, more and more slowly. Is it not possible that if as strong a shock could be applied to a fiber of high irritability without causing it to fire off, it, too, would exhibit a long summation interval? But irrespective of what might be its cause, it is the long summation interval of the fibers of low irritability that puts them in the class of so-called iterative nerves.

Be this as it may, the behavior of the summation interval does not necessarily signify that nerve is made up of two types of fibers responding characteristically to subthreshold shocks.

Refractory phase. The absolutely refractory periods of the fibers contributing to the α, β and γ waves were first measured in our laboratories at a time when the cathode ray oscillograph technique involved stimulation at the rate of 10 to 20 times per second. The values found in the bullfrog’s sciatic were 1.42, 2.06 and 4.46 ms, respectively (Erlanger, Gasser and Bishop, 1924). Later it was found (Erlanger, Gasser and Bishop, 1927) at times, especially with slower stimulation rates, that the differences in the refractory periods were so slight as almost to put them within the error of the method. When fibers of slower conduction were investigated each of the types recognized by Bishop and Heinbecker (1930) were found by them to have characteristic refractory periods, namely, A, 0.8–0.9 (in the bullfrog) and B₁, 0.9–1.1, B₂, 3.5–7.0, and C, 4.5–10.0 ms (in the turtle), the higher values in each case being attributed by them to deterioration of the nerve. An analysis of the recovery process in the individual fibers of a nerve now shows that the rate of recovery at any stage bears an inverse relation to their normal conduction rates. In other words, the slower the fiber, the longer are its absolutely and relatively refractory periods.

The difficulties connected with the determination of relative recovery rates are manifold. A shock imposed on a resting nerve so modifies it as to cause a response. In addition, previous studies (Erlanger and Blair, 1931a) have shown, a shock affects active nerve by changing the curve of
returning irritability. A strong, though at the time, subthreshold, shock delivered during the refractory phase, it was shown, hastens the return to normal at its anode. And in the course of the present investigation it has been found that such a shock produces the reverse effect at its cathode, prolonging the recovery phase. The significance of this effect is demonstrated in figure 11.

Relatively refractory periods are usually determined by producing a response to an initial short shock, adjusting a second similar shock so as to be just threshold for the response, and then approximating the two temporally until the second response fails. This temporal separation of the

![Figure 11](http://ajplegacy.physiology.org/)

**Fig. 11.** Effect of a cathodal shock, delivered during the absolutely refractory phase, on the recovery curve of a single fiber (conduction rate 11.5 m.p.s.). 3/21/33. 23.7°C. Ordinates, threshold voltage in terms of normal fiber threshold; abscissae, separation of initial, $S_1$, and testing shocks. Dots, normal recovery curve following response to $S_1$. A short cathodal condenser charge, $S_2$ (stimulating equivalent, 0.00 $\sigma$ constant current) adjusted to five times the normal threshold, indicated by the horizontal line (or fifteen times threshold of the most irritable fiber of the nerve), is imposed during the absolutely refractory phase and the recovery curve redetermined (triangles). Short, strong cathodal shocks prolong the recovery curve in all its phases.

two shocks has been taken to represent the end of the relatively refractory phase, and the curve of recovery has been determined by plotting the threshold voltage of the testing shock against the separation of the two shocks. The absolutely refractory period has been determined by increasing the testing shock to five times threshold and approximating the two until the second response fails. When, as has been the usual procedure in this laboratory, the two shocks are delivered through the same pair of electrodes, the effect of the initial shock may persist after the first response, and modify recovery. That this happens with very strong initial shocks is demonstrated by a comparison of the recovery curves of single fibers
based first on the results obtained with the two shocks delivered through the same pair of electrodes, and then through different electrodes with the testing shock proximal to the lead. In all cases, the recovery time determined by the first method is the longer. With relatively low voltages no such effect can be demonstrated, even when the shocks are sufficiently long to stimulate fibers of low irritability.

