ANALYSIS OF THE ACTIVITY OF THE CHAINS OF INTERNUNCIAL NEURONS

RAFAEL LORENTE DE NÓ

From the Laboratories of The Rockefeller Institute for Medical Research, New York

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INTRODUCTION

All the neurons in the central nervous system are reciprocally connected by numerous pathways, some having great and others lesser degrees of complexity. This wealth of connections is due not only to the high number of neurons and pathways, but also to the branching of the axons and their collaterals and to the overlapping of the fields of distribution of the branches of the different axons. The number and complexity of central pathways are best described by saying that, with but few exceptions, at least one pathway can be found connecting any two central neurons in a manner so that an impulse may be conducted from one to the other neuron in the direction of axon-synapse-body or dendrite-axon. Obviously many of these complicated paths are physiologically impassable, because the impulses sooner or later fail to reach the threshold of an intervening neuron, but others actually do play an important role in the physiology of the central nervous system. This question was discussed at some length in previous papers (1928, 1933c, 1934a) in which the literature of the subject has been reviewed. Recent advances in the knowledge of the physiology of the synapse (reviewed by Eccles, 1936b, 1937a, b; Bremer and Kleyntjens, 1937; Fulton, 1938; Lorente de Nó, 1938b, c) make it possible to analyze in greater detail the physiological significance of the arrangement of the neurons in synaptic chains.

The interest of the analysis consists in that it is possible to reduce the actual anatomical complexity of the nerve centers to simple diagrams suitable for theoretical arguments. Within the extreme variety of connections established by any one neuron with neurons of the same or of distant pools there is a systematic repetition of two fundamental types of circuit, which may be called the multiple (Fig. 2, M) and the closed chain of neurons (Fig. 2, C). The chains may be longer or shorter, they may contain a larger or smaller number of parallel branches, but in every case they remain essentially the same. Thus it comes about that the cerebellum as an organ is, from the point of view of elementary physiology, a giant chain of internuncial neurons, superimposed upon the reflex arcs in the spinal cord and the medulla (1924). Its activity consists in regulating the transmission of impulses through the shorter arcs. Similarly, the complex anatomical mechanisms found in the reticular substance of the medulla, pons, and midbrain can be reduced to chains superimposed upon the shorter arcs, and it is understandable that if the short arcs have been destroyed through suitable operation, motor reactions can be elicited through the longer chains of the reticular formation (1928; Spiegel,
FIG. 1. Longitudinal section through the medulla (M), pons (P), and midbrain (M.B.) of an adult mouse. Golgi-Cox stain. Drawing made with help of the projection apparatus from a single 80μ thick section. III, IV and VI, the oculomotor nuclei; r.N., red nucleus; Br. conj., crossing of the superior cerebellar peduncles. A, B, C, D, E, F, G, and H nuclei of the reticular substance. A, B, C, D and H belong to the motor correlation system and have connections with the oculomotor neurons. E, F, and G belong to the autonomic system. tr.M., tract of Meynert.
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1929). Nor is it difficult to account for the fact that the internuncial system in the reticular formation may be the locus where inhibition of motor responses is produced (1928, 1931; cf. Sherrington, 1934).

An analysis of the activity of the chains of internuncial neurons has been made in the oculomotor preparation (1935a) which affords an opportunity of stimulating large fiber tracts known to establish synaptic connections with the ocular motoneurons. Diagrammatic representations of the preparation have been given in previous reports (1935a, e) but additional details are needed.

Since in physiological literature the internuncial system has not received the attention that its anatomical importance justifies, it is necessary first to reproduce an actual anatomical picture in which the relative number of motor and internuncial neurons is immediately seen. Fig. 1 reproduces part of a section through the medulla and midbrain of an adult mouse stained after Golgi-Cox. It contains the oculomotor nuclei (VI, IV, and III) and a few of the nuclei of the system of correlation located in the reticular formation of pons and midbrain. In it, it is patent that the motoneurons are outnumbered many times by the internuncial cells* of the reticular formation, which regulate their discharge.

Actual reproductions of pathways connecting these neurons among themselves and with the motoneurons have been published by a number of authors (Cajal, 1909, Fig. 361; 1911, Figs. 151, 155, 156, 157; Whitaker and Alexander, 1932; Lorente de Nó, 1924, 1933a, c, e, etc.). The diagram in Fig. 2 has been constructed on the basis of these data.

The diagram emphasizes several important points: (1) Next to pathways (1, 2, 9, 10, 11) having direct connections with the motoneurons there are pathways (3, 4, 5, 7, 8, 12) that end in the reticular formation without direct connections with the motoneurons. Therefore the impulses which they carry can reach the motoneurons only after having crossed through an additional internuncial neuron. (2) All the pathways that establish connection with the motoneurons also have synapses with cells of the reticular formation, so that

* The name internuncial neuron is ambiguous, because every neuron in the central nervous system, with the exception of the motoneurons, may be called internuncial. But the classification of the cells in each particular case is not difficult if the following argument is considered. Impulses are conducted into a pool of neurons by afferent fibers and out of the pool by efferent fibers, which are axons of some cells of the pool. The cells of origin of the efferent fibers transmit the effect of the activity of the pool and may be called "effector neurons"; all the other nerve cells in the pool are internuncial neurons. Consequently a cell may be called effector or internuncial according to the problem being studied. In the present case the axons of cells in the vestibular and reticular nuclei that run directly to the motor nucleus and are stimulated by the shock are not called internuncials because they are made to play the role of afferent fibers; but if the shocks were delivered to the vestibular nerve, all the cells in the reticular nuclei would be internuncials of the second, third, etc. order, according to the number of synapses crossed by the vestibular impulses on their way to the motor nucleus.

The concept of the internuncial cells is radically different from the concept of the intercalar cell (Schaltzellen of v. Monakow) because, as Cajal long ago (1911, p. 590) pointed out, the cells with short axis cylinders to which v. Monakow referred are not intercalated between the afferent fibers and the cells with long axis cylinder; they form a collateral chain superimposed upon the articulation of afferent fiber-cell with long axon.
whenever an impulse is delivered to a motoneuron, impulses also arrive at internuncial cells. (3) The internuncial neurons are arranged in chains of two types: M (principle of plurality of connections, 1933c, p. 248) and C (principle of reciprocity of connections, 1933c, p. 249), which, with but few exceptions, are also found in every part of the central nervous system.

It is an immediate consequence of the anatomy of the preparation that shocks through electrodes F or Co1 by stimulating axons or cells set up a volley of impulses, called f or c according to the electrodes used, which, after conduction, is delivered to the motoneurons. Furthermore the f or c volley is also delivered to internuncial cells, which may respond and fire new volleys of impulses, necessarily delivered, at least in part, again to the motoneurons. In previous reports (1935a, e) attention was paid especially to the effect of the f or c impulses. Here the effects of the internuncial impulses will be examined in greater detail.

**TECHNIQUE**

The experiments here presented have been made on the oculomotor preparation of the rabbit as previously described (1935a, e), the only difference being that in some experiments the responses were recorded from the trochlear nerve. The stimulating F electrodes on the floor of the fourth ventricle were placed in some experiments on the caudal part of the vestibular nuclei (position F1, Fig. 2), and in other experiments at the level of the abducens nucleus (position F2, Fig. 2). With electrodes in position F1, the number of impulses directly conducted to the motoneurons (f, Fig. 3) is smaller than with the electrodes in position F2, so that the response is established chiefly through the internuncial system. The cathode of the C electrodes introduced in the anterior colliculus was placed approximately as indicated in Fig. 2, Col.
Results

The records reproduced in Fig. 3 were obtained under conditions favoring internuncial discharge. The head of the rabbit was tilted some 40° upwards, so that there was a considerable tonic labyrinthine innervation of the superior oblique muscle, which revealed itself by small irregular waves of the electrogram of the trochlear nerve. The impulses started by a shock through electrodes F1 could thus summate with the constant stream of labyrinthine impulses maintaining the tonus of the superior oblique muscle. Single shocks of progressively increasing strength were delivered at two-second intervals.

For records 1 and 2 (Fig. 3) the stimulus was barely at threshold and there is an indication of response only in record 1; but in records 3 and 4 the response was rather large. As in 1, it consisted in a re-enforcement of the tonic waves lasting for some 4–5 msec. The response increased when the shock was strengthened (5, 6, 7, 8), with the peculiarity that the largest potential waves often appeared at about the middle part of the response. Further strengthening of the shock (9, 10, 11) to maximal (12) and hyper-maximal value (13, 14) caused additional increase of the response. However, the increase of the early potential waves was not accompanied by increase of the late ones; on the contrary, the latest waves disappeared and the response became shorter (cf. records 13 and 14 with 6, 7 and 8).

The type of response shown in records 1 to 8 of Fig. 3 is one that might be expected. The stimulating shock created a volley of impulses partly delivered to the motoneurons and partly to internuncial cells; some motoneurons responded to the volley and their impulses reached the recording electrodes. Some internuncials also fired and caused other motoneurons and internuncials to respond. Likewise, this second volley of internuncial impulses stimulated other motoneurons and internuncials to discharge impulses into their axons, etc. The process was completed when the
internuncial volleys failed to reach threshold value for the next neurons. Since the average synaptic delay of internuncial cells is about 0.7 msec., it is fair to assume that responses such as those shown in records 7 and 8 had involved passage of the impulses through four or five internuncial neurons.

