

THE RÔLE OF FIBER SIZE IN THE ESTABLISHMENT OF A NERVE BLOCK BY PRESSURE¹ OR COCAINE

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A review of the literature on depression of conduction in a nerve trunk reveals the fact that there is a more or less definite order in the susceptibilities of the various fibers. In a cocainized nerve, sensory fibers are described as being more easily depressed than motor fibers, and as having different thresholds among themselves, so that the time of block depends upon the functions mediated. Although the data on this subject are not in complete accord, the order of disappearance which receives the strongest support is, beginning with the most susceptible: pain, cold, warmth and contact. This is the order which was observed by Baglioni and Pilotti (1909) and later by Thöle (1912) to obtain in spinal anesthesia, a condition which is really induced by a perineural application of the anesthetic. That cold is blocked before warmth was also the finding of Ponzio (1908), of Schilder (1913) and of Goldscheider and Hahn (1924); and Bier (1899) described pain as going before temperature and contact. On the other hand, Goldscheider (1886) observed temperature to disappear before pain in the distribution of a cocainized nerve branch.

While cocaine has been most studied, its mode of action is not a feature of cocaine alone. Similar effects have been described for the aliphatic narcotics, phenols, aconitine, etc.; and these effects have therefore been associated with the nature of the nerve fibers themselves. No experimental data have been presented, however, to indicate what this quality of the nerve fibers might be. Cushny in his textbook states that no explanation of the difference between the responses of sensory and motor nerves is known. On the other hand the assumption is widely made (e.g., Gottlieb in Meyer and Gottlieb's text, and Poulsson in Heffter's *Handbuch der Pharmakologie*) that the phenomenon is due to a difference in chemical constitution with a corresponding difference in affinity. But when we see the same order, only reversed, emerging from the data on compression blocks, it is apparent that the postulate of different chemical affinities is not a sufficient explanation.

¹ A preliminary report on the effect of pressure was published in the *Proc. Soc. Exp. Biol. and Med.*, 1927, xxiv, 313.

The data for compression are more fragmentary and less concordant than those for cocaine; but there is evidence that motor fibers are blocked before sensory fibers and that sensations disappear in the order: contact, cold, warmth, pain. The relationship between the susceptibilities of motor and sensory nerves was determined nearly half a century ago by Luederitz (1881). He was stimulated to perform his experiments by the clinical observation that, following mechanical lesions of mixed nerves, motility is more injured than sensation; and he succeeded in duplicating the clinical picture in the sciatic nerve of the rabbit. Although his conclusion—namely, that motor fibers are more susceptible than sensory fibers—has not been confirmed either by Zederbaum (1883), Efron (1885), or Duccesi (1901), the experience obtained in the present research indicates that it is essentially correct. The order designated for the failure of conduction of the various kinds of sensory impulses has been derived from the observations of a number of experimenters. In 1885 Herzen showed that pressure on nerves blocks contact and cold before warmth and pain. In the following year Goldscheider (1886) confirmed the blocking of cold before warmth; but he found that contact, although affected simultaneously with cold, persisted longer so that, with complete anesthesia to the latter, contact and warmth, though subdued, could be felt. More recently Fabritius and Bermann (1913) made the observation that, when the last trace of the contact sense had gone, pain and temperature (including cold and warmth) could still be felt, the pain being very definite.

It is to be expected that the solution of the problem of the mechanism of the differential susceptibility of nerve fibers is to be found in some quality of nerves which varies from fiber to fiber, and this at once suggests a survey of the known characteristics of nerve fibers in search of such a factor. The electrical responses in individual fibers—that is, the axon potentials—are the same in all medullated fibers larger than 5μ (Erlanger, Bishop and Gasser, 1926; Gasser and Erlanger, 1927), and possibly also in some fibers smaller than this; so too are the refractory phases (Erlanger, Gasser and Bishop, 1927): points strongly suggesting that the fundamental chemical or physico-chemical constitution of nerve fibers is the same in all above this size. What varies is the threshold of excitation and the velocity of conduction; but these in turn are dependent upon the fiber size (Lapicque and Legendre, 1913, 1922; Lapicque, Gasser and Desoille, 1925; Gasser and Erlanger, 1927). Thus the physiology of nerve strongly suggests that fiber size should be an important factor in the resistance of nerves to injury.

