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Pioneers in CNS inhibition: Charles Sherrington and John Eccles on inhibition in spinal on supraspinal structures★

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Abbreviations: Anon., Anonymous; ANU, Australian National University; C, century; CNS, central nervous system; JCSMR, John Curtin School of Medical Research; StTHMS, St. Thomas's Hospital Medical School; SUNY, State University of New York

Abstract (296 words)

This article reviews the contributions of the English neurophysiologist, Charles Scott Sherrington [1857-1952], and his Australian PhD trainee and collaborator, John Carew Eccles [1903-1997], to the concept of central inhibition in the brain and spinal cord of mammals. Both were awarded Nobel Prizes; Sherrington in 1932 for "discoveries regarding the function of neurons," and Eccles in 1963 for "discoveries concerning the ionic mechanisms involved in excitation and inhibition in central portions of the nerve cell membrane." Both spoke about central inhibition at their respective Nobel Prize Award Ceremonies. Their subsequent publications of these talks were entitled "Inhibition as a coordinative factor" (Sherrington) and "The ionic mechanism of postsynaptic inhibition" (Eccles). The span of Sherrington's work on central inhibition was 41 years (1893-1934), and for Eccles 49 years (1928-1977). Sherrington first studied central inhibition by observing hind limb muscle responses to electrical (peripheral nerve) and mechanical (muscle) stimulation. He used muscle length and force measurements until the early 1900s and electromyography in the late 1920s. Eccles used these techniques while working with Sherrington, but later used extracellular microelectrode recording in the spinal cord followed in 1951 by co-pioneering intracellular recording from spinal motoneurons to considerably advance understanding of central inhibition. Sherrington's health was poor during his retirement years but he nonetheless made a small number of largely humanities contributions up to 1951, one year before his death at the age of 94. In contrast, Eccles retained his health and vigor until about 3 years before his death, and published prolifically on many subjects throughout his 22 years of ‘official’ retirement. His last neuroscience article appeared in 1994 when he was 91. Despite his afflictions there is evidence that he continued thinking about his life-long interest, the mind-brain problem and was attempting to complete his autobiography until his death at the age of 93.

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1. Introduction

In the previous review in this trilogy (Stuart et al., 2014), we discussed the pioneering role of Ivan Michailovich Sechenov [1829-1905], a Russian scientist who was the first to show convincingly that active central inhibition occurred in the central nervous system (CNS) of non-mammalian vertebrates and humans. About eight decades later the British 1932 Nobel Laureate, Charles Scott Sherrington [1857-1952], who shared his prize with Edgar Adrian [1889-1977] (Hodgkin, 1979), advanced the concept of central inhibition in his studies on reciprocal inhibition in the mammalian spinal cord and his well-considered opinions on the functional role of such inhibition.

In this review provide for the first time our perception of evolution of Sherrington's thoughts on reciprocal innervation, as described in his 14 "note" articles between 1893 and 1909. This work was the foundation for his later thoughts on central inhibition and discussed in his 1932 Nobel Prize lecture, with the prize awarded to both Adrian and him for their separate work on "the function of neurons."

In the case of Eccles, his secure grasp of the nature of central inhibition was established early in his career as revealed in his 1929 Ph.D. thesis, which surprisingly is rarely if ever discussed in previous reviews of his contribution to the central inhibition concept. This was the topic of his Nobel Prize lecture in 1963, with the prize awarded to the team of Hodgkin and Huxley, and to Eccles for their separate "discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral (*Hodgkin and Huxley*) and central (*Eccles*) portions of the nerve cell membrane."

In the third and final article in this trilogy (Graham, Brichta, Schaefer, Stuart and Callister; in preparation), we will discuss the neuropharmacology of central inhibition and the pioneering role of Eccles' Australian trainee and collaborator, David Roderick

Curtis [1927-2017), a gifted neuropharmacologist who advanced understanding of inhibitory transmitters in the mammalian spinal cord and brain.

The reader will readily see that the present review departs from conventional historical reviews by presenting summaries of our two protagonists ever-developing thought processes on central inhibition in tables rather than text. For example, Sherrington's 14 note articles are discussed in Table 1. For Eccles, his inhibition-relevant research and ideas on electrical transmission are evaluated in Table 4. This strategy is somewhat similar to a timeless 1965 monograph entitled "Trails and Trials in Physiology," which written by the 1922 Nobel Laureate, Archibald Vivian (universally called "AV") Hill [1886-1977] (Bassett, 2002). Sherrington and Eccles certainly contributed "trails" to the concept of central inhibition and shored themselves up as they responded to the "trials" they experienced along the way.[1]

(Note: Footnote **2** is in the Fig. 2 legend)

2. Brief summary of Sherrington's academic career

Fig. 1 provides photos of Sherrington at various times throughout his life. Fig. 2 is a timeline of his academic career, research, and theoretical contributions to neuroscience.

Figs.1 and 2 near here.

After initial medical training in 1876-1879 largely at St. Thomas's Hospital Medical School (StTHMS),[3] which was then affiliated with the University of London, Sherrington graduated from the University of Cambridge in 1884 with a B.A., which featured first-class honors in natural science (including botany, human physiology, anatomy, and zoology). His medical M.B. (British Commonwealth Bachelor of Medicine) degree followed at Cambridge in 1885 after additional training in physiology for 9-12 months

with Friedrich Goltz (see 7.1 below) at the University of Strasbourg, which was then part of Germany. His post-M.B. training in 1886-1887 was in bacteriology, neurohistology, and pathology rather than physiology. It was undertaken with Robert Koch (see 6.1.4.) at the University of Berlin.

Sherrington's academic (including teaching) postings were, in their order, at: StTHMS, as an anatomy demonstrator (1883-1884), and later as a lecturer in physiology (1887–1895); in parallel positions at Cambridge as a research fellow and tutor (same time span), and as Physician-Superintendent at the Brown Institution of Preventative Medicine, a University of London veterinary facility (1891-1895); the University of Liverpool as the Professor of Physiology (1895-1912); and finally, the University of Oxford, again as the Professor of Physiology (1913-1935). He resigned his Oxford professorship at the end of 1935 due to severe arthritis (see 6.1.3.), and left the city at the end of 1936 at the age of 79 years. His retirement years were first spent happily in Ipswich, the town of his youth. After the town's severe WWII bombing in 1940 he moved briefly to London. This required another move, as London was also bombed relentlessly, and he was fortunate to return to his former Cambridge College, Caius, where he was a guest in the College Master's own home. After WWII his arthritis was so severe that he spent time in two nursing homes, the first in Droitwich, northeast of London, and then in Eastborne, just east of Brighton. His final days were largely in a home he purchased there near the seashore (for more details see the 1975 article by his son, Carr R. Sherrington). Near his demise, however, he returned to the Eastborne Nursing Home.

Sherrington's first scientific papers were published in 1884 and his last in 1953, one year after his death at the age of 95. In this 69-year span, he had over 320 publications that were mostly in the field of biomedical science.[4]

Although relatively slight of build, Sherringon was from an early age an enthusiastic and accomplished athlete. Most remarkably, he was also a life-long and well-respected classicist, humanist, and poet. This helps explain why in the period between his retirement and death in 1952 he published largely on the interface between neuroscience and philosophical discourse.

More biographical information is provided below in Section 6 even though many people have written about this remarkable and beloved English biomedical scientist. However, it is still possible to provide interesting new information about his life and career. Sherrington possessed key personal qualities, and academic and societal interests, which are worth emphasizing to current (particularly young) investigators in the field of neuroscience.

3. Sherrington's contributions to central inhibition

In Eccles' obituary about Derek Denny-Brown [1901-1981] (Vilensky et al., 1988; Mayer 2001) he commented that "His knowledge of Sherrington's scientific thought was exemplified in his great achievement: *Selected Writings of Sir Charles Sherrington (1939)"*. It was a carefully organized selection with many editorial notes, covering Sherrington's contributions from 1892 to 1933. In that volume the whole of Sherrington's scientific life stands revealed." (Eccles, 1981b; p. 10). We agree this book is a valuable contribution, but to truly understand Sherrington's scientific life we believe much more is needed when discussing his contribution to central inhibition. Indeed, Denny-Brown later stated: "Perhaps his (*Sherrington's*) outstanding single achievement was the measurement, charting, and analysis of spinal inhibition, and the innate pattern of reciprocal innervation" (Denny-Brown, 1957; p. 546).

In what follows we have provided far more detail than in previous biographies on the experiments Sherrington undertook on the study of inhibition and his evolving thoughts on the topic.

3.1. Knowledge of precedents on peripheral and central inhibition

In Stuart et al. (2014), the first review of this trilogy, we emphasized how well the early and particularly 19th C history of work on central inhibition was covered by Smith (1992), and how Sherrington had also read all the key literature on this topic. Sherrington emphasized that Sechenov had made an abrupt jump in advancing the concept in Sechenov (1863), a book Sherrington cited in his own also classic 1906a book, and mentioned later in the second paragraph of Sherrington (1933a**),** his 1932 Nobel Prize lecture.

We also emphasized that Sherrington had a detailed knowledge of the early work on peripheral inhibition, both in vertebrates and invertebrates. However, we have been unable to document how long Sherrington labored, without success, in testing whether mammals had inhibitory motoneuronal connections with peripheral striated muscles, as they do in invertebrates. This work was probably undertaken in part before he began his experiments on central and peripheral inhibition in mammals and it may well have continued intermittently for several more years.

In summary, it seems unlikely that anyone in the United Kingdom, Europe, or the United States had read more extensively on central and peripheral inhibition than Sherrington had when he began his own research on these two topics.

3.2. 1893-1934 span of Sherrington's work and ideas on central inhibition

Tables 1-3 summarize Sherrington's work and ideas on central inhibition. Table 1 summarizes his 14 notes in the belief that he used these articles as the main vehicle for presenting his ideas on this topic between 1893 and 1909, with an emphasis on reciprocal inhibition in spinal reflex pathways.[5] Table 2 summarizes his better known other publications in this epoch that referred to reciprocal inhibition and central inhibition. Next, Table 3 shows the final evolution of his thoughts on central inhibition from 1910 to 1934.

Tables 1-3 near here

Prior to Sherrington's work documented in Table 1 he found it necessary to undertake very painstaking and tedious functional anatomical mapping of sensory input-lumbosacral spinal cord-muscle relationships.[6] This was obvious in his first note, in which Fig. 3 shows the key anatomical arrangement for the work. He had a natural penchant for such mapping work because in many ways Sherrington was much more a functional neuroanatomist/neurobiologist than a neurophysiologist (see 6.1.3. below).

Fig. 3 near here

3.2.1. Reflections on the 14 "note" articles

As one reviews the 14 notes it becomes evident that Sherrington's techniques first relied heavily on literally visualizing muscle activity during electrical stimulation of various sensory inputs.

In retrospect, it is remarkable that this work began with relatively simple observations on the knee jerk in dog and monkey. Today, it is well known that the knee-jerk (tendon-tap) response is a monosynaptic reflex initiated by spindle Ia muscle afferents and expressed by contraction in thigh extensor muscles. When Sherrington began his work on the knee-jerk in the early 1890s, however, most workers thought the motor response to be too fast for a spinally mediated reflex. He proved the response was in fact a reflex and reported this in his first note (Sherrington, 1893b). Interestingly,

he may have encountered his so named "extensor-thrust reflex" during these experiments but he did not describe this in detail until his seventh note (Sherrington, 1905a). He found that this reflex engaged the same muscles as the knee jerk and was best initiated by " ... pushing the finger-tip between the plantar cushion and the toe-pads, especially when the hip and knee, not necessarily the ankle, are resting, passively flexed" (p. 67). He further proposed (p. 68) "The extensor-thrust is probably an important element in the reflex mechanism of the dog's locomotion. One peculiarity it has as compared with other spinal reflexes of the limb is the considerable force which it exerts. In the locomotion of the animal it provides much of the propulsive power required." Many other extensor reflexes in other parts of the body were subsequently described, beginning largely with those that precipitated extensor rigidity in decerebrate preparations. Much later, in Liddell and Sherrington (1924) he described the superposition of individual (“autogenic”) reflex pathways on “composite stretch reflexes.” Today, however, it is known that this idea is not functionally important. Rather, workers now focus on an issue not addressed by Sherrington; namely, analysis of the comprehensive network of extensor reflexes that are linked to the biomechanics of the musculoskeletal system (e.g., Nichols et al. 2014).

In the first note, Sherrington used the term muscle "tonus." This term has caused much mischief in neurophysiology over the years. To Sherrington it meant, albeit not often stated by him, the extent of neural excitatory input to a muscle; with high tonus associated with significant excitatory input and sustained muscle contraction, and low tonus involving diminished excitatory input and barely any muscle activity. Sherrington (1919b) wrote a remarkable review of this topic, extending back to Galen of Pergamon [~131-201 A.D.] (Stone and Mattingly, 1999).

Other key findings in Sherrington's notes included those on lengthening and shortening reactions, which were described in the 12th note (Sherrington,1908a). He showed that rigidity of extensor muscles in acute decerebrate and chronic spinal mammals could be modulated in opposite directions by engaging various reflexes. These could be initiated from the muscle itself via activity in different sets of afferents.

Regulation in one direction was shown by the "lengthening reaction," which is a reflex excited by stretching the muscle; regulation in the other direction is shown by the "shortening reaction," which is a reflex initiated by approximating, either passively or actively, the ends of the muscle.

The first note to include myographic recording of muscle activity (Fig. 4) was his eighth one (1905b). This note included his first sketch of the potential mechanisms of reciprocal innervation and inhibition (Fig. 5).

Figs. 4 and 5 near here

It is very obvious that Sherrington was unusually wordy in his 14 notes, even by the standards of that time.[7] In addition, modern-day electrophysiologists, like the present authors, cannot but wonder if Sherrington could have advanced the concept of central inhibition faster and with more focus on its mechanism(s) if he had not been so intent on establishing the generality of reciprocal innervation in so many muscle groups of the species he used in his experiments (largely the cat, dog, and monkey). Nonetheless, these 14 articles remain a "tour de force," as they brought central inhibition to a much more secure and irrefutable position than had been accomplished by Sechenov in the 19th C. This work also featured Sherrington's first mention of the experimental advantages of decerebrate mammalian preparations as later emphasized by Liddell (1960; pp 127-131) in his valuable history on the use of this preparation and the significance of its mistakenly called decerebrate rigidity, when the term "decerebrate spasticity" is the accurate one.[8]

Sherrington also provided in the 14 notes detailed descriptions of numerous subtleties of spinal reflexes, indeed far more than had been observed previously by Sherrington's then-current peers. It is also noteworthy that in many of these notes Sherrington drew analogies between what he was observing in his mammalian research and findings by others in non-mammalian vertebrates and invertebrates. This broader thinking as a comparative biologist has rarely if ever been commented on in previous

3.2.2. Aside on the flexion reflex

Sherrington introduced results on the flexion reflex in his seventh note (1905a). However, the term "flexion reflex" is far from simple, even in modern times! In summarizing his own results and those of previous workers and his peers Sherrington later stated (1910a; pp. 28-29) "In the spinal cat and dog as in the spinal frog the reflex movement of the limb most readily evoked by stimulation of the skin of the limb or of its afferent nerves is flexion. This reflex may be termed the 'flexion-reflex of the limb.' In the hind-limb the flexion is of hip, knee, and ankle, in the fore-limb of elbow, shoulder, and wrist". He also stated that these observations were also mentioned on p. 28 of the original version of his 1906a monograph. The potential problem with this definition remains that when using electrical stimulation of the skin or its afferent nerve supply it is impossible to separate the effects of activating the lower threshold (and larger diameter) myelinated fibers, which include some innervating low threshold touch and pressure receptors, from the higher threshold (small) unmyelinated fibres, which innervate a substantial number of nociceptive receptors. Much subsequent effort has been expended to develop stimulation techniques that selectively stimulate small diameter nociceptive afferents, however, there is no consensus that this is feasible.

Flexion reflex during stepping. Sherrington was on more secure ground in proposing a common neural basis for the flexor reflex and the flexion phase of stepping. In this case he found that the flexion reflex is initiated by natural, low threshold stimulation of the footpad's skin and musculature such that activation of low threshold myelinated afferents was the unequivocal initiator of the flexion reflex. Duysens et al. (2013; p. 1) reflected that to Sherrington "stepping was basically a series of flexion reflexes, with extension occurring merely as the 'rebound' following the flexion." As emphasized below, this viewpoint was untenable even when first proposed by Sherrington. Another complexity now known is that high threshold cutaneous and muscle afferents (reviewed in Hultborn, 2006) can contribute to flexion reflexes and play a role in the stepping process (see also Orlovsky et al., 1999; pp. 181-182). It seems likely that this observation, which was not made until the 1960s (Jankowska et al,1967 a,b)[9], would have surprised Sherrington!

Flexion reflex following a noxious stimulus. Sherrington (1910a; p.71) used the term "nociceptive flexion reflex" for an ipsilateral hip, knee and ankle withdrawal reflex in

animals. This occurred in response to noxious stimulation of the skin of the limb (especially the foot) by electrical, mechanical, or possibly thermal stimuli of various patterns and duration, including " ... even when a small spring clip affixed to the foot and when therefore the mechanical stimulus is constant." Much later, the nociceptive flexion reflex was shown to operate in humans. (Kugelberg et al.,1960)[10] with subsequent human research on this reflex reviewed by Skljarevski and Ramadan (2002).

The above comments are focused largely on the period known to the present authors as the "Sherrington to Lundberg era". Several modern workers have paid tribute to this era (e.g., Schouenborg, 2002) but understandingly, many have now moved on with little recognition of this early work (e.g., Granmo et al., 2008; Schoenborg, 2008), except for Duysens et al. (2013).

3.2.3. 0ther articles on central inhibition

Five of the 11 Table 2 articles described experimental findings. The first of these (Sherrington, 1894a) described cerebral cortical involvement in reciprocal eye muscle control. The next-described experimental results involved Sherrington's first use of decerebrate preparations (1897a, 1898b) to study aspects of central inhibition, followed by the role of central inhibition in the elaboration of scratching (1906d), and finally the relation between proprioceptive reflexes and central inhibition (1909a).

Fig. 6 shows the striking effect of decerebrate spasticity on the cat's standing posture (Sherrington, 1898a; Fig. 1) and the effects of various brain transections on the degree of this spasticity. Notably, it shows the effects of altering the balance between central excitation and inhibition (Sherrington, 1898b). In virtually all of Sherrington's articles on decerebrate preparations he discussed the role of central inhibition in the manifestation of what he considered to be different types of what we now know as "decerebrate spasticity" (again he mistakenly called it decerebrate rigidity).

Fig. 6 near here

Among the 6 review-type articles in Table 2, three were prestigious lectures or addresses (Sherrington 1898a, 1899, 1904). The 1898a article was possibly the first to

use the term "decerebrate rigidity" while the 1899 article summarized his previous findings on reciprocal innervation and inhibition. The 1904 article introduced Sherrington's now famous concept of motoneurons providing the "final common path" to the musculature.[11]

Among the remaining three reviews, it is of particular interest to compare Sherrington (1897c) to (1900b): i.e., an article compared to a book chapter on central inhibition. In the former, he was particularly cautious about the functional significance of central inhibition, whereas in the latter he was adamant that it was as important as central excitation in the control of movement. A later work, Sherrington (1906a), was one of his best-known publications, "The Integrative Action of the Nervous System." This monograph's Lecture III summarized his views on reciprocal innervation, reflex inhibition, and central inhibition.

Table 3 documents Sherrington's further findings and reflections on central inhibition that appeared in14 further publications over a later 24-year period (1910-1934). Of these, 5 emphasized new experimental findings (all but one between 1910 and 1913), whereas the remaining 9 articles (8 review-type and 1 theoretical) contained further reflections on central inhibition and its importance for normal brain function.

In one review in Table 3 (Sherrington, 1913c) summarized the various techniques he had used to study central inhibition. In retrospect, this article's conceptual Fig. 1 (our Fig. 7) should have appeared in a much earlier article.

Fig. 7 near here

The experimental work in Table 3 (Sherrington, 1910a, 1913a,b and d) was dominated by a focus on the possible ways in which central inhibition might contribute to the control of reflex standing, scratching, and stepping. This work was painstaking, to say the least. For example, Fig. 5 in Sherrington (1910b; our Fig. 8 below) showed how thoroughly he determined the many hindlimb muscles that participated in reflex

stepping. Apparently, he felt he needed this detail for the generalizations that he would later reflect upon.

Fig. 8 near here

Much later, Liddell and Sherrington (1925) pioneered the role of central inhibition in the recruitment and de-recruitment of single and groups of motor units.[12] However, Sherrington's conceptual sketch of a motor unit (Fig. 9) did not appear in print until four years later (Sherrington, 1929).[13] Perhaps Sherrington needed the extra time to reflect on the relationship between the behavior of a single motor unit's motoneuron to that of other motoneurons (innervating other motor units) within its spinal motor nucleus or "pool," as he preferred to call it.[14] Note that much later Duchateau and Enoka (2011) reviewed the initial definition of a motor unit in Liddell and Sherrington (1925), its expansion by Sherrington (1925), and its conceptual precedents in 1905 and 1909 by Keith Lucas [1879-1916] (Adrian,1934) and in 1913 by George Mines [1886-1914] (Acierno and Worrell, 2001).

Fig. 9 near here

Finally, Table 3 lists Sherrington's last two articles on central inhibition. The first was his book chapter in Creed et al. (1932). Its significance is expanded upon in several places throughout the present review. Here, the main point is that this book chapter was Sherrington's swan song on all he held near and dear in the study of reflexes. It clearly documents his preference for reflexes mediated in the spinal cord even though he studied reciprocal innervation and inhibition at virtually all levels of the CNS. Interestingly, when he wrote this chapter he did not permit his co-authors to read a draft and/or edit the chapter (Eccles and Gibson, 1979; p. 65). Clearly his goal was not to have his views altered regarding what he had to say about the spinal cord, his favorite

experimental site in the CNS!

Sherrington's final sole-author and detailed thoughts on central inhibition were expressed in his 1932 Nobel Prize lecture, which appeared in print in 1933.[15] In Eccles and Gibson (1979), Eccles noted succinctly (p. 71):

> The Nobel lecture (*Sherrington's*) was delivered on December 12 (*1932*) and is a masterly review of the role of inhibition in the central nervous system from the earlier suggestions of Descartes up to our most recent investigations. In characteristic manner, there is a superb discussion of the central excitatory and inhibitory processes, which so well foreshadows the discoveries by intracellular recording two decades later: ... "

Eccles closed his comments (p. 72) on the lecture by citing part of Sherrington's conclusion (*actually his second last paragraph on page 11 of the Sherrington (1933a) published version*). Notably, he considered this to be the "essence of his (*Sherrington's*) life's work on the nervous system:"

> 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.

3.3. Aside on disparate views on scratching and stepping of Sherrington and Graham Brown

This information is added here because Sherrington's views on the control of scratching and stepping were strongly influenced by his work on reciprocal innervation and central inhibition in driving spinal reflexes. At the same time, he had to concede (usually reluctantly) the legitimacy of the opposing views of Thomas Graham Brown [1882-1965] (Stuart and Hultborn, 2008; Jones et al., 2011) on the spinal rather than reflex control of both of these types of rhythmic movement.

3.3.1. Scratching.

In regard to our comments on Sherrington (1906d) in Table 2 and his 1910c article in Table 3, we are indebted to Professor Paul Stein, Washington University at St. Louis, for his personal comments to us from which we have extracted the following historical points on the neural control of scratching.

1. Sherrington's 1906d article appears to have been the first to show that a dog's de-afferented hindlimb could produce a well-coordinated scratch when it was spinalized and deafferented (i.e., the same limb's dorsal roots cut and electrical stimulation applied subcutaneously to the spinal cord). His summary point #18 on p. 50 was "The severance of the afferent roots of the scratching limb itself far from impeding or impairing the scratch-reflex renders it brisker and leaves it unaltered in rhythm." In another publication (Sherrington 1947), a much later version of his 1906 monograph, he stated, "The afferent nerves of the muscles which execute the scratching movement do not, when themselves excited, evoke the scratch-reflex; nor does the severance of the afferent nerves of the muscles obviously impair or alter the scratch-reflex."

2. Similarly, Sherrington (1910c) was probably the first report to show that the spinal cord of the (*probably decapitate*) cat with a de-afferented hindlimb could produce a proper scratch. He stated (p. 219) that there was a "... successful elicitation of the reflex after severance of the afferent roots (3rd-9th post-thoracic inclusive) of the scratching-limb; after that severance stimulation behind pinna or faradisation of spinal cord as above described elicits the reflex with little obvious departure from its usual features."[16]

3. Graham Brown was a junior, but independent, researcher in Sherrington's laboratory in 1910-1913. He sometimes collaborated effectively with Sherrington, was a close friend throughout his mentor's lifetime, and always spoke highly of him (e.g., Graham Brown, 1947). However, he felt that Sherrington's scratching results, described

in points 1-2 above, were not based on removal of all the movement-related sensory input associated with a normal scratch. In Graham Brown (1911) he noted (p. 311): for the spinal neural control of stepping (which his experiments showed to be central in origin):

> The suggestion in reality is that the locus of the inhibitory factor is central, and that it is not of essential peripheral origin from proprioceptive stimuli.[17] For the scratch this is in accordance with a previous observation of Sherrington (1906d; p. 1) that the de-afferented hind limb of the cat may be made to scratch (*Graham Brown should have referred to the 1910 Sherrington report on cat scratching rather than the 1906d one that reported on dog scratching*). Although this is perhaps not conclusive--in view of stimuli which arise in the opposite hind limb—he (*Sherrington*) and the present author (*Graham Brown*) have recently demonstrated at a meeting of the Physiological Society a cat in which scratching may be elicited although both hind limbs have been completely de-afferented.[18]

Graham Brown was correct on this point in that Sherrington's above-described results on single limb scratching movements may well have involved the contralateral non-scratching limb receiving mechanically-coupled**,** movement-related signals from the active movements of the scratching limb even though this possibility had been discounted by Sherrington.[19]

Experiments showing that scratching could occur when *all* movement-related sensory inputs were removed had to await the report of Deliagina et al. (1975). This work provided unequivocal results showing a spinal central pattern generator (modern parlance for the Graham Brown findings) for scratching movements existed in the vertebrate spinal cord.[20]

3.3.2. Stepping

D.G.S. has commented extensively in previous articles (Stuart and Hultborn, 2008; Jones et al, 2011) about Sherrington's "on again-off again" comments on the neural control of stepping. Sherrington focused on its reflex control. This contrasts with the

more soundly based views of Graham Brown, who pioneered the view that this control was central in origin. Here, we need emphasize but four points.

1. Graham Brown's views on the central control of stepping were based on his clear cut demonstration that the spinal cord (guinea pig and cat) had the intrinsic capability to generate a stepping output pattern whose timing did not depend upon descending or sensory inputs. Note, for example points 4 and 5 in a summary by Graham Brown (1911; p. 311):

> **Point 4.** The rhythmic sequence of the act of progression is consequently determined by phasic changes innate in the local centres, and these phases are not essentially caused by peripheral stimuli**. Point 5.** The proprioceptive stimuli which are generated by the contraction of muscles taking part in the act (when the appropriate posterior spinal roots are intact) play a regulating and not an intrinsic part in the act. Their chief importance may be in the grading of the individual component movements to the temporary exigencies of the environment.

2. Sherrington accepted the above findings in several of his later publications the most important of which was his "summing-up" 1932 book chapter (recall the quote in Table 3).

3. Early on, however, Sherrington engaged in circular (perhaps agonized) thinking about Graham Brown's view on the central control of stepping: e.g., in Sherrington (1913d; p. 207) he wrote "It is a view that demands careful attention, but, as it seems to remove stepping from the category of reflexes except in so far as concerns regulation, the present argument which proceeds on the assumption that the forms of stepping here dealt with are reflex would be led too far afield by its consideration now." Eccles defended this tortuous reasoning to D.G.S in 1972 with the viewpoint that Sherrington felt that it was premature in the early 20th C to focus on central pattern generating mechanisms when so much work was required on spinal reflex mechanisms. In retrospect, this defense was also tortuous!

4. Sherrington's enthusiasm for the study of reflexes diminished in his retirement years, probably when cerebral cortical studies on conscious human subjects were undertaken in the 1930s, and when such work advanced dramatically in a variety of

species after WWII. Russell Brain [1895–1966] (Henson, 1967) stated during one of the discussion sections at a1958 meeting commemorating Sherrington's contributions (Brain, 1958):

> ... members of the symposium may be interested in a Sherrington reminiscence, which I was reminded of by what was said about reflexes. This was a conversation I had with him and you can attach as much importance to it as you like. He was then over 90 years old, and those who visited him at Eastborne will remember how widely the conversation ranged, philosophy, poetry, recent work in neurophysiology, and so on. He was always particularly interested in Penfield's cortical stimulation observations and he would return to those again and again. This time we talked of reflexes and he said: “The reflex was a very useful idea but it has served its purpose. What the reflex does is so banal. You don't think what we are doing now is reflex, do you? No, no, no.”

3.4. Granit's succinct reflection on Sherrington's contributions to central inhibition

One of the most succinct and accurate summaries of Sherrington's contribution to the concept of central inhibition was that of Ragnar Granit [1900-1991] (Grillner 1995) in his masterful 1966 appraisal of Sherrington's career as an experimental scientist, humanist, and philosopher. Granit's thoughts (p. 83) are repeated here lest future scholars of central inhibition forget them.

> "Whatever other mechanisms could be forced to explain central excitation and inhibition, as the balance of evidence stood when Sherrington, after forty years of experimentation, laid down his tools, it must be concluded that he had definitely established *synaptic* excitation and *synaptic* inhibition as the mirror images of two genuine and opposite processes. These had been endowed with properties which in a decisive manner guided experimentation in this field in the future."

It seems likely that central inhibition was clearly on Sherrington's mind when he was awarded his 1932 Nobel Prize because his talk at the award ceremony and its subsequent 1933 publication were entitled "Inhibition as a coordinative factor." In these contributions, Sherrington certainly emphasized the functional significance of central inhibition.

4. Brief summary of Eccles's academic career

Fig. 10 provides photos of Eccles at various times throughout his life and Fig. 11 provides a timeline of his academic career.

Figs. 10 and 11 near here

Eccles was born and raised in Australia and he went straight from high school to medical school in 1920 at the University of Melbourne when 17 years of age. He completed the 5-year M.B. and B.S. (Bachelor of Surgery) degrees in February 1925. Unlike Sherrington, he was fully committed to a career as a neuroscientist early in his medical training. After 6 months in Melbourne as a Resident Medical Officer he went to Oxford on a 3-year Rhodes Scholarship, specifically to work with Sherrington. This scholarship was awarded in 1924 but delayed by Eccles until he went to Oxford in late 1925. At Oxford, Eccles first undertook an undergraduate honors degree in physiology and biochemistry, which he completed in mid-1927. He then immediately began his PhD research under Sherrington's mentorship. He was supported financially by his Rhodes scholarship in the first instance, which may have overlapped with a 5-year Junior Research Fellowship, and then another overlapping 1931-1934 scholarship. He completed his doctoral dissertation in 1929, and from 1931 to 1934 was supported by another Oxford research fellowship.

Eccles's subsequent academic appointments were, in order: Oxford as a Tutorial Fellow and University Demonstrator (1934-1937); Director of the Kanematsu Institute, Sydney Hospital, Sydney, Australia (1937-1943); Professor of Physiology, Otago University, Dunedin, New Zealand (1944-1951); Professor of Physiology, Australian National University (ANU), Canberra, Australia (1950-1966);[21] Member and head of a research group, A.M.A. Institute of Biomedical Research, Chicago, United States (1966-1968); and Professor of Physiology and Biophysics, State University of New York (SUNY)-Buffalo, United States (1968-1975). His retirement years were spent in Contra, Switzerland (1975-1997), where he remained scientifically active until ill health overtook

him in 1994, almost 3 years before he died in 1997. When considering much of the above, Eccles (1977a; p. 1) reflected "I have been a wanderer over the world for more than 50 years of active scientific life."

Eccles' first scientific paper was published in 1928 when he was 25 years of age and his last in 2003, 6 years after his death at the age of 94 years. In this 75-year span, he had 569 publications[22], most (~80%) in the field of neuroscience and 18% on the mind-brain problem. His work on the latter emphasized the implications of neuroscience on topics that extended into the arts and classical literature.

Eccles was impressively athletic, extraordinarily energetic, and remained so into his early 90s. Most of the experimental work described below required that he and his co-investigators (trainees and other collaborators) have substantial stamina.

More biographical information is provided below in Section 6.2. We do this because we believe Eccles' drive, ambition, intense interest in the nervous system, and ability to bounce back from disappointments and hardships, should serve as inspiration for young investigators entering neuroscience research.

5. Eccles' contributions to central inhibition

5.1. Work prior to the introduction of intracellular recording

The work reviewed in this section was undertaken at three sites: Oxford, Sydney, and Dunedin. During this period (1928-1952) Eccles' expanded his suite of experimental techniques during a progressive transition from extracellular to intracellular recording. This journey involved (1) extra-axonal stimulation of sensory and motor axons in peripheral nerves, dorsal and ventral roots, (2) surface recording from the spinal cord, the cervical stellate ganglion, the retractor smooth muscle of the nictitating membrane in mammals and from nerve trunks in earthworms, (3) intramuscular extracellular multi-

fiber recording from skeletal motor units, (4) extra-axonal recording from ventral roots and their axons (Oxford, 1928-1937), (5) surface recording from striated muscle (Sydney 1938-1943), (6) intraspinal extracellular recording with small-tipped needle microelectrodes (Dunedin 1947-1952), and finally (7) intracellular microelectrodes (Dunedin, 1951-1952).

5.1.1. Initial 1928-1932 Oxford work with Sherrington and his group

It seems likely that Eccles got off to a faster start in the study of central inhibition than any of his preceding or then-current peers. He published seven full-length publications which included central inhibition while at Oxford: (1) in 1928 with Richard Creed [1898-1964] (Anon., 1964); (2-3); in 1929 with Ragnar Granit and in other studies with Derek Denny-Brown [1901-1981] and with Eric Liddell [1895-1981] (Phillips, 1983): (4) in 1929 his PhD thesis; (5-6) in 1931 with Sherrington as a collaborator; and (7) in 1932 by himself.

1. Creed and Eccles (1928) explored the possibilities that (1) inhibitory fractionation of sub-components of motor-units occurred when contracting muscles were inhibited by reflexes set up by electrical stimulation of appropriate afferent nerves, and (2) if present, the inhibition was distributed among all the active units. For this work, they stimulated the test peripheral nerve in a chamber designed by Eccles to maintain the preparation, while it was being stimulated to produce reflex force. This device was described in an Appendix to the article. Their measurements of isometric muscle force (combinations of sub-components of several motor units) were made in decerebrate cats, using a high-frequency torsion-wire device (see Sassa and Sherringon, 1921) connected to an optical recording system. Their main results suggested inhibition operated on a restricted field of motor units composing what was known then as "the flexor half-centre," and that this inhibitory field was overlapped progressively by an excitatory field

as it was increased by afferent nerve stimulation. At that time, this was an entirely original idea.

2. The primary goal of Eccles and Granit (1929) was to study excitatory effects in interactions between the crossed extensor reflexes of thigh extensors in mainly decerebrate, de-afferented cats. Unpublished work of Denny-Brown had shown that these reflexes were far stronger than shown previously, when workers had focused on ankle extensors. Eccles and Granit activated two crossed extensor reflexes either together, apart ("intercurrent"), or partly together. Their recording and stimulating equipment was the best available in the Sherrington laboratory at that time. Eccles and Granit certainly seemed intrigued when they found inhibition occurred during pairing of crossed extension reflexes. Their comments on this raised more questions than answers, with one of their summary points being limited to "The presence of inhibition in some reflexes and the possible influence of its presence on interaction is considered." (p.117). Nonetheless their article is included here because their observations on inhibition between crossed extensor reflexes were quite novel and intrigued their peers. Their collaboration also led to a lifelong friendship (Grillner, 1995).

3. In a study still considered classical, Denny-Brown, Eccles, and Liddell (1929) explored the effects of electrical stimulation of the cerebellar cortex in high decerebrate cats. Their equipment, again the best available to the Sherrington group, included a Berne coil (mentioned above) for activation of bipolar electrodes 2 mm apart with current spread judged to be no greater than 1.5 mm on the cerebellar surface. Their stimuli were focused on the anterior lobe of the vermis and the medial part of the lateral lobes of the cerebellum. For recording isometric muscle force, they used a dual-lead myograph, which was combined in the same optical system as a string galvanometer. Their timing device was not mentioned, possibly because the intershock intervals were rarely shorter than ~20 ms. Points 2 and 3 in their 9-point summary (p. 534) had much

to do with Eccles' much later inhibition research on the cerebellum using intracellular recording. When the cerebellar cortex of these regions was stimulated pre-existing spinal reflex acts or states were modified, but stimulation did not initiate reflexes. Their stimulation produced inhibition and excitation of extensor muscles and reflex inhibition and excitation of flexor muscles. It is probable that this result depended on the stimulation concurrently affecting intermingled nerve units of varying function in the cerebellar cortex.

4. Eccles (1929) was his PhD thesis. This was a study of central excitation and inhibition under the guidance of Sherrington, who assisted in most of the experiments.[23] Some of this work had been reported previously in Eccles and Granit (1929), Cooper and Eccles (1930), and Eccles and Sherrington (1930).[24] The techniques and recording devices were again the best available in Sherrington's laboratory at that time, and Eccles could employ them all. Indeed, the five and one third page methods section of his thesis showed that in only one and a half years of research at Oxford, he had mastered virtually all the spinal cord techniques developed and used by the Sherrington group. These included electromyogram (EMG) recording, which had been developed by Denny-Brown in the Sherrington group and first reported in Denny-Brown (1929). He helped both Sherrington and Eccles learn EMG recording in the latter's PhD research. The following nine and one third pages of Eccles' thesis described preliminary experiments he felt were a necessary adjunct to undertake. This description showed Eccles was well versed in the available literature on the mammalian spinal cord and neuromuscular system. His thesis focused largely on central excitation produced by the interaction of two reflexes. Experiments involved stimulating peripheral afferent nerves and comparing the results of double shocks of varying interval and tetanic frequency to those obtained with single shock stimulation. Inhibition was encountered so frequently that it was evaluated and discussed in its own sections in the thesis, and indeed

included in the thesis title. The inhibition findings included a number of new observations on quantitative aspects of the timing and duration of central inhibition when it interacted with central excitation in the elaboration of flexor and extensor reflexes. The thesis emphasized first for flexor reflexes that the available techniques did not permit demonstration " ... for certain that inhibition can exist as a separate entity apart from its power of removal of excitation." (p. 68). This limitation was then shown also for extensor reflexes. The summary of work on inhibition was presented in the second section on inhibition (pp. 78-86). The final discussion (pp. 87-94) returned largely to excitatory issues. For the present purposes, the most important aspects of his thesis were its continual comparisons of central excitation and inhibition, and the new idea that peripheral afferent input could both excite and inhibit motoneurons by chemical synaptic transmission (pp. 93-94).

Surprisingly, Eccles and others seem never to have subsequently cited his thesis and its results. However, many of the results were incorporated into Eccles (1931) and Eccles' and Sherrington's 1931 sequence of five articles (actually six, the third in the series being Eccles alone in 1931). Two of these studies on the flexor reflex included substantial reference to and work on central inhibition (Eccles and Sherrington,1931b,e). Central inhibition was also covered in Eccles and Sherrington (1931d), mentioned in passing in Eccles (1931) and Eccles and Sherrington (1930**,**1931c), but not in Eccles and Sherrington (1931a).

5-6. It is not necessary to comment on the Eccles and Sherrington (1931b,e) articles because their key results were summarized in Eccles (1932) and one of his three book chapters in Creed et al. (1932). His chapter on central inhibition summarized Eccles' perception of the main results from his 1929 PhD thesis and what he had gleaned in Eccles (1931) and the Eccles and Sherrington (1931a-e) papers. This chapter ended with a general discussion about inhibition, and repeated the ideas in the conclusion of

Eccles and Sherrington (1931e). Two of the themes are provided below as extracts, the first being on central inhibition (Eccles, 1932; pp. 101-102). Note, the use of two terms that Sherrington and Eccles used for central activity: the central excitatory state (c.e.s.) and the central inhibitory state (c.i.s.):

> As a summary of the experimental evidence on inhibition it may be said that: (i) Centripetal volleys in ipsilateral nerves as a rule excite reflex contraction of flexor muscles, and tend to inhibit reflex activity of extensor muscles. On the other hand, centripetal volleys in contralateral nerves excite reflex contraction of extensor muscles and tend to inhibit reflex activity of the flexor muscles. (ii) The inhibitory process in motoneurons can be graded in intensity. It may be latent, i.e. subliminal. (iii) In a motoneuron summation of inhibition may be produced by successive volleys in one or more afferent nerves. (iv) The inhibitory process is quantitatively antagonistic to the central excitatory state, *c.e.s.* In a motoneuron inhibition may slow the rate at which *c.e.s.* is being built up to threshold, i.e. it may slow the rate of reflex discharge, or it may prevent all discharge. According to circumstances, the same motoneuron varies in its susceptibility to inhibition. The more strongly it is excited the more difficult it is to inhibit. (v) The antagonism between the central excitatory and inhibitory states is due to the mutual inactivation resulting from their interaction. (vi) A single inhibitory volley sets up a central condition which can be detected for at least 100 ms. This duration is due partly to the temporal dispersion of the incident inhibitor impulses and partly to the duration of the central inhibitory state set up by any particular inhibitory impulse. (vii) The central inhibitory state undergoes a progressive subsidence. This happens in the absence of incident excitatory impulses, i.e. without removal of c.i.s. by excitatory impulses. (viii) The inhibitory process is unaffected by an antidromic volley 'backfired' up the motor-nerve-fibres. (ix) Inhibition from any afferent nerve does not affect all the motoneurons of one muscle with a uniform intensity.

The second theme covered Eccles' and Sherrington's thoughts on the conceptual similarity between the c.e.s. and the c.i.s. (Eccles 1932; pp.102-103):

> In the following respects *c.e.s.* and *c.i.s.* are analogous**:** (i) They are only produced when nerve-impulses in the terminal branches of one neuron arc incident on a neuron next in series, i.e. at synapses. There is as yet no experimental evidence for the existence of inhibition with neurons other than motoneurons. (ii) Both *c.e.s.* and *c.i.s.* undergo a gradual subsidence. (iii) The *c.e.s.* or *c.i.s.* produced by one impulse sums respectively with the *c.e.s.* or *c.i.s.* produced by other impulses, from either the same or other nerve-fibres ending on that same motoneuron. (iv) As a consequence of summation many grades of intensity of either *c.e.s.* or *c.i.s.* may be produced in a motoneuron**. (v)** When *c.e.s.* and *c.i.s.* interact they suffer a mutual quantitative inactivation. In the following respects *c.e.s.* and *c.i.s.* differ fundamentally: (i) *c.e.s.,* if sufficiently intense, gives rise to the discharge of a nerve-impulse. No corresponding action is known for *c.i.s*. It has no direct effect on the motoneuron – it merely inactivates *c.e.s.* (ii) An impulse passing antidromically up a motor-nerve-fiber to a motoneuron inactivates the *c.e.s.* of that motoneuron, but does not affect the *c.i.s.*

7. The final two thoughts in Eccles' 1932 book chapter on central inhibition are also of particular historical interest. First he emphasized that " ... differences between c.e.s. and c.i.s. have in all probability a common basis. Thus, it may well be that c.e.s. acts as the sole intermediary between c.i.s. and the motoneuron, c.i.s. having no direct action." (p. 103).

The second and final thought returned to the issue of how inhibition was transmitted to motoneurons. Eccles wrote (p.103) that the actual nature of the c.i.s. was unknown and lacked any experimental basis. "It has been suggested that it is a chemical substance ... It may however, receive its ultimate explanation in terms of physical chemistry, e.g., as the stabilizing of a surface membrane ... Certain it is that inhibition can exist independently of excitation." It is easy to imagine that as Eccles wrote these words he was already thinking that his next experiments would be devoted to studying synaptic transmission to motoneurons in both excitatory and inhibitory pathways.

Fig. 12 provides some key figures in Eccles (1932) book chapter, which presumably included material from his 1929 PhD thesis.

Fig. 12 near here

In summary, between 1928 and 1932 Eccles was almost completely immersed in the study of central excitation and inhibition, first as a PhD student in 1927 and later as a postdoctoral research fellow in 1932. In that period, he became thoroughly familiar with the world's invertebrate and vertebrate work on the nature of central excitation and inhibition.

5.1.2. Later 1931-1937 Oxford work as an independent and collaborative investigator

Despite his intense collaboration with Sherrington, Eccles found time in 1931 to begin a collaboration with George Lindor Brown [1903-1971] (Macintosh and Paton, 1974) on the heart beat in mammals (decerebrate cat) during inhibitory input from the vagus

nerve. The reported work (8 abstracts, 5 articles) was undertaken by Eccles alone (4 abstracts), and with Brown (2 articles, and Brown and Eccles, 1934a,b) and Hoff (3 articles). The electrophysiological techniques employed were summarized in Brown and Eccles (1934a,b). The techniques included (1) direct stimulation of the pacemaker, the sino-atrial (s.a.) node (2) recording compound action potentials and electrical excitability of the s.a. node, (3) single shock and repetitive stimulation of single vagal nerve fibers, and (4) extra-axonal recording of action potentials in vagal fibers. They also made indirect inferences about the amount of "A.C. substance" (later proven by others to be acetylcholine (ACh)) released by vagal action onto the s.a. node.

Nothing about this collaboration with Brown and Hoff was mentioned in Eccles' three autobiographies, the most puzzling omission being in Eccles (1977a). However, the articles Eccles wrote with Brown and Hoff, along with several other Brown articles, were mentioned in his review (1936) on synaptic and neuromuscular transmission. In his second far briefer Eccles (1937a) follow-up review of the same topics, the two Brown and Eccles 1934 articles were mentioned several times, again along with several other of Brown's articles. Much later, in Eccles' (1982b) reflection, the importance of the Brown and Eccles (1934a) article is again emphasized and some comments from Brown's biographers were highlighted. We are left thinking that Eccles' five articles with Hoff and Brown on the mammalian heartbeat long-remained in his mind, as did an admiration for these two gifted collaborators.

In another collaboration, Eccles and Hoff (1932) reported on the rhythmic discharge of motoneurons. This work, which was closer to Eccles' future interests, and other articles by Hoff on similar topics (e.g., Hoff, Hoff and Sheehan, 1934) were subsequently covered extensively in Eccles' (1936) first review. For this work, their general techniques had been described in Eccles and Sherrington (1931a), whereas the new additions in Fig. 13A were extensions of the work of Adrian and Bronk (1929) and

Denny-Brown (1929). The decerebrate cat preparation required much surgical skill. This was especially so for the surgery that reduced the innervation of the soleus muscle to a single motor axon as revealed by the compound action potential of muscle fibers innervated by the axon. The motor unit's rhythmic discharge was activated by a sustained cross-extension reflex. By way of comparison, one of Eccles' techniques for work on the stellate ganglion is shown in Fig. 13B.

Fig. 13 near here

The Eccles and Hoff (1932) article had both an experimental and a theoretical component. Experimentally, the rhythmic discharge of single motoneurons was modified by antidromic impulses set up at various times by single or double shocks delivered to the test motoneuron's axon. The data were subjected to mathematical modeling, which improved our understanding of the absolute and relative refractory period following a motoneuron's action potential. As such, the work advanced the Sherrington School's concept of the c.e.s: i.e., in this case "the propensity of the rhythmic centre (*for a single motoneuron in the spinal cord*) to set up a reflex discharge" (their p. 513).

Eccles also collaborated for one year with an Oxford applied mathematician, John H. C. Thompson [1909-1975] (Anon., 1976) on the visco-elastic properties of rubber (Eccles and Thompson,1935). Eccles had hoped that this work could later be related to the mechanical properties of striated muscle. Unfortunately, this was not to be the case and he told D.G.S. in 1966 that he felt in retrospect that this had been "squandered time." However, Stuart et al. (2001; p.138) reflected that this collaboration must have sharpened Eccles' possibly dormant mathematical skills, which were used very effectively in his subsequent championing of electrical synaptic transmission and later work involving differential equations in the Hodgkin-Huxley model of the initiation and conduction of the action potential (see below).

We now return to Eccles' (1936) review on synaptic and neuromuscular transmission. It was a very thorough and masterful 105-page article, covering all that was known and proposed at that time concerning synaptic transmission in the central and peripheral nervous systems (specifically sympathetic ganglia, striated and smooth muscle). Throughout this review, and like articles and reviews written by others at that time, there was a continual focus on arguments for and against both chemical and electrical synaptic transmission. For the latter Eccles began with his "action-current hypothesis," which he claimed (p. 371) to have first espoused in his 1935a abstract, even though the term was not used in that publication. On the same page, he wrote:

> According to the above hypothesis the action-current of a pre-ganglionic volley is itself the synaptic transmitter, which consequently should persist for only a very few milliseconds even when allowance is made for the asynchronism of the volley; hence this hypothesis conforms well with the short limiting value of 6 ms, derived for the duration of the synaptic transmitter from observations on the detonator response.[25] Moreover since the detonator response is closely allied to the local excitatory response of peripheral nerve, which has only been recognized after electrical stimulation, it is arguable that the detonator response is also set up by an electrical stimulus, though of course such an argument is open to the objection that a local excitatory state might also be set up by a chemical substance such as acetylcholine. Further discussion of this hypothesis (*i.e., in this review*) will be postponed until the experiments of Lorente de Nó have been considered for they are particularly significant in respect to the difficult problem of synaptic delay.

After reviewing Lorente de Nó's elegant work on synaptic delay in this review, Eccles argued again in favor of his action-current hypothesis, the forerunner of his electrical synaptic transmission hypothesis, albeit also conceding (p. 398) that "No experiment has yet been performed which definitely excludes one or other of the hypotheses" (*i.e., chemical or electrical transmission*).

Fig. 14 gives two examples of Eccles' thinking at that time. Fig. 14A shows his ideas on the actions of a pre-ganglionic volley of nerve impulses on a stellate ganglion cell. The detonator response was shown as the only primary action. He thought it gave rise to a c.e.s. in the ganglion, which, if strong enough, set up an action potential in the ganglion. He argued that this potential then produced a c.i.s. leading to a refractory

period. Fig. 14B is much simpler. Its purpose was to contrast the extracellular recording situation in spinal motoneurons to that in ganglion cells.

Fig. 14 near here

5.1.3. Focus in Dunedin on the electrical synaptic transmission hypothesis

While it is widely known that Eccles championed electrical synaptic transmission in the spinal cord until late 1951, it is not generally appreciated just how much thought and serious effort he spent on the issue, and how much central spinal inhibition dominated his thoughts while experimenting and writing about electrical transmission. Indeed, before rejecting his own evolving hypothesis, Eccles' thoughts were dominated by its failure to account for central inhibition. Table 4 shows he had six reviews, 17 articles, two key abstracts and a letter to the editor on electrical transmission between 1936 and 1951. Five of these articles and these two abstracts had preliminary findings that supported continuing effort on the topic. It is tempting to propose that his work could not be fully evaluated by many critics of his hypothesis, because they were not as mathematically gifted as Eccles.

Table 4 near here

Eccles began his theoretical work on electrical transmission while still at Oxford. Ludimar Hermann [1838-1914] had suggested the concept in Hermann (1879), a textbook of physiology. However, Hermann remains better known for work in other areas of physiology (Anon., 1920).

According to Eccles (1982b), his own first communicated thoughts on the possibility of electrical transmission were expressed in Eccles (1935a), and then again in the above-mentioned extensive 1936 review, which took into account four other 1935 reports (Eccles, 1935b-e; see below). In Eccles (1937a), a much shorter review with the same title as the 1936 one, he cited the Eccles and Pritchard (1937) abstract, which concluded (pp. 44-45) " ... synaptic delay (*to orthodromic activation of the onset of a*

*motoneuron's action potentia*l) is so short that this discharge must occur before the slow negative wave, which presumably is associated with that increased excitability of neurons due to C.E.S. (*atypically in caps*). Hence it seems that this discharge is not due to C.E.S., but to the rapid initial excitatory process which is called the detonator response (cf. Eccles, 1936)."

After Oxford, Eccles continued to experiment and think deeply about central inhibition. In Sydney, these efforts included a study on synaptic transmission in a sympathetic ganglion, which emphasized the possibility of electrical synaptic transmission (Eccles, 1944a), and a study in the spinal cord with a similar emphasis (Eccles, 1944b).

Fig. 15 shows key components of Eccles' total body of work promulgating electrical transmission, with the majority of the work done in Dunedin. It shows his first use of (1) a conceptual figure on electrical transmission (Fig.15A), (2) a figure to explain his Golgi Cell Hypothesis, which was necessary to justify his original hypothesis for inhibitory transmission (Fig.15B), (3) intraspinal recording with an extracellular needle microelectrode to strengthen both hypotheses (Fig.15C). Two of his final evolving thoughts in Eccles (1949) on the inhibitory hypothesis are shown in Fig.15D. In this article, he made some changes in the details of the excitatory component of the hypothesis, but not the inhibitory component. For the latter, he had to conclude that were still several open questions about how electrical transmission would operate when the Golgi cells were discharging action potentials rather than merely being passive.

Fig.15 near here

Eccles' last article on electrical transmission addressed the possibility that it might occur in the cerebral cortex. However, he had no evidence to support this contention at that time (Eccles, 1951b).

The above body of work includes almost all the research undertaken by Eccles in

Dunedin before his work on intracellular recording. His extracellular microelectrode work with Wilfrid Rall [1922-], which was published in 1950 and 1951, is not included. Rall later became renowned in the USA (Anon., 2014b) for his work on cable theory as applied in particular to mammalian motoneurons, and he is considered one of the key figures in developing modern computational neuroscience. His viewpoints on his Dunedin experience with Eccles are discussed revealingly in his mini-autobiography (Rall, 1992) and a later more-detailed one (Rall, 2006).

In Eccles and Rall (1950) and 3 subsequent articles (Brock, Eccles, and Rall, 1951; Eccles and Rall, 1951a,b) they focused on mechanisms potentially underlying monosynaptic excitatory motoneuron responses to repetitive stimulation. In two of these articles (Eccles and Rall, 1950, 1951b), which are listed in Table 4, there was very brief reference to the possibility that electrical excitatory synaptic transmission was implicated. This was a very cautious implication and given no more weight than the possibility of chemical transmission. (We wonder if this was at the insistence of Rall)!

In summary, Eccles' intense effort in 1936-1951 to explore the possibility of electrical transmission in the spinal cord has left us with the belief that it has a prominent place in the history of work on synaptic transmission. Interestingly, it came to the forefront again in the mid 1970s when research on gap junctions expanded, and showed their ubiquity throughout the mammalian CNS (for review see Dermietzel and Spray (1993) and Connors and Long, 2004.).

5.1.4. Other work in Dunedin of relevance to later intracellular work in Canberra

After his move to Canberra, Eccles co-authored three articles on work which had been undertaken in New Zealand with two talented electrophysiologists; a visiting zoologist from the USA, Dexter Easton [1921-2010], and Eccles' former Dunedin trainee, Kenneth Bradley [1925-1986] (Stuart and Brownstone, 2011; pp. 78 and 76, respectively). The first two articles, which involved extracellular recording, were initiated presumably

before the Brock et al. pioneering 1951-1952 work on intracellular recording (see below). By the third article, however, using the same techniques as the first two, there was reference to the Brock et al 1951-1952 articles. All three of the Bradley/Eccles articles' results were important to Eccles for his use of the same techniques and subsequent interpretation of the results of his later intracellular studies in Canberra.

In the short Bradley and Eccles (1953a) report, extra-axonal recordings were made from muscle nerves and the dorsal root entry zone in the nembutal- anesthetized low spinal cat. The primary goal was to test the effects of strychnine on the fastest (then called direct) inhibitory spinal reflex. For this it was necessary to confirm a Brock, Eccles, and Rall (1951) suggestion that the Ia volley from spindle afferents preceded the Ib volley from Golgi tendon organ afferents. This was claimed to be the case, and they concluded that strychnine inhibited the inhibitory component of the Ia-afferent mediated reflex, rather than augmented the excitatory component of the reflex. Their second report (Bradley and Eccles, 1953b), which done with great care and a much larger sample, used dorsal root volley separation to confirm the different speeds of the Ia and Ib mediated responses. Their final (fourth) conclusion (p. 472) was that " ... the two components are groups Ia and Ib, being respectively the afferent fibres from muscle spindles and Golgi tendon organs. An explanation is offered for the high degree of separateness of these two components in the afferents from thigh muscles in contrast to their much greater admixture in the afferents from leg muscles." The third article in this sequence (Bradley et al., 1953) used the same techniques to evaluate the idea of Lloyd (1946, 1951) and later LaPorte and Lloyd (1951, 1952) that there was a direct (monosynaptic) inhibitory effect from quadriceps Ia afferents to their antagonist biceps-semitendinosis motoneurons. By the time this article was written, the full impact of the initial Brock et al (1951; 1952a,b) intracellular recording articles was known and cited in the article. The conclusion of Bradley et al. (1953) included negation of such a direct

inhibitory effect and (p. 487) the conclusion that there was "no good evidence for the accumulation and persistence of the inhibitory transmitter substance that is assumed to cause direct inhibition." This finding certainly increased the ever-present antagonism between Lloyd and his former PhD mentor, Eccles!

