

Recurrent Inhibition as a Mechanism of Control

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It will be known in this circle that Renshaw, in making the experiments on recurrent inhibition (1941, 1946), which have served as a starting point for much later work, also saw recurrent excitation. This has since been studied by Wilson and his co-workers (Brooks and Wilson 1959; Wilson 1959) and everything points to its being the kind of disinhibition (Wilson *et al.* 1960) that Hartline and Ratliff (1956) first described in the *Limulus* eye.

If I restrict myself to recurrent inhibition, this is because it is far more potent on tonic extensors. In decerebrate preparations, in fact, we hardly ever see recurrent excitation which influences the motoneurons of the ankle extensors, unless it be identified with the rebound which is a common occurrence. Our work has been done with tonically responding extensor neurones and we were led into this field of study by our original interest in the gamma control of tone, which naturally leads to a study of the various aspects of the physiological mechanisms which center round the maintenance of long-lasting tonic discharges and contractions.

It was in this way that we encountered the fact that it was practically always possible to inhibit our tonic motoneurons, isolated in root filaments, by antidromic stimulation of the rest of the ventral root, while the phasic ones quite often proved highly resistant to this influence (Granit *et al.* 1957). We could never influence gamma motoneurons by antidromic stimulation which induced recurrent inhibition. These results were soon confirmed by others (Kuno 1959; Eccles *et al.* 1960 a; Eccles *et al.* 1960 b).

Because tonic motoneurons can be set to discharge at semistationary frequencies over a considerable time, this preparation seemed to offer excellent opportunities for trying to build up something quantitative out of a reflex act, including the principles of regulation shown by recurrent inhibition. It has never been shown that a maintained reflex discharge faithfully reflects the level of depolarization of the active region of the membrane of the motoneuron. In order to examine such a postulate, it was necessary to begin by assuming that it is a valid assumption and then to proceed to prove or disprove it. The idea is, of course, merely the well-known concept of the generator potential. Katz's (1950) experiments with muscle spindles showed that the discharge rate is proportional to the amplitude of the slow potential change at the terminals. This has since been observed in experiments with other sense organs (MacNichol 1956; Fuortes 1958, 1959; Loewenstein 1960; Wohlbarsht 1960). For motoneurons we have the evidence obtained by Frank and Fuortes (1960 and personal

communication) that, when a stimulus is applied through an intracellular electrode, the discharge rate is proportional to the depolarizing current over a considerable range. Eccles *et al.* (1954) have shown that recurrent inhibition is of the polarizing type.

In the experiments the reflex discharge is obtained by tetanizing muscular afferents, some of which may be also inhibitory and may contribute a certain amount of polarizing current P_{pol} . But the large spindle afferents would cause depolarization P_{dep} and this would lead to a tonic discharge in proportion to the net depolarizing current (or depolarizing pressure). Hence we have the fundamental equation for discharge frequency

$$F = k(P_{dep} + P_{pol}) \quad (1)$$

in which k is the proportionality constant, and the expression within brackets represents the net depolarizing current. It is possible to vary F by increasing the rate or strength of the afferent stimulation, so that we obtain, for any one motoneurone, a number of normal values F_n to put into the equation. In order to test our assumption that inhibition and excitation sum algebraically, the next step is to test, as is shown in the diagram of Fig. 1, by a constant antidromic tetanus of the rest of the ventral root. The stimulus frequency must be well above the natural firing rate of motoneurons. This means the introduction into the equation of a constant quantity P'_{pol} . Hence we obtain the inhibited frequency F_i , which is

$$F_i = k(P_{dep} + P_{pol} + P'_{pol}) \quad (2)$$

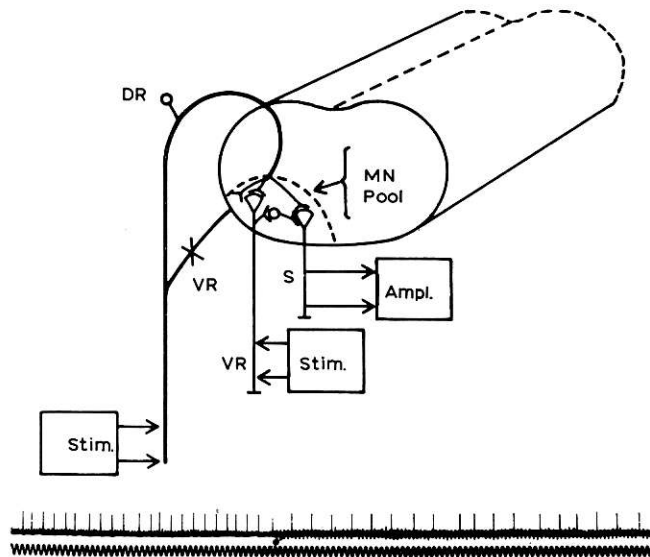


Fig. 1

Experimental arrangement. Stimulating electrodes on severed gastrocnemius nerves and on the ventral root (VR), from which a single fibre (S) has been isolated. DR, dorsal root; the recurrent circuit is diagrammatically shown within the motoneurone pool (MN). Below, record of spike discharging in response to repetitive stimulation of the gastrocnemius nerves; antidromic stimulation at 48/sec inserted at moment marked by dot; time marker, 100 c/sec (Granit and Renkin 1961).

from which it follows that

$$F_n - F_i = -kP'_{poi} \tag{3}$$

Thus, if reflex firing can really be treated quantitatively on the assumptions made, whatever the rate of F_n (above a certain minimum), the difference between it and the inhibited rate F_i should be a constant.

