Nobel Lecture

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Inhibition as a Coordinative Factor

That a muscle on irritation of its nerve contracts had already long been familiar to physiology when the 19th century found a nerve which when irritated prevented its muscle from contracting. This observation seemed for a time too strange to be believed. Its truth did not gain acceptance for ten years; but at last in 1848 the Webers accepted the fact at its face value and proclaimed the vagus nerve to be inhibitory of the heart muscle. Two hundred years earlier Descartes, in writing the *De Homine*, had assumed that muscle was supplied with nerves which caused muscular relaxation. An analogous suggestion was put forward by Charles Bell in 1819. The inhibition suggested was in each case "peripheral". "Peripheral" inhibition, despite its inherent probability, was however to prove void of the fact for skeletal muscle. As just said, it did in fact prove true for the heart; it was found somewhat later to hold good likewise for visceral muscle; and, somewhat later still, was found for the constrictor muscles of the blood vessels. Peripheral inhibition became thus by the sixties and seventies of the 19th century a recognized fact, save for the one important exception of the skeletal muscles.

The first experimental indication of inhibition as a process working *within* the nervous system itself appeared in 1863. Setschenov then noted in the frog that the local reflexes of the limb are depressed by stimulation of the exposed midbrain. Later (1881), somewhat similarly, stimulation of the foot (dog) was found to restrain movements of the foot excited from the brain (Bubnoff and Heidenhain). Matters had, broadly put, reached and remained at that stage, when in the century's last decade experimental examination of mammalian reflexes detected (1892) examples of inhibition of surprising potency and machine-like regularity, readily obtainable from the mammalian spinal cord in its action on the extensors of the hind limb; the inhibitory relaxation of the extension was linked with concomitant reflex contraction of their antagonistic muscles, the flexors. This "reciprocal innervation" was quickly found to be of wide occurrence in reflex actions operating the skeletal musculature. Its openness to examination in preparations with "tonic" background (decerebrate rigidity) made it a welcome and immediate opportunity for the more precise study of inhibition as a central nervous process.

The seat of this inhibition was soon shown to be central, e.g. for spinal reflexes, in the grey matter of the spinal cord. The resulting relaxation of the muscle was found to be both in range and nicety as amenable to grading as is reflex contraction itself. In other words the inhibitory process was found capable of no less delicate quantitative adjustment than is the excitatory process. In "reciprocal innervation" the two effects, excitation and inhibition, ran broadly *pari passu*; a weak stimulus evoked weak inhibitory

relaxation along with weak excitatory contraction in the antagonist muscle; a strong stimulus evoked greater and quicker relaxation accompanying greater and speedier contraction of the antagonist. No evidence was forthcoming that the centripetal nervous impulses which on their central arrival give rise to inhibition differ in nature from nerve impulses giving rise centrally to "excitation", or indeed differ from the impulses travelling nerve fibres elsewhere. An "inhibitory" afferent nerve emerged simply as an afferent nerve whose impulses at certain central loci cause, directly or indirectly, inhibition, while at other central loci the same nerve, probably even the same nerve fibre can produce excitation. There was no satisfactory evidence that an afferent nerve fibre whose end-effect is inhibitory ever for its end-effect at that same locus evokes excitation or indeed any other effect than inhibition. That is to say its inhibitory influence never changes to an excitatory influence, or vice versa. Fixity of central effect, inhibitory or excitatory respectively, has to be accepted for the individual afferent fibre acting in a specified direction, i.e. on a specified individual effector unit. That does not of course exclude the contingency that an inhibitory influence on a given unit may under some circumstances be unable to produce effective inhibition there owing to its being too weak to overcome concurrent excitation.

I will not dwell upon the features of reciprocal innervation; they are well known. I would only remark that owing to the wide occurrence of reciprocal innervation it was not unnatural to suppose at first that the entire scope of reflex inhibition lay within the ambit of the taxis of antagonistic muscles and antagonistic movements. Further study of central nervous action, however, finds central inhibition too extensive and ubiquitous to make it likely that it is confined solely to the taxis of antagonistic muscles.

