"INTEGRATION, THEN AND NOW"

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My title implies an incursion into history which has for its landmark Sherrington's "Integrative Action of the Nervous System." Those Silliman lectures (Sherrington, 1906) given at Yale University now more than forty years ago, have ever since been a beacon in the voyage of neurological discovery. The definition of "integration" cannot be made in one sentence without preface. Sherrington's emphasis on the cell will be remembered. "Nowhere in physiology," he said, "does the cell theory reveal its presence more frequently than at the present time in the study of nervous reactions." Nerve cells have special properties as well as general. They have their own metabolic life like any other cell. They transmit states of excitation. By virtue of that property they integrate behaviour in a multicellular animal, binding its cells into a functional one and whole. That is Integration. But there are other kinds of Integration, as well as the nervous. There is the mechanical combination of unit cells and their chemical combination by endocrines. Nervous Integration is marked for its high speed of reaction and its nicety of adjustment in time and in space. To the clinical observer, Integration is an accepted reality. The whole human animal, integrated by its interdependent systems of nervous activity, blood supply, nutrition, and so forth, with Mind on top of all, can be and often must be studied as a whole, with all the advantages (or disadvantages) of the subject's co-operation. In the laboratory, where isolated phenomena are sought, the very nature of Integration makes isolation difficult because Integration is all-pervading. At every stage of analysis, integrated processes or actions hold a veil against the analysing gaze of the experimenter and resist his penetration. In support of this statement I propose to give a few examples from the history of experimental analysis.

Experimental Analysis

When the "Integrative Action" was published in 1906, unitary studies of cells were technically impossible. On the other hand, to illustrate the

welding, the integration of nervous function, and yet to take from it some complications which could cloud close scrutiny, Sherrington chose for his picture the scratch reflex. Here is his canvas—a spinal cord isolated from high-level influences. That leaves a field for studying nervous integration at low levels. In this reflex no less than thirty-six muscles take part. The number of nerve cells, nerve fibres, and muscle fibres here integrated in allied reflex arcs is very large. They are integrated together and work together for the benefit of the whole organism in order to achieve quietus from skin irritation. As for the stimulus, the flea, we must have a controllable agent. Natural fleas being out of the question, one seeks a substitute. Mechanical stimuli such as a toothed wheel run over the surface of the skin are excellent provokers of the scratch. The end-organ in the skin, what Pavlov would later have called an analyser, can be activated by the electric current which, though less effective than the toothed wheel, is more easily controlled and more certainly repeated.

In passing, let us note that so far electrical stimulation of the bared afferent nerve has not been found to elicit the scratch. The analysing organ in the skin is the needed intermediary. In cataloguing the features of this widely engaging reflex, there is to be remembered for contrast the speed as well as the fatality of a simple nerve-muscle preparation when stimulated directly by its motor nerve. In a nerve-muscle preparation, the response comes rapidly if at all. From what is known of the speed of impulses along nerve-axones, the nerve-paths could carry them from the receptor to the effector in less than a score of milliseconds. But when the electric flea, in the form of a sharp slender pin connected to an inductorium, bites just gently, its modest titillations may sum during as long a period as three and a half whole seconds before the scratching response begins. Here then (but where exactly?) we have a summation of

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stimuli. After that begins the impressive display of integrated movement among all the muscle masses causing rhythmic up-and-down movement of the limb. Moreover, the rhythm itself when reasonably extensive, has a steady rate in a fairly large dog at five beats a second. This vast organization of purposive movement has no counterpart in the spinal nerve-cell observed isolatedly.

If we travel forward in time to recent experiments by Eccles we see the behaviour of spinal nerve-cells subjected to excitation. They respond almost at once, within 0.2 to 0.3 milliseconds of the onset of

FIG. 1.—After Lloyd, 1946. *J. Neurophysiol.*, 9, 426. Lower curve, filled circles, exponential regression of facilitation in flexor and extensor spinal nuclei. The test reflex is the maximum response in a two-neurone arc attainable by stimulation of a particular afferent nerve. The facilitating stimulus is a near-threshold shock applied to large fibres (12–20 μ) in a closely-allied afferent nerve.