If susceptibility to injury be connected with size, then the connection should reveal itself by an order of blocking in relation to the different velocities of conduction, since velocity is a linear function of the diameter of the fibers (Gasser and Erlanger, 1927). This order can be determined

by observation of the conducted action potential, because fibers of different velocities can then be identified on account of their temporal dispersion. If the small fibers be the first to be affected, the potential wave should be shortened from behind; if large fibers be first, the wave should be shortened from the front. Thus the effects of pressure and of cocaine may be predicted. Since they seem to act in a reverse order on the functions mediated by the nerve, they should also affect the action potential in a reciprocal manner, one shortening the front of the wave, the other the tail. Should this occur as predicted, then a comparison of the psycho-physiological observations with the behavior of the action potential should yield information as to the functions mediated by fibers of different sizes.

GENERAL METHOD. The nerve was stimulated at one end and the action potential, after amplification, was recorded monophasically from the opposite end by means of the cathode ray oscillograph. After the normal form of the action potential wave had been recorded, the block was applied to a short stretch of nerve between the lead and the stimulus. The shortness of the block was necessitated by the fact that conduction becomes slower before it is extinguished. To prevent too great confusion from the resulting relative shift of the constituent potentials in the combined wave, it was necessary for the conduction in the depressed area to be as short as practicable in comparison with the total distance of conduction.

In the interpretation of the experiments it should be borne in mind that the impulse is normal until it reaches the depressed area. There it drops in size or is blocked entirely. On emergence the impulse is again traveling in normal nerve and, according to the all-or-nothing law, the process in each active axon must be of normal size and velocity. What is being recorded is normal axon potentials. Any difference between the normal compound wave and one observed after the impulses have passed a depressed area must be due either to inactivity of fibers under the lead, owing to the fact that the impulses have been blocked, or to displacement of axon potentials due to slow conduction in the depressed area.

BLOCK BY COMPRESSION. The method used was a modification of that of Meek and Leaper (1911). Through a brass tube 12 mm. long having a 2.5 mm. bore was threaded a fairly thin-walled rubber tube, whose outside diameter fitted the bore of the brass tube. The ends of the rubber tube were everted over the ends of the brass tube and tied. Since the application of pressure led to protrusion of the rubber tube from its collar and to subsequent bursting, displacement was prevented by metal caps. These were perforated at the center for passage of the nerve. Pressure was applied from an oxygen cylinder through a side-arm of the brass tube, it being quickly, easily and accurately controlled by a reducing valve. To release the pressure after blocking, a needle-valve was inserted in the connecting tubing.

The mechanism of pressure block was not studied, only the results. However, by analogy with the effect of external pressure on thin-walled tubes, where the large tubes would collapse before the small ones, it was to be expected that the large fibers would be the first to be blocked; and such proved actually to be the case.

RESULTS. The effect of pressure was revealed most strikingly when about 25 pounds per square inch were applied rapidly through the cuff. The α wave then seemed to melt away from the fluorescent figure of the action potential on the screen of the tube. But for a careful analysis of the progress of the block it was necessary to build up the pressure more slowly. When this was done very concordant results were obtained, and they can best be presented in the form of an analysis of a single series. Eight of the fifteen records, made in this series during the course of the blocking, are reproduced in figure 1; and for further reference five of them have been redrawn in rectangular linear coördinates and superimposed (fig. 2).

When the pressure was applied the height of the α crest began to decrease; but simultaneously with this the form of the whole wave began to change, showing that the majority of the fibers in the nerve were already affected. When curve 3 was taken, the β crest and the notches on either side were already definitely delayed. This delay increased throughout the period of compression, and it occurred to a relatively greater degree in all the earlier parts of the action potentials. Between records 1 and 6 the α crest was delayed about 0.4σ , while β was delayed 0.2σ , and γ hardly at all. By the seventh record so many α fibers had been blocked, that the crest of the wave had no relation to the peak of the histological distribution curve of the α group; in fact, an approximate correction had to be made to locate the real α crest in record 6.

The course of the β crest could be followed more exactly. The height of the crest decreased slightly, rose again, then progressively fell away. According to the conditions of the experiment these changes can be explained only by a temporal redistribution of the constituent potentials or by blocking. While it is possible that some β fibers may have been blocked out of turn, a comparison of the areas of the waves shows that the initial decrease in height was due mainly to temporal dispersion. The subsequent rise in height was due to a delay of the faster fibers in the compressed area, so that they appeared beyond the block in the same position as smaller, less affected fibers. Later, with the blocking of the β fibers, the whole wave decreased in height just as the α wave had previously undergone the same change.