In instance let us take a reflex especially facile and regular to type, the well-known spinal flexion-reflex of the leg, evoked by stimulation of any afferent.280 1932 nerve of the leg itself Its experimental stimulus may be reduced to a single induction shock evoking a single volley of centripetal impulses in the bared afferent nerve. The reflex effect, observed in an isolated flexor muscle, e.g. of the ankle, is apart from exceptional circumstances, a single contraction wave indicating discharge of a single volley of motor impulses from the spinal centre. This "twitch-reflex", recorded isometrically by the myograph, exhibits a tension proportional to the number of motor units engaged, in other words to the size of the single centrifugal impulse volley. The contraction of each motor unit is on the all-or-nothing principle. The maximal contraction-tension for the reflex twitch will be reached only when all of the motor units composing the muscle are activated. The contraction-tension developed by the reflex being proportional to the number of motor units engaged, an average contraction-tension value for the individual motor unit can be found. The contraction developed by the reflex twitch is less the weaker the induction shock exciting the afferent nerve, in other words the fewer the afferent fibres excited, in short, the smaller the size of the centripetal impulse volley. With a given single-shock stimulus the tension developed by the reflex twitch remains closely constant when sampled at not too frequent intervals. In the case of the spinal flexion-reflex therefore, though with many other reflexes it is not so, a standard reflex twitch of desired size (tension) can be obtained at repeated intervals.

The only index available at present for inhibition is its effect on excitation; thus, a standard twitch-reflex, representing a standard-sized volley of centrifugal discharge, can serve as a quantitative test for reflex inhibition. It serves for this with less ambiguity than does a reflex tetanus. In the tetanus the tension developed will depend within limits on the repetitive-frequency of the contraction waves forming the tetanus. Maximal tetanic contraction is reached only when the frequency reaches a rate which, in many reflex tetani, some of the units do not attain. In reflexes the rate of tetanic discharge can differ from unit to unit in one and the same muscle at one and the same time. The rate will differ too at different stages of the same reflex and according as the reflex is weak or strong. Reflex inhibition acting against a reflex titanic contraction may diminish the contraction in one or other or all of several different ways. In some units it may suppress the motor discharge altogether, in some it may merely slow the motor discharge thus lessening the wave frequency of the contraction and so the tension. The same aggregate diminution of tension may thus be brought about variously and by various combinations of ways, a result too equivocal for analysis. The same gross result might accrue *(a)* from total suppression of activity in some units or *(b)* from mere slackening of discharge in a larger number of units. These difficulties of interpretation are avoided by using as gauge for inhibition a standard reflex twitch. The deficit of contraction-tension then observed shows unequivocally the number of motor units inhibited out of the total activated for the standard. Since the direct maximal motor twitch compared with the standard reflex twitch can reveal the proportion of the whole muscle which the standard reflex twitch activates, we can find further what proportion of the whole muscle is reflexly inhibited. Of course subliminal excitation and subliminal inhibition are not revealed by the test and require other means for detection.

A stable excitatory twitch-reflex as standard allows us to proceed further in our quantitative examination of inhibition. We then find that inhibition can be admixt in our simple-seeming flexion-reflex itself, and indeed usually is so. To detect it we have simply to add to the earlier excitation of the reflex a following one at not too long interval; we then find the response to the second stimulus-volley partly cut down by an inhibition latent in the first.

This is usually evident with intervals between 300-1,200 sigma. The very shortest interval at which the inhibitory effect occurs is difficult to determine, for the reason that the excitatory effect has a subliminal fringe and the second stimulus repeats the subliminal effect of the first, and the two subliminal effects can sum to liminal. The second response is therefore enlarged by summation of subliminal fringe in some of the responsive motor units. This activation by the second stimulus of some motor units facilitated for it by the first though not activated by the first alone tends of course to obscure the inhibitory inactivation; the shrinkage due to the latter is offset by the increment due to the former. The inhibition is traceable only by the net diminution of the second reflex twitch. How quickly the inhibitory element in the stimulus develops centrally is not fully ascertainable, because the sooner the second reflex follows on the first the more the facilitation from it that it gets. This increment will conceal at least in part the decrement due to inhibition. Similarly the beginning of the inhibition may be concealed from observation by concomitant excitatory facilitation. This uncertainty does

not attach to the longer intervals between the two stimuli because the central inhibitory process considerably outlasts the central excitatory facilitation.