Upper curve, crosses, similar but after slightly stronger facilitating stimuli, so engaging smaller afferent fibres, with the result that internuncial neurones (and indirect paths) come into play.

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the electrically polarized state which betokens excitation (Eccles, 1946). They remain in a diminishingly polarized state for less than a score of milliseconds.

Lloyd, working in the same field, finds that the excitation, evidenced by an electric charge on the cell, has declined to one-half in a mere 2.8 milliseconds (Fig. 1, lower curve). Thereafter excitation continues to decline logarithmically and is extinct

FIG. 2.—After Sherrington, "Integrative Action of the Nervous System," New Haven and London, 1906. The reflex response (scratch reflex) is latent, here only for 2.8 seconds, in spite of repeated "fleabites." (This and Fig. 4 are published by kind permission of the author and Messrs. Constable and Co.)

after 13 milliseconds (Lloyd, 1946). The functional closeness of helps to facilitation can be seen when a slightly stronger stimulus, engaging more (and smaller) nerve fibres is applied to the facilitating nerve. The crest of facilitation in the nerve centres is established for a second time (Fig. 1, upper curve). How different a time-chart is this in contrast to the scratch-reflex. The summation period in the latter which may be as much as 3.5 seconds, indicates a high degree of complexity, a long chain of interneurons passing excitation from one to another (see also Fig. 2). As for the rhythmic muscular action, so characteristic a feature of the scratch reflex, we do not derive much information from observations on units of tissue, though one gets a glimpse the quick change from excitation to inhibition, the functional nearness of inhibition to

FIG. 3.—Primary inhibition in an extensor nucleus (middle curve, filled circles), admixed with secondary inhibition (lower curve, hollow circles) and excitation (upper curve, crosses) from internuncial activity. (After Lloyd, 1946.)

excitation, by turning again to Lloyd's records (Fig. 3). The die-away curve of inhibition is the mirror-image of excitation, but by engaging a few more nerve-fibres, by using stronger stimuli, inhibitory influences are annulled and quickly replaced by excitation. Here seems to be, as yet not too clearly focused, a paradigm of the swing from excitation to inhibition, and back again, in the vastly integrated reaction of the scratch reflex. The secret of rhythm is not to be seen in experimental simplicity, so integrated and therefore so complex is its nature. Attempts at analysis and simplification mean, at present, just destruction of the mechanism.

After-discharge.—You will remember that after-discharge, long-continued and rhythmic, is a striking feature of the nerve-cells and nerve-paths concerned in the scratch reflex. Sherrington reported that, for example, after 0.5 seconds of biting, a scratch developed which continued for 2.0 seconds (see also Fig. 4). Again how different is this integrated reflex from the reaction of a single cell or axone. We have a guide but no exact measure of the difference between the two. Of the internuncial paths and neurones engaged in these long-drawn-out effects we have little accurate knowledge.

The Compounding of Reflexes.—Sherrington reminds us that the simple reflex, without internuncial engagement, is "probably a purely abstract conception because all parts of the nervous system are connected together." "The main secret of nervous co-ordination," he said, "lies in the compounding of reflexes. Every reflex is an integrated reaction." It is a common cliché, and true, that "posture follows movement like a shadow." Limb movement can be initiated for example by messages from the pyramidal tract or by messages reaching the spinal cord at its own level, as in the flexor or crossed extensor reflex. But as we know now from Lloyd's work, the messages in those two cases are very different from the direct path of big nerve axones engaged in the postural reflex (Lloyd, 1941). In the former two cases the messages have an anatomically different path in which lie more than one synapse. In posture, only one synapse is concerned, and that at the ventral horn cell itself. Yet in the muscle, in spite of these differences between nerve paths, "every movement begins in posture and ends in posture." The take-over from posture to movement is smooth, the return from movement to posture is smooth.