There are two problems with the above three Bradley articles. First, many subsequent workers began to assume that a clear-cut Ia-Ib volley separation could be achieved in lower leg muscles. This caused much mischief, which continues today, but it certainly cannot be attributed to the three Bradley/Eccles articles. Second, and more important is the subsequent work of others, which challenged the original Bradley/Eccles' finding that such a separation was clear in cat thigh muscle Ia-Ib volleys. This challenge was noted in Stuart et al. (1971). Consult this article for the full citations in the following comments, which appeared on its pp. 124-125:

> There is considerable controversy concerning the composition of afferent nerve volleys as evoked by electrical stimulation. Bradley and Eccles reported that the group I potential recorded at the spinal cord-dorsal root junction following single shock stimulation of nerve to thigh muscles almost invariably has two peaks separated by an interval of 0.2 msec. They felt that the fast-low threshold component was a Ia volley from muscle spindle afferents and the slow-high threshold component a Ib volley from Golgi tendon organ afferents. This discrimination has been employed to study central actions of the two receptor systems. When stimulating the same nerves, Lloyd and McIntyre did not observe bifid volleys, while Laporte and Bessou found all transitions between a split and single volley. From their analysis of isolated afferents, Laporte and Bessou concluded that in preparations exhibiting a split volley the fast-low threshold group comes predominantly from Ia fibers. While they attributed a major component of the slow-high threshold group to Ib activity, a significant component (over 30%) appeared to involve input from Ia and group 1b fibers. Laporte and Bessou's sampling procedures did not exclude the possibility that the fast-low threshold component might receive substantial contribution from Ib fibers. Shugarman et al. found that the mean conduction velocity for group Ia afferents in cat rectus femoris, semimembranosus and semitendinosus, was greater than the mean velocity for Ib afferents. Overlap in distributions was considerable. For the distal nerve to semitendinosus, Coppin et al. found that a differential threshold to electrical excitability does exist, so that a stimulus activating only 30 % of the group I population would be expected to generate a pure Ia volley. Further increase in stimulus strength would recruit to the volley both Ia and Ib fibers. There appears to be more general agreement about the composition of afferent volleys in nerves to calf muscles. Split group I volleys have rarely been observed and would not be expected on the basis of the slight differential conduction velocity reported for Ia and Ib fibers. Taken together these data imply that it is difficult to evoke a group Ia volley by electrical stimulation without some contamination with Ib input. For studies on the 'strength' of synaptic connections between Ia afferents and motoneurons it is necessary to excite all the Ia fibers in a given muscle nerve so that maximum EPSPs and IPSPs can be evoked. An electrical stimulus of sufficient strength to excite all the Ia fibers must also excite Ib and group II fibers. Consequently, the EPSPs and IPSPs produced by Ia action are distorted by the potentials resulting from the additional Ib and group II input. This problem may not be relevant to the

study of the monosynaptic EPSP, since the rise time of this potential is short enough (0.5-2 ms) that it is probably altered but little by that small component of autogenetic Ib IPSP arriving over a disynaptic pathway. In contrast, the di- and tri-synaptic effects excited by Ia fibers in antagonists and on motoneurons innervating muscles that operate at other joints must all be affected or even masked by superimposed Ib and group II potentials.

Eccles expressed his displeasure to D.G.S in Munich in 1971 about the above viewpoints, albeit surprisingly mildly! Another important reservation was that the three Bradley/Eccles articles used nembutalized cats, which provided different results to other anesthetics like those that can be used to simulate the locomotor state. As a result many still believe that Ia afferents invariably excite their homonymous motoneurons whereas Ib afferents invariably inhibit them. This is not correct and in sharp contrast to the concept of alternative spinal reflex pathways as developed subsequently by Lundberg, his trainees (e.g., Hultborn, 2001, 2006), and various other collaborators.

5.2. Post-synaptic inhibition of spinal motoneurons and interneurons

It is customary to attribute the pioneering of intracelluar recording in the CNS (the cat spinal cord) to both Eccles and two of his collaborators, Lawrence Brock [1923-1996] (J. Brock, 2010) and John Coombs [1917-1993],[26] at the University of Otago in Dunedin and to Walter Woodbury [1923-] and Harry Patton [1918-2002] at the University of Washington, in Seattle. (For details on the academic careers of Woodbury and Patton, see Stuart and Brownstone, 2011). Both groups began their work within a few weeks of each other in May-June 1951. The first Dunedin report was an abstract in July 1951, followed by three full-length reports in 1952, whereas Woodbury and Patton published an abstract that was presented at the April 1952 meeting of the Society for Experimental Biology and Medicine (Woodbury and Patton, 1952a). This was followed by an invitation, at short notice, to present a talk (Woodbury and Patton, 1952b) at the highly impactful (Brownstone, 2006; p. 158) June 06-13, 1952 Cold Spring Harbor Symposium on The Neuron.[27] They were given only 10 days to submit an article for the volume that

followed the symposium later that year. In contrast, the other authors were given several months' notice for their contributions. (For details on the reasons for these misfortunes, see Stuart and Brownstone, 2011; p. 71).

The electronics expertize for the above work was provided by Coombs in Dunedin and Woodbury in Seattle. In contrast to Coombs, Woodbury had prior experience during his 1950 PhD thesis in high input impedance intra-axonal recording from myelinated nerve fibers. Similarly, Eccles had substantial (near unique) experience recording extracellularly with steel needle microelectrodes in the cat spinal cord, whereas Patton had none. Another interesting comparison was that the microelectrodes Woodbury designed and used for recording from spinal interneurons were far superior to those used subsequently by Eccles in his initial Canberra studies on interneurons (see below). Woodbury and Patton did not continue their promising initial intracellular CNS research, whereas Eccles subsequently exploited the technique to the fullest possible extent in his own research and his research mentoring of others (see Stuart and Pierce, 2006).

5.2.1. Initial impact of 1951-1953 publications on intracellular recording results undertaken in Dunedin

Only the highlights of this historic research are presented here as this has been detailed in Stuart and Brownstone (2011). Fig. 16 presents several points in the Brock et al. 1951-1953 and Eccles' 1952b article, a 1953 Brock et al. book chapter, and an Eccles 1953 monograph, which created great international excitement in the neuroscience community.

Fig. 16 near here

The Brock et al (1952c) article was presented by Eccles as a talk in a thought-provoking meeting in the United Kingdom. He also chaired the meeting, which was entitled "Contribution to Royal Society Discussion on 'Excitation and Inhibition' on Feb 21, 1952." Eccles' rejection of his electrical transmission hypothesis (see below) was

presented with some very helpful drawings to explain the reason for the rejection. At that time, Eccles still accepted Lloyd's concept of direct inhibition so the focus of the talk and subsequent article was on explaining how impulses in the same Ia afferent fiber from a muscle spindle could act as monosynaptic exciter of homonymous motoneurons and monosynaptic inhibitor on motoneurons supplying antagonistic muscles. This article has been rarely discussed in the literature because Eccles negated direct inhibition shortly thereafter in Canberra (see below). Nonetheless, the article is of historical interest as we trace Eccles' thoughts on synaptic transmission.

Eccles (1952b) included findings first discussed at the above meeting and subsequently presented by Eccles at the June 1952 Cold Spring Harbor Symposium. The article was published in the symposium volume. In it, Eccles presented his first mathematical models and some very helpful hand drawn and retouched intracellular recordings from the Brock et al. (1951-52a,b) results on motoneuron resting potentials, action potentials, and EPSP/IPSPs. This was based on the classic results of Hodgkin (1951) and the Hodgkin and Huxley articles (1952a,b; published in April) on the sodium and potassium currents mediating the resting potential and action potential of the squid (*Loligo)* giant axon*.* Eccles had heard the Hodgkin and Huxley presentations and results (1952c; published in October) at the above-mentioned February 21, 1952 meeting in London. We think it likely that while in London he had acquired as many of the seven Hodgkin/Huxley 1952 articles and relevant abstracts that they would give him! From then on Eccles championed their classic work.[28]

The Brock et al. (1953) book chapter was followed by a full-length article on antidromically activated motoneurons. The chapter included Eccles' penchant for theoretical drawings of potential electrical explanations of cellular events (see Fig 16D), and led in turn to Eccles (1955), a classic article on antidromic effects of motor nerve fibers. We believe that parts of Eccles' (1953) monograph are important in an historical

sense as it gave Eccles an opportunity to review his own and others' work from the perspective of his new 1951-1953 intracellular recording results. Chapter V in Eccles (1953) focused on central inhibition, co-ordination, and transmission of information.[29] Five issues addressed in this chapter are briefly commented upon below. They included (1) direct (a) and indirect (b) inhibition, (2) the mechanism causing inhibitory hyperpolarization, (3) chemical transmitter substances in the central nervous system, (4) the co-ordination of reflexes, and (5) the transmission of information in the nervous system.

1a. Direct inhibition is defined above in footnote c of Table 4 (recall Lloyd, 1941, 1946). It must have been a vexatious trial for Eccles to discuss direct inhibition. He wrote the preface for this monograph in August 1952, just before departing Dunedin for Canberra. At that time, he was preparing a later publication, an extracellular recording study, which raised concerns about the legitimacy of direct inhibition (Bradley et al., 1953). One of the concluding points of the article (p. 487) was "There is thus no good evidence for the accumulation and persistence of the inhibitory transmitter substance that is assumed to cause direct inhibition." At that time, he knew that Birdsey Renshaw, whose meticulous research he held in high regard, had questioned whether direct inhibition was monosynaptic. Renshaw (1942) had experimental evidence for a central latency of 1 ms for direct inhibition. He concluded (p. 496) "It has therefore seemed wise to be noncommittal as to whether or not the tested reflexes were strictly 2-neuron arc discharges, as well as whether the inhibitory effect was necessarily mediated by the direct action of dorsal root fibers on the tested motoneurons." In late December 1953 Eccles submitted his first intracellular evidence that supported Renshaw's 1942 results (Eccles et al.,1954a; see below). As a result, this section of Chapter V in Eccles (1953) is difficult to follow, as it probably was for Eccles at the time.

1b. Eccles (1953) wrote but one paragraph on indirect inhibition attributable to

cutaneous sensory input to motoneurons. He included a figure (no. 55 on p. 160), however, from unpublished observations in the Brock et al. 1951-53 sequence. This figure must have hammered home to readers who had not read this sequence just how significant a presence was active spinal inhibition in the cat spinal cord.

2. This section too must have pained Eccles in subsequent years. He began with what he knew was most likely incorrect at that time: "Since the latent period of the hyperpolarization is too brief to allow for a synaptic relay ... it must be assumed that impulses in collaterals of the group Ia fibres of the antagonistic muscles cause a reaction of hyperpolarization in the surface membrane of the motoneuron." This condemned the rest of this discussion to the dustbowl of history! If the monograph had been submitted a year later this section would have been quite different and far more significant and long-lasting.

3. A brief section was written in Eccles (1953) on the various alternatives that might explain whether excitatory and inhibitory substances had a specificity of action in the CNS, the focus being on mammals. Eccles concluded (p. 173) "It would seem that a decision between these various alternatives will not be possible until the chemical substance or substances have been identified."

4. In this chapter's section on the co-ordination of reflexes, Eccles returned to points emphasized in Sherrington (1906a) and Creed et al. (1932) about the flexor reflex. He wrote (pp. 182-183):

> ... in the ordinary methods of eliciting the reflex, very complex interactions would be occurring in the spinal cord ... For example, on the ipsilateral side, stimulation of a cutaneous nerve usually gives a pure flexor reflex, because the inhibition of extensor motoneuron is adequate to prevent the reflex discharges that would otherwise be evoked by the action of excitatory impulses on the muscle. But it has now been shown that even the stimulation of a small area of skin has often a mixed excitatory effect on both the extensor and flexor motoneuron on the ipsilateral side (Hagbarth, 1952). Moreover, as soon as a muscle begins to contract there will be a change in the afferent barrage of proprioceptor impulses in the spinal cord. Thus, the apparently simple flexor reflex presents extremely complex problems of reflex coordination ...

Interestingly, these problems have not been resolved in modern times, particularly

during natural movements (Hultborn, 2006). Unfortunately, there is probably a tendency to present a naive "straight-jacket" account of this reflex, even when lecturing to graduate students.

5. In summarizing this chapter Eccles (p. 189) likened the nervous system " ... to a telephone system with lines (the nerve fibres) and exchanges (the synaptic components)." He summarized the roles of temporal and spatial summation, and in addition, emphasized the role of inhibition. He stated (p. 192) " ... that excitatory and inhibitory effects are exerted by convergence on to a common locus, the neuron, and there integrated." He concluded the chapter with the argument that “... it may still be difficult to appreciate how the enormous wealth of information is transmitted by a code of dots only. ... It may be stated as a general rule that the number of nerve-fibres in any pathway is related to the wealth of information that has to be transmitted along that pathway."

In summary of the above chapter, and indeed the 1953 monograph as a whole, it is clear that Eccles had a detailed grasp of the contemporary literature and had no problem rejecting ideas he had espoused when he felt better work had become available. His strategy was to accept the new work and develop new hypotheses to advance it

5.2.2. Rejection of the electrical synaptic transmission hypothesis in Dunedin

Of particular historical interest in Brock et al. (1952b), the most widely quoted of their 3 1952 articles, are the authors' comments on the negation of Eccles' electrical synaptic transmission hypothesis (Fig. 17; see their Fig. 12 and text on their p. 452):

> Thus, the potential change observed is directly opposite to that predicted by the Golgi-cell hypothesis, which is thereby falsified. Since the potential produced by the inhibitory volley was reversed by penetrating the membrane, it must have been generated in the membrane ... The increased internal negativity of Fig. 12 thus shows that the inhibitory volley has caused the surface membrane of the motoneuron to give an active anelectrotonic reaction, for the potential reveals that there has been an over-all increase in the membrane polarization. Such an anelectrotonus would of course provide a satisfactory explanation of the inhibitory effect. Presumably the inhibitory impulses produce

subsynaptic anelectrotonic foci by direct action on the motoneuron and these act by preventing the spreading and fusion of excitatory foci, but not their initiation, just as was postulated by the Golgi-cell hypothesis. Note for example the summation, without appreciable interaction, of the potentials produced by the inhibitory and excitatory foci in Fig. 12 E. In fact, all the experimental evidence in support of the Golgi-cell hypothesis (Brooks & Eccles, 1948 (*b,c in our article*); Brooks et al., 1948) merely indicated that the inhibition was attributable to an electrotonic foci on the motoneuron, but did not discriminate between their passive production, as in the Golgi-cell hypothesis, and their active production, as has now been established experimentally. A difficulty, however, arises in attempting to explain the manner in which impulses can produce active anelectrotonic foci. It would seem that the anelectrotonic local responses described by Arvanitaki (1943) are otherwise explicable (Eccles, 1948), and that there is no evidence for an active anelectrotonic reaction by the surface membrane of nerve fibres (cf. Hodgkin, 1938**;** Cole & Curtis, 1941**;** Hodgkin & Rushton, 1946; Katz, 1948**;** Hodgkin et al., 1949). Thus, any electrical explanation of inhibitory synaptic transmission seems to be now excluded. It may therefore be concluded that inhibitory synaptic action is mediated by a specific transmitter substance that is liberated from the inhibitory synaptic knobs and causes an increase in polarization of the subjacent membrane of the motoneuron.

Fig 17 near here

In a later reflection (Eccles, 1976; p. 225) Eccles expressed the above far more succinctly and dramatically:

> Before the test was applied we had recognized that, on the electrical model for inhibitory action, the microelectrode would be in a brief positively going electrical field, whereas on the chemical hypothesis synaptic inhibition would be expected to be due to a brief increase in membrane potential, which means that it would record a brief negatively going potential. Thus, it was a clear test. If the quadriceps volley caused the trace to go up it was electrical, if down it was chemical. It went down. The result was repeatable, graded with stimulus strength and indubitable.

In our opinion, Eccles' abrupt rejection of his electrical transmission hypothesis was admirable, as was his later memory of the events that led up to this rejection. Most remarkably, at the age of ~79, Eccles (1982b) wrote an objective review of the chemical vs. electrical transmission controversy, which gave much credit to all the scientists who participated in it, giving equal weight and credit to the "soup" and "spark" proponents.

Concerning his own participation, he wrote with great feeling about one of his 1935 communications to the Physiological Society when, as revealed in the Eccles (1935a) abstract, he questioned a chemical transmission possibility for the fast initial synaptic phase. Rather, he favoured electrical transmission (pp. 328-329), which he initially called "eddy currents:"

> The climax to this controversy came in May 1935 when there was a very tense encounter. I presented to the British Physiological Society the results of repetitively stimulating the pathway to the nictitating membrane either presynaptically or postsynaptically.... It was argued that ACh accumulation was responsible for the after-discharge ... Two explanations were proposed for the initial fast response: 1. The fast response was also due to ACh. 2. The fast response was due to electrical excitation.

Eccles (1982b) followed with the criticisms espoused in the subsequent discussion

of both possibilities! Interestingly he did not mention in his 1982 reflections that in the same 1935 year four months later, he presented again to the Physiological Society and again came out in favor of "eddy currents" to explain the initial fast synaptic response (Eccles, 1935d). Apparently, the discussion that followed this presentation was not tense. Both of these abstracts were cited in Eccles (1936), his major review on all facets of synaptic and neuromuscular transmission.

5.2.3. Initial follow-up work in Canberra on spinally based central inhibition.

Eccles' progress was remarkable after he began intracellular recording in Canberra in March 1953. He worked on 3 issues more-or-less in parallel, as summarized below. In each case the initial submission was a brief report to the then-obscure (at least internationally) Australian Journal of Science, followed by more detailed research and submissions to leading international journals. We consider Figure 18 to be of particular historical interest because it shows the first published intracellular recording figures for work done in Canberra on these 3 projects.

Fig. 18 near here

First came a report by Coombs, Eccles, and the American-born British biophysicist, Paul Fatt [1924-2014] (Cull-Candy and Ashmore, 2014), the goal being to test for the mechanism underlying motoneuron IPSPs. For this, double-barreled microelectrodes, designed and constructed by Fatt, were inserted into motoneurons.[30] Their first results were submitted for publication on June 24, 1953, the work having begun just 3 months earlier. This short report was followed in 1955 by a sequence of four full-length articles, and an abstract, all dealing with the use of double-barreled microelectrodes to explore the role of predominately Na^+, K^+, and Cl^- ions in generation of the resting and action potentials of motoneurons, and their EPSP and IPSP mechanisms (Coombs et al., 1955a-e). This line of work continued in Eccles' Canberra group for the duration of his

stay there (for the various collaborators, including in particular Curtis, see Stuart et al. (2001).

Many years later Eccles (1975/1992) reflected on his collaboration with Coombs and Fatt (pp. 167-172). A substantial part of this reflection is now provided below because it gives insight into Eccles' approach to experimental work:

> In the first few years at Canberra I had the good fortune to be associated with Coombs and also with Paul Fatt, who had come from Katz's laboratory in London where they had utilized intracellular recording to elucidate the physiological processes involved in neuromuscular transmission in frogs and crustacea ... the work in Canberra with my colleagues Fatt and Coombs, and later David Curtis continued the investigation of the synaptic processes, using much more refined biophysical methods in the attempt to understand the actual nature of synaptic events that brought about a depolarization for excitatory synapses and a hyperpolarization for inhibitory synapses ... Perhaps the most remarkable story about this work concerned our efforts to understand the inhibitory synapses. ... in Dunedin, we had discovered that inhibitory synaptic action produced an increased membrane potential, the IPSP. In one of the early experiments in Canberra, using a rather coarse micro-electrode, I noticed to my amazement that the potential changed over quite quickly after the onset of the intracellular recording, so that what had been an inhibitory potential giving hyperpolarization became a depolarizing potential like that produced by excitatory synapses. My colleagues did not believe my excited report. They had not observed it, being otherwise engaged in the experiment. However, a few minutes later we impaled another motoneuron, and I was careful to have them watch the sequence of events which, I am glad to say, repeated themselves just as I had reported before ... Very quickly we recognized that we had a new discovery, namely that chloride ions diffusing out of the microelectrode (filled as usual with 3M KCL) greatly increase the intracellular concentration of chloride and so cause this inversion of the potential. It is exactly what would be expected if the inhibitory synapses open up ionic gates for chloride ions across the surface membrane of the motoneuron. We realized then that we could inject ions into motoneuron by diffusion out of the microelectrode, provided that the microelectrode was rather larger than normal. The small size of our electrodes in the initial experiments had, of course, prevented this inversion from disturbing and confusing us earlier! So we studied this inversion by diffusion out of coarse microelectrodes—3 to 5 MOhm resistance—in several experiments ... The idea of electrophoretic injection did not come to us until we discovered it by accident. An inadvertent electrical connection onto the microelectrode caused a catastrophic effect on the impaled motoneuron. It was not killed. Instead the inhibitory synapses produced an enormous depolarization. A quick check showed that the current passed through the microelectrode would have caused a large injection of chloride ions out of the microelectrode into the motoneuron. So we had discovered the technique of intracellular ionic injection by accident. It was no longer necessary to use diffusion from the coarse microelectrodes! And we could now also estimate the quantity of ions injected from the coulomb calculation ... I can remember that our initial concept was that chloride was a specific ion for the inhibitory process—an idea that possibly arose from the specificity of the ionic mechanisms demonstrated by Hodgkin and his colleagues for nerve impulses. To test this idea, we filled microelectrodes with various sodium or potassium salts having several different anions and found to our surprise, and even chagrin, that the anions nitrate, bromide and thiocyanate were just as effective as chloride in causing an inversion of the IPSP. On the other hand, there were a number of anions (sulphate, phosphate, bicarbonate, acetate) that were quite ineffective. When we examined the two sets of anions in the physical tables, we discovered to our delight that the anions causing inversion of the IPSP were all small in the hydrated state, whereas those that failed were all large ... Hence, on the basis of tests with some nine anions, we postulated that the inhibitory transmitter substance opens up ionic gates or pores

> in the postsynaptic membrane that allow the free diffusion of anions below a certain critical size in the hydrated state. This hypothesis, of course, demanded experimental testing with other anions in addition to our initial small series. These tests (on 34 species of anions) were performed by my colleagues in Canberra many years later, and revealed only one discrepancy in the critical-size hypothesis ... This arose from the anomalous behavior of the formate ions, which very effectively pass through the inhibitory ionic gates even though they are slightly larger than three other species of anions that are excluded. This formate anomaly (as we now call it) has been demonstrated with other inhibitory synapses both in vertebrates and invertebrates, but it is still unexplained. This investigation of critical ionic size and inhibitory transmitter action is a good example of the way in which Popper's concepts of science have helped me to develop hypotheses that have gone far beyond the data and that have consequently challenged experimental testing. Finally, Paul Fatt derived equations for inhibitory synaptic action that were based on the theory of ionic diffusion across membranes proposed some years before by Goldman, and that formed the basis of the mathematical developments of Hodgkin, Katz and Huxley for ionic diffusion through the surface membrane of nerve fibres. It turned out that these equations predicted with surprising fidelity the effects of a wide range of membrane potentials on the sizes of the IPSPs. Our hypothesis, therefore, was that the inhibitory transmitter opens up ionic gates in the postsynaptic membrane that momentarily allow the free diffusion of anions below a critical size, this ionic movement causing the inhibitory postsynaptic potential. ... We also included small cations in the ionic inhibitory mechanism, but the evidence had a serious flaw, as was later pointed out by Ito. Nevertheless, investigations with Ito many years later led indirectly to the postulate that small cations such as potassium also pass through the inhibitory ionic gates and contribute to the generation of the IPSP.

At that time, Eccles was also collaborating with Fatt and a gifted Japanese neuroscientist, Kyozo Koketsu [1922-] (Kuba, 2007), in the study of Renshaw cells, "which was one of my most satisfying research projects" (Eccles, 1977; p. 8). Their first article was submitted on August 31, 1953 (Eccles et al, 1953). It was followed by the same authors' full-length article (Eccles et al.,1954) and then further work by Eccles, Eccles, Fatt (1956), the second Eccles being his daughter, Rosamund Eccles [1929-]. A few years later (Eccles, Eccles, Iggo, and Lundberg, 1961a) advanced the Renshaw cell story. At that time Ainsley Iggo [1924-2012] (Kelly, 2012) was a renowned neurophysiologist, as was Lundberg [1920-2009] (Alstermark et al., 2010). In a parallel study an allied team (Eccles, Eccles, Iggo, and Ito, 1961) provided new data on Renshaw cells, the gifted Masao Ito [1928-] (see Ito, 1998) being a postdoctoral trainee with Eccles at that time. In all, Eccles' Renshaw cell collaborators and trainees were extremely talented neurophysiologists and biophysicists. For all this work, the various groups employed the large-tipped microelectrodes used to record intracellularly from motoneurons (5-10 μm glass tips), these being suitable for extracellular recordings from

Renshaw cells (Fig. 19A) but problematical for intracellular recording. For this reason, it is not surprising that the first short article in the series (Eccles, Fatt, Koketsu, 1953) contained no intracellular recordings from Renshaw cells and those in their following 1954 article (Fig. 19B) were as good as could be expected, particularly when using whole cat preparations. Interestingly, even with improvements brought by Lundberg when he joined the Canberra group it proved very difficult to study Renshaw cells using intracellular recording (Fig 19C). For example, in the Methods section of Eccles, Eccles, Iggo, and Lundberg (1961a) they stated (p. 462) that "Renshaw cells were recorded from extracellularly, and also, with varying degrees of success, intracellularly."

Fig. 19 near here

Again, much later, Eccles (1975/1992; pp. 172-173) reflected:

> In parallel with these investigations on the biophysics of synapses, we were also working in these early years in Canberra on various neuronal pathways in the spinal cord, following up ideas developed by Paul Fatt while he was reading in the library at Canberra from late 1952 through early 1953 before our equipment was working. This enforced experimental idleness proved to be of great value to us all, because Paul came up with two major problems that led to fascinating experimental developments. The first concerned the cells that Renshaw (1946) had described many years before and that he found to be fired repetitively by an antidromic volley in the axons of motoneurons. Renshaw himself thought they could be the cells responsible for the inhibitory effects on motoneurons that he and Lloyd had (*separately)* found to be produced by these antidromic impulses. However, it was Paul Fatt who very clearly defined the problem. He predicted, in accord with Dale's postulate, that the action of the motor-axon collaterals upon Renshaw cells (as we called them) would be cholinergic, acetylcholine being the transmitter, just as at the peripheral neuromuscular synapses made by these same motor axons. This clear formulation of the problem immediately gave us a clue about how to develop the experimental tests, and in collaboration with Koketsu, who had meanwhile arrived from JPN, we carried out a successful series of experiments (Eccles, Fatt and Koketsu, 1953, 1954). In retrospect, this proved to be one of the most elegant experimental investigations that I can remember being associated with. As illustrated in our earliest diagram ... everything came out as predicted with a full confirmation of all that Lloyd and Renshaw had found, except for the infrequent excitatory action that Renshaw had described. This excitation was later shown by Wilson and Burgess (1962) to be due to a special action of Renshaw cells inhibiting other inhibitory cells of motoneurons. It will be appreciated that the inhibition of a continuous background of inhibition is equivalent to an excitation (technically it is known as a disinhibition). The paper in which we published these experiments is one that I am happy to remember because I feel that it illustrates so well the power of a properly designed experimental attack on a clearly formulated problem.

There is much truth in Eccles' self-congratulatory description of the above work but it is well to remember that he chose to ignore the criticism that the >1000 Hz extracellular

discharge of Renshaw cells, which his group and Renshaw (see below) had documented, was in fact an injury discharge. As a result, this argument invited much skepticism about the existence of Renshaw cells, despite the overall soundness of the reasoning of both Eccles and Renshaw. The skepticism was countered theoretically in a review by Willis (1971) and then anatomically by Jankowska and Lindstrom (1971). Doubts were further laid to rest by several of Jankowska's and Hultborn's 1971-73 articles, which included the existence of recurrent facilitation (Hultborn, 1971; Hultborn et al., 1971a,b,c) and the substantial spinal distribution of Renshaw cell effects (Jankowska and Smith, 1973). As a result, it quickly became well accepted that from the outset Eccles' conception of recurrent inhibition, shown in a model in their 1953 article, which was slightly improved upon visually in their 1954 article (Fig. 20), was indeed a remarkable advancement about recurrent inhibition.

Fig. 20 near here

In yet another collaboration with Fatt, and the initial addition of the Swedish neurophysiologist, Sven Landgren [1921-],[31] Lloyd's claim of direct monosynaptic inhibition in the spinal cord was laid to rest. Their first report was submitted on December 21, 1953 (Eccles, Fatt, and Landgren 1954a). It was followed by a sequence of detailed articles, (Eccles, Fatt, Landgren and Winsbury, 1954b**;** Eccles, Fatt and Landgren, 1956a,b), the last one involving a new research team (Araki, Eccles and Ito, 1960). This was a particularly important set of contributions, as reflected upon in Eccles (1975/1992; p. 173-174):

> “The other problem that Paul Fatt raised early in 1953 concerned the so-called direct inhibition which Lloyd (1946) had discovered and which was remarkable for the very brief time required for its central action. So short was this time that Lloyd had assumed it to be monosynaptic, just as with the excitation described above. In fact, it was produced by impulses in the same large afferent fibres from muscle that are excited by stretch. I too had accepted Lloyd's explanation, even though we had found in our earliest intracellular investigations at New Zealand that the central delay in producing the IPSP was just over 1 ms longer than the central delay for the monosynaptic EPSP. Paul Fatt questioned our explanation that the long latency was due to slow conduction time in collaterals of the

primary afferent fibres in the spinal cord and suggested as an alternative that it was due to the interpolation of an interneuron on the inhibitory pathway. There was just enough time to allow for this synaptic relay. Again, as soon as he raised the problem and had shown its relevance, it was easy for me to design experiments that would test it crucially. The experimental investigations again proved the value of clear formulation of problems, and, in collaboration with Sven Landgren of Sweden, Paul Fatt and I were able to show that the delay of the IPSP was due not to slow conduction but to an interneuronal relay (Eccles, Fatt, Landgren, 1954a), and we found cells in the intermediate nucleus of the spinal cord that had properties appropriate for the postulated interneurons.[32] ... It was later shown by Hultborn, Jankowska and Lindstrom (*1971a*) in Sweden that at least the majority of the inhibitory interneurons lie more ventrally than the interneuronal nucleus we had discovered."

The above two results led to another Eccles' hypothesis the testing of which continued for many years. Eccles (1975/1992; p. 174-176) proudly reflected on the formulation of this hypothesis:

"On the basis of these two discoveries of inhibitory cells, namely Renshaw cells and these inhibitory interneurons that were assumed to be on the so-called direct inhibitory pathways, we formulated the much wider generalization that all inhibitory action in the central nervous system is due to a special class of nerve cells whose sole function is inhibition. Hitherto it had been a general belief that the axons of a nerve cell could excite at some of their synapses and inhibit at others. This erroneous concept was drawn in a classical diagram by Sherrington (1906a, Figure 37) and also in a diagram I published in 1952 (Brock, Coombs and Eccles, 1952b). We now developed the hypothesis that the inhibitory interneuron is required in order to change over the transmitter substance that is being manufactured from the excitatory to the inhibitory substance. We had some other examples of inhibitory pathways in the spinal cord, and, following the scientific methods advocated by Karl Popper, we formulated a general concept for the cell constitution of the mammalian central nervous system, namely, that it was made up of two classes of neurons —excitatory neurons and inhibitory neurons (Eccles, Fatt and Landgren, 1954a, 1956a). This postulate is diagrammed in Figure 9.9 and has been rigorously tested by investigators in many parts of the world. On several occasions falsification of this hypothesis has been claimed, but in every case the claim has itself been shown to be unsound. In a recent survey of the central nervous system over thirty separate species of inhibitory neurons have been identified. In every case it appears that these inhibitory neurons have an inhibitory action at all of their synapses. No ambivalent neurons have been discovered in the mammalian central nervous system. However, several exceptions have now been found in invertebrate nervous systems."

The above three types of work initiated in 1953 are deserving of the summary figures presented in Figure 21. For this figure, we come forward to 1969, when a book was prepared based on Eccles' presentation of The Sherrington Lectures XI at the University of Liverpool. At that time Eccles had no further additions or revisions to make on the work that had begun so promisingly in 1953. In this book, there was no summary of his collaborative 1953-1955 work with Coombs and Fatt, but Fig. 21A is nonetheless reflective of that collaboration. In contrast Fig 21B is an accurate summary of his 1953-

1961 contribution to the Renshaw cell story and Fig. 21C is similarly accurate for his 1953-1961 contribution to refuting the concept of direct monosynaptic inhibition of motoneurons. Given the detailed figure legends provided above for Fig. 18, those for Fig. 21 seem quite brief, just as they were in Eccles' 1969 text.

Fig. 21 near here

The above work preceded knowledge on the role of calcium in any phase of the action potential. Indeed, Eccles had no experimental work on this possibility throughout his subsequent career using intracellular recording in mammalian preparations. However, it is certain that Eccles, like Hodgkin and Huxley, carefully followed the emerging literature on role of calcium currents in vertebrate neuronal discharge.

Calcium currents in invertebrate neurons may have first been considered a possibility in the short report of Oomura et al. (1961), which was publicized by Jung (1967) in another short report. It seems unlikely that Eccles, Hodgkin, and Huxley were initially aware of a subsequent Russian PhD thesis, one of the earliest studies on calcium currents in molluscan neurons (Doroshenko et al., 1973). For vertebrates, the first such work was in the early 1970s' work of Llinas and his colleagues on the Purkinje cells of alligators, followed by that on pigeons (for review, Llinas and Hess,1976; for a valuable review of the early literature on calcium currents, see Lukyanetz (1997)). More akin to our review, the ever-increasing recognition of the role of calcium currents in the resting potential, action potential, and neuronal propagation of mammalian motoneurons began with the first report of Schwindt and Crill (1977). A few years later, Eccles (1983) demonstrated his grasp of the rapidly developing calcium literature in his imaginative attempt to explain the Marr-Albus hypothesis for cerebellar learning (Marr, 1969; Albus, 1971). Here he proposed the existence of a calcium-calmodulin messenger system that could operate on the spine synapses of Purkinje cells.

5.3. Some details on Eccles' work on recurrent inhibition following that of Birdsey Renshaw

Here we provide some reflections on Eccles' contributions to recurrent inhibition following the pioneering work of Birdsey Renshaw (1911-1948).

5.3.1. Renshaw's impressive contributions and tragic ending

Renshaw was an extremely talented American neurophysiolgist, who died tragically at the age of only 37 years. At this stage, he was still developing his considerable experimental skills and it was too early to take advantage of intracellular recording from spinal motoneurons and interneurons as described later by the Eccles' group (1951-1952; motoneurons) and by Woodbury and Patton (1952; motoneurons and interneurons).

Unfortunately, little was written about Renshaw after his death. The Oregon Health & Sciences University has an Archive for him but it is sadly deficient. For example, it does not even contain his CV! The current archival librarians there would eagerly accept much more but it has not been forthcoming.

It is important that current and future neurophysiologists appreciate the quality of Renshaw's research, which was immediately obvious to his PhD mentor and collaborator, Alexander Forbes [1882-1965] (Fenn, 1965). Forbes' (1949) obituary about Renshaw appears below in its entirety:

> In the death of Dr. Birdsey Renshaw on November 23, 1948, science in general, and neurophysiology in particular suffered a major tragedy. It was, I believe, truly said of him that no one in this country offered greater promise of a productive career in this field. Dr. Renshaw's wife and two children had poliomyelitis early in November, and while caring for them he contracted the virus and died within three days of the onset of symptoms. I recall vividly my first meeting him, then a graduate student at Harvard, and hearing him tell of his experiments in growing embryonic nerve fibers in a culture medium. We planned then to explore the possibility of recording the action potential of single nerve fibers with micro-electrodes. His enterprise, eagerness and clear understanding convinced me at once that he was a colleague of rare promise. It was in February 1936 that he first came to the Harvard Medical School to join in our research program, then dealing with cerebral action potentials. His skill and zeal made themselves felt at once, and his brilliant experiments

soon became our major project, in which I was proud to be lending a hand as his assistant. From then until May 1938, when he passed his final examination for the Ph.D., he was working assiduously on the investigation of cerebral action potentials, mastering the techniques of recording with amplifier and cathode ray, and the delicate localization with micro-electrode and micromanipulator. Renshaw's subsequent work on the spinal cord at the Rockefeller Institute is so well known to readers of this Journal (*The Journal or Neurophysiology*) that further commendation is superfluous. Suffice it to say that when he presented his masterly paper on reflex inhibition analyzed with the aid of antidromic stimuli, at the meeting of the American Physiological Society in March 1946, most if not all of those present agreed that it was the "high spot" of the meeting for the neuro-physiologist. Soon after his appointment as Assistant Professor at Oberlin, the war brought a call to Government service in Washington, and this interrupted his research. Moving to Oregon after the war, he eagerly accepted the challenge of enlarging responsibilities, and two months before his death he wrote enthusiastically about the group in which he found himself. No portrait of Birdsey Renshaw is complete if it recounts only his scholarly achievements. Those who were privileged to know him will remember him as a gentleman in the best sense of the word, as a man of the most genuine devotion to service, as a good companion and as a loyal friend.

A distinguished senior American neuroanatomist/physiologist/zoologist at the University of Oregon, William Fitch Allen [1875-1951] (Dow, 1951) wrote an even shorter tribute. It was added to Proceedings of the American Society of Zoologists following their annual meeting in 1948 (Allen, 1949). This brief article also appears below in its entirety:

On the evening of November 20 as Dr. Renshaw was planning to give a dinner at his home in honor of a former teacher, he was stricken with poliomyelitis, which resulted in his death on November 23, 1948. Dr. Renshaw was born in Middletown, Connecticut, October 10, 1911. His father, Rex R. Renshaw, was a biochemist at New York University. Dr. Renshaw was educated at Harvard University, receiving his B.S. degree in 1933; MA 1935; and Ph.D., 1938. From 1938 to 1940 he was a National Research Council Fellow and a Fellow in The Rockefeller Institute for Medical Research. From 1940 to1943 he was a member of the Department of Physiology ((*an error; see below*) at Oberlin College being appointed Assistant Professor in 1941. From 1943 to 1946 he served as Technical Aide (Chemistry) in War Research at Columbia University, and from 1946 to the time of his death he was Associate Professor of Physiology at the University of Oregon Medical School. Dr. Renshaw was a member of the American Physiological Society, American Society of Zoologists, Society of Physiological Neurology, Sigma Xi, and Phi Beta Kappa. His first publication, 1935, with Crozier and Pincus was "Temperature characteristics of heart beat frequency in mice." His second, 1940, with Forbes and Morison was "Activity of

isocortex and hippocampus: Electrical studies with micro-electrodes." Between 1941 and the time of his death he published at least 6 papers on excitation and inhibition mechanisms in the spinal cord as studied with micro-electrodes and the oscilloscope. At the time of his death he had planned to investigate the following problems: (1) Porter phenomenon; this had reached the stage in which he could state that the cross connections for the phrenic nerve were fully as important for respiration as the direct connections. (2) If injury to the motor cell axon would alter the excitability of the cell. (3) Continuation of his studies on an electrical hypothesis for explanation of direct inhibition in the spinal cord. In speaking of his work, Dr. Renshaw would frequently remarked that he was only "a below the neck neurophysiologist," which really signified that he was at work on fundamental problems. Dr. Renshaw is survived by his wife, Janet, and two young sons, Tommy and Bruce Renshaw.

Finally, another valuable 1-page historical note is that of Sarikciogli and Utuk (2009). It includes, e.g., the Renshaw et al. (1938, 1940) citations mentioned in Forbes obituary on Renshaw. These are important because they document Renshaw's mastery in making extracellular microelectrode recordings of single neuron activity in the CNS as early as 1938.

The following epochs summarize Renshaw's brief academic career more accurately and extensively than in the above brief reports: 1933-1938, completion of B.S. (1933), M.A. (1935) and Ph.D (1938; mentor, Alexander Forbes) at Harvard University; 1938-1941, research fellow at the Rockefeller Institute of Medical Research; 1941-1943, Department of Zoology, Oberlin College, Ohio (recruited as an Assistant Professor on July 01, 1941 by Department Head Robert McEwen [1888-1967] (Anon., 1968); 1943-1946, On leave from Oberlin College as Technical Aide in Chemistry, War Research, Columbia University; 1946-1948, Associate Professor of Physiology, University of Oregon Medical School, Portland, Oregon. Renshaw was recruited to Oregon by the Head of Physiology, William Barton Youmans [1910-2006] (Anon., 2003). Fig. 22 shows

two photos of Renshaw, one well before joining the University of Oregon faculty, and one shortly before his death.

Fig. 22 near here

For our present purposes, Renshaw's 1938-1941 time at the Rockefeller Institute is the most relevant because this is when he undertook his three sets of experiments on recurrent inhibition, using cats and rabbits, which had been either decerebrated or lightly anesthetized with pentobarbital sodium. The work, which appeared in three sole-author papers, is now summarized in modern parlance:

Renshaw (1941)
By 1941 anatomical studies had demonstrated spinal motoneurons with axon collaterals that arose close to the soma of motoneurons and terminated in the vicinity of other ventral horn neurons. In this paper Renshaw asked whether impulses in motoneuron recurrent collaterals could influence the activity/excitability of nearby ventral horn neurons. Renshaw relied entirely on extracellular recordings from cut ventral roots as the ‘readout’ of motoneuron activity. Using this approach in decerebrated or lightly anesthetized cats he showed that activation of afferents in dorsal roots or dorsal columns could activate motoneurons and their subsequent discharge could be recorded as a potential in ventral roots. Renshaw hypothesized that he could test the function of motoneuron axon collaterals by stimulating cut ventral roots because ‘the impulse that sweeps over the motor axon must also invade its collaterals’. In a series of very clever experiments he showed that "reflex" motoneuron activity, initiated by stimulating dorsal roots or dorsal columns, was inhibited by antidromic stimulation of ventral roots. Importantly, the inhibitory effect was dependent on the timing of the antidromic stimulation relative to the reflex stimulation – being greatest when the antidromic volley entered the cord several milliseconds prior to reflex stimulation. Renshaw concluded that the axon collaterals produced this inhibition "either by altering the excitability of neurons to synaptic stimulation or by altering the stimuli delivered to post synaptic elements’ (his p.180). These were remarkable insights given that he undertook these experiments without a recording electrode in the spinal cord and without making any reference to what we now know as the 'Renshaw cell.' In the context of our present article he made another important conclusion, ‘the well know detonator (excitatory) process associated with the arrival of impulses at synapses is not the only mechanism by which another active neuron can affect other nerve cells’ (p.181). He was referring to important differences between inhibitory and excitatory synaptic transmission that would be revealed over the next three decades.

Renshaw (1942)
In these experiments Renshaw used techniques employed in the above paper, and additionally introduced an extracellular recording microelectrode (50 um dia. steel needle) into the ventral horn. The extracellular microelectrode provided much more detailed information on current flow in ventral horn neurons than ventral root recording methods. Using this new technique, he wanted to first determine whether spinal motoneurons responded in the same manner as cranial motoneurons (Lorente de No, 1939) when antidromically stimulated. Indeed, they did. A ‘three phase’ extracellular potential could be recorded in the ventral horn. This potential reflected: action potentials in motoneuron axons

as the stimulus travelled into the ventral horn (a sharp downward deflection), action potential invasion of the motoneuron soma and its dendrites (a much broader upward reflection), and finally a small and broad downward defecting potential. Importantly, the middle hump of the potential was the largest and its amplitude could be reduced (by >60%) by high frequency (300 Hz) ventral root stimulation. He went on to stimulate dorsal roots or afferents in muscle nerves, during antidromic motoneuron activation. Most notably, the depression in the middle hump of the extracellular potential could be potentiated or depressed by reflex stimulation (afferents in dorsal roots or muscle nerves) and the nature of the response depended on the 'population of sensory fibers occupied by the conditioning volley', p238). Renshaw's discussion points were framed around what he termed 'retrograde conduction in the motoneurons' (i.e., the middle hump). Because it could be modified he suggested the phenomena had a low 'factor of safety' compared to the 'conduction of impulses along the normal axon' (p.242). He made little comment on the nature of the neurons or circuits involved, but it is clear to the present-day neurophysiologist that he was referring to the capacity of CNS neurons to shape their excitability according to the types of synaptic inputs they receive.

Renshaw (1946b)

For these experiments Renshaw again used antidromic activation of ventral roots or deafferented muscle nerves (i.e., dorsal roots cut), and an extracellular recording microelectrode placed in the ventral horn. His experiments followed from observations made in his 1941 article, which showed discharging motoneurons could influence the excitation of other motoneurons. In his words, he was searching 'for evidences of neural activity in the cord subsequent to the arrival of a volley of impulses travelling centripetally in the axons of ventral roots' (p 191). In some cases, a single shock to a cut ventral root produced 'prolonged spike activity in the ventral horn' (p192). This spiking lasted for ~ 50 ms, occurred at very high frequencies (~ 1500 Hz), and depended critically on the location of the recording electrode – it had to be near the level of entry of the stimulated ventral root. In some experiments, careful positioning of the microelectrode allowed the isolation of action potentials from single neurons after the arrival of the antidromic volley. Again, the same high frequency discharge was observed following single shocks and it persisted for 30-50 ms. Renshaw concluded these observations 'permits the provisional assignment of the action potentials to repetitively discharging interneurons located in the ventral horn' (p195). We now know he was referring to the neuron type called the Renshaw cell – so named his honor by Eccles, Fatt & Koketsu in 1954. The authors speculated these neurons act as a 'significant correlating system with each interneuron being affected by the discharges of many motoneurons' (p. 201). Note that hey also made careful arguments against the high frequency discharge being due damage caused by the microelectrodes (i.e., injury discharge).

The above work was state-of-the-art for 1938-46, specifically for its use of the conditioning volley-test shock approach for inferring spinal connectivity between neurons (Fig. 23A) and recording from single neurons in the spinal cord using extracellular microelectrodes (Fig. 23B), which could follow firing rates as high as 1,500 Hz (Fig. 23C). Clearly, Renshaw was already a particularly promising neurophysiologist when he took his appointment at Oberlin College in 1941.

Fig. 23 near here

After Renshaw began work in Portland in 1948 he planned to return to the study of recurrent inhibition (recall Allen, 1949), but his four publications from Portland (2 abstracts; 2 articles published posthumously) were on a long-standing descending respiratory pathway issue (Porter, 1895), as co-authored with a medical student at the University of Oregon Medical School, Herbert E. Rosenbaum [1924-2014] (Anon., 1973a). These studies used extracellular recording. However, it seems likely that Renshaw would have quickly acquired intracellular recording expertize following its 1951-1952 introduction, and blazed further trails on recurrent inhibition. Sadly, all that remains for us is his masterful pioneering of the phenomenon of recurrent inhibition and the interneuron type that bears his name.

5.3.2. Some historical reflections on Eccles' contribution to the "Renshaw story."

The recurrent inhibition story had begun with work on the central effects of antidromic stimulation of motor nerves and their fibers. Prominent findings before the advent of extracellular microelectrode recording in the spinal cord include those of the pioneer of antidromic stimulation, François Magendie (Dawson, 1908; see also Magendie,1822), followed by others in several countries (reviewed in Eccles, 1955). Then, with the advent of such extracellular microelectodes (a century after Magendie's classic work), the findings of Lorente de Nó (1939), Renshaw (1941, 1942, 1946b), and Lloyd (1943) were on the forefront in noting antridromic effects in the spinal cord.

Eccles' work was prominent throughout the above two epochs. First at Oxford, Eccles and Hoff (1931) used extra-axonal recording from the soleus muscle nerve in the decerebrate cat to show that single (and double under selected circumstances) antidromic shocks could curtail rhythmic soleus nerve discharge (also observed and commented upon in Eccles and Sherrington, 1931c). This finding was followed by

Eccles' and Pritchard's (1937) abstract, which discussed the presumed antidromic responses in motoneurons, seen as spinal cord positive and negative waves recorded from the surface of the spinal cord in response to stimulation of the distal part of the L7 ventral root in the cat. (We assume the cats were in the decerebrate state). Eccles and Pritchard further presumed (p. 43) that “... each antidromic impulse sets up the negative and positive waves only in the soma of its own motoneuron." (Recall their presumption of electrical transmission quoted above).

Later in Dunedin Eccles used extracellular recording in single- and co-authored articles to focus largely on the possibility of spinal inhibitory synaptic transmission (recall Table 4),

The next major jump was the onset of intracellular recording in spinal motoneurons as discussed above. The initial Eccles' findings on the action of interneurons activated by antidromic motor axon discharge appeared in Eccles et al. (1953), as discussed above. Most appropriately, Eccles, Fatt and Koketsu (1954) coined the term "Renshaw cell" for these interneurons, and this term remains to this day.

5.4. Work on presynaptic inhibition following its discovery by Frank and Fuortes

Presynaptic inhibition is another type of inhibition, which is difficult to understand because it involves a mechanism that is very different to postsynaptic inhibition. In essence, presynaptic inhibition diminishes the magnitude of the depolarization in excitatory presynaptic terminals. This reduces the release of presynaptic transmitter substance into the synaptic cleft and diminishes the magnitude of the depolarization in the postsynaptic cell. Together, these two processes decrease the probability that the postsynaptic cell will reach firing threshold.

5.4.1. The pioneering contribution of Frank and Fuortes

The phenomenon of presynaptic inhibition was discovered by Karl Frank [1916-1993] and Michaelangelo Fourtes (1917-1977) at the NIH[34] and first reported by these close friends and successful collaborators (Fig. 24) in a widely read abstract (Frank and Fourtes, 1957). The abstract title introduced the term itself.

Fig. 24 near here

Fig. 25 is the very first figure of this phenomenon, this being in Frank (1959). The figure presented Frank's (and presumably Fuortes') initial view that presynaptic inhibition could result as described above or alternatively by what he termed "remote inhibition": i.e., an EPSP/IPSP interaction occurring so far out on the cell's dendrites that a microelectrode in the cell's soma could not detect the reduction in EPSP amplitude and change in its profile. However, later work from several laboratories largely discounted this possibility (for review, see, e.g., Burke and Rudomin, 1977, their pp. 923-927; also Willis, 2006, pp.192-193).

Fig. 25 near here

Burke (2006, sects. 4, 5,10), Willis (2006, pp. 192-193) and Stuart and Brownstone (2011, p. 83) provided some details on the careers of Frank and Fourtes, and their pioneering contributions to presynaptic inhibition. Interestingly, they did little further work on this phenomenon but rather focussed successfully on other aspects of motoneuron and interneuron neurophysiology.

5.4.2. *Contributions of Eccles' group to presynaptic inhibition in the spinal cord*

Eccles, who had high regard for Frank's neuroscience expertize, became immediately interested in pre-synaptic inhibition when he and his group read the 1957 abstract of Frank and Fuortes. The results were confirmed in Canberra the next day in a single

(apparently unpublished) experiment by R.M. Eccles [1929-] (Eccles' daughter, Rosamund) and Lundberg, who was then on the verge of completing a very successful 1956-1957 collaboration with Eccles and his group before returning to his home laboratory at the University of Lund (Lundberg, 1998; p. 3). Subsequently Lundberg made some important contributions to the early literature on presynaptic inhibition (e.g., Lundberg, 1964; Eide et al., 1968) and there were also valuable later contributions by Lundberg and others in his group (e.g., Lundberg, 1964; Jankowska et al. 1981; Brink et al., 1984).

Frank visited Eccles' Canberra department in 1958 and presented a seminar on presynaptic inhibition (Burke, 2006; p.181), which presumably included all the ideas in Frank (1959). Presumably, Eccles discussed with Frank one of his earlier findings (Brooks, Eccles, Malcolm, 1948) using extracellular recording techniques to infer that presynaptic spikes and excitatory synaptic potentials recorded near spinal motoneurons were reduced by prior inhibitory input. As emphasized by Curtis and Andersen (2001a; p. 447) "This reduction, considered at the time to be of little physiological significance, was attributed to depolarization of excitatory presynaptic fibers (*citing the above article*), later to be referred to as primary afferent depolarization, PAD."

Eccles took up the detailed study of presynaptic inhibition in late 1958 or early 1959, and this continued for a few years (see below). The work had immediate impact as emphasized by Pablo Rudomin [1934-] (for career, see Rudomin, 2013), who has now systematically studied presynaptic inhibition for over 50 years, i.e., Rudomin (1965, 1967a,b) to Contreras-Hernández et al. (2015) and Martin et al. (2015), and advanced the concept and mode of its investigation to a remarkable degree. In one of his several erudite reviews on the topic Rudomin (2009; p. 139) summarized succinctly the key precedents to the concept of presynaptic inhibition, and the contribution of Eccles' group in advancing interest in this ever-evolving topic:

Hagbarth and Kerr (1954) reported that synaptic afferent transmission in the cat spinal cord could be influenced by tonic descending pathways from the bulbar and midbrain reticular formation and the cerebral cortex at the level of the first synapse in the spinal cord (see also Hernández Peon and Hagbarth, 1955). Almost at the same time, Howland et al. (1955) indicated that electrical interactions between afferents could produce conduction block and suggested that some types of inhibition could block afferent nerve impulses before they reached the region of the cells. Shortly after, Frank and Fuortes (1957) showed that Ia EPSPs recorded in motoneurons could be depressed by conditioning volleys to muscle nerves without significant changes in motoneuron properties, and ascribed this depression to presynaptic inhibition. Although later on Frank (1959) proposed remote dendritic inhibition as an alternative mechanism to presynaptic inhibition, the possible existence of extrinsic mechanisms affecting transmitter release of sensory fibers (i.e., of presynaptic inhibition) was a conceptual breakthrough, but it was not until Dudel and Kuffler (1961) when a direct demonstration of presynaptic inhibitory mechanisms possibly operating via a chemical synapse became available. In that same year Eccles and collaborators presented their studies on presynaptic inhibition in the cat spinal cord (*citing Eccles 1961a*). They proposed that the Ia EPSP depression assumed to be due to presynaptic inhibition resulted from *depolarization* of the Ia afferent fibers that decreased *"the size and number of Ia afferent impulses"* (*citing Eccles et al.,1961b*). Later on, they suggested that this presynaptic depolarization (primary afferent depolarization or PAD) was due to the activation of GABAergic interneurons making axo-axonic synapses with the intraspinal terminals of the sensory fibers (*citing Eccles et al., 1963*).

The first report using intra-axonal recordings to register PAD were those of Eccles and Krnjevic (1959a,b). However, the abbreviation PAD was not coined in an Eccles' publication until Eccles, Magni and Willis (1962). This study was a fitting extension of the earlier extracellular recording report of Brooks, Eccles, and Malcolm (1948), as mentioned above. Presumably the potential role of PAD in creating presynaptic inhibition was on Eccles' mind throughout the Eccles and Krnjevic (1959) study.

Eccles (1959a) was a review on excitatory and inhibitory synaptic action. It followed a 1948 symposium in New York City sponsored by the New York Academy of Sciences. Eccles' August 1959 chapter barely mentioned his early research on presynaptic inhibition. The chapter included on its pages 256-257 " ... an exceptional situation arises with the depression of the EPSP by remote inhibitory action (Frank and Fuortes, 1957; R.M. Eccles and A. Lundberg, personal communication (*i.e., see the above mention of their single experiment*). Apparently, this inhibitory action is due to depression of the synaptic excitatory action and is not exerted on the postsynaptic excitatory response; that is, it is exerted further upstream on the excitatory pathway than in all the other

inhibitory actions we have been considering." Similarly, in another book chapter in a widely read publication, the first Handbook of the American Physiological Society, Eccles (1959b) wrote (pp. 68-69):

> It may be noted that conditioning by large afferent volleys causes a fairly long depression in the size of the primary afferent volley and hence depresses its excitatory action (*citing Brooks, Eccles, Malcolm, 1948; Howland et al., 1955; Frank and Fuortes, 1957*). The effect has been attributed to the dorsal root reflex and the dorsal root potential set up by the powerful conditioning volley (*again citing Brooks, Eccles and Malcolm, 1948*) and probably is of little significance with more physiological types of afferent input. Apart from this effect (*i.e., presynaptic inhibition*), it has been shown that inhibitory actions on motoneurons are explained satisfactorily by the transient increase which is produced in their membrane potentials and which has been designated the inhibitory postsynaptic potential IPSP (*citing Brock, Coombs, and Eccles, 1952b; Coombs, Eccles, and Fatt, 1955b,d*).

A year later Eccles' group had completed sufficient work on presynaptic inhibition for him to be more impressed with its potential physiological role and to present internationally his thoughts and some of his group's figures on the relationship between PAD and presynaptic inhibition. These thoughts appeared in his 1960 symposium presentation in the USA, and were more-or-less reiterated in a subsequent 1960 Ferrier Lecture in England. These talks were incorporated into two 1961 publications, a book chapter and an article, respectively (Eccles, 1961a,b). In 1960 Eccles also had two published abstracts of experimentally derived data with no figures (Eccles, Kozak, Magni (1960) and Eccles, Eccles, Magni (1960).

In all, Eccles and his Canberra group advanced understanding of presynaptic inhibition in approximately 40 articles, book chapters, and reviews written between 1959 and 1964.[33] However, only Eccles' 1960 presentations are emphasized here because they showed that from the outset he and his collaborators grasped the relationship between presynaptic inhibition and PAD. They also recognized immediately the significance for advancing understanding of presynaptic inhibition of the findings of Howland et al. (1955) and Hagiwara and Tasaki (1958), if not Dudel and Kuffler (1961). For their historical significance, Figs. 26 and 27 are shown. These figures come from two publications Eccles (1961a,b) that followed the two 1960 presentations.

Figs. 26 and 27 near here.

In 1966 Eccles presented the ninth series of biennial Sherrington lectures at the University of Liverpool. His two lectures, which were entitled "The Inhibitory Pathways of the Central Nervous System", were published in a book in 1969 with the same title. In the book's preface Eccles emphasized that the 135-page book was "greatly expanded from the original two lectures." By the time Eccles submitted his material for the book he and his collaborators had written a substantial number of articles on the cellular neurophysiology of several supraspinal structures. Interestingly, and to some extent puzzlingly, he chose not to address presynaptic inhibition in the subject matter of this book for the reason provided below (Eccles, 1969; pp. 14-15):

> It should be mentioned that, besides the postsynaptic inhibitory action diagrammed in Figures 4 and 5, there is another type of inhibitory synapse operating by a quite different mechanism. Instead of counteracting the postsynaptic depolarization (EPSP) produced by excitatory synapses, this other inhibitory action is effected by the specific synaptic depolarization of the excitatory presynaptic terminals (Eccles1964b; also, *1964b in this review*). The depolarization is produced by axo-axonic synapses, and as a consequence there is a reduction in the output of excitatory transmitter as revealed by a depression of the EPSP. It is postulated that the pathway of this presynaptic inhibition, as it is called, is polysynaptic and that the ootaxon synapses are formed by a specific group of inter-neurons. Interneurons with responses appropriate for the mediators of this presynaptic inhibition have been recognized in the spinal cord (Eccles, Kostyuk and Schmidt 1962), the cuneate nucleus (Andersen, Brooks, Eccles, and Yokota 1964b) and in the thalamus (Andersen, Brooks, Eccles and Sears 1964a). There is pharmacological evidence that these presynaptic inhibitory synapses are mediated by a transmitter different from those mediating postsynaptic excitatory and inhibitory synaptic action (Eccles, Schmidt and Willis 1963b (*1963 in this review*); Schmidt 1963), and, therefore, it is likely that specific interneurons and synaptic mechanisms are involved; hence the presynaptic inhibitory pathways would be distinct from the postsynaptic inhibitory pathways. However, there is as yet very little evidence on these pathways, which in their action are largely restricted to the synaptic terminals of primary afferent fibres, though a small presynaptic inhibitory action has been detected on the afferent pathways relaying in the thalamus (Andersen, Brooks, Eccles and Sears, 1964) and in the lateral geniculate body (Angel, Magni and Strata 1965a,b; Iwama, Sakakura and Kasamatsu 1965). In contrast there is now a wealth of evidence on the postsynaptic inhibitory pathways that alone seem to be responsible for inhibition at the highest levels of the nervous system. The remainder of these lectures will, therefore, be devoted to postsynaptic inhibition.