The reflex therefore, which at first sight seems a purely excitatory reaction, proves on closer examination to be in fact a commingled excitation and inhibition. Usually clearly demonstrable in the simple spinal condition of the reflex, this complexity of character is yet more evident in the decerebrate condition.

We may hesitate to generalize from this example, because a stimulus applied to a bared afferent nerve is of course "artificial" in as much as it is applied to an anatomical collection of nerve fibres not homogeneous in function; and, we may suppose, not usually excited together. If cutaneous, its fibres will belong to such different species of sense as "touch" and "pain" which often provoke movements of opposite direction and are therefore in their effect on a given muscle opposed in effect. That a strong stimulus to such an afferent nerve, exciting most or all of its fibres, should in regard to a given muscle develop inhibition and excitation concurrently is not surprising.

With weak stimuli the case is somewhat different. Such stimuli excite only a few of the constituent fibres of the afferent nerve, and those of similar calibre, presumably an indication of some functional likeness. Nevertheless, as shown above, the reflex result even then exhibits admixed excitatory and inhibitory influence on one and the same given muscle. And this admixture of excitation and inhibition persists when the stimulus is reduced in strength still further so as to be merely liminal. It still is so when the afferent nerve chosen is homogeneous in the sense that it is a purely muscular afferent, e.g. the afferent from one head of the gastrocnemius muscle. But we must remember that the afferent nerve from an extensor muscle has been shown to contain fibres which exert opposite reflex influences upon their own muscle, some exciting and some inhibiting that muscle's contraction. This brings with it the question whether admixture of exciting and inhibiting influence in the reflex effect obtains when instead of stimulation of a bared nerve some more "natural" stimulation is employed.

For this the reflex evoked by passive flexion of knee in the decerebrate preparation has been taken. The single-joint extensor (vasto-crureus) of each knee is isolated; and nothing but that muscle pair thus retained is still innervated in the whole of the two limbs. The preparation thus obtained is a tonic preparation; one of the two muscles is then stretched by passively flexing a knee. This passive flexion excites in the extensor muscle which it stretches a reflex relaxation, i.e. the lengthening reaction; this relaxation at one knee is accompanied in the opposite fellow vasto-crureus by a reflex contraction enhancing the existing "tonic" contraction. The reflex contraction thus provoked is characteristically deliberate and smooth in performance and passes without overshoot into a maintained extension posture. Let however the manoeuvre be then repeated with the one difference of condition, that the muscle contralateral to that which is passively stretched has been deafferented. In the deafferented muscle contraction is still obtained, and more easily than before, but the deafferented condition of the muscle alters the course of its contraction in two respects. The course is no longer deliberate. The contraction is an abrupt rush, with overshoot of the succeeding postural contraction, and this latter is

hardly maintained at all. The severance of the afferent nerve has removed a reflex self-restraint from the contracting muscle. Normally the proprioceptives of the contracting muscle put a brake on the speed of the contracting muscle (autogenous inhibition). The explosive rush and momentum of these deafferented extensor reflexes recall the ataxy of tabes. They recall also the abruptness and overshooting of the "willed" movements of a deafferented limb. In both cases a normal self-braking has been lost along with the deprivation of the muscle of its own proprioceptive afferents. These latter mediate both a self-braking and a self-exciting (autogenous excitation) reflex action of the muscle. Thus here again there is admixture of reflex inhibition and excitation, and in this case the admixture obtains in response to a "natural" stimulation. Here therefore the admixture of central inhibition with central excitation is a normal feature of a natural reflex.

