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Sir Charles Sherrington's The integrative action of the nervous system: a centenary appreciation

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In 1906 Sir Charles Sherrington published The Integrative Action of the Nervous System, which was a collection of ten lectures delivered two years before at Yale University in the United States. In this monograph Sherrington summarized two decades of painstaking experimental observations and his incisive interpretation of them. It settled the then-current debate between the "Reticular Theory" versus "Neuron Doctrine" ideas about the fundamental nature of the nervous system in mammals in favor of the latter, and it changed forever the way in which subsequent generations have viewed the organization of the central nervous system. Sherrington's magnum opus contains basic concepts and even terminology that are now second nature to every student of the subject. This brief article reviews the historical context in which the book was written, summarizes its content, and considers its impact on Neurology and Neuroscience.

Keywords: Neuron Doctrine; spinal reflexes; reflex coordination; control of movement; nervous system organization

Introduction

The first decade of the 20th century saw two momentous events for science. The year 1905 was Albert Einstein's 'miraculous year' during which three of his most celebrated papers in theoretical physics appeared. The following year of 1906 was equally important for neurology and neuroscience. The Nobel Prize in Physiology or Medicine was awarded to two great neuroanatomists, the Italian Camillo Golgi and the Spaniard Santiago Ramon y Cajal. Their duelling Nobel lectures epitomized the emerging triumph of the 'neuron doctrine' espoused by Cajal over the 'reticular theory' that Golgi ardently supported (Liddell, 1960; pp. 29–30). Cajal's anatomical observations and ideas, summarized in his monumental *Histologie du système nerveux de l'homme et des vertébrés* (Ramon y Cajal, 1909, 1911, 1995) had already inspired a young British physiologist, Charles Scott Sherrington, to look at the central nervous system of mammals in an entirely new way. As a result, in 1906 Sherrington published *the integrative action of the nervous system* (Sherrington, 1906), which summarized nearly two decades of his intensive research and thinking. It is no exaggeration to say that Sherrington's book changed the subsequent course of neurophysiology. This note is intended as a centenary appreciation of that seminal event.

The Silliman lectures

Sherrington's 1906 monograph, published simultaneously in London, New Haven and New York, was based on a series of 10 endowed lectures delivered in 1904 at Yale College in New Haven, Connecticut, under the auspices of the Silliman Foundation. In the Silliman bequest, Yale College was

> . . . requested and directed to establish an annual course of lectures designed to illustrate the presence and providence, the wisdom and goodliness of God, as manifested in the natural and moral world. (Unsigned preface to the 1906 edition)

This directive, viewed after more than a century, seems quaint but it suited Prof. Sherrington to perfection. He was then and later in life not only a skilled experimentalist and observer, but also a poet and philosopher, as well as a true humanist in the best sense of the word.

Sherrington was the second Silliman lecturer, the first having been Prof. J. J. Thomson, of Cambridge University, who spoke on 'Electricity and matter'. After a 2-year delay (for which Sherrington makes apology in his brief preface), he prepared the lectures for publication as a monograph. *The integrative action* was subsequently reprinted four times between 1906 and 1920, and re-issued in 1947 by

Cambridge and Yale University Press(es) (Sherrington, 1947), with a new foreword by Sherrington. In this foreword, Sherrington wrote a wide-ranging, philosophical essay '. . . to deal with some ambiguities which have in course of time arisen.' (p. ix in the 1947 edition). Here is how Sherrington, then 90 years old, saw his monograph 40 years after its first appearance:

> The volume here reprinted concerns itself predominantly with the type of motor behaviour which is called 'reflex'; it might give the impression that in reflex behaviour it saw the most important and far-reaching of all types of 'nerve' behaviour. That is in fact not so. But reflex action presents certain advantages for physiological description. It can be studied free from complication by that type of 'nerve' activity which is called autochthonous (or 'spontaneous') and generates intrinsically arising rhythmic movements, e.g. breathing, etc. But taken in comparison with the great field of behaviour in general, pure reflex action of itself cannot be seen to cover such extensive ground as do the instincts actuated by 'urges' and 'drives'. But the mechanism of these has hardly yet been analysed sufficiently for laboratory treatment. The pure apsychical reflex has a smaller role. Studied in that self-contained animal group, the Vertebrates, behaviour seems to become less and less reflex as the animal individual becomes more and more completely individuated. The 'spinal' man is more crippled than is the 'spinal' frog. (pp. ix–x in the 1947 reprint.)