The above small-print section may be considered Eccles' last experimental consideration of presynaptic inhibition albeit he would reflect on his previous work in subsequent reviews.

5.4.3. Emerging perceptions about presynaptic inhibition

It goes without saying that concepts of presynaptic inhibition in the spinal cord have advanced considerably since Eccles' contributions in the 1960s, and these concepts are continuing to expand and become more complex. For the purposes of this review with its focus on central inhibition, it is sufficient to comment on only four recent reports on spinal presynaptic inhibition, and cite but three others.

Rudomin (2009). The advances emphasized in this review, which is Rudomin's most recent on spinal presynaptic inhibition, included (1) differential GABAa control of the synaptic efficacy of muscle, cutaneous and articular afferents, (2) some of the problems encountered when trying to identify interneurons mediating the GABAergic depolarization of the PAD of muscle afferents, (3) the influence of the spontaneous activity of discrete sets of dorsal horn neurons on the pathways mediating the PAD of muscle and cutaneous afferents (see below), and (4) unmasking the cutaneous-evoked responses and associated changes in the tonic PAD that follows the acute and chronic section of cutaneous nerves. Rudomin's concluding comments itemized several problems for future study. These concerned the functional role of presynaptic inhibition and PAD during natural movements, and the nature and role of sensory processing in creating a higher coherence between cortically programmed and spinally executed movements.

Contreras-Hernández, Chávez, and Rudomin (2015). This article examined in anesthetized cats the relationship between ongoing fluctuations of spinal cord dorsal horn neuronal activity (cord dorsal root potentials; CDPs) and the activation of various inhibitory reflex pathways. They found that high levels of synchronization between a technically limited number of CDPs occurred in association with the preferential activation of some of these spinal pathways. This led to PAD and presynaptic inhibition relative to activation of pathways mediating in particular Ib postsynaptic inhibition. It was

suggested that changes in the synchronization of CDPs influenced the interaction of sensory inputs with spinal reflex pathways subserving different functional tasks.

Martin et al. (2015). The seven co-authors of this interdisciplinary article included Contreras-Hernández and Rudomin. Focus was on using a machine learning methodology to explore the functional organization of a far larger number of CDPs in response to nociceptive stimulation, which can elicit presynaptic inhibition. The initial preliminary results showed that the new technique did indeed uncover several more types of CDP than reported by Contreras-Hernández et al. (2015). Prophetically, this suggested to Rudomin (personal communication) that "presynaptic inhibition is not only a mechanism for reducing transmitter release but it is also a mechanism for changing the level of neuronal synchronization in sensory pathways and thereby altering their information content."

Fink et al. 2014. This seven author interdisciplinary article is from the laboratory of Tom Jessell [1951-] (Anon., 2015). It is the first to capitalize on a now widely-used molecular biology approach to identify the presumptive spinal neurons involved in the generation of presynaptic inhibition, delete them using genetic ablation, and then test for possible deficits in motor control. The initial results are of historical importance and potential significance. The authors proposed (p. 43) that presynaptic inhibition provides " ... a genetically hardwired gain control system crucial for the smooth execution of movement:" Two other citations in the Fink article are deserving of comment; Seki et al. (2003) and Azim et al. (2014a,b). (See also Hughes et al., 2012).

Recently, an interesting combined presentation was made by two graduate students in the University of Alberta laboratory of David Bennett. Li and Black (2016) presented evidence on the excitatory role that PAD can play under select conditions in the remote *activation* rather than inhibition of spinal motoneurons. Their evidence

seems in keeping with the multi-faceted role of PAD emphasized in Rudomin's more recent articles on presynaptic inhibition.

In summary, the more recent work described above shows the study of presynaptic inhibition is still at the forefront of contemporary spinal cord neuroscience.

5.5. Work of Eccles' group on inhibitory interneurons in the brain

Despite the lack of detail on presynaptic inhibition, Eccles (1969) is a very useful summary of his foray and thoughts on spinal and supraspinal postsynaptic inhibition from the early 1950s to1967: i.e., beginning with Brock et al. (1952) at the University of Otago, and extending into research undertaken at the ANU in 1952-1966, and the first of his two years at the AMA Institute of Biomedical Research. We have reviewed his spinal work above. His work on supraspinal postsynaptic inhibition continued throughout his second year at the AMA Institute-Chicago and at SUNY-Buffalo until his obligatory retirement there in 1975, with his last experimental article published in 1977. Eccles wrote nostalgically about his work on supraspinal neurons as follows (Eccles, 1976; pp. 13-14):

> The change occurred gradually. At first there were investigations led by Olov Oscarsson on the cells of origin of the spinocerebellar tracts. Cells of origin of another ascending pathway were also studied. Meanwhile Tom Sears was carrying out his refined studies on the control of respiratory movements by employing intracellular recording from motoneurons supplying intercostal muscles. At this time also stimulation of the motor cortex was shown to produce presynaptic inhibition in the spinal cord. However the decisive change occurred with studies on neurons of the brain stem under the leadership of Per Andersen. Firstly, there was synaptic transmission in the cuneate nucleus with ascending actions from the spinal cord and descending from the cerebral cortex. The neuronal machinery involved in these actions was studied in detail. Next came the ventrobasal nucleus of the thalamus on the projection line to the cerebral cortex from the cuneate nucleus. There was study of the neuronal machinery and the role of inhibition in setting the rhythmic activity of the thalamocortical circuits, a theme that Andersen was later to develop so well. The most important study was on the hippocampus, using the new techniques of intracellular recording and field potential analysis. Andersen already had extensive experience on the hippocampus, so good progress was assured. The most interesting discovery was that the basket cells of the hippocampus gave a very large and prolonged inhibitory postsynaptic potential of the hippocampal pyramids. It had been known since the time of Ramón y Cajal that the basket cells formed a dense terminal plexus (or basket) around the somata of pyramidal cells, which he believed to exert an intense excitatory action. The combination of depth profile and intracellular studies convincingly demonstrated that the action was an intense inhibition. So for the first time an inhibitory cell with its synaptic terminals had been identified histologically. At that time Renshaw cells had not yet been recognized histologically. Having accomplished that identification so satisfactorily, I asked: where else

> are there basket cells? The answer being the cerebellum, we (Andersen, Voorhoeve, and myself) immediately in early 1963 changed our attention to the cerebellum. It was a more complex study than the hippocampus; nevertheless the clear answer came that the basket cells there are also inhibitory, this again being shown by depth profile and intracellular recording. Per Andersen had to return to Norway, so we made a pact. He was to have the hippocampus for his field, and I and my associates, the cerebellum. I regret to report that in 1975 I broke the pact by again working on the hippocampus in a final electrophysiological study on the ionic mechanism of postsynaptic inhibition. It was an appropriate and very successful termination of my experimental life with my colleagues Allen, Nicoll, Oshima, and Rubia (*see Allen et al., 1977*).

There is no doubt that Eccles' work with Andersen was important scientifically. It also had a substantial effect on Andersen's subsequent career and his sustained appreciation for Eccles' postdoctoral mentoring (see Andersen, 2006). However, in the present authors' opinion, Eccles' work on the cerebellum was the most significant of his forays outside the spinal cord. About the beginning of this period he reflected (again Eccles, 1977; p.14) as follows.

> The beautifully organized structural pattern of the cerebellum was a great opportunity for an analytical study of the mode of operation of the two input lines, by mossy fibers and by climbing fibers, and of the five species of neurons. Of particular importance was Szentagothai's evidence for the origin of climbing fibers from the inferior olive. Remarkably clean results were obtained by stimulating through an electrode inserted into the inferior olive. The mossy fiber input gave a more complex picture, but, by utilizing various sites of stimulating together with depth profile recording and intracellular recording from Purkinje cells, a satisfactory picture emerged that enabled us to make models of the mode of operation of the neuronal machinery in the cerebellar cortex. With but minor variations this model still holds, so the comprehensive book published in 1967 with Ito and Szentagothai, "The Cerebellum as a Neuronal Machine**,"** still does not need extensive revision. This analysis of the neuronal operation in the cerebellum was greatly aided by a principle that I had proposed as early as 1954: that all the synapses formed by a neuron in the mammalian central nervous system have not only the same transmitter (Dale's Principle), but also the same action, either excitatory or inhibitory, there being no ambivalent neurons. So we could generalize from our analytical experiments and propose models of circuits that displayed the essential features of operation in all the complex interactions of the neuronal machinery.

Eccles certainly blazed a new trail between1963 and1967 when he and his colleagues in Canberra used intracellular and extracellular stimulating and recording techniques to uncover many of the main features of the circuitry of the cerebellar cortex, as shown in Fig. 28.

Fig. 28 near here

This new trail, which included Eccles' 1967 monograph, "The Cerebellum as a Neuronal Machine" for which he invited Ito and Janos Szentágothai [1912-1994] (Pasik

and Pasik, 1995) to be his co-authors, was certainly impactful. It was widely read because its wiring diagrams were postulated to be fundamental to the machine-like function of the cerebellum. This emphasis encouraged other neuroscientists to test the validity of the wiring diagrams. It also encouraged theoreticians to develop models of cerebellar function that might explain the machine function of the structure.

Making a serious advance in our understanding of cerebellar circuitry was not Eccles' only major contribution to advancing understanding of this intriguing brain structure. Rather, his postdoctoral mentoring of Ito in the rigors of intracellular recording in spinal motoneurons in surgically reduced cat preparations had greatly expanded this talented Japanese neuroscientist's experimental techniques such that his initial cerebellar research had instant impact. Furthermore, by inviting Ito to coauthor the above book on the cerebellum opened new doors for Ito's progress in this field of endeavor.

Ito worked with Eccles in Canberra in 1959-1962 during which time they published several papers on cellular neurophysiology. Apparently, Ito displayed much native talent in this work because in subsequent years Eccles emphasized many times to D.G.S that he felt Ito had a natural talent for demanding neuroscience research from the cellular to the behavioral level of enquiry.

Ito (1998; pp.173-174) wrote of his Canberra experience as follows:

> John Eccles' department attracted about seventy researchers from abroad. Its alumni association list includes the names of numerous eminent individuals presently considered leaders in the world of neuroscience. Among these, Per Andersen, Tatsunosuke Araki, Platon Kostyuk, Olov Oscarsson, Tomokazu Oshima, John Phillis, Tom Sears, Rod Westerman, and Bill Willis were my contemporaries. It seems to me to have been one of those rare occasions in which a single scholar attracts a large number of young talents who then became the leaders of the next generation. During the first year of my stay I had a precious opportunity to work as part of a team with John Eccles and his daughter, Rose. We studied the ionic permeability of cat spinal motoneuron membranes by injecting two ion species in combination through double-barrelled microelectrodes, each barrel filled with a different solution (*see Eccles, Eccles, Ito, 1964a,b*). I learned the energetic and organized ways to conduct cat experiments. In addition, during the English-style tea time - often held at midnight during a break from an experiment - John Eccles often talked about his days in Oxford, and especially about Charles Sherrington. Apparently, John Eccles was taking Sherrington as his role model. Eccles, born in 1903, used to ask how he could stop working when Sherrington had started to fully work only after the age of sixty. During the second year of my stay, I continued ionic permeability studies using electrophoretic injection

> techniques (Araki et al., 1960**;** Ito et al., 1962). We tested 34 different anion species and found a sharp distinction between permeant and nonpermeant ions through inhibitory subsynaptic membranes, proof of the sieve-membrane hypothesis. During the third year, I recognized a peculiar multiple exponential behavior of motoneuron membrane for current steps, and devoted a considerable amount of time to analyzing it (Ito and Oshima, 1965). The 3 years passed quickly and fruitfully and, in 1962 I decided to return home.

Ito returned to his position at the University of Tokyo in early 1963 and subsequently worked almost exclusively on cerebellar neurobiology. He joined Eccles on two major cerebellum projects, which he explained as follows (Ito, 1998; pp.176-177):

> When I started to work on Deiter's neurons in Tokyo (*in late 1963*) I was not aware that John Eccles had moved his focus to the cerebellum after I had left Canberra. He came to Tokyo in 1965, on the occasion of the 26th IUPS (International Union of Physiological Sciences) Congress, and we organized an IBRO (International Brain Research Organization) - sponsored symposium on the neuronal mechanism of the cerebellum. It was a fantastic meeting, attended by internationally renowned authorities on neuroscience such as Ragnar Granit, John Szentagothai, Robert Dow, Charles Phillips, Francis Schmitt, John Brookhart, Vernon Brooks, and a number of young researchers, including Kris Krnjevic, Per Andersen, Jan Jansen, and Rodolfo Llinas. Our studies in Tokyo were well received, and no one doubted that Purkinje cells are inhibitory. The 1965 meeting on the cerebellum brought me two big rewards. One was that John Eccles asked me to write a monograph on the cerebellum with him and John Szentagothai, which was published by Springer Verlag in 1967 as "The Cerebellum as a Neuronal Machine." The other reward was invitations to participate in three meetings in 1966: a 1-week workshop on the cerebellum held in January in a suburb of Boston as part of the Neuroscience Research Program (NRP), a second 4-week NRP workshop held that summer in Boulder, Colorado (both organized by Francis Schmitt), and the Nobel symposium on structure and function of inhibitory neuronal mechanisms organized by Curt von Euler, in Stockholm. To attend these meetings and visit many laboratories around the world, I left home for six months. John Eccles brought to Boston a number of chapters, which he had written for the monograph. As we discussed the structure of the book, I saw his inspiration emerge and grow. These discussions were some of the most vivid scenes in which I recall this fabulous hero of neuroscience, who passed away in May 1997 at the age of 94.

Ito's contribution to present-day understanding of the cerebellum includes >170 refereed articles between 1964 and the present. This work was summarized in two monogaphs he wrote after the one with Eccles and Szentágothai. In their chronological order Ito's monographs addressed largely (1) the cerebellum's role of long-term depression and its control of the vestibular-ocular reflex (Ito, 1984), which suggested to Ito that the cerebellum was capable of learning and that the cerebellum could perform particularly complex computations, as shown a few years later (for review see Kawato,

1999), and (2) the book planned to be his final one on the cerebellum (Ito, 2011) in the preface of which (pp. x-xi) he provided a cogent and thought-provoking summary of his thoughts on the cerebellum up to 2011:

> This 2011 monograph discusses advances made since 1964 in the overall study of neuronal circuits and the adaptive and model-based control of movement. It also presents new developments concerning the involvement of the cerebellum in motor actions and cognitive functions. The subtitle of the book, "Brain for an Implicit Self," reflects my current view of the cerebellum. Its role in the adaptive control of movement is performed unconsciously. Even though voluntary movements, such as those needed to ski, ice skate, or play a piano, and so on, are performed under conscious awareness (or at least some components of the movements), there is no such awareness when these movements become more refined due to their practice. A similar situation prevails for our thoughts. When we think about some topic repeatedly, the thought becomes more and more implicit: that is, it requires less and less conscious effort, as in intuition. This suggests that the cerebellum aids the self in both movement and thought, but covertly, by use of its internal models. The question of just how neuronal circuits of the cerebellum can accomplish such an all-encompassing role will be a major challenge in the coming decades.

Clearly, and much to Eccles' satisfaction, Ito advanced the cellular and molecular understanding of the cerebellum to a remarkable degree, and combined this progress with the use of behavioral techniques to uncover cognitive aspects of the still far-from-resolved issue of the overall functions of this intriguing structure. His philosophical approach to this research is shown in Fig. 29.

Fig. 29 near here

5.6. Eccles' reflections on central inhibition after conclusion of his experimental work

5.6.1. Overview of 1975-1999 contributions

Between 1975 while concluding his sojourn at SUNY-Buffalo until ill health impaired him in Contra in late 1993 the quantity and quality of Eccles' non-experimental contributions, which were written in largely English, German, and Italian, were quite remarkable, albeit with very little of it addressing central inhibition. To appreciate this, we added to the 134 such relatively substantial publications (including one posthumous publication) listed in Curtis and Andersen (2001; their pp. 468-473) the additional largely short 79 publications listed in Eccles' own Archives and Private Library, which have been housed

since 2010 in the Institute of the History of Medicine, Heinrich-Heine-University, Düsseldorf, GER (see Freund et al., 2011). (Short articles, like prefaces in symposium volumes, are included because they show Eccles' mindset and favored areas of emphasis until the last of his writings). We collated idiosyncratically this total of 213 publications into 8 topics. They are organized here according to topic and their number of published articles: mind-brain viewpoints and issues (65 contributions); neuroscience-oriented and political philosophical viewpoints (62); fundamental and clinical neuroscience (49); autobiographies and other largely neuroscience reflections (16); neural control of movement (9), biosketches and obituaries (7); book author or co-author (4); an editor or co-editor of two books and one symposium volume (3). In analyzing this material we were not surprised that the first two topics topped the list, given Eccles' interest in these subjects since his medical school days (see 6.2.3.). But it was surprising to learn that the third topic of emphasis was clinical and basic neuroscience; a feat of intellectual discipline that we find remarkable for this ever-active neuroscientist. He wrote science-centered articles in both 1990 and 1994. Eccles (1990), which appeared in December 1990 (date of submission not known), was a reflective historical review on synapses. For this he reviewed relevant articles up to 1989, including key ones on inhibition. Eccles (1994a) was a thoughtful article on the human experience of pain. It followed a presentation he made at an international symposium held on April 23-28 in Geneva, Switzerland, with his subsequent article including review of purely neuroscience articles up to 1990. Surprisingly, it made no mention of inhibition. In addition, some neuroscientists (and many psychologists and philosophers) would argue that in his collaboration on potential quantum processes in the brain, with the German theoretical physicist Friedrich Beck [1927-2008] (Anon., 2016), Beck and Eccles (1992) was a demanding intellectual feat for an article submitted by Eccles on July 21 that year. In Beck and Eccles (1998) Beck stated "This article was prepared by, and reviews work of, both authors on quantum aspects of brain activity. Since Sir John Eccles passed away during

preparation, responsibility for text is due to first author. Friedrich Beck (Institut fur Kemphysik, Technical University Darmstadt)." This suggests that even while his health was failing in 1994-1997 Eccles attempted to keep working with Beck on quantum mechanics.

5.6.2. Aside on 1975-1984 motor control articles

Eccles first article with Creed in 1928 addressed the effect of central inhibition on the spinal territory of motor units. This article was followed by many more on the role of central inhibition in the supraspinal and spinal control of movement and the motoneuron's role in the peripheral neuromuscular system. For these reasons it seemed appropriate for us to look for work on central inhibition in eight of the nine articles Eccles published on this topic between 1975 and 1986, after cessation of the experimental phase of his career. They appear below listed chronologically in the year of their publication. (Eccles (1984) was not available to us). It surprised us that central inhibition was barely mentioned in these articles. Below we provide a potential explanation as it may give insight into his mindset after his experimental career had ended.

Eccles, 1975. Eccles was originally asked by the organizers of an interdisciplinary symposium on creativity in science and medicine to give examples of creativity in biology and medicine. He chose, however (p. 61) " ... to illustrate creativity in the action of scientific problems related to the control of movement." The 23-page chapter that followed in the symposium volume is an insight into how Eccles preferred to think about neuroscience for the remainder of his life. He proposed roles in the control of movement for 7 hierarchical levels, beginning with (1) the motor unit and ascending rostrally to (2) simple spinal reflexes, (3) long spinal and supraspinal circuits, (4) the cerebellum for posture and automatic movements, including the only place where inhibition was considered for selected connections between neurons, (5) the motor cortex and pars intermedia of the cerebellum, (6) cerebrally initiated movements with separate consideration of (6A) the cerebrum's

association cortex interacting with the cerebellar hemispheres, (6B) the basal ganglia, and (6C) various circuits contributing to cerebro-cerebellar interactions (6C) and finally (7) freely willed actions as revealed in neurophysiological investigations and in philosophical thinking about free will. Eccles argued somewhat vaguely (p. 84) that " ... We have therefore examples of creative imagination exhibited in a complex structure of integration and organisation." The article is written clearly, albeit his discussion of levels 1 and 2 demonstrated that he was not keeping up with the then-current literature in these areas. Rather, his main interest was in level 7 and even here his main interest was in the philosophical rather than neurophysiological aspects of free will. He conceded (p. 84), however, that " ... It must be recognised that the story as here told is still at a rather primitive level."

Eccles, 1977b. An attempt was made to correlate fundamental advances in cerebellar neurobiology based largely on 1950s-1970s work in the cat and non-human primates with earlier clinically-based views and findings of the British neurologist, Gordon Holmes [1876-1965] (Walshe, 1966). The latter's views on cerebellar function were influenced strongly by his collection of the brains of deceased British WWI soldiers. The collection consisted of brains with 80 localized gunshot wounds, plus 20 cases of localized cerebellar lesions in patients whose deficits were examined thoroughly. In Holmes' (1939) he related his clinical findings to fundamental science research. (Holmes is perhaps best known for emphasizing three main deficits attributed to cerebellar malfunction: hypotonia, asthenia and muscle fatigue, and abnormalities in the rate, regularity and force of voluntary movement). In Eccles' article inhibition is only mentioned twice and with little emphasis. He concluded (p. 177) " I am sure that Holmes would have felt that we have not advanced very far beyond the explanations he was able to develop before the analytical successes of recent times. The understanding of cerebellar function can be attempted only when there have been synthetic studies to match the analytical." It seems that while Eccles was justifiably proud of the electrophysiological advances made by

his and other groups on the cerebellar circuitry of experimental animals (mainly cat and non-human primates) it frustrated him that these advances still had so little clinical relevance.

Eccles, 1981a. The physiology of motor control was considered again in hierarchical terms involving (1) a paragraph on the motor unit and (2) slightly more information on spinal reflex mechanisms (2 paragraphs), including mention of recurrent and presynaptic inhibition but no mention of the action of low-threshold Golgi tendon organs. The subsequent hierarchical levels were again presented far more expansively, but with no mention of inhibition! They included (3) brain stem mechanisms; (4) cerebellar vermis and cerebrocerebellar controls, (5) via the pars intermedia, and (6) via the cerebellar hemispheres and the basal ganglia.

Eccles, 1981c. Citing only seven references, the hypothesis was proposed (p. 24) that " ... in all voluntary movements the initial neural event is exclusively in the supplementary motor area (SMA) of both hemispheres." This idea was based largely on the findings of Deeke and Kornhuber (1978), Brinkman and Porter (1979) and Roland et al. (1980). Each of these studies used a different technique to register neural activity and emphasized that the earliest neural events prior to different types of voluntary movement occurred in the SMA. At the outset, Eccles stated (p. 24) "I am not going to expatiate on the definition of voluntary movement ... Recently Richard Jung (1980) has written very wisely on this theme." In this scholarly article Jung [1911-1986] (Creutzfeldt, 1986), a neurologist with a strong basic science bent, did not address the hypothesis proposed by Eccles. It would have been valuable if his SMA hypothesis had been contrasted to the concept of motor equivalence, i.e., the multiple ways humans and animals can perform a movement to achieve the same goal. This was first described in the classical 1933 review of the American psychologist, Karl Lashley [1890-1958] (Bartlett, 1960), with the concept further refined in the1947/1967 books of the Russian physiologist and mathematically-gifted movement neuroscientist, Nikolai Bernstein [1896-1966] (Gurfinkel and Cordo, 1988).

Motor equivalence is not necessarily at odds with the SMA hypothesis, a point that was neglected by Eccles.

Eccles, 1982c,d. As expansions of Eccles (1981c), with 42 and 45 citations respectively vs. seven in the earlier article, these two clearly written articles were near-identical in their treatment of the SMA. In the 1982d article, Eccles reflected on Sherrington's much earlier use of the term "liaison" in describing a brain site where there was interaction between the abstract concept of "mind" with investigable neural ("brain") activity. Eccles used Sherrington's earlier views to support his contention that the SMA was the liaison for the initiation of a voluntary movement. The problem remains, of course, to determine the neural event(s) that drive the SMA's essentially efferent contribution to voluntary movement, i.e., to determine the still unknown neurobiology of intention and how it interacts with known brain structures and cellular mechanisms. Eccles (1982d) proposed (p. 169) " ... in order to bring about the desired movement the intention has to exert a specific patterned influence (*on selected SMA neurons*) required for the desired movement that must differ for each of the diverse motor programs (the subroutines) require for the desired movement."

Eccles, 1986. In this article, three distinct phenomena were included under the rubric of motor learning. The first was automatic movement, in which the whole process was considered to be subconscious from the beginning, as in a corrective vestibulo-ocular reflex. Inhibition was mentioned vaguely as explaining insufficient opening of calcium channels between climbing fibers and Purkinje cell dendrites, which were considered essential for this reflex. Second was motor skills performed by animals with an emphasis on neuronal responses of the cerebrum and cerebellum, where disinhibition of mossy fiber excitation of Purkinje cells was thought to play a role in monkey hand movements. For an animal making adjustments to unexpected perturbations like walking on uneven ground, disinhibition was also mentioned as a component of the cerebro-cerebellar-cerebrum pathway. It seems unlikely that Eccles read much in the 1980s on the role of

spinal mechanisms for coping with unexpected perturbations (e.g., Hasan and Stuart,1988). Third was human skills again with an emphasis on the automatization of skills like walking, swimming, cycling, and skiing and again emphasizing the interactive role of the cerebrum and the cerebellum. There was no mention of inhibition or disinhibition. Eccles began this article with the apology (p. 15) that " ... because of inadequate knowledge, the emerging story will be more fragmentary than in the two preceding sections."

In summary, we believe Eccles did relatively well with his "cherry-picked" selections of articles, but he totally neglected work on spinal motor learning in animal models: for relevant theory and citations when Eccles was still active, see, e.g., Wolpaw and Carp (2006), and for even more recent work, see Brownstone et al. (2015). He also neglected the need to consider the biomechanics of the learned movements of tested subjects, be they human or animal models (see, e.g. Hasan et al.,1985). As a result his analysis of motor learning in this article is very idiosyncratic, being focused on his passion for the existence of unproven supraspinal mechanisms.

In summary on the above eight articles, we are left with the impression that even though Eccles remained remarkably cognizant of advances in cellular neuroscience and retained his ability to write meaningfully about them until ill health intervened in his early 90s, it was not his preference to do so. Rather, as his health declined he gave full vent to his passion for the brain-mind problem and the possibility that he could advance this field of endeavor, which interestingly had remained far from attractive to his peers and close colleagues in the field of neuroscience.

In support of our speculation, the two books he wrote near the end of his career did not address any aspect of central inhibition. Rather, both addressed the mind-brain problem. Eccles (1989), entitled "Evolution of the Brain: Creation of the Conscious Self," was on display in the publisher's booth at the IUPS Helsinki Meeting in 1989.[34] The

second book (Eccles 1994b), "How the self controls its brain," was published when Eccles' health was beginning to deteriorate, due possibly in part to cerebral arteriosclerosis. At that time he was working on his (*unpublished*) autobiography, and also continuing his collaboration with Beck on the mind-brain problem. Interestingly, there is evidence that Eccles retained much of his mental faculties until very near the end of his life. Note for example excerpts from the following three reports.

Mennis (2008; p. 167):

> The next time I saw Dad was in Easter 1997, a month before his death. ... I had a long visit with him in the hospital in Locarno. We had not seen each other for five years and, at first, he did not recognise me. He was happy I had come and asked how I knew where he was and how I managed to get in to see him. He was pleased when I told him how many people in Australia wanted to know how he was and were praying for him. Sue de Viana (*a friend of Mennis*) took some photos and went out to get water for the flowers. We stayed and talked for over an hour and no-one came near us except for a nurse with two tablets for Dad. We had brought some eucalyptus foliage in the bunch of flowers and he rubbed the leaves and remembered Australia ... Overall, it was a successful visit, but a sad time. (*In a subsequent March 22, 2016 email to D.G.S. Mennis emphasized that during her over one-hour talk with her father he was "quite lucid*").

Mombelli (2000; pp.183-184):

> I was Sir John's doctor during the last years of his life. I cared for him at various occasions in the hospital the last months until his death. But I have followed him as an out-patient, seeing him regularly in my practice ... He was happy to meet me and tell me that he managed to go on the whole more or less well. ... The last visits of Sir John were marked with motoric difficulties. His mind was clear, the features of his face kept having the expressive and mild nobility, but the body was bent and the prognosis was uncertain. Nevertheless, Sir John continued to live and work in his house, isolated in the woods above Contra.... Sir John worked on his autobiography. ... Each time after the medical control, I always used to ask him about his work. ... Rewriting his life, it seemed reliving all the past sadness and pain and for short moments he could fall down in his spirit. These were, however, short moments only…. he was turning on his great problems of his research and thinking: soul, reason, consciousness and self-consciousness — all the abstract terms of untouchable superiority - and then the brain in its most complicated but still material appearance. Then his eyes have always become intense and most serious. His thinking - it was so obvious - has managed to set himself apart from all the human miseries and lift up his spirit towards the endless and creative scientific theories and solutions. *(Dr. Giorgia Mombelli [1943-] (see: http://tinyurl.com/hsnn855) is an Italian-born internist located in Locarno, CHE).*

Monotti (2000; pp. 185-186):

> I went to visit Sir John on Sunday afternoon, five days before he died. He seemed to be sleeping and was physically in ever greater difficulties. He said: "Life is a mystery, it's a mystery, it's a mystery and I will get it". ...I didn't know that these were the last words I would hear from him. Only after his death did I remember that he had also spoken of the mystery (the mystery of human life, of man) in an intense meeting in Rimini in April 1982. And I also recalled the enthusiasm of a few friends of mine who had gone to

interview him in Contra, in spring '84. To a question about his opinion at the end of life, he had replied: "Even in tragic circumstances, life is a mystery. Each one of us is a mysterious being. Life is a total mystery and this is why we can't think in terms of pure opportunism or convenience. We must have the courage to continue to live and to die when we are called to die ..." ... Those words were the ultimate act of a man who looked on the Mystery and recognised it as something which can be met, as the fulfillment of life with all its tensions and dramas; as the fulfillment of reason which, open to the whole of reality, seeks the truth; therefore, his words were the fulfillment of the work of a man who was free because he recognised his own creativeness. *(Dr. Rita Monotti [1956-] (see: http://tinyurl.com/jomr2on) is a Swiss internist located in Locarno, Switzerland).*

5.7. Reflections of Ito and Curtis on Eccles' contribution to central inhibition

Most would agree that Eccles' major contribution to central inhibition was demonstration of the intracellularly recorded IPSP in spinal motoneurons of the cat. We are not aware of a paragraph as succinct as that provided above by Granit for Sherrington's contribution to central inhibition. However, the viewpoints of two of Eccles' best-known trainees and collaborators deserve mention. Ito (2000), when reflecting on his time with Eccles in Canberra (1959-1962) provided an intriguing historical vignette (p.31): "The circumstances under which excitatory synaptic transmission was discovered were described by Jack Coombs at an informal (*Canberra*) party held in June of 1961 to celebrate the tenth anniversary of this discovery. The invitation to the party was printed at the margin of a reprint of the first report of the discovery ..." (*i.e., Brock et al., 1951*). Inhibitory synaptic transmission followed shortly thereafter in August 1951 (Stuart and Brownstone, 2011; p.74).

In another reflection, Curtis (2003; p. 171) wrote "The opposite polarity of excitatory and inhibitory postsynaptic potentials convinced Eccles that synaptically released chemical transmitters were responsible. He immediately and dramatically rejected his theories of electrical excitation and inhibition which he had strongly defended for many years." Curtis continued (*same p. 171*) "Eccles moved to Canberra in late 1952 and began experiments in temporary laboratories in March 1953. With Coombs and Paul

Fatt he brilliantly exploited and extended intracellular recording techniques to establish the biophysical properties of the motoneurone membrane and the changes in membrane permeability which generated excitatory and inhibitory synaptic potentials. Spinal afferent fibres were established as excitatory and interneurones as being either excitatory or inhibitory. This work essentially led to his sharing the 1963 Nobel Prize for Physiology or Medicine with A.L. Hodgkin and A.F.Huxley."

Eccles certainly believed this as the reason for his award because his presentation at the Nobel ceremony was entitled "The ionic mechanism of postsynaptic inhibition." This title and talk were fitting tributes to his mentor, Sherrington, who was honored in the first paragraph of his subsequent Nobel article (Eccles, 1964c).

6. More on the life and times of Sherrington and Eccles

6.1. Sherrington biosketch

Much has been written about Sherrington since his death in 1952. For example, there are four valuable in-depth reports written by four of his trainees. These include: 1) a biographical memoir by Liddell (1952a[35]), an Englishman who was first an undergraduate student (1914-1918) greatly influenced by Sherrington and later his research assistant and collaborator (1921-1926, 1932); 2) the above mentioned book by Denny-Brown (1939), Sherrington's New Zealand PhD trainee (see also Denny-Brown, 1957); 3) a 1966 book by the 1967 Nobel Laureate, Ragnar Granit, a Finn and later Swedish postdoctoral trainee (1928) of Sherrington and later a visiting researcher; and 4) a book by Eccles and Gibson (1979), with the Australian Eccles having been first an honors undergraduate and predoctoral trainee of Sherrington, and then his major research collaborator (1925-1931). The Canadian Gibson was advised informally by

Sherrington in 1935-1936 and later became his close friend and frequent visitor during Sherrington's retirement years (1936-1952).[36] Another valuable book is that of Judith Swazey (1969), an English physician and well-known medical historian.

Three of us (A.M.B., D.G.S., R.J.C.) contributed to this biographical effort in a book chapter (Stuart et al., 2001) and several interesting articles addressed facets of his contributions on the centenary of his birth (e.g., Penfield, 1957) and fifty years later (e.g., Burke, 2007; Fuller, 2007; Gibson, 2007, Zerman, 2007; see also Molnár and Brown 2010). Sherrington's son, Carr Sherrington [1897-1973] (1957), also contributed unique insights in a touching memoir about his father's personality.

In view of the above substantial biographical material, the following biosketch is quite succinct, and includes some points not made in the above publications.

6.1.1. Life and times

Sherrington grew up in the Victorian era when Great Britain was at its wealthiest. The borders of the British Empire were far reaching and the level of intellectual activity and enquiry in London, Cambridge, Oxford, and Edinburgh was at its height with an emphasis on philosophical and scientific thought, the humanities, and fine arts. As an older man, Sherrington experienced civilian life in WW I, albeit with a war-related research assignment, and in his old age he experienced the devastation of WW II and the substantial social changes in Great Britain that came immediately thereafter.

6.1.2. Physique, athleticism, and personality

Sherrington was slight of build, and ~5' 6" tall as an adult. He was very athletic, playing soccer for his high school,[37] rugby union football for both St. Thomas's Hospital and Caius College at Cambridge, and he also rowed for the latter. In rugby, he played as a

forward, his bad eyesight preventing him from playing at the more appropriate half back position. Later, he took on in order skiing, cycling, tennis, and golf. It seems likely that this ruggedness was one of the reasons that he was so popular with his peers, superiors, and trainees at the various stages of his career. Similarly, he probably appreciated the athleticism of his trainees and other students, including Rhodes Scholars from then "colonial" countries. Throughout Sherrington's career his Rhodes Scholar trainees were selected primarily on the basis of their scholarship and leadership potential, but were also expected to have performed well in an athletic pursuit (Gibson, 1996; p. 111)

Sherrington's athleticism and ruggedness carried over into his research experiments. He always worked well into the night, even before his final arduous experiments with Eccles when he was in his early 70s (see Eccles and Gibson, 1979; p. 56). However, there was much more to Sherrington's personality than his athleticism. He had common sense, innate kindness, a generosity of spirit, a sound general knowledge, a well-developed sense of humor, and was a popular raconteur (see, e.g., Sherrington (1953), which was published after his demise). He also had an intense interest in the careers of his research trainees and the medical students he taught. He had a quiet confidence that inspired the respect of those who expected or needed him to succeed in a variety of endeavors.

Denny-Brown wrote fondly (1957; p. 546):

> He was short in stature, about 5 feet 6 inches, very precise and neat in all his movements, and he tended to peer through rimless spectacles though not severely shortsighted. He had lively, humorous grey eyes and a light, easy, friendly manner. He was one of the mildest men I have ever known, rarely being vexed and at most saying, “Dear me” or “That is most annoying.” He seldom if ever made a derogatory remark about any colleague, at most saying, “He must be mistaken” or turning the conversation to some anecdote including the person under discussion, very humorous but never unkind, preceded always by a little pulling in of the lips and suction of breath which were the sign that something good was coming."

6.1.3. Early life, academic training and appointments

Sherrington was born in Islington, London, England on November 27, 1857 while his mother and probably Sherrington's true father (Dr. Caleb Rose) were visiting the city. It is generally stated that this father was James Norton Sherrington a clinician in Caister, Great Yarmouth, who died while his son, Charles, was quite young. This is not correct, however, because he died well before our Sherrington was born.[38] In 1880 Dr. J.N. Sherrington's wife, nee Anne Chington [1817-1907] (C.E.R. Sherrington, 1975) remarried Dr. Caleb Rose [1820-1895], a clinician, noted classics scholar, and archeologist to whom Sherrington was always closely attached and most responsive. Dr. Rose's home was in Ipswich, an ancient, pleasant town by the ocean in the southeast section of England. Sherrington lived there with his parents, two younger brothers who became lawyers, and a stepbrother, who was later well known as a dramatist and drama critic. Their home was ideal for a future academician and all-round scholar as it was filled with a variety of biological and physical collections befitting an archeologist of note, and frequented by artists and scholars. In all ways theirs was a happy and fulfilling home.

Sherrington excelled in his demanding secondary 5-year education at the Ipswich Grammar (High) School (1870-1875). For example, in his senior year he passed general education courses usually taken at that time in early medical school tertiary training. In addition, his high school headmaster, the Rev. Hubert Ashton Holden M.A., LL.D [1822-1896] (Anon., 1896), the editor of *Aristophanes* instilled in Sherrington a lifelong love of classical literature. Similarly, another teacher there, Thomas Ashe [1836-1889] (Lee, 1901), who was a poet of considerable talent, encouraged Sherrington's own poetic efforts, and urged him to seek and enjoy foreign travel and to read all manner of books.

Normally, Sherrington would have gone from high school to the University of Cambridge for a broad tertiary experience. However, a bank failure diminished the

family's finances. This meant that Sherrington, as the oldest son, needed to join the work force as soon as possible. For this reason, he entered medical school a year after he completed high school. After initial medical training (1876-1879) at StTHMS, the University of Edinburgh, and then back to StTHMS,[39] his family's finances had improved sufficiently for him to begin attending Cambridge in October 1879 as a non-college student. After three terms (more-or-less equivalent to 3 quarters in the USA college system), the family finances were apparently sufficient for him to become a member of a Cambridge college, Gonville & Caius. Sherrington graduated from Cambridge with a B.A. in 1884. It included first-class honors in natural science (mostly botany, human physiology and anatomy, and zoology) in 1884. His Cambridge medical M.B. degree followed in 1885. Later, he was awarded a Cambridge M.D. degree in 1893, which apparently recognized his earlier University of London dissertation (Sherrington, 1891b) for work undertaken at StTHMS.

Sherrington was greatly impressed by the quality of the Cambridge physiologists who worked in the laboratory of the first Cambridge Professor of Physiology, Michael Foster [1836-1907] (Sherrington, 1907a; Hawgood, 2008; for comments on Foster's laboratory, see Swazey,1969; her pp. 5-8). Sherrington's primary research mentors there were in a broad sense Foster, and more specifically John Langley [1852-1925] (Sherrington, 1925b; Todman, 2008), who contributed substantially to late-19th C neuroscience, particularly on the mammalian autonomic nervous system and Walter Gaskell [1847-1914] (Langley, 1915; Geison 1972), a cardiovascular, autonomic nervous system, and comparative neurobiologist. Sherrington wrote long after Gaskell's demise (Liddell, 1952a; pp. 244-245):

> My own work began by chance at the wrong end – the cortex-pyramidal degenerations, etc. It was certainly through Gaskell that I very soon felt that…the cord offered a better point of attack physiologically…he was still always a bulwark to me about inhibition and voluntary muscle…In a hundred ways I owe him help and inspiration.

Sherrington was also strongly influenced by the writings of Santiago Ramón y Cajal [1852-1934] (Sherrington, 1935b), whom Sherrington met only twice (Spain in 1885; London in 1894), even though his work was essential for the development of Sherrington's own theoretical contributions on the synapse (Sherrington, 1935b; Liddell, 1956).

A prestigious fellowship enabled Sherrington to interrupt his advanced medical training in 1884-1885 to undertake further research training in Germany. He began by spending one-two relatively unprofitable months with the renowned German physiologist and pioneer of vagal inhibition, Eduard Pflüger [1829-1910] (Rothschuh, 1974), at the University of Bonn. (In retrospect, we wonder if they discussed CNS inhibition)! Sherrington then spent 9-12 very scientifically rewarding months at the University of Strasbourg (then part of Germany) with the German physiologist, Friedrich Goltz [1834-1902], whose considerable abilities and contributions to physiology have been relatively neglected in the historical literature, except for a biography by his former student. the German physiologist, Ernst Ewald (1855-1921).

After completing his Cambridge M.B. degree Sherrington returned to Germany in 1886 to strengthen his then primary interest in biomedical research, which was not physiology (see footnote 41 below), but rather neurohistology and pathology. He began by spending two months with the renowned "father of pathology," Rudolf Virchow [1821-1902] (Schultz, 2008) in the Pathological Institute, Charité Hospital, Berlin. This was an unsatisfactory experience because by then Virchow was more engaged in national politics than in his science. However, Virchow encouraged and helped Sherrington move to another laboratory, that of the founder of modern bacteriology and a later 1905 Nobel Laureate, Robert Koch [1843-1910] (T. Brock, 1988), with whom Sherrington spent a very productive and rewarding year at the University of Berlin. After this experience, Sherrington felt he was well prepared to take on a full-time university

appointment as a biomedical academician, with a focus on both teaching and research.

Sherrington's Cambridge medical training and research experiences in Germany were undertaken more or less in parallel with valuable and adventurous clinical experiences in Spain in the summer of 1885 and Italy in the summer of 1886. In 1885, he and two friends, Charles Roy [1854-1897] (Brown, 1897) and John James Graham Brown (Anon., 1925), were authorized by the Association of Research in Medicine, the Royal Society, and the University of Cambridge to look into and report on an outbreak of cholera in Spain. In all, they performed 25 autopsies in the town of Aranjuez near Madrid. Their work, which was hampered by the local authorities because of its emphasis on sanitary precautions, showed that the causative bacteria were in the feces and nasal mucosa of these fatal cases (Roy et al., 1886). See also Sherrington (1953) for descriptions of the more adventurous aspects of this experience.

Sherrington returned to Europe for two summer months in 1886 at Foster's request and with some funds provided by the Royal Society, to report on an outbreak of the same disease in Italy (Sherrington, 1887). He examined 22 fatal cases of Asiatica cholera in the Province of Puglia and three fatal cases in the Province of Venetia. These cases did not involve true cholera, however. His detailed pathological examination of this material revealed Sherrington's nascent skill and interest in pathology and bacteriology. It also revealed his expediency, because being short of money for this assignment he practiced medicine there for a short time!

Sherrington's academic (including temporary teaching) postings were, in their order, at*:* StTHMS as an anatomy demonstrator (1883-1884), and later as a lecturer in physiology (1887–1895).[40] He also had in parallel positions as the Professor/ Superintendent of a veterinary facility, the Brown Institution of Preventative Medicine, University of London (1891-1895), and at Cambridge University as a fellow and tutor

(1887-1895); the University of Liverpool as the Professor of Physiology (1895-1912); and, the University of Oxford as the Professor of Physiology (1913-1935). He voluntarily gave up first his Oxford physiology laboratory in June 1935, then his professorship in December 1935, and finally his stay at Oxford in December 1936 the age of 79. It seems likely that he would have stayed longer[41] but for rheumatoid arthritis, which first afflicted him in 1933 shortly after the death of his wife of 41 years, and later permanently crippled his left arm.

6.1.4. Research career

Sherrington published on all manner of biomedical topics, including, for example, not only basic science and clinical articles on the CNS and cardiovascular function in the brain and spinal cord but also clinical (including public health) articles on bacteriology, cholera, diphtheria, emotion, fatigue, hygiene, infectivity of oysters, leucocytes, neuropharmacology (of chloroform, strychnine, and tetanus-toxin), and scar tissue.[42] His major findings, however, were on the control of movement, from which he extrapolated several features of overall brain and spinal cord function.[43] His main emphasis was on the study of spinal reflexes, but this work was not evident until his first report on the knee-jerk reflex (Sherrington, 1891a). This report was preceded by 21 reports, most of which employed histological techniques. Interestingly, 12 of these reports had then-important implications for the role of the cerebral cortex, descending pathways, and the spinal cord in the control of movement. The first two of these reports (Langley and Sherrington 1884a,b) were prepared while Sherrington was still a medical student. They followed a very public dispute between Goltz and David Ferrier [1843-1928] (Sherrington, 1928) in 1881 about the functional organization of the motor cortex (see Wilkins, 1964).

Sherrington's first sole-authored article was published shortly after completion of his M.B. degree, using brain tissue provided to him by Goltz (Sherrington, 1885). It is important to note that by 1891 Sherrington had decided that he would focus on the study of spinal reflexes as his "way into the CNS." This required that he undertake a series of painstaking experiments on the organization of the lumbosacral plexus and its afferent and efferent pathways to the musculature because the available information on this topic and then-current dogma were simply incorrect (recall footnote 6).

Previously three of us (A.M.B., D.G.S, R.J.C.) found it useful to divide Sherrington's movement neuroscience contributions into three themes: overall neuroscience, with emphases on the synapse and CNS inhibition; suprasegmental motor control; and segmental motor control (Table 11.1 in Stuart et al., 2001). The latter was divided into three areas, according to the modern-day definition of the segmental motor system: 1) the properties and central actions of posture- and movement-related sensory feedback from the body's somatic structures; 2) interneuron and motoneuron discharge properties, motor unit recruitment properties, and the associations between motoneuron, muscle fiber, and motor unit properties for the graded development of muscle force; and 3) segmental pattern generation for the elaboration of intrinsic/rhythmic and learned/skillful movements (Stuart, 1999; 2007). Sherrington contributed to all three areas either experimentally or theoretically. Early on, this effort included bringing motoneurons to the forefront of spinal cord research (see e.g., Clarac and Barbara, 2011)

Sherrington's most important contributions to neuroscience were emphasizing the importance of synapses in reflexes and behavior, a variety of potential mechanisms of spinal cord function (they required later verification and further clarification using intracellular recording), and inhibition as a coordinative CNS mechanism. Much of this work was summarized in a book and two book chapters (Sherrington (1906a, 1932,

1933a, respectively).

Robert Burke [1934-] (Garnett, 2005) strongly emphasized the significance of the 1906a book in an article (Burke, 2007) beginning (p. 887) with:

> 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.

The second summary (Sherrington, 1932) was Sherrington's book chapter contribution in Creed et al. (1932), which was subsequently evaluated by Eccles and Gibson (1979; pp. 65-69). Here, Sherrington reviewed his perception of the major features of spinal cord function as based on his 1884-1931 period of exacting research. These included his so-called "concealed reflexes" (reversal and rebound of reflex effects), the quantitative adjustment of reflex contraction (scale of adjustment, grades of reflex excitation, sub-tetanic reflex responses, single vs. multi-muscle reflex responses, reciprocal innervation, the speed of movement, tremor, rhythmic reflexes including the scratch reflex and stepping), the significance of decerebrate rigidity, and the overall spinal state. Interestingly, he did not include his essential prerequisite to all of the above work, which he had found boring. This work included the anatomy of spinal cord-muscle function, an area where he cleared up many preceding misconceptions. However, the first 100 pages of Denny-Brown (1939) summarize this work, which was edited informally by Sherrington.

The third chapter was his 1932 Nobel Prize lecture, which was published in 1933. We discussed and cited from this contribution in Section 3.2. above.

Sherrington elaborated on synapses, largely based on the work and thoughts of others, particularly in collaboration with two renowned textbook writers and editors, Foster and Edward Schäfer [1850-1935]. The latter changed his surname in 1918 to Sharpey-Schäfer (Sherrington, 1935a). Both Foster and Sharpey-Schäfer are listed in Table 5 along with his other 26 co-authors on articles and book chapters. These co-

authors are grouped according to the focus of their articles with Sherrington providing contributions in the general areas of either (1) suprasegmental and descending and ascending pathways or (2) segmental mechanisms. These 28 co-authors helped him write ~80 articles. Many of these articles were related either directly or indirectly to central inhibition, as compared to the 46 articles on CNS inhibition he wrote largely as a single author (recall Tables 1-3 above).

Table 5 near here

Eccles and Gibson (1979) may have overstated the case that from the age of 68 in 1925 until 75 in 1932, Sherrington was regarded internationally as "… the great integrator of knowledge of the central nervous system …" (p. ix). Thereafter, until late 1936 at Oxford, he returned to his far earlier neuro-histological interests, albeit with no publications in this area. His last and only scientific paper after 1935 was an histological article on spinal border cells (Cooper and Sherrington, 1940). Cooper had been his former postdoctoral trainee, so Sherrington's contribution was presumably made several years earlier (~1931-1932). However, Sherrington continued to publish an impressive body of work for a man of his age with a deteriorating physical condition and continuing service contributions to society (see below). In all, until his death in 1952 he published 19 articles (one was posthumous) and one book (Sherrington, 1946). He also scrutinized and made comments about the collection of his scientific writings that was organized and edited by Denny-Brown (1939), and did similarly for the second edition of five of his books. His post-retirement articles were largely brief biographical sketches, which are of particular historical interest because of his close association with his subjects (for further details see Liddell, 1952a; pp. 269-270). However, in these last years of his life, he never lost contact with the advances and rigor of neuroscience research. This is exemplified in the precision and fervor of his 1948 BBC radio lecture on the then-current status of neuroscience, which he delivered at the remarkable age of

91 years (Sherrington, 1948).[44]

It is also interesting to reflect on Sherrington (1953). This was his final publication, a book chapter of reflections and reminiscences, which was published after his death. He wrote it in 1946 at the age of 89 but carefully re-edited the chapter just before he died. In it, he recalled with much good humor and enthusiasm his cholera work and adventures in Spain in 1885 and 1886, and his 1914 interactions with Pavlov in St. Petersburg. Sherrington also recounted dramatically how he had saved the life of one of his nephews in 1884, by giving him an anti-diphtheria serum that he had prepared in a horse housed at the Brown Institution.[45] This chapter ended with an appreciative remembrance of his chief laboratory technician, George Cox, who came to Sherrington's St. Thomas's laboratory in 1887 as a "laboratory lad" after completing elementary school and remained with Sherrington as his head laboratory technician for the remainder of his laboratory life.

One aspect of Sherrington's research publications that has rarely been discussed was his tendency to engage in circular thinking about topics where the issue(s) were still open, at least in his mind. One example was his ambivalence about the possibility of reflex reversals: i.e., low threshold and non-nociceptive reflexes being context- and phase-dependent with the CNS selecting motoneuron input-output pathways appropriate for the movement task (see Stuart, 2002; pp. 250-251). More widely known and discussed was his difficulty in fully accepting Graham Brown's pioneering 1910-1915 work, which showed the intrinsic capability of the spinal cord in the guinea pig and cat to generate a stepping output pattern did not depend upon descending or sensory inputs (for review see Orlovsky et al., 1999; Stuart and Hultborn, 2008; Jones at al., 2011). It is generally thought that the reason for his ambivalence about Graham Brown's findings was his belief that the best strategy for advancing knowledge about CNS function was through the study of reflexes. Another possibility was suggested in Stuart

et al. (2001; p. 336). Sherrington, like most of his British neuroscience peers, strongly favored a single-cell (vs. systems) approach to the study of the CNS even though he had no way to activate or record from single neurons. This inside-out approach was most successful in setting the stage for post-World War II advances using the intracellular microelectrode, but its supporters had little insight into the potential significance and value of Graham Brown's outside-in approach (Stuart and Hultborn, 2008; Jones et al., 2011).[46] However, this uncertainty in no way precluded the friendship and lifelong mutual respect that existed between Sherrington and Graham Brown.[47]

Another intriguing aspect of Sherrington's body of work was the evolution of his research techniques. His pre-1920s' neurophysiology work was undertaken with quite simple electrical stimulation equipment combined with visual observations of muscle contractions: He used “… careful surgery … meticulous care … and a mind which pondered.” (Liddell, 1952a; p. 253; also Liddell, 1960; pp. 100-143). He was one of the first to quantitate reflex outputs in terms of muscle length changes of antagonistic muscles, and, taking the lead from an 1875 article by David Ferrier [1843-1928] (Sherrington, 1928), he was also one of the first to use repetitive (then called “faradic") stimulation of peripheral nerves, rather than the previously used sustained (then called “galvanic”) stimulation. Sherrington did not use an accurate muscle length-measuring device, however, until arriving at the University of Oxford in 1914. This was a spring-loaded isotonic myograph, with muscle twitch recordings made on a stationary smoked drum, as described in Sherrington and Sowton (1915).[48] Liddell (1960; pp.117-118) also wrote about this equipment "Sherrington initiated use of the myograph and continued to use it for the remainder of his life. It was an adjunct which had never been employed much by anyone till then for recording reflex action. His abundant results with it opened a new era."

By 1918, he was working with his own newly developed isometric torsion-wire optical myograph (Sassa and Sherrington, 1921). In the late 1920s he combined the myograph technique with the EMG (with Eccles) – “Together we learnt the technique of electrical recording from muscle, one of us near the end of his experimental life, the other near the beginning.” (Eccles and Gibson, 1979; p. 56). The EMG was first applied to the

study of spinal reflexes by Sybil Cooper [1900-1970] (Brading,1993) and Adrian (1924) at the University of Cambridge. In Sherrington's group at Oxford, combined EMG and force measurements first appeared in the 1926 paper of Fulton and Liddell.

A final thought about Sherrington's circular thinking has not been discussed in previous biographies. He hated to be "wrong."[49] This may not have been for egotistical reasons, given his many favorable personal attributes. Rather, he may have felt that "being wrong" slowed progress, a viewpoint not shared by Eccles or the authors of this review.

6.1.5. Mentoring and collaborating record in neurophysiology and neuroscience

From all accounts, Sherrington was an ideal and most successful mentor of those who worked in his laboratory, both for their research and the articles they co-wrote as co-authors or independently. They are listed above in Table 5 if their focus was on neurophysiology, neuroscience, or closely allied topics.

Several further features of Table 5 deserve emphasis.

1. By modern-day standards, Sherrington co-authored relatively few neurophysiology and neuroscience articles with his formal trainees, except for the 11 with Eccles, who was his last and favorite PhD student.

2. He also wrote few articles with his other junior and senior peers.

3. However, he certainly gave advice on article-writing to the people (~28) who worked in his laboratory for various lengths of time and independently published the work generated in his laboratory.

4. Virtually all of the above people became leading figures in neuroscience in several countries such that Sherrington's overall international impact was quite substantial.

5. Three of the above group became Nobel Laureates; Florey in 1945, Eccles in 1963, and Granit in 1967, thereby making Sherrington still the leading "Nobel Prize Mentor!" Interestingly, Sherrington wrote no articles with two of his other "Laureates," Florey and Granit.

Table 5 does not include several visitors to his laboratory, most of whom focused either then or subsequently on the administration of either basic biomedical or clinical science disciplines and medical school administration. It is likely that Sherrington had a profound effect on them. This group included among others:

> James Olmsted [1886-1956] Physiology, UC-Berkeley, USA; Emile Holman [1890-1957] Neurosurgery, Stanford University, USA; Wilburt Davison [1897-1972], First Dean, Duke University Medical School, USA; Franc Ingraham [1898-1955] Neurosurgery, Boston Childrens' Hospital-Harvard University, USA; John Balsdon [1901-1908] Ancient History, University of Oxford, GBR; John H. Wolfenden [1902-1989]. Chemistry, Dartmouth University, USA; and Karl Matthes [1905-1962] Cardiovascular Research, University of Heidelberg, GER.

Most of the people in Table 5 and the above small-print section felt they had a lifelong debt to Sherrington for his advice, mentoring, and never-ending support of their careers.

We conclude this section by citing Liddell's (1952a; p. 259) point that as a mentor, Sherrington wanted to know his trainees' "… thoughts and problems and not just live on a pedestal above them." In modern parlance, Sherrington emphasized "… putting students and their needs first …" (Kennedy, 1997; p. 287).

6.1.6. Classroom and laboratory teaching

According to Eccles and Gibson (1979), Sherrington took his teaching duties at Oxford very seriously (delivered to medical and graduate students, and often undergraduates in the same course). In a section written by Eccles he reflected (pp. 45-46) that in his probably overly generous opinion, based on his Oxford experience from 1925 to 1935, Sherrington was a good lecturer up to 1930 (*when he was 73 years of age*) but he then became obtuse and confusing to most of his students who stopped going to his lectures. However, this problem came far earlier at Oxford. For example, Phillips (1983; pp. 333-334) commented about Liddell that "As an undergraduate (*in 1914*) ... (*Liddell*) came under the spell of Sherrington ... and unlike the majority of students learned how to derive inspired instruction from those lectures, composed like a sandwich, of

coincident tiers of different materials: facts, thoughts for research and general philosophical reflections.[50] A little later Denny-Brown reflected quite amusedly (1957; p. 546) about Sherrington's lecturing and discussion style at scientific meetings:

> He (*Sherrington*) was a disappointing lecturer, much too prone to digression, so that, for example, at one meeting of the Physiological Society when he had defended Head's views on sensation in discussing a paper given by Schäfer he had thought of a better way of putting his objection half way through the first, and ended by thoroughly confusing the audience, including Schäfer, and Barcroft who was chairman. A heated discussion, in which it was clear that none of those present had understood what Sherrington was trying to say, was terminated only by adjournment for lunch.

Where Sherrington did excel in the teaching arena was in the laboratory exercises he designed for his students. Eccles and Gibson (1979; p. 47) emphasized the uniqueness and value of his approach:

> In his later years at Liverpool Sherrington had been concerned with the obsolescence of the traditional physiological practical course for medical students. He incorporated some experimental work on cats in the Liverpool classes. Taking advantage of this early experience, he was at Oxford able to develop a systematic experimental course in Mammalian Physiology that became world famous. During the war there were few students, so there was excellent opportunity to work with them in evolving the course. The tracings of blood pressure, of secretion and movements were recorded on a smoked drum kymograph, and the best specimens were carefully fixed by varnish and framed with the names of the students responsible. As soon as the war was over, it was possible to produce a printed laboratory manual giving the experimental procedures and the physiological interpretations with the chosen illustrations of the pioneer investigators. The book *Mammalian Physiology: A Course of Practical Exercises* published in 1919 was the text for this quite unique practical course. Nowhere else in the world was there anything like it.