The γ wave was progressively delayed, but this delay did not become marked until the β wave was rapidly decreasing. Even in the late records the γ wave was essentially intact; but encroachments of the more delayed

faster fibers had filled up the notch between it and β , and had probably raised its crest.

In the late records it is seen that, beginning at the time of the start of the normal action potential, there is a long low potential lasting up to the start of the β wave. The most probable explanation of this is that a few fibers of very varied sizes had a more sheltered position with respect to the compression. Their number was small however, and the majority of the fibers followed the rule.

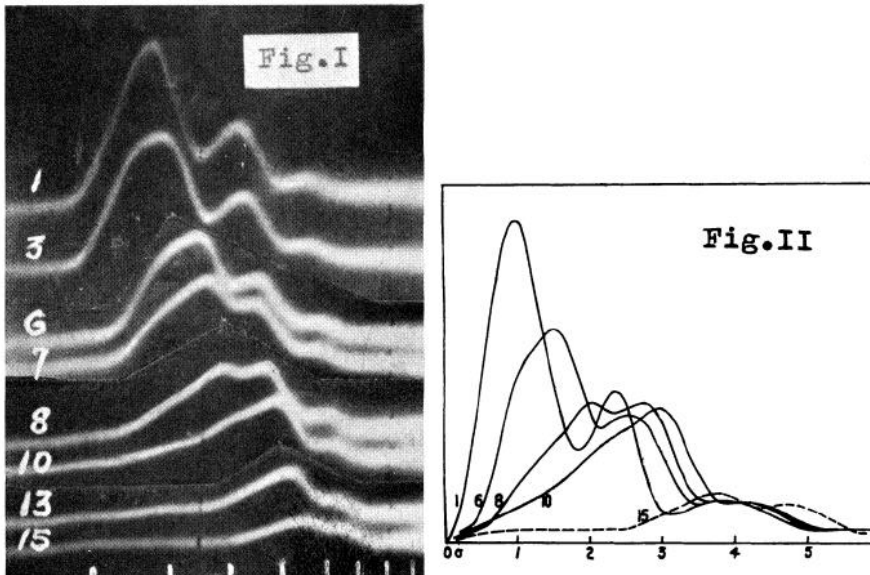


Fig. 1. Action potentials of a bullfrog nerve (10/28/26). 1 mf. 5000 ω . Conduction 7.8 cm. Time in sigma in all figures, 1, 12:54 normal; 12:55 compression started with 10 pounds per square inch. 3, 1:02; 1:09 pressure increased to 25 pounds per square inch. 6, 1:10; 7, 1:10:30; 8, 1:11:15; 10, 1:12:30; 13, 1:14:45; 15, 1:34.

Fig. 2. Records 1, 6, 8, 10 and 15 of figure 1, redrawn in rectangular linear coordinates and superimposed at their origins.

BLOCK BY COCAINE. For the application of the cocaine solution the nerve was threaded through two perforations in the side of a small vulcanite cylinder. When the cylinder was filled, the surface film at the openings was sufficient to maintain a column of liquid high enough to cover the nerve. Taking into consideration the amount of spread of solution along the nerve, the length actually in contact with the drug could not have been over 1 cm. The experiments on frog nerves were performed at room temperature, and those on mammalian nerves at 37° unless otherwise noted.