Finally, the 1947 edition was once again reprinted in its entirety in 1961, appearing as a paper bound volume issued by Yale University Press. This remarkable publication history is testament not only to a landmark classic in physiology, but also to the continuing relevance of Sherrington's ideas about the way in which the central nervous system operates.

Sources

Despite the fact that, as Liddell tells us, '. . . Sherrington said repeatedly with great earnestness that he hoped no one would write his biography' (Liddell, 1960, preface), his colleagues and former students have given us an enviable number of articles and books that convey the facts of his life and commentaries on his approach to science and the world in general (Adrian, 1957; Cohen, 1958; Denny-Brown, 1957; Eccles, 1957, 1982; Eccles and Gibson, 1979; Granit, 1966; Liddell, 1960). There are also more recent evaluations of Sherrington's scientific contributions taken in context of current ideas in neurophysiology (Swazey, 1969; Stuart *et al.*, 2001; Breathnach, 2004; Stuart, 2005). After his death in 1952 at age 94 years, numerous obituary notices appeared, again written by former students and eminent colleagues, that give important information about Sherrington's life and thought (see Selected References in Eccles and Gibson, 1979). Liddell's extensive obituary notice (Liddell, 1952) is particularly eloquent and informative. These writings convey deep and sincere affection for Sherrington as a person as well as a scientific mentor. Of particular note is the volume entitled *The Discovery of Reflexes* by E.G.T. Liddell (Liddell, 1960), which provides a remarkable review of the scientific legacy that shaped Sherrington's thinking at the time that he delivered his Silliman lectures.

Finally, Derek Denny-Brown, a Sherrington student who became an eminent clinical neurologist, compiled an annotated *Selected writings of Sir Charles Sherrington*, first published in 1939 by Hamish Hamilton for the Guarantors of Brain and reprinted by Oxford University Press in 1979 (Denny-Brown, 1979). This invaluable collection encapsulates Sherrington's scientific writings, many of which are difficult to obtain in the original, in a way that deserves a place on every neuroscientist's shelf.

Some background

Charles Scott Sherrington was born into a middle class English family on November 27, 1857. He received training as a physician in Cambridge and at St Thomas's Hospital in London. During his Cambridge studies, Sherrington took a First in both parts of the Natural Sciences Tripos and managed, despite his diminutive stature (5′6″; see Granit, 1966; p. 3), at the same time to be a fierce competitor for his college in both rugby and rowing. His first two papers were published in 1884, both with his Cambridge mentor J. N. Langley, on histological studies of the canine brain contributed by Prof. Goltz of Strasbourg (Denny-Brown, 1979). Sherrington later spent over half a year with Goltz, doing anatomical work and absorbing Goltz's ideas about localization of function, or lack thereof, in the cerebral cortex.

After qualifying as a physician in 1885, Sherrington became interested in studies of infectious diseases such as diphtheria and cholera, and their amelioration with newly developed vaccines. In that year, he joined his friends C. S. Roy and J. Graham Brown in a summer excursion to Spain to examine a purported vaccine for the Asiatic cholera that had broken out there. Although reports differ (e.g. Liddell, 1952; p. 245), Eccles and Gibson (1979; p. 4) state that Sherrington did not meet Ramon y Cajal during that trip, noting that his only direct encounter with the great Spanish neuroanatomist took place later during Cajal's visit to England in 1894. In the following summer, Sherrington went on a similar expedition to Italy, which resulted in an extended visit with the eminent pathologist Rudolf Virchow in Berlin. Virchow sent him to the laboratory of Robert Koch, one of the foremost bacteriologists of the day, where he spent a full year (Granit, 1966; p. 15).