The appended diagram (Fig. 2) perhaps helps us to understand what this means.

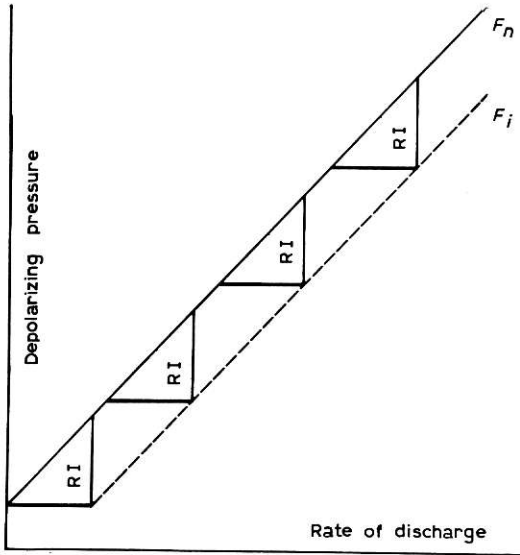


Fig. 2

Diagrammatic. Depolarizing pressure ($=P_{dep} + P_{poi}$) plotted against the rate of discharge of a single motor cell responding to it. The curve marked F_n shows their relationship without the addition of experimental recurrent inhibition. When RI , which is a constant amount of recurrent inhibition ($= P'_{poi}$), is subtracted, the curve shifts to the dashed line marked F_i .

The firing rate is plotted on the abscissa against the net depolarization on the ordinate (upper curve). If we then subtract a constant amount of recurrent inhibition (RI in the graph), this amounts to removing a constant amount of depolarizing current and the inhibitory curve will be shifted downwards by a constant amount.

Actually the experimental results have been plotted as in Fig. 3. F_n will be found on the abscissa and F_i on the ordinate. Now, if there were no recurrent inhibition, F_n would always be equal to F_i and the curve would be a 45° line with its proportionality constant 1.0. This curve is the upper one in the graphs of Fig. 3. The lower curve, obtained by the method of least squares, is drawn through the experimental values, and it is clear that our assumptions mean that it can only be moved downwards by a fixed amount. It should, therefore, also possess a regression coefficient of 1.0. This is seen to be so. The regression coefficient is given in the left upper corner; below it is the standard error, which is defined as the standard deviation divided by the square root of the number of observations (N). With eighteen cells and a total of 470

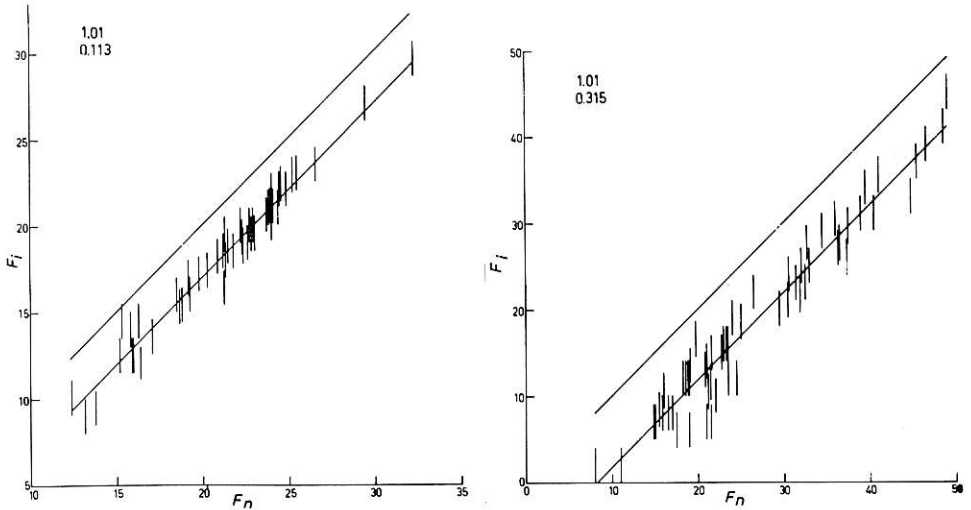


Fig. 3

Decerebrate cat. Single tonic motor cell. Two experiments plotted to show F_n as a function of F_i and the regression line drawn through the data. The upper line represents $F_n = F_i$ or a 45° line with its proportionality constant = 1.00. The theoretical value of the regression coefficient should also be 1.00. The actual value in both these experiments is 1.01 (upper, left corner). The figure below shows the standard error (Granit and Renkin 1961).

observations, sixteen cells gave a regression coefficient which fell inside the limits 0.9–1.1.

If we regard all the experiments with the eighteen motoneurons as being part of one experiment devoted to testing the validity of our equation, the regression coefficients should be weighted with respect to the number of observations (N) in order to obtain their true average value. This proved to be 0.996, which may well be called an unexpectedly good approximation to the theoretical 1.0. Apparently, in order to have cancelled out so well, systematic errors must have been small. The average inhibitory effect in the whole material was

$$F_n - F_i = 5.5 \text{ impulses/sec}$$

Thus it seemed possible, on the assumptions used, to turn reflexology into a simple piece of algebra. As some of you may remember, Sherrington used to think of inhibition and excitation as truly opposite processes which sum algebraically upon the motoneurone, but the time was not yet ripe for putting these general notions to an experimental test.