The results obtained with cocaine were not as uniform as was the case for

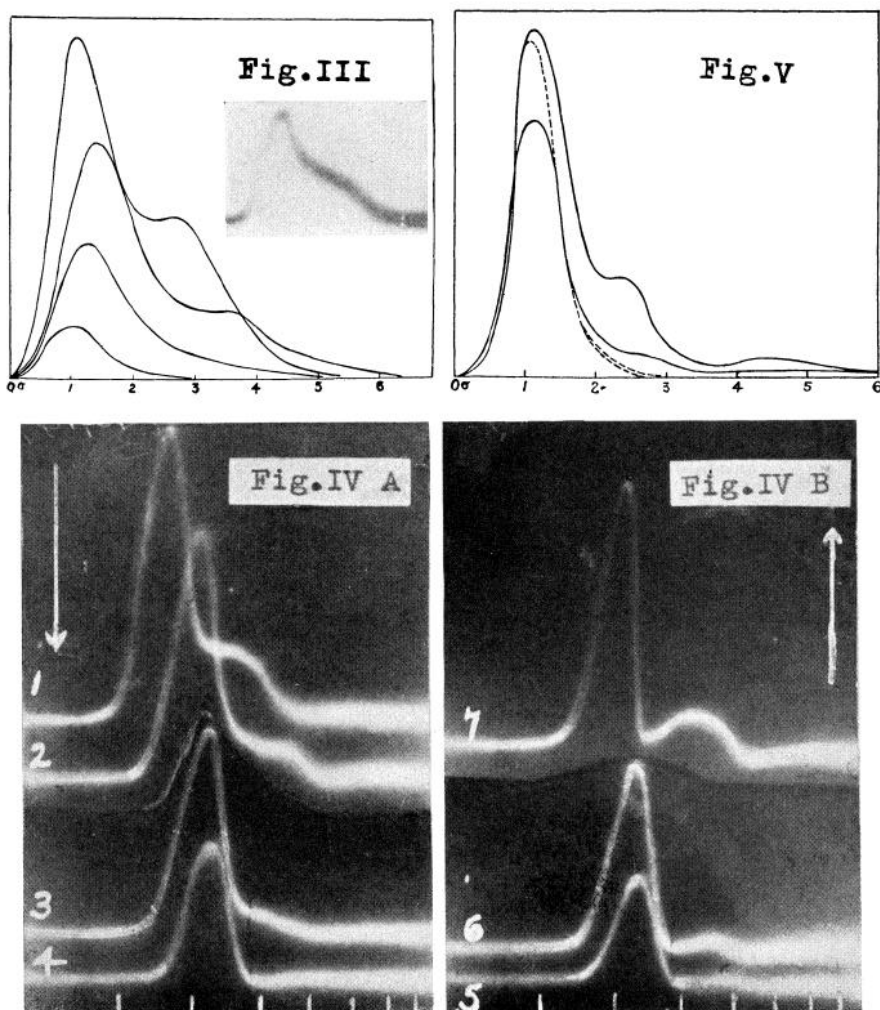


Fig. 3. Four stages of the compound action potential of a dog's saphenous nerve undergoing a block in 1/1000 cocaine HCl (10/9/26). Conduction 9 cm. The records were taken 4, 13, 17 and 21 minutes after the application of the drug. The largest wave differs from normal in having a deeper notch between the β and γ waves (first and second waves in saphenous). The form of the normal wave is seen in the reproduction of the actual record in the inset.

Fig. 4. Dilute cocaine on the sciatic nerve of the bullfrog (10/14/26). 1 mf. 5000 ω . Conduction 7.8 cm.

A. Period of block. 1, normal, 10:23. At 10:28 1/10,000 cocaine HCl; at 11:58, 1/2000 cocaine HCl. 2, 12:37; 3, 1:20; 4, 2:03.

B. Period of recovery beginning at 3:00. 5, 3:23; 6, 3:50; 7, 5:00.

Fig. 5. Dilute cocaine on the sciatic nerve of the bullfrog (10/15/26). Conduction 8.2 cm. Records redrawn in rectangular linear coördinates. — whole action potential. - - - α group only. The first parts of these are coincident with the whole action potential.

pressure. The amount of differential action was variable, and in some frog nerves was insignificant or zero. However, a differential action was visible in every mammalian nerve studied; and wherever it occurred, in nerves of all species, it was the same in kind: small fibers were blocked before large ones.

The experiments were performed in two series. The first series depended upon the fact that the conducted action potential occurs in waves, the method being to note the time at which each of these waves disappears. The first three waves α , β , and γ are very close together and represent the potentials of fibers larger than $5\ \mu$. Following the γ wave and well separated from it is a fourth wave which was described by Erlanger (1927) in the saphenous nerve of the dog and labeled δ . This wave also occurs in other nerves and is best revealed in records made with four panel (100,000 fold) amplification.

For the separation of the α and β waves, the branches of the crural nerve promised to afford a favorable preparation, as Erlanger had observed that the muscle-branch receives only the first or α wave, while the saphenous branch receives fibers whose fastest component corresponds to the β wave of a mixed nerve. Accordingly, the preparation was arranged so that the undivided portion passed through the cocaine chamber in such a way that the proximal end could be stimulated electrically, and each of the two branches could rapidly be connected in turn to the amplifier.