Similarly the effect of the testing shock acting through the utilization and latent periods may modify recovery time. By analogy with simple responses, latency should be expected to increase with an increase in threshold during the relatively refractory period, thereby giving a longer time for the testing shock to produce an effect on the recovery before the second response develops. That this happens is shown by the disappearance of a consistent threshold response of a low irritability fiber stimulated during the relatively refractory period by a strong, short testing shock, when this shock is still further increased in strength. Indeed, when the strength of a testing shock from a coreless Porter inductorium is increased to five times threshold for the purpose of determining the absolutely refractory period of a fiber of low irritability the recovery time usually increases so that the second response disappears at a shock separation that is as great as or at times even greater than, the determined relatively refractory period. The durations, therefore, of the absolutely and relatively refractory periods of a fiber, determined by such a method, may be alike (see table 1). In view of this fact, and of the irreversible damage which very
strong, short shocks produce in all fibers, such shocks are impractical for
the investigation of refractoriness. With longer shocks, though, while the
longer utilization and latent periods provide a longer period for effective
polarization, the relatively low voltage required reduces the necessary cur-
rent to such an extent that there is no demonstrable effect on the recov-
er curves even when the strength is increased some fifteen times the
threshold of the most irritable fiber. It must be pointed out, however,
that in the case of the slower shocks the relatively longer utilization and

Fig. 12. Recovery curves of 6 axons of a nerve with conduction rates given by the
numerals on the curves. Ordinates, thresholds in relative volts; abscissae, \( \sigma \).

For the curve marked by triangles the ordinates are the absolutely refractory
phases of the fibers determined by the extrapolations, the abscissae, the conduction
rates of the fibers.
latent periods associated with the initial and testing shocks probably are not exactly the same, and, therefore, the separation of the two shocks is not an entirely valid index to the duration of refractoriness.

Figure 12 presents the recovery curves of single fibers in a typical experiment at 21.3°C. Threshold voltages are plotted against separation of the two shocks. Stimulation was by a pair of condenser charges, each adjusted to have a stimulating value equivalent to a constant current of 0.25\(\sigma\). The rate of stimulation chosen, once in four seconds, was such that the threshold of the least irritable fiber, as shown by the response to the initial shock, remained constant. The nonpolarizable stimulating electrodes were placed on the unbranched portion of the sciatic, and the axon spikes recorded from the plantar nerve. The voltage of one charge was set just above the threshold of the least irritable fiber under observation, and the key arranged to close coincidentally with the initiation of the spread of the time line. The key controlling the second charge was moved to give different separations of the two shocks and their temporal separation determined (see determinations of conduction times). With each separation the threshold voltages were determined for the six individual fibers. Readings were scattered both temporally and as to order of determination. At frequent intervals the thresholds with infinite separation of the shocks were determined.

It is seen 1, that as the conduction rate (indicated by the numerals above the curves) decreases, the thresholds ("infinite" separation) increase as previously described; and 2, that the recovery curves, as indicated by the voltage thresholds of the different fibers, are of a similar hyperbolic type, the recovery time increasing in continuous series with increasing threshold and decreasing conduction rate. To avoid complications due to polarization the maximum voltage was not carried beyond 13 times the threshold of the most irritable fiber or hardly twice that of the least irritable one. As previous work has indicated a supernormal phase may or may not be present. Of the six fibers, those conducting at the rates of 18.1, 15.9 and 12.9 m.p.s., show supernormal phases, indicated by a lower threshold with 7\(\sigma\) separation of stimuli than with "infinite" separation. As with the strength-duration curves, single points have little meaning here; the end of the recovery phase of fibers having no supernormal phase cannot be determined with any accuracy because of the asymptotic character of the curves; and the values thus found can be in no way comparable with the readings secured by employing the sharp beginning of the supernormal phase, when it is present, as the sign of the end of the recovery phase. Determination of absolutely refractory phases by increasing the shock to 3 or 5 times threshold and decreasing the separation of shocks until no response is obtained leads to error because of the effect of polarization by the testing shock on recovery.
From the curves, absolutely refractory periods were approximated by extrapolation (broken lines) and the values thus obtained (triangles), plotted against conduction rate on the inside coordinate system of figure 12 (small print). This curve, as well as those from other experiments, is without discontinuities.

Experiments have not been performed specifically for the purpose of determining the relation of the absolutely refractory periods to the temporal configurations of the axon spikes (see below). Comparison of the two values as obtained in different preparations under conditions not always exactly comparable, shows that the refractory periods are at least 2 to 3 times as long as the crest times of the spikes throughout the entire range.