What *a priori* could not be expected is that strengthening of the shock, *i.e.*, increase of the size of the *f* volley, would cause the response to lose the late waves (records 9 to 14). This has only one explanation, namely, that the motoneurons, which in weak responses fired upon arrival of late internuncial volleys, in response to strong shocks fired when stimulated either by the impulses of the initial (*f*) volley or by the early internuncial volleys, and they could not fire again for the remainder of the response. The late internuncial volleys were lost because they were delivered to refractory neurons.

This result is expressed in graphic form in the diagram at the bottom of Fig. 3. The fiber marked *f* belongs to the posterior longitudinal bundle and is supposed to reach a motoneuron eventually engaged in the response to the *F* shocks. *i.1., i.2., i.3., and i.4.* are those few internuncial pathways which are crossed by the impulses in their way to the motoneurons. It is seen in the diagram that if the motoneuron (*N.*) does not respond to the *f* impulses, it may respond to the internuncial impulses after a latency equal to one, or to the sum of several synaptic delays; but if it is fired by the *f* impulses it will not reappear in the response as long as the *i* impulses find it in a refractory state.

Since even the strongest responses (*12 to 14*) contained only a small fraction, *i.e.*, scarcely one-third, of the total cell population of the motor nucleus, the diagram also illustrates the fact that the internuncial volleys were delivered in great density again and again to a small number of neurons, or in other words, that despite the many possible channels for conduction into branches (Figs. 1 and 2) the impulses remained confined within a few selected channels, so that the majority of the neurons of the motor pool received only subthreshold stimuli. Using a term introduced by the Oxford school (Cooper, Denny-Brown, and Sherrington, 1926) it may be said that during activity the internuncial and motor pools become *fractionated* into active and inactive groups, part of the latter group constituting a *subliminal fringe* (Denny-Brown and Sherrington, 1928), the activation of which demands stimulation by another set of pathways. In the particular case under consideration the fractionation was already established by the tonic labyrinthine innervation in which, as in other tonic innervations (cf. Denny-Brown, 1929; Adrian and Bronk, 1929), a small number of motoneurons are continuously engaged. Apparently the shock delivered to the posterior longitudinal bundle and other secondary vestibular paths temporarily altered the fractionation by causing some motoneurons of the subliminal fringe to enter into the active group. But still the additional impulses were unable to reach the threshold of neurons that were not already in the subliminal fringe. As a result, when a large number of the facilitated motoneurons responded (Fig. 3, *12 to 14*), the later internuncial volleys became ineffective.

The diagram of Fig. 3 deserves especial consideration because it repre-
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sents the relatively simple type of chains of neurons in which the internuncial system becomes fractionated during transmission of impulses. It has been substantiated by a number of other experiments. That the impulses of successive internuncial volleys actually are delivered repeatedly in great numbers to a small number of motoneurons is demonstrated in a most conclusive manner by the records in Fig. 4 obtained by successive delivery of two F1 shocks. Either shock alone (records 1 and 2) set up a response as in Fig. 3, 10 and 12 respectively. When both shocks were delivered in succession at intervals of 0.5 msec. or more, the response to the second shock increased considerably, but only in its early wave; the late waves were considerably reduced even when the facilitation was greatest (record 5). At that moment the response to the testing shock became a practically synchronous spike somewhat less than half the maximal nerve spike. As there can be no doubt that the testing volley was followed by successive volleys of internuncial impulses, the lack of late waves in the facilitated response demonstrates that the impulses were delivered to the same motoneurons that had responded to the f volley.

Records 7 to 10 correlate the duration of the period of facilitation and the duration of the response to the conditioning shock. As shown by record 8, the total duration of the conditioning response was about 4–5 msec., which also was the duration of the period of facilitation. In record 7, where the interval between shocks was 3.52 msec., the facilitation was still great; but in record 10, where the interval was 5.3 msec., there was no appreciable increase of the testing response. Evidently in the oculomotor preparation the increase in strength of stimulation necessary to bring motoneurons of the subliminal fringe into the active group is so small (cf. 1938c) that unless some motoneurons are engaged in the response, the extension of the subliminal fringe is negligible.

Since the period of the summation of impulses delivered at different synapses is extremely short (1935c, d; for sympathetic ganglion cells see Eccles, 1937b), there can be no doubt that the height of the initial wave in the facilitated response (records 3 to 7) measures the number of inter-
nuncial impulses entering the motor nucleus at different moments after delivery of the conditioning F shock. The testing volley of f impulses was of course constant, because the testing shock was maximal, and consequently the number of responding motoneurons was roughly proportional to the number of i impulses arriving at the motor nucleus simultaneously with the f impulses. The temporal course of facilitation demonstrates that the internuncial volleys had more or less the densities indicated in the diagram in Fig. 3, the largest volleys being i1 and i2 after the impulses had crossed through one or two internuncial neurons.

The records in Fig. 5 obtained in another experiment also are very demonstrative. In this experiment the electrodes were placed in position F2 (Fig. 2), with the result that the initial f volley was large enough to cause the appearance of a considerable f wave, while the waves of internuncial origin were small (Fig. 5, 7, 8). Nevertheless, it could be demonstrated that the f volley was followed by powerful i volleys which remained ineffective because they were delivered almost exclusively to those motoneurons that had been made refractory by their response to the f impulses. The experiment was based on the following argument (1936, Fig. 4; cf. Eccles, 1931, p. 582). An antidromic shock was delivered to the motor nerve in order to create refractoriness of the motoneurons, and at different moments during the period of recovery an F response was elicited. The impulses of the initial f volley reached the motoneurons while their threshold was still high and failed to elicit responses, but the i volleys, which arrived at the motor pool after delays of 0.6 msec. or more, found the motoneurons at a more advanced state of recovery and were able to set up responses. By properly choosing the interval between the antidromic and the F shocks it was possible to obtain F responses in which the f wave was small, while the i waves were large (Fig. 5, 9, 10); as the rate of recovery of the motoneurons is rather slow (1935c; Lorente de Nó and Graham, 1938), it must be concluded that the i volleys were almost as
The actual experiment is illustrated by the records shown in Fig. 5. Two F2 (Fig. 2) shocks (F1 and Ft) were delivered in succession at the constant interval of 0.8 msec., and a maximal antidromic shock was delivered at three different intervals (1.30, 0.8, and 0.6 msec.) before the first F1 shock. Both the conditioning (Fig. 5, record 1) and the testing shock (record 2) set up responses with a large f wave followed by small i waves; but in a similar manner as in the experiment of Fig. 4 when the F shocks were delivered in succession, the i waves in the response to the testing shock disappeared (record 3).

The maximal antidromic shock when delivered 1.30 msec. before F1 prevented any response to this shock (record 4); but when F1 was followed by Ft, the response to the latter contained a large f wave (with slightly lengthened latency) and, in striking contrast with the response in record 3, also well marked internuncial waves (i). When F1 was omitted, the response to F1 (record 6) contained only i waves.

When the antidromic shock was approached to the F1 shock (record 7) the response to F1 changed in a spectacular manner; the early f wave decreased, while the internuncial waves increased considerably. If F1 was omitted no response was obtained (record 8). Further decrease of the interval between the antidromic and the F1 shock to 0.6 msec. resulted in a further decrease of the f1 wave, without reduction—there rather was an increase—of the internuncial waves (records 9 and 10).

The fractionation of the internuncial and motor pools is maintained even in the case of repetitive stimulation creating strong activity. In the experiment illustrated by the records in Fig. 6 a rhythmic series of shocks was delivered through C electrodes (Fig. 2, Col). The responses were recorded from the left trochlear nerve and the C cathode was placed in the reticular formation in front of the left oculomotor nucleus. Since the nucleus of the left trochlear nerve is located on the right side, the shock did not stimulate trochlear motoneurons, but stimulated trochlear axons shortly after they had crossed the middle line. This response is labeled i on records 13, 14, 17. Synaptic responses of trochlear motoneurons, labeled a, had of course a longer latency.

Single shocks of any strength or tetanic stimulation at low frequency failed to set up synaptic responses, but when the frequency of the series was raised (1 to 9) synaptic responses appeared after a period of recruitment including never less than three shocks; after a further period of increase, the responses remained at rather constant level, roughly proportional to the frequency of the series.

The recruitment was obviously attributable to the same process which underlies the facilitation of responses of motoneurons to two shocks in succession (1935c, e). The first shock created impulses which lowered the threshold of some internuncial cells to synaptic and electrical stimuli; therefore the second shock was able to stimulate a larger number of internuncials and create
Fig. 6. Oculomotor preparation; responses recorded from the trochlear nerve. Electrodes in position Col. (Fig. 2) (3-9-36). Tetanic stimulation. The records on the right side were obtained at higher sweep speed than those on the left. Time (1/60 and 1/1000 sec.) below each series of records. Note that downwards deflection indicates negativity at the active electrode. $n$, response of directly stimulated trochlear fibers; $s$, synaptic responses.

A greater facilitation of the third shock, etc. The process was cumulative and soon the internuncial bombardment became large enough to enable the motoneurons to respond to the impulses of the direct volley (c) of impulses started by each C shock in internuncial axons or cells (cf. discussion, e). However, the recruitment did not progress beyond a certain limit; here as in the case of reflex responses fractionation took place. In fact the responses in the
experiments of Fig. 6 did not include more than a third of the total number of cells of the motor pool.