The next question is: how does the frequency of the antidromic stimulation influence a constant firing rate of a motoneurone. This question is relevant only within the range of firing frequencies in reflex action. Below 5 impulses/sec no tonic motoneurons fire steadily and a large number does not seem to be able to maintain a discharge below 10/sec. At these low rates of stimulation each antidromic shock leads to a pause which is generally succeeded by a brief rebound increase of frequency, which compensates for the loss of spikes during the pause. Thus the net effect in terms of frequency may

be zero. It is well known that the discharge of the Renshaw cells in response to isolated shocks is a high-frequency burst which gradually disappears within some 30–50 msec, but, when the rate of repetition of the antidromic stimuli approaches some 8–10 impulses/sec, the whole character of the discharge changes. The tail drops out and the shock produces only a couple of impulses. From then onwards, up to some 30–40 shocks/sec, the effect of the antidromic stimulation measured as $F_n - F_i$ tends to be, as Fig. 4 shows, proportional to the shock frequency. This is the best we have been able to do at the moment.

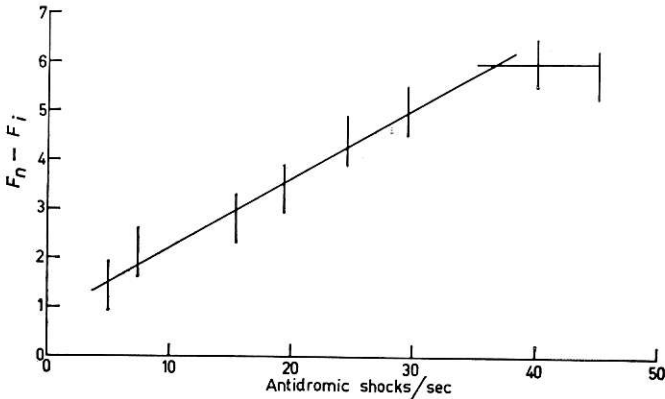


Fig. 4

Experiment as in Fig. 3 but with F_n kept constant and the frequency of antidromic stimulation varied (abscissa). On the ordinate the effect on the recurrent inhibition in terms of $F_n - F_i$ (Granit and Renkin 1961).

It is a striking fact that both the results presented above form a perfect analogy to the findings of Hartline and his co-workers (Hartline 1949; Hartline and Ratliff 1956) with lateral inhibition in the eye of the horseshoe crab *Limulus*. The amount of inhibition is proportional to the firing rate of the inhibiting ommatidium, but is independent of the frequency of discharge of the inhibited ommatidium. It seems to be of considerable interest that it is the frequency of discharge which emerges as the decisive factor and lends itself to treatment in terms of simple linear equations. In *Limulus*, Hartline and his group have explored these possibilities in great detail. Because lateral inhibition is mutual and proportional to the firing rate of the two cells concerned, the cell which discharges more slowly will inhibit its fellow less than the latter inhibits in return. The sum total of the two effects can be obtained not only by experimentation, but also by solving two simultaneous equations after their constants have been obtained by experimentation. Mutual inhibition implies, in effect, a mechanism of sensory contrast. In a similar way recurrent inhibition will, as is easily understood from a consideration of Fig. 5, act to produce motor contrast.

In Fig. 5 the abscissa is the frequency of stimulation of the motor nerve to the soleus and the ordinate is the isometric tension of the muscle. For this nerve-muscle preparation — values from Matthews (1959) — the curve drawn between the experimental

points shows that there is a critical region, which begins around 5–10 impulses/sec, from which tension, as a function of stimulus frequency rapidly rises asymptotically to reach a maximum around 30 shocks/sec. This is the firing range of the soleus motoneurones (Denny-Brown 1929; Granit 1958).

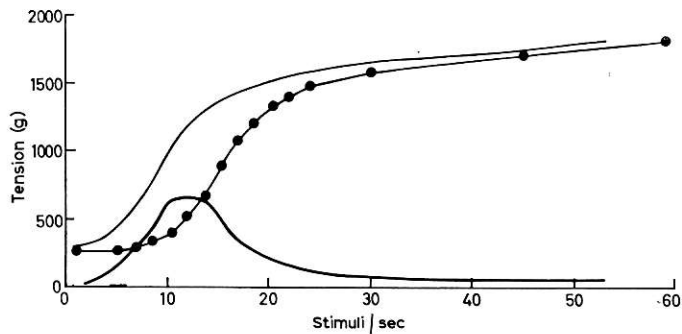


Fig. 5

Curve with observations in filled circles (from Matthews 1959) which illustrates the isometric tension (ordinate) plotted against the stimulus frequency to the muscle nerve (abscissa) of the soleus at an initial length determined by a tension value below 50 g. It is assumed (see Text) that the abscissa also represents the natural firing frequencies across the soleus motoneurone pool, the range being from 25–5 impulses/sec from the centre to the edge of the pool. An approximate idea of what the experimental curve would have looked like in the absence of recurrent inhibition is obtained by subtracting for all points in the curve 6 impulses/sec. This is the upper curve. The lower one is the difference between the two others (Granit and Renkin 1961).

