

FIBRE INTERACTION IN INJURED OR COMPRESSED REGION OF NERVE.

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It has long been known in classical electrophysiology that severance of the nerve is a factor of significance for the excitability of the frog's nerve-muscle preparation. Thus Pflüger's (1859) observation that the upper end of the nerve is more excitable than the end towards the muscle was accounted for by Heidenhain (1861) by his finding that nerve excitability is increased in the region near a cross section. With modern methods Adrian (1930) showed that the excitability at the cut end of a nerve is sufficiently high to cause a spontaneous discharge of impulses, and Adrian as well as Skoglund (1941) demonstrated that cross sections of *sensory* nerves are far more efficient impulse generators than those of *motor* nerves.

But the most remarkable experiment in this field was published as long ago as in 1882 by Hering: he cut the sciatic plexus of a frog, tied a knot around the nerve at the knee and stimulated through a pair of electrodes just above the knot. Muscles *above* the knee were then found to contract, signifying that impulses caused by the stimuli had ascended the nerve fibres to the cut end of the plexus in the pelvis there to pass over into adjacent motor fibres innervating muscles above the knee region. Nerve fibre interaction thus may take place at an injured region which in this respect serves as an artificial synapse. Hering added that the experiment only succeeded with especially excitable preparations. Uexküll (1894) confirmed this effect and found that it disappeared when the cut end was shunted with a solution of 0.5 per cent. NaCl.

Since the possibility of fibre interaction in a pathologically altered region of a nerve is a question of considerable importance for clinical neurology (causalgia, sciatica and other neuralgic pains, referred pain) it is surprising how little attention has been devoted to experimentation in this field, and how commonly either central effects or fibre dichotomy are invoked to explain every apparent exception to the classical law of isolated conduction in nerve fibres. The experiments to be presented in this paper contain some new observations on fibre interaction in mammalian nerve which also emphasize clinical aspects of this problem.

The recent history of research in this field is relatively brief. It has been shown by Jasper and Monnier (1938), Arvanitaki (1940) and Katz and Schmitt (1939-40) that cross excitation between adjacent fibres can easily be demonstrated in crab nerves. In frog nerve this does not happen normally (Holzer, 1936) but if the excitability in a certain region of the nerve is increased by stimulation with a constant current (Otani, 1937), by dehydration, or by treatment with various hypertonic solutions (Kwassow and Naumenko, 1936) stimulation of some fibres induce activity in others. Similarly Rosenblueth (1941) has shown that after application of a constant current to any region of a cat's nerve the impulses carried by some fibres may stimulate other adjacent fibres. In an interesting paper Renshaw and Therman (1941) have modified Hering's original experiment and demonstrated that impulses passing up along the dorsal columns are reflected at a cross section in the spinal cord and thrown back into other column fibres so that they can be picked up from the dorsal roots.

TECHNIQUE.

In this work nerve activity is recorded with an amplifier and a cathode ray oscillograph. The electrical stimulus to the nerve (1-2 per second) has been synchronized with the sweep circuit of the cathode ray so that each time the beam of the cathode ray passes horizontally across the face of the tube this movement starts at the moment of stimulation of the nerve. The impulse activity is pictured at right angles to the sweep movement so that the effect of the stimulus can be observed as a standing vertical wave on the horizontal abscissa written by the cathode ray. Thus, when the film slowly passes vertically across the beam of the oscillograph a series of successive pictures is obtained such as in fig. 2, illustrating the moment of stimulation to the left and the volley discharged into the amplifier after a latent period measurable in milliseconds somewhere in the middle of the picture. The time marking in the figures is always in milliseconds.

Cats have been used throughout as experimental animals. The details of the operation will be given below. The animals have been in a metal box the floor of which formed the bottom of a water-bath heated from the outside. A moist atmosphere and high temperature were thus secured.

RESULTS.

(1) *The standard experiment. Some precautions. The effect of the anæsthetic.*

The best anæsthetic was found to be chloralose, a 1 per cent. solution, injected intravenously. About 5-6 c.c./kg. were given. Then the spinal cord was exposed, the dura opened, and the dorsal and ventral roots from L1 to S5 severed. Knots were tied around the ends of L6 and L7. In most cases the L7 pair of roots was used. The sciatic stem was exposed and branches severed up to the bony canal.