An analysis of the response can be made on the basis of records 10 to 19 which contain the middle part of responses similar to those on the left side, photographed at higher sweep speed.

At frequencies of less than 100 per second there was no synaptic response following the n wave (10), but at the frequency of 120 per second (11) the n wave began to be followed by an asynchronous synaptic response including several wavelets. The same type of response was observed at frequencies up to 145 per second (15). In terms of the diagram in Fig. 3 this type of response indicates that the initial volley of c* impulses was sufficient to reach the threshold of only a small number of motoneurons, while the following i, ii, etc., volleys were able to fire a larger number. It is important to note that in record 13 the synaptic response, despite its small size, appeared after the minimal synaptic delay (cf. 1938b).

Increase of the frequency of the series resulted not only in an increase but also in a shortening of the duration of the synaptic response, which soon (17 to 19) became a synchronous spike. Evidently the c impulses set up by each C shock met at the motoneurons a large internuncial volley due to the preceding shock and were capable of firing a large number of motoneurons. The following i volleys, being delivered with great density only to refractory neurons, failed to set up new responses. Here again, as in the previously studied, cases despite the great internuncial activity the i impulses arrived in large numbers only at a discrete number of neurons.

The fractionation of the motor nucleus was accentuated by the progressive increase of threshold (summation of subnormality) of the neurons engaged in tetanic activity. Although there is no conclusive proof, it is most likely that the motoneurons were following each shock of the series. As indicated by records 10 to 15, at low frequencies some motoneurons, obviously those near the subliminal fringe, alternated; but at higher frequencies the motoneurons must have followed every shock, otherwise some of them would have responded after the minimal synaptic delay, as in record 13, and not after the maximal delay, as in records 17 to 19. The frequency of the series necessary for effective recruitment was well above the critical one for summation of subnormality, i.e., about 100 (cf. Lorente de Nó and Graham, 1938) so that once the motoneurons responded to two shocks in succession, their threshold became so high that they could respond again only to very strong stimuli, which apparently were created only by the coincidence of a c and an i volley. In the absence of c volleys, the i volleys would have been subliminal for any of the motoneurons engaged in the response. And in fact it is consistently found in experiments of this type that, despite the strong internuncial activity

* The volley of impulses set up by direct stimulation of axons or somata of internuncial neurons is called f or c according to the position of the stimulating electrodes (F or Col. Fig. 2). Later volleys which cross through one or more internuncial synapses are always called i.
created by the tetanus, after the end of the series of shocks the electrogram of the nerve, or muscle, showed a silent period of some 15 to 20 msec. duration, followed by a long-lasting tonic discharge (Fig. 9, 5, 13).

Experiments such as that illustrated by the records of Fig. 4 make the assumption likely that facilitation ends when the internuncial bombardment ceases. However, this demands careful consideration, because according to the observations of Eccles (1936a, b, 1937b), subliminal stimulation of the ganglion cell after the period of effective summation of impulses arriving at different synapses—called by Eccles “period of summation of detonator responses,” produces a long-lasting state of lowered threshold (Eccles’ c.e.s.). The fact must also be considered that the duration of the period of effective summation has been determined by studying the interaction of only two volleys of impulses, and it is thinkable that continued bombardment may lead to different results because it might produce a cumulative change in the motoneuron.

With ocular motoneurons it has as yet been impossible to demonstrate the existence of an enduring effect of subliminal impulses comparable to Eccles’ second phase of facilitation (c.e.s.), perhaps because in the cases studied internuncial bombardment and facilitation were inseparable. An instructive experiment will be mentioned here.

The series of records in Fig. 7 illustrate one type of interaction of F and C shocks. In isolation the F shock (3, 5, 18) caused the appearance of a response as shown in Fig. 3; the tonic discharge down the trochlear nerve was increased during a period of several msec. The C shock, however, caused a response composed of an almost synchronous spike potential followed by a silent period of several msec., during which the tonic discharge ceased (1, 2, 7, 21).

The F and the C shocks may have in part stimulated the same fibers, but there can be no doubt that they also stimulated different internuncial axons, because when delivered at simultaneity (22) more neurons responded than when either shock was delivered in isolation. When the F preceded the C shock, the response to the latter was facilitated (4 to 12), the period of facilitation lasting as in Fig. 4 through the period of increased tonic activity which followed the initial f discharge.

The results were different when the C preceded the F shock. At an interval of 0.2 msec. (20) the F response was greatly reduced even in its early wave, and it was practically abolished at an interval of 0.49 msec. (19). At greater intervals (17, 16, 15, 14, 13) the F response was totally abolished, as was the case also when the C response included only a small number of motoneurons (15). The F response began to reappear at an interval of about 4 msec. between shocks, and up to the last interval studied (5 msec.) it did not show signs of being facilitated.

The effect stated cannot be ascribed to the presence of some “inhibitory” impulses in the C volley, because when the F and the C shocks were delivered simultaneously (22) there was a marked summation. The assumption of “inhibitory” impulses in later internuncial volleys following the initial c volley also would be in conflict with the results of the experiment shown in Fig. 6
FIG. 7. Oculomotor preparation; responses recorded from the trochlear nerve. Two stimulating electrodes in positions F1 and C0 (Fig. 2) respectively (same experiment as in Figs. 3 and 4). The responses to the C and F shocks in isolation have been reproduced in records I, 2, 3, 5, 7, 18, and 21. There was a certain variation of height of the C response due to the discontinuous character of the tonic labyrinthine innervation, the response being of course larger when the c impulses happened to coincide with a large internuncial volley. Record 1 reproduces the largest observed response to a C shock in isolation. The numbers of the right hand side of the records indicate the order in which they were obtained; between each two consecutive records there was an interval of two seconds. For records 4 to 12 the F shock preceded the C shock at the intervals indicated in msec. on the records. For records 13 to 22 the C shock preceded the F shock. Time in 0.2 and 1. msec. below.

and of other experiments, in which it was found that the C shock may create a long-lasting facilitation of the F shock. For example, Fig. 8 reproduces records from an experiment in which the C shock was followed by a markedly enduring facilitation of the F response (I, 3, 4, 6), greater than the facilitation of the C response by the F shock (9, 10).

The striking difference between the experiments in Fig. 7 (13 to 20) and Fig. 8 (I, 3, 4, 6) finds its explanation in the fact that in Fig. 8 the C response
was followed by a period of increased tonic activity, obviously due to internuncial bombardment, while in Fig. 7 the C response was followed by a silent period which indicated absence of internuncial bombardment; even the transmission of the tonic labyrinthine impulses had been blocked. Evidently the c volley in this experiment was not followed by internuncial volleys; while it arrived as well at motoneurons as at internuncials, the latter failed to respond, or if they did respond their impulses were blocked at some internuncial link made refractory by the shock (cf. 1936). Since the f volley, no matter how powerful it may be, in the absence of a background of subliminal stimulation cannot set up response in any motoneuron, the F response became "inhibited" as soon as the period of summation of the c and f volleys was finished. Comparison of records 20 and 21 demonstrates that summation was poor, indeed scarcely possible when the c and f volleys were delivered 0.2 msec. apart. This result and the "inhibition" of the F response in records 13 to 17 do not demonstrate that the c impulses did not cause a long-lasting lowering of threshold of some motoneurons, but they do demonstrate that if a long-lasting effect such as this had been produced, it was considerably weaker than the immediate effect of a mild (i.e., subliminal for the majority of the motoneurons), internuncial bombardment.

The limited strength of durable effects also is apparent after long-lasting bombardment of the motoneurons, as in the case of vestibular nystagmus. During that reflex the agonistic eye muscles show a series of slow contractions of long duration, interrupted by rapid relaxations of short duration—no more than 100 msec. Thus, it may be said that the motoneurons are submitted to a constant bombardment by impulses interrupted by short periods of no bombardment. Should continued bombardment after it stops be followed by a long-lasting lowering of threshold, then during the periods of relaxation at least those motoneurons which did not fire during the
nystagmic contraction would respond to F shocks. But in fact they do not so respond; the response to an F shock is always large during the periods of contraction, while it is small or absent during periods of relaxation (1935a, Fig. 2).

Under the conditions of the present experiments, in which the stimulating shock always creates a powerful volley of impulses delivered to the motor-neurons, facilitation and increase of the tonic waves in the electrogram of the motor nerve or the muscle have been inseparable phenomena, even when facilitation lasted for several seconds. For that reason, facilitation in every case could be explained as the result of instantaneous summation of the testing volley of impulses with impulses of the internuncial bombardment, the existence of which was revealed by tonic discharge of some motoneurons. Fig. 9 reproduces records from a representative experiment in which long-lasting facilitation was observed after a short tetanic stimulation through the C electrodes. In order to avoid strong motor reactions the preparation was kept under light ether narcosis, which is known to reduce the tonic internuncial activity.*

Although during ether narcosis single F shocks are ineffective (Fig. 9, 11, 16) two F shocks in succession may set up strong responses (Fig. 9, 1), undoubtedly because the first shock starts an internuncial bombardment of the motor nucleus. Its duration is usually brief (from 1.25 to 5 msec.), the impulses being able to cross only a few internuncial synapses, but tetanic stimulation leads to the creation of internuncial bombardment and facilitation of several seconds’ duration (Fig. 9).

