H ERBERT S. GASSER

Mammalian nerve fibers

Nobel Lecture, December 12, 1945

In this review of the classification of nerve fibres the discussion will be restricted to mammalian fibers, as the most recent work on the subject in my laboratory has been turned in that direction. The later experiments were performed against the background of the earlier experiences with frog and mammalian nerve fibers, in the long and happy collaboration with Professor Erlanger; and much of what I will have to say is based directly on findings in our joint investigations. During the early period it became evident that the action potential (i.e. the variation during activity of the potential difference between two electrodes in contact with the nerve) was characterized not only by the initial rapid negative deviation which was called the "spike", but also by a subsequent sequence of low potential changes which were called the "after-potentials". The latter in their standard form consist in a negative after-potential followed by a positive after-potential. And, as we shall see later, their existence has shown itself to be useful in fiber classification.

Interest in mammalian fibers extended beyond the fibers as such to the consideration that any detailed analysis of central nervous system activity would involve a thorough knowledge of the properties of the units of which it is constructed. And this consideration in turn imposed the condition that the fibers must be studied in a state as close as possible to that obtaining in their natural position in the body. The spike potential is not easily disturbed, but the after-potentials are extremely labile. They are particularly sensitive to asphyxia, pH changes, ionic content of the surrounding medium, and to previous states of activity. The manner in which they are modified by the first three of these factors was beautifully worked out by Dr. Jörgen Lehmann. In the routine technique the nerves were examined after as rapid transfer as possible to an atmosphere of 5% carbon dioxide in oxygen, fully saturated with water vapor, and maintained at body temperature.

How well the natural conditions were imitated in the artificial environment was a question that had to be answered. Previous experience had demonstrated that there is a correlation between two sets of measurements of nerve activity: the potential changes and the excitability changes. As the

potential cycle is made up of the spike, the negative after-potential, and the positive after-potential, so what we have called the excitability cycle is made up of the refractory period, the supernormal period, and the subnormal period (described by H. T. Graham). And the temporal correspondence between the steps is excellent. It was argued that, if the potential cycle recorded from the isolated nerve matched the excitability cycle measured on the nerve with its natural perfusion of blood in the body, the technique was adequate. Experiments of this sort were performed by Dr. Grundfest and the necessary assurance was obtained.

For designation of fiber groups it has been necessary to invent names. Only a detailed history of the growth of information about the fiber constitution of nerves, its shadows as well as its lights, could fully elucidate the evolution of the terminology. The latter started before all the groups were known; and it now survives with the minimum of adjustment necessary to cover the extensions and clarifications. When all uncertainties will have been eliminated it may be desirable to invent a completely new terminology. At present, however, it seems more practical to adhere to the system as it has grown up, with the addition of definition where it is necessary for precision of meaning.
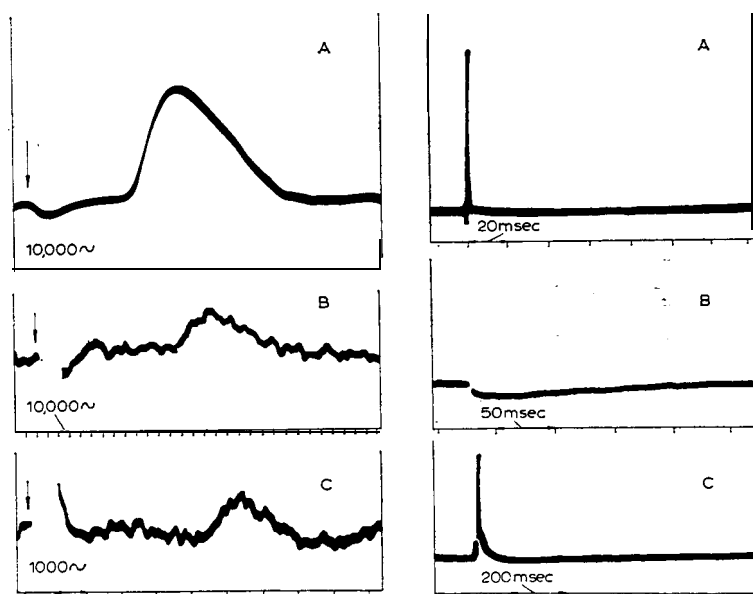
Fig. 1. *(Left)*: Spikes of unit axons of the A-, B-, and C-groups. *(Right):* Spikes and afterpotentials of the A-, B-, and C-groups in multiple fiber preparations.