If at this phase of the operation, stimulating electrodes are applied to the motor root of L7 and leads are taken to the oscillograph from the sensory root of L7, as in fig. 1 (the picture marked "Standard"), stimula-

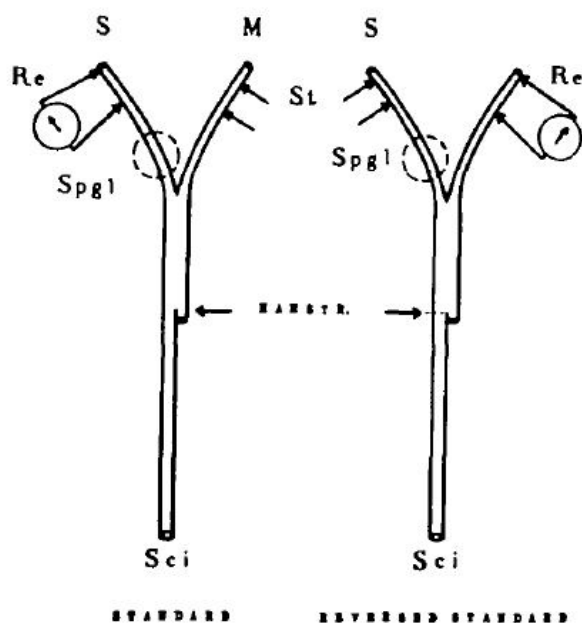


FIG. 1.—Diagram of placement of stimulating electrodes (St) and recording electrodes (Re) on Motor (M) or sensory (S) root, Sci, sciatic nerve; Spgl, spinal ganglion (see text).

tion of the motor root causes a volley of impulses to appear in the sensory root. It can be shown that this volley is a "back-response" from the gastrocnemius muscle (absent in the figure). Its latent period is so brief that the whole process is over long before the muscle has had time to contract and stimulate its stretch receptors. We noted this "back-pressure" here but soon found that it had been described before by Lloyd (1941) whose pictures are identical with our own. The "back-response" is due to electrical cross-stimulation in the muscle, probably at the region of the motor end plate.

From the point of view of this work this interesting back-response from the muscle is a source of error. Hence complete denervation of the limb must be carried out with the utmost care and the muscles around the hip joint and spine have to be cut at their insertions. When this has been done a preparation is obtained such as the one marked "Standard" in fig. 1. The severed ends of the hamstring and sciatic nerves are shown in the figure to emphasize that these are the important regions with which this paper will deal.

After complete denervation our "standard" experiment can be carried

out. The motor root of L7 is again stimulated. The leads on the sensory root (fig. 1) then record a discharge such as the one illustrated in fig. 2 *a*

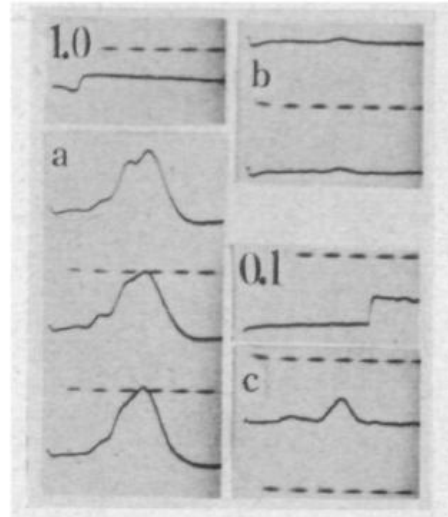


FIG. 2.—Above *a*, calibration to 1.0 mV. Time in this and all records to follow in msec. *a*, response to stimulation of motor L7 picked up in sensory L7 (standard); *b*, reversed standard (*see text*). 0.1 calibration to 0.1 mV; *c*, reversed standard.