Amplitude and temporal configuration of axon spikes. From favorable preparations of plantaris it rarely is possible to obtain more than four to six spikes separated cleanly and, therefore, suitable for measurement of height and configuration. This number is insufficient, particularly in view of the many exceptions to the rule, to define a curve.

Relation of amplitude to conduction rate. In general one finds for each nerve that the slower the rate of conduction the lower is the spike in terms of microvolts. Illustrations of this relationship in individual nerves are seen in figures 3, 13, 14 and 16. The maximum recorded amplitude from fibers in small nerves has been of the order of 400 μv. In order to obtain more information regarding this relationship, for each of a number of nerves with differing absolute values an average amplitude for fibers of the same conduction rate was assigned a single representative axon spike and in each case this value (circles in fig. 17) has been used as a base for the expression of the relative amplitudes of the other spikes of that nerve. Justification for this method of treatment is derived from the assumption that axons conducting at a given rate under the same conditions develop the same potential. When the data from the different experiments are thus correlated and plotted on the same system of coordinate, the points fall, though rather widely, to be sure, about a straight line. There is no

Fig. 13. Contact print showing 5 cleanly separated axon spikes. 4/17/33. Conduction distance 129 mm. 24.3°C. S is the shock artifact. V in this and in subsequent records is the threshold. The coordinate system, shown by the lines ruled in the lower left hand corner, is not squared with the page.

Fig. 14. Series of axon spikes from a nerve refrigerated for 24 hours. 12/31/33. 23°C. Number 7 is probably cut short by the diphasic artifact. A comparison of 3 and 6 demonstrates the difficulty of obtaining comparable measurements of crest time from spikes of different configurations.

The conduction rates and basic irritabilities of the fibers producing spikes 3 and 5 were identical. It was possible to obtain separate pictures because sometimes one spike, sometimes the other, appeared alone at the lead.

Fig. 15. Axon spikes of three fibers in a skin nerve. Amplification and speed same for all. 1/25/33. 24.7°C.
Figs. 13-15
Fig. 16. Series of axon spike records from a fresh nerve. 1/16/33, 24°C. 1 and 5, diphasic, the latter distorted by noise. 2, 3 and 4, typical spikes.

Fig. 20. Atypical spike records. A. Spikes from three unlike daughter axons resulting from stimulation of the single high irritability parent fiber. The third spike lies in the diphasic artifact of the second. B. Similar record, but with lower irritability parent axon. There seem to be three daughter branches. C. High amplitude (45μV) spike of slow conduction. Possibly the result of multiple branching near the lead. First figure under the wave, end of rising phase; second, beginning of falling phase. A type encountered not infrequently.
evidence of any discontinuity in their arrangement. The meaning of this result in relation to fiber diameter and conduction rate is considered in the discussion.

Relation of time to maximum to conduction rate. In individual nerves crest time in general increases as conduction rate slows, though, as in the case of amplitude, there are many exceptions to the rule. We are confronted here, however, with the difficulty that there is no perfectly valid way of correlating the data from different nerves. Our procedure, there-

![Fig. 17. Relation of the relative amplitudes of axon spikes to conduction rates. For method of construction see text. The points appear to fall about a straight line (see fig. 21).](image1)

![Fig. 18. Relation of time to maximum of axon spikes to conduction rate. Room temperature. The points indicate a curve of the hyperbolic type (see fig. 21).](image2)

fore, has been simply to plot on the same system of coordinates the data from a number of experiments performed under reasonably comparable conditions (20 to 25°C.). The curve indicated (fig. 18) is of the hyperbolic type; the slower the fiber the longer is its time to maximum. The time range in plantaris has been from about 0.3 up to about 4.0σ. The curve is without recognizable discontinuities.

Falling phase. The asymptotic approach to the base line of the falling phase of the spikes and the influence of diphasicity upon it stand in the
way of even reasonably accurate measurement of this part of the spike. The topic may be dismissed with the statement that the falling phase in general seems to increase as conduction rate slows.