As already mentioned, in the experiment illustrated by the records in Fig. 9 the conditioning tetanus was delivered through C electrodes, the C cathode being placed in front of the oculomotor nucleus, but far enough away to prevent electrical stimulation of motoneurons or motor axons. The response was recorded from the right internal rectus muscle. A series of C shocks at low frequency (Fig. 9, 2, 3) did not cause motor response or long-lasting facilitation of F shocks, but series of low frequency during the period of increased internuncial activity following a previous stimulus, or series at high frequency caused motor responses similar to those in Fig. 6 and also long-lasting facilitation of the F shock (Fig. 9, 5, 8, 13). During the period of facilitation, except in the silent period immediately following motor discharge, the electrogram of the muscle showed tonic waves caused by the response of a few motoneurons. Facilitation was strong while the tonic discharge was great (6, 9, 14), but it decreased when the tonic waves diminished in size (7, 10, 15), and disappeared when the tonic waves ceased (11, 16). It is important to mention

* The effect of ether is rapidly apparent; it has, in fact, been observed after 15 seconds of inhalation of a mixture of ether and air so weak that it did not cause disappearance of the corneal reflex after prolonged inhalation. A specific action of ether on some neurons of the vestibular system must, therefore, be assumed. However, the motoneurons are but little affected, because they readily respond when internuncial bombardment is created by suitable stimulation. Furthermore, results similar to ether narcosis are obtained when the background of subliminal stimulation is suppressed by destroying the reticular substance in the pons. The selective effect of anesthetics is also suggested by the experiments of Bremer and Moldaver (1933).
Fig. 9. Oculomotor preparation; responses recorded from the internal rectus muscle (negativity downwards). Two stimulating electrodes in positions F2 and Col. (Fig. 2) respectively (6-5-36). Light ether narcosis. 1, response to two F shocks in quick succession; 2, 3, the same response conditioned by a series of shocks through the C electrodes at low frequency; 4, the same as 3 but the series delivered during a period of internuncial activity following a previous C stimulation at high frequency. The F response is facilitated. 5, facilitation by a series of 13 C shocks at a frequency of 500 per second; 6, two seconds later; 7, four seconds later. Note the tonic activity in records 6 and 7. 8, 9, 10, 11, facilitation of the response to one F shock immediately and 2, 4 and 6 seconds after a series of 13 C shocks at a frequency of 475 per second. Note that the F shock remained ineffective (11) when the electrogram of the muscle did not reveal the existence of tonic discharge. 12, timing film (1/60 and 1/1000 second) for records 1 to 11; 13, 14, 15, 16, a similar set of records, also obtained at two second intervals, illustrating facilitation of a subliminal F shock (16) after delivery of tetanic stimulation (13) through the C electrodes; 17, timing film (1/60 second) for records 13 to 16.
that each facilitated response (6, 9, 13) was followed by a silent period in the electrogram, indicating that the impulses set up by the F shocks fired those motoneurons which were taking part in the tonic discharge. Here again facilitation extended only to the motoneurons reached by large internuncial volleys.

In view of the evidence presented here the conclusion must be reached that the internuncial bombardment, despite the short duration of the effect of the individual impulses, constitutes a statistically constant stimulus for the motoneurons of the active group; each neuron responds to it rhythmically at a frequency determined by two factors: (1) strength of the bombardment and (2) rate of recovery of the neuron. An almost ideal confirmation of this conclusion is given by the records in Fig. 10. The cathode of the stimulating (C) electrodes was placed near the oculomotor nucleus, so that certain motoneurons were capable of responding to the summated effect of induction shocks and internuncial impulses.

**Fig. 10.** Oculomotor preparation: responses recorded from the internal rectus muscle (negativity downwards) (6-1-36). Tetanic stimulation through the C electrodes. Time (1/60 second) in record 9. The small sharp downward deflections are shock artifacts. Further explanation in text.
In records 10, 11, and 12 the shocks were strong enough to stimulate some motoneurons. The responses did not, however, follow the rhythm of the stimulating series; they appeared in groups of two and sometimes three responses, separated by intervals including four or five shocks during which only a mild tonic discharge was visible. The grouping of discharges was obviously attributable to summation of subnormality; two or three responses in quick succession raised the threshold of the motoneurons to a high level and no further response could take place until the threshold had recovered.

In records 1 to 8 the strength of the shocks was reduced so that they did not reach the electrical threshold of the motoneurons without first increasing the internuncial bombardment. The frequency of the stimulating series was progressively increased from record 1 to record 8. In record 1 the electrical threshold of the motoneurons was not reached until the tenth shock of the series, and it was not attained again during the remainder of the series. In record 2 the response appeared earlier (seventh shock) and there was a grouped discharge followed by a long silent period. A similar effect is seen in records 3 and 4. In record 5 the frequency of the series was sufficient to create a strong internuncial bombardment, with the result that the responses were regularly grouped in pairs. Nevertheless two responses in quick succession were sufficient to create a subnormal threshold which remained for periods of over 40 msec. above the stimulating value of the shocks.

Further increase in the frequency of the series (6, 7, 8) reinforced the internuncial bombardment to a degree so that the groups of responses contained three equal twitches, but here again after the third twitch the threshold of the motoneurons became so high that a silent period, of 40–50 msec. duration, followed each third twitch. While records 1 to 12 were being taken, the preparation was kept under mild ether narcosis which prevented the increase of internuncial activity above unwanted limits; but before taking records 13 to 15, the narcosis was discontinued. The strength of the shocks was reduced below the value used for records 1 to 8; nevertheless the groups of responses contained three or four twitches before subnormality increased sufficiently to prevent further response. The great amount of internuncial activity created by the series of shocks also revealed itself in the powerful tonic discharge lasting throughout the series.

Although the records were obtained at two-second intervals, the effect of the stimulus was cumulative and the tonic discharge at the end of the series increased progressively in each record (13, 14). Finally, in record 15 the internuncial bombardment was so great that the three first shocks of the series reached the threshold of all the motoneurons of the nucleus, resulting in an abortive group formation; but the internuncial bombardment raised the stimulating effect of the shocks to maximal value and the remainder of the response consisted of maximal twitches at the frequency of the series. The internuncial activity was so great that despite the high threshold of the motoneurons no silent period appeared after withdrawal of the stimulus. Furthermore it continued to increase and soon spread through the whole
reticular formation, with the result that the preparation showed violent convulsions.

The grouping of discharges also may be observed in the pure synaptic responses of motoneurons. In the experiment shown in Fig. 11 the responses were recorded from the right trochlear nerve; the C cathode was placed in front of the right oculomotor nucleus. In record 1 the frequency of the series (about 300 per second) was almost subliminal, only two small responses being present after the sixth and the tenth shock. Strong responses began to appear in record 3 when the frequency of the series was about 350 per second; the discharge of the motoneurons took place in two groups separated by an interval of about 15 msec. Increase in the frequency (4, 5, 6) caused the responses to appear early and to grow in size, but it did not change the grouping of the discharge. At high frequencies the discharges, although clearly grouped as before, became irregular (11, 12).

The mechanism of the production of groups is understandable. Single shocks being ineffective to create sufficient impulses to reach the threshold of the motoneurons, successive recruitment was necessary, until finally the internuncial bombardment became strong enough to bring the threshold of the motoneurons down to the stimulating value of the volleys created by the C shocks. But the tetanic activity of the internuncial neurons soon created in them a high threshold, with the result that the internuncial impulses were
blocked at some of the cells and the bombardment ceased. Response of the motoneurons could not take place until after a second period of recruitment. This effect is very interesting in that it reveals the existence of a process by means of which a pool of internuncial neurons may reduce the frequency of the impulses it transmits at the same time that it changes the character of the afferent stream from a practically continuous bombardment by asynchronous impulses into a series of powerful volleys of synchronous impulses at low frequency.

**DISCUSSION**

(a) **Bombardment of motoneurons by internuncial impulses as a source of continuous stimulation.** The period of summation of the impulses arriving at neighboring synapses is short. For example, in the experiment illustrated in Fig. 7, 20 and 21, most of the $f$ and $c$ impulses failed to summate and to reach threshold when delivered at 0.2 msec. intervals. Nevertheless internuncial bombardment may constitute a constant stimulus, because the great number of internuncial cells ensures the delivery of impulses in large numbers and at high frequencies. For example, in the case of Fig. 3, following the initial $f$ volley, internuncial impulses entered the motor nucleus in successive volleys at intervals of about 0.7 msec., which is the average delay of internuncial neurons. Furthermore, the internuncial volleys, owing to slight differences in the delays at the individual neurons and to differences in the speed of conduction in axonal branches of various calibers, necessarily were highly asynchronous. The frequency of arrival of the impulses at the individual neurons was correspondingly high, for the frequency of the wavelets in records 5 and 6 in Fig. 3 was over 2000 per second, and the majority of the internuncial impulses remained below threshold for the motoneurons. Thus it may be said that the internuncial impulses arrive at the individual motoneurons in a constant stream, so that the $f$ impulses created by the second, testing, $F$ shock, delivered at any moment during the period of facilitation which follows the conditioning shock, always meet at the motoneurons internuncial impulses with which they can sum. The situation is exactly the same for the internuncial neurons, because as previously mentioned (Fig. 2), all the fibers having synapses on motoneurons also have synapses on internuncial cells, so that whenever motoneurons receive impulses at their synapses, internuncial neurons necessarily are also stimulated.