This makes it clear that for the study of normal nervous coordinations we require to know how central inhibition and excitation interact. As said above, the centripetal impulses which evoke inhibition do not differ in nature from those which evoke excitation. Inhibition like excitation can be induced in a "resting" centre. The only test we have for the inhibition is excitation. Existence of an excited state is not a prerequisite for the production of inhibition; inhibition can exist apart from excitation no less than, when called forth against an excitation already in progress, it can suppress or moderate it. The centripetal volley which excites a "centre" finds, if preceded by an inhibitory volley, the centre so treated is already irresponsive or partly so.

A first question is, are there degrees of "central inhibitory state"; and are they, like central excitatory state, capable of summation. This can be examined in several ways. Thus: against the central inhibition caused by a given single volley of inhibitory impulses a standard single volley of excitatory impulses can be launched at an appropriate interval. The relatively long duration of the central inhibitory state allows a second inhibitory volley to be interpolated between the original inhibitory volley and the standard excitatory volley. The standard excitation is found to be then diminished (as shown by the twitch-contraction which it evokes) more than it is if subjected to either one inhibitory volley only. This holds even when the second inhibitory volley, launched from the same cathode as the first, is arranged to be clearly smaller than the first. Since the distribution of the effect of the smaller impulse volley (launched from the same cathode as the larger) among the motoneurones of the centre must lie completely included within that of the first, the added inhibition due to the second volley indicates that the combined influence of the two volleys prevents activation of some motoneurones which neither inhibitory volley acting alone was able to prevent from being activated. Evidently therefore central inhibition sums; consequently it is capable of subliminal existence. Also, successive subliminal degrees of inhibition can by temporal overlap sum to supraliminal degree. In these ways central inhibition presents analogy with its converse "central excitations"; both exhibit various degrees of intensity in respect to the individual motoneurone.

Summation of inhibition is well exhibited when a given twitch-reflex is evoked at various times during and after a tetanic inhibition. The cutting down of the reflex twitch is progressively greater, as within limits, the inhibitory tetanus proceeds. After cessation of

the tetanus the inhibitory state, similarly tested, passes off gradually, more quickly at first than later.

The relatively long persistence of the central inhibitory state induced by a single centripetal impulse volley allows examination of the effect on it of two successive excitation volleys as compared with one of the two alone. An excitatory volley is interpolated between the inhibitory volley and a subsequent standard excitatory volley. The interpolated excitatory volley is found to lessen the inhibitory effect upon the final excitatory volley. The interpolated excitation volley neutralizes some of the inhibition which otherwise would have counteracted the final test excitation. Just as central inhibitory state (c.i.s.) counteracts central excitatory state (c.e.s.) so c.e.s. neutralizes c.i.s. The mutual inactivation is quantitative. There occurs at the individual neurone an algebraic summation of the values of the two opposed influences.

It is still early to venture any definite view of the intimate nature of "central inhibition". It is commonly held that nerve excitation consists essentially in the local depolarization of a polarized membrane on the surface of the neurone. As to "central excitation", it is difficult to suppose such depolarization of the cell surface can be graded any more than can that of the fibre. But its antecedent step (facilitation) might be graded, e.g. subliminal. Local depolarization having occurred the difference of potential thus arisen gives a current which disrupts the adjacent polarization membrane, and so the "excitation>. travels. As to inhibition the suggestion is made that it consists in the temporary stabilization of the surface membrane which excitation would break down. As tested against a standard excitation the inhibitory stabilization is found to present various degrees of stability. The inhibitory stabilization of the membrane might be pictured as a heightening of the "resting" polarization, somewhat on the lines of an electrotonus. Unlike the excitation-depolarization it would not travel; and, in fact, the inhibitory state does not travel.

The quantitative character of the interaction between opposed inhibition and excitation is experimentally demonstrable. Thus: a given inhibitory tetanus exerted on a certain set of motoneurones fails to prevent their excitation in response to strong stimulation of a given afferent nerve; but when the stimulation of the excitatory afferent is weaker the given standard inhibitory tetanus does prevent the response of the motor neurones to the excitatory stimulation. With the weaker stimulation of the afferent nerve there are fewer of its fibres acting, and therefore fewer converge for central effect on some of the units. On these the standard c.i.s. has therefore less c.e.s. to counteract.