Let us now imagine that the scale of the abscissa also represents a variation in the firing rate from the edge to the centre of the soleus motoneurone pool. The most active focal neurones which fire at high rates are in the centre. These will dominate and so let us, for a first approximation, subtract their constant recurrent inhibition of 6 impulses/sec. This is the upper curve. The lower one is the difference between the two and it shows that the recurrent inhibition has been most potent at the lower frequencies of discharge coming from cells which contribute but little to the tension. If we add the fact that the recurrent inhibitions are mutual, we realize that the motoneurones which fire at low frequencies have been able to suppress those in the centre of the pool but little, while they themselves have been struck by the full inhibitory force of the neurones which fire at high rates. In this sense there is motor contrast. The just liminal fringe of motoneurones will be suppressed and the active focus will be emphasized.

In motor contrast there is another mechanism of considerable importance which tends, like the one just explained, to suppress activity within the fringe. I shall take but one experiment to illustrate it. In Fig. 6 the abscissa is the running time and the ordinate is the impulse frequency of a single tonic cell responding to stretching of the ankle extensors. It is seen that the discharge soon settles down to a constant value for the period between the two horizontal lines. This discharge has been recorded as open circles. The small oblongs on the abscissa show the times when the recurrent

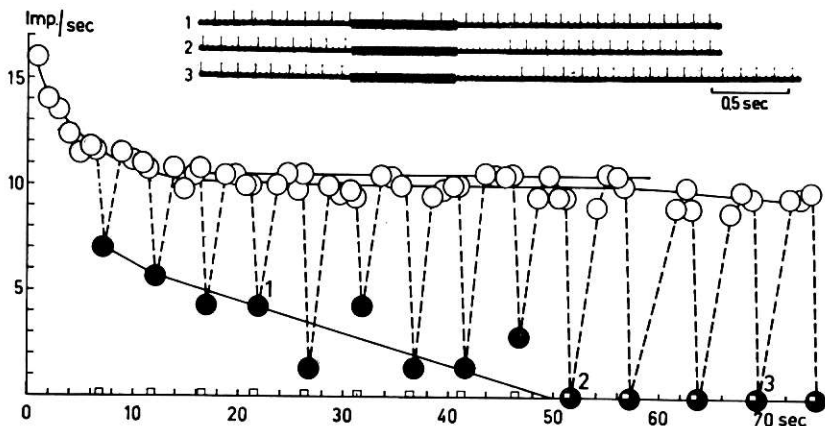


Fig. 6

Motoneuron responding to a steady pull of 15 mm on the ankle extensors. Tetanic antidromic inhibition at 114/sec inserted for 0.7 sec at regular intervals, as marked by rectangles on the abscissa (running time). Frequency of discharge constant between the two parallel horizontal lines. ●, number of impulses (imp/sec) during the periods of recurrent inhibition. Inset: original records at moments marked 1, 2 and 3 in the diagram. Note that, when delayed recovery after recurrent inhibition begins, discharge frequency fails to reach its original level (at this rate of repetition of the antidromic stimulation periods). Discharge stopped for good with the last period of stimulation, having been five times temporarily silenced (Granit and Rutledge 1960).

inhibition was inserted. The points 1, 2 and 3 refer to moments cut out from the film and given in the inset.

Consider now our equation. Because the impulse frequency is constant, the depolarizing pressure is also constant. Recurrent inhibition must therefore remove a constant fraction of it, as, indeed, it will often do, provided that there is enough excitatory drive. But in this situation the effect of the recurrent inhibition increases along the curve. In the original paper (Granit and Rutledge 1960) we have given the evidence for our conclusion that there must be a certain surplus or margin of excitatory drive before a neurone can withstand inhibition and fully recover afterwards. If the term be forgiven me, I could call it presynaptic excitation. We have taken it to express the idea that a constant depolarizing pressure can be maintained with a large or a small margin of support. When the margin decreases too much, recovery from the inhibition at first is delayed and later becomes difficult, and finally impossible. This is seen in the inset of Fig. 6, which gives the moments 1, 2 and 3 in the discharge.

It is clear from Fig. 6 that, whenever the excitatory surplus is low, the cell falls an easy prey to recurrent inhibition and we have reason to assume that this at first happens with the feebly supported neurones in the fringe. Thus the mechanism here described will contribute to the enhancement of motor contrast as established by the algebraical rules for mutual inhibition described in the previous paragraphs.

So far we have been reasoning as if the recurrent inhibition were an automatic circuit which operates, in spite of its intercalated internuncial, the Renshaw cell, as the lateral ramifications of the *Limulus* optic nerve fibres do. But the spinal cord is like a

grand piano which requires a virtuoso to handle its layed-out connexions. We must therefore proceed to give the player in the brain a chance of showing what he can do. This we did by studying not only individual Renshaw cells, but also the full recurrent circuit. The first line of approach differed but little from the one hitherto described. It was part of a set of experiments devoted to the study of the frequency limitation in the motoneurons (Granit *et al.* 1960). The second line was the approach with conventional microcapillaries (Haase and Van der Meulen 1961).