Sherrington also wrote several articles (three as a committee member) about how to teach physiology in a university setting, and the relationship between public health and public education, in general. Clearly, he had a keen interest and commitment to teaching, which appears, however, to have outshone his prowess as a teacher.

6.1.7. Service contributions

Sherrington's bibliography highlights his intramural and extramural (including international) commitment to the societal value of universities in general, and medical schools, in particular. This commitment found specific expression in only ~12 articles.

However, the >20 obituaries and biographical articles he wrote often included the commitment of his subjects to service. Furthermore, as President of the Royal Society (1920-1925), his responsibilities and published comments in newspapers and journals helped strengthen political and public support for tertiary education and university research.

Sherrington also had a broader service commitment to his country's societal needs. For example, during WWI he did what he could as a civilian scientist, as mentioned by Liddell (1952a; p. 256):[51]

> During the First World War, as Chairman of the Industrial Fatigue Board, he used to speculate with some curiosity upon the nature and even existence of industrial fatigue. At the beginning of that war, he might have experienced industrial fatigue himself, since he worked for some weeks in a shell factory at Birmingham. The day shift was thirteen hours, the Sunday shift nine hours. He was then fifty-seven. ... Later during the war he helped the Liquor Control Board in its scientific inquiries, and wrote part of the book *Alcohol. Its action on the human organism.*[52]

6.1.8. Contributions to the humanities and social sciences

Sherrington's father and their home's many talented visitors encouraged his interest as a youngster in the fine arts (particularly all manner of art), the humanities (especially poetry and literature) and the social sciences (particularly philosophy). These interests and his personal contributions to poetry and philosophy continued throughout his life and were unabated in their quality up to the year before his death (Sherrington, 1953). The reader is referred to Graham Brown (1947), Eccles (1952a), his son Carr Sherrington (1975), Fuller (2007), and Zerman (2007), for these essential components of Sherrington's contributions and interests.

6.2. Eccles Biosketch

Much has also been written about the academic career and contributions to neuroscience of Eccles and his trainees and collaborators, including some outstanding memoirs and reflections (e.g**.,** Andersen and Lundberg, 1997; Curtis and Andersen,

2001a,b; Karczmar 2001a,b; H. Eccles and Biersack, 2000; Fillenz, 2000 and 2012; Ito, 2000; Strata, 2000; and Mennis, 2003 and 2008). One of us has contributed to this overall effort (Stuart et al., 2001, Stuart and Zigmond, 2006; Stuart and Brownstone, 2011). Eccles, himself, provided three autobiographical accounts that are cited in the present review (Eccles, 1975/1992, 1976, 1977). Note that Mary R. Mennis [1942-] was the third of Eccles' daughters and a well-known writer in Australia. She wrote about Papua New Guinea and its people and that Marianne Fillenz [1924-2013] a distinguished neuroscientist at the University of Oxford (Stein, 2013) was one of Eccles' first medical student researchers at the University of Otago.

6.2.1. Quintessential transnational academician

Eccles' post Australian M.B. training career was at 6 institutions in four countries (United Kingdom, Australia, New Zealand, Australia, United States) and Switzerland when retired. Throughout his research career he trained and collaborated with 180 mostly research academicians from 21 countries (listed in Stuart et al., 2001). He performed with distinction, had many close friends, and was very much at home in all five of these countries and developed many other close friendships with neuroscientists in additional countries which he relished visiting including, in particular, Canada, France, Germany, Hungary, Italy, Japan, Norway, and Sweden.[53] Eccles was far more than an advocate of internationalism. He was a true trans-nationalist, perfectly at home in counties with different customs, languages, and histories.

6.2.2. Athleticism and personality

Eccles was about 6'1" in height, lean in stature, and projected an imposing and often aggressive image. While a medical student he set an Australian Universities' pole vault

record. Like many Australians of his era he was an avid and competent tennis player and always relished folk and ballroom dancing, and swimming. When visiting D.G.S. at UC-Davis in his early 60s, he exhibited strong and endurance-challenged freestyle swimming, and in later trips to the University of Arizona in his early 70s he enjoyed long hikes in Southern Arizona. He remained hale and hearty until the age of ~91. His energy and endurance for long experiments with many over 24 hours) are noted below.

Eccles' personality has often been commented upon, both to his credit and discredit. However, several of his biographers, trainees and collaborators have commented that his personality had a positive effect on the research training and mentoring environment in his laboratory (e.g., Curtis and Andersen, 2001a; pp. 452-453).

One of Eccles' closest friends, Alex Karczmar [1917-] (Costa, 2007) wrote revealingly about Eccles' personality.[54]

> Eccles was tall and his face was typically Australian: rugged and handsome, and his accent remained throughout his life unmistakably from down-under. He exuded physical strength and energy: he was a very good tennis player, assiduous folk dancer, his stride was fast, his voice penetrating, and he could carry out his work for days with just about no sleep. Altogether, John Eccles' personality was somewhat overwhelming, and he could be quite direct and threatening in the course of scientific discussions. His repartees with David Nachmansohn and Harry Grundfest at the 1959 Rio De Janeiro Symposium were most unyielding; at the Federation Symposium of 1968 Eccles was very aggressive refuting the notion of Forrest Weight that the Renshaw cell did not exist. In everyday life Eccles was focused, driven and concerned with his own goals. This was counterbalanced by his old-fashioned courtesy, warmth and humor, conversational talents, and loyalty and generosity with respect to his friends. And, there were Eccles' spiritual and religious aspects; occasionally, when on a Sunday he found himself in strange surroundings he would go to some pains to find a church where he could attend a Mass. The complexity of Eccles' persona was expressed by his social attitudes; while essentially apolitical and a conservative anticommunist, Eccles was an old-fashioned liberal, perhaps even a libertarian. Altogether, as a scientist, philosopher and person, Eccles is unforgettable.

6.2.3. Pre-and post-medical training

November 1850 was the beginning of the Australian line of the Eccles family, with the marriage of Henry Eccles and Mary Jane Ingram in Melbourne (Mennis, 2008). Our Eccles was born in Melbourne, Australia, as were his parents William J. Eccles [1866-

1946] and Mary (nee Carew) [1868-1952], who were first generation Australians, of English and Irish ancestry. Both parents were in the teaching profession. Early in 1911 William Eccles was transferred to Koriot, an attractive township about 10 miles northwest of the port town (city designation in 1918) of Warrnambool, which is on the coast of Victoria, about 130 miles southwest of Melbourne.

Like Sherrington, Eccles excelled academically in high school, first for four years at Warrnambool High School where he boarded during the school week and usually took a train home on the weekends to his parents' home in Koriot (Mennis, 2008). He spent his final high school year at the still renowned Melbourne High School. Eccles was very interested and capable in mathematics but chose medicine for his dual 5-year M.B. and S.B. degrees at the University of Melbourne. During this period he began to consider the mind-brain problem and conscious experience (defined and discussed below), and decided to become a neuroscientist and work under Sherrington at Oxford. His Rhodes Scholarship enabled him to do this. Sherrington was one of his lecturers while he completed a two-year honors undergraduate degree in physiology and biochemistry (1925-1927). He received research training in late 1927, while working on spinal inhibition with Richard Creed, and on the cerebellum with Denny-Brown[55] and Liddell. More-or-less simultaneously, Sherrington accepted Eccles as his Ph.D. student and supervised his doctoral thesis. However, Sherrington was Eccles' collaborator rather than supervisor for much of the experimental work in this thesis (Eccles, 1929).[56] They then remained collaborators throughout 1928 and subsequently until late 1931.[57] Indeed, it can be argued that Eccles was really a semi-independent investigator while undertaking his doctoral research. From late 1927 onwards Creed, who was in the process of changing his research focus to visual neurobiology, gave him his modest spinal cord research laboratory.

6.2.4. Research career

Like Sherrington, Eccles's contributions to neuroscience are everlasting. In a collation of articles edited by Stuart and Zigmond (2006) his major contributions were considered to be the firing properties of motoneurons (Brownstone, 2006), the understanding of central synaptic transmission (Burke, 2006), spinal cord pre-synaptic transmission (Willis, 2006), mechanisms and concepts on spinal reflexes (Hultborn, 2006), plasticity from muscle to brain (Wolpaw and Carp, 2006), inhibitory circuits in the thalamus and hippocampus (Andersen, 2006), cerebellar circuitry and function (Ito, 2006), perspectives on the forebrain and skilled movement (Wiesendanger, 2006), and the brain-mind problem (Libet, 2006), which we discuss in the next section.

An interesting issue when considering Eccles' career is the patience and self-discipline he showed in delaying his move from the spinal cord to the suprapspinal structures and functions that really fascinated him. As noted above the 'mind-brain problem' and 'consciousness' had compelled him as a medical student to consider a career in neuroscience. From 1928 to 1961 his focus was on the spinal cord and the peripheral neuromuscular system. Presumably, he felt compelled to continue work on the spinal cord after his initial success with intracellular recording in 1951. Much later in one of his autobiographies, he wrote that: "After some ten years of intracellular recording in the spinal cord I was happy to move into the *much more complex and challenging problems* (*our italics*) presented by higher levels of the nervous system" (p. 13 in Eccles, 1977). This statement, which may be considered naive by current spinal cord neurobiologists, is a reflection of Eccles' primary interest in the fundamentals of synaptic transmission and their relation to the mind-brain problem (see below). However, it remains puzzling why, given the insight that Eccles had gained from his work on the spinal cord's interaction with the peripheral neuromuscular system, he did

not wax enthusiastic about the role of the spinal cord in the control of locomotion and the importance of work on spinal pattern generation for advancing understanding of central inhibition's interaction with central excitation at the spinal level. For example, in a particularly spirited, one-on-one conversation in Tucson in 1972, he could not be persuaded by D.G.S. about the significance of the early 20th C work of Graham Brown on spinal pattern generation for locomotion (Stuart and Hultborn, 2011). During that same interaction Eccles also could not also be persuaded to watch the movie made by Graham Brown in the late 1930s on the treadmill locomotion of high decerebrate cats (Lundberg and Phillips, 1973), nor consider its importance, which had been so readily apparent to Sherrington in the late 1930s, as expressed in an enthusiastic and encouraging letter to Graham Brown (Jones et al., 2011).

Here, our focus is on Eccles' contributions to central inhibition after first reflecting on his ideas on electrical synaptic transmission in mammals and the significance of how he came to reject it.

Eccles' work on electrical transmission was discussed above and previously, it has been well reviewed by Curtis and Andersen (2001a,b) and Bennett (2001), the latter a prominent Australian neuroscientist like Curtis [1927-2017].

This work began at Oxford in 1935 on the superior cervical sympathetic ganglion. From the outset, Eccles accepted the convincing work of many others that the slow component of the synaptic response was mediated by acetylcholine (ACh). However, since the ACh esterase blocker, physostigmine, did not seem to prolong the fast component and for several other seemingly plausible reasons, he came out with a mathematically-based "detonator" model for electrical transmission of this fast component (summarized in Eccles, 1936). This was quickly extended to the spinal cord and for the activation of striated smooth muscle (Eccles, 1937b). In Sydney, he devised the means to record end-plate potentials from the surface of striated muscle strips, first

in support of his detonator theory (Eccles and O'Connor, 1939), but later rejecting it for this preparation (Eccles et al., 1942). In contrast he claimed his detonator theory was correct for the cat stellate ganglion (Eccles, 1944a). In Dunedin, he continued work on his detonator theory for several years with his approach being strongly influenced by the widely read and highly respected philosopher Karl Popper [1902-1994] (Thornton, 2014), who was originally a Jewish Austrian refugee from Nazism with an academic post in Canterbury University College, Christchurch (1937-1945) and later two posts in England (1946-1969).[58] Eccles met Popper in Dunedin in 1944 and from then on his approach to research was forever changed as expressed with great feeling in Eccles (1975/1992; p. 162):

> Through my association with Popper I experienced a great liberation in escaping from the rigid conventions that are generally held with respect to scientific research. Until 1944 I held the following conventional ideas about the nature of research: First, that hypotheses grow out of the careful and methodical collection of experimental data. ... Second, that the excellence of a scientist can be judged by the reliability of his developed hypotheses, which, no doubt, need elaboration as more data accumulate, but which, it is hoped, stand as a firm and secure foundation for further conceptual development. Finally, and this is the important point, that it is in the highest degree regrettable and a sign of failure if a scientist espouses an hypothesis that is falsified by new data so that it has to be scrapped altogether. When one is liberated from these restrictive dogmas, scientific investigation becomes an exciting adventure opening up new visions; and this attitude has, I think, been reflected in my own scientific life since that time.[59]

Accordingly, Eccles continued to espouse and improve upon his detonator theory in a sequence of hypothesis-driven reports, the last of which was the most complete and novel, with fast synaptic inhibition requiring a Golgi type 2 interneuron supplying the current required for the inhibition of neighboring motoneurons (Eccles, 1949). Shortly thereafter Eccles was able to abruptly reject his long-held idea of electrical transmission for a fast synaptic event in his own laboratory with his own mastery of intracellular recording from motoneurons in the cat spinal cord (Brock et al.,1952b; their Fig. 12 and p. 452; for comments see Burke, 2006; p. 176; Stuart and Brownstone, 2011; p. 66). In our opinion, this evolution of Eccles' imaginative and controversial work on electrical transmission, which he sustained from 1935 to late 1951, and his own abrupt rejection

of it was the epitome of how scientific research should be conducted, and this by one co-awarded a Nobel Prize in 1963! Even today most investigators still have difficulty rejecting their own work and pet theories. Later, of course, electrical transmission in the mammalian CNS became an established fact as more become known about gap junctions.

Turning now to Eccles' pioneering work on central inhibition it is intriguing that his first publication on this topic was his first-ever publication from Oxford in 1928 in Creed's laboratory, their topic being the inhibition of motor units (Creed and Eccles, 1928). More-or-less in parallel, his work in Denny-Brown's laboratory on the cerebellar cortex included a component on inhibition (Denny-Brown et al., 1929). Similarly, his doctoral dissertation the same year addressed inhibition to the same extent as excitation. This focus on CNS inhibition continued during his 1928-1931 collaboration with Sherrington on the flexor reflex and his chapter on central inhibition in Creed et al. (1932).[60]

Indeed, throughout Eccles 1928-1937 Oxford experience he published ~30 full-length manuscripts almost all of which addressed some aspect of central inhibition in the spinal cord, or peripheral inhibition in the heart or autonomic ganglion. This emphasis continued at his subsequent sites for experimental work; Sydney, Dunedin, Canberra, Chicago, and Buffalo. An important transition for Eccles occurred in Canberra in 1961-1963 when he turned from studying neurons in the mammalian spinal cord to supraspinal interneurons in the hippocampus and cerebellum.[61] At these supraspinal centers, his focus was far more on excitatory and inhibitory synaptic mechanisms than on function, albeit he eventually ventured into cerebellar function in a book (Eccles et al., 1967) written with his research collaborators, Ito and János Szentágothai [1912-1994] (Pasik and Pasik, 1995). Eccles et al. (1977), which was based on collaborative experiments undertaken in Buffalo, was his final experimental report on central

inhibition. Thus, his experimental work on central inhibition spanned 49 years; from 1928 to 1977.

When Eccles retired to Switzerland in 1975 he became very active in writing, travelling (largely within Europe, but also in the United Kingdom, Japan, and the United States), and lecturing at many institutions, including those where he had visiting appointments (e.g., The Max Planck Institute for Biophysical Chemistry in Göttingen, the Max Planck Institute for Brain Research in Frankfurt, and the Universities of Basel, Genoa, and Wurzburg). One of his major contributions was to introduce the concept of ionotropic and metabotropic synaptic transmission; the former by directly opening ion channels, and the latter indirectly by producing intracellular metabolic reactions. These concepts were developed with the Canadian clinician and neuroscientist, Patrick McGeer [1927-] and his wife, the neurochemist and later all-round neuroscientist, Edith McGeer [1923-] (see McGeer et al., 1978; Eccles and McGeer, 1979; McGeer and McGeer, 2001).

In all, Eccles' publications after his retirement amounted to over 145 articles and book chapters, and 9 books (3 as an editor), a remarkable feat in his fields of endeavor. Note, in particular, his ability to keep up with the explosion of findings in cellular and molecular neuroscience, which occurred from the 1970s onward, and his penchant for using his own often controversial extension of peer-reviewed findings by others into the realm of his own imagination. For example, at the age of 85 he wrote a book chapter (presumably non-refereed) in which he modified a well-accepted model of long-term potentiation (LTP; see Wigström and Gustafsson, 1985) and used his version of it to develop a model of cognitive memory. Up until this time his ideas were potentially acceptable as a plausible explanation of memory consolidation in the cerebral cortex. However, his next step, relating this exercise to the brain-mind problem (see below), had far less support among his neuroscience peers. However, his late-age writing was

not always controversial. For example, in Eccles (1990) he traced developments in cellular and later molecular neuroscience from Sherrington (1906) to two articles in 1989; one on long term depression in the cerebellar cortex (Ito, 1989), and one on the molecular cloning of a neurotrophic factor (Leibrock et al., 1989). This is truly inspirational for an 89-year-old!

6.2.5. Contributions to the mind-brain problem

Eccles' contributions to the study of the mind-brain problem, dualism, and conscious experience[62] are beyond the scope of this review. They do, however, deserve at least some comment because about 18% if his publications addressed these issues. His first two publications on such topics appeared while he was in New Zealand (Eccles, 1947a, 1951a), whereas the sustained surge came after his retirement to Switzerland in 1975, albeit with some isolated work that created substantial interest and comment along the way (e.g., Eccles, 1966).

Most of Eccles' peers, research collaborators, and trainees in the field of neurophysiology criticized Eccles' work on the mind-brain problem because his ideas on the topic were not really testable, while they continued to heap praise on his work in cellular neurophysiology (e.g., Libet, 2006). Curtis and Andersen (2001a; pp. 450-452) have provided a detailed and objective discussion of the evolution of Eccles' thoughts on the brain-mind problem. Rather than repeat these views we focus on two aspects of Eccles' approach that deserve emphasis.

First, beginning shortly after Eccles met Popper in NZL in 1944, they had mutually rewarding discussions on the mind-brain problem. This continued until Popper's death in 1994, when Eccles himself was on an irreversible decline. Together they wrote an intriguing book on the topic (Popper and Eccles, 1977), which included their disparate viewpoints on selected issues. Second, we are impressed with the thoughts of our late

colleague, Mario Wiesendanger [1931-2017] (Hepp-Reymond and Marini, 1997), who also wrote objectively about Eccles' ideas on the mind-brain problem and his interaction with Popper. See Wiesendanger on p. 318 in Stuart and Zigmond (2006):

> The mind–brain problem has been debated for centuries and it may never be resolved. But to remain open-minded is always a good thing. Recall the words of Shakespeare: ‘‘There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy’’ (Act 1, scene 160 of Hamlet)! There is an abundant critical literature on this theme. As mentioned above, the philosopher, Ryle (1949), characterized the dualistic concept as a myth – ‘‘the ghost in the machine!’’ Criticism concerning the role of quantum mechanics in the mind–brain interaction came also from science and technology (e.g., Borck, 1998), quantum physics (Hepp, 1999), cognitive psychology (Wilson, 1981), neuroscience (Bennett and Hacker, 2002; Libet, 2006), and philosophy (Bunge, 1980). In retrospect, at the end of the 1988 Vatican conference, Eccles presented his thoughts about the mind–brain interaction. As a guest at the conference, Bartholomew Kiely, Professor of Psychology and Moral Theology at the Pontifical Gregorian University in Rome, made the following remark: ‘‘We have two epistemological lines of access to what goes on in the brain: one given in the methods of neuroanatomy, neurophysiology, and neuropsychology, and one given in our direct experience of ourselves in action’’ (p. 583 in Eccles and Creutzfeldt, 1990). At the age of 90, Eccles was forced to give up much of his previous activities, reducing also much his travels. I visited him in 1994 at the hospital in Locarno, near from his home in Contra, which was built on the mountain near Lago Maggiore. His book, ‘‘How the Self Controls Its Brain’’, was on his table, fresh from the publisher. He was obviously happy and proud about its publication, as expressed in the book (Eccles, 1994, p.147; *1994b in this review*): ‘‘This chapter represents the culmination of my life-long quest to find the scientific explanation for dualism’’. It was my last encounter with Sir John Eccles. I am much indebted to him for his generosity, his warm friendship, and his immense knowledge."

6.2.6. Research mentoring

One of the distinguishing characteristics of the fields of cellular neurophysiology and neuroscience before the advent of molecular biology was the relatively small number of pre- and postdoctoral trainees and visiting faculty working at any one time with a prominent scientist in these allied fields. Viewed in this light it is remarkable that throughout his career Eccles trained and collaborated with over 180 people from 21 countries. Communications received by Stuart et al., (2001) from many of this group revealed that Eccles' research mentoring was not limited to his pre-and postdoctoral trainees but usually included visiting faculty as well. Since most of these trainees and faculty went on to have distinguished careers it follows that Eccles' research mentoring had a major impact following WWII on the development of neuroscience into a major discipline.

It is interesting that most of Eccles' trainees were not put off by his forthright and often aggressive mannerisms. Curtis and Andersen (2001a; pp. 452-453) emphasized this point:

> His infectious enthusiasm over a new or unexpected finding, his extensive knowledge of virtually all experimental neurophysiology, which he gladly shared, and above all, his ideas for further experimentation were both instructive and formative for his younger colleagues ... Most major investigations involved two long experiments each week, beginning very early in the morning and often lasting 16–20 hours, occasionally longer and extending well into the following day. He regularly took part in the animal preparation, and took considerable pride in his anatomical knowledge and surgical expertise.

The above assessment was in keeping with the communications that Stuart et al., (2001) received from those he mentored successively in New Zealand, Australia, and the United States. These communications, both written and in person, included several from his Japanese trainees and collaborators, who emphasized Eccles concern for and interest in their welfare and the field of neuroscience in Japan. It seems likely that by far the majority of Eccles' trainees and visiting faculty considered him a most valuable mentor and emerged as scientists who were highly motivated, self-confident, and immune to blunt criticism.

6.2.7. Teaching contributions

Eccles' wrote enthusiastically about his teaching assignments at Oxford, including his participation as a demonstrator in Sherrington's laboratory exercises for students (Eccles and Gibson, 1979; pp. 47-48). He was also quite proud of what he provided in teaching and research experiences for medical students at the University of Otago, where he had a demanding teaching load in the medical school (Eccles, 1977; pp. 5-6). His subsequent positions required no formal classroom teaching, albeit he presented innumerable lectures on a wide variety of topics.[63]

Eccles was gifted in explaining ion movements across the nerve membrane during resting and action potentials. For example, Fig. 30 shows a resting potential diagram in

Eccles (1957; its Fig. 8), which he probably devised in the early 1950s.[64] Later it was extended to include the action potential (with its subsequent hyperpolarization). He presented these models throughout the 1950s-1960s in varying levels of detail depending on the qualifications of those attending his lectures. His figures were subsequently used by those teaching these topics at many institutions throughout the world. Many such faculty, including the present authors have used this figure and those in two Scientific American articles (Eccles, 1958, 1965b) to introduce undergraduates, graduate students, and medical students, to the cellular neurophysiology of single neurons. Indeed these articles are timeless despite the explosion of more recent articles on ion channel neurobiology.

Fig. 30 near here

6.2.8. Service contributions

Curtis and Andersen (2001a,b) listed Eccles' innumerable honors and awards from many countries, including decorations (1958 Knighthood in the United Kingdom and its equivalent in 1987 in Japan and 1990 in Australia), membership and leadership of learned academies and professional bodies (including editorship of leading peer-review journals), honorary degrees, international lectureships, and visiting professorships. They and the other biographical material cited above give insight into Eccles' extramural service contributions, which were extensive to say the least. This is not surprising, given his extraordinary energy and enthusiasm for international projects and activities, and the fame he enjoyed as a leading neurophysiologist from the early 1930s onwards (Stuart and Zigmond, 2006). Of course, his greatest technical contribution was the role he played as a co-pioneer of intracellular recording in the mammalian CNS and his rapid exploitation of the technique (Stuart and Brownstone, 2011). Below we focus on those of his service contributions that have not been considered in previous biographies.

As a faculty member at Oxford Eccles' activities were focused on research and teaching and his various autobiographical accounts of his time there say nothing about intramural service. He did emphasize, however, the value of the intellectual camaraderie he experienced at his college with leading workers and thinkers in a wide range of disciplines. He wrote of his Oxford college days (Eccles, 1977, pp. 1-2):

> Exeter College was my delightful academic home for the next seven years (*1928-1935*). We were a small band of Fellows, but in their association I was able to mature culturally in that natural manner characteristic of Oxford at its best. There were at Exeter famous scholars such as Farnell, Marrett, Madariaga, Dawkins, Soddy, Barber, Balfour, and Tolkien, but the closest associates were my contemporaries: Neville Coghill, John Wolfenden, Dacre Balsdon, Bill Kneale, and Jim Bessant who represented, respectively, the fields of English, chemistry, classics, philosophy, and theology!

From then on Eccles was perfectly at home in his intellectual interactions with university personnel spanning Nobel Laureates to beginning undergraduates and his exchanges with university presidents, deans, boards of trustees, those that funded universities, and so forth (see below).

Eccles had little opportunity for intramural service while directing the pathology department at the Kanematsu Institute in 1937-43, except for setting up research laboratories on the top floor of the building. His disappointment about this institution's potential as a vibrant research center was expressed in Eccles (1977; p. 4): "I thought my position in the Kanematsu Institute of Sydney Hospital was secure; however under new management Sydney Hospital proceeded in 1943 to make my position untenable. Unbeknown to me, living quarters for hospital residents were to be constructed on top of my Institute, preventing any postwar development ...." The situation changed dramatically, however, when he took up his next position as the Professor of Physiology and Biochemistry at Otago University in New Zealand. His remarkable intramural service record there in 1944-1951 is documented in Stuart et al. (2001; p. 140; see also Fillenz, 2000, 2012). Similarly, Eccles provided very effective and indeed essential intramural service in the 13+ years (1952-1966) that he spent as the Professor of

Physiology at the fledgling ANU.[65] His subsequent two years at the A.M.A. Institute of Biomedical Research (1966-1968) did not provide opportunities for intramural service but it should be noted that in the City of Chicago he was treated like a fellow faculty member at Loyola University, the University of Chicago, and the University of Illinois-Chicago Circle. At these institutions he made substantial contributions in the form of lectures, and arranging seminars and conferences (Stuart et al, 2001; pp. 145-146). Much the same can be said of his final academic appointment at SUNY-Buffalo.

We are left with the impression that Eccles' natural inclination and ability to render effective intramural service of long-lasting significance found its "official" expression at only two of his academic sites: the University of Otago and the ANU. However, this was compensated for by his behavior when he was "on the road". On these trips he visited countless universities to present lectures, meet and encouraged faculty irrespective of their discipline,[66] and behaved similarly with trainees from the undergraduate to the postdoctoral level. He also emphasized to research university administrators the importance of fully supporting the research enterprise and optimizing the research environment for faculty and trainees alike. In all such activities his "intramural" service was outstanding at the host university.

6.2.9. Last meeting with Sherrington

It is fitting to conclude this section with an unpublished letter written by Eccles about his last meeting with Sherrington because of the strong influence each had on the other, particularly Sherrington on Eccles. This letter was published by Mennis (2008; p.147) and appears below *in italics*.

> In 1952 ... Dad, accompanied by Rose, went to visit Charles Sherrington. ... Dad described his visit (*on pp. 170-171 of his unpublished autobiography; see also Eccles and Gibson, 1979; p. 258*): *"On arrival in England (in 1952) after almost 15 years absence I had a visit to*

Sherrie as a high priority. ... My daughter Rose was then doing research on intracellular recording from sympathetic ganglia in Hodgkin's laboratory. She had visited Sir Charles at his Eastbourne Nursing Home that was run by Catholic nuns. So we went together to see Sherrie on Sunday, February 3. ... I was rather apprehensive to see him so deteriorated as I had heard. However, once we started to talk all was well. Rose then left us alone for some time before the hour-long visit was over. We talked much about the second shortened edition of his great book "Man on his Nature," 413 reduced to 300 pages. He initially remarked "I must have been a garrulous old man when I wrote it in 1939!" All too soon the time of our visit was up and I promised to come again soon. I came alone on Sunday February 24. We had good open talk as Sherrie was annoyed at some of the reviews of his book, the second edition. The materialist establishment rejected the sections dealing with the mind and the mental world as the delusions of an old man who had once been a good scientist. Sherrie was particularly unhappy at a review by Prof. J.Z.Young, saying to me "when will this YOUNG ever grow up"? I took several photos that he reluctantly agreed to and we discussed the great problem of the design and functioning of the brain that gave it the transcendent property of being in liaison with mind and the mental world. He was of course as strong a dualist as I had been right from the start. So I had to leave with the frustration that I should have come with a tape recorder. There were entrancing discussions that should not have been lost. But I would come with one next time, but there was to be no next time! Nine days later on March 4 in the early morning I heard the Magdalen death toll, and suspected at once that their greatest Fellow had died, which I soon confirmed and saw the Magdalen flag at half-mast out of my window across St. Swithins quadrangle. I went to the Ceremony in the College chapel and some days later to the memorial service in St. Margaret's Church Westminster. ... the Sherrington genes have gone, but his great creative and imaginative work is immortal, as also I believe in his Soul. At our last meeting he told me: "For me, Jack, the only reality now is the human soul." (*Note: the above quote is longer than the one provided by Mennis*). It was fitting that he be there at that time and visit Sherrington who had had such a tremendous influence on his life.

8. Summary thoughts on Sherrington and Eccles

"He has searched long and happily and found much. His kind comes to the world not often in centuries." These thoughts were applied most appropriately to Sherrington by Liddell (1952b; p. 284) in one of his obituaries about his professor and later collaborator. A slight modification of this quote[67] was repeated again most appropriately for Eccles by Andersen and Lundberg (1997; p. 325) in their obituary about their collaborator (Lundberg) and mentor/collaborator (Andersen).

In retrospect, it is intriguing that they were such good personal friends with a long-standing correspondence after Sherrington retired from Oxford in 1936. Admittedly, it is

well known that Sherrington would have preferred for Eccles to succeed him as the Professor of Physiology at Oxford.[68] They had very different personalities, albeit their collaboration brought out the best in both of them, and their talent in the field of neuroscience was of equal luster in their respective spans of international influence. For health reasons, this span was greater for Eccles than Sherrington, but perhaps unfairly Sherrington remains more "beloved" than Eccles, probably because the latter often displayed his innate aggressiveness on the international stage, at least before he mellowed in his 60s. Clearly, they were both key protagonists, indeed immortal ones, in the study of central inhibition.

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Footnotes

Note to the proof setter: *The footnotes are to appear at the bottom of the text page on which the no. of the footnote appears. In some cases the footnote will have to continue onto the bottom of the next page.*

[1]Basset (2002; p.1580) cited from Hill's (1965) preface "The implication of 'trails' is obvious, sometimes false sometimes genuine. That of 'trials' is deliberately equivocal; mostly the word relates quite simply to tests, to experiments, but it would be a reminder also of vexations, failures, and frustrations that were part of the job. How often did one waste a day, or a month, in fruitless experiments? How often were one's facts mis-interpreted or one's theories found wanting? (and one was lucky if one discovered that for oneself). In undertaking difficult experiments (and few others are really much fun) such trials are inevitable, and it may be comforting for people to realize that others have experienced them too. Often I have told my young friends that when they have found something they cannot understand at all. Instead of being cast down they should jump in the air for joy; for that is how discoveries are made. Research must indeed be planned; but the most interesting things can emerge when the plan does not work, providing a test not only of tenacity but of understanding."

[2]The terms “segmental motor control” and “segmental motor system” are relatively modern terms but valuable for considering Sherrington's main contributions. It is now considered useful in both invertebrate and vertebrate motor control neuroscience for summarizing work on (1) the properties and central actions of posture-and movement-related sensory feedback from the body's somatic structures, (2) interneuron and motoneuron discharge properties, motoneuron recruitment properties, and the associations between motoneuron, muscle fiber, and motor unit properties for the graded development of muscle force, and (3) segmental pattern generation for the elaboration of intrinsic/rhythmic and learned/skillful movements.

[3]StTHMS was founded about 1550. It did not become affiliated with the University of London until 1900. Much later, it was merged in 1982 with the Guys College Medical School and subsequently absorbed in 1998 into the King's College London School of Medicine.

[4]The most complete list of Sherrington's references appears to be those in Liddell (1952a), as compiled largely by his trainee, John Fulton [1899-1960] (Todman, 2009). It is necessary to add Sherrington (1897d and 1953). The latter was published posthumously. Note, that the Liddell list of Fulton's extensive compilation includes many abstracts and other short notes, including obituaries.

[5]The animal models, equipment, and muscle and reflex terms used by Sherrington in his 14 "note" and other articles discussed in this review are rarely considered in modern-day neuroscience. Except for his laboratory exercise manual (Sherrington, 1919a), he provided virtually no details in his publications on the specifics of his surgical procedures. He went to great lengths, however, in describing the spinal reflexes that he studied and their relation to previous and then current work undertaken by others on both vertebrates and invertebrates. He first used the term "decerebrate rigidity" in his 4th note, and the terms "decerebrate cat," and "decerebrate animal" in the 8th note.

These terms were then used innumerable times thereafter. Sherrington (1898b) appears to be the article in which he pioneered use of the term "decerebrate." However, the preparation, itself, had been used much earlier as reviewed by Liddell (1960; pp. 127-131). Early on, Sherrington used other midbrain preparations, including ones in which the brainstem transections ranged from the pontine level to the "crus cerebri" (defined by Sherrington as the white matter of the cerebral peduncles). In the modern era it is customary to consider a decerebrate preparation as one with a brain transection from the mid-collicular level dorsally to the posterior margin of the mammillary bodies ventrally. This followed Sherrington's later statement (1920a; p. 29) that "By the decerebrate preparation is understood one in which the whole brain in front of the posterior colliculi has been removed"(see also Sherrington 1919a; pp. 147-151). Spinal preparations lower than decapitate ones were also used by Sherrington. These involved a transection usually at the thoracic level, which we presume was at its mid-level, with the animal studied several days or weeks after the transection when either conscious or lightly anesthetized.

6Between 1890 and 1898 Sherrington reported on the anatomical relationships among the lumbosacral portions of the spinal cord, the ventral and dorsal root arrangement in the lumbosacral plexus, and the motor and sensory nerves to hip and hind limb muscles. For this effort, using largely the cat, he combined painstaking surgery, electrical stimulation of ventral and dorsal roots and their subcomponents in the spinal cord, and visual observations of subsequent muscle movements. "In later life, Sherrington was known to say that this early work on spinal roots and the innervation of muscles (*needed to challenge the so-called 'Laws of Pflüger'*) was dull and boring but he had to do it because anatomical knowledge of the time was so inaccurate and useless" (Liddell, 1952a; p. 247). However, his painstaking 1892 report " ... was one of the longest and most substantial that he ever wrote " (Liddell, 1960; p, 117). Note, however, that Denny-Brown (1979) devoted a substantial amount of his book to Sherrington's anatomical work. Similarly, we would draw the reader's attention to a selected number of these publications including Sherrington (1890; 1891; 1892a,b,c; 1893d, 1897c,e,g,h,j; 1898a) because they document his passion for functional anatomy and the steadfastness of this research motivation.

7Liddell (1960; p. 127) reflected that a first reading of Sherrington's articles up to 1895 gave the impression of " ... an untidiness in thought and writing. But it soon becomes clear that what was unusual was the profusion of results and of ideas jostling crowdedly for expression. He saw bright exciting possibilities on the nature of function, but the foundations of structure were not yet sure enough. ... So, what a reader in his first glance may judge to be grey repetition, is found on careful reading to consist of restatements with differences and sparkles of fresh material brimming up." In the present authors' opinion, these comments were overly generous!

8Liddell's 1960 comments on decerebrate preparations (pp. 127-131) included a revealing translation of an 1823 citation of François Magendie [1783-1855] (Haas, 1994). "If the section be made immediately in front of the optic tubercles ... the animal falls on its side, with its head thrown back, the feet stretched out stiffly and pointed forwards. I have seen young rabbits remain several hours in this position." Liddell also commented that "Olmsted... portrayed a perfect sketch of a man 'with his head thrown back, back arched, arms folded, legs and feet rigidly extended." This account appeared in Olmsted and Olmsted (1944).

9This work was undertaken in the laboratory of Anders Lundberg [1920-2009] (Alstermark et al., 2010), who played a key role in advancing understanding of the neural control of locomotion in the post WWII era, and paving the way for further such advances. These advances included the considerable ones of his former PhD student, Sten Grillner [1941-] (Kavli Foundation, 2008), who integrated comparative, evolutionary, and modeling/simulation approaches (e.g., Grillner and Jessell, 2009; Robertson et al., 2014).

10Two of these Swedish authors have contributed substantially to clinical neurology and movement neuroscience. They are Eric Kugelberg [1913-1983] (Edstrom and Grimby, 1985), and Lennart Grimby [1933-]. Nothing has been written about Grimby's movement neuroscience contributions even though he wrote 44 high-quality such articles between 1959 and 1997. He retired in 1998 from the Department of Neurology, Karolinska Hospital, Stockholm, Sweden where he spent his last few years engaged solely in clinical practice.

11The term "final common path" was coined by Sherrington (1904). The concept was and remains that the motoneuron integrates its excitatory and inhibitory inputs, and as such, serves as the final path to the musculature for its excitation, easement or abatement of action. In modern times, there is more of an emphasis on the net effect of last-order interneurons on motoneurons (both excitatory and inhibitory) as being the more prominent final common path to the musculature, albeit via motoneurons (Burke, 1985; Stuart and Hultborn, 2008; see their Fig. 5). This modern conception of last-order interneuron function was not entirely ignored in Sherrington (1904), and even today much is still to be learned about interactions between interneurons and motoneurons during the elaboration of postures and movements.

12Re the innervation of skeletal muscle in Fig. 8, Sherrington later wrote (1913c; p. 54) "The state of the skeletal muscle reflects faithfully the state of its motor centre. Its motor centre is the only source whence impulses can reach it. Upon that motor centre many nerve-paths converge, transmitting to it nervous impulses from various receptive points and from centres elsewhere. Of these nerve-paths some excite, others inhibit. The latter, by quelling or moderating the discharge from the motor centre, quell or moderate the contraction of the muscle. The inhibition of the skeletal musculature is therefore always reflex; and the study of skeletal inhibition falls wholly under the head of reflex action. The motor centre is a convergence point for various reflex influences competing, so to say, for dominance over the musculature. The motor centre lies as an instrument passive in the hands of opposing forces of excitation and inhibition, exerted by nerve channels which impinge upon it. Sometimes the one influence and sometimes the other influence prevails; often the two are simultaneously in action, and then these opponents partially cancel, either spatially in proportion to the relative intensity of their respective stimulations, or temporally by alternating with each other rhythmically in their dominance over the motor centre, thus producing rhythmic reflexes."

13It is surprising that this sketch of a motor unit did not appear in either Liddell and Sherrington (1925), when they used the term for the first time and defined it (albeit somewhat in passing), or shortly thereafter when Sherrington (1925a) provided a more clear-cut definition.

[14]The term "pool" was probably used because it was known at that time that the motoneuron nuclei providing innervation via their axons to a single muscle often overlapped with those innervating other muscles in both the brainstem and spinal cord. Some modern workers have retained the pool terminology whereas others prefer the term "motor nucleus" and write of overlapping motor nuclei.

[15]Below there is discussion of the six experimentally based articles published by Eccles and Sherrington in 1932. We presume that Sherrington, who participated in all the experiments, contributed substantially to the preparation of these reports and received credit for this effort from the Nobel Prize Committee.

[16]In retrospect it may seem strange to modern movement neuroscientists that in neither of the above two reports did Sherrington ascribe the spinal neural control circuitry to be central in origin. Rather his focus was on rigidly maintaining that scratching, like locomotion (see below), was essentially due to the operation of interacting spinal reflexes, even though he recognized the validity of Graham Brown's counter 1911 findings.

[17]The adjective "proprioceptive" requires discussion. Sherrington (1906c) provided definitions of proprioceptors as distinct from exteroceptors, and the reflex effects of both. He argued that exteroreceptors are embedded in or near structures (a field) external to the body, such as tactile receptors in the skin, where they respond often strongly to external stimuli (p. 470), "which abound in the general environment at work on the... outer surface." In contrast, he emphasized that proprioceptors are embedded in structures (another field) deep within the body and included muscle spindles, Golgi tendon organs, and joint receptors in vertebrates and a variety of muscle receptor and chordotonal organs in invertebrates. He argued (p. 472) that these receptors were of low threshold and " ... the (*quite mild*) reactions produced by the receptor organs of the deep field are results primarily due to the stimulation of the organism by itself, but secondarily due to the stimulation of the organism by the environment." Edward Evarts [1926-1985] (Thach, 2000) later reviewed the significance of Sherrington's earlier (1904) proprioceptor definition in Evarts (1981), pointing out that it has often been forgotten in post WWII work on muscle spindles and Golgi tendon organs. Even later, François Clarac [1938-] and two colleagues showed that force-sensitive receptors in the exoskeleton of many invertebrates can function as proprioceptors (Libersat et al.,1987). This point was taken into account by Hasan and Stuart (1988) who proposed (p. 217) that across crabs, cats, and humans "The problems of movement control involve many levels of analysis. The role of proprioceptive information too is multifarious, but may be broken down into two categories. One involves the smoothing and stabilization of internally generated motor patterns, by way of rectification of certain peculiar properties of muscle, compensation for lever-arm variations, and correction for interjoint interaction effects. The other category is comprised of the roles of proprioception with respect to the physical environment. Resistance to unexpected perturbations is only one such role. Perhaps more importantly, proprioceptive signals can help select the appropriate "synergy" of response, and can even be used to assist external forces; the assistance may be important in interlimb coordination in the presence of the mechanical coupling among the limbs provided by the environment." These propositions are still open issues but it seems likely that Sherrington and Evarts would have agreed with them!

[18]Stuart and Hultborn (2008) pointed out that no published abstract of the Physiological Society at that time referred to this demonstration. This point in no way implies that the demonstration did not occur.

[19]It seems likely, albeit not specifically stated so by Graham Brown, that the demonstrated bilateral hindlimb de-afferented cat that scratched was indeed a spinal preparation. So, his objection to Sherrington's 1906d and 1910c results was based upon the presumption that sensory structures in the limb contralateral to the de-afferented ipsilateral limb producing a scratch would have received movement-related inputs from the scratching limb due to passive coupling. Sherrington (1910c) had looked at contralateral muscles during a scratch of the ipsilateral limb and did not find any rhythmicity in those muscles. He reported (p. 215) " ... the contra-lateral hind-limb is also usually engaged by the reflex. In this contra-lateral limb the effect of the reflex is extension, not clonic, but steady and maintained so long as the stimulus is applied." It is now known, however, that some muscles in the contralateral limb are indeed rhythmically active during a scratch of the ipsilateral limb in the cat. For example, in Fig. 7 of Deliagina et al. (1981b) there is clearly rhythmic motor activity supplying the contralateral hindlimb when the ipsilateral hindlimb is performing a fictive scratch. This result contrasts with the above-mentioned Sherrington observation. Similarly, Deliagina et al. (1981a) showed rhythmic motor output in the non-scratching contralateral limb when the ipsilateral limb produces a scratch. Stein et al. (1995) also showed rhythmic activation of certain contralateral motor neurons during an ipsilateral fictive scratch in a spinal turtle. Graham-Brown (1911) was correct when he claimed that bilateral de-afferentation was more effective than unilateral de-afferentation in removing movement-related sensory inputs during an ipsilateral hindlimb scratch. Was this the first unequivocal demonstration that the vertebrate spinal cord contains a central pattern generator for hindlimb scratching? The answer is no because all movement-related sensory inputs from the scratching limb were not taken into account. There is spinal sensory input from the tail, thorax, and neck that enters the spinal cord in dorsal roots both rostral and caudal to the hindlimb enlargement. Sherrington and Graham Brown did not transect these dorsal roots. It is likely that some muscles in these peripheral structures are rhythmically activated during a hindlimb scratch (e.g., in neck muscles of the cat; see Carlson-Kuhta and Smith JL, 1994).

[20]De-efferentation via neuromuscular blockade is an unequivocal method for removing all movement-generated sensory input. Deliagina et al. (1975) accomplished this by demonstrating a fictive scratch rhythm in both a spinal and decerebrate cat immobilized with Flaxedil. Similarly Stein and Grossman (1980) demonstrated a fictive rostral scratch in the spinal turtle immobilized with the same agent. A second unequivocal method for removing all movement-related sensory inputs is an in vitro method in which a portion of the spinal cord is removed and placed into a bath of physiological saline in the absence of all muscles. For the vertebrate scratch produced by the spinal cord, the first report of an in vitro fictive spinal scratch was Keifer and Stein's (1983) report on the turtle.

[21]In December 1951 Eccles accepted the professorship and headship of the Department of Physiology, John Curtin School of Medical Research (JCSMR), Australian National University (ANU), Canberra, Australia. An arrangement between

ANU and the University of Otago allowed his laboratory group to continue working in his Dunedin research facilities throughout much of 1952. This included several months that he spent in the UK and USA, returning in late June 1952 to Dunedin, and then taking up residence in Canberra in September 1952. The temporary building for his Canberra department became available for occupancy and the resumption of research in March 1953. For more on this early history of ANU and the JCSMR see Fenner and Curtis, 2001; pp. 1-34).

22This number is listed in Curtis and Andersen's (2001a) Eccles' bibliography. It includes a few of his more frequently cited abstracts, and even less of them are listed in the present reference section. Their bibliography ends with an article published after Eccles' death (Beck and Eccles, 1998). An expansion of this article appeared in Beck and Eccles, 2003). The present review lists two abstracts not listed by Curtis and Andersen but located in Eccles' private collection of his publications (see below).

23The copyright holder (Lady Helena Eccles, 1925-2016) of Eccles' (1929) Ph.D. thesis gave us permission to share between us a single electronic copy of this report, as prepared by the Bodleian Library, University of Oxford. Unfortunately, the 53 figures for this thesis have been lost or mislaid at Oxford and there is no record of when or where this happened. It seems likely that these figures were originally sent to the relevant Oxford library in a separate package. Some of them may have re-appeared in Eccles' (1932) book chapter, which summarized his 1929-1931 results and ideas about central inhibition (see text below).

24Eccles had considerable angst several years later about one aspect of the Eccles and Sherrington (1930) research, when gamma motoneurons were shown by Lars Leksell [1907-1986] (Sabbatini, 1997) to innervate intrafusal rather than extrafusal muscle fibers (Leksell, 1945; for more history see Matthews, 1972; pp. 196-204). Sherrington and Eccles had wrongly concluded that gamma motoneurons were very small alpha motoneurons that innervated a very small number of striated muscle fibers. However, this did not unduly compromise the conclusions drawn in Eccles' Ph.D. results.

25The term "detonator response" was introduced in Eccles (1936) to emphasize that the c.e.s. alone could not initiate an action potential. Rather in addition to sufficient c.e.s. an explosive additional detonator response was required. The same idea was elaborated a little earlier by Lorente de Nó but without introduction of an acronym. In Eccles (1936) the term was applied to the postsynaptic excitatory response of both a ganglion cell (p. 358) and an oculomotor motoneuron (p. 376). In Eccles (1937a,b) he discussed his concept of ganglion detonator responses in great detail. For motoneurons he favored from the outset electrical transmission resulting in the detonator response, as emphasized in Eccles & Pritchard (1937).

26It is unfortunate that a biography has not been written about Coombs' life and stellar career. In Stuart and Brownstone (2011), footnote 14 mentions that "Further information on Coombs is available upon request to his younger brother Douglas Coombs, Emeritus Professor and former Head (for 34 years), Department of Geology, University of Otago (doug.coombs@stonebow.otago, ac.nz.).

27Later, Stuart and Brownstone (2011; p. 65) reflected that "Four of the attendees went

on to receive Nobel Prizes, including Eccles and Hodgkin in 1963, Keffer Hartline [1903–1983] in 1967, and Bernard Katz [1911–2002] in 1970. (The co-1963 Nobel Laureate, Huxley, did not attend this meeting. He was, however, a co-author of Hodgkin's presentation and resultant publication). Recall that Eccles was an excellent mathematician so the Hodgkin-Huxley differential equations were meat and drink for him in contrast to many of his research peers, except for Coombs, with whom he must have had innumerable discussions about the equations' significance. Interestingly, Woodbury, too, as a highly competent PhD biophysicist explained and promulgated the equations to medical students and their instructors across the entire USA (see Stuart and Brownstone, 2011; footnote 11 on p. 72).

28Rall told Robert Brownstone in 2010 that he remembered Eccles' "... excited reporting to us when he returned to Dunedin after this meeting (*the 1932 Cold Spring Harbor Symposium*). He was so impressed that he included much of H & H in the Dunedin lectures he presented and published in Oxford a year later. He made use of pre-publication access to the classical (*J. Physiol. Lond.)* H & H papers. It is clear that he actively associated himself with H & H" (*cited with a minor omission here and more fully by Brownstone (2006) and Stuart and Brownstone (1911)*).

29In this monograph, Chapters VI, VII, and VIII were respectively on prolonged functional changes (plasticity) in the nervous system, the cerebral cortex, and the mind-brain problem. Eccles' peers gave him high marks for the former two, and low marks for the final chapter (see below).

30For the history of the first use of double-barreled microelectrodes in motoneurons see footnote 23 in Stuart and Brownstone (2011).

31Despite its science-supported society, Sweden has no publications like American Men and Women of Science and Dictionary of Scientific Biography. Hence, there is no biosketch about Sven Landgren's contributions to neurophysiology, which seems a great pity. His refereed publications spanned at least 50 years; from ~1950 to ~2000. Apparently his first published experience with intracellular recording was in his collaboration with Eccles and Fatt. His neural focus was approximately in the order of intestinal motility (1950), cardiovascular control, corticofugal outputs and corticopetal inputs to the cerebral cortex, masticatory control, trigeminal nucleus inputs and outputs, epilepsy, and hippocampal inputs and outputs (to 2000).

32For the 1972 edition of Creed et al (1932) Lloyd added some annotations. His note 29 (p. 196) was that definitive evidence that inhibition could occur at neurons other than motoneurons had to remain until summarized in Eccles (1964b). Also, his note 30 (also p. 196) stated that " Except for the examples of 'presynaptic inhibition" and for the inhibition of interneurones it is no longer held that inhibitory action has no direct effect upon the motoneuron." In our opinion, he should have cited classical Eccles' 1950s-1960s work on these two points!

[33]The number is approximate because it includes 12 review-type articles written by Eccles, which the present authors judged to have been impactful for a wide international readership. Less approximate are the neuroscientists who collaborated with him in the experimental work on presynaptic inhibition. They included in their alphabetical order Per Andersen [1930-], Chandler McC. Brooks [1905-1989], Rosamond M. Eccles [1929-], Platon G. Kostyuk [1924-2010], Wlodzimierz M. Kozak [1927-], Kresimir Krnjevic [1927-], Franco Magni [1930-], Tomokazo Oshima [1932-], Thomas A. Sears [1928-], C. Norman Shealy [1932], Robert F. Schmidt [1935-], William D. Willis [1934-2015], and Tokikatsu Yokota [1931-].

[34]With much enthusiasm Eccles, who was then 86 years of age, dragged D.G.S. from his poster presentation at this IUPS meeting to the publisher's booth so that he could proudly show his figures in the book on the neural control of movement. Others gathered around thereby prompting Eccles to vigorously give an impromptu seminar on the overall aims of his book, which focussed on the brain-mind problem.

[35]In addition to this full length biographical memoir about Sherrington, Liddell wrote three short obituaries about his mentor and later collaborator. In each he brought out somewhat different features of Sherrington's life and accomplishments (Liddell, 1952b,c,d).

[36]Gibson [1913-1909] was Eccles' Ph.D. trainee and later his co-author. For more on Gibson's subsequent distinguished career in Canada as a neurologist see Gunn (2009).

[37]In his widely read and quoted biography of Sherrington, Liddell (1952a; p. 241) wrote "He played soccer for Ipswich town ...)." This was an error, according to the archives of this team. It was his brother George who played for Ipswich town."

[38]The lifespan of Sherrington's alleged father, Dr. James Norton Sherrington, was 1807-1948, so he was clearly not our Sherrington's father. In the 1861 census Ann Sherrington (age 43) was listed as the "Head" of a household, which included Caleb Rose (age 40, a "visitor") and Charles Scott (age 4). It seems likely that Rose was Sherrington's true father.

[39]There is still mystery about the relative duration of time that Sherrington spent in initial medical training at St. Thomas's and the University of Edinburgh. Records of the former were destroyed by an air raid in WWII and the latter does not have records of beginning medical students in the 19th C. Similarly, it is not known whether he was happy in Edinburgh, as claimed by Graham Brown (1947; p. 810) or as more often reported unhappy as mentioned by his son (E.R. Sherrington, 1957; p. 46). Perhaps it is safe to conjecture a compromise of sorts in that while in Edinburgh it seems possible that Sherrington began his life-long friendship with the Graham Brown family (Gareth Jones et al., 2011; footnote 5, p. 192), and particularly with Dr. John James Graham Brown [1854–1925] (Anon., 1925), an Edinburgh Medical School graduate, later a lecturer in neurology, and in 1912 President of the Royal College of Physicians of Edinburgh.

[40]It is generally written that Sherrington immediately resumed his physiological research when he returned in 1887 from Berlin to St. Thomas's. However, according to his life-

long friend, colleague, and former junior collaborator in 1911-1913, Graham Brown, he " ... came home with enthusiasm for bacteriology and participated at St. Thomas's in Path. Dept. - PM room chiefly. But he got repeated eczema of hands (scars still there) and finally could not go on. He therefore took to Physiology and lectured at St. T." We are indebted to Emeritus Professor Dr. J. Gareth Jones for this citation, which appears in the jottings of Graham Brown while on a 1931 trip with Sherrington to several European laboratories. These jottings are available in the Graham Brown Collection at the National Scottish Library in Edinburgh.

41At Oxford Sherrington was actually quite secretive about his age because " ... he had been appointed for life, before a retiring age became general in universities, and felt his younger colleagues who had reached retiring age must criticize his continuing at his Post" (Denny-Brown 1975; pp. 547-548).

42Sherrington's co-authors in areas of clinical importance with a non-neuroscience-focus included in the chronological order of his and their participation: *cholera pathology*, with Charles Roy and John Graham Brown; *scar tissue and other forms of pathology and bacteriology* with Charles Ballance, Ammand Ruffer, William Herdman, Sydney Hickson, Rupert Boyce, and Ronald Ross; *blood, heart, and circulation*, Sydney Copeman, Edward Schäfer, Stanley Kent; *fatigue*, with William MacDougall and Sara Sowton; *chloroform anesthesia*, with Joseph Barr and Sara Sowton; *cancer biology*, with Sydney Copeman; and *evolutionary biology***,** with Francis Mason.

43A case can be made for Sherrington having made important contributions to suprasegmental aspects of CNS function (e.g., Granit, 1966; Porter and Lemon, 1993), and it was indeed recognized internationally that he thought profoundly about the nervous system as a whole. For example, for many years he carried on hand-written correspondence with many of the world's leading contributors to CNS research. Nonetheless, his own work focused largely on the spinal cord rather than the CNS as a whole (see, e.g., Clarac and Barbara, 2011). This viewpoint was also the opinion of Denny-Brown (1975; p. 543).

44Originally recorded on 12/29/1948 at the BBC, London, GBR onto three 78 rpm discs. These discs were transferred on 10/28/1997 to a cassette tape by Professor A. Taylor, Sherrington School of Physiology, St. Thomas's Hospital Medical School, London, Great Britain. We had this tape converted into an audio file, which is available upon request to the authors.

45The following citation is an editorial note (p. 551) by the editor of Sherrington's (1953) book chapter. "Goodall *(A short history of the epidemic infectious diseases,* London, 1934, p. 75) stated that the first cases to be treated with (*antidiptheria*) serum in England numbered about twenty. This was in the summer of 1894, and the treatment was used at the Eastern Hospital, Homerton. *(The Director of this hospital)* Goodall *[Edward W.,1861-1938]* used serum supplied to him by Sir Joseph *Lister [1827-1912]*, who had obtained it from *(the French bacteriologist/immunologist at the Pasteur Insitute)* Roux *[Emile, 1853-1933]*. He also stated that in the autumn of the same year Ruffer *[Marc A.,1859-1917]* prepared antitoxin at the British Institute of Preventive Medicine, now the Lister Institute, and this serum was first used at the Eastern Hospital on 23 October 1894. From the information quoted above it is evident that Sir Charles

Sherrington used for therapeutic purposes serum manufactured in this country on 15 October 1894. His name must therefore in future find a place in the annals of diphtheria."

46Sherrington was in his 70s before the Swiss 1949 Nobel Laureate, Walter Hess [1881-1973] (Stuart, 2005), began to report in German on his conceptual advances in the late 1920s and early 1930s using an outside-in approach to study the functional organization of the diencephalon (Hess, 1963; pp. 415-416). The same could be said even more so of Nicolai Bernstein [1896-1966] (Gurfinkel and Cordo, 1998), the Russian movement neuroscientist with a strong background in clinical medicine, mathematics, and biomechanics, whose 1920s' articles were written in Russian and largely ignored in western countries like the UK until the 1960s (Stuart, 2005). Their work came too late to influence Sherrington's viewpoints in his later years, as in his contribution to Creed et al. (1932). Indeed, the inside-out and outside-in approaches to the control of movement did not converge in international pre-WW II neuroscience, in general, and it came late to British neuroscience well after WWII (Stuart, 2007). Interestingly, the renowned German neurologist, Richard Jung [1911-1986] (Creutzfeld, 1986), commented in a thoughtful memoir that while he was most impressed with the scientific rigor of leading pre-World War II British neuroscientists, who he met in Great Britain in 1936 (but apparently not including Sherrington), he was forever influenced later by his personal change from " ... fact-oriented (*i.e., unitary cellular*) British physiology to the systems-oriented physiology of W. R. Hess ... (*who*) considered single facts (*i.e., single-cell results*) only in their context with functional systems or in their significance for the organism." (Jung, 1975/1992; pp. 488-489).

47For example, in a letter Sherrington wrote to Graham Brown in January 1938 he was enthusiastic about the latter's work on the treadmill locomotion of high decerebrate cats (for details about this unpublished work see Lundberg and Phillips, 1953 and Jones et al., 2011). Similarly, in a letter Sherrington wrote to Eccles in the mid-1930s he mentioned with pride a difficult climb that Graham Brown had made in the Swiss Alps (for more on Graham Brown's mountaineering prowess, see Jones et al., 2011).