After returning to England in 1887, Sherrington was appointed as lecturer in physiology at St Thomas' Hospital and was elected to a fellowship at Gonville and Caius College, Cambridge. He turned again to neuropathological studies of the human brain and published a number of reports on this subject over the next 5 years. It was during this period that Sherrington's interest moved from the cortex to the spinal cord, using experimental physiology

as well as neuroanatomical methods. In this, he was much influenced by W. H. Gaskell, who was a lecturer in Sir Michael Foster's Department of Physiology at Cambridge. Later on, in 1918, Sherrington wrote to his friend Henry Head that '[m]y own work began by chance at the wrong end - the cortex-pyramidal degenerations, etc. . . . [o]ne could not talk to him [Gaskell] long without realizing that the cord offered a better point of attack physiologically.' (quoted in Liddell, 1952; p. 244).

In 1891, Sherrington was appointed Superintendent of the Brown Institute of the University of London, a veterinary hospital that afforded him a large material for experimental work. He was elected to fellowship of the Royal Society during this time and caused this body to invite Prof. Cajal to give its Croonian Lecture in 1894. Cajal's adventures in England are memorably described in Eccles and Gibson' biography of Sherrington (1979; pp. 10–12).

It was during this period at the Brown Institute that Sherrington's passionate interest in the physiology of the nervous system finally crystallized. Between 1889 and 1895, he published an accelerating series of papers that began to include specific work on reflexes. Of special importance were two papers on the knee jerk (Sherrington, 1893*a*, *b*), in which he provided key evidence that this well-known clinical phenomenon was indeed a reflex (then in some dispute) that depended on afferents arising in the contracting knee extensor muscles, and that activation of afferents from the antagonist knee flexor muscles reduced or abolished the extensor jerk. He took advantage of the availability of great apes and lesser primates in the institute, as well as other species, to work out in detail the segmental patterns of afferent and efferent innervation of specific muscles, as well as the interanimal variations that were critical to interpretation of later reflex studies (Sherrington, 1892, 1894).

Sherrington was invited, in 1895, to become Professor of Physiology at University College, Liverpool. Here he was to remain until 1914, when he left to assume the Chair in Physiology at Oxford. Although the latter period is better known, particularly because of commentaries by the illustrious students who worked with him during the Oxford era (Denny-Brown, 1957; Eccles, 1957, 1982; Eccles and Gibson, 1979; Granit, 1966), Sherrington's friend and fellow Nobel Prize recipient E. D. Adrian commented that '. . . it was when he held the chair of Physiology at Liverpool that he was at the height of his powers as an investigator' (Adrian, 1957; p. 212). Sherrington's son Carr has written that both of his parents found life in Liverpool far more congenial than that experienced in London: '. . . the years in Liverpool were, I believe, the happiest in his life, and my mother's too . . .' (see Appendix 17 in Eccles and Gibson, 1979). The same article shows how busy Sherrington was outside as well as inside the laboratory during the period of gestation for *The integrative action* (see also Liddell, 1960; pp. 127–143).

What did Sherrington say in 1906?

Overview

The integrative action of the nervous system consists of 10 chapters, each covering one of the 1904 lectures at Yale. The book was dedicated to David Ferrier, one of Sherrington's scientific heroes '. . . in token of recognition of his many services to the experimental physiology of the central nervous system.' Sherrington, in his Preface, attributed the 2-year delay to 'The pressure of varied work . . . . I take this occasion of expressing my regret at the delay.' Because of the lecture format, there is a certain amount of repetition in succeeding chapters. In addition, Sherrington's unique style of writing, undoubtedly influenced by his education in the classics and his skill as a poet, is sometimes difficult. Lord Adrian remarked in a centennial tribute on the occasion of Sherrington's 100th birthday: '*The integrative action of the nervous system* . . . is not light reading but it is and will remain one of the major classics of physiological literature.' (Adrian, 1957; p. 214).

The following represents an attempt to summarize the content of the book, viewed from the perspective of the time at which it was published. Each of the 10 lectures is preceded by an 'argument' in which Sherrington encapsulates the major points to be made. The text includes numerous citations to previous work by others as well as himself. There are 314 references in the bibliography, ranging from Descartes in the 17th century to the early 20th century, including citations in French, German, Italian and Spanish, in all of which Sherrington was literate. The page references given below are for the 1961 reprint, because this is probably the version most accessible for current readers.