Discussion of the difficulties in the way of comparison of configurations.

a. Nerve diameter, as a factor affecting the recorded height of axon spikes, is a difficulty to which reference has already been made.

b. The thickness of the nerve also has a definite effect on the configuration of the axon spikes, as may be seen in figure 19, A and B. Nerve thickness may affect the picture in several ways: 1. The axon spike from the larger nerve, A, has a more distinct foot; 2, sometimes there is a distinct angle, as at the point 2, figure 15, A, where the foot joins the steeper rise; 3, and where this angle is marked the foot may even be slightly convex upwards. The factors determining these three pictures are not at all clearly understood. With respect to 1, it is possible that in thick nerve the foot, which presumably is due to spread of potential from the active region, is merely relatively higher with respect to the recorded spike potential than in thinner nerve and becomes prominent because the amplification is increased in order to bring the height of the axon potential record up to that obtained from small nerve. 2. The angle that sometimes appears between the foot and the quicker rise possibly is to be attributed to some condition which in effect puts the lead off of the path of the active axon (Bishop and Gilson, 1929). This possibility is supported, and 3, light shed on a possible explanation of the occasional convexity upwards of the foot, by the fact that in one experiment, by shunting plantaris with a large nerve, a normal axon potential was converted into one preceded by a positive wave. The axon potentials recorded by Matthews (1929) from the median peroneal nerve frequently exhibit such a preliminary positive wave.

Fig. 19. Axon spikes redrawn in linear coordinate systems. A, is record A of figure 15 (from a relatively thick nerve). B, is record I of figure 14 (from a slender nerve). Amplitude is without significance.

![Axon spikes](http://ajplegacy.physiology.org/Downloadedfromhttp://ajplegacy.physiology.org/)
The question that concerns us here is how to take the foot into consideration in measuring the records of axon potentials temporally. The total time to maximum of spikes measured from the beginning of foot to crest in large nerves where the foot is conspicuous is of about the same order of magnitude as the time to maximum in plantaris where the foot often is not obvious and cannot be distinguished from a more rapid rise. If the foot is due to spread of potential it should not be included in the time measurements and has not been where it has been possible to recognize it; but it is not possible to exclude it in the case of plantaris axon potentials. Even where the foot is fairly obvious (fig. 15, A) it is difficult to define exactly the time to maximum. If the end of the foot indicates the time of arrival of the active process at the lead the ordinate values of figure 18 are all too large.

Exceptional configurations. Exceptional configurations not infrequently account for unusual values for height and duration. Some of these unquestionably are to be accounted for by damage in preparation. In such cases further changes frequently develop in the shape of the spike, and the refractory phase at the lead is apt to be abnormally long as evidenced by occasional failure of the response to reach the lead. The data obtained from axons behaving in this way have been discarded.

But exceptional spike configurations are by no means all referable to damage, for atypical configurations are seen also in records from skin nerves. The pictures obtained from one and the same fiber in such a nerve fluctuate somewhat in height and in configuration, but scarcely more than can be accounted for by noise and variations in the lead. But the pictures yielded by different fibers of the same nerve are apt to have characteristically different configurations. Figure 15 shows contact prints of three different axon spikes from a skin nerve with the same leads, amplification and time axis. Spike A has a slowly rising initial phase, with possibly a faint indication of an angle, 2, and a relatively sharp crest; B has a sustained falling phase showing an elevation; C has a sharp start, and an indefinite crest between 2 and 3. These particular variations are not referable to differences in amplitude because they are quite as apparent when the amplification is adjusted so that the different spikes have the same amplitudes. Since the nerve is not damaged at the lead and is uniform in diameter, the differences must be referable to unlike active processes, to uneven sheaths, or to differences in the relation of the electrodes to the fibers. In the absence of evidence, our inclination is in the direction of assigning them rather to anatomical factors, such as sheath thickness and to the relation of the lead to nodes, than to inherent differences in the local process.

A much wider range of variation has been seen in plantaris preparations, possibly because they have been subjected to a more thorough scrutiny,
though, as has been stated, damage may be a factor here. A variation
which has been observed on several occasions is illustrated by 3, figure 14;
the spike is too high and too long in relation to companion potentials. The
maintained falling phase gives the impression that the fiber is damaged,
but the amplitude is greater even than normal. In one experiment on
a skin nerve, a group of similar fibers of intermediate irritability (about
10 in number) had spikes which were regularly double-crested, while all
other spikes were normal in configuration.

Branched axons. Perfectly, or not quite perfectly, superimposed po-
tentials from branches of a single parent axon may lead to error in the
determination of spike configuration. When the superposition is imperfect,
as in figure 20, A and B, the condition is easily identified. Multiple branch-
ing near the lead might produce much more complicated pictures; possibly
this is the explanation of record C, an exemplar of a configuration seen not
infrequently.