Distinctly different sets of constants clearly point to the existence of three main groups of fibers. These have been named A, B, and C. Differences have been found as between both the spikes and the after-potentials. The durations of the spikes measured in presumably single axons may be given, omitting random variations, as 0.45 msec for A, about 1.2 msec for B, and about 2.0 msec for C (Fig. 1). For technical reasons the accuracy cannot be as great for the very small fibers as for the larger ones.

The after-potentials are smallest in the A-fibers; and in low-gain records taken so that the spike may be seen at the same time, as in Fig. 1, they are scarcely visible. There is a negative after-potential ending (in the saphenous nerve of the cat) at about 12-15 msec, followed by a positive after-potential ending at about 70 msec. At its maximum the latter has a value equivalent to 0.1-0.4 per cent of the spike height. B-fibers normally have no visible negative after-potential; though one may be developed by special procedures. The potential curve as seen in the records drops promptly to a level of positivity equivalent to 1.5-4 per cent of the spike height, and then returns to the base line over a period of 100-300 msec. In the C-fibers of visceral nerves there is again a well-developed negative after-potential. It lasts 50-80 msec, and is followed by a positive after-potential larger than in A-fibers but not so large as in B-fibers. Its maximum is equivalent to about 1.5 per
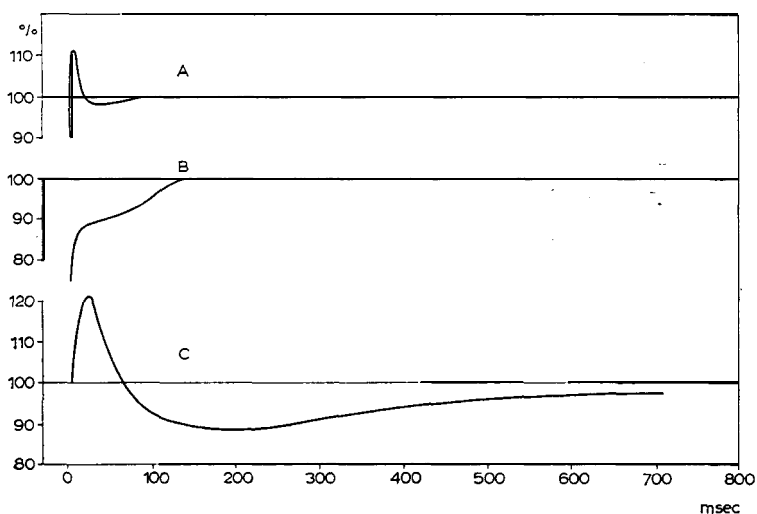

Fig. 2. Recovery of excitability after a single response.

cent of the spike height and it is traceable for 1 to 2 seconds. About the after-potentials in C-fibers of dorsal root origin little is known.

As would be expected from the configurations of the action potentials the excitability cycles are equally distinctive. After an absolutely refractory period commensurate with the spike duration the subsequent course of the excitability follows the curves set forth in Fig. 2. A return to normal through supernormality followed by subnormality holds for the A- and C-fibers, though on quite different time scales. In B-fibers without a negative after-potential refractoriness merges into subnormality without an intervening rise of excitability to or above the resting level.

Thus far no mention has been made of the difference between nerve fibers that is the most obvious of them all: the velocity of conduction. Over the range of the three groups all velocities are known between 115 and 0.6 m.p.s. (meter per second). Within each of the three groups the variations are 115 m.p.s. to about 10 m.p.s. for A, 15 m.p.s. to about 3 m.p.s. for B, and 2+ m.p.s. to about 0.6 m.p.s. for C.