In locomotor ataxia we see a state of affairs when the absence of correlation between movement and posture is strikingly illustrated. That picture needs

no further mention. The close correlation of posture to movement, of static to phasic contraction, is well seen in the laboratory by testing the stretch-reflex response after a brief elicitation of the crossed extensor response. The stretch reflex is found to be much enhanced by the previous elicitation of crossed extension reflex and the enhancement continues to be marked, though to a diminishing degree, for 60 seconds or so (Liddell and Olmsted, 1929). Whether the same or kindred neurones are employed in the two reflexes we do not know. But the co-operative correlation in the two muscle responses is clear enough, and implies close correla-

FIG. 4.—After Sherrington, 1906. The "flea" bites here for 0.25 sec. between S and S', but nearly all the responding reflex is subsequent to the stimuli, and lasts for 1.75 sec.

tion, if not the same identities, among the final neurones.

Readiness for Integration.—Thus we see proximity of action, the policy of good neighbours, as it were, the blending which is integrated action of one kind of response with an allied kind of response into smooth movement from rest and back to rest again. But not only at these spinal levels is integrated action evident. Readiness, or fitness to be integrated, can be seen in still

more simplified preparations. In the skeletal muscle of the frog, Bronk found that the heat economy increased parallel with the mechanical tension, both reaching a maximum when the rate of stimulation was 4 a second, the muscle being at 0° C. (Fig. 5) (Bronk, 1930). Here we seem to have an example of mechanical integration of kinetic character, not just the static mechanical integration provided by the body's skeletal framework. In the cat, Cooper and Eccles found that the slow soleus muscle stimulated peripherally did not show much increase in tension after a stimulation rate as low as 10 a second had been reached,

FIG. 5.—After Bronk, 1930. *J. Physiol.*, **69**, 311. Frog muscle at 0°. Upper curve, relation between economy and frequency of stimulation. Lower curve, maximum tension developed at various frequencies of stimulation. (By kind permission of the author, and the Editor of the *Journal of Physiology*.)

whereas the rapid gastrocnemius muscle had to be stimulated at a rate of 35 a second before the rate of increase ceased to rise rapidly (Cooper and Eccles, 1930). These different rates for the two muscles are very suggestive of their being optimally attuned, as it were, to rates of natural stimulation appropriate for their functions, the slow soleus being concerned, as Denny-Brown showed, more with posture and the rapid gastrocnemius more with movement (Denny-Brown, 1929).

Readiness to co-operate and fitness to be integrated are again exemplified by observations of Gordon and Holbourn. They observed single reflex muscle units during slight progressive stretch. The first two reflex discharges are double discharges, so that by the summing of stimuli the increase in the muscle's mechanical tension is

accelerated at the time when it is most needed by the organism (Gordon and Holbourn, 1948). Denny-Brown had earlier noted similar double discharges in reflex units at the inception of stretch (Denny-Brown, 1929).

Long Nerve Paths.—To integrate the behaviour of a long multi-cellular organism, long nerve paths seem to be an implicit necessity. Sherrington's oft-quoted words are profoundly true—the brain is the head ganglion of the distance receptors. The leading segments of the animal in its progress through its world are, as he said, exposed more to external influences than the hinder parts which follow. The leading segments meet more objects, receive more stimuli. The reactions of the distance receptors in the leading segments integrate the whole series of somatic segments. Conducting arcs pass from the cephalic receptors to the contractile masses of the body so that the distance receptors are the inaugurators of reaction. They integrate the individual not merely because of the wide ramifications of their arcs to effective organs, they integrate because of their great connexions in the high cerebral centres.

In this picture the pyramidal tract is an international path. But there are many other international paths, though of less notoriety. In the scratch reflex where, as we have seen, the cord has been isolated from all cephalic connexions, long intra-spinal paths with perikarya in the cord convey impulses from the receptive area on the skin of the back to the motoneurons which control the muscles of the hind limb. These are the long descending proprio-spinal fibres which lie in the lateral region of spinal white matter. For the scratch reflex of the spinal animal, Sherrington suggested the co-operation of at least three neurones, the efferent, the proprio-spinal, and the final common path to the muscle. In light of modern knowledge concerning the fleeting states of activity in single neurones, contrasted with the slow tempo of processes in the integrated scratch reflex, it is clear that many side-chains of interneurons must nowadays be postulated.