In two of three preparations from the dog the waves in the saphenous branch disappeared before any great involvement of the muscle-branches. In the third preparation such a differentiation was absent, although there was good differentiation as to the time of disappearance of the waves within the saphenous nerve itself. This lack of uniformity was very possibly due to the existence of an uncontrolled variable in the connective tissue sheath of the nerve, as the sheath is a very important factor affecting the rate of the action of drugs applied perineurally. The branches of the crural nerve still have their own sheaths in the undivided portion of the nerve and therefore any variation in their thickness or holes at the points of cut branches would produce a serious complication. The sheaths on the two branches are about the same in thickness; but there are many divisions of the muscle branch at this level, while there are none of importance in the saphenous. This would place the muscle branch at a relative disadvantage.

In the saphenous nerve the δ wave always disappeared before the $\alpha\beta\gamma$ complex; and it was also seen to behave similarly in the tibial nerve of the cat and in the sciatic nerve of the frog.

The second series of experiments was limited to a closer analysis of the changes in the $\alpha\beta\gamma$ complex. In general, γ was more affected than β , and β more than α ; but during the blocking of the slower waves the faster

waves were undergoing alterations in form. It was therefore necessary to make a special study, to determine whether or not some fibers in the faster waves were blocked before all the fibers in the slower ones.

In figure 3 are recorded the effects of cocaine on the portion of the $\alpha\beta\gamma$ complex found in the saphenous nerve, that is on the β and γ fibers. The experiment was performed at 25.5°C. Four records were selected from the series, enlarged optically, redrawn in linear coördinates, and then plotted so that they all start at the same point; although actually, when the last record was made, the fastest fibers took 0.6 σ longer than was normally necessary to traverse the 90 mm. distance of conduction. This meant that the fastest fibers had a mean velocity in the cocainized stretch of about 13.3 m.p.s., a value 30 per cent of normal. Block is anteceded by a great retardation in velocity.

A mere glance at the figure shows that the γ wave was blocked before the β wave, but that at the time of block the β wave was much reduced in height. This decrease in height can be explained in part by the greater temporal dispersion of the constituent fibers. But is it entirely so explained? To obtain an answer to this question some reconstructions were made of the action potential which would be predicted by the histological constitution of the nerve. The method for this procedure has been previously published (Gasser and Erlanger, 1927); and the data contained in figure 15 of that paper were employed. After a preliminary reconstruction, made for the conditions obtaining in a normal wave, had provided a control theoretical curve in satisfactory correspondence with the one actually recorded, reconstructions were made of the action potentials in partially blocked nerves, on the assumption that the velocity in fibers of each size would be the same fraction of normal as occurs in the fastest fibers. These reconstructions made it quite apparent that the fall in the height of the β wave could not possibly be accounted for on the basis of spread, either on the assumption selected or on any one employing a set of velocities which would permit the crests of the waves to fall in their proper positions.

Some of the large fibers might possibly be blocked ahead of small ones because of a position in the nerve trunk more accessible to the poison. They might, for instance, lie at the concentrated end of a diffusion gradient; but, if that be so, the effect should become minimal when very dilute solutions are employed to produce the block. Accordingly, an experiment was done on the sciatic nerve of the bullfrog, in which the block was started with 1/10,000 cocaine-HCl and finished with 1/2000. Records selected from this experiment are reproduced in figure 4 so that the abscissae correspond. The delay in the fastest fibers is therefore evident. The secondary waves decrease progressively in height, but in spite of the slow action of the poison the α wave also decreases in height as they disappear;

and it does not elongate sufficiently to explain the decrease. As the last record was taken $3\frac{1}{2}$ hours after the start of the cocaine action, opportunity was almost surely given for an even distribution of the drug throughout the perineural spaces. Therefore, the blocking of some of the fast fibers before the slower ones cannot be explained as due to a diffusion gradient.

The recovery series for this experiment is also included in figure 4. As is usually the case the late waves are the last to recover; but in this particular experiment, part of the changes in form between the initial and final records must be due to changes independent of cocainization, as the total period of observation of the nerve was $6\frac{1}{2}$ hours.

As a further test of the order of fiber disappearance, 1/2000 cocaine-HCl was applied to another bullfrog sciatic nerve and records made not only of the whole action potential but also of the α group alone, the latter being obtained by the use of an appropriately submaximal stimulus (Erlanger, Gasser and Bishop, 1924; Gasser and Erlanger, 1927). The drug acted very slowly and a few β fibers were still conducting after three hours. The records taken for figure 5 were made after a period of action of the drug lasting $2\frac{1}{2}$ hours; they are redrawn in rectangular linear coordinates. The delay of the fastest fibers in passing the cocaine cell was small in this experiment, but the amount present has been eliminated in the figure so as to start all the curves at the origin.