The possibility that velocity is a function of fiber size was first proposed by Göthlin in 1907, long before means for testing it became available. With the advent of the modern methods, the fruitfulness of the idea soon became apparent; but the answer to the central question - what function of fiber size - was not directly to be forthcoming. The conclusion from our first experiments, which as far as it goes is still deemed to be correct, namely that velocity is in approximately linear relationship with the fiber diameter, was derived from an analysis of what was later learned to be an incomplete listing of the fibers in the A-group. After the catalogue of the three groups was completed it became apparent that the system of analysis that had been used was not adequate to establish the conclusion as valid even for the A-group alone. To find what the source of the difficulty might be was the object of the more recent experiments.

The approximate validity of the linear diameter-velocity relationship was shown by Hursh. He checked the maximal velocity with the size of the largest fiber in mammalian nerves selected to yield a wide range of maximal velocities. When these velocities, with values from 8 to 117 m.p.s., were plotted against the fiber diameters the points could best be connected by a calculated regression line with a slope of 6.

Encouraged by this observation, the original method pursued with Dr. Erlanger, which is a very sensitive test of the merits of a postulated velocity-size relationship, was reexamined with the collaboration of Dr. Grundfest.

The method consists in mapping the distribution of the fiber sizes, plotting for a given conduction distance the potentials contributed by the fibers of each size at the times fitting the velocities assigned to them, summing the potentials, and comparing the result with the recorded action potential from the same nerve at the conduction distance in question. Because the method is sensitive it is exacting. An error of a fraction of a micron in the size of a small fiber will throw the potential contributed by the fiber badly out of position, on account of the rapid dispersion at low velocities. But it is the method that must be adopted if ability to predict the form of the action potential from the histology be set as the solution of the problem.

In the revision of the procedure the principle innovation was to enter the potential contributed by each fiber as proportional to the diameter, inasmuch as the spike height of single axons had been shown to be proportional to the velocity (Erlanger and Blair for frog fibers, Zotterman and then ourselves for mammalian fibers), and the velocity in turn was known to be closely related to the diameter. In this way the necessary area was obtained for the late part of the action potential. With the innovation the action potentials constructed on the basis of a linear diameter-velocity relationship were now close enough in configuration to the recorded action potentials to justify the slight shifting of the velocities necessary to cause the fibers to make their proper contributions to the potential form. An empirical velocity-diameter curve was thereby derived which had a characteristic serpentine deviation from linearity. The initial concavity (Fig. 3) was traced to the variation in the axon-diameter/fiber-diameter ratio to which attention had been called by Arnell; and it could in the greater part be removed by using the axon diameter as the reference parameter.