The technique used in the first approach emerges from Fig. 7. It looks very much like Fig. 1, but differs from it in that the discharge from the single fibre *S* is connected through an amplifier to the stimulator *Stim.* for the rest of the ventral root. This means that we make an extra recurrent circuit emphasize the inhibitory effect in proportion to the rate of firing of the single cell selected. Below is shown an original record of a stretch reflex (*1*), and in *2* the same reflex is repeated with the recurrent circuit connected. It is seen that the discharge is slowly strangled, inhibition increasing in a cumulative fashion. In the experiments it proved an advantage to cut the muscle nerve and to use electrical stimulation of the muscular afferents instead of pull on a muscle

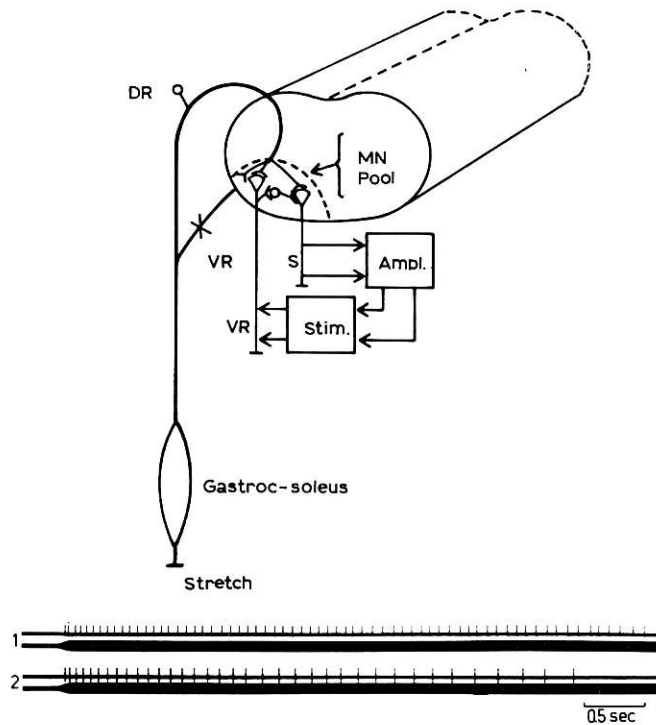


Fig. 7

Arrangement differing somewhat from that of Fig. 1. Here the amplified spike *S* from the single, tonic ventral horn cell is connected to the stimulator *Stim.*, which therefore fires antidromically into the rest of the ventral root, *VR*, at the rate of discharge of *S*. Below, two records of stretching with a length-recorder, indicating the change in the muscle. The upper one is the control; in the lower one the antidromic shock is triggered by *S* in the manner described and the spike is silenced (Granit and Rutledge 1960).

It is then easier to obtain the amount of surplus excitation needed to make the recurrent effect analyzable. If again we plot F_i against F_n with the shock triggering the recurrent feedback, results such as those shown in Fig. 8 are obtained. The relations are linear, but they vary a little in slope because of the variation in the firing frequency of the triggering cell.

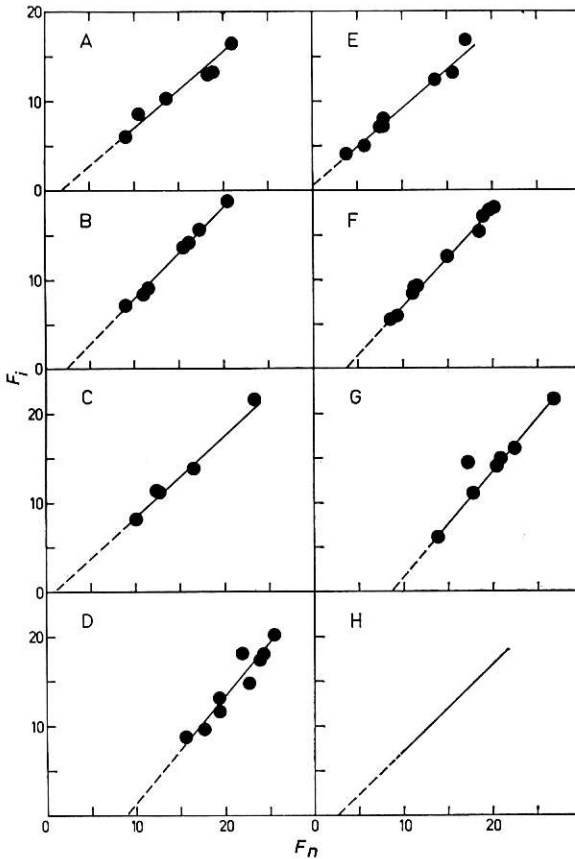


Fig. 8

Graph of F_i against F_n from seven experiments (A-G), in which the antidromic shock is triggered by the tonic spike (see Fig. 7) but, instead of stretching the muscle, electrical stimulation of the cut nerve to the ankle extensors is used for starting the spike at various rates of F_n . Curve H is an average from 33 experiments with different tonic spikes (Granit *et al.* 1960).