Many features characteristic of reflex myographic records of various type become interpretable in light of the stimulus volley from a single afferent nerve trunk, even small, evoking an admixture of inhibition and excitation, with consequent central conflict and interaction between them. Features which find facile explanation in this way are the following. (A) The flexion-reflex (spinal) commonly has a *d'emblée* opening; that is, a steep initial contraction passes abruptly into a plateau, giving an approximately rectangular beginning to the myogram. Here the initial reflex excitation is closely followed by an ensuing reflex inhibition commingled with and partially counter-acting

the concurrent excitation. (B) Allied to this and of analogous explanation is the so-called "fountain"- form of flexion-reflex. After the first uprush of contraction a component of reflex inhibition grows relatively more potent and the contraction-tension drops low before continuing-level. Between these extreme forms there are intermediates. The key to the production of them all is admixture of central excitation with central inhibition; the excitation is prepotent earlier, and later suffers from encroaching inhibition.

(C) Again, the typical opening of the crossed extensor reflex (decerebrate) "recruits". A variably long latent period precedes a contraction which climbs slowly, taking perhaps seconds to reach its plateau. Here, struggling with excitation, inhibition has the upper hand at first. The action currents of the muscle marking the serial stimuli to the afferent nerve are not choked by secondary waves of after-discharge. The concurrent inhibition cuts them out. The inhibition is traceable partly to the proprioceptive reflex mechanism attached to the contracting muscle itself; the progress of the reflex contraction is partly freed from inhibition by deafferenting the muscle, but still not wholly freed. A residuum of inhibition in the reflex is traceable to the crossed afferent nerve employed. This again illustrates the ubiquitous commingling of inhibition and excitation in the spinal and decerebrate reflexes evoked by direct stimulation of afferent nerves.

An instance of combination of excitation and inhibition for coordinative effect is the rhythmic reflex of stepping. In the "spinal" cat and dog there occurs "stepping" of the hind limbs; it starts when the "spinal" hind limbs, lifted from the ground, hang freely, the animal being supported vertically from the shoulders. The extensor phase in one limb occurs with the flexor phase in the other. This "stepping" can also be evoked by a stigmatic electrode carrying a mild tetanic current to a point in the cross-face of the cut spinal-cord. The "stepping" then opens with Aexion in the ipsilateral hind limb accompanied by extension in the contralateral. To reproduce this stepping movement by appropriately timed repetitions of tetanization of, for instance, a flexion producing afferent of one limb or an extension-producing afferent of the other never succeeds even remotely in exciting the rhythmic stepping. In the true rhythmic movement itself, which has been examined particularly by Graham Brown, the contraction in each phase develops smoothly to a climax and then as smoothly declines, waxing and waning much as does the activity of the diaphragm in normal inspiration. But although this rhythmically intermittent tetanus affecting alternately the flexors and extensors of the limb and giving the reflex step cannot be copied reflexly by employing excitation alone, it can be easily and faithfully reproduced and with perfect alternation of phase and with its characteristic asymmetrical bilaterality, by employing a stimulation in which reflex excitation and reflex inhibition are admixt in approximately balanced intensity. The result is then a rhythmic sea-saw about a neutral point. The effect on the individual motor unit appears then to run its course thus: if we start to trace the cycle with the moment when c.e. and c.i. are so equal as to cancel out, the state of the motoneurone is a zero state, for which the term "rest", although often applied to it, is perhaps better avoided. With supervention of preponderance of c.e. over c.i. the motor neurone's discharge commences and under progressive increase of that preponderance the frequency of discharge increases in the individual motor neurone, and more motor neurones are "recruited" for action until in due course the preponderance of c.e. begins to fail and c.i. in its turn

asserts itself more. The recruitment and frequency of discharge begin to wane, and then reach their lowest, and may cease, and an interval of zero state or quiescense may ensue. The quiescence may be inhibitory or merely lack of excitation. Which of these it were could be directly determined only by testing the threshold of excitation. However brought about, it is synchronous with the excitation-phase in the antagonistic muscle and with the excitation-phase in the symmetrical fellow muscles of the opposite limb. Since reciprocal innervation has been observed to obtain between these muscles, the phase of lapse of excitation is probably one of filer active inhibition. The rhythm induced by stimulation of the "stepping"-point in the cut face of the lateral column of the cord would seem to act therefore by evoking concurrently excitation and inhibition, and so playing them off one against the other as to induce alternate dominance of each. Intensifying the mild current applied to the point quickens the tempo of the rhythm, i.e. of the alternation.