48Little information is available about Sarah C.M. Sowton [1854-1929], who was 2 years older than Sherrington. They co-authored several articles between 1906 and 1915. In the 1920s she worked for the UK's Medical Research Council's Industrial Fatigue Research Board where her professional title was "British Medical and Psychological Researcher" (Ogilvie and Harvey, 2000; p. 1928).

49In September 2006, D.G.S. had his last conversation with Anders Lundberg, his latter-day mentor. Lundberg told him another vignette about being offered the Chair of Physiology at Oxford in the early 1960s. While visiting there about this potential appointment, Lundberg discussed Sherrington's ambivalence and circular thinking on several issues with a few physiologists who had had known Sherrington well. They all agreed that he hated to ever be "wrong."

50We have no documentation on the quality and student response to Sherrington's classroom teaching prior to his Oxford years. It seems likely, however, that the opinion of Granit (1966; p. 19) that Sherrington "was never known as a good lecturer" extended back to his initial efforts at St. Thomas's Hospital Medical School, even though he was

admired and respected by his classroom audiences.

51Swazey (1969; pp. 23-24) also had interesting comments on Sherrington's WWI-related work, citing material in C. Sherrington (1957; pp. 58-59) and Forbes (1916; pp. 545-546).

52This book was published in 1918 by Longmans, Green and Co., New York. The publication designated no author or set of editors. However, the first two pages explained that the Liquor Traffic Unit of the UK Central Control Board prepared the book, as based on input from a 9-person advisory committee that included Sherrington.

53These comments are based on extensive discussions between Eccles and D.G.S. in various countries between 1966 and 1989.

54This material was provided to D.G.S. by Professor Karczmar for publication in Stuart and Pierce (2006; p. 152). The editor(s) deleted the material from the published version of Karczmar (2001a) without informing Dr. Karczmar. Because of its historical importance, he appends his comments on Eccles' personality to requested reprints of his article.

55Eccles emphasized to D.G.S. that he owed a great debt of gratitude to Denny-Brown from whom he learned the most at Oxford about all aspects of the experimental techniques potentially available to Sherrington's group, including, in particular, electrophysiological recording (see also Eccles 1975/1992, p. 160). It is often forgotten that Denny-Brown (1929) reported on single motor unit recording the same year as the widely quoted Adrian and Bronk (1929) article. Eccles made similar recordings in his six 1931 reports with Sherrington on the flexor reflex, and his 1932 report with Hebbel Hoff [1907-1987] (Valentinuzzi, 1987) on rhythmic motoneuron discharge (for their respective recording techniques, see Eccles and Sherrington, 1931a; Eccles and Hoff, 1932).

56The title page of Eccles' 1929 doctoral dissertation ends with the following statement in parenthesis. "(With the exception of some of the preliminary experiments done with Miss S. Cooper, and the experiments on the Crossed Extensor Reflex done with Dr. R. Granit, most of the other experimental work has been performed in collaboration with Sir Charles Sherrington.)"

57Eccles (1975/1992; p. 160) later reflected on their " ... three years of continual collaboration (1928-1931). I learned from him his unique insights into the mode of operation of the nervous system, his many skills in investigation, and also, very importantly, the cultural outlook of a scholar." (*In a previous article, however, Eccles (1982) listed the continual research collaboration as being for 4 years, 1928-1931*). Eccles reflected much later (1977a; p. 2) " At first the equipment was restricted to optical isometric myographs and a plate camera plus induction coils for single and repetitive nerve stimulation. We also had a massive antique pendulum for giving accurate timing for two induction shocks (to 0.1 msec). In 1928 Sherrington fitted up the research room with a string galvanometer-the height of luxury in those far-off days-and also with a Lucas spring pendulum. We began our collaboration studying first the motor unit and then the excitatory and inhibitory mechanisms of spinal reflexes from 1928 to

1931."

58In1946 Popper moved to England to teach at the London School of Economics. In 1949, he became professor of logic and scientific method at the University of London. He retired from this post in 1969 but remained active as a lecturer, writer and broadcaster until his death in 1994.

59This philosophy was far different than that espoused by Sherrington (recall footnote 49 above) and in our opinion it is still far too rare among experimentalists in our field!

60Eccles wrote 3 chapters in Creed et al. (1932). We presume that one of them was chapter VI on central inhibition.

61The following footnote appeared previously as no. 20 (p. 78) in Stuart and Brownstone (2011). "In one of Eccles' autobiographies, he wrote that: 'After some ten years of intracellular recording in the spinal cord I was happy to move into the *much more complex and challenging problems* (*our italics*) presented by higher levels of the nervous system' (p. 13 in Eccles, 1977a). This statement, which is considered naïve by current spinal cord enthusiasts, including ourselves, is more a reflection of Eccles' primary interest in the fundamentals of synaptic transmission and their relation to the mind-brain problem, which is not covered in this article (see pp. 456–452 in Curtis and Anderson), than to the realities of SC research. He recognized the major contribution made to his Canberra group by the presence of Lundberg (see Alstermark et al., 2010) but he had no detailed insight into the 1960s–onward contributions of other key spinal cord and movement neuroscience workers, which have been profound to say the least (see, e.g., Delcomyn, 1980; Stuart, 2007; Grillner et al., 2008; Grillner and Jessell, 2009)."

62For a valuable set of definitions about the mind-brain problem, see Gould (2009). In this non-paginated Internet article Gould espouses the viewpoint that the mind-brain problem is actually the consciousness-brain problem, with consciousness defined as the " ... personal awareness of our: 1. perceptions (of our external and internal environments), 2. thoughts (information processing), 3. feelings (emotions), 4. motivations (drives), and of 5. a unique self having those experiences, (i.e., a sense of self, and thus self-awareness -- the “I” as experienced by an individual)."

63D.G.S. heard one such lecture in 1967, as presented in an 8:00 am lecture to first-year medical students at the University of Chicago. The topic was the ionic bases for the generation and propagation of the nerve action potential. The lecture was remarkably clear and readily comprehended by the medical students. For teaching purposes, Eccles was gifted in designing visual models of the Hodgkin-Huxley mathematical equations on the action potential and other neurophysiological concepts and results. See, for example the figures in his 1963 Nobel lecture (Eccles, 1964a).

64This model appeared again in Eccles (1973), his book entitled "The Understanding of the Brain." He referred to the source as "From Eccles, 1957," but did not list this citation in the reference list. To our knowledge, he did not publish a modified model between 1957 and 1973, and it seems unlikely that he changed the model in his subsequent

talks and lectures.

65Bart Bok [1906–1983] (Millman, 1984) was Professor and Head of Astronomy at ANU in 1957–1966, and then held the same positions at the UA (1966–1983). In a conversation at the UA in 1967 he gave examples to D.G.S. of the singular importance of Eccles' innumerable intramural service contributions in the solidification of the ANU as a major research university.

66D.G.S. noted this behavior first hand in 1966 while Eccles was a visiting professor for a week at the University of California-Davis. Early on his first morning there, he was unexpectedly asked by a well-known professor of veterinary anatomy, Walter Tyler [1925-] (Anon.,1973b) to visit his laboratory for a short time to give advice re the analysis of some data on the respiratory biology of horses. Eccles ended up spending the entire day with this professor and his trainees; reviewing their data, discussing future research strategies and possibilities, and listening to impromptu presentations by the trainees. This was an exhilarating experience for both the Tyler group and Eccles!

67Andersen and Lundberg (1997; p. 325) modified this quote (probably unintentionally) to read: "He has reached long and found much. His kind comes to the world not often in centuries."

68This point was continually stressed by Lundberg to D.G.S. throughout the 38 years of their interactions (1971-2009). It is verified by inspection of the many letters from Sherrington to Eccles as obtainable in the Sherrington fonds of the Woodward Library at the University of British Columbia.

Figure legends

Fig. 1 – Photographs of Sherrington at various times throughout his life. Top left panel: A photo taken in his late teens. Top right panel: A Wikipedia photo taken in his 40s. Bottom left panel: An oil painting by Reginald Grenville Eves (1876-1941) for which Sherrington posed when he was about 70 years of age, and which is hung in the National Portrait Gallery, London and approved by this gallery. Bottom right: A photo taken in Sherringtons 93th year, and used in Granit (1966). Permissions not required for three of the four panels.

Fig. 2 – A time line of selected academic events in Sherrington's life. Details about these events are covered in the text. The blue shadings are epochs of his academic activity and appointments. The orange shadings show the research areas he focused on between his first publications (with Langley) in 1884 and his last one in 1953, which was posthumous. This time line should be viewed in conjunction with that of Molnár and Brown (2010), which had a somewhat different focus and purpose. The present figure's blue shadings include the years of his birth (1857) and death (1953) and 8 epochs within this lifespan. 1857-1870: An idyllic childhood in the academically emphasized home of his presumed father, Dr. Caleb Rose. 1870-1875: Five years at Ipswich Grammar School where he excelled in all of his coursework, poetry, and several sports. 1876-1879: Premedical studies at St. Thomas's Hospital-University of London. Then medical school, which was first briefly at the University of Edinburgh and then back at St. Thomas's Hospital. 1879-1887: University of Cambridge for B.A. (1884), M.B (1885), M.A. (1887) and a variety of other clinical and research experiences at Cambridge and in London and Europe. 1887-1895: Lecturer in Systemic Physiology at St. Thomas's, and conjunctive appointments in 1891-1895 as Director of the Brown (Veterinary) Institution of Preventative Medicine, University of London, and as a research fellow and tutor, University of Cambridge. 1895-1912: Professor of Physiology, University of Liverpool. 1913-1935: Professor of Physiology, University of Oxford. 1936-1952: Retirement successively (1) as a homeowner in Ipswich for almost 4 years (1936-1940), (2) leaving this town due to its initial WWII bombing and spending a brief period in the more heavily bombed London (1940), (3) fortuitously becoming a guest in the Master's Lodge of his former Cambridge College, Caius (~1940-1946); (4) needing a degree of care for his painful arthritis in nursing homes in first Droitwich (northeast of London) and then Eastborne (~1946), just east of Brighton; and (4) finally a degree of serenity and many visitors at a home purchased in Eastborne near the seashore (~late 1946-1952; see C.R. Sherrington, 1975). The orange shadings show the tripartite evolution of Sherrington's main research and conceptual contributions, taking into account the analysis of Stuart et al. (2001; their Table 11.1). These contributions were approximately in overlapping epochs. 1884-1948: Suprasegmental motor control, including the functions of the cerebral cortex, the cortico-motoneuronal system, and the cerebellum, and the segmental convergence of descending command and sensory feedback signals; 1884-1932: Segmental motor control**2**, including striated muscle being a sense as well as a force organ, the properties of muscle receptors, central excitatory vs. inhibitory states, the presence and significance of disynaptic spinal pathways, the final common path, integrative reflex actions, spatiotemporal summation of reflex activity, the motor unit and its muscle component, the discharge zone of motoneurons and their subliminal fringe. 1897-1932: the overall function of the brain and spinal cord, including the role of synapses in reflexes and behavior, and active inhibition as a coordinative CNS mechanism. 1936-1953 (1 posthumous article): discourse on the nature of humankind as viewed from the perspective of the interface between neuroscience and humanistic/philosophical reasoning.

Fig. 3 – The anatomical arrangement for Sherrington's 1893b first note article. Shown from rostral to caudal on his Fig. 1 (p. 561) are several mixed (sensory and motor) nerves connecting the lumbosacral portion of the spinal cord to a muscle and a muscle group of the upper hindlimb (Va. Cr., vastus crureus; Hamstring group). His test nerves included: A.c., anterior crural nerve trunk, with its cutaneous (C') and muscular (m') branches including one to vastus crureus; Sc, Sciatic nerve trunk, with its divisions to P. (popliteal nerve), hamstring muscles, which include a cutaneous (c') branch, and divisions to the I.P. (internal popliteal) and E.P. (external popliteal) nerves. This and subsequent relevant figures have been reprinted with permission of the publishers.

Fig. 4 – The first myographic recordings published by Sherrington on reciprocal innervation in his 1905b 8th note. (Top panel) The "flexion reflex" was observed in Fig. 1A as a reflex contraction (excitation) of the flexor muscle of the knee and in Fig. 1B (Bottom panel) as a reflex relaxation (inhibition) of the extensor muscle of the knee. The stimulated nerve was a twig of the internal saphenous below the knee. The stimulation for both panels was by a series of break induction currents, the number and frequency of which are shown by the top sawtooth traces in both panels. We have replaced the original time scale in both panels by a 200 ms scale bar. The bottom panel observation was made from the same preparation as in the top panel and about 4 minutes later. We have used an arrow to indicate for both panels the start of the1-s sweep, in which ~6 shocks were delivered just before the reflex contraction set in. The intensity of the stimulating shocks was feeble, hence the relatively long latent period.

Fig. 5 – Sherrington's first conceptual figure of reciprocal innervation and inhibition in the same 1905b 8th note article. The Fig. 8 diagram indicated connections and actions of two afferent spinal root-cells, α and α^1, in regard to their reflex influence on the extensor and flexor muscles of the two knees. Other labels include: α, the same root-cell afferent from skin below knee, i.e., in hamstring nerve; e and e^1, efferent neurons to the extensor muscles of the knee, left and right ; δ and δ^1, efferent neurons to the flexor muscles; E and E^1, extensor muscles ; F and F^1, flexor muscles (note faintness of the F and F^1 labels). The sign **+** indicates where the afferent fibres α and α^1 excite the motoneuron to discharging activity, whereas the sign **–** indicates where they inhibit the discharging activity of the motoneurons.

Fig. 6 – Various postures of decerebrate cats under different circumstances. (Top panel) Plate 3-Fig 1 in Sherrington 1898a.The posture assumed in decerebrate rigidity (see p.159 and p.174 in1898a text). (Bottom panel) Fig. 1 in Sherrington (1898b). a. Position of animal after transection at calamus scriptorius. b. Position of animal after ablation of both cerebral hemispheres when decerebrate rigidity had developed. c. Position of animal after ablation of one cerebral hemisphere when decerebrate rigidity had developed. d. Effect on decerebrate rigidity of severance of afferent spinal roots of left fore-limb.

Fig. 7 – Fig. 1 in Sherrington (1913c) showed his approach to the study of central spinal inhibition in vertebrate preparations. He compared the direct excitatory and inhibitory innervation of visceral and vascular smooth muscle from the CNS and peripheral ganglia (top panel) to the excitatory and inhibitory innervation of skeletal muscle via its motoneurons in the spinal cord (bottom panel). (He had sought long and hard for direct inhibitory innervation to skeletal muscles in vertebrates as observed in invertebrate preparations). Note that for motoneuron innervation he did not connect the inputs to the generalized cell body of a motoneuron, a collation of which he termed a "motor centre"

(dotted circle) even though he had conjectured on this in Fig 5 above (1905b paper). From Fig. 1 in Sherrington (1913c).

Fig. 8 – Sherrington's 1910b model of the nature of reflex stepping. Sketches show the muscles he found to be active in the flexion (A) and extension (B) phases of the reflex step of the cat. Muscles in the A group included: A, tibialis anterior; B, biceps femoris posterior; E, extensor brevis digitorum; F, tensor fascia femoris brevis; G, gracilis; I, psoas; L extensor longus digitorum; M, gluteus minimus. Those in the B group included: 0, quadratus femoris; 1, crureus; 2, vasti; 3, adductor minor; 4, adductor major (a part); 5, semimembranosis; 6, biceps femoris posterior; 7, gastrocnemius; 8, soleus; and 9, flexor digitorum longus.

Fig. 9 – Possibly, Sherrington's first sketch of a motor unit (recall footnote 14). His Fig.1 legend in Sherrington (1929) read: "Schema of convergence point and motor unit. M, mirror-myograph. G, galvanometer." In his drawing the neuronal component of the motor unit was shown to begin at the axon hillock and terminate as axon collaterals innervating the axon's "own" muscle fibers. The cell body of the motoneuron is shown within the "pool" (area within dotted circle) of motoneuron cell bodies supplying a single muscle. (The modern definition includes the motoneuron's soma and dendrites). The figure shows that Sherrington clearly understood that the motoneuron's cell body and possibly dendrites were where the motor unit integrated the unit's excitatory and inhibitory input (arrow-tipped lines entering the pool and representing either excitatory or inhibitory inputs) as was in keeping with his concept of a motoneuron pool as the "final common path" to its portion of the musculature.

Fig.10 – Photographs of Eccles at various times throughout his life. (Top left) In Melbourne, Australia with his parents and sister, Rose, in ~1910, when he was 7 (Mennis 2003; pg. 8). (Top middle) At the University of Melbourne in 1924 during his early 20s, and completing his M.B. and S.B degrees (Mennis 2003; pg. 9). (Top right) In his early 30s in the UK when visiting the recently retired Sherrington at his Ipswich home in 1936 (Granit, 1966; plate 10). (Bottom left) With Stephen Kuffler (1913-1980; Nicholls, 1998) on his right and Bernard Katz (1911-2003; Sakmann, 2007) on his left in downtown Sydney, Australia in the early 1940s on the way to giving a lecture to medical students at the University of Sydney (multiple sources). (Bottom middle) In his early 60s at the ANU after being awarded a Nobel Prize in Physiology in 1963. See: < https://www.google.com/?gws_rd=ssl#q=Photographs+of+John+Carew+Eccles >. (Bottom right) Eccles at the age of ~83 years (On book cover of H Eccles and HJ Biersack, 2000). Reprinted with permission, respectively, of Mary Mennis, Nobel Foundation, and Professor Biersack.

Fig.11 –A time line of selected academic events in Eccles' life. This figure is organized like that for Sherrington in Fig. 2, using some of the same and other standard abbreviations. The blue shadings include the years and locale of his birth (1903) and death (1997), and his approximate years of academic training and subsequent appointments. ISO3166-1 3-letter country abbreviations are used for the 5 countries he lived in throughout his lifetime. Note that there were 12 epochs within this lifespan. 1903-1914: A stable academically and athletically oriented childhood in Melbourne and then Warrnambool, a town (later city) south west of Melbourne in the State of Victoria. 1915-1919: Four years at Warrnambool High School and a fifth (final) year at Melbourne High School emphasizing science and mathematics. 1920- 1925: Medical School at the University of Melbourne followed by a 6-month post M.B.-S.B residency at St.Vincent's Hospital, Melbourne. 1926-1927: Honors Undergraduate Program Rhodes Scholar @

Magdalen College-University of Oxford, graduating in mid-1927 with First Class Undergraduate Honors in Physiology and Biochemistry. In this epoch his academic advisor was Sherrington. 1927-1934: Junior Research (1927-1929) and Medical (1932-1934) Fellow w/ Christopher Welch University Scholarship (1927-1929) & Staines Medical Fellowship (1932-1934). Latter @ Exeter College-University of Oxford. PhD in 1929, and research with Sherrington till late 1931. 1934-1937: Tutorial Fellow at Magdalen College and University Demonstrator in Physiology (collectively presumably equivalent to an assistant professor in North American universities). 1937-1943: Director of the Kanematsu Institute of Diagnostic Pathology, Sydney Hospital, in central Sydney, Australia. Strangely, he had no formal association with the University of Sydney even though he gave lectures there and in 1938 was elected a Foundation Fellow of the Australasian (Australia and New Zealand) College of Physicians. 1944-1951: Professor of Physiology and initially Biochemistry, University of Otago, Dunedin, New Zealand 1950-1966: Professor of Physiology, and Head of the John Curtin School of Medical Research (JCSMS), Australian National University (ANU), Canberra, Australia (1950-1966). An arrangement between the ANU and the University of Otago allowed him to remain in his Dunedin laboratory until temporary space became available at the ANU in late 1952. 1966-1968: Member and Head of own research group, A.M.A. Institute of Biomedical Research, Chicago, United States. 1968-1975: Professor of Physiology and Biophysics, State University of New York (SUNY)–Buffalo, United States. 1975-1997: Retirement years in own home in Contra, Switzerland, with several visiting appointments, including German ones at the Max Planck Institutes in Frankfurt and Göttingen, and at the Universities of Basel-Switzerland, Genoa-Italy and Wurzburg-Germany. The orange shadings show the evolution of Eccles's main research and conceptual contributions, which were mostly in overlapping epochs. 1928-1977: Central inhibition studied with progressively more refined techniques, from surface recording with various types of bipolar electrodes to EC- and then IC-recording in the CNS with microelectrodes. 1928-1963: Spinal reflexes, mechanisms, and concepts, including 1928-1931 training and collaboration with Sherrington on spinal central excitatory and inhibitory states, spinal reflexes in general, and the spinal flexion reflex in particular. 1934-1937: Mechanisms controlling rhythmicity in the mammalian heart. 1934-1952: Electrical vs. chemical synaptic transmission in the CNS and the peripheral neuromuscular and neuroganglionic nervous systems. 1944-1962: Muscle and brain plasticity.1947-1998: Mind-brain issues (one posthumous article). 1951-1975: Application of intracellular recording to study the neurophysiology (including function and circuitry) and neuropharmacology of spinal motoneurons and interneurons, and supraspinal neurons in largely the brainstem, hippocampus and cerebellum. 1975-1989: Role of the forebrain**,** in particular the supplementary motor area, in the initiation and control of voluntary movement.

Fig.12 – Representative figures in Eccles' 1932 book chapter of responses in spinal cats. (Top panel) Read from right to left. Panel shows electrical and mechanical responses of the tibialis anticus muscle to single electrical shocks applied in two conditions. The upper 3 traces show stimulation of the ipsilateral popliteal nerve, whereas the lower 3 traces show stimulation of the contralateral peroneal nerve 50 ms before stimulation of its ipsilateral equivalent. (The middle two traces are not explained in the figure legend and text). (Second from top panel) In Fig. 49 the upper trace showed complete inhibition in a spinal cat of the knee jerk reflex for a period of 0.8 s after a single electrical shock (lower trace, at asterik) was applied to the ipsilateral hamstring nerve. The time (T) vertical bars had intervals of 0.1 s. (Third from top panel) Fig 51 showed inhibition of the vastus crureus muscle's stretch as brought on by 50/s electric shocks (beginning at asterik) of the small sciatic nerve for about 7.4 s

(downward deflection of lower trace). (Bottom panel) The lower continuous trace (Fig. 55) showed inhibition of the crossed extensor reflex of the vasto-crurues cat muscle, as evoked by repetitive electrical stimulation between E and E^1. At I, a single electrical shock was applied to an inhibitory nerve. The broken line trace shows what would have been the profile of the control (uninhibited reflex).

Fig.13 – Examples of preparations and techniques acquired by Eccles during his Oxford years as illustrated in his 1932 spinal cord report with Hoff and his 1935 superior cervical ganglion report**.** Many of the techniques were described in Eccles and Sherrington (1931a) but not the motor unit work now described. (Top panel) Fig. 1 in Eccles and Hoff (1932) showed tetanic reflex responses of the soleus muscle elicited by repetitive stimulation through electrodes E of the contralateral popliteal or peroneal nerve. Using silver pins in the muscle, the extracellularly recorded multi-motor unit muscle action potentials were led to a string galvanometer, and photographed with a falling plate camera at a plate speed of ~150 mm/s. The nerve supply to soleus was then dissected down until there remained but one reflexly active motor unit. This was indicated by the succession of identical multi-fiber action potentials, with a fairly regular rhythm at ~10-20/s. (*Not shown in this figure*). The dissection was done either peripherally where the nerve branched into the muscle or centrally by dividing the relevant ventral root filaments (*Presumably at d in the figure*). Antidromic impulses to soleus motoneurons were set up by stimulation of the intact left- side popliteal nerve by electrodes (A in figure), usually using supramaximal electric shocks. (Bottom panel) The left side drawing in Fig. 1 of Eccles 1935b showed that both stimulating and recording leads were raised from the cat in a study on the stellate ganglion. The arrow in the right side figure indicated the stimulus artifact, which can barely be detected about 6 ms before the action potential. 1 calibration sawtooth cycle = 10 ms.

Fig.14 – Figures in Eccles' (1936) first major review on synaptic and neuromuscular transmission. (Top panel) The Fig. 4 diagram showed a generalized ganglion cell with 2 synapses and the location of some responses. The arrows inside the square soma diagram show Eccles' perception of the spread and summation of his so-called "detonator responses," as occurring at the two synapses. (Bottom panel) The simple Fig. 10 diagram showed the relation of extra-spinal recording leads (at arrows) from the dorsum of the cat spinal cord to nerve cells of the gray matter, the text focus being on motoneurons. The point of this diagram was to contrast the extracellular recording situation in spinal motoneurons to that in generalized ganglion cells (see pp. 386-387).

Fig.15 – Evolution from 1945 to 1949 of Eccles' ideas about the role of electrical synaptic transmission in central excitation and inhibition in the cat spinal cord**. (Top left panel)** Figs. 1-3 in Eccles (1945) were his first conceptual overview of electrical synaptic transmission. In this panel Fig. 1 showed a horizontal view of the terminal end of a nerve fiber at a synaptic junction with the text providing its capacitive and resistance values and his reason that inductance could be ignored. The model proposed that the current generated by an impulse penetrated in part the effector cell and gave a diphasic action, first an anodal focus at the junctional region with a cathodal surround (Fig. 2a*),* which quickly reverses (Fig. 2b) when the peak of the impulse reached the junction. This latter cathodal current of high density evoked an intense local response of the effector cell which outlasted the second phase of penetrating current flow, and provided a relatively enduring focus of very low polarization and resistance through which adjacent regions of the effector membrane proceeded to discharge (his Fig. 3). (Top right panel) Fig. 1 in Brooks and Eccles (1947a) showed a sketch of a very-short-axon Golgi Type 2 cell (G) to explain inhibitory electrical synaptic transmission. An

inhibitory afferent (I) was envisioned with excitatory contact to a Golgi cell which, in turn, made contact with a motoneuron (M). When the interneuron was subliminally depolarized (i.e., no action potentials generated), inward current in the soma was envisioned to flow down the short axon to make low resistance electrical coupling with a motoneuron (M), thereby producing hyperpolarization via outward current. (Middle left panel) Fig. 5 in Brooks and Eccles (1947b) was an example of Eccles' first use of extracellular intraspinal needle electrodes, which were inserted into a spinal motor nucleus to record the integrated synaptic response of several motoneurons The figure showed the ventral root extra-axonal response (a) and the extracellular focal synaptic response in the spinal cord (b) to a stimulus just maximum for the large afferents of the quadriceps muscle. The cat was deeply anesthetized to ensure the Golgi cell's excitatory responses did not reach action potential firing levels. It was claimed (p. 271) on somewhat dubious grounds that all of the observations made in this study agreed "closely with the predictions of the electrical hypothesis of synaptic transmission." Nonetheless, this article is of particular historical significance because Eccles' use of needle electrodes enabled his analysis of focal synaptic potentials, which was essential for facilitating his later intracellular recording studies. (Middle right and bottom panels) Figs. 7 and 9 in Eccles (1949) were sketches based on experimental testing of the Golgi cell hypothesis shown when these cells were discharging impulses rather than being passive. Fig 7 (middle right panel) showed inhibitory paths without synaptic relay from antagonistic muscles to vicinity of the quadriceps motoneuron nucleus (Q). H and G were input from large proprioceptive fibers of hamstring and gastrocnemius muscles and C was an indirect cutaneous inhibitory pathway with additional interpolated interneurons. The results suggested, but did not prove, that this input was to first-order Golgi cells near a motoneuron nucleus, with the authors stating (p. 581) "There is as yet no adequate neuro-histological study of this problem." Fig 9 (bottom panel) was a sketch of the post-synaptic surface of a motoneuron, with 2 excitatory knobs, E, separated by an inhibitory knob, I, which, according to the Golgi Cell Hypothesis, produced an anelectronic focus on the post-synaptic membrane. Eccles' experiments suggested that such an anelectronic focus had no action, not only on initial generation of local membrane responses, but also on discharge of a motoneuron's membrane into electrical sinks so produced: i.e., development of a catelectronic surround. When local excitatory responses attempted to spread along the membrane, however, the anelectronic focus under the inhibitory (I) knob limited further excitation. "Thus the inhibitory hypothesis would predict that, in inhibited motoneurons, synaptic potentials show no depression until the latter part of their rising phase" (p. 581).

Fig. 16 – Some key points in the Brock et al. (1951-1953) and Eccles' (1952b) manuscripts, and the Eccles' 1953 book. (Top panel) Figs. 1 and 2 in Brock, Coombs, and Eccles (1951) were the first published figures of the intracellularly recorded action potential of a mammalian (cat) spinal motoneuron. The authors commented " …With motoneurons in good condition … the negative after-potential reverses at about 4 ms to a positive after-potential (*this term was later considered a misnomer and changed to afterhyperpolarization (AHP)*), reaches 3–4 mV at 20 ms, the total duration being about 120 ms" (p. 15 in Brock et al., 1951). (Second from top panel) Fig. 5 in Brock, Coombs, Eccles (1952b) showed recordings of clear-cut AHPs in motoneurons supplying a hamstring (A) and a calf (B) muscle. The time scale is for both records. (Middle panel) Eccles (1952b) presentation at the impactful Cold Spring Harbor 1952 symposium on neuron biology. The Fig 1 diagram showed his perception of the mechanism for the resting membrane potential of a generalized neuron. The left-side showed the electrical equivalent of a small piece of surface membrane, a capacitor in parallel with a resistance-battery component. When potassium concentrations were as indicated, the battery voltage given by the diffusion potential would be 87 mV. The right side inwardly

and outwardly directed arrows gave respective magnitudes of inward and outward potassium fluxes. The fluxes were equal at a membrane potential of 87 mV, which was thus the equilibrium potential for potassium. The relative changes in inward and outward potassium fluxes for hyperpolarization to 94 mV and a depolarization to 80 mV were shown by the respective length of the arrows. (Second-lowest panel) Eccles' (1952b) Fig 2 diagram showed time courses of depolarization (a) and hyperpolarization (b) produced by small rectangular currents which were applied for 0.5 ms. They were respectively outwardly and inwardly directed across the surface membrane of the model. The resting potential was shown at 87 mV and the applied current caused a change of 7 mV, which on cessation of the applied current decayed back to baseline on account of the resulting imbalance of the resting ionic fluxes. The larger outward current caused depolarization to the critical level (10 mV) at which there was a self-regenerative activation of the sodium carrier, with a resulting further potential change in the same direction (shown by the arrow), which would approach the sodium equlibrium potential. Zero (0) on the time scale marks the end of applied currents. (Bottom left panel) Fig. 4A in Brock, Coombs, and Eccles (1953) showed a motoneuron's postulated lines of current flow during the rising phase of the "small simple spike." The isopotential line at earth potential is drawn orthogonally and marked "0." Fig 4B showed the falling phase of the small simple spike. The rapid repolarization of the active motoneuron membrane caused it to act as a source of external current, so aiding in the repolarization of the soma-dendritic membrane. (Bottom right panel) Fig. 62 in Eccles' (1953) monograph showed that while he still accepted Lloyd's claim of direct (monosynaptic) inhibition but he had come to grips with the early gamma motoneuron literature. The diagram showed a large motoneuron (LM) and a small (gamma) motoneuron (SM) in the spinal cord with axons innervating respectively a large muscle fiber and a small one, a muscle spindle. (The convention was filled knobs being excitatory and open knobs inhibitory). The group Ia afferent axon of the annulo-spiral endings of the polar region of the muscle spindle was shown ending monosynaptically on the LM, and possibly also on the SM. (*At that time, however, Eccles did not know about beta motoneurons*). The polysynaptic connections of cutaneous afferents from two skin areas were shown to motoneurons, one being excitatory, and the other inhibitory. Note also excitatory and inhibitory input to both motoneurons from fiber collaterals of ventro-lateral tracts. Finally, the plus (+) and minus (–) signs indicated stretch (the arrow within the muscle spindle pointing to tendon) vs. contraction (the arrow within the large muscle fiber pointing in the opposite direction).

Fig. 17 – Recordings that contributed to Eccles' instant rejection of his electrical transmission hypothesis for cat motoneurons. Note the respective sizes of the biceps semitendinosis (BSt) monosynaptic EPSP set up by a small afferent volley in the BSt nerve (1) as compared to a disynaptic IPSP in the same MN (2) produced by a much larger afferent volley in the quadriceps muscle nerve. The same time scale is used in both records but the potential scales are different. Excerpted and modified from Fig. 12 in Brock et al. (1952b) with permission of the publisher.

Fig. 18 – The first intracellular recordings published in each of the three 1953 studies initiated in Eccles' Canberra laboratory. The recordings were composed of 40-50 faint traces to eliminate random noise. (Top panel) Fig.1A-C in Coombs, Eccles, and Fatt 1953) showed intracellularly recorded motoneuron potentials generated by a direct inhibitory volley. The progressive change in IPSP profile was attributed to diffusion of Cl^- out of a relatively large-tipped microelectrode filled with 3M KCl, the membrane potential remaining constant at 44 mV and the IPSP reversing to a small EPSP. The voltage calibration in this panel was 5 mV. The unlabelled time calibration was stated as in ms, but this had to be incorrect**.** (Middle panel) Fig. 1A in Eccles, Fatt and Koketsu (1953)

was composed of intracellular recordings from a biceps-semitendinosus motoneuron as it responded to antidromic volleys, from above downwards, of the motor axons of biceps semitendinosus, semimembranosus and plantaris (no response). The motoneuron was not invaded antidromically by an impulse in its own motor axon so in the uppermost record there was no complication of an AHP. Time scale was in ms, and the voltage scale was 5 mV**.** Fig. 1B was organized similarly. It showed a motoneuron's hyperpolarization set up by an antidromic volley fired through the 7th lumbar ventral root. The upper record was the control response, a long period of postsynaptic inhibition. The lower reduced inhibitory trace was after the i.v. injection of dihydro-β-erythroidine hydrobromide, a nicotinic ACh inhibitor. Voltage scale was 5 mV. Note the slower time scale,10 ms intervals. (Lower panel) Fig 1 in Eccles, Fatt and Landgren, (1954a) compared the latency of monosynaptic EPSPs and the so-called "direct" IPSPs in the cat spinal cord. The intracellular recordings were from a biceps-semitendinosis motoneuron at the upper S1 level showing EPSP (Fig. 1A) and IPSP (1B) responses to afferent volleys from biceps-semitendinosis and quadriceps, respectively. The EPSP in A rose quickly to a spike (latent periods 0.55 and 1.45 ms, respectively, for A and B). The time scale below B had 1 ms intervals (also for A)**.** Fig.1C showed extracellular recording at higher amplification and faster speed just outside the motoneuron shown in A-B, downward deflection being negative. The latent period of the spike attributable to presynaptic terminals (1.1 ms) was measured between the two arrows (time in ms). Fig. 1D-E showed intracellular recording as in Fig 1 A-B, of EPSP and IPSP responses, but evoked by the same afferent volleys in a flexor motoneuron at the upper L3 level (probably a sartorious motoneuron). Extracellular recording showed that the initial less-steeply sloped deflexion in E was due to the potential field of the focal synaptic potential generated by adjacent quadriceps motoneurons, the IPSP beginning at the arrow. Time as in Fig.1B.

Fig. 19 – Examples of recordings in the recurrent Renshaw circuit achieved in Eccles laboratory. (Top left panel) The top trace in Fig. 2B of Eccles, Fatt and Koketsu (1953) showed the high signal-to-noise ratio of extracellular recording of a Renshaw cell's discharge in response to an antidromic volley from motor axons of the biceps-semitendinosis muscle. The lower three traces showed the less efficacious effects in the same interneuron of similar volleys in motor axons of respectively the gastrocnemius muscle, the flexor digitorum longus muscle, and the deep peroneal group of muscles. Calibrations: ms and 0.5 mv. (Top right panel) Fig. 6 F-J of the same authors' 1954a article showed intracellulary recorded responses of a Renshaw cell to a maximum volley in the 7th lumbar ventral root, the upward deflection indicating positivity of the microelectrode recording to an indifferent electrode this being the reverse of conventional extracellular recording. In F note that the upper trace extracellular surface recording is also shown inverted. Three different sweep speeds are shown for F, G, and H. The smaller H responses are due to progressive failure of the cell. In F-H the amplitude calibration is 5 mV. I and J show potentials just inside (as in F-H) and just outside, respectively, another Renshaw cell with the recordings at a much slower sweep speed (time scale intervals 1 ms). The voltage bar is 1 mv. (Bottom left panel) Fig 1A-F in Eccles, Eccles, Iggo, and Lundberg (1961) showed intracellular recording responses of a Renshaw cell evoked by submaximal α volleys from the medial gastrocnemius nerve, of increasing size from A to D and by maximal volleys in E and F. (Bottom right panel) Fig 4 A-D in the same article showed a series of Renshaw cell responses recorded intracellularly as evoked by antidromic volleys set up by stimulation of the L7 ventral root, submaximal in A-B and maximal in C (all at the same sweep speed). D is the same response as C but at a faster sweep speed as shown above it. The same voltage calibration applied to all 4 recordings.

Fig. 20 – The Fig. 18 sketch of the recurrent Renshaw circuit in Eccles, Fatt, and Koketsu (1954) was a slight visual improvement of the one published in their 1953 article. It summarized the postulated sequence of events from an impulse in a motor axon to the inhibition of a motoneuron. All events were plotted on the time scale shown on the abscissa, and the corresponding histological structures are shown diagrammatically to the left (note the matching arrows). The six plotted time courses were for the following events: A, the electrical response of an impulse in a motor-axon collateral; B, the effective concentration of the acetylcholine which it liberates at a synaptic terminal; C, the electrical response evoked in a Renshaw cell by the cumulative effect of acetylcholine at many synapses, showing impulses superimposed on a background depolarization; D, the effective concentration of inhibitory transmitter substance which these impulses liberated at a synaptic terminal of the Renshaw cell, showing summation at the high initial frequency; E, the IPSP generated in the motoneuron by the Renshaw cell discharge and the inhibitory transmitter shown in C and D, respectively; F, the aggregate IPSP evoked in a motoneuron that is repetitively bombarded by many Renshaw cells which progressively become more asynchronous so smoothing the latter part of the ripple shown in E. The morphological diagram to the left shows converging synapses both on the Renshaw cell and on the motoneuron.

Fig. 21 –This figure emphasized spinal inhibitory pathways described in Eccles' (1969) monograph, which summarized research initiated in 1953**.** Top panel: This was Fig. 5 in Coombs, Eccles and Fatt (1955). It showed diagrammatically their perception of an activated synaptic knob. The synaptic cleft was shown at 10 times the scale for width vs. length. The current was thought to pass forward along the cleft and into the cell across the activated subsynaptic membrane. Elsewhere it was shown to pass outward across the membrane, and in doing so generated depolarization of the EPSP**.** 5B was a similar diagram showing the reverse direction of current flow for an activated inhibitory knob and its associated IPSP**.** The ordinate showed the equilibrium potentials for sodium (E_{Na}), potassium (E_K) and chloride (E_{Cl}) ions, together with the equilibrium potential for postsynaptic inhibition (E_{IPSP}). The equilibrium potential for the EPSP (E_{EPSP}) was shown at zero. 5C showed an EPSP when generating a spike potential at about 18 mV. The 5D diagram showed an EPSP and IPSP alone (broken lines) and then when interacting with each other (solid line). As a result of the depressant effect of the IPSP, the EPSP that had alone generated the spike shown in 5C was thought to be no longer able to reach the threshold level for spike initiation. Middle left panel: Fig. 6A sketched the inhibitory pathways to motoneurons via their axon collaterals and Renshaw cells. 6B showed extracellular recording of a Renshaw cell being excited by an antidromic volley in the motor axons of the later gastrocnemius muscle. Middle right panel: Fig. 2 in Eccles, Fatt, Landgren and Winsbury (1954a) was a sketch of a transverse section of the cat spinal cord in the lower lumbar region with one microelectrode positioned in a motoneuron receiving disynaptic inhibition from interneurons in the intermediate nucleus and another microelectrode positioned outside an interneuron in the intermediate nucleus where it is monitoring excitatory Ia afferent input to the intermediate nucleus. (Bottom panel) Fig 11B-O in the same article provided examples of excitatory and inhibitory motoneuron responses as dependent on where the microelectrodes were positioned. In Fig. 11L-O the stimulus was applied through the microelectrode in the intermediate nucleus (work of Eide, Lundberg and Voorhoeve, 1961).

Fig. 22 – Two photos of Renshaw. Sources and exact years not known. (Left) About 1941-1943, while in the Department of Zoology at Oberlin College. (Right) About 1948 while a faculty member at the University of Oregon School of Medicine (now the Oregon

Health & Science University) in Portland, Oregon.

Fig. 23 –Some features of Renshaw's work on recurrent inhibition. (Top left panel). Fig. 6D in Renshaw (1941) showed his perception of the spinal pathways in his first demonstration of recurrent inhibition in a cat under light barbiturate anesthesia. The experiment involved conditioning motor discharges of the crural nerve by antidromic volleys in other branches to the quadriceps. The caudal cord had been transected, and all sacral and lumbar dorsal roots on the tested side were cut. The tested "reflexes" were initiated by stimulation of the dorsal columns at L4. The diagram showed all the neurons and synaptic connections which might have been concerned in the production of the recurrent inhibition. (Top right panel**).** Fig 1 in Renshaw (1942a) showed responses in a decerebrate cat of motoneuron somas (a,c) vs. motor axons (b,d). Records a and c were obtained with a microelectrode in the ventral horn whereas b and d were recorded by a small Ag-AgCl ball electrode on ventral root axons. An upward deflection indicated negativity at the microelectrode. The stimuli were single (a,b) and repetitive (c,d) shocks, maximal for α fibers, as delivered to the ventral root. The voltage amplification for records a and c was 5 times that for b and d, with the time scale equal for both sets of records. (Bottom panel) Fig 7 in Renshaw (1946b) showed excitation of ventral horn interneurons by primary afferent and antidromic motor volleys in an anesthetized cat with a severed ipsilateral dorsal root. Record a, stimulation of L6 dorsal root; b, stimulation of the deafferented crural nerve; c and d*,* stimulation of L6 dorsal root followed by stimulation of the deafferented crural nerve. Note, the presence of a marked conditioning effect in record c and the absence of such a definite effect in record d*.*

Fig. 24 – Some photos of Karl Frank and one of Michelangelo Fuortes, who co-authored several refereed articles and book chapters with Frank while at the NIH in 1955-1961. (Top left). Frank shown when 40 working in his NIH laboratory. (Top right) Frank when 65 attending an NIH function. (Bottom left). Frank steering his yacht across the Atlantic Ocean in 1972 with a crew of four. (Bottom right) Fuortes when 55 on the same yacht and voyage, as part of the crew. The figures were kindly provided by Eric Frank, the son of Karl Frank, and also a prominent neurophysiologist, like his father.

Fig. 25 – Fig. 5 in Frank (1959**)** was the first in the literature showing the clear-cut existence of presynaptic inhibition as described in Frank and Fourtes (1957). Frank's idea was that this might be a form of what he termed *remote inhibition.* The left side of Fig. 5 was a diagram of the mechanisms of direct excitation and inhibition. Activity in one group of nerve cells was shown to arrive at the junctions or synapses of the large motoneuron via the fine terminal fibers with their specialized processes, the *boutons terminaux.* These were indicated in the diagram by the small filled and open circles plastered over the cell membrane of the motoneuron (*these are not clear in the figure*). Excitatory or depolarizing incoming volleys were envisioned to arrive via the fibers indicated with solid lines and open circles. Direct inhibitory neural inputs shown by the dotted lines and filled circles. Below, the diagram tracings were of the potentials recorded by the intracellular micropipette within the soma of the cell. It showed the combined effect of such volleys on the cell's overall potential. The top trace showed the cell's response to an excitatory volley initiated by an electrical shock at E, which arrived at the motoneuron in about 2 ms and produced the transient depolarization shown. If this EPSP was large enough to reach threshold, an action potential was produced. For the case illustrated, the volley was inadequate to reach threshold. In the bottom trace, the effect of an inhibitory volley was illustrated. Here the negative resting potential

inside the cell became more negative and the transient in potential was the IPSP. The center trace showed the principle underlying this direct type of inhibition. A given excitatory volley was made less effective in bringing the cell membrane to its critical firing level by the competing inhibitory synaptic potential (produced by a shock at I). Both of these synaptic potentials were interpreted as being caused by chemical transmitter substances, which were thought to change the specific ion conductances of the cell membrane. (*Note that when Frank published this portion of the figure the nature of these chemical transmitters was not known for transmission in the CNS*). The right side of the figure showed the new type of inhibitory mechanism, which Frank called *remote inhibition.* This differed from direct inhibition in the implied site of its action. In the upper trace on the far right side a standard EPSP is shown. The middle trace showed his idea that the effect of the test volley was reduced if a test excitatory volley (initiated at E) was preceded by an inhibitory volley to a selected nerve (initiated at I), i.e., the EPSP was reduced. However, as shown in the lower trace, the inhibitory volley alone produced no change in the potential across the cell membrane. This is what would be expected were the inhibitory nerve impulses interacting with the excitatory volley before the latter reached the surface of the motoneuron. This possibility was illustrated in the diagram labeled *presynaptic remote inhibition*. Frank thought that no change was produced in the cell membrane by the inhibitory volley alone since this volley never reached the cell. An alternative hypothesis was illustrated on the far right, labeled *dendritic remote inhibition.* Here it was supposed that interaction occurred between the inhibitory and excitatory volleys but at sufficient distance from the cell body that the effect of the inhibitory volley alone could not be "seen" by the microelectrode. Subsequent work in several laboratories showed that *dendritic remote inhibition* does not normally occur and that the more appropriate terminology for the other possibility was best termed *presynaptic inhibition.* Note, that the two time intervals (lowermost traces) were 1 ms apart.

Fig. 26 – Presumably, the first figures about presynaptic inhibition that Eccles presented to his peers. They appeared in the 1961a volume that followed an international symposium entitled "Nervous Inhibition," which was held at Friday Harbor, Washington, USA on May 31-June 04, 1960. The presumption is required because the editor of this volume, Ernst Florey [1927-1997] (Rheinberger, 1998), pointed out (p. vi) that "The published papers are not necessarily identical with the talks as they were given at the symposium; several of them have been worked over and some of them were expanded." (Top panel) Fig. 6A-E in (Eccles 1961a) was based on the unpublished work of Eccles, Kozak, and Magni. The upper traces in A-C showed dorsal root records and the lower traces showed EPSPs produced by a gastrocnemius afferent volley to a gastrocnemius motoneuron. Compared with the control response (c) in A, the EPSP was diminished when preceded by a biceps-semitendinosis volley. Also the effect of a group Ia volley (B; stimulus strength at 1.4 x threshold) was much less than that of a Ia+Ib volley (C**;** stimulus strength at 2.2.x threshold). In D-E biceps-tendinosis volleys of Ia (D) and Ia+Ib (E) composition were shown setting up dorsal root reflexes in the nerve to gastrocnemius. These were much larger for the Ia+Ib volley**.** Note the difference in time scales for the left and right side responses in D and E. (Second from top panel) Traces A-H were parts of Fig. 7 in the unpublished work of Eccles, Eccles, and Magni (1960). These traces showed spike potentials recorded in the nerve to the flexor digitorum longus muscle. These were evoked by stimulation with brief pulses through a microelectrode in the flexor digitorum motor nucleus. Since the ventral roots were severed, these spikes were produced by group Ia afferent fibers that were excited in the central ramification in the motor nucleus. A gave the control spike size and in B-H the same (shown in the third panel from the top) stimulus was applied at the indicated

intervals in ms after conditioning by a group I afferent volley in the biceps semitendinosis nerve. (Third from top panel) As a continuation of the above figure, I showed the time course of the potentiation of the spike, which gave the time course of the depolarization of the Ia afferent terminals. (Bottom panel) J continued the above figure 7. It showed field potentials (upward deflections signaling negativity) recorded by a microelectrode against an indifferent earth lead at the indicated depths below the cord dorsum; and produced by five goup ! afferent volleys in the posterior biceps semiitendinosis nerve. Each record was formed by the superposition of about ten faint traces.

Fig. 27 –The two diagrams in Fig. 8 of Eccles (1961a) showed possible pathways for presynaptic inhibitory action, which were assumed to have an interpolated interneuron (IN). The axon of the interneuron in A was shown making a chemical transmitting synapse on a Ia afferent fiber close to its termination on a motoneuron (MN). In B Eccles' perception of electrical transmitting synapses are shown from the Ia fiber to the IN and from the axon of the Ia fiber near its termination. Arrows indicated the paths of the presumed intracellular current flow.

Fig. 28 – Figs. 20-21 in Eccles (1961b) were used in his Ferrier Lecture, which was given in the United Kingdom on June 10, 1960. These figures came from the about-to-be published work of Eccles, Eccles, and Magni (1960). (Top panel) Fig 20 A-H showed intracellular recording of an EPSP which a gastrocnemius Ia afferent volley evoked in a gastrocnemius motoneuron, there being about ten superimposed traces for each record. In B-H this volley was preceded at the intervals marked in ms by a maximum group 1 biceps-semitendinosis volley. (Second-from-top panel) A plot of the time course of the EPSP depression that was illustrated for brief intervals in A-H above. (Third-from-top panel) The A-H part of Fig. 21 showed EPSP depression produced in the same motoneuron as in figure 20, but the testing interval was fixed at 9 ms, and the strength of the stimulus applied to the biceps-semitendinosis nerve was varied relative to the threshold as shown for each record. (Fourth-from-top panel). A plot of the percentage depression of the EPSP plotted against stimulus strength relative to threshold for the series partly illustrated in A to H**.** (Bottom panel) The conclusion of Fig. 21 showed on the same threshold scale the percentage sizes of the Ia (filled circles) and Ib (open circles) components of the afferent spikes , as determined by the double volley test.

Fig. 29 – The Fig. 1 diagram of Eccles, Llinas, and Sasaki (1966) showed the principal features that the authors postulated for cerebellar neuronal circuits. Their work showed that the Golgi, stellate and basket cells were all inhibitory in action and conventionally labeled black. The diagram was drawn from a section along the folium such that the main distribution of the basket and stellate cells would be perpendicular to the plane of the diagram. They were also distributed as shown, i.e., to a band of several Purkinje cells along the folium. Arrows indicated the direction of impulse propagation. PAC was for Purkinje axon collaterals.

Fig. 30 – (Top panel) Fig. 4 in Ito's (2011 final book on the cerebellum was his concept of a decomposition/reconstruction cycle, as used in neuroscientific enquiry. He reasoned (p. 6) "Research on the CNS usually starts with the experimental breakdown of a complex system into its simpler elements." He defined a system " ... as a CNS unit (e.g., a spinal segment, the pineal body, the oculomotor system) while it is undertaking a specific operation. ... The dissected elements are assorted to construct models of the original system by means of theories and simulations." His approach was what others call the *inside-out approach* (Stuart, 2007). To Ito, this circular approach may be based on " ... observation-inspired models, model-based predictions, or experimental testing of

a prediction. The model is continuously refined until it simulates accurately the first cycle (outer trajectory), an intermediate (middle) cycle, and the most refined (inner) cycle." (Bottom panel) Fig 5 was Ito's summary of decomposition/reconstruction cycles. For this he showed levels of reconstruction that extended from gene regulation (his -2 on the left side), to the cellular molecular- (-1) neuronal- (0), simple circuit- (+1) and finally, complex circuit (+2) level of analysis. Major examples of research at levels -1 to +1 are also shown.

Fig. 31 – Eccles (1957; p. 26) first published diagrammatic representation of K^+ and Na^+ fluxes through the surface neuronal membrane in the resting state. The slopes in the flux channels across the membrane represented the respective electrochemical gradients. At the resting membrane potential (-70 mV) the electrochemical gradients, as drawn for the K^+ and Na^+ ions, corresponded respectively to potentials, which were 20 mV more positive and about 130 mV more negative than the equilibrium potentials (note the potential scale). The fluxes due to diffusion and the operation of the pump were distinguished by the direction of hatching. The outward diffusional flux of Na^+ ions would be less than 1% of the inward current. This was too insignificant to be indicated as a separate channel in this diagram, because the magnitudes of the fluxes were indicated by the widths of the respective channels.

References

Acierno, L.J., Worrell, L.T., 2001. George Ralph Mines: Victim of Self-Experimentation? Clin. Cardiol. 24, 571–572.

Adrian, E.D., 1924. Some recent work on inhibition. Brain 47, 399-416.

Adrian, E.D., 1934. Cambridge 1904-14. In: Fletcher, W.M. (Ed.), Keith Lucas. Heffer, Cambridge, pp. 88-108. Note: This book was originally written in 1916 but not published until after Fletcher's death.

Adrian, E.D., Bronk, D.W., 1929. The discharge of impulses in motor nerve fibers. Part II. The frequency of discharge in reflex and voluntary contractions. J. Physiol.

Allen, W.F., 1949. Birdsey Renshaw 1911-1948. Anat. Rec. 103, p. 235. .

Allen, G.I., Eccles, J.C., Nicoll, R.A., Oshima, T., Rubia, F.J., 1977. The ionic mechanisms concerned in generating the i.p.s.ps of hippocampal pyramdal cells. Proc. R. Soc. Lond. B 198, 345-361.

Alstermark, B., Hultborn, H., Jankowska, E., Pettersson, L.-G., 2010. Anders Lundberg (1920-2009). Exp. Brain Res. 200, 193-195.

Andersen, P., 2006. Inhibitory circuits in the thalamus and hippocampus: An appraisal after 40 years. Progr. Neurobiol. 78, 264-271.

Andersen, P., Lundberg, A., 1997. John C. Eccles (1903–1997). Trends Neurosci. 20, 324–325.

Andersen, P., Eccles, J.C., Sears, T.A., 1964. The ventrobasal complex of the thalamus: types of cells, their responses and their functional organization. J. Physiol. (Lond.) 174, 370-399.

Andersen, P., Brooks, C. McC., Eccles, J.C., Sears, T.A., 1964a. The ventro-basal nucleus of the thalamus: potental fields, synaptic transmission, and excitability of both presynaptic and postsynaptic componenets. J. Physiol. (Lond.) 174, 348-369.

Andersen, P., Eccles, J.C., Schmidt, R.F., Yokota, Y., 1964b. Identification of relay cells and interneurones in the cuneate nucleus. J. Neurophysiol. 27, 1080-1095.

Angel, A., Magni, F., Strata, P. 1965a. Excitability on intrageniculate optic tract fibres after reticular stimulation of the midpontine pretrigeminal cat. Arch. Ital. Biol. 103, 668-693.

Angel, A., Magni, F., Strata, P. 1965b. Evidence for presynaptic inhibition in the lateral geniculate body. Nature 208, 495-496.

*Anon., 1893. Walter Baugh Hadden, M.D., F.R.C.P., 1893. Brit. Med. J. June 3, pp. 1200-1201.

Anon., 1896. The Times/1896/Obituary/Hubert Ashton Holden. The Times Issue 35065, P. 6, Col. D.

*Anon., 1914. Obituary. Walter Holbrook Gaskell, M.D., F.R.S., Hon. LL.D. Edin. and McGill. Brit. Med. J. September 26, 559-560.

Anon., 1920. Obituary notices of fellows deceased – Ludimar Hermann, 1838-1914. Proc. R. Soc. Lond. B No. 641, pp.xxxviii-xl.

Anon., 1925. Obituary. J. J. Graham Brown, M.D., F.R.C.P.Ed., Consulting Physician, Edinburgh Royal Infirmary. Brit. Med J. March 14, p. 537.

Anon., 1952. Obituary. Herbert Eldon Roaf – M.D. Toronto. D. Sc. Lpool. Lancet 260, p. 784.

Anon., 1964. Obituary. Richard Stephen Creed, T.D., M.A., D.M. Oxon. Lancet July 25, p. 211.

Anon., 1968. Robert Stanley McEwen. Ohio Acad. Sci. 68, p. 244.

Anon., 1973a. Rosenbaum, Herbert E. Biographaphical Directory of the Fellows and Members of the American Psychatric Association. Jaques Cattell Press, New York/London, p. 769.

*Anon., 1973b. Tyler, Walter S(teele). In: American Men & Women of Science. 13th Edition, Vol. 6, p. 4577. R.R. Bowker, New York.

Anon., 1976. Papers and correspondence of John Harold Crossley Thompson, 1909-

1975. See: http://archiveshub.ac.uk/data/gb476-200/1

Anon., 2003. Youmans, William Barton. In: American Men & Women of Science: A Biographical Directory of Today's Leaders in Physical, Biological and Related Sciences. 21st Edition, Vol. 7, p. 653. Thomson/Gale, Detroit, MI.

*Anon., 2014a. Walter Holbrook Gaskell. Brit. Med. J. pp. 559-560.

Anon., 2014b. Rall, Wilfrid. In: American Men & Women of Science: A Biographical Directory of Today's Leaders in Physical, Biological and Related Sciences, 32nd Edition, Vol. 6, p. 42. Gale/Cengage Learning, Detroit, MI.

Anon., 2015. Vilcek Foundation honors Professor Thomas Jessell for biomedical research. Columbia News. See URL first downloaded on February 16, 2016: http://news.columbia.edu/content/vilcek-foundation-honors-professor-thomas-jessell-biomedical-research (First downloaded on February 16, 2016).

Anon., 2016. Friedrich Hans Beck (16 February 1927-20 December 2008). See URL first downloaded on January 19, 2016 : http://research.omicsgroup.org/index.php/Friedrich_Beck

Araki, T., Eccles, J.C., Ito, M., 1960. Correlation of the inhibitory postsynaptic potentials of motoneurones with the latency and time course of inhibition of monosynaptic reflexes. J. Physiol. (Lond.) 154, 354-377.

Arvanitaki, A., 1943. Reactions au stimulus anodique. Étude de la réponse électrique locale de signe positif. Observations sur l'axone isolé de *Sepia* [Reactions to the anodal stimulus. [Study of the local electrical response of positive sign. Observations on the isolated axon of *Sepia*]. J. Physiol. Path. Gén. 88, 147-170.

Azim, E, Jiang, J., Alstermark, B., Jessell,T.M., 2014a. Skilled reaching relies on a V2a propriospinal internal copy circuit. Nature. 509, 43-48.

Azim, E., Fink, A.J.P., Jessell, T.M., 2014b. Internal and external feedback circuits for skilled forelimb movement. Cold Spring Harb. Symp. Quant. Biol. 79, 81-92.

*Bacq, Z. M.,1935. La transmission chemique des influx dans le systeme nerveux autonome [The chemical type of impulse transmission in the autonomic nervous system]. Ergebn. Physiol. 37, 82-185.

Barakan, T.H., Downman, C.R.B., Eccles, J.C. 1949. Electrical potentials generated by antidromic volleys in quadriceps and hamstring motoneurons. J. Neurophysiol. 12:393-424.

Bartlett, F.C., 1960. Karl Spencer Lashley 1890-1958. Biogr. Mem. Fellows R. Soc. 5,

Basset, D.R. 2002. Scientific contributions of A.V. Hill: exercise physiology pioneer. J. Appl. Physiol. 93,1567-1582.