in three consecutive pictures cut out from a long series. The slight variations seen are characteristic. The calibration to 1.0 mV. above the picture shows that the volley is of a large order of magnitude. Somewhere in the nerve the volley of impulses set up in the motor fibres at the root have been transmitted to the sensory fibres and thus have become measurable at the sensory root. In the next row (*b*) the stimulus has been shifted to the sensory root and the leads to the motor root. We shall refer to this arrangement (fig. 1) as "Reversed standard." The two consecutive uppermost records of the series show a very small hump on the baseline. We therefore increase amplification so that calibration to 0.1 mV. (above *c*) now gives a deflection about twice the size of the deflection to the ten times larger voltage used for series *a*. The lowermost picture *c* then shows that a volley of somewhat less than 0.1 mV. can be seen in the motor root upon stimulation of the sensory root. In many, if not in most cases, nothing whatever can be observed in the reversed standard when large volleys are noted in the standard combination. In general, therefore, there is far more resistance to transmission by fibre interaction in the direction sensory \rightarrow motor, than in the direction motor \rightarrow sensory.

Where does the fibre interaction take place? There are several methods available for answering this question but one of the most direct ones is used in the experiments illustrated in figs. 3 and 4. The stimulating

electrodes are on the motor root as in the standard experiment but the leads to the oscillograph have been shifted down the nerve as shown in fig. 3. The electrical shock to the motor root will then elicit a typical direct diphasic wave (fig. 4 *a*) at the leads. In the figure this is the first

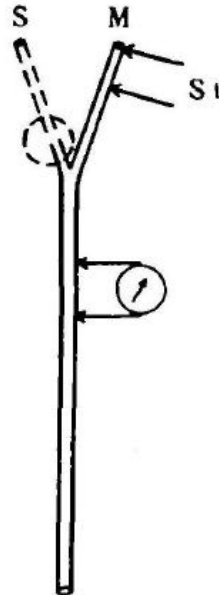


FIG. 3.—Recording galvanometer (oscillograph) placed on the sciatic nerve, stimulating electrodes on the motor L7, as described in text.

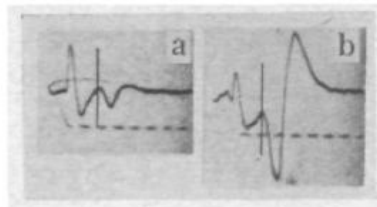


FIG. 4.—Records taken with stimuli and leads as in fig. 3. Record *a*, first follows "direct wave" from motor root; after vertical line, wave with opposite phase leading and hence reflected from end of nerve. In *b* stimulus for "direct wave" weakened. Reflected wave generally augmented by cutting end of nerve.

wave that begins with an upward swing, signifying that the travelling volley has reached the upper lead in fig. 3. It is followed by the well-known change of sign with a smaller swing in the downward direction when the wave of activity passes the lower lead on the nerve. This first and direct diphasic wave in fig. 4 *a* is followed by a small wave (after 2 msec.) travelling in the *opposite* direction. This conclusion can be drawn from the fact that the first phase of the second diphasic wave is a *downward* swing of the oscillograph, and the second smaller phase an upward move-

ment. Hence in this case the *lower* lead on the nerve has been influenced before the upper one. The second wave in fig. 4 *a* is therefore relayed somewhere from the end of the cut sciatic nerve. In this region it must have been transmitted from motor fibres into sensory fibres by fibre interaction. The long interval between the first and the second wave place this region at the cross section of the sciatic nerve. (Fig. 4 *b* showing a much larger second or relayed wave will be discussed below.)

In the type of experiment presented in figs. 3 and 4, with leads on the nerve below the hamstring level, the evidence conclusively points to the cut end of the *sciatic* being the region where the volley to the motor fibres is transmitted into the sensory fibres. But in the standard experiment with leads on the sensory root it has turned out that the cut end of the hamstring or some nerve severed above this level also is an exceedingly active region of transmission. In most cases the relayed response consists of two volleys as in fig. 5. Sometimes they are separated from each