The shortness of the period of effective summation of two impulses excludes the possibility of the summation of impulses that have arrived in succession through the same fiber. Hence the strength of the stimulation by internuncial bombardment depends upon the density of the latter, i.e., on the number of fibers conducting impulses simultaneously; and all gradations are possible, ranging from subliminal (i.e., only maintaining facilitation) to liminal (i.e., causing discharge of resting neurons) and supraliminal (i.e., causing discharge of refractory neurons). Internuncial bombardment must necessarily cause rhythmic discharge of motoneurons, because each responding motoneuron will fire again as soon as its threshold is reached by the stimulus.
Internuncial bombardment (Forbes, 1922; but cf. Forbes, 1934, 1936) has all the properties of c.e.s. (Sherrington, 1925; Eccles and Sherrington, 1931b; Bremer and Homès, 1932), and since a motoneuron despite any possible lowering of threshold due to previous, intrinsic or extrinsic activity does not fire unless impulses are delivered to its synapses (cf. 1938b), there is no doubt that the "central excitatory state" leading to motor discharge is due to internuncial activity and bombardment. Furthermore, it has been shown in this paper that subliminal c.e.s., i.e., excitation demonstrable only by its ability to facilitate the response to an intercurrent stimulus, is always accompanied by internuncial bombardment, which under the conditions of the present experiments overshadows the effect of any other factor capable of lowering the threshold of the neurons.

For this reason the present discussion is conducted on the following principles: The mechanism of the stimulation of neurons is the delivery of impulses at their synapses. The effect of the individual impulses is brief, but the continuous arrival of impulses ensures constant stimulation. The neuron responds whenever the stimulating effect of the impulses that arrive within a period of effective summation reaches its threshold. The neurons as well as their axons (Gasser, 1935a, b; cf. Eccles, 193620, p. 392) have two thresholds, the resting and the subnormal threshold which develop during tetanic activity (Lorente de Nó and Graham, 1938). The creation of a high subnormal threshold does not necessarily demand a long-lasting activity; two discharges at high frequency are sufficient to raise the threshold of the motoneurons to a high level (loc. cit., Figs. 5 and 6).

The existence of a third threshold, even lower than the resting threshold, although it has not yet been demonstrated for motoneurons is likely, because it has been found to exist with sympathetic ganglion cells, with the neuromuscular junction, and with nerve fibers. With sympathetic ganglion cells Eccles (1936a, b, 1937b) observed after delivery of subliminal synaptic stimuli at the end of the period of effective summation, which Eccles has called summation of detonator responses, a second period of summation termed by him c.e.s.,* that appeared to be caused by a lowering of threshold of the ganglion cells. It never resulted in the setting up of an impulse. Bremer and Kleyntjens (1937) offer convincing arguments in favor of the view that the process underlying this second period of summation is the same as the process responsible for the passage of a second impulse across the partly curarized neuromuscular junction of the frog (Bremer, 1930; Bremer and Homès, 1932), or the neuromuscular junction of the crab (Lucas, 1917).

With nerve (Gasser, 1938), a second period of summation after subliminal stimulation can regularly be demonstrated under certain conditions, for example, after tetanization. Therefore the assumption lies at hand that the second period of summation is a general property of excitable tissues which

* The suggestion of Eccles to apply the term c.e.s. to the second period of summation is not followed here, for the reason that the term has been widely used with a different significance.
may influence synaptic transmission. However, in blood-perfused trochlear nerve the second period of summation is not demonstrable unless the recovery curve shows a supernormal phase, or unless the nerve has previously been tetanized (1938e). Under ordinary conditions it is absent; absence of peripheral recruitment is shown in Fig. 6. On the other hand, the effect of the lowering of threshold during the second period of summation is qualitatively the same as a mild internuncial bombardment (cf. Bremer and Kleyntjens, 1937, Gasser, 1938), and consequently not demonstrable in the presence of the latter (cf. Eccles, 1936b, p. 376). Since under the conditions of the experiments reported here the internuncial bombardment is always present, there is no immediate need for considering the second period of lowered threshold; although it is realized that under given conditions it might play a pre-eminent role. For example, the remarkable observation of Kleyntjens (1937) made on the frog that tetanization of the motor nerve increases the reflex response, indicates that at least under certain conditions, after prolonged tetanization a period of lowered threshold develops in the motoneurons. Another factor likely to play an important role in determining the threshold of the neurons is a change of metabolic conditions (Dusser de Barenne, McCulloch, and Nims, 1937). Its significance is not minimized by disregarding it in the present discussion, but more precise information is needed before it can be successfully considered in theoretical arguments.

The main difference between the concept of c.e.s as used by the Oxford school (Creed et al. 1932) and that of continuous stimulation by internuncial bombardment is that c.e.s. was assumed to develop and accumulate within the individual neurons, while internuncial bombardment places the excitatory and facilitatory mechanisms outside of the cell (1935b, p. 607). For many theoretical arguments the difference may be overlooked; in fact, the result obtained is essentially the same, whether the one or the other concept is used. In his review Eccles (1936b), while re-examining the physiology of the spinal cord in the light of recently acquired knowledge, found it necessary to alter but few of the original theoretical arguments. The concepts of recruitment, fractionation, subliminal fringe, etc. can be kept with their original meaning and have been repeatedly used in this paper. Nor is it necessary to alter the discussion of the transmission of impulses across the cerebral cortex made elsewhere (1934a) on the basis of Sherrington's c.e.s. As a matter of fact, if the recruitment and successive fractionated discharge of the various groups of cortical neurons had to be described entirely in terms of the internuncial bombardment responsible for it, the diagrams, owing to the very large number of neurons to be considered, would lose their didactic value.

However, there are cases in which the concept of c.e.s. as an enduring state of excitation of single cells cannot be used, not even to simplify theoretical arguments, as for example, when the simultaneity of arrival of two volleys of impulses is the necessary condition for threshold stimulation (cf. later discussion of inhibition), or when the response of the neuron depends more on
the spatial distribution of the active synapses than on the total number of impulses (1938c).

(b) The multiple chains of internuncial cells (M, Fig. 2) as elementary units of transmission. The question so often mentioned in the literature, as to whether a two-neuron (one synapse) arc sets up motor responses, can now be satisfactorily answered. Since the temporal summation of impulses arriving in succession through the same synapse is hardly possible, there can be no doubt that some cells in the nervous system are stimulated above threshold when a sufficiently strong synchronous volley of impulses through a homogeneous path is delivered to them. Obviously the cells with one-to-one transmission are those having either large synapses with individual fibers, or those having large sections of their soma covered by synapses of fibers from one homogeneous pathway (1933b). The rest of the neurons will fire only when impulses arrive simultaneously through several different pathways.

In the spinal cord it can be established (1938c) that the motoneurons have synapses of heterogeneous origin, so that conduction of impulses through a single pathway cannot result in the activation of all the synapses in any discrete zone of the soma, while many internuncials, especially in Cajal's intermediate nucleus and in the posterior horn, have homogeneous synapses. These cells must fire when a sufficiently large synchronous volley of impulses enters into the cord through the posterior roots; and in fact they do so, because (1) subliminal stimuli cause facilitation, and (2) internuncial potentials precede motor discharge and are obtained at a lower strength of stimulation (Gasser and Graham, 1933; Hughes and Gasser, 1934a, b).

When anatomical conditions prevent the convergence of impulses and therefore make it impossible for a two-neuron arc, such as that formed by fiber f and the motoneuron of Fig. 3, to transmit impulses, the additional activity of one internuncial neuron (i1, Fig. 3) may result in transmission. If the first impulse through fiber f fires cell i1, the motoneurons will respond to a second f impulse arriving simultaneously with the i1 impulses, but obviously a transmission unit containing only one internuncial neuron cannot transmit impulses at a frequency below 1000 impulses per second. Increase in the number of links in the internuncial chains diminishes the frequency, and yet in the case of the oculomotor preparation, the frequency of shocks delivered to the posterior longitudinal bundle and adjacent pathways must be rather high, i.e., 100 per sec. (Figs. 6 and 9.) Transmission of impulses at lower frequency demands the activation of much more complex chains of neurons, which are found only in the so-called primary nuclei of the sensory nerves—the posterior horn of the spinal cord, etc. The urgent need for including in physiological diagrams these nuclei, which form the most complex part of the medulla and cord, is herewith emphasized.

The concepts of the two-neuron arc, or of an arc with a fixed number of internuncials, lose their physiological meaning. On the one hand the impulses may set up responses of the motoneurons after having crossed a variable num-
ber of synapses, depending upon the state of the centers; and on the other hand, the internuncials are not intercalated between afferent fibers and effector cells. They form collateral chains superimposed upon the shortest path which, if a sufficient background of facilitation exists, is undoubtedly passable.

(c) Fractionation of the internuncial and motor pools into active and inactive groups. The elementary phenomenon responsible for fractionation consists in this, that threshold stimulation of a neuron is obtained only by summation of impulses delivered at several synapses. Of the neurons reached by the fibers of the active tracts only those respond upon which convergence of impulses takes place; the other neurons remain in the subliminal fringe (Sherrington, 1931). However, since each internuncial axon branches out and establishes connections with a large number of other internuncial neurons, it is difficult to understand how during continued stimulation the impulses may fail to spread into neighboring channels and engage a progressively increasing number of neurons producing avalanche conduction (Cajal, 1909; Herrick, 1926). 