On account of the identifiable features in its action potential a sensory nerve, as the saphenous, is the most favorable material for constructions of the action potential from the distribution of fiber sizes. The end result for one saphenous nerve of a cat is shown in Fig. 3, together with the fiber analysis of the nerve, and the axon-diameter velocity curve, alongside of two similar curves from other nerves. As the correspondence between the derived and the recorded potential form is close, the interest centers on the correlation curves. Collectively their principal deviation from linearity is a slight concavity downwards; that is, on the basis of a strictly linear relationship the potentials would be dispersed slightly too rapidly. To define the curve more closely will require much greater refinements and a mathematical treatment of conduction. For practical purposes a surprisingly good result can be ob-
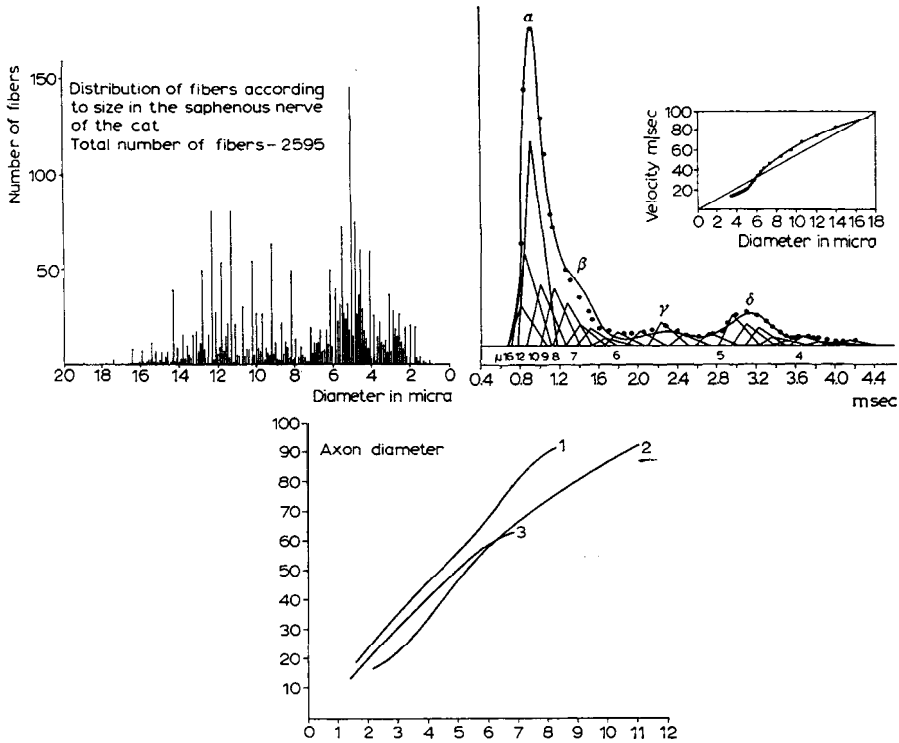
Fig. 3. *In the upper-right graph the continuous line* gives the action potential (saphenous nerve of the cat) recorded at 6 cm of conduction; the dots give the summation of the triangles. The location of the potentials according to fiber size is indicated under the construction. In *the curve in the inset* there is reported the velocities assigned to the fibers in terms of diameter. *Curve 2 in the lower graph* gives the relationship of the assigned velocities in terms of the axon diameters. Curves 1 and 3 represent the results of two other constructions of action potentials of the saphenous nerve: (1) cat; (3) rabbit. (Gasser and Grundfest.)

tained simply by using a constant times the axon diameter. And the approximate action-potential form for human nerves can be derived with some assurance from the published fiber analyses. As yet fiber analyses have not been extended beyond the A-group. However, the variation in fiber sizes is undoubtedly great enough to account for the range of velocities in the B- and C-groups.

In the foregoing presentation it was tacitly assumed that the A-fiber system is homogeneous except for size. To question the assumption is to call up for review the whole system of classification into three groups. The specific question is: within a group are there other variables than the size of the fibers.

Outstanding among the properties to be considered is the spike duration. Extrapolation back to zero time of the saphenous action potential reveals a constancy of duration of the spikes of all components (Fig. 4); and the collection of single-fiber A spikes in Fig. 5 shows durations falling between 0.4 msec and 0.5 msec without a systematic difference with respect to velocity.
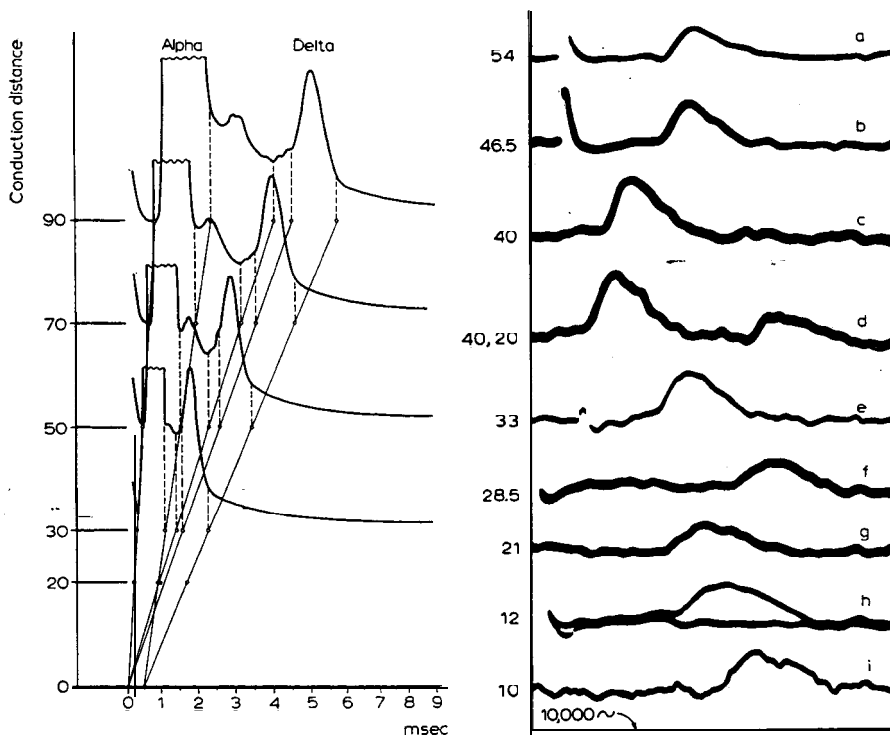