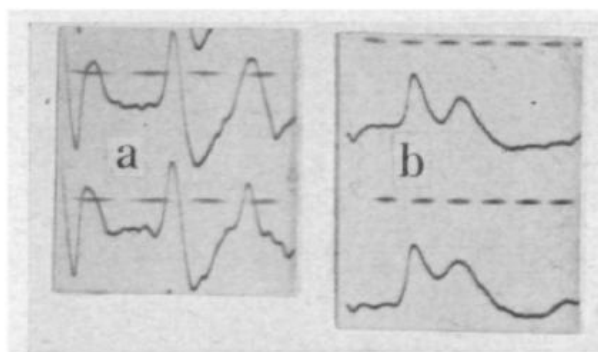


FIG. 5.—“Standard” arrangement of fig. 1. Record *a* begins with unusually large shock artefact from stimulus. Explanation in text.

other by a definite interval, as in 5 *a*, sometimes, and more generally, the response is expanded and contains two separate peaks, as in 5 *b*. By measuring both the latent periods of the two relayed waves as well as the actual impulse velocities it is possible to separate the hamstring cross-section from the sciatic cross-section as source of relayed volleys. In the standard combination the latent period of the response relayed from the cut end of the hamstring nerve is of an order of 1.8 msec., whereas it lasts about 3 msec. before a volley from the motor root can be picked up from the sensory root if cross-excitation has taken place at the cut end of the sciatic nerve in the knee region. By making a fresh section of the nerve in the regions concerned it is often possible to find out whether the “artificial synapse” was localized to the one or the other nerve cross-section. This question will be taken up below.

The experiments have thus shown that fibre interaction is a normal process at an injured region of a mammalian nerve. Hering saw this happen only in the plexus ischiadicus of hyperexcitable frogs. Our results have added the theoretically and practically significant fact that impulses with much greater ease are transmitted in the direction motor \longrightarrow sensory (our standard combination) than in the reversed direction. This "artificial synapse" at the cut end of the nerve behaves like other synapses in that it is very sensitive to the anæsthetic. Some decerebrate animals were used in order to study fibre interaction without complications of this nature. The standard experiment was successful in all these cases. Dial was tried and found to be unsatisfactory. Sometimes the effect was present, sometimes absent. But decerebrate and chloralosed animals are both extremely reliable preparations, provided that the cat is in good condition. If the cat is asphyctic or too heavily narcotized fibre interaction disappears before the nerve ceases to transmit impulses.

(2) *The immediate effects of cutting or crushing a nerve.*

We return to the combination illustrated in fig. 3 in which (fig. 4 *a*) a direct diphasic wave is followed by a relayed wave starting with the opposite phase leading. The direct wave of fig. 4 *a* is next diminished by diminishing stimulus strength, as in fig. 4 *b*, but immediately afterwards the end of the sciatic is cut through with a pair of scissors. There is now in 4 *b* a very large increase of the second diphasic wave relayed from the freshly established cut, meaning that the number of fibres, involved in cross-excitation from motor to sensory fibres, has risen in a very considerable manner owing to the renewal of the injury.

The same experiment is repeated in fig. 6, but this time in the standard combination of fig. 1. In fig. 6 *a* is shown the relayed response transmitted

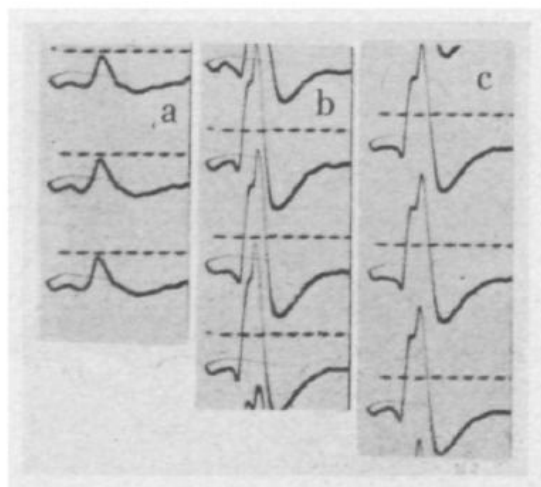


FIG. 6.—"Standard" arrangement, *a*, before, *b* and *c* after fresh section of nerve.

in the direction motor \longrightarrow sensory some time after the nerves had been severed. The main sciatic stem is then cut across with a sharp pair of scissors. The increase of the relayed wave, that follows in 6 *b*, by 4 times exceeds the control. The records 6 *c* are taken about a minute later. The amplification or "facilitation" of transmission at the "artificial synapse" by a fresh cut lasts from five to ten minutes or more. The duration of this period varies a great deal from animal to animal. Cross-sections at the upper portion of the nerve tend to give far more facilitation than those at the lower portion.