The fractionation of the neurons of a pool into active and inactive groups is found not only in reflex physiology, but is a general feature of the activity of the nervous system. A most demonstrative example is the recent observation of Marshall, Woolsey and Bard (1937; cf. Bard, 1938) on the physiological projection of the surface of the body onto the sensory cortical areas. Despite the many possible channels for the dispersion of impulses, only a discrete portion of the cortex becomes active. This indicates that here, as in the case of the retinal projection, the fractionation is successively maintained in each internuncial station (cf. 1934b, Fig. 36).

One of the most remarkable features of fractionation is that, once established, it continues in the absence of peripheral stimulation. For example, stimulation of a single semicircular canal results in a response of the motor apparatus of the eye producing nystagmus with a component, the "nucleus," invariable for each canal and another component, the "appendage," which may be reversed by concurrent stimulation of another canal (1933e) or even by stimulation of static receptors (1931). The interesting fact is that if the appendage of a response has been reversed by the concurrent stimulation of another canal, the reversal is maintained after concurrent stimulation stops. Likewise, the appendage of a response may be reversed by the after-discharge of a previous stimulation. This indicates that certain labyrinthine impulses may enter into two different channels, but once they have entered one of them they do not leave it during the remainder of the response. Even more, they force other impulses to use the same channel, with the result that they summate; and two stimuli in isolation apparently antagonistic, when delivered simultaneously give rise to a stronger response.

How the reversal is initiated it is not difficult to understand. In Fig. 12, $f_1$, $f_2$, and $f_3$ are fibers of the vestibular nerve and it is assumed that two synapses must be activated in order to insure the passage of the impulse across the synapse. It is clear that stimulation of fiber $f_3$ will always fire cell $N$, setting up the nucleus of the response and that concurrent stimulation of
fibers $f_1$ and $f_2$ will cause response of cell $I$, setting up the appendage $A_1$, while concurrent stimulation of $f_1$ and $f_3$ must set up appendage $A_2$.

Now it is known (1933c, Figs. 4 and 8) that the pools of neurons of the reticular formation send numerous recurrent (centrifugal) fibers back to the primary nuclei, thus forming a closed chain of type $C$ (Figs. 2 and 12); and it is also known (1928, 1931, 1933) that lesions in the reticular substance, destroying among others those recurrent pathways, modify the transmission of impulses through the primary nuclei. The assumption lies therefore at hand that when the $f_3$ fiber stops conducting, the impulses brought back to the vestibular nuclei through the $C$ chain maintain the state of facilitation of cell

Fig. 12. I. Diagram explaining the production of reflex reversal by concurrent stimulation of two fibers ($f_1$ and $f_2$ or $f_1$ and $f_3$) from different peripheral sense organs and its maintenance by the impulses conducted by closed chain $C$, after fiber $f_3$, which initiated the response of cell 3, ceases conducting. Each one of the links in the closed chain represents a multiple chain of neurons ($M$, Fig. 2) such as is illustrated in the diagram of Fig. 3. Collateral $d$ by lowering the threshold of cell $a$ and thus causing two impulses to cross through cell 3 in quick succession may produce inhibition, for cell 3 will acquire a high subnormal threshold.

II. Diagram of Gasser (1937c) explaining reciprocal innervation. It is assumed that threshold stimulation of neurons with normal threshold requires simultaneous activation of two synaptic knobs, but three knobs are required to stimulate a neuron having subnormal threshold. When fiber I conducts a rhythmic series of impulses at low frequency neuron $F$ is stimulated by the $b$ and $c$ impulses and the flexor muscle contracts, but if fiber II then becomes active, cell $b$ will be forced to discharge an extra impulse and to acquire subnormal threshold. Henceforth cell $b$ will be able to respond only to the impulses conducted by fiber II, the result being that the extensor muscle contracts, while the flexor muscle relaxes because the $b$ and $c$ impulses reach neuron $F$ at intervals longer than the period of effective summation of impulses delivered at neighboring synapses.
3 and raise to threshold value the stimulating effect of the $f_2$ impulses, which continue setting up the appendage $A_2$ as if the $f_2$ impulses were still being delivered.

In systems having an extensive anatomical distribution such as the internuncial nuclei in the medulla and pons or in the spinal cord, analysis of the individual closed chains of neurons cannot be made, but in other organs, such as the cerebral cortex, the study may be carried out much farther. It is found (1934a, 1938d) that the arrangement of afferent fibers and cortical dendrites and axons in closed chains is such that the successive volleys of internuncial impulses must be delivered again and again in great density to the cells—internuncials and effectors—reached by the afferent volley, while the neighboring cells, which receive only small and infrequent volleys, must remain in the subliminal fringe. Thus it must be concluded that in the cerebral cortex the arrangement of the internuncial cells in closed chains, which force the impulses to use the same pathways repeatedly, is an anatomical mechanism leading to fractionation; and there is evidence to show that the same mechanism is operative also in subcortical centers.

(d) Long-lasting facilitation, after-discharge. At present it is generally believed (cf. 1935c; Eccles, 1936b, p. 394; Fulton, 1938 Chap. IV) that long-lasting facilitation and after-discharge are maintained by internuncial bombardment. The bombardments of relatively short duration can be satisfactorily explained by open chains of neurons having a few links. As a rule (cf. Kemp, Coppée and Robinson, 1937) it may be calculated that the passage of impulses through each internuncial station in the medulla and midbrain demands 1 msec. or slightly more (synaptic delay plus conduction time). Consequently, open internuncial chains such as are illustrated in Fig. 3 will be able to maintain facilitation and after-discharge for 4 msec. But long-lasting bombardment necessarily demands repeated passage of the impulses through the same internuncial cell (Bremer and Rijlant, 1926; Forbes, Davis, and Lambert, 1930). The internuncial chains through which the impulses circulate have been called reverberating circuits (Ranson and Hinsey, 1930) and closed self-reexciting chains (1933c).

Since the summation of subnormality progresses but slowly at low frequencies, a closed chain having a large number of links can remain in activity for considerable periods of time; but short chains, in which the impulses circulate at high frequency, must have a short time constant, because the passage of only a few impulses will create a high threshold and stop conduction. Inhibition must then result (1936). For example, in the diagram of Fig. 12 impulses may circulate through the closed chain $C$ at different rates. If the circuit should be closed through cells $a$ the rate would be high, because the impulse initiated in cell 3 would return in about one msec. to the same cell after crossing cells $a$; but if the cell 3 impulse should fail to reach the threshold of cells $a$ and return through $b$, the rate would be lower. With a long chain, i.e., one with many internuncials in series, or a chain including long fiber paths, the rate of circulation may be low enough to allow activity for considerable
periods of time, especially when fiber $f_2$ or $f_3$ also is conducting a series of impulses. However, if while chain $C$ is working at low frequency, facilitation of cells $a$ by impulses through collateral $d$ should force the impulse from 3 to cross these cells and to restimulate cell 3, the activity must cease, because two discharges at the rate of 1000 per second create in cell 3 so high a threshold that further transmission through this cell is blocked.

Thus, the activity of closed chains of internuncial neurons leads, under certain conditions, to facilitation, and under other conditions to inhibition. For this reason it seems best to drop the qualifications "reverberating" and "self-reexciting," which have too strict a meaning. The function of the closed chains of neurons must be analyzed in each particular case, as it must be determined by experiment whether a certain system of closed chains may become rhythmically active in the absence of peripheral stimulation or of impulses arriving from other centers.

There is evidence that in the case of the internuncial system regulating the discharge of ocular motoneurons, the closed chains of neurons in the reticular formation and vestibular nuclei are dependent for the initiation and maintenance of their activity on the constant stream of impulses set up in static receptors such as the labyrinth, the proprioceptors of the neck muscles, etc., so that even when by suitable operation the closed chains are made short, their activity may continue for long periods of time. This point deserves detailed consideration, for it leads to the problem of the nature of after-discharge. Is after-discharge the continuation of a newly created activity, or is it simply a particular case of reflex reversal which maintains the impulses, ordinarily passing through certain channels, in another set of channels?

It has been shown (1928, 1933c, p. 22) that vestibular after-discharge may be enormously prolonged by destroying parts of the reticular formation. The neurons left after the operation still formed closed loops (1933c, Fig. 8) but evidently short ones. With the now available knowledge of the recovery cycle of motoneurons, if an attempt is made to explain the after-discharge in terms of autochthonous activity of the closed circuits, the result becomes paradoxical. The destruction of internuncial cells shortens the chains and favors the creation of a high, subnormal threshold, because in order to maintain the internuncial bombardment, the remaining neurons must discharge at high frequency; nevertheless, the after-discharge is prolonged. The explanation is prompted by diagram I of Fig. 12, which indicates that if impulses started somewhere else are fed into them, the closed chains do not need to maintain circulation of impulses at the high frequency which autochthonous activity would demand. Fiber $f_2$ now represents one of the fibers from static labyrinthine receptors which set up the tonus of the external rectus eye muscle by firing the few motoneurons reached by the axon of cell $N$. The intercurrent stimulation of fiber $f_3$ brought in the motoneurons innervated by $A_3$, and the contraction of the muscle increased. When the stimulus of fiber $f_3$ was withdrawn, the impulses conducted back to the primary nuclei through the $C$ chain maintained facilitation of cell 3 and the $f_3$ impulses were still capable
of crossing that synapse, with the result that muscle remained contracted
(after-discharge) until subnormality was created in some neuron of the C
chain. If the bombardment of cell 3 by the C chain (cells a, b and c) is mild,
the \( f_i \) impulses will set up discharges of cell 3 at low frequency; but under or-
dinary conditions, when the C chains are complete, many synapses of the 3 cells
are simultaneously activated and the impulses are forced to circulate at higher
frequency. The result is that subnormality is more rapidly created and after-
discharge stops earlier.