The variation of F_n obtained by varying the stimulus rate or strength to the afferent muscle nerve gives a good range over which the effect of supraspinal stimulation can be tested. Fig. 9 shows tetani to the anterior lobe of the cerebellum from which some places give excitation, others inhibition, as can be seen from the slope and location of the curves obtained during stimulation when these are compared with the controls. A full explanation is given in the legends. On the whole it was easier to obtain inhibition (as in Fig. 9), but excitation also occurred.

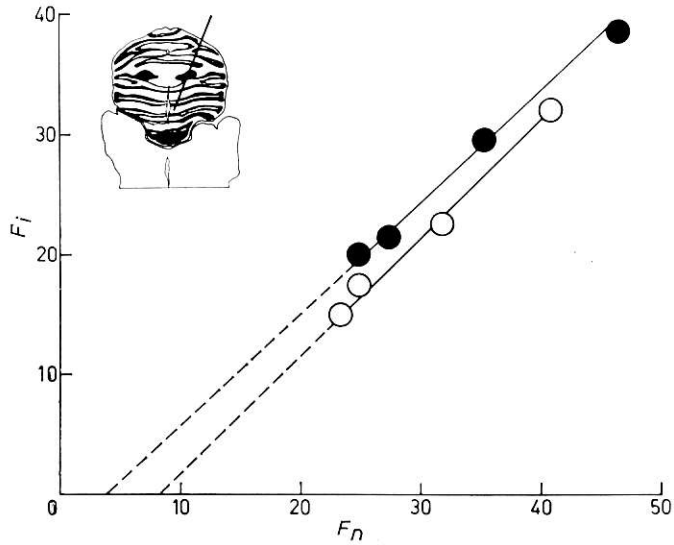


Fig. 9

Afferent stimulation maintained for 50 sec, during which time the antidromic shock was locked to the discharging spike for brief intervals only, as tests. Values from such tests were averaged over four consecutive 10 sec periods from control runs (O), before and after one series during stimulation (●) of the point in the frontal part of the anterior cerebellum illustrated as inset. This well isolated spike had an exceptionally high initial frequency of discharge of around 40/sec, but fell, during maintained afferent stimulation, to values between 20–25 impulses/sec. The point stimulated proved to be in the anterior lobe of the cerebellum (electrocoagulated), as is shown by the inset, in which it is marked by a pointer. The stimulus frequency during the experiment was 300/sec, with a strength of 0.45 V through the tip of the thin coated needle against the ground. By increasing the stimulus strength the discharging spike itself was ultimately inhibited. The effect of stimulation reduces the recurrent inhibition by 4.2 impulses/sec. Co-ordinates scaled in impulses/sec (Granit *et al.* 1960).

Finally let us look briefly at some of the results obtained by Haase and Van der Meulen (1961), who supplemented this work with a study of single Renshaw cells and used conventional microcapillaries to locate them. The method of choice proved to be to maintain an automatically repeated antidromic test shock while Renshaw cells, identified as belonging to the gastrocnemius nerve, were studied. We see the characteristic burst of such cells in the two figures taken from the paper (Fig. 10 and 11). For definition the latent period of the burst had to be 0.6–0.8 msec and the discharge had to be steady, in order to provide a reliable background for the effect of the stimulation of either the cerebellum or else the ventro-medial area of the reticular formation in a region extending from the superior colliculi to the medulla oblongata.

Fig. 10, *A* and *C* (upper) show the effect of a weak antidromic shock eliciting 1–2 spikes, *A* before, *C* after, the record *B* that was taken during cerebellar stimulation of the point marked by a square in the section. It should be noted that cerebellar conditioning in *B* was by a single shock. Facilitation of the test response was considerable. In the lower part of the same figure *A* is the control and in *B* recording had been preceded by a tetanus, which is repeated also in the interval between *B* and *C*. Tests take place at a frequency of 1/sec and the records are from successive sweeps.

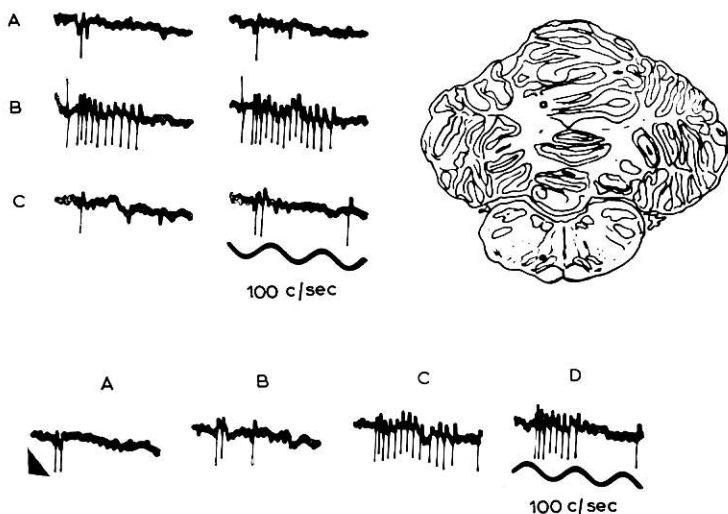


Fig. 10

Deafferented decerebrate cat. Single Renshaw cell. *Upper part*: *A*, the antidromic test shock to the gastrocnemius nerves was adjusted so that only one or two discharges appeared in control. *B*, cerebellar conditioning by a single shock to point marked by a square in section, results in strong facilitation. *C*, after cessation of the cerebellar conditioning the original rate of discharge re-appeared. *Lower part*: successive sweeps at rate 1/sec; the same experiment continued with tetanic stimulation at 48/sec for 0.5 sec in intervals *A-B* and *B-C*. Thus *A* and *D* are controls, but the effect lingers on in *D* (Haase and Van der Meulen 1961).