In the next experiment we are using the standard arrangement and proceed to tie a series of knots around the sciatic nerve beginning just at the end. Fig. 7 shows in *a* the control, a relayed volley with two peaks, the

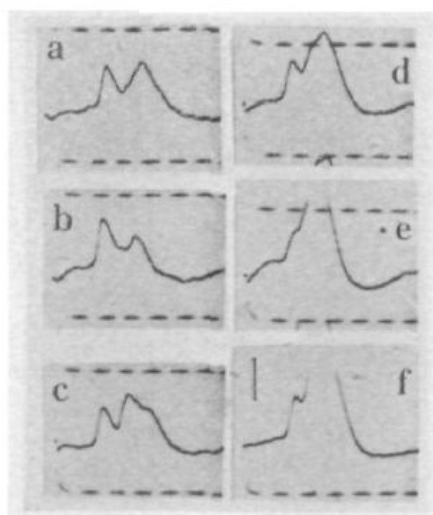


FIG. 7.—"Standard" arrangement. Records fully explained in text. Calibration to 1.0 mV. marked in record *f*.

first coming from the cut end of the hamstring, the second from the end of the sciatic. In *b* the second peak (sciatic) diminishes somewhat when a loose knot with a thread at the end of the nerve is tightened. The same procedure is repeated 1 cm. up the nerve in *c*. Now the wave relayed from the crushed region definitely increases. A fresh knot is made 1 cm. further up, and in *d* a large increase of the wave relayed from this knot is seen to occur. Finally the nerve is tied still higher up in *e*. This last knot on the main sciatic stem is now so near the reflecting region at the cut end of the hamstring that the first wave from the latter merely is indicated as a hump on the rising phase of the wave relayed from the crushed region under the knot on the sciatic. The relayed response is now

so large as to fall outside the picture. In order to show that the first phase of this large wave actually is relayed from the hamstring and not from the sciatic the hamstring is freed and a knot is tied around it 1 cm. higher up. This shifts the transmitting region further up by the same amount. The effect is shown in *f*. The first phase of the wave is now again better set off from the rest of the response and, besides, has increased in magnitude.

It is concluded from this experiment that a crushed region obtained by tying a knot around the nerve, is equally effective as a cross section in setting up an artificial synapse and that in both cases transmission in the direction motor \rightarrow sensory undergoes a very considerable transitory facilitation by cutting or crushing the nerve in a fresh place. This effect is not always seen at the extreme end of the nerve where sometimes a fresh cut may cause a diminution of the relayed wave or no effect whatever but it is well marked in the proximal region. In experiments of the type illustrated above the facilitating effect of a fresh cut affords the best means of localizing the origin of a relayed wave. (Exceptions will be described below.) It is of practical significance that this facilitation is of a very large order and sometimes must involve most if not all fibres of a nerve. The facilitation diminishes with time, first rapidly, then slowly along an asymptote which cannot be followed for a sufficiently long period in acute experiments (with a nerve kept in good condition).

In order to study the relayed waves in the "reversed standard" which are very much smaller than in the "standard" arrangement it is convenient to utilize the facilitation caused by a fresh section. In fig. 8 *a* a loose knot

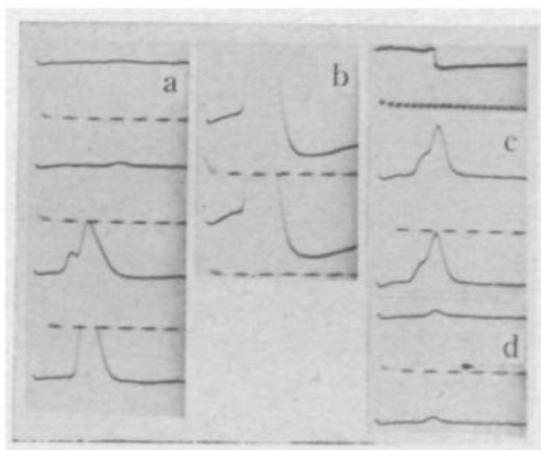


FIG. 8.—Fully explained in text.