In how far this argument applies to the spinal cord cannot be determined
without direct experiments. It is likely, however, that the argument has gen-
eral application, for the reason that long-lasting after-discharge hardly ever
appears without a background of tonic activity (decerebrate rigidity, etc.),
which obviously is due to a continuous stream of impulses arriving either
from the periphery or from other centers.

e) Rhythmic reflexes. Stimulation of the semicircular canals results in a
rhythmic reflex, nystagmus, characterized by a succession of contractions and
relaxations of the eye muscles. The records of the action potentials of the eye
muscles or of their motor nerves during nystagmus are similar to the records
in Figs. 10 and 11, the similarity being enhanced by the fact that the grouped
discharges in Figs. 10 and 11 were obtained during continuous stimulation in
the same way as nystagmus is produced in the presence of a continuous stream
of labyrinthine impulses. Both sets of phenomena seem to have the same
explanation.

In the classical theory of the production of rhythmic reflexes (Graham
Brown, 1914; Forbes, 1922; Spiegel, 1929) the attempt was made to explain
simultaneously reciprocal innervation and rhythm on the basis of a succession
of states of activity and rest, as due to the fatigue of certain cells. This ex-
planation is consistent with present knowledge, although rhythm and re-
ciprocal innervation must be accounted for separately. Rhythm is generally
accompanied by reciprocal innervation but it may appear without it, even
when the antagonistic muscles contract and relax simultaneously. The fol-
lowing discussion, therefore, refers to a frequent form of nystagmus which is
perhaps the fundamental one, in which the agonist muscle shows a succession
of slow contractions and quick relaxations of short duration, while the an-
tagonsist muscle shows only quick contractions (Fig. 13, II; cf. 1935f).

A number of significant facts are known: (1) During the slow phase of
nystagmus the contraction of the agonist is due to an increase of the number
of active motor units and to an increase in the frequency of their discharge.
The speed of the contraction, \( i.e., \) the speed of the recruitment of the motor
units, is directly proportional to the strength of the stimulus, while the dura-
tion of the contraction is inversely proportional to it. Many things seem to
indicate that the onset of the quick phase is caused by a trigger-like mecha-
nism, which becomes active when the contraction has reached a certain level
dependent upon the strength of the stimulus. (2) The relaxation of the agonist
and the contraction of the antagonist during the quick phase are very fast,
i.e., the recruitment of the motor units of the antagonist proceeds rapidly, the
discharge of the motoneurons taking place with a great deal of synchronism.
The duration of the quick component varies between narrow limits (McCouch
and Adler, 1931) from 100 msec. in weak nystagmus to 80 msec. in strong

Fig. 13. I. Diagram explaining the production of rhythm during vestibular nystagmus. Fiber f is sup-
posed to carry the continuous series of impulses started at the cristae of the semicircular canals which set up
the nystagmus. Fibers f₁ are supposed to be main-
taining the tonus of the antagonistic muscle; 1a, 1b,
2a, 2b, 3a, 3b are branches of the axons of cells 1, 2
and 3, 4a, 4b, 4d, 4e are branches of the axon of cell 4;
f₁, f₁, f₁, are branches of fiber f.
II. Diagram of the rhythmic succession of con-
tractions and relaxations of the antagonistic muscles
during the nystagmus explained by diagram I. Rising
of the line indicates contraction. The interval between
turning points a and b is never less than 3 to 4 msec.;
the interval between turning points c and d may be
50 msec. long.
nystagmus (1935f). (3) The stream of impulses created in the vestibular nuclei is a constant one. The interrupted discharge of the motoneurons is attributable to the activity of neurons located in the reticular formation. In fact, if part of the reticular formation or of its pathways is destroyed, the nystagmus is converted into a monophasic reflex, the agonist remaining contracted as long as the peripheral stimulus lasts (1933c). (4) The relaxation of the agonist is not attributable to an active inhibitory process but only to a lack of excitatory impulses (1933d). (5) The turning points in the antagonistic muscles are not synchronous (1935f) (Fig. 13, II).

In view of these facts it is not difficult to construct a diagram explaining the production of rhythm. In Fig. 13, \( f \) represents the fibers of the semicircular canals which, after interruption in the primary vestibular nuclei, reach the motor pool of the agonist and the internuncial pool (cells 1, 2, 3). In order to simplify the diagram, only a few internuncial cells have been included and it must be assumed, therefore, that, although successive impulses through the same synapse never summate, the period of summation of impulses arriving through different synapses is of long duration. This is identical with making the linkage between neurons through chains of type \( M \), as in Fig 3. Cells 4 and 5 to 9 also belong to the internuncial system, and fibers \( f \) represent those from static receptors such as the labyrinth and proprioceptors of the neck, which maintain the tonus of the antagonist. The effectiveness of stimulation is indicated by the size of the synaptic knobs. It is assumed that the synapses formed by a large terminal knob, representing a number of simultaneously active ordinary knobs, are one-to-one synapses, while those formed by small knobs demand summation of the effects at two adjacent knobs in order to fire the underlying neuron.

When fiber \( f \) starts to conduct, its rhythmic series of impulses successively recruits internuncial and motoneurons: the first \( f \) impulse does not set up any response of motoneurons, neither does it fire cells 2 and 3, but it fires cell 1; the second \( f \) impulse summates with the impulses delivered by the branches of 1 and fires some motoneurons and cells 1 and 2; the third \( f \) impulse summates with the impulses of 1 and 2 and fires a larger number of motoneurons and cell 3. The fact that cell 3 responds means that after completion of its synaptic delay cell 4 also fires and consequently cells 1, 2, and 3 must fire again. For this reason the fourth \( f \) impulse finds the motor nucleus in a greater state of facilitation, as it has just received two impulses from each internuncial cell and is capable of setting up a response of a large number of motoneurons. The contraction of the muscle is then strong; but, a relaxation must immediately follow because the discharge of two impulses by cells 1, 2, and 3 in quick succession, at an interval of about 1.2 msec., which is equal to the synaptic delay at 4 plus the synaptic delay at 3, 2, or 1, has created in them a strong subnormality, so that the \( f \) impulses cannot reach their threshold. Consequently since no internuncial impulses are produced, the facilitation of the motor nucleus ceases and the following \( f \) impulses alone fail to set up a response of the motoneurons. As long as the subnormal state of neurons 1, 2,
and 3 lasts, i.e., no more than 100 msec., the muscle remains relaxed, but as soon as recovery has been completed the same process is started once more; internuncials and motoneurons are successively recruited* and the contraction of the muscle increases until the discharge of 4 again creates a state of subnormality in 1, 2, and 3. Evidently if by means of suitable lesions the connections of cell 4 with cells 1, 2, and 3 are severed, a sudden development of subnormality becomes impossible and the muscle will remain contracted as long as the / impulses are being produced.

The contraction of the antagonist is explained by the existence of branches 4d and 4e of the axon of cell 4. When this cell fires it not only causes the relaxation of the agonist, but also produces a contraction of the antagonist, for it sets into activity chains of neurons 5-6-7 which on the one hand deliver volleys of impulses to the antagonistic pool and on the other hand lower the threshold of cells 8 and 9, thus increasing the transmission of the tonic (f.) impulses to the motor pool. The antagonistic muscle contracts rapidly, but it must relax again very soon because the impulses cross through the short chains formed by cells 5 to 9 at high frequency and the rapidly created subnormality prevents further conduction of impulses to the motoneurons.

There is extensive experimental evidence to show that neurons 4 to 8 are located at least in part in the reticular substance in the pons. Moreover, it was found possible to place lesions in the vestibular system allowing those groups of neurons to become rhythmically active in the absence of stimulation of the semicircular canals (1928, p. 90; 1933c, p. 29). The eye muscles showed then a peculiar form of nystagmus; the antagonistic muscles underwent a rhythmic succession of fast and short-lasting simultaneous contractions, separated by longer phases of relaxation. Stimulation of the labyrinth did not produce any other result than increase of the frequency of the contractions; but when an additional part of the reticular substance was destroyed, the spontaneous nystagmus ceased and the labyrinth was again able to produce either a monophasic reflex consisting of a steady contraction of the agonist, or even a rhythmic nystagmus in which the contraction of the agonist was partially checked by small quick relaxations.

The relaxation of the agonist begins earlier than the contraction of the antagonist, because the discharge of cell 4, which makes cells 1, 2, and 3 subnormal, does not result in contraction of the antagonist until after some recruitment has taken place in chains 5 to 7. The interval between the beginning of relaxation of the agonist and the start of contraction of the antagonist is smaller the stronger the nystagmus, but even in the case of a strong reflex the difference is not less than 3 to 4 msec., indicating that the transmission of impulses from cell 4 to the antagonist pool takes place through at least three or four internuncial neurons.