Fusion of similar spikes. Two fibers with identical irritabilities, con-
duction rates and spikes may fuse to form smooth curves of the usual
configuration but with a higher voltage than that expected of a single
response from a fiber of corresponding irritability.

Diphasic artifact. When the diphasic artifact is marked its effects upon
the height and shape of the axon potential can be discounted, but not its
unrecognizable effects. The limitation set by the amplifier input resist-
ance makes it impossible in the case of small nerves to record brief poten-
tials with the two phases cleanly separated even if there were available a
sufficient length suitable for the purpose.

Demarcation potential. To reduce the diphasic artifact the nerve must be
freshly killed proximal to the grid electrode, and injury modifies the ampli-
tude of spikes recorded even as far away as 4 or 5 mm. It is quite possible
that this uncontrolled influence varies not only from nerve to nerve, but
differentially affects axon responses.

Amplifier noise. The relatively greater shunting in the case of slowly
conducting fibers so reduces their spike amplitudes that the inherent noise
of the amplifier produces significant distortion. In such cases the con-
figurations can be ascertained only by a comparison of several records and
then, often, only roughly.

Summary. The complications in the way of determining the amplitude
and the time to maximum of the axon potential have been reviewed in part for
the purpose of indicating that a certain amount of scattering of the points on
the graphs correlating these with conduction rate is inevitable. In support
of the plotted data it may be said that the experiments in which records
were made and which serve as the basis for the data in the graphs form only
a small fraction of the total performed. There are available over 200
additional experiments done with the other ends of this investigation in
view. In all the behavior of the axon potentials observed on the screen has been in complete agreement with the quantitative observations used in this section.

**Theoretical Considerations. Relation of fiber diameter to conduction rate.** If it be assumed that the intrinsic potential of action attains the same amplitude in all fibers then, if the whole nerve acts as a homogeneous shunting resistance, the measured potential, \( Y \), would vary as the cross areas of the fibers, or as the squares of their diameters, \( D \), (Gasser and Erlanger, 1927). But experiment indicates that the amplitude, \( Y \), of the recorded axon potentials varies directly as the conduction rate, \( X \). It, therefore, follows that the conduction rate varies as the diameter squared. Expressed with symbols:

\[
Y = CD^2
\]

and

\[
Y = C'X
\]

hence

\[
D^2 = C''X
\]

Gasser and Erlanger, however, came to the conclusion that "to a first approximation the velocity in the fiber is determined by the diameter." The basis for this conclusion was the reasonably close resemblance of theoretical reconstructions of the action potential waves to the actually recorded waves. The fibers they measured for this purpose extended down to \( 5\mu \) in diameter and included only those contributing to the \( \Lambda \) wave. Later, when the potentials of fibers of slow conduction were found, Erlanger and Gasser (1930) extended the analysis to include all of the myelinated fibers. The latter reconstructions exhibited another elevation but it fell considerably earlier than the \( B \) elevation of the record from the same nerve, and it was, therefore, concluded that "the velocity of conduction in the small fibers is slower than the one calculated on a size basis from the velocity of the fastest fibers."

Recalculation of the data of the one experiment of which all of the necessary data are available (fig. 9 of Erlanger and Gasser, 1930), on the basis of proportionality of conduction rate to the cross area of the fibers (diameter squared), throws the \( B \) wave into just about the position it occupies in the record, but the reconstructed \( \alpha, \beta \) and \( \gamma \) waves of \( \Lambda \) then fall somewhat too late. The deviation is not sufficient, in our opinion, to invalidate the applicability of the diameter squared rule to this portion of the action potential. But to decide a question fraught with such a large experimental error and based upon so many assumptions a much more careful consideration will be required than we have been able to give it thus far. It is
felt, however, that the evidence is not definitely opposed to the possibility that all of the fibers of the nerve conduct at rates which roughly are proportional to the squares of their diameters.

Relation of axon potential amplitude to fiber diameter. Through an argument similar to that employed above one derives the equation

\[ \text{Amplitude of action potential} = CD^2 \]

In other words, the amplitude of the action potential also is proportional to the diameter squared.