has been passed round the end of the nerve, set up in the "reversed standard" arrangement. The two first records show that the relayed

response originally is very small. Between the second and the third record the knot is quickly tightened with the result that the relayed response immediately undergoes a very great amplification. Already in the second response a second later (the fourth in record *a*) the relayed response has reached its maximum and the beam of the cathode ray is thrown just out of focus. In *b* this effect is compared with the "standard," taken immediately afterwards. In the standard arrangement the relayed response is a great deal larger. Finally, in *c*, the sensitivity is decreased (calibration to 10 mV.) and the standard (*c*) is quantitatively compared with the reversed standard *d*. The relayed response in the standard combination is of the order of 25 mV., a truly impressive effect, as against the more than ten times smaller response in the reversed standard. Fibre interaction may thus under favourable conditions mobilize practically the whole sensory input of a large nerve such as the sciatic. Facilitation disappears at a very much faster rate in the "reversed standard" than in the "standard" arrangement.

(3) *Compression without loss of conductivity.*

For fibre interaction it is not necessary to cut the nerve or crush it till it has lost its capacity to conduct impulses through the damaged region. Some experiments, designed to imitate pressure by the pulp of a vertebral disc on the roots in sciatica, were carried out in which the nerve itself was pressed against a plate of ebonite by an ebonite edge of 1 mm. operated by a lever. Pressures between 50-100 gr. were used but their actual values are of less importance because the biologically significant factor is conductivity under the compressed region and not pressure as such, and conductivity was measured directly. To this end stimulating electrodes were placed in the distal region of the cut sciatic, the leads in the usual manner being on the sensory root. The weighted lever was placed somewhere in the middle of the nerve between stimulus and leads. A submaximal volley is first sent from the stimulating electrodes at the end of the nerve to the leads at the root. Let the size of this volley in an actual experiment be 18 mm. Then the lever is weighted with 50 gm. The volley from the end of the nerve is reduced by this pressure to 12 mm. Finally the lever is removed, the nerve treated with warm Ringer solution and after a brief while it is found to let through the full 18 mm. volley again. With pressures up to 110 gr. there is a larger reduction of the direct volley but this volley can still be greatly augmented by slightly increasing stimulus strength, and the nerve shows full recovery after removal of the lever. We are thus concerned with reversible effects of a compression

which, according to the biological test applied is of a relatively moderate order of magnitude.

In order to present a case which as nearly as possible imitates selective pressure on sensory fibres of the sciatic nerve the effect of compression will here, in fig. 9, be illustrated with the aid of the less usual combination

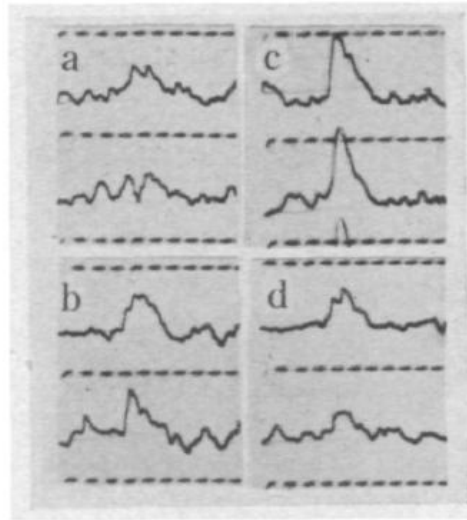


FIG. 9.—Fully explained in text.

sensory \rightarrow sensory. The sensory root S1 of an apparently post-fixed cat was stimulated and the leads were on the sensory root L7. It is a convenient arrangement also because the relayed response from the cut end of the sciatic is of a moderate order though somewhat variable, as shown by *a* in fig. 9. Then the lever is dropped and a weight of 60 gr. applied to the nerve by the lever. Fig. 9 *b* shows the effect on the relayed wave immediately afterwards; 9 *c*, after one minute. The volley sweeping through the compressed region has doubled in size. Finally the lever is removed, the nerve washed with warm Ringer; and eight minutes later the record 9 *d* is taken, showing that the facilitating effect of the compression has passed over, and that the relayed response again is of the same order as in 9 *a*.