It is clear that the tetanus has mobilized a facilitation of the Renshaw cell which is maximal in *B* and lingers on in *C* after cessation of stimulation.

Fig. 11 shows in a similar manner inhibition of a submaximal discharge by tetani to the medial point marked by the medial filled circle in the inset. In these experiments spontaneous activity was continuously followed by another channel which wrote on a stationary spot on moving paper, but there was surprisingly little of it, the explanation probably being that the spinal cord of these decerebrate animals was de-afferented

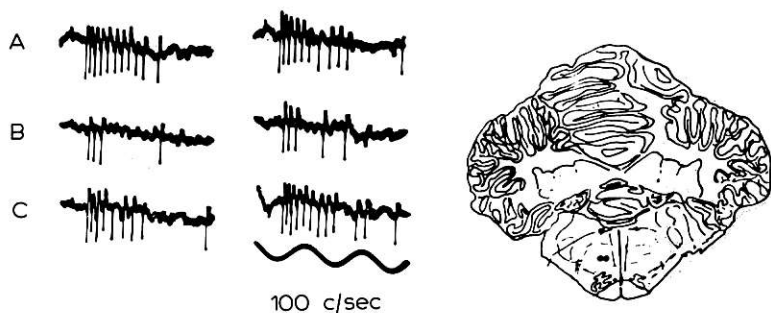


Fig. 11

As Fig. 10, but another experiment. Tetani, as in the lower part of Fig. 1. These were delivered to the medial point in inset. *A* and *C*, controls. *B*, test preceded by tetanus; discharge is inhibited (Haase and Van der Meulen 1961).

over the lumbar and sacral segments. Only occasional and highly irregular bursts were seen. It is important to note that none of the experiments showed the spontaneous activity influenced by the supraspinal stimuli used, nor was it ever possible to detect a supraspinal effect on Renshaw cells, unless they were actually tested antidromically. The effects were therefore never in themselves supraliminal. All these facts seem to demonstrate conclusively that the supraspinal effects on the Renshaw cells were not indirect in the sense that they presupposed an activation of the motoneurons.

We therefore conclude that the recurrent circuit is at the disposal of the supraspinal centres. The limitation of the study to Renshaw cells of the ankle extensors and the central regions mentioned also gives some indication of the general functional significance of the supraspinal mechanism in the control of the mechanisms of tone. An interesting finding was that one of the Renshaw cells, which could be driven both antidromically and orthodromically (from the dorsal root), so that it thus allowed a comparison of both the tests, was, when it was driven orthodromically, facilitated only from a point in the ventromedial part of the reticular formation. This finding, and the absence of direct effects on the Renshaw cells, suggests that the supraspinal mechanisms of control operate through fairly specific internuncial organizations.

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DISCUSSION

J. C. ECCLES:

It is very encouraging indeed to see how the negative feed-back through Renshaw cells, that was initially developed on a purely qualitative basis, has, in Prof. Granit's hands, become a subject for quantitative investigation, and moreover has given the opportunity for such an elegant theoretical development. I would also like to say that at first I was very much surprised by the evidence that cerebellar stimulation can cause changes, either an increase or decrease, in the discharge which antidromic volleys produce in Renshaw cells. However, on further consideration, it seems that this could occur by action on the interneurons that have now been shown by Curtis *et al.* (1961) to excite Renshaw cells by non-cholinergic synapses. In their experiments these interneurons were probably excited by high threshold muscle afferents acting through interneuronal pathways. A likely explanation of the effects of cerebellar stimulation would be that the descending volley from the cerebellum acted through these interneurons, so potentiating or inhibiting the Renshaw cell discharge. The potentiation is thus readily explicable. The inhibition would arise if the volley inhibited a tonic excitatory action of these interneurons on the Renshaw cell. I think these results of Prof. Granit are of great interest for they show for the first time that this homeostatic control of motorneuronal activity is susceptible to influences from higher centres.

CURTIS, D. R., PHILLIS, J. W. and WATKINS, J. C. Cholinergic and non-cholinergic transmission in the mammalian spinal cord. *J. Physiol (Lond.)*, **1961**, *158*: 296–323.

F. BREMER:

The observation on activation of the Renshaw type of spinal interneurons by impulses of cerebellar origin seems to me particularly interesting. While it emphasizes the difficult problem of the mediator, it suggests that the inhibition of spinal motor neurons produced by the stimulation of the anterior lobe of the cerebellum or of the "descending" reticular system could include a component of post-synaptic inhibition. This component of direct inhibition explains the fact that, although fundamentally strychnine-resistant, inhibition of cerebellar origin may be slightly reduced by the convulsive alkaloid. This explanation is not the only possible one, however, for when — as Terzuolo did — we examine the effect of stimulation of the anterior lobe of the cerebellum or of the inhibitory reticular formation on the rhythmic spinal potentials of strychnine tetanus in curarized cats, we observe not a trace of attenuation of the central inhibitory process.