Other long intraspinal paths have recently been scrutinized with modern methods by Lloyd and McIntyre (1948). They have studied in the cat the time taken for a stimulus to a nerve of the fore limb to make its presence felt in motor neurones controlling the lower limb. The first sign of facilitation is detected after 8 milliseconds, and the effect on the lower limb's motoneurons is strongest at 15 milliseconds after the application of the stimulus. After 25 milliseconds the effect is over. The great pyramidal pathway has time relations which are

not much different. Stimulation of the pyramid at the cephalic end of the spinal cord is carried by fibres with a velocity of conduction in the cat of 60/65 milliseconds. Facilitation measured electrically of lower limb motoneurons begins 12 milliseconds after such stimulation, and the effect is gone after 35 milliseconds. Additional stimuli coming in singly after the first at 2.5-millisecond intervals do not alter the time-relations, but they increase the magnitude of the facilitating effect from the first stimulus. Three additional stimuli sent down the pyramidal tract, at 2.5-millisecond intervals, double the amount of facilitation, five nearly treble it (Lloyd, 1941). Increased inter-neurone speed, however, plays a part as well as increase in electrical activity and gives a clear picture of a double process in integration. Where the pyramidal fibres end at the dorsal group there is at first a latency of 4.5 milliseconds, and a latency of 3 milliseconds in the intermediate group of neurones, so that the total internuncial delay is 7.5 milliseconds. Subsequently, however, with repeated stimulation the total delay drops to be only 1 millisecond (Lloyd, 1941). "The more the better and faster" seems to be the integrated reply to repetitive stimuli.

It is well realized that we are only at the beginning of knowledge as to the functioning of that long big integrating pathway of pyramidal fibres. In 1909, only a few years after Sherrington's "Integrative Action" was published, Holmes and May wrote: "The cortical origin of the pyramidal fibres is not accurately known but the descriptions given of it are vague and discordant" (Holmes and May, 1909). Lassek's recent figures show that in man among the total count of 688,000 fibres in one pyramid only 30,000 fibres are of diameter as large as 9-22 μ ; 85 per cent. of pyramidal fibres are 1-4 μ in diameter, 61 per cent. are not myelinated (Lassek, 1942). What is the provenance, destination, and function of these numerous small fibres? At least we can safeguard the future by refusing to assume that an anatomical entity of structure need imply a physiological unity of function. The small pyramidal fibres need not have and do not appear to have just the same function as the large.

Of long integrating paths outside the anatomical limits of the pyramid, knowledge begins to accumulate. An overall stimulation of the cerebral hemispheres and basal ganglia does appear to activate extra-pyramidal paths. Dr. Phillips and I have recently observed electrically induced epileptic fits in cats and made cinematograph film records (Liddell and Phillips, 1948). Before any section of the pyramidal path, the cerebral and sub-cerebral discharge registers its maximum effect in the body's musculature. After acute section of one pyramidal

path, the limbs corresponding have much diminished movement. When both pyramids are acutely sectioned, muscle movement is almost absent, but nevertheless is not completely absent. From the *commotio cerebri* produced, excitation is travelling down the spinal cord by other routes. In preparations which have been made some months previously, the hind limb, with unilateral section, is still almost but not quite immobile, though the difference between the fore limbs is now less marked, owing presumably to the opening-up of other descending routes. When both pyramids have been sectioned some months previously, movement of muscles still persists. It is not until the cerebral and sub-cerebral nerve-masses are thrown out of action by deprivation of their blood supply (ligation of carotid and basilar arteries) that complete immobility of the body's skeletal musculature is achieved. Thus by this way of total stimulation combined with partial or total deprivation of pathways, we glimpse briefly the fields of control achieved by pyramidal and non-pyramidal intervention. Integration by long paths does not depend on only one anatomical path. To take but one example, the ever watchful vestibular apparatus is always at work in modifying the use of the limbs and the trunk so that the organism's total reactions resist gravity.

The Future

Full elucidation of the complex integration by long paths in the highest of all multicellular organisms, in man, is a problem for the future. No simple picture will be revealed eventually, but it seems safe to prophesy that the interdependence of function at every level of activity as well as fitness for the purpose can be expected as the prelude to integration throughout the nervous system. In Sherrington's brief phrase, "Each and every part of the animal is integrative."

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