The lectures

The first three lectures deal with 'Co-ordination of the simple reflex'. Sherrington boldly states the overall message of the entire monograph in the famous first sentence of Lecture I: 'Nowhere in physiology does the cell-theory reveal its presence more frequently in the very framework of the argument than at the present time in the study of nervous reactions.' From the beginning of his scientific career, Sherrington was convinced that neurons were separate entities and not, as envisioned by the 'reticular theory', parts of a continuous meshwork of directly connected conduits through which signals passed unimpeded. He presents the view that the central nervous system '. . . works through living lines of stationary cells along which it dispatches waves of physico-chemical disturbance . . . of relatively high speed . . .' (p. 3 of the 1967 reprint). He defines the reflex arc as a '. . . whole chain of structures – receptor, conductor, and effector . . .' and goes on to assert that '[t]he unit reaction in nervous integration is the reflex' (p. 7). Sherrington immediately qualified the notion of a simple reflex as '. . . probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of

reaction with affecting and being affected by various other parts, and it is a system certainly never absolutely at rest.' And finally, he adds '[t]he main secret of nervous co-ordination lies evidently in the compounding of reflexes' (p. 8). Thus, in a few pages, Sherrington presents his broad conception of the central nervous system which forms the basis of the rest of the monograph.

The remainder of the first lecture deals with such crucial concepts as the specificity of sensory receptors, central latency of conduction in reflex arcs that is slower than nerve conduction itself, unidirectional conduction in contrast to bidirectional conduction in nerve fibres, after-discharge, temporal summation during repeated stimuli, reflex fatigue, reflex threshold and its variability and dependence of reflexes on intact metabolism and the effect of drugs like anaesthetics. He uses all of these features to emphasize that there must be a '... nexus between neurone and neurone ...' (p. 17), i.e. a 'synapse' that accounts for unidirectional conduction in reflex arcs. He notes that he had introduced the term earlier in the 1897 edition of Sir Michael Foster's *Text-book of physiology*. Sherrington illustrates his experimental evidence for all of the 'arguments' throughout the first three lectures with elaborate illustrations of his myographic recordings. The text is embellished by references to the existing literature, with examples ranging from jellyfish to dogs and cats.

Lecture II continues Sherrington's exposition of the contrasts between reflex action and what might be anticipated from conduction through a reticular network, stressing again the properties of irreversibility, summation of subliminal stimuli, facilitation of successive stimuli and long-lasting actions that result from brief stimuli. Using the scratch reflex as the example, he notes the importance of a 'refractory phase' during which subsequent stimuli fail to evoke the reflex output. As a striking indication of his ideas about the central organization of reflex pathways, he provides a proposed circuit diagram for the stretch reflex (Fig. 13B) that includes three sequential neurons: the afferent 'receptive neurone', a long descending 'propriospinal neurone' and the 'final common path' motor neuron. He supposed that there are two central synapses in this circuit and therefore describes it as a 'disynaptic arc' (p. 53). Such a specific proposal would have been literally unthinkable in a reticular nervous system. Because neither the afferents nor the motor neurons display the prolonged refractory period in the scratch reflex, Sherrington concludes that '... the seat of the refractory phase of the scratch reflex lies "... in the central nervous organ itself, somewhere between the motor neurone to the muscle and the receptive neurone from the skin"' (p. 65). The modern reader will forgive Sherrington's suggestion that successive refractory phases explain the cyclic limb movements of scratching and 'probably' (p. 65) stepping. As noted later, his view a century ago did not include central circuits that can produce such repetitive movement patterns.

In the final section of Lecture III, Sherrington introduces what he may have regarded as his greatest discovery—reciprocal inhibition (Granit, 1966; p. 50). This he defined as a reflex of 'simultaneous double-sign', with excitation of one or more agonist muscle(s) and simultaneous inhibition of the antagonists acting at the same joint. He was able to show that the locus of this inhibition was in the spinal cord, and not peripheral as found by others in some invertebrates. Sherrington describes reciprocal inhibition when superimposed on the exaggerated extensor tonus found in 'decerebrate rigidity' (another Sherringtonian neologism still used today) as well as in the phasic knee jerk and other hindlimb reflexes. Equally important, he demonstrated that the afferents involved travelled in the nerve that innervates the responding muscle. Such afferents are, in his term, 'proprioceptive' because they are activated by the organism's own movements, as distinguished from 'exteroceptive' afferents that convey information from the environment. Sherrington carefully describes the caveat that testing for the presence of reciprocal inhibition must take into consideration the mechanical action of the agonist/antagonist muscle pairs so as to avoid mistakes from looking at muscles that cross two joints (those now known as bifunctional or multifunctional muscles). The lecture ends with tests of the convulsant drug strychnine and the action of tetanus toxin. He comments that his observations '... incline me to the inference that the action of the alkaloid is to convert in the spinal cord the process of inhibition – whatever that may essentially be – into the process of excitation - whatever that may essentially be' (p. 112).