Fig. 4. Projection of the events in the action potential of the saphenous nerve of the cat, as recorded at the conduction distances indicated in millimeters on the ordinates, to zero conduction distance. The alpha and delta elevations subtend the same time on the abscissas. (Gasser and Grundfest;)

Fig. 5. Unitary axon spikes in fibers with velocities indicated in Fig. 4 in m.p.s. (Gasser and Grundfest). A spike of a 90 m.p.s. fiber is shown in Fig. 1.

However, Hursh recorded definitely mounting spike durations in kitten A-fibers conducting at less than 20 m.p.s. Furthermore there is an increase in the period of absolute refractoriness in the fibers with slow conduction as compared with the fibers of fast conduction, just as Blair and Erlanger found in frog fibers. If these findings cannot be traced to technique or to fiber

dimensions then the possibility must be entertained of a continuous series with change occurring abruptly only among the small fibers. Information about variation in the B-group is too meagre to be introduced into the argument.

In a continuous series the inference would be that all properties would be tied to the velocity; and the inference cannot be supported. Overlapping is described of velocities associated in one case with A properties, and in the other cases with B properties. The fibers in both groups are myelinated, and there is no method of differentiating them histologically. Moreover, the sizes of fibers known to give B potentials in visceral nerves correspond to the smallest sizes in the saphenous nerve which are A. No transitions have been seen in the after-potential configuration and the accompanying excitability cycle. The after-potentials in the fibers forming the last elevation in the A series conform to the group type, while the B after-potentials are quite different. For the refractory period the abruptness of transition was vividly shown by Bishop and Heinbecker in visceral nerves, where proximity in velocities can cause fibers of the two groups to contribute to the same elevation. The separateness of the contributions could readily be demonstrated by the refractory periods. Indeed, this observation was one of their reasons for their original differentiation of B from an elevation in A-fibers now known as delta. In a similar situation the change in the positive after-potential has been shown by Grundfest.

C-fibers stand apart not only because of the constants that have been described but also on account of their unmyelinated structure and their relative resistance to asphyxia, which holds in spite of their small size. The B-fibers most adjacent in size and velocity are more sensitive to asphyxia than are A-fibers. B is more closely related to A than to C. But the balance of evidence is in favor of regarding them as a group separate from A rather than a focal point of interest in a continuous transition. Consequently the original classification into A-, B-, and C-groups still seems to be the most practical one. But one should not lose sight of the fact that further classification on the basis of criteria not here considered is on the way. These forms of differentiation have not been included in my own experiments.