Bayliss, W.M., 1919. The electrical changes in active tissues. Brit. Med. J. May 31, 670-671.

Beck, F., 2008. My odyssey with Sir John Eccles. NeuroQuantology 6, 161-163.

Beck, F., Eccles, J.C., 1992. Quantum aspects of brain activity and the role of consciousness. Proc. Natn. Acad. Sci. USA 89, 11357-11361.

Beck, F., Eccles, J.C. (deceased), 1998. Quantum processes in the brain: A scientific basis of consciousness. Cognitive Studies 5, 95-109. See also an expansion of this article in Osaka, N. (Ed.), Neural Basis of Consciousness. John Benjamin Publishing Co., Philadelphia. 99,141-165.

Beck, F. Eccles, J.C., 2003. In: Osaka, N (Ed.), Neural Basis of Consciousness. John Benjamins Publishing Company, Amsterdam.

Bell, J., Bell C., 1826. The Anatomy and Physiology of the Human Body. Vol. 3. 6th edit. Longman, Rees, Orman, Brown, and Green (Paternoster Row address), and Cadell (Strand address), London. Note: The 1st. edition was by John Bell alone in 1802, as published by Longman, Rees, Orman, Brown, and Green, London. The 6th edition was almost completely rewritten by his brother, Charles Bell.

Bennett, M.R., 2001. History of the Synapse. Harwood Academic Publishers, Newark

(NJ), USA.

Bennett, M.R., Hacker, P.M.S., 2002. The motor system in neuroscience: a history and analysis of conceptual developments. Prog. Neurobiol. 67, 1–52.

Bernstein, N. A. (1947). O postroenii dvizhenii [On the construction of movements]. Medzig, Moscow: (Available only in its original Russian language)

Bernstein, N. A. (1967). On the co-ordination and regulation of movements. New York: Pergamon (A collection of English-translated papers published previously in Russian and German journals and monographs).

Borck, C., 1998. John C. Eccles (1903–1997): neurophysiologist and neurophilosopher (obituary). J. Hist. Neurosci. 7, 76–81.

Brading, A., 1993. Sybil Cooper – 1900-1970. In: Bindman, L., Brading, A., Tansey, T. (Eds.), Women Physiologists. Portland Press, London, pp. 115-117.

Bradley, K., Eccles, J.C., 1953a. Strychnine as a depressant of primary inhibition. Nature (Lond.) 171, p. 1061.

Bradley, K., Eccles, J.C., 1953b. Analysis of the fast afferent impulses from thigh muscles. J. Physiol. (Lond.) 122, 462-473.

Bradley, K., Easton, D.M., Eccles, J.C.,1953. An investigation of primary or direct inhibition. J.Physiol. (Lond.) 122, 474-488.

Brain, R., 1958. See discussion following Magoun, H.W. Early developments of ideas relating the mind to the brain. In: Wolstenholme, G.E.W., O'Connor, C.M. (Eds.), Ciba Foundation Symposium on the Neurological Bases of Behavior in Commemoration of Sir Charles Scott Sherrington. Little, Brown and Company, Boston, p. 24.

Brink, E., Jankowska, E., Skoog, B.,1984. Convergenve onto interneurones subserving primary afferent depolarization of group I afferents. J. Neurophysiol. 51, 432-449.

Brinkman, C., Porter, R., 1979. Supplementary motor area in the monkey: activity of neurons during performance of a learned motor task. J. Neurophysiol. 42, 681-709.

Brock, J. (Ed.), 2010. Lawrence Gordon Brock 192-1996. The Gordon Brocks, pp. 16-21. (Privately prepared family memoir available upon request to J. Brock < jgb@ihug.co.nz>).

Brock, L.G., Coombs, J.S., Eccles, J.C., 1951. Action potentials of motoneurones with intracellular electrode. Proc. Univ. Otago Med. Sch. 29, 14–15.

Brock, L.G., Coombs, J.S., Eccles, J.C., 1952a. Synaptic excitation and inhibition. J. Physiol. (Lond.) 117, P8.

Brock, L.G., Coombs, J.S., Eccles, J.C., 1952b. The recording of potentials from motoneurones with an intracellular electrode. J. Physiol. (Lond.) 117, 431–460.

Brock, L.G., Coombs, J.S., Eccles, J.C., 1952c. The nature of the monosynaptic excitatory and inhibitory processes in the spinal cord. Proc. R. Soc. Lond. B 140, 169–176.

Brock, L.G., Coombs, J.S., Eccles, J.C., 1953a. Antidromic propagation of impulses into motoneurones. In: Wolstenholme G.E.W., Ed., The Spinal Cord. Ciba Symposium Foundation, pp. 120-129. Churchill, London.

Brock, L.G., Coombs, J.S., Eccles, J.C., 1953b. Intracellular recording from antidromically activated motoneurons. J. Physiol. (Lond.) 122, 429-461.

Brock, L.G., Eccles, J.C., Rall, W. 1951. Experimental investigations on the afferent fibres of muscle nerves. Proc. R. Soc .Lond. B 138, 453-475.

Brock, T.D., 1988. Robert Koch: A Life in Medicine and Bacteriology. Springer, Berlin.

Brooks, C. McC., Eccles, J.C., 1947a. An electrical hypothesis of central inhibition. Nature 159, 760-764.

Brooks, C. McC., Eccles, J.C., 1947b. Electrical inverstigation of the monosynaptic pathway through the spinal cord. J.Neurophysiol. 10, 251-274.

Brooks, C. McC., Eccles, J.C., 1947c. A study of the effects of anesthesia and asphyxia on the monsynaptic pathway through the spinal cord.J.Neurophysiol. 10, 349-360.

Brooks, C. McC., Eccles, J.C., 1948a. An analysis of synaptic excitatory action. J. Neurophysiol. 11, 365-376.

Brooks, C. McC., Eccles, J.C., 1948b. Inhibitory action on a motor nucleus and focal potentials generated therein. J.Neurophysiol. 11, 401-416.

Brooks, C. McC., Eccles, J.C., 1948c. Inhibition of antidromic responses of motoneurones. J.Neurophysiol. 11, 431-444.

Brooks, C. McC., Eccles, J.C., Malcolm, J.L., 1948. Synaptic potentials of inhibited motoneurones. J.Neurophysiol. 11, 417-430.

Brooks, C. McC., Downman, C.B.B., Eccles, J.C., 1950a. After-potentials and excitability of spinal motoneurones following antidromic activation. J. Neurophysiol. 13, 9-38.

Brooks, C. McC., Downman, C.B.B., Eccles, J.C., 1950b. After-potentials and excitability of spinal motoneurones following orthodromic activation. J.Neurophysiol. 13, 157-176.

Brown, G.L., Eccles, J.C., 1934a. The action of a single vagal volley on the rhythm of the heart beat. J. Physiol. (Lond.) 82, 211-241.

Brown, G.L., Eccles, J.C., 1934b. Further experiments on vagal inhibition of the heart. J. Physiol. (Lond.) 82, 242-257.

Brown, L., 1897. Charles Smart Roy, M.A., M.D., F.R.S. Brit. Med. J. Oct. 9, pp. 1031-1032.

Brownstone, R.M., 2006. Beginning at the end: Repetitive firing properties in the final common pathway. Prog. Neurobiol.78, 156-172.

Brownstone, R.M., Bui, T.V., Stifani, N., 2015. Spinal circuits for motor learning. Curr. Opin Neurobiol. 33, 166-173.

Bunge, M., 1980. The Mind–Body Problem. Pergamon, Oxford.

Burke, R.E., 1985. Integration of sensory information and motor commands in the spinal

cord. In: Stein, P.S.G. (Ed.), Short Course Syllabus – Motor Control: From Movement Trajectories to Neural Mechanisms. Society for Neuroscience, Bethesdaa, MD, pp. 44-46.

Burke, R.E., 2006. John Eccles pioneering role in understanding central synaptic transmission. Progr. Neurobiol. 78, 173-188.

Burke, R.E., 2007. Sir Charles Sherrington's The integrative action of the nervous system: a centenary appreciation. Brain 130, 887-894.

Burke, R.E., Rudomin, P.,1977. Spinal neurons and synapses. In: Kandel, E.R. (Ed.). Handbook of Physiology. The Nervous System. Cellular Biology of Neurons. Sect. 1, Vol.1, Pt. 2. Am. Physiol. Soc., Bethesda, MD, pp. 877-944.

Carlson-Kuhta, P., Smith,J.L., 1994. Coordination between head and hindlimb motions during the cat scratch response. Exp. Brain Res. 101, 279-290.

Clarac, F., Barbara, J.-G., 2011. The emergence of the "motoneuron concept": From the early 19th C to the beginning of the 20th C. Brain Res. 1409, 21-41.

Cole, K. S., Curtis, H. J., 1941. Membrane potential of the giant squid axon during current flow. J. Gen. Physiol. 24, 551-563.

Connors, B.W., Long, M.A., 2004. Electrical synapses in the mammalian brain. Ann. Rev. Neurosci. 27, 393-418.

Contreras-Hernández, E. Chávez, D., Rudomin, P., 2015. Dynamic synchronization of ongoing neuronal activity across spinal segments regulates sensory information flow. J. Physiol. (Lond.) 153 (10), 2343-2363.

Coombs, J.S., Eccles, J.C., Fatt, P., 1953. The action of the inhibitory transmitter. Aust. J. Sci. 16, 1–5.

Coombs, J.S., Eccles, J.C., Fatt, P., 1955a. The electrical properties of the motoneurone membrane. J. Physiol. (Lond.) 130, 291–325.

Coombs, J.S., Eccles, J.C., Fatt, P., 1955b. The specific ionic conductances and the ionic movements across the motoneuronal membranr that produce the inhibitory posy-synaptic

potential. J. Physiol. (Lond.) 130, 326–374.

Coombs, J.S., Eccles, J.C., Fatt, P., 1955c. Excitatory synaptic action in motoneurones. J.Physiol. (Lond.) 130, 374-395.

Coombs, J.S., Eccles, J.C., Fatt, P., 1955d. The inhibitory suppression of reflex discharges from motoneurones. J. Physiol. (Lond.) 130, 396-413.

Coombs, J.S., Eccles, J.C., Fatt, P., 1955e. The inhibitory suppression of reflex discharges from motoneurons. J.Physiol. (Lond.) 130, 396-413.

Coombs, J.S., Eccles, J.C., Fatt, P., 1955f. The ionic permeability of the motoneurone membrane. J. Cell Comp. Physiol. 46, 362-363.

Coombs, J.S., Curtis, D.R., Eccles, J.C., 1959. The electrical constants of the motoneurone membrane. J. Physiol. (Lond.) 145, 505–528.

Cooper, S., Adrian, E.D., 1924. The electric response in reflex contractions of spinal and decerebrate preparations. Proc. R. Soc. Lond. B 96, 243-258.

Cooper, S., Eccles, J.C.,

Cooper, S., Sherrington, C.S., 1940. Gower's tract and spinal border cells, Brain 63, 123-134.

Cooper, S., Denny-Brown, D.E., Sherrington, C.S., 1927. Interaction between ipsilateral spinal reflexes acting on the flexor m.s of the hind-limb. Proc. R. Soc. Lond. B 101, 262-303.

Costa, E., 2007. An interview with Alexander G. Karczmar. Placed on the Internet by the author on December 08, 2007 when Karczmar was 90 years of age.

Creed, R.S., Eccles, J.C., 1928. The incidence of central inhibition on restricted fields of motor units. J. Physiol. (Lond.) 66, 109-120.

Creed, R.S., Sherrington, C.S. 1926. Observations on concurrent contraction of flexor muscles in the flexion reflex. Proc. R. Soc. Lond. 100, 258-268.

Creed, R.S., Denny-Brown, D., Eccles, J.C., Liddell, E.G.T., Sherrington, C.S., 1932. Reflex Activity of the Spinal Cord. Clarendon Press, Oxford. Note: Reprinted in 1972 by Oxford University Press, Oxford.

Creutzfeld, O., 1986. Richard Jung, 1911-1986. Exp Brain Res. 64, 1-4.

Crozier, W.J., Pincus, G., Renshaw, B.1935. Temperature characteristics for heart beat characteristics in mice. J. Gen.Physiol.20, 491-497.

Cull-Candy, S., Ashmore J. 2014. Paul Fatt 1924-2014. Nat. Neurosci. 17, 1634.

Curtis, D.R., 2003. John Carew Eccles, Nobel Laureate (1903–1997). J. Clin. Neurosci. 10, 171–173.

Curtis, D.R., Andersen, P., 2001a. John Carew Eccles 1903–1997. Hist. Rec. Aust. Sci. 13, 439–473. (~12,000 words with Eccles' full bibliography of 568 publications up to 1998). Note: The citations do not include Eccles' 1929 PhD thesis.

Curtis, D.R., Andersen, P., 2001b. Sir John Eccles, A.C. 27 January 1903 – 2 May 1997. Biogr. Mem. Fellows R. Soc. 47, 159–187 (~7,000 words with a selected bibliography of 96 publications).

Dawson, P.M., 1908. A Biography of Francois Magendie. A.J. Huntington, New York.

Deeke, L., Kornhuber, H.H., 1978. An electrical sign of participation of the mesial 'supplementary' motor cortex in human voluntary finger movement. Brain Res. 159, 473-477.

Delcomyn, F., 1980. Neural basis of rhythmic behavior in animals. Science 210, 492–498.

Deliagina, T.G., Feldman, A. G., 1981a. Activity of Renshaw cells during fictive scratch reflex in the cat. Exp. Brain Res. 42, 108-115.

Deliagina, T.G., Orlovsky, G.M., Perret, C., 1981b. Efferent activity during fictitious scratch reflex in the cat. J. Neurophysiol. 45, 595-604.

Deliagina, T.G., Feldman, A. G., Gelfand, I.M., Orlovsky, G.M., 1975. On the role of

central program and afferent inflow in the control of scratching movements in the cat. Brain Res. 100, 297-313.

Denny-Brown, D., 1929. On the nature of postural reflexes. Proc. R. Soc. Lond. B 104, 252-301.

Denny-Brown, D. (Ed.), 1939. Selected Writings of Sir Charles Sherrington. Hamish Hamilton Medical Books, London. Note: The most recent edition of this book was published in 1979 by Oxford University Press.

Denny-Brown, D. 1957. The Sherrington School of Physiology. J. Neurophysiol. 20, 543–548.

Denny-Brown, D., Eccles, J.C., Liddell, E.G.T.,1929. Observations on electrical stimulation of the cerebellar cortex. Proc. R. Soc. Lond. B 104, 518-536.

Dermietzel, R., Spray, D.C., 1993. Gap junctions in the brain: where, what type, how many and why. Trends Neurosci. 16, 188-192.

Doroshenko, P.A., Kostyuk, P.G., Krishtal, O.A., 1973. Dejstvie kal'cija na membranu somy gigantskih nejronov molljuskov. [Effect of calcium on the somatic membrane of giant neurons of mollusc]. Nejrofiziologija [Neurophysiology] 5, 621-627.

Dow, R.S., 1951. William Fitch Allen, PhD., Sc.D. J. Neurophysiol. 14, 333-334.

Duchateau, J., Enoka, R.M., 2011.Human motor unit recordings: Origins and insight into the integrated motor system. Brain Res. 1409, 42-61.

Dudel, J., Kuffler S.W., 1961. Presynaptic inhibition at the crayfish neuromuscular junction. J.Physiol. (Lond.) 155, 543-562.

Duysens, J., De Groote, F,, Jonkers, I., 2013. The flexion synergy, mother of all synergies and father of new models of gait. Front. Comp. Neurosci. Published March 13, doi:10.3389/fncom.2013.00014.

Eccles, H., Biersack, H.J. (Eds.), 2000. Sir John Eccles in Memoriam– A Tireless Warrior for Dualism. Ecomed, Landsberg, GER.

Eccles, J.C., 1929. Investigations on Excitation and Inhibition in the Nervous System with Special Reference to the Features of Interaction between Excitatory and Inhibitory Reflexes. Ph.D. Dissertation, University of Oxford, Oxford.

Eccles, J.C., 1931. Studies on the flexor reflex. III. The central effects produced by an antidromic volley. Proc R. Soc. B, 107, 557-585.

Eccles, J.C., 1932. Chapter VI. Central inhibition. In: Creed, R.S., Denny-Brown, D., Eccles, J.C., Liddell, E.G.T., Sherrington, C.S.,1932. Reflex Activity of the Spinal Cord. Clarendon Press, Oxford. pp. 84-103 Note: Reprinted in 1972 by Oxford University Press, Oxford, with annotations by D.P.C. Lloyd (pp. 84-103 in this latter version). It seems certain that Eccles wrote this chapter.

Eccles, J.C., 1935a. After discharge from the superior cervical ganglion. J. Physiol. (Lond.) 84 (Suppl.), 50p-52p.

Eccles, J.C., 1935b. The action potential of the superior cervical ganglion. J.Physiol. (Lond.) 85, 179-206.

Eccles, J.C., 1935c. Facilitation and inhibition in the superior cervical ganglion. J. Physiol. (Lond.) 85, 207-238.

Eccles, J.C., 1935d. Slow potential waves in the superior cervical ganglion. J. Physiol. (Lond.) 85, 464-501.

Eccles, J.C., 1935e. Actions of antidromic impulses on ganglion cells. J. Physiol. (Lond.) 85 (Suppl.), 32p-34p.

Eccles, J.C., 1936. Synaptic and neuro-muscular transmission. Ergebn. Physiol. 38, 339-444.

Eccles, J.C., 1937a. Synaptic and neuro-muscular transmission. Physiol. Rev. 17, 538-555. Note: This review includes substantial reference to the previous much longer review with the same title (Eccles, 1936).

Eccles, J.C., 1937b. The discharge of impulses from ganglion cells. J. Physiol. (Lond.)

91, 1-22.

Eccles, J.C., 1939. The spinal cord and reflex action. Annu. Rev. Physiol. 1, 363-384.

Eccles, J.C., 1943. The nature of synaptic transmission in a sympathetic ganglion. J. Physiol. (Lond.) 101, 465-483.

Eccles, J.C., 1944a. The nature of synaptic transmission in a sympathetic ganglion. J. Physiol. (Lond.) 103, 27-53.

Eccles, J.C., 1944b. Synaptic tranmission in the spinal cord. Nature (Lond.) 153, 432.

Eccles, J.C., 1945. An electrical hypothesis of synaptic and neuromuscular transmission. Nature (Lond.) 156, 680-682.

Eccles, J.C., 1946a. Synaptic potentials of motoneurons. J. Neurophysiol. 9, 87-120.

Eccles, J.C., 1946b. An electrical hypothesis of synaptic and neuromuscular transmission. Ann. N.Y. Acad. Sci. 47, 429-455. Note: This review makes reference to its preliminary report (Eccles, 1945).

Eccles, J.C., 1947a. Man and freedom. Twentieth C. 2 (No. 2), 5-23.

Eccles, J.C., 1947b. Acetylcholine and synaptic transmission in the spinal cord. J. Neurophysiol. 10, 251-274.

Eccles, J.C., 1948. Conduction and synaptic transmission in the nervous system. Annu. Rev. Physiol. 10, 93-116.

Eccles, J.C., 1949. A review and restatement of the electrical hypothesis of synaptic excitatory and inhibitory action. Arch. Sci. Physiol. 3, 567-584.

Eccles, J.C., 1950. The responses of motoneurones. Br. Med. Bull. 6, 304-311.

Eccles, J.C., 1951a. Hypotheses relating to the mind-brain problem. Nature (Lond.) 168, 53-57.

Eccles, J.C., 1951b. Interpretation of action potentials evoked in the cerebral cortex. Electroenceph. Clin. Neurophysiol. 3, 449-464.

Eccles, J.C., 1952a. Obituary. Sir Charles Sherrington, O.M., F.R.S., 1857-1952. Br. J, Philos. Sci. 3, 298-301.

Eccles, J.C., 1952b. The electrophysiological properties of the motoneurone. Cold Spring Harb. Symp. Quant. Biol. 17, 175-183.

Eccles, J.C., 1953. The Neurophysiological Basis of Mind: The Principles of Neurophysiology. Clarendon Press, Oxford. Note: Based on his 1952 Waynflete Lectures.

Eccles, J.C., 1955. The central actions of antidromic impulses in motor nerve fibres. Pflug. Arch. 260, 385-415.

Eccles, J.C., 1957. The Physiology of Nerve Cells. The Johns Hopkins Press, Baltimore. Note: Based on three lectures presented at Johns Hopkins University in the fall of 1955.

Eccles, J.C., 1958. The physiology of imagination. Sci. Am. 199, 135-146.

Eccles, J.C. 1959. Potential changes recorded inside primary afferent fibres within the spinal cord. J. Physiol. 149, 250-273

Eccles, J.C., 1959a. Excitatory and inhibitory synaptic action. Ann New York Acad Sci. 81, 247-264.

Eccles, J.C., 1959b. Neuron physiology – Introduction. In: Field, J., Magoun, H.W., Hall, V.E. (Eds.). Handbook of Physiology. Sect. 1. Neurophysiology, Vol. 1. Am. Physiol. Soc., Washington, D.C., pp. 39-74.

Eccles, J.C., 1961a. Inhibitory pathways to motoneurones, In: Florey, E. (Ed.), Nervous Inhibition. Pergamon Press, New York, pp. 47-60.

Eccles, J.C., 1961b. The nature of central inhibition. Proc. R. Soc. B 153, 445-476.

Eccles, J.C., 1964a. The Physiology of Synapses. Berlin, Springer-Verlag.

Eccles, J.C., 1964b. Presynaptic inhibition in the spinal cord. In: Eccles, J.C., Schadé,

J.P. (Eds.), Physiology of Spinal Neurones. Prog. Brain Res. Vol. 12, Amsterdam/London/New York, Elsevier, pp. 65-91.

Eccles, J.C., 1964c. The ionic mechanism of postsynaptic inhibition. Nobel Lecture, December 11, 1963. In: Liljestrand, G. (Ed.), Les Prix Nobel en 1963. Nobel Foundation, Stockholm, pp. 261-283. (In 1963, Also in Aust. J. Sc. 27, 121-131.

*Eccles, J.C., 1965a. Pharmacology of central inhibitory synapses. Brit. Med. Bull. 21, 19-25.

Eccles, J.C., 1965b.The synapse. Sci. Am. 212, 56-66.

Eccles, J.C. (Ed.), 1966. Brain and Conscious Experience. Springer-Verlag, New York. Note: This book is based on the Sept. 28-Oct. 4 1964 Study Week at the Pontifical Academy of Sciences, Vatican City.

*Eccles, J.C., 1968. Professor Ragnar Granit's contributuions in the field of motor control. Am. J. Phys. Med. 47, 3-7.

*Eccles, J.C., 1969. The Inhibitory Pathways of the Central Nervous System. Charles C. Thomas, Liverpool, England.

Eccles, J.C., 1973. The Understanding of the Brain. McGraw-Hill, New York.

Eccles, J.C., 1975. Hierarchical concepts on the control of movement. In: Krebs, H.A., Shelly, J.H. (Eds.), The Creative Process in Science and Medicine. Exerpta Medica, Amsterdam, pp. 61-85.

Eccles, J.C., 1975/1992. Under the spell of the synapse. In: Worden, F.G., Swazey, J.P., Adelman, G. (Eds.), The Neurosciences: Paths of Discovery. MIT Press, Cambridge (USA), pp. 158–179 (and Birkhäuser, Boston, 1992 (Vol I), pp. 159–179).

Eccles, J.C., 1976. From electrical to chemical transmission in the central nervous system. Notes Rec. R. Soc. Lond. 30, 219–230.

Eccles, J.C., 1977a. My scientific odyssey. Annu. Rev. Physiol. 39, 1–18.

Eccles, J.C., 1977b. Cerebellar function in the control of movement (with special reference to the pioneering work of Sir Gordon Holmes). In: Rose, F.C. (Ed.), Physiological Aspects of Clinical Neurology, Blackwell Scientific Publications, Oxford, pp. 157-178.

Eccles, J.C., 1977c. Chapter E. Voluntary movement. In: Popper, K.R., Eccles, J.C. The Self and Its Brain. Springer-Verlag, Berlin, pp. 275-294. (Note: we assume that Eccles wrote this chapter independent of Popper).

Eccles, J.C., 1981a. Physiology of motor control in man. Appl. Neurophysiol. 44, 5-15.

Eccles, J.C., 1981b. Obituary: Derek Denny-Brown (1901-1981). IBRO News 9 (4), 9-10.

Eccles, J.C., 1981c. Voluntary movement. Freiburger Universitatsblatter, 74, 24-28.

Eccles, J.C., 1982a. Life in Sherrington's laboratory – his last decade at Oxford 1925-1935. Trends Neurosci., 5, 108-110.

Eccles, J.C. 1982b. The synapse: From electrical to chemical transmission. Annu. Rev. Neurosci. 5, 325–339.

Eccles, J.C., 1982c. The initiation of voluntary movements by the supplemenary motor area. Arch. Psychiatr. Nervenkr. 231, 423-441. PMID: 6812546

Eccles, J.C., 1982d. The liaison brain for voluntary movement: the supplementary motor area. Acta Biol. Acad. Sci., Hung. 33, 157-172.

Eccles, J.C., 1982e. The future of studies on the cerebellum. Exp. Brain Res. Suppl. 6, 607-620.

Eccles, J.C., 1983. Calcium in long-term potentiation as a model for memory. Neuroscience. 10, 1071-1081.

Eccles, J.C., 1984. Voluntary movement. 12, 1-9. Note: This article is not available to requesting libraries.

Eccles, J.C., 1986. Learning in the motor system Progr. Brain Res. 64, 3-13.

Eccles, J.C., 1988. Mammalian systems for storing and retrieving information. In: Woody, C.D., Alkon, D.L.,McGaugh, J.L. (eds.), Cellular Mechanisms of Conditioning and Behavioural Plasticity, Springer-Verlag, Berlin, pp. 289-302.

Eccles, J.C., 1989 The Evolution of the Brain: Creation of the Conscious Self. Routledge, London/New York.

Eccles, J.C., 1990. Developing concepts of the synapses. J. Neurosci. 10, 3769–3781.

Eccles, J.C., 1994a. How the brain gives the experience of pain. Int. J. Tissue React. 16, 3-17.

Eccles, J.C., 1994b. How the Self Controls its Brain. Springer-Verlag, Berlin/New York. Eccles, J.C.(deceased), 1999. The discipline of biological science with special reference to the neurosciences. Riv. Biol. 92, 458-459.

Cooper, S., Eccles, J.C., 1930.The isometric responses of mammalian muscles. J. Physiol. (Lond.) 69, 377-385.

Eccles, J.C., Creutzfeld, O., 1990. The Principles of Design and Operation of the Brain. Pontificia Academia Scientiarum, Vatican City.

Eccles, J.C., Gibson, W.C., 1979. Sherrington — His Life and Thought. Springer-Verlag, Berlin.

Eccles, J.C., Granit, R., 1929. Crossed extensor reflexes and their interaction. J. Physiol. (Lond.) 67, 97-118.

Eccles, J.C., Hoff, H.E., 1931. Rhythmic responses of motoneurones. J. Physiol. (Lond.) 71, xxi.

Eccles, J.C., Hoff, H.E., 1932. The rhythmic discharge of motoneurones. Proc. R. Soc. Lond. B 110, 483-514.

Eccles, J.C., Hoff, H.E., 1934. The rhythm of the heart beat. I. Location, action potential and electrical excitability of the pacemaker. Proc. R. Soc. Lond. B 115, 307-327.

Eccles JC, Kjnjevic K., 1959a. Presynaptic changes associated with post-tetanic

potentiation in the spinal cord. J. Physiol. 149, 274-287.

Eccles JC, Kjnjevic K., 1959b. Presynaptic changes associated with post-tetanic potentiation in the spinal cord. J. Physiol. 149, 250-273.

Eccles, J.C., Magni, F., Willis, W.D., 1962. Depolarization of central terminals of group 1 afferent fibres from muscle. J. Physiol. 160, 62-93.

Eccles, J.C., McGeer, P.l., 1979. Ionotropic and synaptic transmission. Trends Neurosci. 2, 39-40.

Eccles, J.C. 1939. Responses which nerve impulses evoke in mammalian striated muscles. J. Physiol. (Lond.) 97, 44-102.

Eccles, J.C., O'Connor, J.C., 1939. Responses which nerve impulses evoke in mammalian striated muscle.

Eccles, J.C., Pritchard, J.J., 1937 Action potential of motoneurones. J.Physiol. (Lond.) 89, pp. 43-45.

Eccles, J.C., Rall, W., 1950. Post-tetanic potentiation of responses of motoneurones. Nature (Lond.) 166, 465-466.

Eccles, J.C., Rall, W., 1951a. Repetitive monosynaptic activation of motoneurones. Proc. R. Soc. Lond. B 138, 475-498.

Eccles, J.C., Rall, W., 1951b. Effects induced in a monosynaptic reflex path by its activation. J. Neurophysiol. 14, 353-376.

Eccles, J.C., Sherrington, C.S., 1930. Numbers and contraction values of individual motor units examined in some muscles of the limb. Proc. R. Soc. Lond. B 106, 326-357.

Eccles, J.C., Sherrington, C.S., 1931. Studies on the flexor reflex. I. Latent period (1931a); II. The reflex evoked by two afferent volleys (1931b); III (see Eccles, 1931); IV. After discharge (1931c); V. General conclusions (1931d); VI, Inhibition (1931e). Proc. R. Soc. Lond. B 107, pp. 511-544 (a), 535-536 (b), 586-596 (c), 597-605 (d);

B109, 91-113 (e).

Eccles, J.C., Thompson, J.H.C., 1935. An investigation on the mechanical properties of rubber. Proc. R. Soc. Lond. A 148, 171-185.

Eccles, J.C., Eccles, R.M., Fatt, P., 1956. Pharmaclogical studies on a central synapse operated by acetylcholine. J. Physiol. (Lond.) 131, 154-169.

Eccles J.C., Eccles, R.M., Ito, M., 1964a. Effects of intracellular potassium and sodium injections on the inhibitory postsynaptic potential. Proc. R. Soc. Lond. B 160, 181-196.

Eccles, J.C., Eccles, R.M., Ito, M., 1964b. Effects produced on inhibitory postsynaptic potentials by the coupled injections of cations and anions into mtoneurons. Proc. R. Soc. Lond. B 160, 197-210.

Eccles, J.C., Eccles, R.M., Lundberg, A., 1960. Types of neurone in and around the intermediate nucleus of the lumbosacral cord. J. Physiol. (Lond.) 154, 89–114.

Eccles, J.C., Eccles, R.M., Magni, F., 1960. Presynaptic inhibition in the spinal cord. J. Physiol. (Lond.) 154, 28P.

Eccles, J.C., Eccles, R.M., Magni, F., 1961. Central inhibitory action attributable to presynaptic depolarization produced by muscle afferent volleys. J. Physiol. (Lond.) 159, 147-166.

Eccles, J.C., Eccles, R.M., Iggo, A., Lundberg, A., 1961a. Electrophysiological investigations of Renshaw cells. J.Physiol. (Lond.) 159, 461-473.

Eccles, J.C., Eccles, R.M., Iggo, A., Ito, M., 1961b. Distribution of tecurrent inhibition amomg motoneurones. J. Physiol. (Lond.) 159, 479=499.

Eccles, J.C., Fatt, P., Koketsu, K., 1953. Cholinergic and inhibitory synapses in a central nervous system pathway. Aust. J. Sci. 16, 50-54.

Eccles, J.C., Fatt, P., Koketsu, K., 1954. Cholinergic and inhibitory synapses in a pathway from motor-axon collaterals. J. Physiol. (Lond.) 126, 524-562.

Eccles, J.C., Fatt, P., Landgren, S., 1954a. The ‘direct’ inhibitory pathway in the spinal cord. Aust. J. Sci. 16, 130-134.

Eccles, J.C., Fatt, P., Landgren, S., Winsbury, G. 1954b. Spinal cord potentials generated by volleys in large muscle afferents. J. Physiol. (Lond.) 125, 590-606.

Eccles, J.C., Fatt, P., Landgren, S., 1956a. The central pathway for the direct inhibitory action of impulses in the largest afferent nerve fibres to muscle. J. Neurohysiol. 19, 75-98.

Eccles, J.C., Fatt, P., Landgren, S., 1956b. The inhibitory pathway to motoneurones. In: Kappers, A. (Ed.). Progress in Neurobiology. Proceedings of the First International Meeting of Neurobiologists, pp. 73-82. Published under the auspices of the Netherlands Society for Psychiatry and Neurology as supplement no. 2 to the journal "Folia Psychiatrica, Neurologica et Neurochirurgica Neerlandica." Elsevier, Amsterdam.

Eccles, J.C., Ito, M., Szentagothai, J., 1967. The Cerebellum as a Neuronal Machine. Springer-Verlag, New York.

Eccles, J.C., Katz, B., Kuffler, S.W, 1942. Effects of eserine on neuro-muscular transmission. J. Neurophysiol. 5, 211-230.

Eccles, J.C, Kozak, W., Magni, F, 1960. Dorsal root reflexes in muscle afferent fibres. J. Physiol. (Lond.) 153, 48P-49P.

Eccles J.C., Eccles R.M., Iggo, A., Ito, M.,1961. Distribution of recurrent inhibition among motoneurones. J. Physiol. (Lond.) 159, 479-499.

Eccles, J.C., Kostyuk, P.G., Schmidt, R.F., 1962. Central pathways responsible for depolarization of primary afferent fibres. J. Physiol. (Lond.) 161, 237-257.

Eccles, J.C., Llinas, R., Sasaki, K., 1966. Intracellularly recorded responses of cerebellar Purkinje cells. Exp. Brain Res. 1, 161-183.

Eccles J.C., Eccles R.M., Iggo, A. et al., 1961. Electro-physiological investigations on Renshaw Cells. J. Physiol. (Lond.) 159, 461-478.

Eccles, J.C., Schmidt, R.F., Willis, W.D, 1963. Pharmacological studies on the presynaptic inhibition. J. Physiol. (Lond.) 168, 500-530.

Eccles, J.C., Allen, G.I., Nicoll, R.A., et al., 1977. The ionic mechanisms concerned in generating the i.p.s.p.s of hippocampal pyramidal cells. Proc. R. Soc. Lond. B 198, 363-384.

Edstrom, L., Grimby, L, 1985.Obituary. Erik Kugelberg, 1913-1983. Muscle Nerve 8, 258.

Eide, E., Lundberg, A., Voorhoeve, P., 1961. Monosynaptically evoked inhibitory postsynaptic potentials in motoneurones. Acta Physiol. Scand. 53, 185-105.

Eide, E., Jurna, I., Lundberg, A., 1968. Conductance measurements from motoneurons during presynaptic inhibition. In: Euler, C. von, Skoglund, S., Södeberg, U. (Eds.), Structure and Function of Inhibitory Neuronal Mechanisms. Pergamon Press, Oxford/New York.

Evarts. E.V., 1981. Sherrington's concept of proprioception. Trends Neurosci. 4, 44-46.

Fenn, W.O., 1965. Alexander Forbes (1882-1965). Biograph. Mem. Nat. Acad. Sci. USA 40, 113-141.

Fenner, F., Curtis, D.R., 2001.The John Curtin School of Medical Research. The First 50 Years, 1948-1998. Brolga Press, Gundaroo, NSW, Australia.

Ferrier, D., 1875. Experiments on the brain of monkeys. Proc. R. Soc. Lond. 23, 409-430.

Fillenz, M., 2000. Memories of Sir John Eccles in New Zealand. In: Eccles, H., Biersack, H.J. (Eds.), Sir John Eccles in Memoriam– A Tireless Warrior for Dualism. Ecomed, Landsberg (Germany), pp. 11-28.

Fillenz, M., 2012. Memories of John Eccles. J. Hist. Neurosci. 21, 214-226.

Fink, A.J.P., Croce K.R., Huang, J. et al., 2014. Presynaptic inhibition of spinal sensory feedback ensures smooth movement. Nature 509, 43-48.

Frank, K., 1959. Basic mechanisms of synaptic transmision in the central nervous system. IRE Trans. Med. Electron. 6, 85-88.

Frank, K., Fourtes, M.G.G., 1957. Presynaptic and postsynaptic inhibition of monosynaptic reflexes. Fed. Proc. 16, 39-40.

Fulton, J.F., Liddell, E.G.T., 1926. Observarions on ipsilateral contraction and "inhibitory rhythm. Proc. R. Soc. Lond. B 98, 214-227.

Forbes, A., 1916. The laboratory reacts. Atl. Monthly. 118, 544-551.

Forbes, A., 1922. The interpretation of spinal reflexes in terms of present knowledge of nerve conduction. Physiol. Rev. 2, 361-414.

Forbes, A.,1949. Birdsey Renshaw 1911-1948. J. Neurophysiol. 12, p. 81.

Freund, H.-J., Koppitz, U., Labisch, A., (Eds.), 2011. The Legacy of John C. Eccles. Shaker-Verlag, Aachen.

Fuller, J., 2007. The poetry of Sir Charles Sherrington. Brain 130, 1981-1983.

Garnett, S.E., 2005. Burke says goodbye after 41 years. NIH Record, June 17, 2005.

Goodall,E.W., 1934. A Short History of the Epidemic Infectious Diseases. See: https://openlibrary.org/publishers/John_Bale,_Sons_&_Danielsson,_Ltd.

Hagiwara, S., Tasaki, I., 1958. A study on the mechanism of impulse transmission across the giant synapse of the squid. J. Physiol. (Lond.) 143, 114-137.

Hasan, Z., Stuart, D.G., 1988. Animal solutions to problems of movement control: the role of proprioceptors. Ann. Rev. Neurosci. 11, 199-233.

Hasan, Z., Enoka, R.M., Stuart, D.G., 1985. The interface between biomechanics and neurophysiology in the study of movement: Some recent approaches. Exerc. Sport Sci. Rev. 13, 169-234

Hill, A.V., 1966. Trails and Trials in Physiology: a Bibliography, 1909-1964. Williams and

Wilkins, Baltimore, MD.

Hughes, D.I., Sikander, S., Kinnon, C.M. et al., 2012. Morphological, neurochemical and electrophysiological features of parvalbumin-expressing cells: a likely source of axo-axonic inputs in the mouse spinal dorsal horn. J. Physiol. (Lond.) 590, 3927-3951.

Hultborn, H. 2006, Spinal reflexes, mechanisms and concepts: From Eccles to Lundberg and beyond. Prog. Neurobiol. 78, 215-232.

Jones, J.G., 2010. Selected writings of Thomas Graham Brown. (Unpublished manuscript). Available from J.G.J upon request.

Jones, J. G., Tansey, E.M.T., Stuart, D.G., 2011. Thomas Graham Brown (1882-1965): Behind the scenes at the Cardiff Institute of Physiology. J. Hist. Neurosci. 20:188-209.

Gasser, H.S., 1973a. The control of excitation in the nervous system. Harvey Lect., 32, 169-193 (also published same year by Bull. N. Y. Acad. Med. 13, 324-48

Gasser, H.S. 1973b. Sequence of potential changes, Chapts. IV () and V (). In: Erlanger, J., Gasser, H.S. (Eds.) Electrical Signs of Nervous Activity. Philadelphia, U. Penn. Press.

Geison, G.L., 1927. Walter Holbrook Gaskell. In: Gillespie, C.C. (Ed.), Dictionary of Scientific Biography, Vol. 5. Charles Scribner's Sons, Detroit, pp. 279-284.

Gibson, W., C., 1996. No Time to Slow Down. UBC Alumni Association, Vancouver.

Goltz, F., 1874. Ueber die functionen des Lenden markes des Hundes [About the functions of the lumbar cord of the dog]. Pflüger's Archiv. 8, 460-498.

Gould, J., 2009. Mind-brain problem and conciousness. An 5-page set of definitions and opinions put on the Internet on 06/15/09.

Graham Brown, T., 1911. The intrinsic factors in the act of progression in mammals. Proc. R. Soc. Lond. B 84, 308–319.

Graham Brown, T., 1947. Sherrington – the man. Brit. Med. J. pp. 810-812.

Granit, R.,1966. Charles Scott Sherrington: An Appraisal. Thomas Nelson and Sons, London. Note: Reprinted in 1967 by Doubleday & Co., New York, with a cover entitled " Charles Scott Sherrington: A Biography of a Neurophysiologist."

Granmo, M., Petersson, P., Schouenborg, J., 2008. Action-based body maps in the spinal cord emerge from a transitory floating organization. J Neurosci. 28, 5494-5503.

Grillner, S., 1995. Ragnar Granit 30 October, 1900 – 11 March 1991. Biogr. Mem. Fell. R. Soc. Lond. 41, 185-197.

Grillner, S., Jessell, T.M., 2009. Measuring motion: searching for simplicity in spinal locomotor networks. Curr. Opin. Neurobiol.19, 572–586.

Grillner, S., El Manira, A., Kiehn, O., Rossignol, S., Stein, P.S.G. (Eds.), 2008. Networks in motion. Brain Res. Rev. 57, 1–269.

Gunn, S.W.A., 1909. Dr. William C. Gibson 1913-2009. BC Med. J. 51, pp. 338 and 344.

Gurfinkel, V.S., Cordo, P.J., 1998. The scientific legacy of Nikolai Bernstein. In: Latash, M.L. (Ed). Progress in Motor Control: Bernstein's Traditions in Movement Studies. Human Kinetics, Champaign, IL, pp. 1-19.

Hagbarth, K.E., 1952. Excitatory and inhibitory skin areas for flexor and extensor motoneurons. Acta Physiol. Suppl. 1952. 26, 1-58.

Hagbarth, K.E., Kerr, D.I.B.,1954. Central influence on spinal afferent conduction. J. Neurophysiol 17, 295-307.

Hagiwara, S., Tasaki, L. 1958. A study on the mechanism of impulse transmission across the giant synapse of the squid. J. Physiol. (Lond.), 143, 114-137.

Haas, L. F., 1994. François Magendie (1783-1855). J. Neurol. Neurosurg. Psychiatr. 57, p. 692.

Hawgood, B.J., 2008. Sir Michael Foster MD, FRS: the rise of the British school of physiology. J. Med. Biograph. 16, 221-226.

Heidenhain, R. P. H., 1882. Untersuchengen über den Einfluss des Nv. Vagus auf die Hertzhatigkeit [Studies on the influence of the vagus nerve on heart rate]. Pflüg. Archiv. 27, 383-412.

Henson, R.A., 1967. Obituary – Russell Brain, DM, FRCP, FRS. JAMA Neurol. 16, 559-560.

Hepp, K., 1999. Toward the demolition of a computational quantum brain. In: Blanchard, P., Jadczyk, A. (Eds.), Quantum Future. Springer, Berlin, pp. 92–104.

Hepp-Reymond, M.-C., 1997. The pyramidal tract: past, present and perspective – an introduction to the symposium in honor of Mario Wiesendanger. In Hepp-Reymond, M.-C., Marini, G., Perspectives of Motor Behavior and its Neural Basis. Karger, Basel, pp. 1-18.

Hering, H.E., Sherrington, C.S.,1897. Über Hemmung der Contraction willkürlicher Muskeln bei electrischer Reizung der Grosshirnrinde [About inhibiting the contraction of voluntary m.s by electrical stimulation of the cerebral cortex]. Arch. Gesamte. Physiol. 68, 222–228.

Hermann, L., 1879. Handbuch der Physiolgie (Handbook of Physiology). Vol. 2. Verlag von F.C.W. Vogel, Leipzig.

Hernández Peon, R., Hagbarth, K.E., 1955. Interaction between primary afferent and cortically induced reticular responses. J. Neurophysiol 18, 44-55. 1955.

Hess, W. R., 1963. From medical practice to theoretical medicine. An autobiographic sketch. Perspect. Biol. Med 6, 400–423.

Hill, A.V., 1965. Trails and Trials in Physiology. E. Arnold Ltd., London

Hodgkin, A.L., 1938. The subthreshold potentials in a crustacean nerve fibre. Proc. R.

Soc. Lond. B 126, 87–121.

Hodgkin, A.L., 1951. The ionic basis of electrical activity in nerve and muscle. Biol. Rev. 26, 339-409.

Hodgkin, A.L, 1979. Edgar Douglas Adrian, Baron Adrian of Cambridge. 30 November 1889-August 1977. Biogr. Mems. Fell. R. Lond. 25,1-73.

Hodgkin, A.I., Huxley A.F., 1952a. Currents carried by sodium and potassium ions through the membrane of the giant axon of Loliga. J. Physiol. (Lond.) 16, 449-472.

Hodgkin, A.I., Huxley, A.F., 1952b. The dual effect of membrane potential on sodium conductance in the giant axon of Loliga. J. Physiol. (Lond.) 16, 497-506.

Hodgkin, A.I., Huxley A.F., 1952c. Propogation of electrical signals along giant nerve fibres. Contribution to Royal Society Discussion on "Excitation and Inhibition." Proc. Roy. Soc. B 140, 177-183.

Hodgkin, A. L., Rushton, W. A. H., 1946. The electrical constants of a crustacean nerve fibre. Proc. R. Soc. B 133, 444-479.

Hodgkin, A. L., Huxley, A. F., Katz, B., 1949. Ionic currents underlying activity in the giant axon of the squid. Arch. Sci. Physiol. 3, 129-150.

Hoff, E.C., Hoff, H.E., Sheehan, D., 1934. Reflex interruption of rhythmic discharge. J. Physiol. (Lond.) 83, 185-191.

Holmes, G., 1939. The cerebellum of man. Brain 62, 1-30

Howland, J., Lettvin, J.T., McCulloch, W.S., Pitts, EW., Wall P.D., 1955. Reflex inhibition by dorsal root interaction. J. Neurophysiol. 18, 1-17

Hughes, D.I., Sikander, S., Kinnon, C.M. et al., 2012. Morphological, neurochemical and electrophysiological features of parvalbumin-expressing cells: a likely source of axo-axonic inputs in the mouse spinal dorsal horn. J. Physiol. (Lond.) 590, 3927-3951.

Hultborn, H. 1971. Neuronal pathway of recurrent facilitation of motoneurons.

J. Physiol. (Lond.) 218, 495-514.

Hultborn, H. 2001. State-dependant modulation of sensory feedback. J. Physiol. (Lond.) 533, 5-13.

Hultborn, H. 2006. Spinal reflexes, mechanisms and concepts: From Eccles to Lundberg and beyond. Progr. Neurobiol. 78, 215-232.

Hultborn, H., Jankowska, E., Lindstrom, S. 1971a. Recurrent inhibition of interneurones monosynaptically activated from group Ia afferents. J. Physiol. (Lond.) 215, 613-636.

Hultborn, H., Jankowska, E., Lindstrom, S. 1971b. Relative contribution from different nerves to recurrent depression of Ia IPSPs in motoneurones. J. Physiol. (Lond.) 215, 637-664.

Hultborn, H., Jankowska, E., Lindstrom, S. 1971c. Neuronal pathway of the recurrent facilitation of motoneurones. J. Physiol. (Lond.) 281, 495-514.

Huxley, A.F., 2000. Sir Alan Lloyd Hodgkin, O.M., K.B.E. 5 February 1914 – 20 December 1998: Elected F.R.S. 1948. Biogr. Mems. Fell. R. Soc. 46, 219–241.

Ito, M., 2006. In: Stuart, D.G., Zigmond, M.J. (Eds.), 2006. The Contributions of John Carew Eccles to Contemporary Neuroscience. Prog. Neurobiol. 78, 135–326.

Ito, M., 1984. The Cerebellum and Neural Control. Raven Press, Hew York.

Ito, M., 1989. Long term depression. Annu. Rev. Neurosci. 12, 85-102.

Ito, M., 1998. Autobiography. In: Squire, L.R. (Ed.), The History of Neuroscience in Autobiography, Vol. 2. Academic Press, San Diego/London, pp. 168-190.

Ito, M., 2000. My years with Sir John. In: Eccles, H., Biersack, H.J. (Eds.), Sir John Eccles in Memoriam — A Tireless Warrior for Dualism. Ecomed, Landsberg, Germany, pp. 29–36.

Ito, M., 2011. The Cerebellum: Brain for an Implicit Self. FT Press, Upper Saddle River, New Jersey.

Ito, M., Oshima, T.,1965. Electrical behaviour of the motoneurone membrane during intra-cellularly applied current steps. J. Physiol. (Lond.) 180, 607-635.

Ito, M., Kostyuk, P.G., Oshima, T., 1962. Further study of anion permeability of inhibitory postsynaptic membrane of cat motoneurones. J. Physiol. (Lond.) 164, 150-156.

Iwama, K., Sakakura, H., Kasamatsu, T., 1965. Presynaptic inhibition in the lateral geniculate body induced by stimulation of the cerebral cortex. Jap. J. Physiol. 310-322.

Jankowska, E., 1959. Instrumental scratch reflex of the deafferented limb in cats and rats. Acta Biol. Exp. (Warsaw) 19, 233-247.

Jankowska, E., Lindstrom, S., 1971. Morphological identification of Renshaw cells. Acta Physiol. Scand. 81, 428, 430.

Jankowska, E., Smith, D.O., 1973. Antidromic activation of Renshaw cells and their axonal projections. Acta Physiol. Scand. 88, 198-214.

Jankowska, E., Jukes, M.G.M., Lund, S., Lundberg, A., 1967a. The effect of DOPA on the spinal cord. 5. Reciprocal organization of pathways transmitting excitatory action on motoneurons of flexors and extensors. Acta Physiol. Scand. 70, 369-388.

Jankowska, E., Jukes, M.G.M., Lund, S., Lundberg, A., 1967b. The effect of DOPA on the spinal cord. 6. Half-centre organization of interneurons transmitting effects from the flexor reflex afferents. Acta Physiol. Scand. 70, 389-402.

Jankowska, E., McCrea, D., Rudomin, P., Sykova, E., 1981. Observations on neuronal pathways subserving primary afferent depolarization. J. Neurophysiol. 46, 506-516.

Jones, J.G., Tansey, E.M.T., Stuart, D.G**.,** 2011. Thomas Graham Brown (1882-1965): Behind the scenes at the Cardiff Institute of Physiology. J. Hist. Neurosci. 20,188-209.

Jung, R., 1975/92. Some European neuroscientists: a personal tribute. In: Worden, F.G., Swazey, J.P., Adelman, G. (Eds.),The Neurosciences: Paths of Discovery, I. Birkhäuser, Boston, pp. 477-511. Note: First published by MIT Press in 1975.

Junge, D., 1967. Multi-ionic action potentials in molluscan giant neurones. Nature (Lond.) 215, 546—548.

Karczmar, A.G., 2001a. Sir John Eccles, 1903–1997. Part 1. Onto the demonstration of the chemical nature of transmission in the CNS. Perspect. Biol. Med. 44, 76–86.

Karczmar, A.G., 2001b. Sir John Eccles, 1903–1997. Part 2. The brain as a machine or as a site of free will? Perspect. Biol. Med. 44, 250–262.

Katz, B. 1948. The electrical properties of the muscle fibre membrane. Proc. R. Soc. B 135, 506-544.

Kavli Foundation, 2008. The Kavli Prize in Neuroscience. See: http://www.kavlifoundation.org/2008-neuroscience-citation (Downloaded on February 04, 2016).

Kawato, M., 1999. Internal models for motor control and trajectory planning. Curr. Opinion Neurobiol. 9, 718-727.

Keifer, J., Stein P.S.G., 1983. In vitro motor program for the rostral scratch reflex generated by the turtle spinal-cord. Brain Research 266: 148-151.

Kelly, J.S., 2012. Ainsley Iggo. FRS, FRSE, FRCPE, M. Agr.Sc. (NZ), BSc (Otago), PhD (Aberdeen), D.Sc (Edinburgh). Obituary prepared for the Royal Society of Edinburgh. See: http://www.royalsoced.org.uk/cms/files/fellows/obits_alpha/iggo_A.pdf

Kennedy, D., 1997. Academic Duty. Harvard University Press, Cambridge (MA).

Kuba, K., 2007. Excitable membranes and synaptic physiology since the dawn of a new age – History of studies by Dr. Kyozo Koketsu. J. Physiol. Soc. Jpn. 69 (12), 362-377. (In Japanese).

Kugelberg E, Eklund K, Grimby L., 1960. An electromyographic study of the nociceptive

reflexes of the lower limb: mechanism of the plantar responses. Brain 83, 394–410.

Lance, J.W., 1990. What is spasticity? Lancet 335 (8689), 606.

Langley, J.N., Sherrington, C.S., 1884a. On sections of the right half of the medulla oblongata and the spinal cord of the dog which was exhibited by Professor Goltz at the International Medical Congress in 1881. Proc. Physiol. Soc. J. Physiol. (Lond.) 5, vi.

Langley, J.N., Sherrington, C.S., 1884b. Secondary degeneration of nerve tracts following removal of the cortex of the cerebrum of the dog. J. Physiol. (Lond.) 5, 49-65.

Langley, J.N., 1915. Walter Holbrook Gaskell 1847-1914. Proc. R. Soc. Lond. B 88, xx vii – xxxv.

LaPorte,Y., Lloyd, D.P.C. 1952. Nature and significance of the reflex connections established by large afferent fibres of muscular origin. Amer. J. Physiol. 169, 609-621.

Lashley, K.S. 1933. Integrative function of the cerebral cortex. Physiol. Rev. 13, 1–42.

Lee, S., 1901. Ashe, Thomas (1836-1889). Dict. Nat. Biograph. 1901 Suppl. Smith, Elder & Co., London.

Leibrock, J., Lottspeich, F., Hohn, A. et al.,1989. Molecular cloning and expression of brain-derived neurotrophic factor. Nature 341, 149-152.

Leksell L., 1945. The action potential and excitatory effects of the small ventral root fibres to skeletal muscle. Acta Physiol. Scand.10 (Suppl. 31), 1-84.

Li, V., Black, S., 2016. Presynaptic facilitation of the monosynaptic reflex. Joint presentation at Neurohike 2016 – Kananaskis. University of Alberta, Edmonton.

Libersat, F, Clarac F, Zill S., 1987. Force-sensitive mechanoreceptors of the dactyl of the crab: single unit responses during walking and evaluation of function. J. Neurophysiol. 57 (5):1618-1637. GET PDF

Libet, B., 2006. Reflections on the interactions of mind and brain. Stuart, D.G., Zigmond, M. J., (Eds.). Progr. Neurobiol. 78, 322-326.

Liddell, E.G.T., 1952a. Charles Scott Sherrington 1857-1952. Biogr. Mems. Fell. R. Soc. Lond. 8, 241-270.

Liddell, E.G.T., 1952b. Sir Charles S. Sherrington 1857-1952. Oxford Magazine 70 (May 01), 282-284.

Liddell, E.G.T., 1952c. Sir Charles Sherrington – 1857-1952. Brit. Med. Bull. 8, p. 379.

Liddell, E.G.T., 1952d. Sir Charles Scott Sherrington – An appreciation. The Sunday Times. March 9, pg. 6.

Liddell, E.G.T., 1954. Physiology in Oxford. Oxf. Med. Sch. Gaz. 5, 3-11.

Liddell, E.G.T., 1956. Cajal and Sherrington. Lectures on the Scientific Basis of Medicine 6, 100-115.

Liddell. E.G.T., Sherrington, C.S., 1924. Reflexes in response to stretch (myotatic reflexes). Proc. R. Soc. B 96, 212-242.

Liddell. E.G.T., Sherrington, C.S., 1925. Recruitment and some other aspects of reflex inhibition. Proc. R. Soc. B 97, 488-518.

Liddell, E.G.T., 1960. The Discovery of Reflexes. Oxford University Press, London.

Llinas, R., Hess, R.,1976. Tetrodotoxin-resistant dendritic spikes in avian Purkinje cells. Proc. Natl. Acad. Sci. USA. 73, 7, 2520-2523.

Lloyd, D.P.C., 1941. A direct central inhibitory action of dromically conducted impulses. J. Neurophysiol. 4, 184-190.

Lloyd, D.P.C., 1943. The interaction of antidromic and orthodromic volleys in a segmental spinal nucleus. J. Neurophysiol. 6, 143-151.

Lloyd, D.P.C., 1946. Facilitation and inhibition of spinal motoneurones. J. Neurophysiol. 9, 421-438.

Lloyd, D.P.C., 1951.Electrical signs of impulse conduction in spinal motoneurons. J. Gen. Physiol. 35,255-288.

OFFICE *Lloyd, D.P.C., LaPorte, Y. 1951. Disynaptic reflex link between muscles of a myotatic unit. J. Physiol. (Paris). 43, 786-

Lorente de Nó, R., 1935a. The synaptic delay of the motoneurones. Am. J. Physiol. 111, 272-282.

Lorente de Nó, R., 1935b. The electrical excitability of the motoneurones. J. Cell. Comp. Physiol. 7, 47-71.

Lorente de Nó, R., 1935c. Facilitation of motoneurones. Am. J. Physiol. 113, 505-523.

Lorente de Nó, R., 1939. Transmission of impulses through cranial motor nuclei. J. Neurophysiol. 2, 402–464.

Lucas, K., 1917. The Conduction of the Nerve Impulse. Longmans Green, London (Note: "This book is based on a series of lectures that Lucas had given at University College London and was edited posthumously by Adrian" (McComas, 2011; p. 336).

Lukyanetz, E.A., 1997. Development of the concepts of voltage-operated calcium channels. Neurophysiology, Kiev 29, 45-56.

Lundberg A., 1964. Supraspinal control in reflex path paths to motoneurons and primary afferents. In: Eccles, J.C., Schadé, J.P. (Eds.), Prog. Brain Res. Vol. 12, Physiology of Spinal Neurons, Elsevier, Amsterdam/London/New York,. pp. 197-221.

*Lundberg A., 1982. Inhibitory control from the brain stem of tranmission from primary afferents to moroneurons, primary afferents terminals and ascending pathways. In: Sjoland H., Bjorklund, A. (Eds.) Brain Stem Control of Spinal Mechanisms. Elsevier Biomedical Press, Amsterdam, pp. 179-224

Lundberg, A. 1998. Introduction. In: Rudomin, P., Romo, R., Mendell, L.M. (Eds.)

Presynaptic Inhibition and Neural Control. Oxford University Press, New York. pp. 3-10.

Lundberg, A., Phillips, C.G., 1973. T. Graham Brown's film on locomotion in the decerebrate cat. J. Physiol. (Lond.) 231, 90P–91P.

Macintosh, F.C., Paton W.D., 1974. George Lindor Brown (1903-1971. Biogr. Mem. Fellows R. Soc. 20, 41-73.

Magendie, F., 1822. Expériences sur les fonctions des racines des nerfs qui naissent de la moelle épinière [Experiments on the functions of nerve roots that arise from the spinal cord]. J. Physiol. Exp. Pathol. (Paris) 2, 366-371.