In Lecture IV, Sherrington begins his consideration of how reflexes interact, which he notes is a '... main problem in nervous co-ordination' and introduces what he calls '... the principle of the common path.' (p. 117). He distinguishes between 'private' paths from individual sensory receptors and neurons within the spinal cord that represent, to various degrees, 'public' pathways, i.e. neurons that receive input that converges from multiple afferents. For motor reflexes, the motoneurons that activate muscles necessarily represent the 'final common path' but Sherrington takes pains to note that 'internuncial neurons' (now more commonly called interneurons) also represent common paths that receive convergent inputs, not only from afferents, but also from other sets of interneurons. With this background, he examines experimental results from reflexes that '... act harmoniously together ...', called 'allied reflexes', in contrast to 'antagonistic reflexes' that preclude or interrupt one another. Because all of these operate through the same *final* common path, the motoneurons, he argues that the central mechanisms must involve interactions between interneuronal common paths that receive different combinations of afferent inputs. He draws a sharp contrast between the divergence of afferent inputs as they enter the cord and the convergence of those inputs onto neurons in a variety of common paths that eventually feed onto motoneurons that are the final common path. Sherrington presents data to show that allied

reflexes of the same 'type' (e.g. the scratch reflex from different parts of the receptive field) exhibit reinforcement, or what he terms 'immediate spinal induction', which increases as the distance between stimulated points decreases. Although he notes that '... the intimate nature of the mechanism ... is difficult to surmise ...' (p. 143), Sherrington uses circuit diagrams (Figs 38, a repeat of Fig. 13 in Lecture II, and 44) to illustrate how interneuronal convergence could be the basis for positive and negative reflex interactions. It is Sherrington's thinking about central neuronal pathways that transformed phenomenology into the science of neurophysiology that we follow to this day.

Lecture V continues Sherrington's discussion of interactions between reflexes as reflections of intraspinal circuitry, with the idea of synaptic strength as the key to observed threshold differences in reflex interactions (his Fig. 46). He formulates five 'rules involved in the spread of impulses in spinal reflexes' which mostly concern the segmental localization of afferent and efferent limbs of the arcs. He also debunks Pflüger's 'four laws' related to the same subject (see Liddell, 1960; pp. 84–87), stating that '[t]hese so-called ''laws'' of reflex irradiation were so generally accepted as to obtain a doctrinal eminence which they hardly merit' (p. 165). This is one of the few times that Sherrington, usually reticent in such matters, engages in a frankly polemical argument. He discusses his concept of 'reflex figures' in which the posture of animals with supraspinal transections at bulbar or spinal levels is explained by simultaneous combinations of 'harmonious' long and short arc reflexes. Sherrington also negates the widely held (at the time) view that such harmonious combinations can be explained by combinations of individual spinal roots (i.e. segments).

In Lecture VI, Sherrington turns from the idea of simultaneous reflexes to deal with coordination through temporal sequences of reflexes, getting closer to his goal of explaining the role of reflexes in motor behaviour of behaving mammals. He stresses that combinations of successive reflexes can include both 'allied' and 'antagonistic' reflexes that are '... linked together by more than the mere external ... stimulus. In such a sequence the *threshold of each succeeding reflex is lowered by the excitation just preceding its own*.' (p. 185; emphasis in the original), resulting in smooth transitions that produce coordinated movement. In the middle of the lecture (pp. 196–200) Sherrington turns abruptly to a fascinating examination of then-current ideas about the mechanism of central inhibition which has a surprisingly modern tone. Evidently such sudden digressions were not uncommon in Sherrington's lectures (Granit, 1966; p. 19; see also Eccles and Gibson, 1979; p. 46).