In the A-group another terminology has grown up from the designation of the features of the frog action potential by Greek letters at the time when all the known fibers were within the compass of what is now known as the A-group. As extended to mammalian nerves it has little significance beyond convenience of designation of the elevations, which are very constant in their

appearance in the action potentials of a given nerve. The elevations do not represent blocks of fibers consistently recognizable as such from nerve to nerve: and there is but little correlation of them with function. Somatic sensory, motor, and mixed nerves regularly have a first high elevation called alpha. But even this does not in each case represent the same fibers, as can be seen in Fig. 6 which is prepared from records of the action potentials of the saphenous and peroneal nerves of the cat obtained under the same conditions at 4 cm of conduction. The two alpha elevations end at about the same time; but the one from the peroneal nerve starts earlier, with a maximal velocity of 101 m.p.s., as compared with 85 m.p.s. for the saphenous nerve, because of the inclusion in the former of larger motor and afferent fibers to muscle. While in the saphenous nerve there follow after alpha, three other elevations that have been named beta, gamma, and delta, they cannot be identified in the peroneal nerve except for a delta difficult to discern the amplification
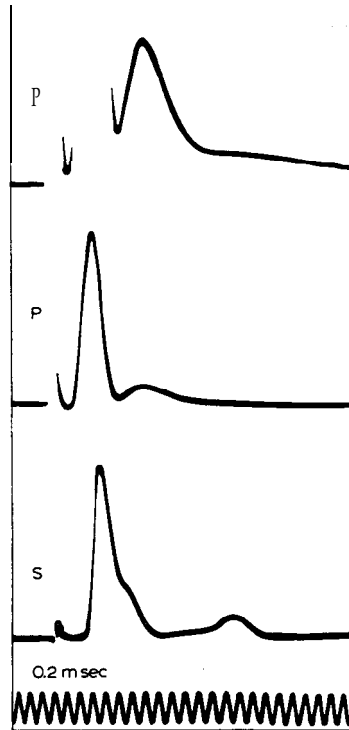

Fig. 6. Action potentials of the saphenous and perineal nerves from the same cat, recorded under identical conditions. Conduction distance, 4 cm. Upper peroneal record like the lower except for greater amplification.

used for recording. An elevation in the delta position can be identified in all somatic nerves. It is prominent in sensory nerves; and nerves to muscle contain both sensory and motor nerves with this velocity.

When the prominent delta elevation in sensory nerves was first described it was confused with B, largely because there is a B in a similar position in the action potentials of frog nerves; and in the earlier publications it was labelled B. After Bishop and Heinbecker, through studies of visceral nerves, identified a B analogous to the frog B, and showed the saphenous elevation was of dorsal root origin, the B designation had to be abandoned. The elevation is now called delta. In records of the dorsal roots, where all the fibers are involved, no elevation of like prominence appears. Nevertheless the presence of delta fibers in the roots is readily demonstrable. When the roots are stimulated the action potential pattern appearing in a-sensory nerve is typically that obtained on stimulation of the nerve itself. Most probably the explanation of the appearance is in the selection of fibers for distribution in the skin. In sensory nerves about one-half of the medullated fibers are involved in and about the delta peak. The importance of the peak is out of proportion to its height.

If B-fibers occur at all in mammalian somatic nerves there can be but few of them. No elevation recognizable as B has been seen in the action potential of any nerve, and the evidence for their presence is limited to the irregular appearance of a potential in the B position when the gray rami are stimulated. The subject needs a thoroughgoing reinvestigation, with proof that the potentials observed really belong to B-fibers. In visceral nerves the B potential, as it is seen in most records, appears as a single elevation. At long distances of conduction, Bishop and Hembecker, and Eccles, find that it breaks up into closely approximated peaks with components relaying with different sets of postganglionic fibers.

The exact configuration of the C elevation has been but little examined. Among the somatic nerves the elevation appears most prominently in the sensory nerves to the skin. Compared with the C elevation in muscle nerves it is found to be of the order of ten times as high, as related to the preceding A elevation. Ranson and Davenport found after sympathectomy a ratio of the unmyelinated to the myelinated fibers of 3.7 to 1 in the saphenous nerve of the cat as opposed to a ratio of 0.4 to 1 in a muscle nerve. It is this difference, uncompensated by the higher proportionality in the muscle nerves of unmyelinated fibers of sympathetic origin to those of dorsal root origin, that must account for the difference between the action potential heights.