One might use the data on the time to maximum of axon potentials to work out still other interrelationships. This development, however, will be postponed until the opportunity comes to obtain records of the spike potentials on a linear time line, when it will become possible to obtain the slope of the ascending limb without having to replot the curves on Cartesian coordinates.

Discussion. Although there are many observations on record of responses of single axons, there is, so far as we know, only one other contribution to the general subject of this paper. Matthews (1929), employing his oscillograph, has determined the conduction rates and recorded the potentials of cutaneous and proprioceptive axons in the frog’s sciatic. He found the two functionally different axons to conduct at rates around 12 and 16 m.p.s, respectively (ca 13°C.), thus confirming the conclusion reached by Erlanger (1927) that proprioceptive fibers are among the fastest of the sensory fibers. His crest times are longer than those reported here, probably due to inertia, but the relative times agree fairly well with the present data.

We have next to consider more fully the differences between our and Bishop and Heinbecker’s points of view. Apparently they recognize histologically four general types of fibers, A, B1, B2 and C, (although they leave open the possibility of transitional varieties) with properties which are more or less characteristic, the less characteristic being conduction rate and irritability, the more characteristic duration of spike potential and especially the duration of the refractory period, the most abrupt change in properties occurring between the B1 and B2 groups where the differences in the case of some of the measures employed is “in the ratio of least 4 to 1.” (Bishop and Heinbecker, 1930.)

We have not concerned ourselves with histology. However, the opinion seems to be growing among histologists that there is every gradation between heavily myelinated fibers and completely naked axis cylinders (Verzár, 1932). Our findings are in keeping with that opinion, in that by every measure we have applied we find that the properties of the axons vary in a perfectly continuous manner from one end of the range to the
other. The two apparent exceptions, namely, chronaxies and summation intervals, do not fit the scheme of Bishop and Heinbecker, for the sudden discontinuities that occur in the curves occupy different positions, neither of which lies quite in the B1-B2 gap of Bishop and Heinbecker.

Figure 21 visualizes our and what we take to be their points of view. The properties of fibers, as we have measured them, with conduction rate as the base, are represented as continuous curves (indicated by large type). In the same system are blocked out the comparable values for the A, B1, B2 and C types of fibers as given by Bishop and Heinbecker (small type). Their four blocks form extended points on, or not far from, our curves. The blocks furthest removed from their corresponding curves are those representing Bishop and Heinbecker’s crest time values. The reason for this divergence will be considered in a subsequent paper.

![Graph of the relation of threshold, amplitude and crest time to conduction rate](http://ajplegacy.physiology.org/)

Fig. 21. Graph of the relation of threshold, amplitude and crest time to conduction rate (see text).

In their latest publication (1933) Bishop and Heinbecker say that our differences are quantitative ones; that “if one reads ‘groups’ in place of ‘types’ . . . . these would be unimportant.” With this we, indeed, agree if they consider their “axon types” as aggregations of fibers with similar properties from out of the general mass of fibers whose properties range continuously along smooth curves as described in this paper.

It may be of interest to direct attention to the bearing of the concept of a numerical grouping of fibers with a continuous range of properties on the development of certain phases of our knowledge regarding the constitution of nerves. The first observations with the cathode ray oscillograph, made when the effective amplification was 10 mm. per millivolt, disclosed three elevations in the continuous maximum conducted action potential of the frog’s sciatic, very rarely a fourth (Erlanger, Gasser and Bishop.

For the sake of convenience these were designated $\alpha, \beta, \gamma$ and $\delta$. Later (Erlanger and Gasser, 1930), when amplification was increased so that 1 mv. deflected the spot 100 mm., two additional elevations, B and C, of the continuous potential were described, but then Erlanger and Gasser failed to find the $\delta$ wave. Even with the high amplification now available the present authors do not find in the frog's sciatic a discrete elevation corresponding with $\delta$'s position. Simultaneously Bishop and Heinbecker (1930) described in the action potentials of certain autonomic nerves the elevations designated by them, A, $B_1$, $B_2$ and C. Later (1931) they say that a potential with the properties "of the original delta wave" or $B_1$ "is invariably present in the sciatic of the frog," and that "for reasons not apparent" they "fail to support the position of Erlanger and Gasser in which they now deem it expedient to disregard the delta wave. . . . ."