Of particular interest to modern readers is Sherrington's brief discussion of the 'stepping reflex', by which he means the sequential extension and flexion of the limb in the spinal dog when suspended above the ground. He mentions this as an example of adaptation of reflexes to a particular action, in this case locomotion. His discussion suggests, but does not clearly state, that he viewed this action as dependent on limb proprioceptors since it can occur without an obvious external stimulus. He also notes that 'We have as yet no satisfactory explanation of this.' Others (Stuart *et al*., 2001) have recently noted that it seems odd that Sherrington largely ignored the issue of autonomous spinal stepping in 1906 as well as later, although this problem was investigated by Thomas Graham Brown in pioneering work begun in Sherrington's department in Liverpool (Graham Brown, 1916). An answer may be found in Sherrington's philosophical foreword to the 1947 reprint of *The integrative action* (pp. x, quoted above) in which he deliberately excluded such ''autochthonous'' actions from consideration.

Internally generated rhythmic movements indeed represent actions that result from complex neuronal circuits, as current work on what are now called 'central pattern generators' clearly demonstrates. Sherrington obviously thought that the scratch reflex, which occupies much attention in *The integrative action*, was fundamentally different (although clearly a complex rhythmic action) because it was triggered by an external stimulus like any other reflex. Rhythmic scratching is now believed to be a triggered response that involves a central pattern generator closely related to that underlying locomotion. In mammals, these central circuits are still elusive despite modern techniques of electrical and optical recording from single and multiple neurons. They were quite out of reach given the relatively primitive experimental approaches available in Sherrington's day. It is no wonder that Sherrington, even in 1947, preferred to stick with his view that a '... train of motor acts results therefore from a train of successive external situations' (p. xi).

In his remarkable Lecture VII, Sherrington deals with three disparate issues. First, he tackles the knotty teleological problem of the 'why' of reflexes. Rejecting earlier notions of 'psychical powers of the spinal cord', he suggests that Darwinian 'adaptation under natural selection' provides an explanation for the existence of 'purposive neural mechanisms' (pp. 236 and 237). He combines persuasive philosophical arguments with multiple examples to illustrate his case. Next, he jumps to consider the nature of spinal shock that follows spinal transection, noting the relative lack of alterations above the lesion in contrast to the dramatic changes below it. He notes the phenomenon is much more profound and long lasting in primates than in 'lower' species, and that it affects nociceptive reflexes much less than others, such as the scratch reflex. After a brief discussion of subtle differences that depend on the locus of stimulus, termed 'local sign', Sherrington launches into an extended essay on the neural basis of emotion. He defines 'pseudoaffective reflexes' as the responses in decerebrate animals to stimuli that would be expected to produce pain were the animal intact. The outward signs are similar to those seen in intact animals but '... they

never amount to an effective action of attack or escape' (p. 253). Using spinal lesions in such preparations, Sherrington concludes that nociceptive pathways ascend to the brain through the lateral columns only, more via that contralateral to the stimulus than ipsilateral. He also concludes, using evidence from others (notably Goltz), that the centres involved in nociception lie lower in the neuraxis than those dedicated to perception of pleasure. This leads him into an extensive discussion of three then-current theories of emotional perception: (1) the external stimulus produces the emotional percept in the brain which consequently produces the visceral (autonomic) accompaniments; (2) the stimulus generates the percept and the visceral responses simultaneously or (3) the stimulus produces the visceral responses which in turn are appreciated by the brain as the emotional percept, as argued by William James and, somewhat differently, by Lange and Sergi. Sherrington uses his pseudoaffective reflex model to examine the question in animals with spinal and vagal transections. The experimental results are described in great detail, leading Sherrington to the conclusion that '... the visceral expression of emotion is *secondary* to the cerebral action occurring with the psychical state' (p. 266; emphasis in the original). In a single lecture, Sherrington makes a daring leap from a detailed treatment of the internal working of reflexes in the spinal cord into a much more philosophical and, to some extent speculative, essay on 'higher nervous function' in the brain.