The recording of the C complex is fraught with technical difficulties of a degree out of all proportion to those holding for the A complex. There is no way of getting a monophasic lead. Killing the nerve between the leads does not remove the second phase. It merely obliterates its features, and makes the locus of origin of the potential uncertain. In the face of this difficulty the best procedure, as long as one cannot eliminate the second phase, has been to use it. A convenient method is, for example, to set the two leads at two and four centimeters of conduction. The beginning of the potential distribution is obtained from the first lead and the end from the second lead. Then by making the necessary corrections for conduction, the form of the whole
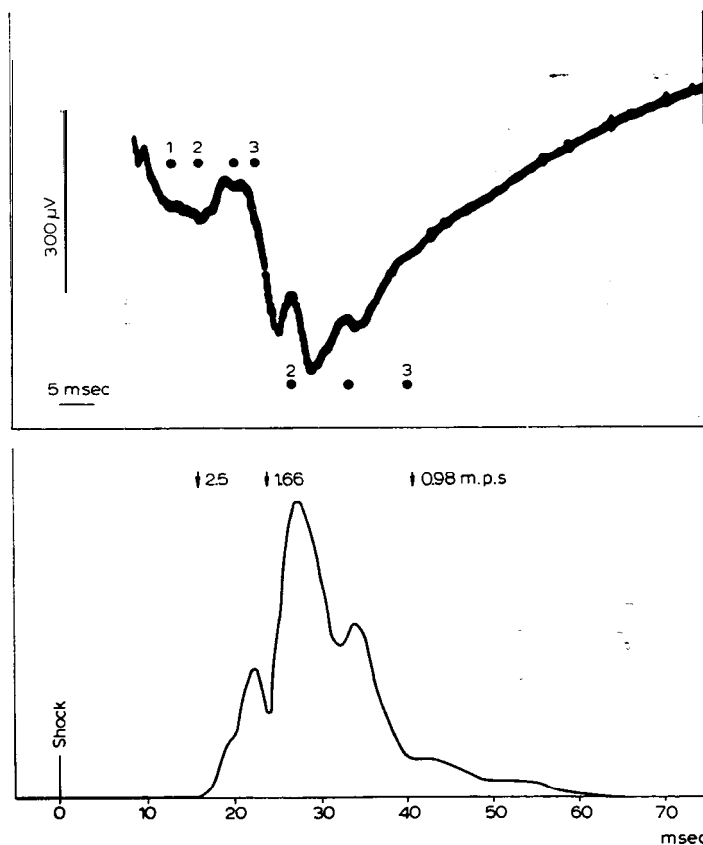

Fig. 7. (*Above*): Action potential of the C-fibers in the saphenous nerve of the cat. Diphasic leads at 2 and 4 cm conduction distances. The *dots* aid the identification of the events in the second phase with those in the first. *(Below)* : Attempt at derivation of the monophasic form of the action potential after 4 cm of conduction.

picture can be estimated with little error as to time, but with considerable uncertainty as to the magnitude of the components.

In some recent estimations of this sort the observations have yielded potential pictures which, though they lack the machine-like reproducibility of the A potential, still are consistently in agreement in having a basic pattern with only secondary variations. A fair sample is shown in Fig. 7. There is a large first component made up of action potentials conducted at velocities between 2 m.p.s. and 1 m.p.s., and this is followed by a smaller one with velocities between 0.9 m.p.s. and 0.6 m.p.s. The first component regularly divides at conduction distances long enough to permit the dispersion into two elevations with the second one starting at about 1.5 m.p.s. These three elevations are also seen in the action potentials of the dorsal roots. In the latter the C potential is much smaller than it is in the skin nerves as the ratio of the unmyehnated fibers to myelinated fibers is smaller (1.2-2.1 to 1, according to Ranson and Davenport), and the centrally directed unmyelinated branches of the dorsal root ganglion cells are finer than the peripherally directed ones. The fineness shows itself physiologically in that the velocities must be multiplied by a factor of about 1.7 to obtain the velocities of the corresponding components in peripheral nerves.