From the present standpoint it is of no importance whether or not the sciatic action potential presents a wave in the $B_1$ situation. The point we wish to make is that such potential as there may be in that position is produced by fibers all of whose properties, we believe, are known if their conduction rates, for example, are known. Erlanger and Gasser never regarded the region in the conducted potential of the frog's sciatic (or of any other large nerve) between A and B as free of potential, nor, as a matter of fact, the region between B and C (see their fig. 3, 1930); but they did not regard the A to B region as any more worthy of a special name than did Bishop and Heinbecker the region between $B_2$ and C.6

In our opinion the emphasis that has been placed on specific elevations or waves or types has had the effect of obscuring correlations which otherwise would have been obvious, and has given rise to certain unwarranted inferences both on our part and on the part of others.4 When the statement has been made by workers in this field that a given elevation on a conducted action potential is made by fibers devoted to a given function (and to be specific, let us say to voluntary motion) it was never intended to mean that all of the motor potentials are confined to that elevation. That they are not confined to the $\alpha$ wave, but actually contribute to a very extensive stretch of the record, was clearly recognized, and proved by the analysis of the sizes of the fibers in a motor root that is free of sympathetic fibers, such as VIII in the frog (see fig. 8a, Gasser and Erlanger, 1927). The sizes of the fibers in motor VIII range from 20$\mu$ down to 2$\mu$ or even less, though there are very few so small. On the diameter squared basis the

4 Italics ours.
5 Those interested in following this matter further should compare the region between $\gamma$ and B in figure 1d of Erlanger and Gasser (1930), making due allowance for noise there, with the part of Heinbecker's figure 1 (1930) labelled $B_1$, making due allowance in this case for the diphasic artifact of the $A$ wave.
6 The writers assume entire responsibility for the opinions here expressed.
conduction rate range of these fibers would be from, say, 42 to about 1 m.p.s., on the basis of proportionality to diameter, 42 to 4.2 m.p.s. The fibers mediating other functions presumably range as widely in their conductive
tivity. Concerning this, however, we know less, and want to direct
attention to but one aspect of it, one with which we have had some experi-
ence, though still only in a qualitative way.

In sufficiently small skin nerves of the frog it is possible to determine the
physiological properties of every one of the constituent axons. In any
one such nerve the grouping of the axon potentials after conduction is
perfectly constant but the pictures from the different nerves differ strik-
ingly one from the other. The main point of interest at the moment, how-
ever, is the conduction rate of the fastest fiber. This, at comparable tem-
peratures, has ranged all the way from 22 to 6 m.p.s. It seems justifiable
to conclude, therefore, that the conduction rate range of the fibers of the
skin sense that is conducted fastest is wider than from 22 to 6 m.p.s. In
large skin nerves, it should be added, the variations exhibited by the small
nerves are smoothed over and their action potentials, therefore, have a
configuration that is more or less typical (Erlanger, 1927).

While there is every reason for believing that the conduction rates of
fibers mediating a given function often are clustered in such a way as to
make it possible to recognize their potentials by an elevation in the con-
ducted action potential of a large mixed nerve, there nevertheless is evi-
dence, such as that given by skin nerves, indicating that in different small
nerves and presumably, therefore, in branches of a large nerve, the par-
tition of the fibers may differ to such an extent from that obtaining in the
parent nerve as to throw the elevations they produce into very different
relative positions.

To cite an instance— when the sciatic nerve of the frog is stimulated the
resulting action potential led from a connecting sensory root presents three
elevations which have, and rightly, we believe, been regarded as the equiva-
lets of the \( \alpha \), \( \beta \) and \( \gamma \) elevations in the sciatic (Erlanger, Bishop and Gasser,
1926). However, the specific configurations of the two sets of waves are
very different (compare fig. 2, Erlanger, Bishop and Gasser, 1926 with
fig. 2a, C and D, Erlanger, Gasser and Bishop, 1924). And when the
conduction rates of the apparently corresponding waves are determined
by measurements made in two ways, namely, from the stimulating elec-
trodes on the peripheral end of the sciatic \( I \), to a lead just peripheral to the
posterior root ganglion, and \( 2 \), to a lead on the central end of the root, the
results obtained are not alike. At the time this subject was being studied
no obvious explanation of these observations occurred to us. Now the
differences can be attributed to a numerical grouping of the sensory fibers
in the root that differs from that obtaining in the nerve.