Such experiments do not always succeed but from time to time positive results are obtained showing that fibre interaction *can* be caused by moderate pressure in sufficiently excitable nerves.

(4) *The length of the facilitating interaction. Distance effects.*

Hitherto the facilitation has been described as an effect localized exclusively to the cut or crushed region. In a number of experiments,

such as, for instance, the one illustrated in fig. 4, this localization has also been experimentally verified. In such cases the "artificial synapse" must cover a relatively short stretch of nerve. But there is a large number of experiments in which cutting or crushing the sciatic facilitates the relayed response from the end of the hamstring and *vice versa*. This means that in suitable preparations a distance effect can amount to 3-4 cm., maximally perhaps up to 6 cm. In some cases the effect of the one nerve upon the other is a reduction of the relayed response instead of an increase. Why this should be so is not yet understood.

In order to throw some light upon this particular aspect of the general problem of fibre interaction an experiment of the type illustrated in fig. 10

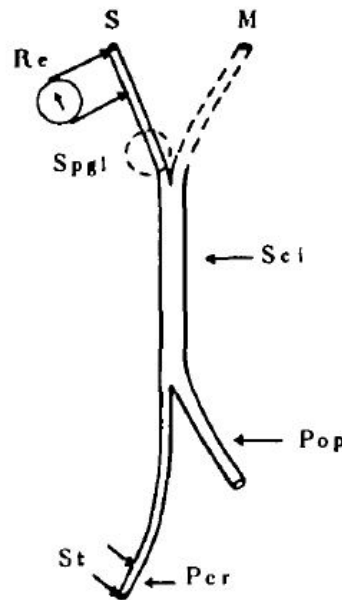


FIG. 10.—St, stimulating electrodes on peroneal nerve, Re, recording electrodes on sensory root.

was set up. The stimulating electrodes are on the peroneal branch (Per) of the sciatic which has been dissected free from the popliteal branch (Pop), the leads, in the usual manner, being on the sensory root. The experimental problem is simply: How does cutting or crushing the popliteal branch affect a volley set up, electrically in the peroneal branch of the sciatic? In most cases it was found that cutting the popliteal with a pair of scissors augmented the response started at the end of the peroneal nerve. There were, however, some cases in which the effect was a diminution instead of an augmentation.

DISCUSSION.

In this work we have selected a number of facts from our experiments on fibre interaction at injured or compressed regions of nerve which describe some of the fundamental features of this process of transmission, those, namely, that would seem to be of interest to the clinical neurologist. Two of us have completed the work with an extended analysis of impulse transmission at the artificial synapse from the points of view of theoretical neurophysiology. The facts selected for the present work do not therefore represent everything that at the moment could be said about this phenomenon. Those interested in following other aspects of the work are referred to a paper in course of publication (Granit and Skoglund, 1944).

The clinical aspects are so obvious that little need be said about them: an injured or compressed region forms a critical point at which impulses can be reflected centrifugally or centripetally by engaging other fibres by interaction, in particular sensory ones. Similar processes will occur in centres too. With these facts uppermost in mind the neurologist may be able to localize critical points of this character by observing what regions of the body are engaged in anomalous reactions.

But why, in particular, are the sensory fibres so easily engaged by interaction? The explanation of this fact probably lies in Skoglund's (1942) demonstration with cats that sensory fibres have lower threshold and far less accommodation than motor nerves. At any rate this explanation must be given serious consideration.