There is little danger of overestimating the importance of the C-fibers in sensory nerves. As compared with A-fibers, they are far more numerous, and there is a similar variation in the relative velocities. Equivalent variation in A-fibers would necessitate inclusion of the velocities from 15 to 60 m.p.s.; and this range is believed to take care of the mediation of a great deal of the detailed information about peripheral states. Whatever may be the proper interpretation of the groupings in the A-fibers, the problem appears to be repeated in the C-fibers.

Progress in the determination of the participation of sets of fibers in the carrying of sensory messages is retarded for want of a directly objective method. Much of the present information is precariously based on comparisons of what observers say they feel with neural events recorded under analogous conditions in animals. My principal contact with the functional problem has been to view the observations of others in relation to the order in which fibers are blocked by cocaine and by asphyxia. Cocaine blocks the C-fibers first, then the A-fibers in the order of their size, beginning with the smallest ones. The precision of the order is not perfect, however. Asphyxia, on the contrary, blocks the A-fibers first, with the order within the group the same as that holding for cocaine, while the C-fibers are the most resist-

ant. A brief account will now be given of how the reports of observers working with these agents on their own nerves appear from this viewpoint.

One finding stands out in bold outline, and the conclusion from it is amply supported otherwise: pain messages are carried both by A- and C-fibers. The part of the A-group most often associated with pain is the delta elevation because of several lines of converging evidence: reflexes evoked through sensory nerves stimulated under oscillographic control, histological findings as notably Sjoqvist's analysis of the trigeminal bulbospinal tract, stimulation of human nerves with shocks of controlled strength (Bishop, Heinbecker, and O'Leary), and the single axon potentials set up by stimuli that would be painful to man (Adrian, Zotterman). With this point in mind let us now examine the order in which deficits in sensation appear following the asphyxiation of nerves under a sphygmomanomegr cuff (Zotterman, Lewis, and Pochin). The first effect is numbness and with it come in rapid succession a rise in threshold of stimulation with the von Frey hair, and impairment of the responses to stimulation of the temperature spots and of fast pain. When a sensory nerve, the action potential of which is being recorded, is similarly asphyxiated the fibers in the delta elevation are the first to be blocked; and the block comes at a similar time. Hence, there is strong reason for assuming that all four modalities may be represented in the delta complex.

Due weight is not generally given to the experimental support for the representation of touch among the small fibers. Interpretation to this effect follows directly from the findings in asphyxia, and the view is supported by the single fiber delta spikes recorded by Adrian and by Zotterman following stimuli for light touch. To entertain this view in no way negates the involvement of large fibers also well supported by single fiber experiments, and by the fact that touch is the last sensation to be blocked by cocaine.

Experiments with cocaine theoretically reveal the relative upper limits of the velocities at which the several modalities are conducted. They tell nothing about the absolute position of the limits. The same relative limits should be revealed in the asphyxia experiments; but, as they do not appear even when the survival of the C-fibers is discounted, the subject will be passed over. There remain, however, two inferences that may be worthy of mention. One is that, inherent in the findings in both the asphyxia and the cocaine experiments, there is a warning against setting too low an upper velocity limit to the conduction of pain impulses. The other is that it is difficult to account for the long survival of the temperature senses in asphyxia without

postulating the mediation of these modalities by C-fibers. Goldscheider described double cold and double warm, but the phenomenon is nowhere nearly as vivid as that of double pain. In my own experience double cold seemed to be recognizable. It would be valuable to have the reports of more observers.

From the foregoing review it appears that attempts to identify modalities with definite segments of the velocity spectrum have not been very successful. We are left faced with evidence for conduction of single modalities at very different velocities, and inclusion of a number of modalities within a narrow band of fibers.

What then is the significance of the wide velocity range? Is it timing? Reflection on this, the most obvious interpretation of all, causes it to loom progressively larger. One need but consider the speed with which posture is controlled in preparation for the reception of oncoming detailed information and the adjustment of fine movement; or again the mode of transmission of excitation through any central ganglion. The more one sees of the exquisite precision with which events take place in the central nervous system the more one is impressed by it. The more the idea of timing grows in meaning content the more it becomes a directive for future exploration. Differential axonal velocities must play their part in the mechanism. Be this their only contribution to integration, it is still a large one.