TERZUOLO, C. Influences supraspinales sur le tétanos strychnique de la moelle épinière. *Arch. int. Physiol.*, 1954, 62: 179-196.

H. H. JASPER:

This beautiful quantitative demonstration and theoretical treatment of the algebraic summation of excitation and inhibition in the control of tonic motoneurons of the cord, determining their rate of continuous discharge, is a model which must be applicable also to motoneurons of the cerebral cortex, if it could be tested there.

In the studies of cortical motoneurons in the monkey during conditioned movements (to be mentioned later from experiments by Drs. Ricci and Doane) I have had the impression that one might make a distinction between "tonic" and "phasic" neurons also in the motor cortex. I would like to ask if there is further evidence that this may be true.

However the patterns of cortical neuronal firing are often so complex that their firing rates must be determined by other than simple summation of excitatory and inhibitory states, unless one reduces this principle to a very brief time scale. It would seem that the time constants of neuronal nets and circuits and peripherally imposed temporal patterns may be of greater importance in most instances. One may well ask whether the "tonic" action of the ascending reticular formation may, however, fit into this theory, especially since ascending inhibitory effects seem to be as important as facilitatory effects from the reticular system.

JASPER, H., RICCI, G. and DOANE, B. Microelectrode analysis of cortical cell discharge during avoidance conditioning in the monkey. *Electroenceph. clin. Neurophysiol.*, 1960, Suppl. 13: 137-155.

J. C. ECCLES:

According to the suggestions which I made earlier the inhibitory action of the cerebellar stimulation on the Renshaw cell response can be regarded as a dis-excitation, for it was postulated that it removed a tonic excitatory action evoked by a background of interneuronal activation.

R. JUNG:

Prof. Granit has mentioned that there is a contrast mechanism in the motor system analogous to sensory contrast. This mechanism is so important in nearly all sensory systems that one would also suspect it to be at work in sensory-motor integration.

The well known mechanism of lateral inhibition may explain most of these contrast phenomena together with reciprocal inhibition, as we have found in the visual system.

R. JUNG to H. H. Jasper:

I am very glad that Prof. Jasper has brought cortical neurones into this discussion. They provide good examples of these contrasting and reciprocal inhibitions. As Hering, Froehlich and Ebbecke used Sherrington's spinal mechanisms for an explanation of sensory contrast phenomena we might be allowed here to proceed in a reverse manner and use cortical neurons to illustrate these spinal mechanisms.

All who have worked with microelectrodes in the cortex have seen phenomena similar to the ones Prof. Jasper has just described: Inhibition of one neuron simultaneous with the excitation of neighbouring neurones. It seems to be common that these reciprocal neurones lie rather near together so that you get them with the same microelectrode, pushed some microns further. This may also be due to their mutual inhibitory synaptic relation. However, we have not yet any good examples of recurrent inhibition in cortical neurones except in the Ammons horn and no Renshaw mechanism has been demonstrated in the cortex, although there must be plenty of negative feed back mechanisms to prevent a convulsive explosion in the immense cortical neuronal apparatus and its synaptic powder barrel.

G. GRANIT's replies

To J. C. Eccles

There is little more to add to Sir John's comments than the admission that his suggestions seem entirely plausible and deserve to be tested by experimentation.

To F. Bremer

Has cerebellar inhibition a component run by the Renshaw cells? This may or may not be the case. There are places in the cerebellum that excite, and others that inhibit these cells. No comparison has yet been made with the effects from corresponding cerebellar sites on motoneurons controlled by a definite set of Renshaw cells.

To H. H. Jasper

The first question regarding tonic and phasic neurones in the cortex I cannot reply to, even though I am inclined to suspect that this is a classification that applies to a large number of organised aggregates of neurones. It seems such a sensible subdivision of elementary tasks. Phillips has found evidence for recurrent action in the motor cortex but the spinal cord is unique in providing a situation that can be handled in quantitative terms. This proviso is essential because from it alone has it become possible to deduce from the experiments that recurrent inhibition definitely is a mechanism serving discrimination by what, for short, we may call *contrast*, motor or sensory, as the case may be.

To R. Jung

This very point is raised by Professor Jung's remarks. I entirely agree that similar mechanisms, wherever they be found, must serve the same purpose, sc. contrast. The recurrent or lateral inhibition in *Limulus* does it, although this preparation is an invertebrate eye lacking also the internuncial cells of the motoneurons in the spinal cord. In fact, any recurrent inhibition, randomly distributed within an aggregate of neurones devoted to the same function, should behave as in the two examples mentioned, because its action is tied to frequency of firing and is mutual with respect to adjacent neurones in possession of recurrent collaterals. A very attractive feature of the findings is that they can be simply expressed in terms of impulse frequency which, with some justification, may be called the fundamental quantity of the code in which nervous messages are clothed. This has also been emphasized by Hartline and his co-workers.

HARTLINE, H. K., RATLIFF, F. and MILLER, W. H. Inhibitory interaction in the retina and its significance in vision. In E. FLOREY (Editor). *Nervous Inhibition*. Pergamon Press, New York, 1961: 241-284.

PHILLIPS, C. G. Actions of antidromic pyramidal volleys on single Betz cells in the cat. *Quart. J. exp. Physiol.*, 1959, 44: 1-25.