Accommodation may be defined as the resistance a nerve puts up to stimulation. If the accommodative resistance is low the nerve easily responds, even to slowly rising stimuli, if high, the nerve only responds to currents rising at a very fast rate. Fig. 11 from Skoglund's work illus-

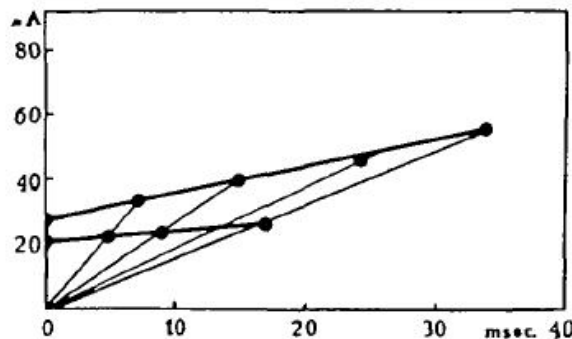


FIG. 11.—“Accommodation curves” for motor (upper) and sensory nerves (lower) of cat. Ordinates, stimulus strength in microamp., abscissae, stimulus duration in milliseconds. The linearly rising stimuli drawn in the figure. (From Skoglund, *Acta. physiol., Scand.*, 1942, 4, Suppl. 12.)

trates the differences in accommodation between motor and sensory nerves. On the abscissa is found the time during which the linearly increasing stimuli to a nerve rise, on the ordinate the strength to which at any particular moment, given by the abscissa, the stimulus has risen. The linearly rising stimuli to the nerve (cat) are also inserted in the figure. This shows that it has been necessary to compensate decreased rate of rise of the stimulus by increasing current strength. The lower curve, referring to sensory nerves, shows that the rate of rise of the stimulus is of much less significance there than for motor nerves (upper curve). These "accommodation curves" express an important aspect of what is generally called "excitability." The absolute threshold or rheobase is also seen to be lower for sensory than for motor nerves as shown by the difference in initial values. The motor nerve thus has both higher rheobase and in addition accommodates or puts up resistance to stimulation, so that the slower the rise of the stimulus the more compensation necessary to overcome accommodation. The sensory nerves have this capacity to resist stimulation far less developed.

The lower rheobase and accommodation of the sensory nerves suggest a natural explanation of the directional properties of the artificial synapse at the cut end of a nerve. Recently Kugelberg (1944) has completed an extensive analysis of accommodation in man under various conditions and for motor and sensory nerves found differences identical with those in cats. As the small pain fibres of the so-called C-group apparently are practically lacking in accommodation (Grundfest, 1940) it is natural to expect them to be easily excited by fibre interaction. Some symptoms of causalgia would thus receive a very simple explanation on the basis of this view.

Cross-stimulation in the direction sensory \dashrightarrow sensory has been demonstrated by Renshaw and Therman (1941) at a cut surface in the spinal cord, as mentioned above, and even seems to occur without destruction of a path or a centre if accommodation has been diminished in the spinal cord, e.g. by cooling the cord. An instance of this is the so-called "dorsal root reflex," first described by Barron and Matthews (1935, 1938), then further elucidated by Tönnies (1938, 1939) and from the point of view of accommodation by Barron and Matthews (1938 *b*) and by Skoglund and Uvnäs (1943).

It was repeatedly noted that the effect of cutting or crushing a nerve was far more pronounced in the proximal than in the distal region of the nerve. This may have been due to better circulation further up the nerve but, on the other hand, it deserves to be pointed out that in Kugel-

berg's (1944) work on accommodation in man the nerves were found to lose their accommodation a great deal easier in the upper region of the arm than in the lower region in experiments on hyperventilation and compression with pneumatic cuffs, and that spontaneous activity leading to positive Trousseau sign, fasciculations, etc., then started in the same region.

SUMMARY.

In experiments on cats it is shown that nerve impulses, set up in a motor root are transmitted to the sensory fibres in a cut region of the nerve and can be picked up in the sensory root of the same segment. The cut region thus serves as an "artificial synapse."

Fibre interaction of this character also takes place at a crushed region, for instance, when a knot is tightened around a nerve somewhere along its course.

Fibre interaction is also described in a region subjected to mechanical pressure of a moderate order.

The transmission in the damaged region is of a much smaller order, if present at all, if the discharge is forced in the reversed direction, i.e. from sensory to motor fibres.

The effect is greatly facilitated in a freshly damaged region where most if not all sensory fibres can be excited to discharge by a volley passing them in motor fibres.

The fibre-fibre interaction is impeded by deep narcosis or general deterioration of the preparation.

The significance of this process for certain neuralgic symptoms, referred pain, causalgia, etc. is pointed out.

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