In Lecture VIII, Sherrington concludes his ascent of the neuraxis with a detailed discussion of the areas of the 'motor cortex' that he and others had shown to produce specific movements when electrically activated at specific and reproducible cortical loci. He summarizes his work at the Brown Institute with a variety of great apes, emphasizing that such loci can be precisely mapped even though they are not reliably related to cortical sulci and convolutions (except for the central sulcus) in individual animals. Much of this lecture is devoted to the issue of reciprocal inhibition in the responses elicited by cortical stimulation. Sherrington stresses that the patterns of reciprocal inhibition between 'true' antagonist pairs are much the same whether elicited by cortical stimulation or peripheral inputs to the spinal cord. Despite the fact that cortical stimulation generally promotes excitation of flexor groups there is corresponding inhibition of the antagonist extensors. Sherrington uses the similar effects of strychnine and tetanus toxin on segmental (called 'local') reflexes and responses to cortical stimulation to postulate that the reciprocal inhibition found in both is effected by segmental mechanisms. The last part of the lecture gives a detailed description of decerebrate rigidity, which he uses to postulate '[t]wo separable systems of motor innervation...' (p. 312), both of which require intact afferents: a 'tonic' system that activates antigravity muscles throughout the body, and the other a 'phasic' system that produces the multiple 'local' reflexes discussed in the earlier lectures. He speculates on a dichotomy between the cortex and the cerebellum, such that '... cerebellum is the centre for continuous movements and the cerebrum for changing movements' (p. 303).

Lecture IX, entitled 'The physiological position and dominance of the brain', is a *tour-de-force* essay on the general principles of organization in the central nervous system in the animal kingdom, from protozoa to man. In it, Sherrington steps back from the details that occupy most of the preceding material to present a grand panorama of nervous systems through the phylogenetic sequence. He brings together the ideas developed in the preceding lectures, summarized with exceptional clarity. Early on, Sherrington notes that '... by its branching the motor neurone obtains hold of many muscle-fibres' (p. 309), which is the essential idea behind his later introduction of the term 'motor unit' (Liddell and Sherrington, 1925). Progressing through ideas already discussed about exteroceptive and proprioceptive afferents, and the organization of spinal segments and basic motor reflexes, Sherrington introduces the critical importance of the labyrinths as detectors of position in space acting in concert with, and part of, the proprioceptive system ruled by the cerebellum. However, his goal is to expound on the role of the cerebral hemispheres, referred to as 'the brain'. Sherrington views the distance receptors (including but not limited to the visual, auditory and olfactory systems) as essential to the success of the organism for survival in its environment. It is the brain that integrates their information to guide the action of the 'after-coming segments'. He says: '[t]he brain is always the part of the nervous system which is constructed upon and evolved upon the "distance receptor" organs' (p. 325). There is so much here that it really defies summary. If one reads nothing else in *The integrative action*, it should be this lecture. Anyone with even passing interest in the brain will find here a marvelous interweaving of facts and cogent analysis, expressed in beautiful language.

The final lecture, entitled 'Sensual fusion' would, at first glance, appear to be something of an anticlimax after the above but it represents Sherrington's attempt to go beyond the motor system to the realm of psychical events, i.e. sensation and perception. At the outset he says:

> But we may agree that if such sensations and feelings or anything at all closely like them do accompany the reactions we have studied, the neural machinery to whose working they are adjunct lies not confined in the nervous arcs we have so far traced but in fields of nervous apparatus that, though connected with those arcs, lie beyond them, in the cerebral hemispheres (pp. 353–354).

Ever the experimentalist, he begins with a detailed description of his work on perception of contrast in flickering visual stimuli presented to both eyes simultaneously. In contrast to his clarity in the preceding lecture, Sherrington describes his apparatus and the results of a long list of protocol variations in elliptical language that

makes for difficult reading. However, he then clarifies his goal, which is to show that the observed effects are not due to peripheral interactions but rather phenomena resulting:

> . . . only after the sensations initiated from right and left 'corresponding points' have been elaborated, and have reached a dignity and definiteness well amenable to introspection, does interference between the reactions of the two (left and right) eye-systems occur. The binocular sensation attained seems combined from right and left uniocular sensations elaborated independently. (p. 379) . . . . The cerebral seats of right-eye and left-eye visual images are thus shown to be separate. (p. 380)

As in his work on reflexes, Sherrington is thinking in terms of neural circuits, albeit undefined:

> The unification of a sensation of composite source is evidently associated with a neurone arrangement different from that which obtains in the synthesis of a reflex movement by the convergence of the reflexes of allied arcs upon its final common paths. . . . Pure conjunction in time without necessarily cerebral conjunction in space lies at the root of the solution of the problem of the unity of mind (p. 381).