Marr, D., 1969. A theory of cerebellar cortex. J. Physiol. (Lond.) 202, 437-470.

Martin, M., Contreras-Hernández, E., Javier Béjar, J., et al., 2015. A machine learning methodology for the selection and classification of spontaneous spinal cord dorsum potentials allows disclosure of structured (non-random) changes in neuronal connectivity induced by nociceptive stimulation. Front. Neuroinform. 9, 1-15.

Matthews, P.B.C., 1972. Mammalian Muscle Receptors And Their Central Actions. Williams & Wilkins, Baltimore.

Mayer, R.F., 2001. The motor unit and electromyography – the legacy of Derek Denny-Brown. J. Neurol. Sci. 189, 7-11.

*McComas, A., 2011. Galvani's Spark. Oxford University Press, Oxford/New York.

McGeer, L.D., McGeer, E.G., 2001. Joint autobiography. In: Squire, L.R. (Ed.), The History of Neuroscience in Autobiography, Vol. 3. Academic Press, San Diego/London, pp. 330-363.

McGeer, P.I., Eccles, J.C., McGeer, E.G., 1978. Molecular Neurobiology of the Mammalian Brain. Plenum Press, New York.

Mendel, L.B., 1897. Professor Rudolph Heidenhain. Science 6, 645-648

Mennis, M.R., 2003. The Book of Eccles. A Portrait of Sir John Eccles. Australian Nobel Laureate and Scientist. LaLong Enterprises, Aspley, Queensland, AUS.

Mennis, M.R., 2008. Hullo Eccles – The Eccles Family 1850 to 2000. Ed. 3. LaLong Enterprises, Aspley, Queensland, AUS.

Millman, P.M, 1984. Obituary – Bart Jan Bok, 1906-1983. J. R. Astron. Soc. Can., 78, No.1, 3-7.

Molnár Z., Brown R.E., 2010. Insights into the life and work of Sir Charles Sherrington. Nature Rev. Neurosci. 11, 429-426.

Mombelli, G., 2000. The last months of Sir John – Memories of his physicians. In: Eccles, H., Biersack, H.J. (Eds.). Sir John Eccles in Memoriam– A Tireless Warrior for Dualism. Ecomed, Landsberg, GER. pp. 183-184.

Monotti, R., 2000. Testimony. In: Eccles, H., Biersack, H.J. (Eds.). Sir John Eccles in Memoriam– A Tireless Warrior for Dualism. Ecomed, Landsberg, GER. pp. 185-186.

Munk, H., 1903. As to the consequences of the sensitivity loss of the limbs for their motility. Sitzungsberb. d. Königl. Akad. der Wissensch. z. Berlin. 40 pp.

Nicholls, J.G.,1998. Stephen W. Kuffler. 1913-1980. A Biographical Memoir. National Academies Press, Washington, D.C.

Nichols, T.R., Bunderson, N., Lyle, M.. 2014. Chapter 4. Neural regulation of limb mechanics – Insights from the organization of proprioceptive circuits. In: Prilutsky, B., Edwards, D.H. (Eds.), 2014. Neuromechanical Modeling of Posture and Locomotion. Springer, New York. In Press.

Ogilvie, M., Harvey, J. (Eds.), 2000. The Biographical Dictionary of Women in Science – Pioneering Lives from Ancient Times to the Mid-20th Century. Routledge, New York.

Olmsted,J.M.D., E.H. Olmsted, 1944. Francois Magendie, Pioneer in Experimental Physiology and Scientific Medicine in XiX Century France. Schuman, New York.

Oomura, Y., Ozaki, S., Maeno, T., 1961. Electrical activity of a giant nerve cell under abnormal conditions. Nature (Lond.) 191, 1265-1267.

Orlovsky, G.N., Deliagina, T.G., Grillner, S. 1999. Neuronal Control of Locomotion – From Mollusk to Man. Oxford University Press, Oxford.

Pasik,T., Pasik, P., 1995. János Szentágothai (1912-1994): A personal tribute. J. Comp. Neurol. 356, p.165.

Penfield, W, 1957. Sir Charles Sherrington, poet and philosopher. Brain 130, 402-410.

Philippson, M., 1905. L'autonomie et la centralisation dans le svstème nerveux des animaux [Autonomy and centralization in the nervous svstem of animals]. Trav. Lab. Physiol. Inst. Solvay (Bruxelles) 7, l-208.

Phillips, C.G., 1983. Edward George Tandy Liddell – 25 March 1895-17 August 1981. Biogr. Mems. Fellows R. Soc. Lond. 29, 333-359.

Popper, K.R., Eccles, J.C., 1977. The Self and Its Brain. Springer-Verlag, Berlin.

Porter, A.T., 1895. The path of the respiratory impulse from the bulb to the phrenic nuclei. J. Physiol. (Lond.) 17, 455-485.

Porter, R., Lemon, R. 1993. Corticospinal Function and Voluntary Movement. Monographs of the Physiological Society, Vol. 45. Oxford University Press, New York. Note: See historical section on pp. 1-34.

Rall, W., 1992. Path to biophysical insights about dendrites and synaptic function. In: Samson, F., Adelman, G. The Neurosciences: Paths of Discovery. II. H. Birkhäuser, Boston, pp. 214-238.

Rall, W., 2006. Autobiography In: Squire, L.R. (Ed.), The History of Neuroscience in Autobiography, Vol. 5. Academic Press, San Diego/London, pp. 551-611.

Renshaw, B., 1940. Activity in the simplest spinal reflex pathways. J. Neurophysiol. 3, 373-387.

Renshaw, B., 1941. Influence of discharge of motoneurons upon excitation of neighbouring motoneurons. J. Neurophysiol. 4, 167-183

Renshaw, B., 1942. Effects of presynaptic volleys on spread of impulses over the soma

of the motoneuron. J. Neurophysiol., 5, 235-243.

Renshaw, B., 1946a. Observations on interaction of nerve impulses in the gray matter and on the nature of central inhibition. Am. J. Physiol. 46,443-448.

Renshaw, B., 1946b. Central effects of centripetal impulses in axons of spinal ventral roots. J. Neurophysiol. 9, 191-204.

*Renshaw, B., Rosenbaum, H., 1948a. Does injury to an axon promptly induce altered excitability in its cell of origin? Fed. Proc. Pt. 1, 100-101.

*Renshaw, B., Rosenbaum, H., 1948b. Respiratory pathways in the cervical spinal cord. Anat. Rec. 101 (4), 738.

*Renshaw, B., Rosenbaum, H., 1952. Does injury to an axon promptly induce altered excitability in its cell of origin?

*Renshaw, B., Therman, P.O., 1941. Excitation of intraspinal mammalian axons by nerve impulses in adjacent axons. Am. J. Physiol. 133,96-105.

Renshaw, B., Forbes, A., Drury, C., 1938. Electrical activity recorded with microelectrodes from the hippocampus. Am. J. Physiol. 123, 169-170.

*Renshaw, B., Forbes, A., Morison, B.R., 1941. Activity of isocortex and hippocampus, electrical studies with microelectrodes. J. Neurophysiol. 3, 74-105.

Rheinberger, H.-J., 1998. Ernst Florey, 1927-1997 (obituary). In: Reports on the History of Science, Vol, 21, p 46 (Translated from German).

Robertson, B., Kardamarkis, A., Capantini, L., Péréz-Fernandez, J., Suryananayana, S.M., Wallén, P., Stephenson-Jones, M., Grillner, S., 2014. The lamprey blueprint

Roland, P.E., Larsen, B., Lassen, NA, SkinHøj, E.,1980. Supplementary moto area and other cortical areas in organization of voluntary movements in man. J. Neurophysiol. 43, 118-136.

*Rosenbaum, H, Renshaw, B.1949. Descending respiratory pathways in the cervical spinal cord. Am. J. Physiol.157, 468-476.

Rothschuh, K. E. (1974). Eduard Friedrich Wilhelm Pflüger. In: Gillespie, C.C. (Ed.), Dictionary of Scientific Biography, Charles Scribner's Sons, New York, 1970-1990, vol. 10, pp. 578-80.

Roy, C.S., Graham Brown, J., Sherrington, C.S., 1886. Preliminary report on the pathology of cholera Asiatica (as observed in Spain). Proc. R. Soc. Lond. 41, 173-181.

Rudomin, P., 1965. Recurrent laryngeal nerve discharges produced by cutaneous and vagal afferent stimulation. Acta Physiol. Lat. Am. 15 (2), 158-170.

Rudomin, P., 1967a. Primary afferent depolarization produced by vagal visceral afferents. Experientia 23, 117-119.

Rudomin, P., 1967b. Presynaptic inhibition induced by vagal afferent volleys. J. Neurophysiol. 30, 964-1981.

Rudomin, P., 2009. In search of lost presynaptic inhibition. Exp. Brain Res. 196 (1), 139-151.

*Rudomin, P., Schmidt, R.F., 1999. Presynaptic inhibition in the spinal cord revisited. Exp. Brain Res. 19, 1-37.

Rudomin, P., Romo, R., Mendell, L.M., 1998. Presynaptic Inhibition and Neural Control. Oxford University Press, New York.

Ryle, G., 1949. The Concept of Mind. Hutchinson, London.

Sabbatini, R.M.E., 1997. A brief biography of Lars Leksell. htm Brain & Mind.com

Sakmann, B., 2007. Bernard Katz. 26 March 1911-20 April 203: Elected 1952. Biogr. Mems. Fell. R. Soc. 53, 185-202.

Sarikciologli, L., Utuk, A., 2009. Birdsey Renshaw (1911-1948) and his eponym. J. Neurol. Neurosurg. Psychiat. 80 (1), p. 79.

Sassa, K., Sherrington, C.S., 1921.On the myogram of the flexor-reflex evoked by a single break-shock. Proc. R. Soc. Lond. B 92, 108-117. (Note: The first name and lifespan of K. Sassa are not known to us).

Schmidt, R.F., 1963. Pharmacological studies of primary afferent depolarization of the toad spinal cord. Pflüg. Arch. ges. Physiol. 277, 325-346.

Schouenborg, J., 2002. Modular organization and spinal somatosensory imprinting. Brain Res. Rev. 40, 80-91. NO REPRINT IN MY FILES

Schouenborg, J., 2008. Action-based sensory encoding in spinal sensorimotor circuits. Brain Res. Rev. 57,111-117.

Schultz, M., 2008. Rudolph Virchow (1821-1902), Emerg. Infect. Dis. 14, 1480–1481.

Schwindt, P., Crill, W.E., 1977. A persistent inward current in cat lumbar motoneurons. Brain Res.120, 173-178.

Sechenov, I.M., 1863. Physiologische Studien über die Hemmungsmechanismen für die Reflexthätigkeit des Rückenmarks im Gehirne des Frosches [Physiological Studies about Inhibitory Mechanisms in the Brain of Frogs for Spinal Reflex Activity]. Hirschwald, Berlin.

Seki, K., Perlmutter, S.!., Fetz, E.E., 2003. Sensory input to primate spinal cord is presynapptically inhibited during voluntary movement. Nature Neurosi. 6, 1309-1316.

Sherrington, C.E.R., 1975. Charles Scott Sherrington: Memories. Notes Rec. R. Soc. Lond. 30, 45-63. Note: Also published privately in 1957 by the author, Carr Sherrington, who was Sherrington's son.

Sherrington, C.S., 1885. On secondary and tertiary degenerations in the spinal cord of the dog. J. Physiol. (Lond.) 6, 177-191.

Sherrington, C.S., 1887. Note on the anatomy of Asiatica cholera as exemplified in cases occurring in Italy in 1886. Proc. R. Soc. Lond. 42, 474-477.

Sherrington, C.S., 1890. On outlying nerve-cells in the mammalian spinal cord. Proc. R. Soc. B57,144-146.

Sherrington, C.S., 1891a. Note on the knee jerk. St. Thom. Hosp, Rep. 21, 145

Sherrington, C.S., 1891b. II. On out-lying nerve cells in the mammalian spinal cord. Phil. Trans. R. Soc. B 8, 181, 33-48. (Followed by several plates and figures). Note: This article was based on Sherrington's University of London dissertation.

Sherrington, C.S., 1892a. The nuclei in the lumbar cord for the m.s of the pelvic limb. Proc. Physiol. Soc. 13, viii-xxi.

Sherrington, C.S., 1892b. Note on the functional and structural arrangement of efferent fibres in the nerve-roots of the lumbo-sacral plexus. Proc. Royal Soc. 51, 67-78. Note: Full report in Sherrington (1892c).

*Sherrington, C.S., 1892c. Experiments in examination of the peripheral distribution of the fibres of the posterior roots of some spinal nerves. Proc. Roy. Soc. 52, 333-337. Note: Preliminary to Sherrington (1893d).

*Sherrington, C.S., 1893a. In memorium W.B. Hadden M.D. Lond. F.R.C. P. St. Thom. Hosp. Rep. 22, xix-xxi. Note: This obituary was unsigned by Sherrington.

Sherrington, C.S., 1893b. Note on the knee-jerk and the correlation of action of antagonistic muscles. Proc. Roy. Soc. Lond. B 52, 556-564.

Sherrington, C.S., 1893c. Further experimental note on the correlation of action of antagonistic muscless. Proc. Roy. Soc. Lond. B 53, 407-420.

Sherrington, C.S., 1893d. Experiments in examination of the peripheral distribution of the fibres of the posterior roots of some spinal nerves. Phil. Trans. R. Soc. Lond. B 184, 641-763.

Sherrington, C.S., 1894a. Experimental note on two movements of the eye. J. Physiol. (Lond.) 17, 27-29.

Sherrington, C.S., 1894b. On the anatomical constitution of nerves of skeletal muscles; with remarks on recurrent fibres in the ventral spinal nerve-root. J. Physiol. (Lond.), 17, 211- 258.

Sherrington, C.S., (1897a). Cataleptoid reflexes in the monkey. Proc. Roy. Soc. Lond. 60, 411-414.

Sherrington, C.S., 1897b. The spinal cord. In: Foster, M. assisted by Sherrington, C.S. A Text Book of Physiology, 7th ed., Bk. III, Chpt. 1, Macmillan, London, pp. 915-1000.

Sherrington, C.S., 1897c. Experiments in examination of the peripheral distribution of the fibres of the posterior roots of some spinal nerves. (Preliminary abstract). Proc. R. Soc Lond. 60, 408-411. Full report in Sherrington (1898a).

Sherrington, C.S., 1897d. On reciprocal innervation of antagonistic m.s. Third note. Proc. Roy. Soc. B60, 414-417.

Sherrington, C.S., 1897e. On reciprocal action in the retina as studied by means of some rotating discs. J. Physiol. (Lond.) 21, 33-54.

Sherrington, C.S., 1897g. Double conduction in the central nervous system. Proc. R. Soc. Lond. 61, 243–246. Note: This report was also published the same year in a German journal: Doppelte Leitung im Centralnervensystem [Double conduction in the central nervous system]. Mschr. Psychiat. Neurol. 1, 503-506.

Sherrington, C.S., 1897h. Further note on the sensory nerves of m.s. Proc. R. Soc. Lond. 61, 247-249.

Sherrington, C.S., 1897i. On the question whether any fibres of the mammalian dorsal (afferent) spinal root are of intraspinal origin. J. Physiol. (Lond.) 21, 209-212.

Sherrington, C.S.,1897j. Antagonistic m.s and reciprocal innervation. Fourth note. Proc. R. Soc. B 62, 183-187.

Sherrington, C.S., 1898a. II. Experiments in examination of the peripheral distribution of the fibres of the posterior roots of some spinal nerves. Part II. Phil. Trans. Roy. Soc. Lond. B 190, 1-186. Note: This article is preceded by Sherrington (1893d, 1897c). Also, Section IV of this article formed the material for Sherrington's Croonian Lecture, which was entitled "The mammalian spinal cord as an organ of reflex action" and presented to the Royal Society the previous year on April 01, 1897.

Sherrington, C.S.,1898b. Decerebrate rigidity, and reflex co-ordination of movement. J. Physiol. (Lond.), 22: 319-332.

Sherrington, C.S., 1898c. Further note on the sensory nerves of the eye muscles. Proc. R. Soc. Lond. 64, 120.

*Sherrington, C.S., 1898d. On the reciprocal innervation of antagonistic muscles. Fifth note. Proc. R. Soc. B 64, 179-181.

Sherrington, C.S., 1899. Marshall Hall Lecture – On the spinal animal. Med.-Chir. Trans. 82, 449-477.

Sherrington, C.S., 1900a. On the innervation of antagonistic muscles. Sixth note. Proc. R. Soc. Lond. B 66, 66-67. (Read in 1900; published in 1899).

Sherrington, C.S., 1900b. The spinal cord. In: Textbook of Physiology. Vol. 2. Schäfer, E.A. (Ed.), Pentland, London, pp. 783-883.

Sherrington, C.S., 1904. The correlation of reflexes and the principle of the common path. Brit. Assoc. Adv. Sci. Rep. 74:1-14. Note: Abstracts of this report appeared in in three other journals (see Liddell, 1952; p. 264).

Sherrington, C.S., 1905a. On reciprocal innervation of antagonistic m.s. Seventh note. Proc. R. Soc. B 76, 160-163.

Sherrington, C.S., 1905b. On reciprocal innervation of antagonistic muscles. Eighth note. Proc. R. Soc. B 76, 269-297.

Sherrington, C.S., 1905c. Über das Zusammenwirken der Rückenmarksreflexe und das Prinzip der gemeinsamen Strecke [About the interaction of the spinal reflexes and the principle of the common path]. Ergebn. Physiol. 4, 797-850.

Sherrington, C.S., 1906a. The Integrative Action of the Nervous System. Yale University Press. Note: Composed of the 10 Silliman Lectures given by Sherrington at Yale University in 1904. It was published simultaneously in New Haven, New York, and London, with several further publications between 1906 and 1920). Sherrington (1947) is the same book published much later by Cambridge University Press.

Sherrington, C.S., 1906b. On innervation of antagonistic muscles. Ninth note – Successive spinal induction. Proc. Roy. Soc. B 77, 478-497.

Sherrington, C.S., 1906c. On the proprioceptive system, particularly its reflex aspect. Brain 29, 467-482. Note: This volume is called "The Hughling Jackson Number."

Sherrington, C.S., 1906d. Observations on the scratch-reflex of the spinal dog. J. Physiol. (Lond.) 34, 1- 50.

Sherrington, C.S., 1907a. Appreciation of Sir Michael Foster, Brit. Med. J. Feb. 09, p. 351. Note: This appreciation follows the obituary, which begins on p. 349.

Sherrington, C.S., 1907b. On reciprocal innervation of antagonistic m.s. Tenth note. Proc. Roy. Soc. B 79, 337-349.

Sherrington, C.S., 1907c. On reciprocal innervation of antagonistic muscles. Eleventh note – Further observations of successive induction. Proc. Roy. Soc. B 80, 53-71.

Sherrington, C.S., 1907d. Address on 'Inhibition' to the Royal Society of Edinburgh. The Scotsman, 26 October. Note: This was a newspaper summary of the address.

Sherrington, C.S., 1908a. On Reciprocal Innervation of Antagonistic Muscles. Eleventh Note – Further Observations on Successive Induction. Proc. R. Soc. Lond. B 80, 53-71.

Sherrington, C.S., 1908c. Reciprocal Innervation of Antagonistic Muscles. Twelth Note. – Proprioceptive Reflexes. Proc. R. Soc. Lond. B 80, 552-564.

Sherrington, C.S., 1908c. Reciprocal Innervation of Antagonistic Muscles. Thirteenth Note. – On the Antagonism between Reflex Inhibition and Reflex Excitation Proc. R. Soc. Lond. B 80, 565-578.

Sherrington, C.S., 1909a. On plastic tonus and proprioceptive reflexes. Quart. J. Exp. Physiol. 2, 109-156.

Sherrington, C.S., 1909b. On the reciprocal innervation of antagonist m.s. Fourteenth note. On double reciprocal innervation. Proc. R. Soc. Lond. B 81, 249-268.

Sherrington, C.S., 1910a. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J. Physiol. (Lond.) 40. 28-121.

Sherrington, C.S., 1910b. Remarks on the reflex mechanism of the step. Brain 33, 1-25.

Sherrington, C.S., 1910c. Notes on the scratch reflex of the cat. Quart. J. Exp. Physiol. 3, 213-220.

Sherrington, C.S., 1913a. Reciprocal innervation and symmetrical m.s Proc. R. Soc. Lond. B 86, 219-232.

Sherrington, C.S., 1913b. Nervous rhythm arising from rivalry of antagonistic reflexes: reflex stepping as a result of double reciprocal innervation. Proc. R. Soc. B 86, 233-261.

Sherrington, C.S., 1913c. Reflex inhibition as a factor in the co-ordination of movements and postures. Quart. J. Exp. Physiol. 6, 251-310.

Sherrington, C.S., 1913d. Further observations on the production of reflex stepping by combination of reflex excitation with reflex inhibition. J. Physiol. (Lond.) 47, 196-214.

Sherrington, C.S., 1913e. Reciprocal innervation. XVIIth International Congress of Medicine – London: 1913. Section II. Part I. Frowde, Oxford University Press, and Hodder and Stoughton, London, pp. 85-98.

Sherrington, C.S., 1919a. Mammalian Physiology – A Course of Practical Exercises. Oxford University Press, Oxford. Note: The 2nd edition of this manual was co-authored with E.G. T. Liddell in 1929.

Sherrington, C.S., 1919b. Note on the history of the word "tonus" as a physiological term. In: Contributions to Medical and Biological Research Dedicated to Sir William Osler in Honor of His Seventieth Birthday by his Students and Co-Workers. Vol.1. Hoeber, New York, pp. 261-268. Galen is discussed in this article. For his biography see: http://www.historylearningsite.co.uk/claudius_galen.htm. (Retrieved on 12/08/14).

Sherrington, C.S.,1925a. Remarks on some aspects of reflex inhibition. Proc. R. Soc. Lond. B 97, 519-545.

Sherrington, C.S., 1925b. J.N. Langely, Sc. D., Hon. M.D., LL. D., F.R.S. Brit. Med. J. Nov. 14, p. 295.

Sherrington, C.S., 1927. Lucas, Keith (1876-1916). In: Davis H.W.C., Weaver, J.R.H. (Eds.), Dictionary of National Biography, 1912-1921. (Suppl. III). Oxford University Press, London. p. 347.

Sherrington, C.S., 1928. Sir David Ferrier. Proc. R. Soc. Lond. B 103, viii-xvi.

Sherrington, C.S., 1929. Ferrier lecture. – Some functional problems attaching to convergence. Proc. R. Soc. Lond. B 105, 332-362.

Sherrington, C.S.,1931a. Hughlings Jackson Lecture. – Quantitative management of contraction in lowest level of co-ordination. Brain 54, 1-28.

Sherrington, C.S., 1932. Lower reflex co-ordination. In: Creed, R.S., Denny-Brown, D., Eccles, J.C., Liddell, E.G.T., Sherrington, C.S., 1932. Reflex Activity of the Spinal Cord. Clarendon Press, Oxford. Note: Reprinted in 1972 by Oxford University Press, Oxford. pp. 104-159 in the latter version w/ knowledge that Sherrington wrote this

chapter (Eccles and Gibson, 1979; pp. 65-69).

Sherrington, C.S., 1933a. Inhibition as a coordinative factor. Nobel Lecture, December 12, 1932. In: Santessan, C.G. (Ed.), Les Prix Nobel en 1932. Nobel Foundation, Stockholm, pp. 278-289.

Sherrington, C.S., 1933b. The Brain and its Mechanism. The Rede Lecture delivered before the University of Cambridge, December 5, 1933. Cambridge University Press, Cambridge, 36 pp. Note: The second issue of this article was in November,1937.

Sherrington, C.S., 1934. Reflex inhibition as a factor in co-ordination of muscular acts. Rev. Soc. Argent. Biol. Suppl.10, 510-513.

Sherrington, C.S., 1935a. Sir Edward Sharpey-Schäfer and his contributions to neurology. Edinb. Med. J. 42, 393-406.

Sherrington, C. S. 1935b. Santiago Ramón y Cajal. 1852-1934. Obit. Notices Fell. R. Soc. 1, 425-441.

Sherrington, C.S., 1946. The Endeavour of Jean Fernel. Cambridge University Press, Cambridge, UK.

Sherrington, C.S., 1948. Introduction to BBC Third Program series entitled “The Physical Basis of Mind.” Original recording (14 min) on 3 sides of 78 rpm discs. Copies available upon request from the British National Sound Archive, and the Wellcome Institute for the History of Medicine. Also available as a digital MP3 disk upon request to the authors.

Sherrington, C.S., 1953. Marginalia. In: Underwood., E.A. (Ed.), Science, Medicine and History, Vol. 2. Oxford University Press, London, pp. 545-553. Note: Sherrington wrote this article in 1946 and corrected the proofs shortly before his death in 1952.

Sherrington, C.S., Hering H.E., 1897. Antagonistic muscles and reciprocal innervation. Fourth note. Proc. Roy. Soc. Lond. B 62, 183-187.

Sherrington, C.S., Sowton, S.C.M.,1915. Observations on reflex responses to single break-shocks. J. Physiol. (Lond.) 49, 331-348.

Skljarevski, V., Ramadan, N.M., 2002. The nociceptive flexion reflex in humans – review article. Pain 96, 3-8.

Smith, R,1992. Inhibition–History and Meaning in the Sciences of Mind and Brain. University of California Press, Berkeley/Los Angeles.

Stein, J., 2013. Marianne Fillenz (1924-2013). Physiology News – Winter. p. 53.

Stein, P.S.G., 1983. The vertebrate scratch reflex. In: Roberts, A., Roberts, B. (Eds,), Neural Origin of Rhythmic Movements. Society for Experimental Biology, UK, pp. 383-403.

Stein, P.S.G., Grossman, M.L., 1980. Central program for scratch reflex in turtle. J. Comp. Physiol. A 140, 287-294.

Stein, P.S.G., Victor, J.C., Field, E.C., Currie, S.N., 1995. Bilateral control of hindlimb scrarching in the spinal turtle.: contralateral spinal circuitry contributes to the normal ipsilateral motor pattern of fictive rostral scratching. J. Neurosci. 15, 4343-4355.

Stone, D.S., Mattingly D.J.,1999. Life, Death, and Entertainment in the Roman Empire. University of Mchgan Press, Ann Arbor, p. 3. p. 63.

Strata, P., 2000. Recollections of my life with Sir John Eccles. In: Eccles, H., Biersack, H.J. (Eds.), Sir John Eccles in Memoriam - A Tireless Warrior for Dualism. Ecomed, Landsberg, Germany, pp. 13–47.

Stuart, D.G., Willis, W.D., Reinking, R.M., 1971. Stretch-evoked excitatory postsynaptic potentials in motoneurons. Brain Res., 33, 115-1125.

Stuart, D.G., 1999. The segmental motor system – advances, issues, and possibilities. Prog. Brain Res. 123:3-28.

Stuart, D.G., 2002. Reflections on spinal reflexes. Adv. Exp. Med. Biol. 508, 249-257.

Stuart, D.G., 2005. Integration of posture and movement: Contributions of Sherrington, Hess, and Bernstein. Hum. Mov. Sci. 24, 621-643.

Stuart, D.G., Zigmond, M.J. (Eds), 2006. The contributions of Sir John Carew Eccles to contemporary neuroscience. **Prog Neurobiol**, 78: 135-326

Stuart, D.G**.,** 2007. Reflections on integrative and comparative movement neuroscience. Integr. Comp. Biol. 4, 82-504.

Stuart, D.G., Brownstone, R.M., 2011. The beginning of intracellular recording in spinal neurons: facts, reflections, and speculations. Brain Res. 1409, 62-92.

Stuart, D.G., Hultborn, H., 2008. Thomas Graham Brown (1882-1965), Anders Lundberg (1920-), and the neural control of stepping. Brain Res. Rev. 39, 74-95.

Stuart, D.G., Pierce, P.A., 2006. The academic lineage of Sir John Carew Eccles (1903–1997). Prog. Neurobiol. 78, 136–155.

Stuart, D.G., Zigmond, M.J. (Eds.), 2006. The Contributions of John Carew Eccles to Contemporary Neuroscience. Prog. Neurobiol. 78, 135–326.

Stuart, D.G., Schaefer, A.T., Graham, B.A., Callister, R.J., 2014. Pioneers in CNS inhibition: 1. Ivan M. Sechenov**,** the first to demonstrate inhibition arising in the brain and spinal cord. Brain Res. 1548, 20-48.

Stuart, D.G., Pierce, P.A., Callister, R.J., Brichta, A., McDonagh, J.C., 2001. Sir Charles Sherrington: humanist, mentor, and movement neuroscientist. In: Latash, M.L., Zatsiorsky, V. (Eds.), Classical Papers in Movement Science. Human Kinetics, Champaign, pp. 297–374.

Swazey, J.P.,1969. Reflexes and Motor Integration – Sherrington's Concept of Integrative Action. Harvard University Press, Cambridge (MA).

Thach, W.T., Jr., 2000. Edward Vaughn Evarts – 1926-1985. Biogr. Mems. Nat. Acad. Press 78, 1-15.

Thornton, S., 2017. Karl Popper. The Stanford Encyclopedia of Philosophy (Spring 2014

Edition), Edward N. Zalta (ed.), See http://plato.stanford.edu/archives/spr2014/entries/popper/. Retrieved on 12/08/14.

Todman, D.H. 2008. John Newport Langely (1852-1925). IBRO History of Neuroscience. See: http://www.ibro.info/Pub/Pub_Main_Display.asp?LC_Docs_ID=2572). (Retrieved on 12/02/14).

Tucker, A., 2012. Sir Andrew Huxley obituary. The Guardian May 31.

Valentinuzzi, M.E., 1987. Hebbel E. Hoff (Dec. 1st, 1907– May 1st, 1987) Physiologist, Historian, Teacher, Scientist, Scholar. IEEE Eng. Med. Biol. Mag. 6, p. 55.

Vilensky, J.A., Gilman, S., Dunn, E., 1988. Derek Denny-Brown (1901-1981): his life and influence on American neurology. J. Med. Biographr. 6, 73-78. See also: http://users.ipfw.edu/vilensk/dbwebintro.htm

Walpaw, J.R., 2006. Plasticity from muscle to brain. Progr. Neurobiol. 78, 233-263.

Walshe, F.M.R., 1966. Gordon Morgan Holmes 1876–1965. Biogr. Mems. Fell. R. Soc. 12, 311-319.

Wiesendanger, M., 2006. Eccles' perspectives on the forebrain: its role in skilled movements, and the mind-brain problem. Progr. Neurobiol. 76, 304-321.

Wigström, H., Gustafsson, B., 1985. On long-lasting potentiation in the hippocampus: A proposed mechanism for its dependence on coincident pre- and postsynaptic activity. Acta Physiol. Scand. 125, 159-12.

Wilkins, R.H., 1964. Neurosurgical classic – XXII. J. Neurosurgery 21, 724-733.

Willis, W.D., 1971. The case for the Renshaw Cell. Brain Behav. Evol. 4, 5-52.

Willis, W.D., 2006. John Eccles' studies of spinal cord presynaptic inhibition. In: Progr. Neurobiol. 78, 189-214.

Wilson, J.A., 1981. Eccles's physiological evidence for a self-conscious mind. Brain Behav. Evol. 18, 33–40.

Wilson, V.J., Burgess, P.R., 1962. Disinhibition in the cat spinal cord. J. Neurophysiol. 25, 392-404.

Wolpaw, J.R., Carp, J.S., 2006. Plasticity from muscle to brain. Progr. Brain Res. 78, 233-263.

Woodbury, J.W., Patton, H.D., 1952a. Properties of spinal cord elements studied with intracellular ultramicroelectodes. Fed. Proc. 11, 175.

Woodbury, J.W., Patton, H.D., 1952b. Electrical activity of spinal cord elements. Cold Spring Harb. Symp. Quant. Biol. 17, 185-188.

Zerman, A., 2007. Sherrington's philosophical writings – a 'zest for life.' Brain 130, 1984-1987.

Table 1 – Sherrington's fourteen "note" articles on reciprocal innervation in their chronological order.

Note no. Citation	Preparation(s).	Main results & their interpretation by Sherrington
01. 1893b	Monkey & cat; surgery not explained.	Proved knee jerk was a reflex event, viz. 1892b article. Results showed (p. 563) " ... the degree of tension in one muscle of an antagonistic muscle intimately affects the degree of 'tonus' in its opponent, not only mechanically, but also reflexly, through afferent and efferent channels and the spinal cord."
02. 1893c	Monkey & cat; anesthetized & conscious preps.	Further support for knee jerk a reflex event. Followed w/ analysis of reciprocal inhibition in eye muscles. An **addition**[a] emphasized earlier discovery of reciprocal inhibition in eye muscles by Bell & Bell (1826). (Terms "reciprocal inhibition" & "reciprocal innervation" not used in Bells' article or this note). Further experiments then undertaken, which supported earlier 1826 work of Charles Bell [1774-1842]. (John Bell [1763-1820] had died prior to the 1826 sixth edition of Bell & Bell).
03. 1897c	Unanesthetized cat after brain transection @ high midbrain level.	First note to use terms "reciprocal innervation" & "extensor rigidity." Reciprocal inhibition (term not used) confirmed for knee & elbow extensors. The term "decerebrate rigidity" was also not used.
04. 1897d	Anesthetized (ether or ether + chloroform) monkey & cat w/ brain exposed subdurally.[b] Additional exps. on unanesthetized cats w/ decerebrate rigidity.	Electrical stimulation of selected sites in cortex & internal capsule had reciprocal effects on forearm biceps & triceps, & on hindlimb quadriceps components that produced hip flexion vs. knee extension. An **addendum** added further stimulation sites in cat, including optic radiations, Rolandic & occipital (visual) cortex, & internal capsule. In cats w/ high midbrain transection producing decerebrate rigidity[c] similar reciprocal effects shown in various combinations of muscle agonists/antagonists by stimulation of skin & skin nerves, muscles & their afferents, cerebellum, & crusta cerebri (i.e., anterior portion of cerebral peduncle containing the motor tracts).
05. 1898c	Deep chloroform narcosis of conscious monkey & cat after section of nerves to various eye muscles.	Demonstrated reciprocal innervation between eye opening (levator palpabrae superioris) & eye closing (orbicularis palpebrarum (oculi)) muscles during eye closing. Had previously shown reciprocal innervation between these muscles during eye opening (Sherrington, 1894a).

06. 1900a	Conscious spinal cat, dog, & frog.	Hind limb posture examined after spinal transection in response to sensory stimulus arising from passive movement. In cat, flexion predominated for first few weeks after cervical or upper thoracic transection. Later, hip extension often observed. If initial passive posture included hip & knee flexion major observations (p. 67) were (1) " ... the direction which a spinal reflex movement elicited by stimuli similar in all respects, including 'locality,' may take, is in part determined by the posture already obtaining in the limb at the time of the application of the stimulus," & (2) " ... the influence of the posture of the limb upon the spinal condition & reaction is not traceable to the nerves of the cutaneous sense-organs of the limbs. There still remain the afferent nerves subserving muscular sense, and connected w/ the sense-organs in muscles, tendons, and joints."
07. 1905a	Conscious spinal dog.	Extended 1900a results by examining active rather than passive movements brought on by both mechanical stimulation of plantar surface of foot & electrical stimulation of afferent nerves. Pinprick of plantar foot surface produced flexion reflex, whereas light mechanical tap produced "extensor thrust." If latter elicited before & after former reflex, a post inhibitory rebound of latter was seen. Effect also seen in crossed extension associated w/ the ipsilateral flexion reflex. Latter finding thought associated w/ conversion from F to E1 phase of step (terminology of Philippson, 1905).
08. 1905b	Presumably conscious & anesthetized spinal dog & decerebrate cat.	Further work on idea (p. 269) that inhibition " ... is part and parcel of the normal reflex process, so that in a reflex it goes on side by side with excitation of other muscles opposed to those which are inhibited." **I.** Prep. had hindlimb movements restricted to knee flexion in one limb & knee extension in the other during "direct-flexion reflex." Single-, multiple-shock, & sustained electrical stimulation of a skinfold field produced knee flexion in homonymous limb, whereas stimulation of same site in opposite limb produced inhibition of knee extension in that limb. Other examples shown for various mechanical stimuli, both noxious & non-noxious. **II–III.** Further details discussed about flexion reflex. **IV.** Discussion about knee jerk's spinal pathway. **V.** Experiments described using strychnine to support notion that spinal inhibition an active process & separate from spinal excitation. **Addendum**. Tetanus toxin shown to have effects on spinal reflex pathways similar but not identical to that of strychnine. Similar results obtained for effects of cerebral cortical stimulation on spinal pathways. This was the first paper in the notes sequence to include myographic recordings (Fig. 3) & a conceptual figure of possible spinal pathways for reciprocal innervation & inhibition (Fig. 8).

09. 1906b	Chronically maintained spinal cat & dog w/ section at thoracic level.	Examples provided of post-inhibitory rebound (called "exaltation" or "after-exaltation") in flexor & extensor muscles & reflexes that followed a short period of mildly noxious inhibition in same muscle & reflexes, w/ spinal prep. In various postures; e.g., spine vertical or horizontal & limbs hanging freely or supported at knee, or animal lying on side w/ no mechanical strain on flexors & extensors. Coined term "successive spinal induction" for post-inhibitory rebound not due to excitatory stimulation during preceding period of inhibition. Inferred (p. 483) "The reflex arc whose reaction is inhibited and the reflex arc which inhibits are both found when separately examined to use the same final common path, but to different effect." (The "principle of the common path" had been elaborated in 1904 article). **Addendum.** Provided evidence that successive induction & rebound contraction might explain natural alternating reflexes, presumably to him as in stepping,
10. 1907b	Mostly spinal cat & dog w/ section presumably at thoracic level. Also some decerebrate preps.	**I.** W/ previous studies on reciprocal innervation/inhibition focusing on muscles acting on one joint (usually knee), similar results now obtained for gastrocnemius (knee flexor, ankle extensor) as opposed by ankle flexor, tibialis anterior. **II.** Similar results also obtained in several other muscle combinations & within some muscles when divided into two sections. **III.** Main finding (p. 340) was " ... reflex inhibition is not confined to one single muscle, but involves a number of muscles, just as the reflex contraction is not confined to one single muscle, but involves a number." Two groups of muscle afferent fibers encountered w/ both activating reciprocal effects in antagonistic muscle combinations; one group provided homonymous excitation & the other homonymous inhibition. **IV.** Several other antagonistic muscles of the lower limb provided similar results & attention then directed to which reflex fields were "exteroceptive" vs, "exteroceptive plus proprioceptive," as defined in 1905c article & 1906a book. Additional reflections on features of muscles strongly inhibited by reciprocal innervation (i.e., extensors that counteract gravity in habitual standing posture), the scratch reflex, the crossed & uncrossed flexion reflex, features of decerebrate rigidity in the cat, dog, monkey & rabbit, including ankle clonus. **V.** Observed in several muscle combinations (p. 344) " ... the distribution of the reflex effect is in the crossed reflex mainly, if not entirely, to the same muscles as those affected by the uncrossed reflex, but that the incidence of excitation & inhibition upon the motor neurons of those muscles is converse in the two reflexes." **VI.** Studied role of reciprocal inhibition in extensor thrust reflex of decerebrate cats. **VII.** More observations on rebound effects following reciprocal innervation effects in several muscle combinations. **Addendum.** Provided examples of reciprocally produced inhibition of muscles not counteracting gravity (e.g., thigh adductors & external rotators).

11. 1907c	Briefly maintained cat & dog w/ pontine transection of brainstem.	Goal was to demonstrate "successive induction" in extensor hindlimb muscles of preparations studied within few hours after brainstem transection, rather than several days later as in previous notes. After reducing chloroform narcosis following surgery (p. 55) "The movement of active flexion (*produced by stimulation of nerves to antagonistic flexors*) is followed by a movement of active extension. During the active flexion the extensor muscles are relaxed by central inhibition; during the active extension the extensor muscles contraction." This finding resulted from even a very brief single electric shock (*50 ms*), albeit smaller than when using repetitive stimuli. Proposed (p. 66) " If a reflex A not only temporarily inhibits a contraction B antagonistic to it, but also induces in the arc of B, as an immediately subsequent result, an excitation, we have a process qualified to link together simpler reflexes, so as to form from them reflex cycles of action such as characterise the reflex play of the limbs in locomotion." **Addendum.** W/ co-author, Canadian biochemist/anesthesiologist Herbert E. Roaf [1881-1952] (Anon., 1952), described post-inhibitory rebound of extensor muscles resulting not only following cessation of reciprocal inhibition from flexor input to the spinal cord, but also from reducing levels of inhibition. Again, effect proposed relevant to reflex activity during stepping.
12. 1908a	Acute decerebrate cat w/ only one extensor muscle (mostly crureus) intact in hind limb & all other muscles acting on the ipsilateral & contralateral knee paralyzed by section of their n. supply. Also spinal dog after abatement of spinal shock.	Two opposite reflexes in rigid decerebrate cat described largely for crureus muscle (vastus intermedius). **I.** Crureus alone maintained limb in partial or complete extension; removed by activation of antagonist flexor muscles deprived of sensory input to spinal cord. Post-inhibitory rebound then not evident. Rather, muscle exhibited a reflex "lengthening reaction" (p. 553): i.e. (p. 544), " There exist in the nerve of vasto-crureus afferent fibres which, under mechanical and electrical stimulation, cause relaxation of the vastocrureus muscle itself." (*Reaction first described without term "lengthening reaction" in 1906b note*). **II.** In contrast, reflex "shortening reaction" produced sustained contraction of crureus, brought on by shortening muscle actively or passively. Latter used afferent fibers in crureus but not same ones used for lengthening reaction. **III.** Same result for hind limb, shoulder, & elbow extensors. **IV.** Similar results for knee & hip extensors of spinal dog after abatement of spinal shock.[d] **V.** The two reactions considered analogous to those observed in non-striated limb muscles of several invertebrates studied by others & even visceral smooth muscle of vertebrates. **VI.** Such lengthening & shortening reactions thought to be instigated in extensor muscles by their proprioceptive reflexes, properties of which were first fully described in 1906a book (chpts. 4 & 9), & 1907b note.

13. 1908b	Crureus muscle prep. in decerebrate cat as in note 12.	Crureus muscle responses measured during reflex activation & inhibition (graded stimulation of central end of contralateral popliteal & ipsilateral peroneal nerve, respectively), both singly & together. Inhibition in the class I category of Rudolph Heidenhain [1834-1897] (1882; for biosketch see Mendel, 1897); i.e., it antagonized excitatory process by decreasing or suppressing its action. Noted (p. 578) " ... the point of collision of the antagonistic influences ... either ... lies at a synapse, in which case the opposed influences may be thought of as altering oppositely the permeability of the synaptic membrane, or that it lies in the substance of the 'central' portion of a neurone, probably of the motoneurone itself, meaning by " central" that part of the neurone which lies in the reflex centre. In either case ... The net change which results there when the two arcs are stimulated concurrently is an algebraic sum of the *plus* and *minus* effects producible separately by stimulating singly the two antagonistic nerves."
14. 1909b	Knee extensor (crureus) & flexor (semitendinosis or posterior part of biceps femoris) muscles in spinal cat after abatement of spinal shock,[e] & in decerebrate cat	**I.** Sherrington (1908c) results in decerebrate preparations also seen in spinal (decapitate) ones. To observe inhibition some reflex excitation (brought on by electrical stimulation of appropriate set of afferents or strychnine injection) was necessary because spinal preparations lacked tonus. **II.** First of Sherrington's notes and other studies showing graded active inhibition of flexor muscles interacting w/ graded excitation. **III.** When combining excitatory & inhibitory stimuli for a selected reflex, equilibrium was reached, wherein the two opposing reflex influences balanced each other at a certain level of contraction or relaxation, the length of the muscle then remaining constant. Arguments presented that decerebrate preparations have a natural inhibitory tonus in flexor muscles. **IV.** First demonstration of "double reciprocal innervation" in a single limb (i.e., sensory input activating extensor muscles & inhibiting flexor muscles & vice versa for a different sensory input).

[a]This addition, later Roman numerals (I, II, etc.), and addenda presented **in bold** in Main results column (Sherrington used this style on occasion to number observations &/or opinions & arguments). [b]Description very vague about this preparation, [c]Term "decerebrate rigidity" first used in note 4. [d]Earlier, Sherrington (1898a; p. 134) wrote "The best explicit account of the condition (*i.e., shock*) is contained in the papers of Goltz. By him temporary paralysis following injuries of the brain or cord are all classed as Hemmungserscheinungen (*inhibition phenomena*), and these collectively may be considered to compose the phenomenon of "shock." Goltz's (*Pflugers Archiv, Vol. 8*) descriptions of spinal shock are masterly, but they refer entirely to the dog, and to transection below the middle of the back. “As it is in the monkey that the phenomenon appears at maximum, and especially consequently to high cervical transection, I shall give a description of it as so seen. No more remarkable nervous condition can be imagined." Today our definition of spinal shock is more-or-less the same.

Table 2 – Sherrington's other articles and book chapters that emphasized central inhibition, reciprocal innervation, and inhibition throughout the 1893-1909 epoch of his note articles. **1**

Citation	Article type	Main results & their interpretation by Sherrington
1894a	Experimental	Electrical stimulation of cerebral cortical sites evoked coordinated left rectus externus (lateral rectus) muscle movements with those of right eyeball muscles in lightly anesthetized monkey w/ cerebral cortical cuts & left lateral rectus only active muscle to left eyeball. Inhibition of test muscle in selected eye movements shown to be of subcortical origin & thought to operate during volitional eye movements.
1897a	Experimental	In decerebrate monkey w/ cerebral hemispheres removed & time delay to obviate shock described condition of "decerebrate rigidity" without mentioning this term or anesthesia used initially (probably chloroform). Provided examples of reflexes that evoked inhibition of various muscle groups.
1897b[a]	Textbook chapters	Chapters included short section on phenomenology of supraspinal inhibition of spinal reflexes in various animals including humans (pp. 987-990) & very brief (indeed cautious) mention of spinal inhibition between antagonistic muscles (p. 1000): "Indeed the study of the various instances of antagonistic muscles in the body brings to light increasing evidence that the spinal cord (and other parts of the central nervous system) influences the tone of muscles; the contraction of a muscle has for its concomitant an inhibition (more or less pronounced) of its antagonist. Thus, in the movements of the eye, the contraction of one rectus muscle (internal or external) is associated with an inhibition of its antagonist rectus (external or internal). It would seem that the 'tone' of skeletal muscles and its regulation, inhibition or augmentation, plays a not unimportant part in the due carrying out of the various movements of the body."
1898a	Published Croonian Lecture	Focused on spinal cord reflexes producing contraction of extensor muscles and producing inhibition of flexor muscles & vice versa in several species &/or preparations. Relative extent of each effect varied from one muscle group to another. Possibly first use, by Sherrington or any study, to use terms "decerebrate," "tonus," & "decerebrate rigidity." A preparation illustrating decerebrate rigidity was shown in photos (e.g., cat in note's Fig. 6), & the cerebellum was implicated in one form of associated rigidity.

1898b	Experimental	Claimed first description of decerebrate rigidity in a 1896 note read to the Royal Society. This was an error. The note was no. 4 (1897d). Possibly first-ever study to show the extensor-dominated posture of decerebrate rigidity in the 5 species studied, it being similar & dependent on afferent input. See note's Fig. 1. Examples shown of various sensory inputs relaxing the rigidity. Emphasized that source of condition not determined.
1899	Published Marshall Hall Prize Address	120-page scholarly spinal cord chapter included a section on inhibition & facilitation of spinal reflexes & their invertebrate ganglia equivalents (pp. 837-834). Cited succinctly relevant literature on that point, including supraspinal findings. The advancement is quite remarkable in Sherrington's surety of thinking on central inhibition since his 1897 book chapter.
1900b[b]	Book chapter	Focus on integrative function of nervous system in several species &/or preps, & Sherrington's belief that its unit of action was the uni-directional reflex, which was composed of reflex arcs of sensory or descending origin. Proposed for first time (p. 9) "Reflex arcs show therefore the general feature that the initial neurone is a private path exclusive for a single receptive point; and that finally the arcs embouch into a path leading to an effector organ, and that this final path is common to all receptive points wheresoever they may lie in the body, so long as they have any connection at all with the effector organ in question. Before finally converging upon the motor neurone arcs usually converge to some degree by their private paths embouching upon internuncial paths common in various degree to groups of private paths. The terminal path may, to distinguish it from internuncial common paths, be called *the final common path.* The motor nerve to a muscle is a collection of such final common paths." Examples provided of central spinal inhibition & reciprocal innervation, as he understood them at that time.
1904	Published address to British Association for Advancement of Science	This article addressed inhibition only sparingly. Rather, it focused on Sherrington's ideas to date on the correlation of reflexes, with an emphasis on the scratch reflex, and his principle of motoneurons operating as the final common path in several species &/or preps. For Sherrington this was a well-written and not so wordy contribution.
1906a	Monograph[c]	Burke (2007) provided a succinct summary of this monograph's chapters & their significance. Here the main points are that the concepts of central inhibition, reciprocal spinal innervation, & reciprocal spinal inhibition were well covered in this monograph. Even today, they continue to reach a far wider international readership than Sherrington's previous articles on these topics.

1906d	Experimental	Demonstrated scratching movements of a single hindlimb in spinal dog that was de-afferented. Claimed that the control contralateral hind limb had no mechanical coupled scratching movements. Discussed role of central inhibition in helping create alternating movements during scratching.[d]
1909a	Experimental	Discussed proprioceptive reactions of (**I**) spinal dog, (**II**) decerebrate cat, (**III**) de-afferented knee extensor of various preps, & **(IV**), reflex nature of the above. Many examples provided of reflex inhibition in **I-V**, particularly for lengthening & shortening reactions.

[a]Sherrington was the sole author of all the chapters he wrote for this textbook by Foster. Title page lists Sherrington as assisting Foster. [b]Sherrington wrote 4 chapters in this Textbook of Physiology edited by E.A. Schäfer. [c]Based on 10 lectures given at Yale University in 1904. [d]For further discussion see section 3.4 in the text.

Table 3 – Sherrington's other articles & book chapters on reciprocal innervation/inhibition after the 1893-1909 epoch of his fourteen note articles. **1**

Citation	Article type	Main results & their interpretation by Sherrington
1910a	Experimental	93-page article summarized much of what Sherrington had learned about central inhibition, reciprocal spinal innervation & inhibition, & decerebrate rigidity, as applied to the flexion & crossed extension reflexes & their potential use in reflex standing & stepping in largely dog & cat preparations. Article contained valuable technical details for later researchers undertaking intracellular spinal cord research well into the 1980s.
1910b	Address**a**	Condensed summary of 1910a findings on several animal preps.
1910c	Experimental	Description of scratch reflex attributed its operation to spinal pathways featuring reciprocal & double reciprocal spinal innervation & inhibition in largely decapitate cat preparations. Scratching shown to be more intense than observed previously in spinal dog (Sherrington 1906d). No mention of reciprocal spinal mechanisms in dog work. In neither study was there discussion of the possibility that scratch reflex was driven by a spinal pattern-generating mechanism, as had been demonstrated for several species by the end of the 19th C (for citations, see Jankowska, 1959; Deliagina et al., 1975; Stein, 1983).
1913a	Experimental	Addressed situations in which right and left hind limb muscles are subject to reciprocal vs. identical innervations to produce alternate vs. co-contactile activity (presumably in decerebrate cat). Examples showed how reflexes could be adjusted so one or the other effect predominated as dependent on relative strength of its reflex effect (see article's Fig. 7).
1913b	Experimental	Reflex stepping movements in decerebrate cat w/ intact hindlimb muscles limited to bilateral vastus crureus (vastus intermedius) produced by simultaneous repetitive 40 Hz stimulation of same right & left afferent nerves; one producing sustained excitation of the muscle on its side, & the other producing sustained reciprocal inhibition of the same muscle: "In the rhythmic reflex the right and left muscles each contract and relax alternately and move reciprocally ... This rhythmic reflex is shown clearly to be reflex stepping." (p. 261). Results showed clear role of reciprocal inhibition in stepping.
1913c	Review	Sherrington's most complete & best article on central inhibition in various animal preparations. Summarized all his experimental work on topic to date & set stage for later articles & lectures. Conclusions included "In all these uses of inhibition we see it as an associate of, and a counterpart or counterpoise to, excitation. Whether we study it in the more primitive nervous reactions which simply interconnect antagonistic muscles, or in the latest acquired reactions of the highly integrated organism, inhibition does not stand alone but runs always alongside of excitation." (pp. 307-308).

Table 3. Contd.

1913[d]	Experimental	Reflex stepping again demonstrated – same preparation as 1913b except for also deafferenting the 2 test vasti muscles & several possible notions presented, including Graham Brown's 1911 argument for central control. Sherrington favored idea that "two reflex influences one excitatory the other inhibitory are concurrently at work in closely balanced intensity; & that in the presence of these the intrinsic processes of 'fatigue' & 'successive induction' occurring in the nerve-centres produce an alternate predominance of effect of the one & then of the other of the two opposed extrinsic influences" (p. 214).
1913e	Review[b]	Same information as that covered in 1913 review.
1925[c] (w/ Liddell)	Experimental	Presented findings on how reflex inhibition initiated by the crossed extensor reflex affected motor unit recruitment in knee extensor muscles of decerebate cat. Main result was that inhibitory recruitment behaved quite similarly to excitatory recruitment. Paper is of considerable historical interest for first definition of a motor unit (p. 511) "Styling as 'motor unit' the motoneurone-axon and its adjunct muscle fibres."
1925a	Theoretical	Paired his views on the reflexive nature of central inhibition with ideas of others who focused on views like his (e.g., Graham Brown, 1924) or who focused on potential cellular mechanisms (Lucas, 1917; Adrian, 1918; Forbes, 1922; Cooper & Adrian, 1924). Also of historical interest for refining the above definition of a motor unit (p. 519) to "The term 'motor-unit' includes, together with the muscle-fibres innervated by the unit, the whole axon of the motoneurone from its hillock in the perikaryon down to its terminals in the muscle."
1929	Theoretical	Provided reasoning on how interplay between excitation & inhibition could affect phenomenon of convergence. Argued (p. 361) " ... though trains of impulses are the sole reactions which enter and leave the central nervous system, nervous impulses are not the sole reactions functioning within that system. States of excitement which can sum together, and states of inhibition which can sum together, and states which represent the algebraical summation of these two, are among the central reactions. The motoneurone lies at a focus of interplay of these reactions and its motor unit gives their net upshot, always expressed in terms of motor impulses and contraction. The central reactions can be much longer lasting than the nerve impulse of nerve-trunks." Further historical interest for possibly first sketch of a motor unit (Fig 1 in article; Fig 9 in present text).
1932[d]	Book chapter	Reviewed previous work on reciprocal & double reciprocal innervation & reciprocal inhibition in several preparations. No reference made to a preceding chapter on central inhibition written by Eccles. Conceded correctness of Graham Brown's work on spinal control of stepping (p. 146). "The nervous mechanism answerable for the essential rhythmicity of the scratch reflex & stepping seems a central spinal one, not requiring *rhythmic* (*his italics*) pulsation from outside." Graham Brown (1914) has insisted on this.

Table 3. Contd.

1933a	Published Nobel Prize address	First summarized CNS situations in which reciprocal innervation could occur with emphasis on spinal reflexes. Next discussed (1) interaction between inhibition & excitation including possibilities that their cellular mechanisms were similar, albeit the reverse of each other, and (2) their antagonism could produce both & brake "release" phenomenon of Hughlings Jackson.[e] "When disease or injury has caused a deficit of excitation, a re-adjustment of concurrent inhibition offers a means of arriving once more at the normal quantity (*of excitation*)) required." (p. 11).
1934	Brief review	Same information covered in many earlier articles but possibly influential w/ appearance in the journal Scientific American. Also of historical interest as Sherrington's last comments on the topic of central inhibition, ending with "The whole quantitative grading for the due execution of a muscular act appears to rest on mutual interaction between the two central processes of *excitation* & *inhibition*." (p. 513).

[a]Presidential Address to Neurological Section of Royal Society of Medicine. [b]Published summary of presentation at XVIIth International Congress of Medicine, held in London. [c]Authors in alphabetical order; i.e., Liddell and Sherrington (1925). [d]Sherrington's chapter is in a book with him as a co-author. For the book (Creed et al. 1932), itself, the authors were in alphabetical order. [e]**For** review, see Sherrington (1931a).

Table 4 –Eccles' publications on the case for electrically–based synaptic transmission 1

No. Year	Article type[a]	Main results & their interpretation by Eccles & his co-authors
		At Oxford
01. 1935a	RA (P)	Focused on role of ACh in chemical transmission of contractions of nictitating membrane in cats. Results strongly supported this role but claimed (p. 52) " ...no evidence for ... assumption" that ACh could affect initial fast acting transmission and suggested alternative hypothesis that " ... preganglionic impulses excite ganglion cells by ... eddy currents, the ions conveying these eddy currents being the synaptic transmitters ...." Note: his 02 review (p. 371) claimed this abstract was birth of his action-current hypothesis but the term itself was not mentioned in this 01 abstract.
02. 1936	REV	Major review of synaptic & neuromuscular transmission included argument (p.398) for initial electrical rather than chemical transmission at motoneuron synapses (he argued for his "action-current hypothesis," which he claimed was used, e.g., by oculomotor motoneurons, citing Lorente de Nó (1935a,b). He conceded, however, at the end of his review that "No experiment has yet been performed which definitely excludes one (*chemical transmissio*n) or the other (*electrical transmission*) hypothesis."
03. 1937 w/ Pritchard	AB(P)	Volume conducted ventral root version of motoneuron action potentials recorded during their activation by dorsal root stimulation. Synaptic delay considered too short for chemical transmission but rather an electrically transmitted form of "detonator response".[b]
04. 1937a	REV	Brief summary of evidence for chemical transmission at synapses w/ long duration action vs. electrical transmission at neuroglandular, neuromuscular, & CNS synapses of short duration. Emphasized limitations of electrical transmission evidence.
		At Sydney
05. 1939	REV	Brief update of evidence about chemical vs. electrical transmission. Claimed " ... general agreement on the essential similarity of the transmission processes at the synapses in sympathetic ganglia and in the spinal cord." However, he warned (p. 382) " In view of the paucity of experimental data further discussion of these rival hypotheses of synaptic transmission–the chemical and the electrical–is unwarranted."
06. 1943	RA(P)	Surface recording of output in cat stellate ganglion during sympathetic cardiac-nerve stimulation revealed synaptic potential when action potentials blocked by curare. Experimental results suggested transmitter action w/ two phases: a brief high intensity one due to detonator action, & a prolonged low intensity phase, possibly involving same overall transmitter mechanism.
07. 1944a	RA	Extension of 06 procedures showed eserine blocked prolonged low intensity phase of transmitter action but not preceding brief high intensity phase, which was attributed to electrical transmission.