The difficulties encountered in the search for the source of the fibers
making the B wave of the mammalian saphenous nerve can be accounted for in a similar manner. The B wave in the saphenous is an outstanding feature (see fig. 6, Erlanger and Gasser, 1930). It was natural to suppose, therefore, that it is formed by the potentials of sensory fibers. But we failed to find in mammalian sensory roots a “wave consistently occupying the position of B.” Examination of the root records, however, (for example, fig. 12c, Erlanger and Gasser, 1930) discloses an abundance of “potential” between the A and the C waves. Furthermore, in records obtained by stimulating an appropriate root and leading peripherally from mixed nerve in the cat “nothing resembling a B wave” was ever seen. The possibility that these intermediate fibers from the several contributory sensory roots might on redistribution be so grouped in the saphenous as to produce the B wave did not occur to us. On the other hand, upon stimulation of an appropriate gray ramus a wave occupying the B position occasionally appeared in the peripheral nerve, and the search, therefore, was concluded with the statement that “whatever the meaning of this experience may be, our experiments have disclosed no other source of B fibers than the gray rami.” While these experiments do show that in the cat axon potentials contributing to the B elevation may occasionally reach peripheral nerves via the gray rami they do not, we now feel, prove that sensory root fibers contribute nothing to B.

SUMMARY

Individual axons of small nerves of the frog have been identified by their action potentials through the cathode ray oscillograph after amplification up to 2,200,000 times and their properties determined.

To brief threshold shocks an axon responds with a latency that shifts spontaneously from a maximum of about 0.5σ in the case of the fastest fibers to over 2.4σ in slower fibers. The shift diminishes as shock strength increases and the response is stabilized at a latency, plus utilization period, of 0.06 to 0.1σ. A greater shift is observed in the case of fibers stimulated by a threshold constant current.

The irritability of axons also varies spontaneously through a narrow range; presumably this and the latency variations are an expression of spontaneous alterations in reactivity.

The characteristics studied are referred to conduction rate, as a base. Axon branching, examples of which are given, may, when unrecognized, lead to erroneous correlations.

The thresholds of individual axons, measured by induction shocks and condenser charges, increase as conduction rate decreases, along smooth curves of the hyperbolic type. There may be rather wide random variations.

The chronaxies, as conduction rate diminishes, fall uniformly from 0.3σ
to about 0.2σ at conduction rates of about 10 m.p.s., and then rapidly increase. The curve differs wholly from other irritability curves.

The curves expressing the relation of current strength to current duration for individual axons form a continuous series, the slower the fiber the further from the axis is its curve. The curves are not all quite identical in form.

The summation interval of a fiber fluctuates somewhat, but in different fibers shortens as the conduction rate slows, down to 2 m.p.s., and then lengthens rapidly. The lengthening is regarded as an effect of the high potential needed to stimulate the fibers of low irritability. The summation interval of nerve does not seem to be a measure of the speed with which the excitatory process subsides.

The determination of the relative recovery rates of axons after a response is complicated by the action of the second (testing) shock when, as in the case of the low irritability fibers, it must be made inordinately strong. It then delays the recovery process, even when delivered during the refractory period, with the result that in fibers of low irritability the absolutely refractory period, as measured, is as long as the relatively refractory period. The plotted recovery curves of individual axons form a continuous series, the slower the conduction rate of the fiber the further from the axes is its curve. The recovery curves are not all alike in form.

The recorded amplitude of the potential of axons diminishes as their conduction rates. The relation seems to be linear, but the variations are wide.

The time to maximum of the spike increases as conduction rate slows, the plotted points falling rather widely around a curve of the hyperbolic type. The difficulties in the way of correlating the above two values are considered, and some exceptional configurations of axon spikes are described.

It is pointed out that if the relation of the recorded spike height to conduction is linear the conduction rate in a fiber, granting certain assumptions, must vary as the square of its diameter.

By the measures that have been applied the properties of nerve fibers have been found to vary in a perfectly continuous manner from one end of the conduction rate range to the other. If there are fiber types they cannot be differentiated by their axon potentials.

Consideration is given to the bearing of these results on the interpretation of the significance of the elevations appearing on the conducted action potentials of nerves.

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