Sherrington concludes this final lecture with a discussion of volitional control of reflexes, or as he carefully states '. . . reflex arcs are controllable by mechanisms to whose activity consciousness is adjunct' (p. 386). He points to this as the mechanism by which we acquire new motor skills, making man '. . . the most successful animal on earth's surface at the present epoch.' (p. 389) His concluding sentence is still true:

> It is then around the cerebrum, its physiological and psychological attributes, that the main interest of biology must ultimately turn (p. 390).

The impact

In 1957, a number of publications appeared to celebrate the centenary of Sherrington's birth. Among them were the following commentaries with regard to the impact of *The integrative action* on the physiological sciences.

Lord Adrian, who shared the Nobel Prize in 1932 with Sherrington, commented:

> It was fortunate for neurology that he [Sherrington] had been invited to Yale in 1904 to give the Silliman lectures, He had brought these together in a book with the title *The integrative action of the nervous system* and it is in this book that the plan [Sherrington's overview of motor control in response to afferent signals] is set out. It was a new approach to the understanding of the nervous system, the approach which is now so familiar that we take it for granted in all our discussion. (Adrian, 1957; p. 214)

Sir John Eccles, who began his scientific career with Sherrington and was later (1963) a Nobel Prize recipient, wrote:

> It has been claimed that Sherrington's achievement has been to construct the secure foundations for the physiology of the central nervous system, and even that *The integrative action of the nervous system* has had an influence comparable with that of *De motu cordis*. . . . Sherrington's investigations on the nervous system were conceived in terms of the anatomical concepts of the neurone and the synapse, and it was he who showed the way in which these concepts are significant for function. In fact it was the clarity of his functional thinking in terms of neurons and the synaptic links between them that distinguished Sherrington from all contemporary neurophysiologists. (Eccles, 1957; p. 216 and 218)

Prof. Derek Denny-Brown, who also began his career with Sherrington before becoming one of the pre-eminent clinical neurologists of his day, noted:

> Already by 1906 . . . Sherrington almost single-handed had unravelled the chief patterns of spinal reflexes and their interaction. This was a stupendous achievement, and so was its clear and classic exposition in the *Integrative action*, published in 1906 when Sherrington was 49 years old. (Denny-Brown, 1957; p. 544–545)

Postscript

There is little that this writer can or should add to such eloquent appraisals. But perhaps I may be permitted a personal comment. I became a Sherrington disciple by osmosis while in medical school in the late 1950s. By that time, physiologists had thoroughly absorbed Sherrington's approach to the nervous system, looking beyond the details of experimental data to what they might mean in terms of central mechanisms. I had determined to learn more about the spinal cord because of encounters with patients suffering from amyotrophic lateral sclerosis. During a research year out from the medical curriculum, I did an honours thesis on supraspinal control of some spinal reflexes under my mentor and friend, the late Dr Wilbur K. Smith, a clinical neurologist and neuroscientist. Through reading for the project and allied clinical material, my scientific heroes became Sir John Eccles and Prof. Ragnar Granit in neurophysiology, and Dr Derek Denny-Brown in clinical neurology. Only later, after I had begun my own work in neurophysiology at the National Institutes of Health, did I realize that all three had begun their scientific careers with Sherrington. By that time, I had purchased the 1961 reprint of *The integrative action* and was intellectually ready to understand it. However, it was only with time and multiple re-readings that I was fully able to appreciate its beauty and impact. It will be a revelation for modern students to find in it so many basic concepts and terminology that are now so thoroughly ingrained in the literature as to be second nature. I am indebted to the editor of *Brain* for giving me the

opportunity to write this centenary tribute to a classic work of science and to Sir Charles Sherrington, who literally revolutionized how we all look at the brain.

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