After its relaxation the agonist again begins to contract when cells 1, 2,

* It should be noted that the period of relaxation of the agonist is made up of two parts: (1) the time during which the transmission of impulses is blocked; and (2) the time necessary for the recruitment of internuncial neurons.
and 3 recover from subnormality, while the contraction of the antagonist ceases when cells 5 to 7 become subnormal. Since the creation of subnormality demands less time than recovery from subnormality, it is to be expected that the contraction of the antagonist should be briefer than the relaxation of the agonist. In fact differences as great as 50 msec. have been found.

Despite its simplicity, the diagram in Fig. 13 explains why the rhythm may be profoundly modified by intercurrent stimuli. The rate of recruitment of neurons 1 to 4 and of neurons 5 to 9 depends not only upon the impulses conducted by fibers $f$, but also upon the impulses conducted by all the other fibers having connections with the internuncial cells; and the amount of subnormality necessary to block conduction of impulses also depends upon the amount of pre-existent internuncial activity.

Although the available information, especially the anatomical data, is not sufficient to warrant the application of the diagram given in Fig. 13 to other rhythmic activities of the nervous system, it seems likely that some of the elementary phenomena are in every case essentially the same (cf. Sherrington, 1906; Wachholder, 1924; Bronk and Ferguson, 1935) and that other rhythmic reflexes differ from nystagmus only in the rates of recruitment of the motor units during the alternating phases.

(f) Inhibition, reciprocal innervation. At present it is generally believed (cf. Eccles, 1936b; Beritoff, 1937; Fulton, 1938; Lorente de Nó, 1936) that specific inhibitory impulses, even if there were specific inhibitory fibers (Kato, 1934), do not exist. Inhibition must, therefore, be explained in terms of processes created by the same impulses that create excitation. The problem of inhibition has been submitted to careful analysis by Gasser (1935a, b, c, 1938) who has suggested several diagrams accounting for different types of the phenomenon. Two elementary processes are considered: (1) rise in threshold of the neurons due to summation of subnormality; 2) lowering of the stimulating value of a synchronous volley of impulses by its fractionation into two volleys delivered at an interval longer than the effective period of summation of impulses arriving at different synapses.

Since the motoneurons and presumably all other neurons work at threshold, there is no doubt that either of the two processes will cause a deficit of response (inhibition). Several instances have been mentioned in this article as well as in previous papers, in which it was necessary to attribute the absence of response of ocular motoneurons to reduction or cessation of internuncial activity (Fig. 7, 13 to 22); and the diagrams in Figs. 12, I, and 13 explain how a closed chain of neurons including only a few links may act as an inhibitory mechanism. Summation of subnormality, however, will lead to the production of rhythm (Figs. 10 and 11) rather than to sustained inhibition, unless it is produced and maintained in cells which are common links of antagonistic chains of neurons.

The diagram suggested by Gasser (1938c) which is reproduced in Fig. 12, II, includes a link of this type in cell $b$; subnormality of that cell will allow activation of cell $E$ or cell $F$, but not a simultaneous activation of both.
A similar linkage between paths $A_1$ and $A_2$ (Fig. 12, I) would explain the reciprocal exclusion of the appendages of vestibular nystagmus, and the same type of linkage between fibers $f$ and $f'$ (Fig. 13) would explain the initial relaxation of the antagonist, which accompanies the initial contraction of the agonist in certain forms of nystagmus. The existence of an additional linkage ensuring reciprocal innervation is likely, because as previously mentioned, destruction of certain internuncial nuclei may abolish reciprocal innervation and cause co-contraction without abolishing rhythm.

Inhibition through the subnormality of cell $b$ (Fig. 12, II) is very different from inhibition produced by a Wedensky block (Lucas, 1917, Fig. 22). Under certain conditions increase in the frequency of a train of impulses in nerve establishes the Wedensky block; and once established, the block is impassable for any impulse.* Subnormality, on the contrary, produces a block for weak stimuli only, and no matter how strong the subnormality may be, it will be "broken through" if the stimulus is strengthened (Fig. 10, 15).

In principle, then, the problem of inhibition does not offer insurmountable obstacles, and the fact that it is due to excitation of certain neurons explains the similarity found by Sherrington (1925) and by Eccles and Sherrington (1931c) between c.e.s. and c.i.s. Inhibition must have all the properties of excitation, i.e., recruitment, subliminal fringe, etc., the only difference being that inhibition does not set up motor responses. Furthermore, inhibition must be maintained chiefly by internuncial bombardment, but other factors (cf. Dusser de Barenne and McCulloch, 1937; Dusser de Barenne, McCulloch, and Nims, 1937; Gerard, 1936a) may also become operative under given conditions.

The difficulties in the explanation of reciprocal inhibition appear when an attempt is made to identify the anatomical mechanisms, because inhibition by fractionation of synchronous volleys of impulses arriving at different synapses demands that excitation of some cells be brought about through pathways insuring a perfect synchronism of the arrival of impulses, despite the causes for the temporal dispersions responsible for the statistically constant bombardment observed during facilitation (cf. above, sub a). The timing of the arrival of the impulses to the neurons responsible for inhibition must indeed be accurate. Fig. 14 reproduces records of an experiment in which the stimulating value of a synchronous volley of impulses was reduced by dividing it into two volleys delivered at variable intervals.

The diagram at the top explains the conditions of the experiment (cf. 1935c, Fig. 2). An F shock ($F_1$) capable of firing fibers $f_1$ and $f_2$ (records 1, 5, 7) or $f_3$, $f_4$, and $f_5$ (9) was preceded by a smaller F shock ($F_1$) capable of firing only fiber $f_1$ (record 4). The conditioning shock was weak so that the $f_1$ volley was not perfectly synchronous, which caused an apparent increase of the duration of the period of summation of the impulses delivered at neighboring synapses (cf. records 6 and 7). Nevertheless, there was an interval between

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* Several convincing reasons why a Wedensky block cannot be considered as the elementary mechanism underlying inhibition were given by Fulton (1926).
shocks (records 3 and 10) during which the response to F, was clearly diminished. This interval was short, because the bombardment through internuncial cells i, started by shock F, caused the arrival to the motor nucleus of impulses which summated with the F, impulses and gave rise to a facilitated response (records 2 and 8).

The existence of synchronizing mechanisms has been mentioned in previous paragraphs (p. 226). It is, however, not improbable that future research will lead to the discovery of still other, as yet unknown, synchronizing factors and of other agencies capable of maintaining inhibition.* Synchronization of

* Observations made on peripheral nerve (1938a) suggest that subliminal stimulation may play a role in the maintenance of inhibition. When a train of subliminal shocks is delivered to a nerve, each shock is followed by a period of local summation and a period of postcathodal depression, but the duration of the period of summation diminishes with each successive shock of the train, at the same time that the depth of the postcathodal depression decreases.
a large number of elements is a prominent characteristic of the activity of the cerebral cortex (cf. Bishop and O'Leary, 1936; Bishop, 1936). Gerard (1935a, b) has made a thorough analysis of the various factors, which in addition to the play of nerve impulses on neurons may be operative in modifying cortical rhythms. They belong into the class of enduring changes and therefore lie beyond the scope of the present paper (cf. above, parag. a).

**SUMMARY**

An attempt is made to correlate data on the anatomy of the central nervous system with the results of physiological experiments.

The nervous system is composed of an exceedingly large number of interlacing pathways, which offer numerous opportunities for the conduction of impulses into divergent paths; but during activity it becomes fractionated into a group of active and another group of inactive neurons. The active neurons are arranged in convergent chains of relatively simple composition, which may be called the multiple (M, Fig. 2) and the closed chain (C, Fig. 2) through which impulses circulate. The fractionation is attributable to the fact that stimulation of a neuron requires the activation within a short period of time, which for the motoneurons is less than 0.3 msec., of several synapses having a determined spatial distribution on the neuron. The rigidity of the conditions necessary for the effective summation of impulses delivered to synaptic junctions is such that the impulses circulating through the active chains, despite their being very numerous, remain subliminal for the neurons of the inactive group.

Impulses circulating through the chains of neurons of the internuncial system create a statistically constant stimulus of motoneurons and internuncials, as both classes of neurons are submitted to a constant bombardment by impulses being delivered at their synapses. The neurons respond rhythmically at a rate dependent upon the strength of the bombardment and the rate of their recovery.

The multiple chain of neurons (M, Fig. 2) is the elementary unit of transmission; it supersedes the classical reflex arc with a fixed number of synapses. The rate at which a multiple chain may transmit impulses depends upon the number of neurons it contains; the greater the number of links, the lower being the minimal rate.

The closed chain of neurons (C, Fig. 2) may play different roles according to the number of links that it contains. If the number is small, activation of the chain may result in inhibition, but if the number of links is large enough it may result in sustained facilitation or discharge. It is indicated that after-discharge does not necessarily require autochthonous activity of closed chains of neurons; after-discharge must rather be interpreted as an especial depression increases. If these phenomena should take place during synaptic transmission, subliminal stimulation would maintain the high subnormal threshold in the periods between discharges. The neurons would then be accessible only to strong stimuli constituted by the absolutely synchronous arrival of several impulses.
case of reflex reversal, maintained by closed chains of neurons which keep the constant stream of impulses that have arrived from the periphery or from other centers within channels opened by the intercurrent stimulation.

The participation of the internuncial system in the establishment of reflex reactions is explained in some detail on the basis of diagrams designed to account for the production of vestibular nystagmus.

The elementary mechanisms underlying inhibition are discussed.

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