The area of any part of the curve represents the area of the fibers in the nerve trunk which was responsible for that part. Therefore, with the aid of a planimeter, the areas of both the whole waves and of their corresponding α waves were measured. In the curve for the normal nerve the α wave constituted 58 per cent of the total, a value in good agreement with the percentage area of the α fibers in the nerve (vide Gasser and Erlanger, 1927, fig. 10). In the cocainized nerve the area rose to 83 per cent of the total, not, however, before the blocking of some fibers within the wave, as the wave-area was only 90 per cent of normal. In the meantime the whole action potential had fallen to 63 per cent of normal, which means that it contained the potentials of fibers other than α fibers amounting to 5 per cent of the original area.

The sum of the experiments shows that in general small fibers are blocked before large ones, but that the blocking is not effected with any precision. Fibers of all sizes are found to be unable to conduct as long as smaller ones. Thus, while fiber size is a determining factor in nerve susceptibility to poisons, it is not sufficiently differentiating to cause the fibers to drop out on a strictly size-basis. It may be for this reason that the psychophysiological findings are not in better accord.

DISCUSSION. The foregoing experiments show that, in so far as there is a differential action of cocaine on the fibers of a nerve trunk, it is the small fibers which are most affected. This might be due to the fact that their

thinner myelin sheaths would permit easier access to their axial protoplasm, but it is not necessary to make use of the myelin sheaths in formulating a sufficient explanation. If we assume that cocaine acts by chemical combination with the protoplasm, then, since the surface per unit volume increases directly as the diameter decreases, the smaller the fiber the greater the accessibility. At first sight, such an hypothesis suggests that when the nerve is washed the same factor would also cause the small fibers to be the first to recover. But this is definitely not the case. Recovery begins in the large fibers and proceeds in an order the reverse of that of the blocking, thereby corresponding with what has long been known with respect to the return of function. However, further consideration of the accessibility hypothesis suggests that a possible consequence would be that the protoplasm of the small fibers combines with the poison not only to the point of block but to a point far beyond this. The effect is progressive; block is preceded by varying degrees of slower conduction and it may be followed by a greater disorganization of function. Thus a longer period of washing would be necessary either to remove the excess drug or to allow more time for reorganization.

Such a simple mechanism as has just been described should cause the fibers to be blocked systematically on a size-basis; and since this does not rigidly hold the problem can be considered to be only partly solved. Some other as yet undetermined factor must be operating.

However, the relationship of the ease of blocking to the size of the fibers is sufficiently precise to explain the origin of the notion that sensory nerves are more easily blocked than motor. Small sensory fibers have been compared with large motor fibers; and, had it so happened that it would have been equally easy to compare vasomotor and proprioceptive fibers, the reverse notion could easily have arisen. In fact Dixon (1905) has described cardio-inhibition as disappearing more easily, on cocainization of the vagus nerve, than the reflexes modifying respiration. A motor function has disappeared before a sensory one, which probably means that it is mediated by smaller fibers.

LOCATION OF THE VARIOUS SENSORY FIBERS IN A NERVE TRUNK. Since the observations on the relative intensities of the action of pressure on the conduction of the sensations of cold and warmth cannot be made to fit with the action of cocaine, these two senses must be considered collectively as temperature. With this simplification, the two sets of data, derived from pressure and cocaine experiments, indicate that the senses in a nerve trunk are located, with respect to the fibers of various sizes, in the order, contact, temperature, pain. Use can be made of this order, provided the ends of the series can be located. Unfortunately this can only be done by inference. The most probable location of the upper end is in the β group, because this is the fastest wave in a cutaneous sensory nerve. The

lower end is more difficult to locate; but Ranson and Billingsley's observation (1916) that pain is mediated through the lateral division of the dorsal root, which is made up only of unmyelinated and small myelinated fibers, gives an indication as to its position. The other senses must fall in the intermediate fiber groups.

SUMMARY

An important factor, determining the relative susceptibility of the constituent fibers in a nerve trunk to a pressure and to cocaine, is their size. Pressure exerts its greatest effect upon the large fibers, cocaine upon the small ones. These facts offer an explanation of the order in which functions have been observed to be depressed, and they provide an aid to the location of these functions among the fiber groups.

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