Another class of events revealing inhibition as a factor wide and decisive in the working of the central nervous system is presented by the "release" phenomenon of Hughlings Jackson. The depression of activity called "shock" supervenes on injury of a distant but related part; conversely there supervenes often an over-action due likewise to injury or destruction of some distant but related part. "Shock" is traceable to loss of excitatory influence, which, though perhaps commonly subliminal in itself, lowers the threshold for other excitation. The over-action conversely is traceable to loss of inhibitory influence, perhaps subliminal in itself and yet helping concurrent influences of like direction to maintain a normal restraint, the normal height of threshold against excitation. Where the relation between one group of muscles and another, e.g. between flexors and extensors, is reciprocal, the effect of removal (by trauma or disease) of some influence exerted by another part of the nervous system is commonly two-fold in direction. There is "shock", i.e. depression of excitability in one field of the double mechanism and "release", i.e. exaltation of excitability, in another. Thus spinal transection, cutting off the hind-limb spinal reflexes from prespinal centers inflicts "shocks" on the extensor half-centre and produces "release" of the flexor half-centre. In this case the direction both of the "shock" and of the "release" runs aborally ; but it can run the other way, as in the influence that the hind-limb centres have on the fore-limb. Which way it runs, of course, depends simply on the relative anatomical situation of the influencing and the influenced centres.

The role of inhibition in the working of the central nervous system has proved to be more and more extensive and more and more fundamental as experiment has advanced in examining it. Reflex inhibition can no longer be regarded merely as a factor specially developed for dealing with the antagonism of opponent muscles acting at various hinge-joints. Its role as a coordinative factor comprises that, and goes beyond that. In the working of the central nervous machinery inhibition seems as ubiquitous and as frequent as is excitation itself. The whole quantitative grading of the operations of the spinal cord and brain appears to rest upon mutual interaction between the two central processes "excitation" and "inhibition", the one no less important than the other. For example, no operation can be more important as a basis of coordination for a motor act than adjustment of the quantity of contraction, e.g. of the number of motor units employed and the intensity of their individual tetanic activity. This now appears as the outcome of nice

co-adjustment of excitation and inhibition upon each of all the individual units which cooperate in the act.

In reflexes, even under simple spinal or decerebrate conditions, interplay between excitation and inhibition is commonly induced even by the simplest stimulus. It need not surprise us therefore that variability of reflex result is met by the experimenter. Indeed, that it troubles him by being partly beyond his control, need not surprise him in view of the multiplicity and complicity of the sources of the inhibition and of the excitation. This variability seems underestimated by those who regard reflex action as too rigid to provide a prototype for cerebral behaviour. It is in virtue of their containing inhibition and excitation admixt that, in accord with central conditions prevailing for the time being, a limb-reflex provoked by a given stimulus in the decerebrate preparation can on one occasion be opposite in direction to what it is on another, e.g. extension instead of Aexion ("reversal") Excitation and inhibition are both present from the very stimulus out-set and are pitted against one another. The central circumstances may favour one at one time, the other at another. Again, if the quantity of contraction needed normally for a given act be reached by algebraic summation of central excitation and inhibition, it can obviously be attained by variously compounded quantities of those two. Hence when disease or injury has caused a deficit of excitation, a readjustment of concurrent inhibition offers a means of arriving once more at the normal quantity required. The admixture of inhibition and excitation as a mechanism for coordination thus provides a means of understanding the remarkable "compensations" which restore in course of time, and even quickly, the muscular competence for execution of an act which has been damaged by central nervous lesions. More than one way for doing the same thing is provided by the natural constitution of the nervous system. This luxury of means of compassing a given combination seems to offer the means of restitution of an act after its impairment or loss in one of its several forms.

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