At Dunedin		
08. 1944b	LET	Non-peer-reviewed letter to editor described experiments on spinal cord of decerebrate cat & isolated spinal cord of frog w/ motoneurons activated by dorsal root volleys after single, double, & high frequency shocks. Motoneuron discharge recorded extra-axonally from ventral roots. Experimental results suggested possibility of electrical transmission of presumed monosynaptic motoneuron discharge.
09. 1945	RA	First "Popper-encouraged" hypothesis fully committed to electrical excitatory transmission at spinal & glandular synapses, & neuromuscular junction (see text Fig. 15A) w/ examples of requisite experimental tests. Emphasized key problem was explaining curare's action & noted (p. 683) "Mathematical development has been beyond my competence and may be premature, though it should be possible ..."
10. 1946a	RA	Work on unanesthetized decerebrate cat and frog suggested (p. 118) " .. acetylcholine probably plays no significant role in synaptic transmission in the spinal cord. The evidence presented in this paper accords with the hypothesis that synaptic transmission in the spinal cord is due to the action currents of the pre-synaptic impulses."
11. 1946b	RA	Theoretical extension of 09 article began w/ overstatement (p. 429) "There is now good evidence that the transmission of (*excitatory*) impulses, at all these synapses, is mediated by catelectrotonic potentials set up at the synaptic membrane of the post-synaptic cell – the end-plate potentials of skeletal muscle (*6 refs.)* and the synaptic potentials of ganglion cells (*2 refs.)* and motoneurones (*3 refs.).* Six theoretical figs. supported transmission sequence involving (p. 442) " ... (1) Impulse in pre-synaptic nerve fiber generates a current which gives a diphasic effect at the synaptic region of the post-synaptic cell, with a total duration of probably not more than 1 msec, in mammalian muscle and the spinal cord; initial anodal focus, with cathodal surround; more intense cathodal focus, with anodal surround. (2) This cathodal focus sets up a brief and intense local response at the synaptic region. (3) From this local response, a catelectrotonus spreads decrementally over the post-synaptic cell membrane (4). A propagated impulse is set up in the post-synaptic cell, if this catelectrotonus is above a critical value. If it is below, then, as the local response subsides, the catelectrotonic surround decays passively." Concluded realistically (p. 450) " ... both the chemical (acetylcholine) and electrical hypotheses ... are unsatisfactory."
12. 1947b	RA	Showed convincingly that ACh is not the synaptic transmitter in the spinal cord thus supporting electrical synaptic transmission in the spinal cord.
13. 1947a w/ Brooks	RA	Addition to 09 & 11 proposed the original electrical transmission hypothesis for central spinal inhibition. It required a first-order Golgi (short-axon interneuron) cell's inhibitory connection with relevant motoneurons (see FIG 12_). Accepted others' work on monosynaptic sensory activation of motoneuron and Lloyd's concept of direct (monosynaptic) inhibition.[c] No limitation of their " Golgi Cell Hypothesis" proposed.

14. 1947b w/ Brooks	RA	His first use of an intraspinal extracellular needle microelectrode electrodes,[d] as used by others to record motoneuron's focal potentials, & first attempt to interpret this potential's tri-phasic waveform. Deep anesthesia used to emphasize possibility of direct inhibitory synaptic transmission.
15. 1947c w/ Brooks	RA	Extension of 14 using deep anesthesia and asphyxiation to provide a preparation appropriate for studying direct electrical spinal inhibition, albeit no discussion of this hypothesis.
16. 1948	REV	Review of previous work on membrane of nerve & muscle fibers, ACh metabolism in nerve impulses, & nerve impulse theory set stage for new work on junctional transmission in muscle, ganglia, and spinal cord. No conclusions on ganglionic transmission but proposed (p. 112) " .. electrical theory of synaptic transmission provides a satisfactory explanation for the spinal cord, which contrasts with the neuromuscular junction where transmission appears to be exclusively cholinergic ..."
17. 1948a w/ Brooks	RA	Using techniques like those in articles 10 & 14, measured interactions between 2 monosynaptic reflexes activated at different brief times. Showed distinction between local detonator responses & the c.e.s., thereby giving credence to central spinal inhibition, albeit not specifically mentioned in this paper.
18. 1948b w/ Brooks	RA	In study considered "preliminary," used techniques like those in 14 to activate Golgi cells by large proprioceptive sensory (Group1) afferents w/ less certainty of activation by cutaneous input.
19. 1948c w/ Brooks	RA	Antidromic and reflex inhibition of cat motoneuron discharge, recorded extracellularly with a micro-electrode as in 14, differed in 3 respects. Presented 3 well thought out theoretical arguments that accommodated the Golgi Cell Hypothesis.
20. 1948 w/ Brooks, Malcolm	RA	Techniques used in 14 repeated to test experimentally several aspects of Golgi Cell Hypothesis. Results thought to comply with hypothesis, as based again on theoretical reasoning, which was difficult to counter by those opposed to electrical synaptic transmission.
21. 1949 w/ Barakan, Downman	RA(P)	With same paper 14 techniques, recorded field potentials of cat spinal motoneuron action potential responses to maximum antidromic activation. Presumed soma-dendritic responses and blocks provided valuable experience for eventual intracellular recording & rejection of electrical transmission and Golgi cell hypotheses.
22. 1949	REV	Final elaboration of electrical hypothesis. Note his quotes: (p. 569) "small size of synaptic knobs ensures that any local responses generated on the subjacent post-synaptic membrane would be well below the critical area necessary for growth of a propagated impulse;" (p. 576) " ... present formulation of the excitatory hypothesis is deficient in that it attributes no properties of the pre-synaptic terminals ... necessary for electrical transmission," and "Until more precise data is available, it does not yet seem expedient to attempt the necessary modification of the excitatory hypothesis ... ;" (p. 582) " ... no depression of antidromic propagation into motoneurons at a time when they exhibit a considerable intensity of inhibition;" (p. 583) was " ... to provide a widely distributed return circuit that, flowing from synaptic knobs, penetrate the subjacent of that neurone and set up there the catelectronic or anelectronic foci that are postulated by the excitatory and inhibitory hypotheses."

23. 1950a w/ Brooks, Downman	RA (P)	Frequent mention of previous Eccles' work on electrical excitatory synaptic transmission (including paper 11 & 14), but main focus provided essential preliminary work for the shortly following intracellular studies. Motoneuron antridromically activated after potential (later to be known as "afterhyperpolarization"), recorded using either ventral root leads or extracellular micro-electrodes positioned in or near a spinal motor nucleus, using techniques described in paper 14. Argued that positive after-potential located on soma and proximal dendrites. Claimed first satisfactory study to show that a prolonged facilitation state could be abolished by an after-potential, but ended (p.36) with caution that " ... a definitive result is only possible with the investigation of single motoneurones."
24. 1950b w/ Brooks, Downman	RA	Continuation of 23 using orthodromically activated motoneurons to study their after-potentials. Claimed (p. 173) to show that "after-positivity and associated depression following reflexly subliminal activation is, according to the electrical hypothesis, likewise attributable to the positive after-potential following subsynaptic areas of the motoneurone. On the available evidence the prolonged phase of depression is located in the presynaptic pathway."
25. 1950	RA	Review of motoneuron properties emphasized that their monosynaptic orthodromic excitation (p. 304) "satisfactorily explained by the electrical hypothesis of synaptic transmission" (citing papers 13 and 22). No new evidence provided on the excitatory hypothesis & no mention of inhibitory hypothesis.
At transition from Dunedin to Canberra		
26. 1951a	RA(P)	Began with self-revealing premise "that basically the responses of neurones are similar throughout the central nervous system, and that the more easily analysed responses of motoneurones provide the data for a satisfactory explanation of the electrical responses evoked in the cerebral cortex by all conditions of stimulation: by direct electrical stimulation; by afferent volleys; and by antidromic volleys." Conceded from outset that it would be more difficult to explain the spontaneous electrical activity of the cerebral cortex. Had advantage of the first intracellular findings of the Brock et al. (1951) abstract, which were discussed substantially throughout the text. Experiments showed antidromic volley responses of cortical cells were easier to interpret than the other 2 techniques. Conclusions based also on knowledge of cortical neurohistology. Reference to electrical synaptic transmission was minimal and subtle, but article included in this table because it influenced proposed mechanisms for superficial and deep responses of cortical cells to antidromic volleys (see Figs. 1 & 2 in article.)
Articles w/ Rall		
1. 1950	RA	Cautious possibility raised that excitatory synaptic transmission may be electrical, but with an emphasis on the possibility that post-tetanic potentiation of extracellularly recorded motoneurons by repetitive stimulation of afferent muscle fibers attributable to presynaptic impulses becoming " ... a more effective synaptic exciter because repetitive stimulation temporarily alters the spatial relationship of the synaptic knobs to the postsynaptic membrane; for example, the knobs may become larger and/or in closer apposition thereto." (p. 466).

2. 1951b	RA	Extension of their 1950 article raised possibility of either chemical or electrical excitatory monosynaptic synaptic transmission to motoneurons. Emphasis, however (p. 375), was again on possibility that " ... the presynaptic impulse becomes a more effective synaptic excitator because repetitive stimulation temporarily alters the spatial relationship of the synaptic knobs to the post-synaptic membrane, the knobs becoming larger and/or in closer opposition thereto." Note similarity of this wording to that in 1950 paper!

a Types included: RA, research article; AB, abstract; LET, letter to editor; REV, review; and (P), a relevant preliminary article or abstract.

b The term "detonator response" was introduced in this review to emphasize that the c.e.s. alone could not initiate an action potential. Rather in addition to sufficient 'central excitatory states' (c.e.s.) an explosive additional detonator response was required. The same idea was elaborated a little earlier by Lorente de Nó (1935a,b) but without introduction of an acronym. In Eccles (1936) review the term was applied to the postsynaptic excitatory response of both a ganglion cell (p. 358) & an oculomotor motoneuron (p. 376). In Eccles (1937a) he discussed his concept of ganglion detonator responses in great detail. For motoneurons he favored from the outset electrical transmission resulting in the detonator response, as emphasized in Eccles & Pritchard (1937).

c Direct inhibition was defined by Lloyd (1941,1946) as the monosynaptic inhibitory action produced by spindle Ia afferents in their contralateral motoneurons. However, he used extracellular recording from motoneurons for this assertion and the pathway was eventually discounted in Eccles' Canberra laboratory using intracellular recording (Eccles et al., 1954a, 1956b; Araki et al.,1960).

d They explained that their "needles (*steel, stainless steel or tungsten*) were ground so that the terminal 2 or 3 mm had a uniform calibre of 50 μ or slightly less and then insulated to the tip by enamel that was baked on the tip and then ground to a sharp chisel point of bare metal." Strangely, no attempt made to provide approximate diameter of uninsulated tips of their needle microelectrodes.

Table 5 – Sherrington's co-authored experimental contributions on suprasegmental and segmental topics in the fields of neurophysiology and neuroscience.

Epoch[a]	Suprasegmental & descending/ascending pathway topics		Segmental topics	
	Topic(s)	Co-author(s)[b]	Topic(s)	Co-author(s)[b]
1884-1895	Brain/spinal cord interconnections; optic nerve damage	Langley[c] 1884a/b, 1891; Hadden 1886, 1888	Spinal canal size; pilomotor nerves; motor effects of sensory input	Reid 1890; Langley 1901; Mott 1895
1895-1913	Overall CNS; cerebral func/localiz; desc effects of motor ctx & decerebrate rigidity; spino-cerebellar tract; effects of chloroform & tetanus toxin on lock-jaw & other muscles	Foster 1897; Hering 1897a/b, 1899; Fröhlich 1901, 1902; Grünbaum[d] 1901a/b, 1902, 1903; Laslett 1902, 1903b; Sowton 1906; Roaf 1906a/b; Mott 1911, Schuster 1911; Graham Brown 1911a/b, 1912a	Spinal cord; properties of nerve cells; spinal reflexes interaction & inhib; cranial nerve receptors/affs; drug responsiveness in intact & transected spinal cord	Foster 1890, 1897; Hering 1897c; Sharpey-Schäfer 1900; Laslett 1903a; Woodworth 1904; Tozer 1910; Roaf 1910; Sowton 1911a/b/c; Graham Brown 1912b; Owen 1911
1913-1935	Cerebral cortex functions; acoustic reflexes; motor cortex & its descending effects	Graham Brown 1913a/b; Forbes 1914; Leyton[d] 1917	Deglutition & spinal reflexes; muscle affs; reflex inhib, motor units	Miller 1915; Sowton 1915; Dreyer 1918; Sassa 1921; Liddell 1923a/b/c/d, 1924, 1925a/b.1929, 1932; Creed 1926, 32; Cooper 1926, 1927, 1932; Denny-Brown 1926, 1927, 1928, 1932; Eccles 1929, 1930a/b/c; 1931 a/b/c/d/f/g, 1932; Fulton 1930, 1932
1936-1952	None	None	Spinal border cells	Cooper 1940

Abbreviations: affs, afferents; ctx, cortex; inhib, inhibition [a]Epoch sites were: **1884-1887**, University of Cambridge, St Thomas's Hospital Medical School, & Europe; **1887-1895**, St. Thomas's Hospital Medical School & the Brown Institution of Preventative Medicine; **1895-1913**, University of Liverpool; **1913-1935**, University of Oxford; **1936-1952**, academic retirement years - largely in Ipswich, Cambridge & Eastbourne. [b]The publications with co-authors are listed in chronological order, and many are mentioned in the text and listed in the references. See Liddell (1952) for those not listed in the references. [c]Langley was one of Sherrington's primary research mentors. He published no research articles with his other primary research mentor, Gaskell, albeit he had a committee report with him & others (1897) that focused on nerve cells. [d]Sherrington published several articles on corticospinal connections between 1901 & 1917, the experimental work being the most definitive in Leyton (nee Grünbaum) & Sherrington (1917). This work was completed over a decade earlier in 1901-1903.

Figure 1

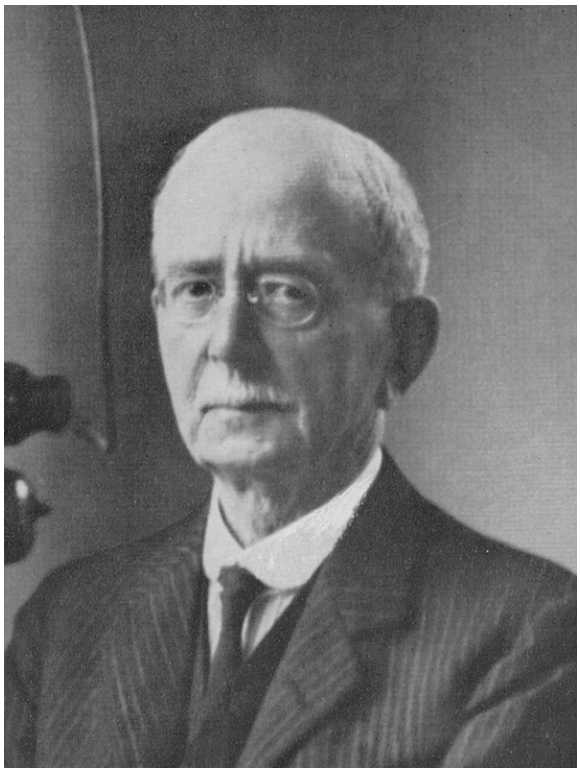


Figure 2

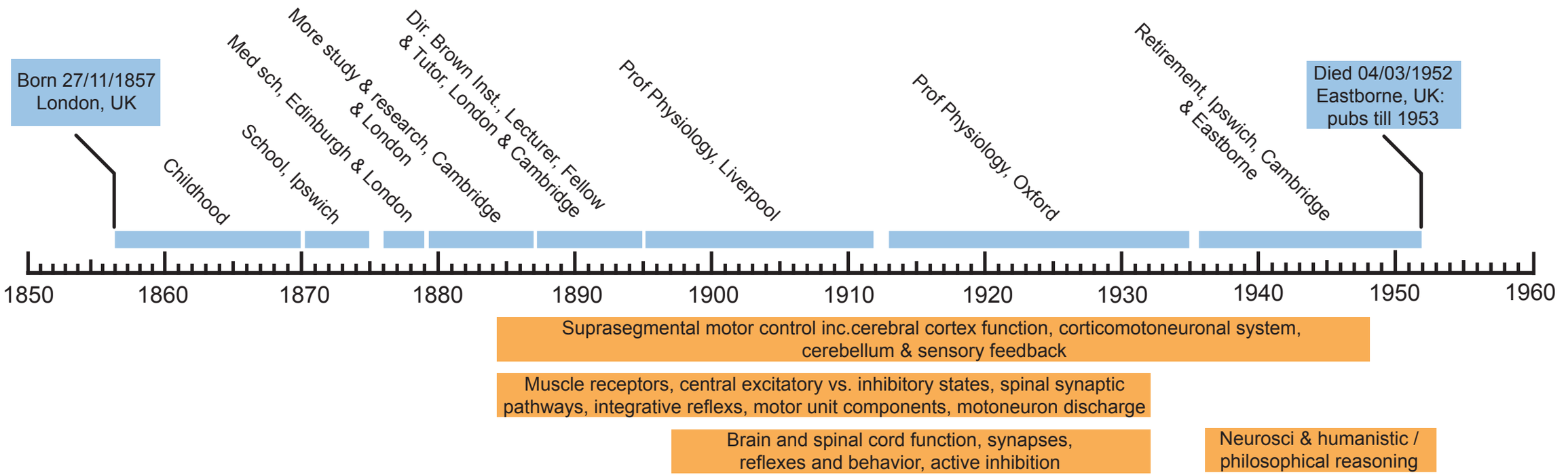

Born 27/11/1857
London, UK
Childhood
School, Ipswich
Med sch, Edinburgh & London
More study & research, Cambridge & London
Dir. Brown Inst., Lecturer, Fellow & Tutor, London & Cambridge
Prof Physiology, Liverpool
Prof Physiology, Oxford
Retirement, Ipswich, Cambridge & Eastborne
Died 04/03/1952
Eastborne, UK:
pubs till 1953
1850
1860
1870
1880
1890
1900
1910
1920
1930
1940
1950
1960
Suprasegmental motor control inc.cerebral cortex function, corticomotoneuronal system, cerebellum & sensory feedback
Muscle receptors, central excitatory vs. inhibitory states, spinal synaptic pathways, integrative reflexs, motor unit components, motoneuron discharge
Brain and spinal cord function, synapses, reflexes and behavior, active inhibition
Neurosci & humanistic / philosophical reasoning

Figure 3

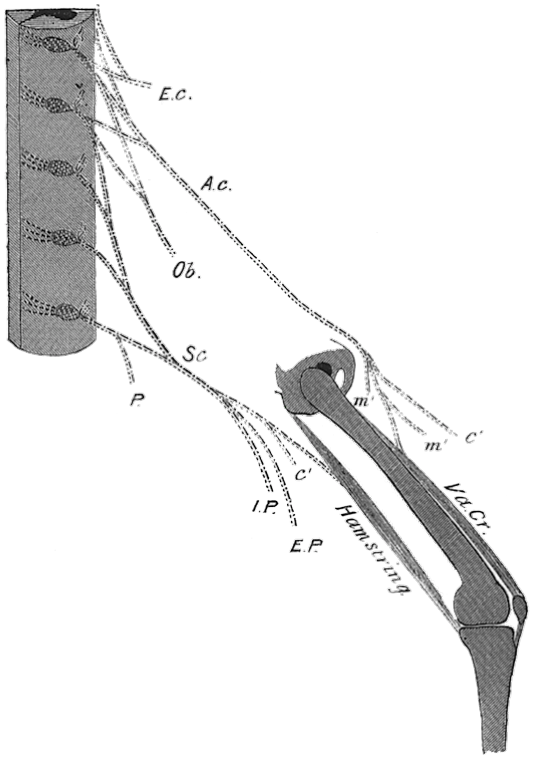


Figure 4

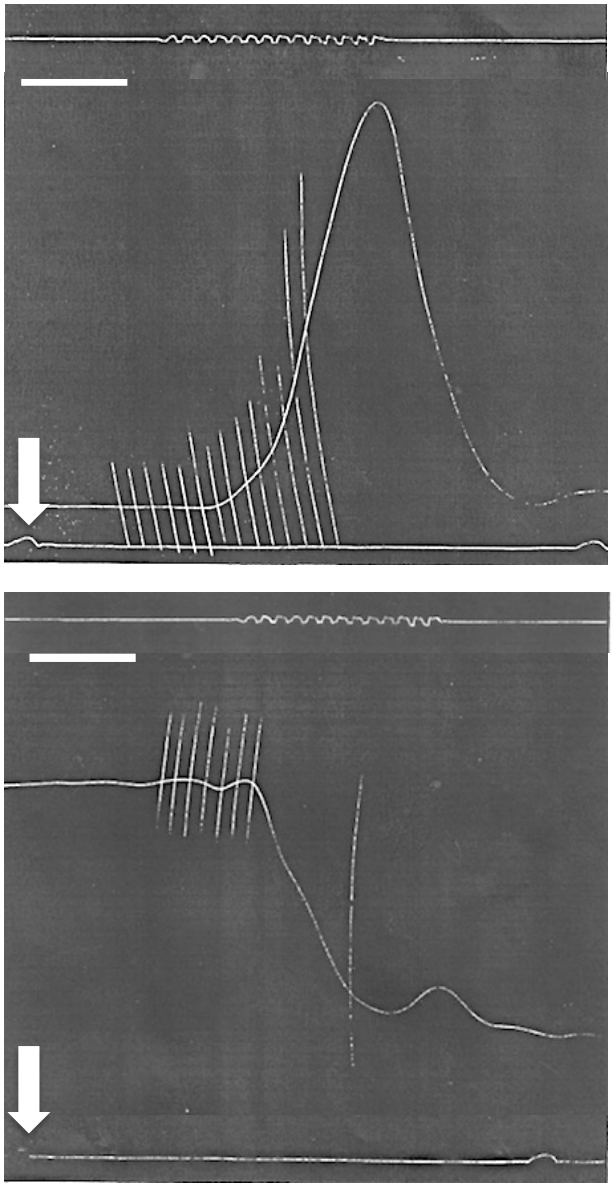
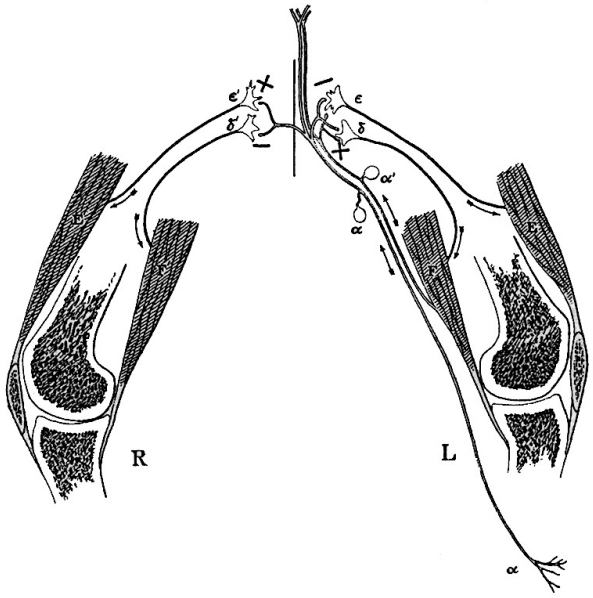


Figure 5



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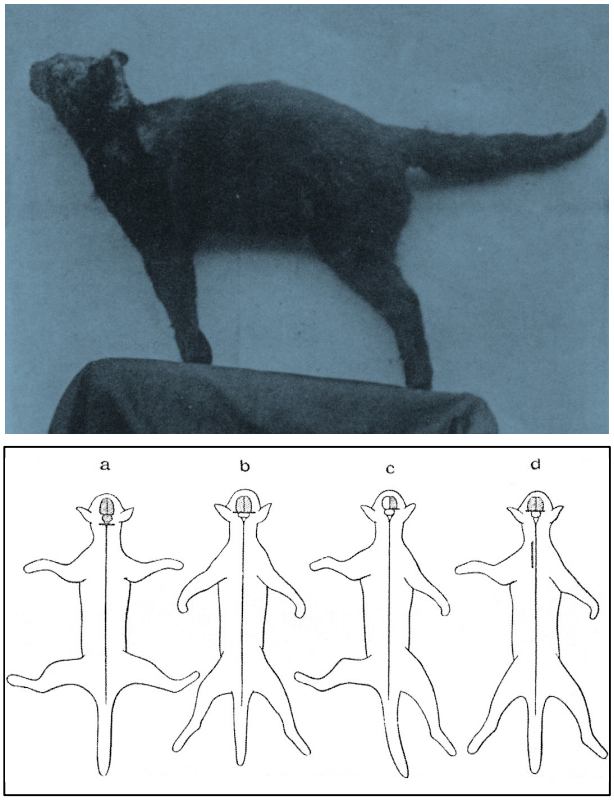

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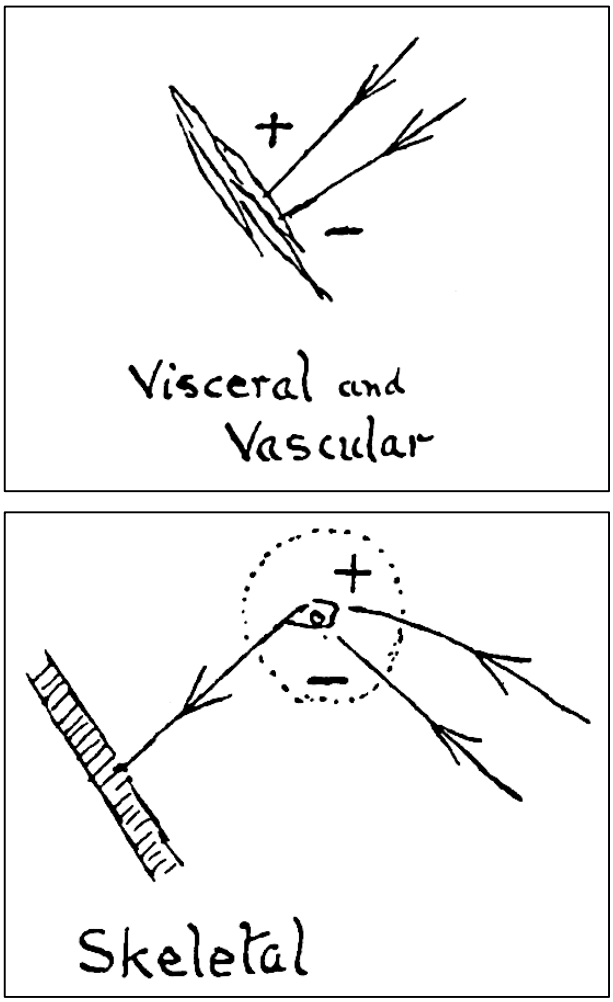


Figure 8

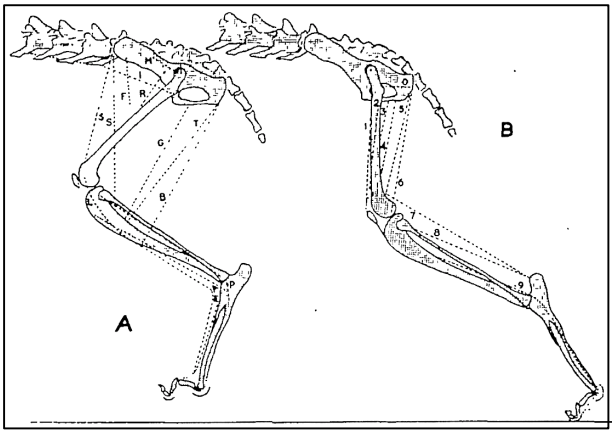


Figure 9

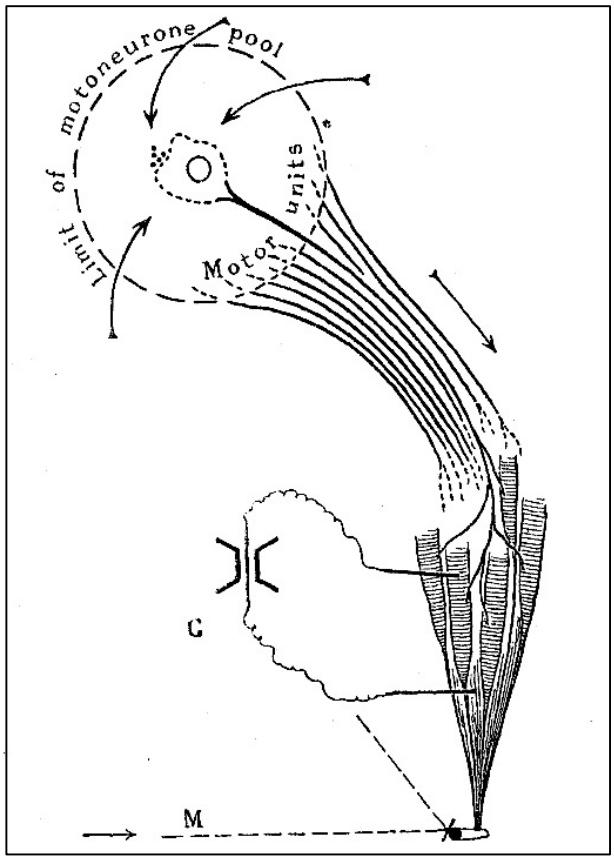


Figure 10

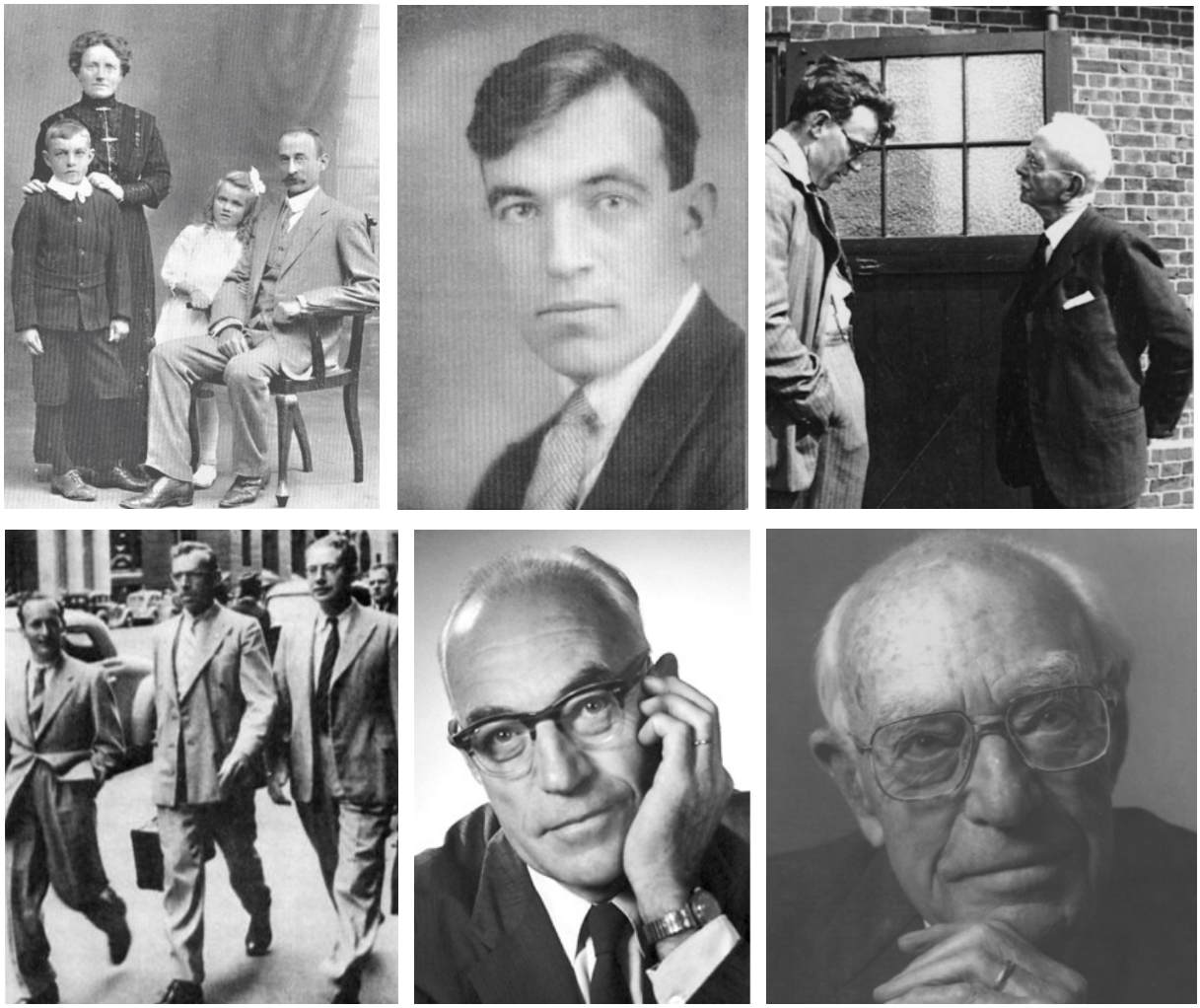


Figure 11

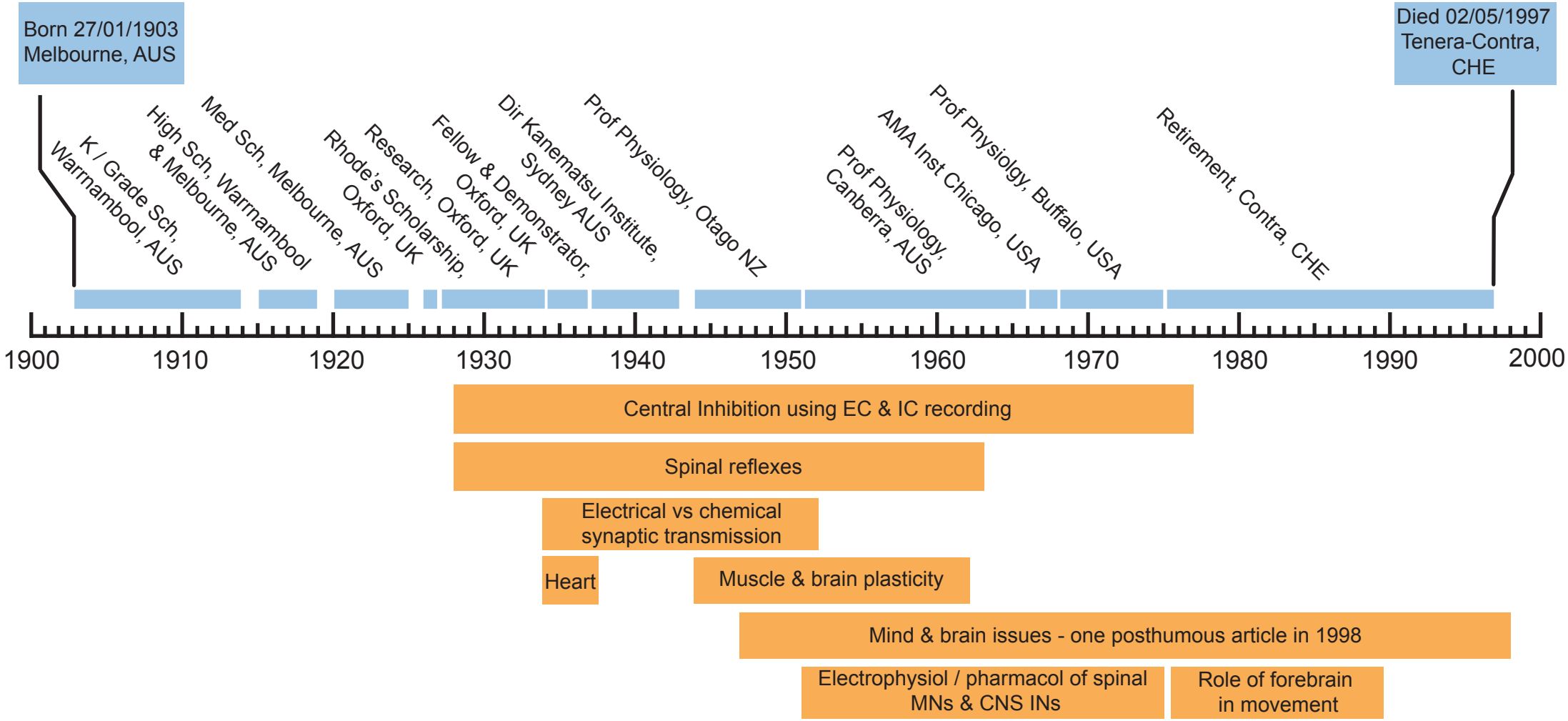

Born 27/01/1903
Melbourne, AUS
Died 02/05/1997
Tenera-Contra, CHE
K / Grade Sch, Warrnambool, AUS
High Sch, Warrnambool & Melbourne, AUS
Med Sch, Melbourne, AUS
Rhode's Scholarship, Oxford, UK
Research, Oxford, UK
Fellow & Demonstrator, Oxford, UK
Dir Kanematsu Institute, Sydney AUS
Prof Physiology, Otago NZ
Prof Physiology, Canberra, AUS
AMA Inst Chicago, USA
Prof Physiology, Buffalo, USA
Retirement, Contra, CHE
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
Central Inhibition using EC & IC recording
Spinal reflexes
Electrical vs chemical synaptic transmission
Heart
Muscle & brain plasticity
Mind & brain issues - one posthumous article in 1998
Electrophysiol / pharmacol of spinal MNs & CNS INs
Role of forebrain in movement

Figure 12

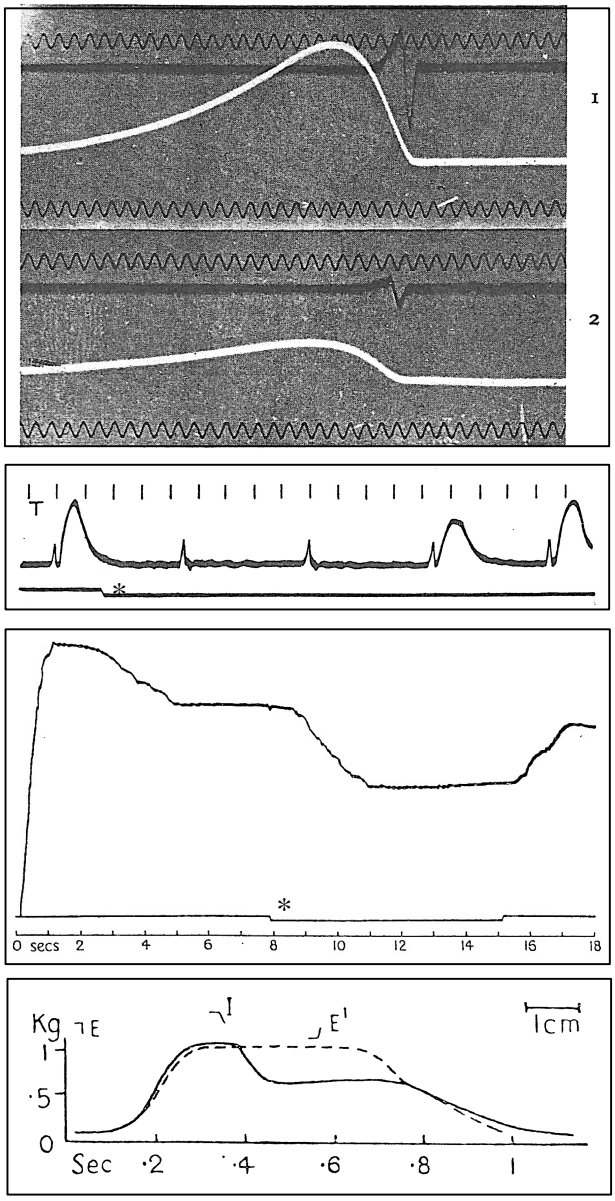


Figure 13

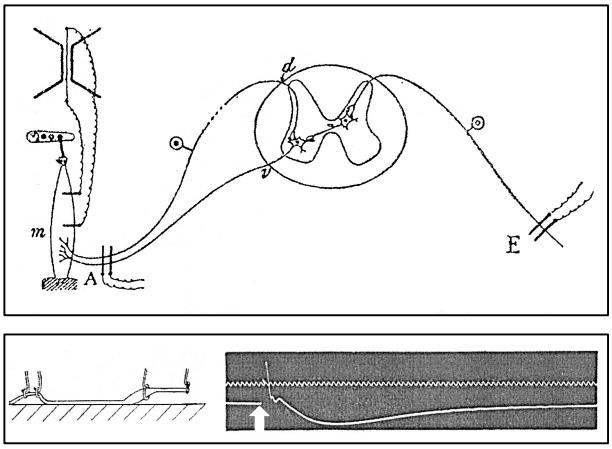


Figure 14

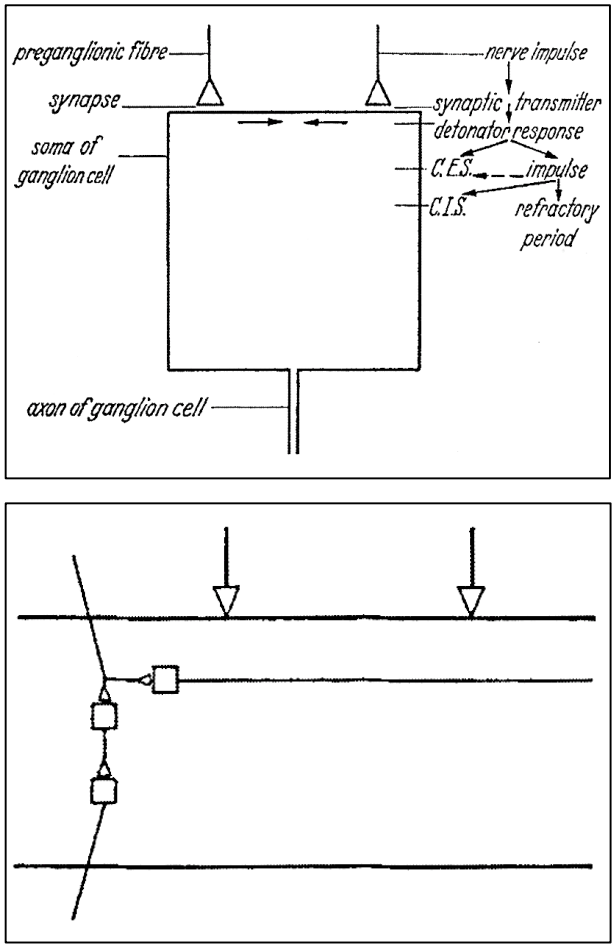

preganglionic fibre
synapse
soma of ganglion cell
axon of ganglion cell
nerve impulse
synaptic transmitter
detonator response
C.E.S.
impulse
C.I.S.
refractory period

Figure 15

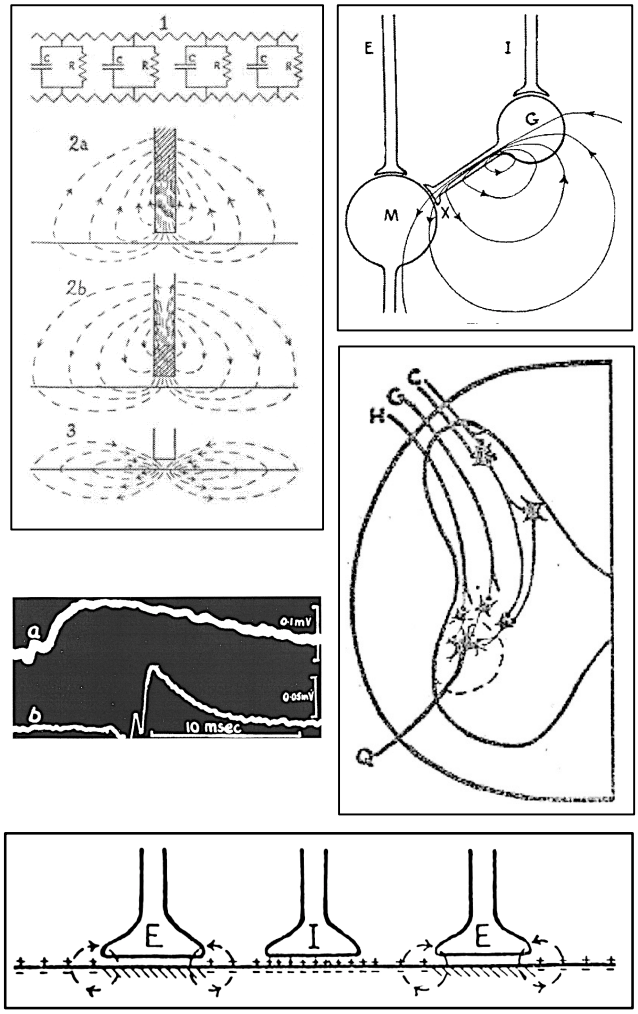


Figure 16

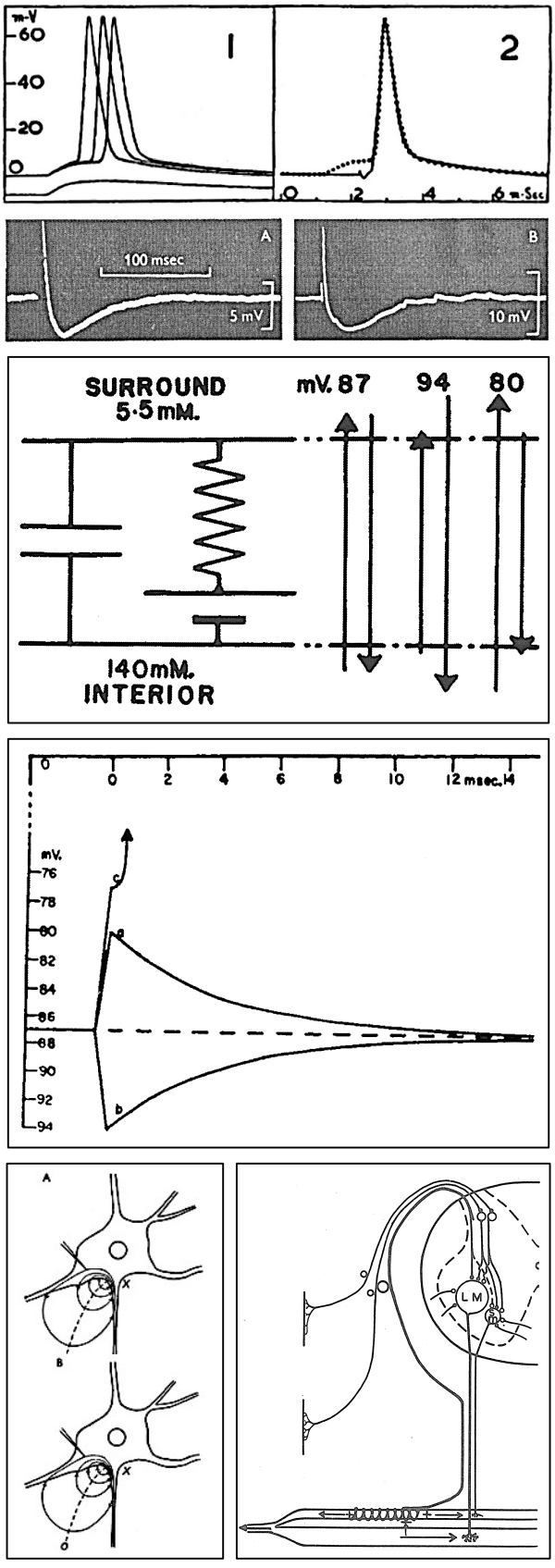

m-V
60
40
20
0
1
2
A
100 msec
5 mV
B
10 mV
SURROUND
5·5 mM.
mV. 87
94
80
140mM.
INTERIOR
0
2
4
6
8
10
12 msec.
14
mV.
76
78
80
82
84
86
88
90
92
94
a
b
c
A
B
X
X
LM

Figure 17

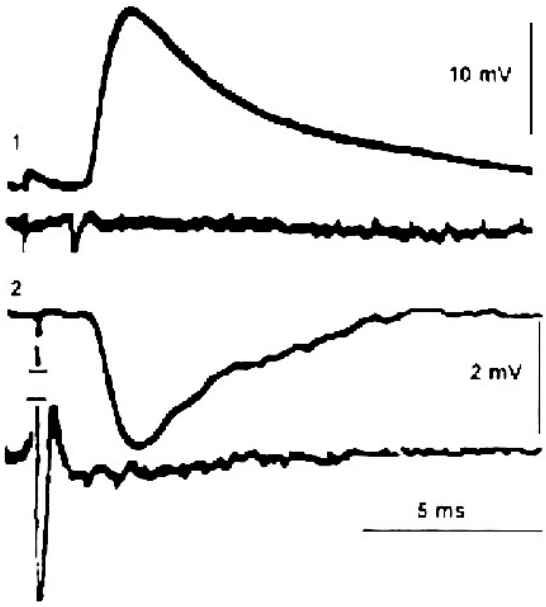


Figure 18

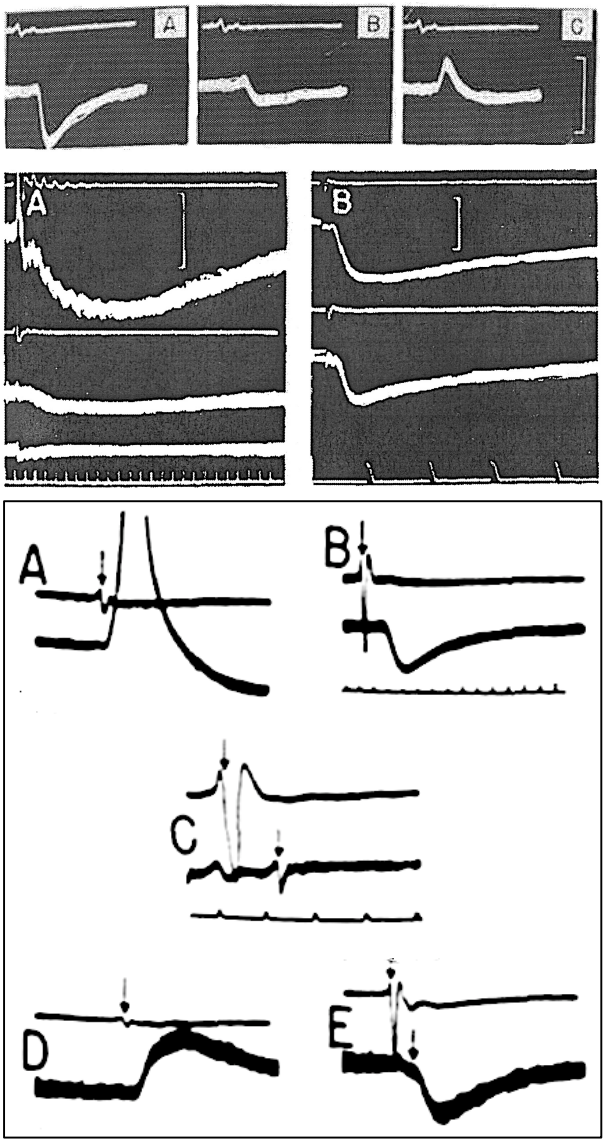


Figure 19

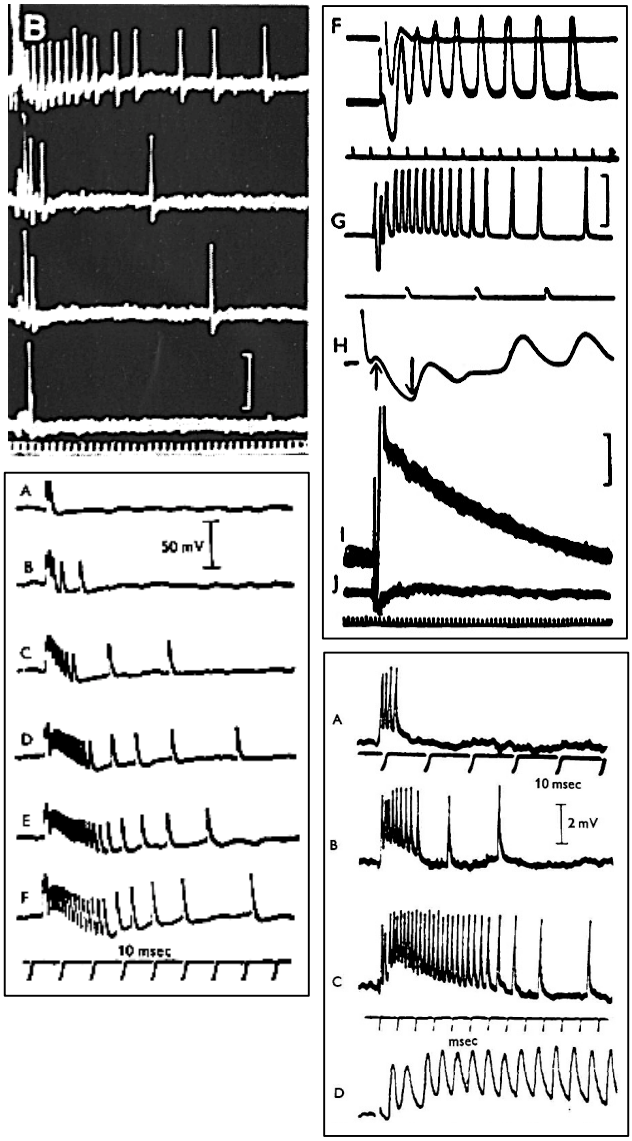


Figure 20

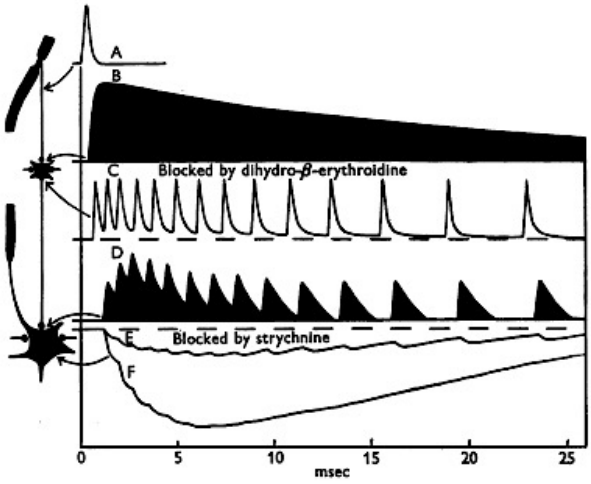

A
B
C
Blocked by dihydro-β-erythroidine
D
E
Blocked by strychnine
F
0
5
10
15
20
25
msec

Figure 21

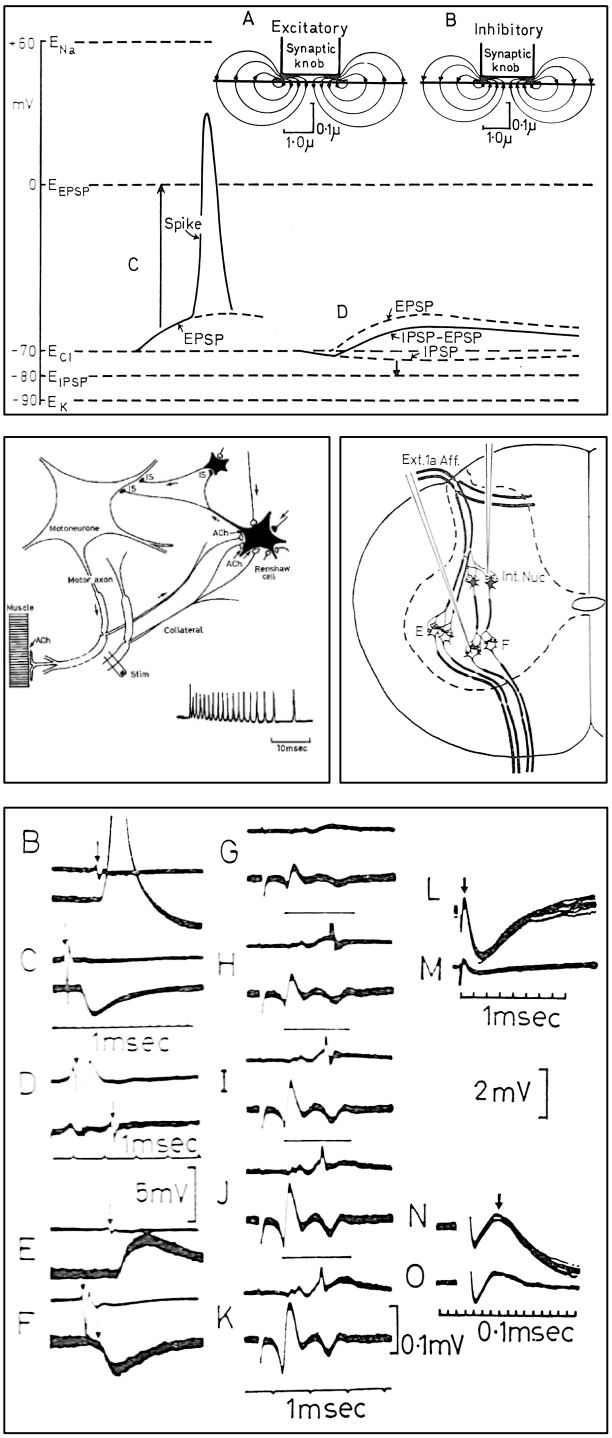

A
Excitatory
Synaptic knob
B
Inhibitory
Synaptic knob
0·1μ
1·0μ
+60
E_{Na}
mV
0
E_{EPSP}
Spike
C
D
EPSP
IPSP-EPSP
IPSP
-70
E_{Cl}
-80
E_{IPSP}
-90
E_K
Motoneurone
Motor axon
Muscle
ACh
Renshaw cell
Collateral
Stim
10msec
Ext.1a Aff.
Int. Nuc.
E
F
B
C
D
E
F
G
H
I
J
K
L
M
N
O
1msec
2mV
5mV
0·1mV
0·1msec

Figure 22

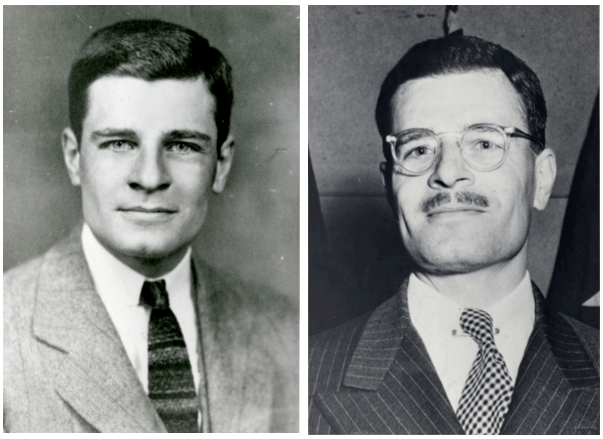


Figure 23

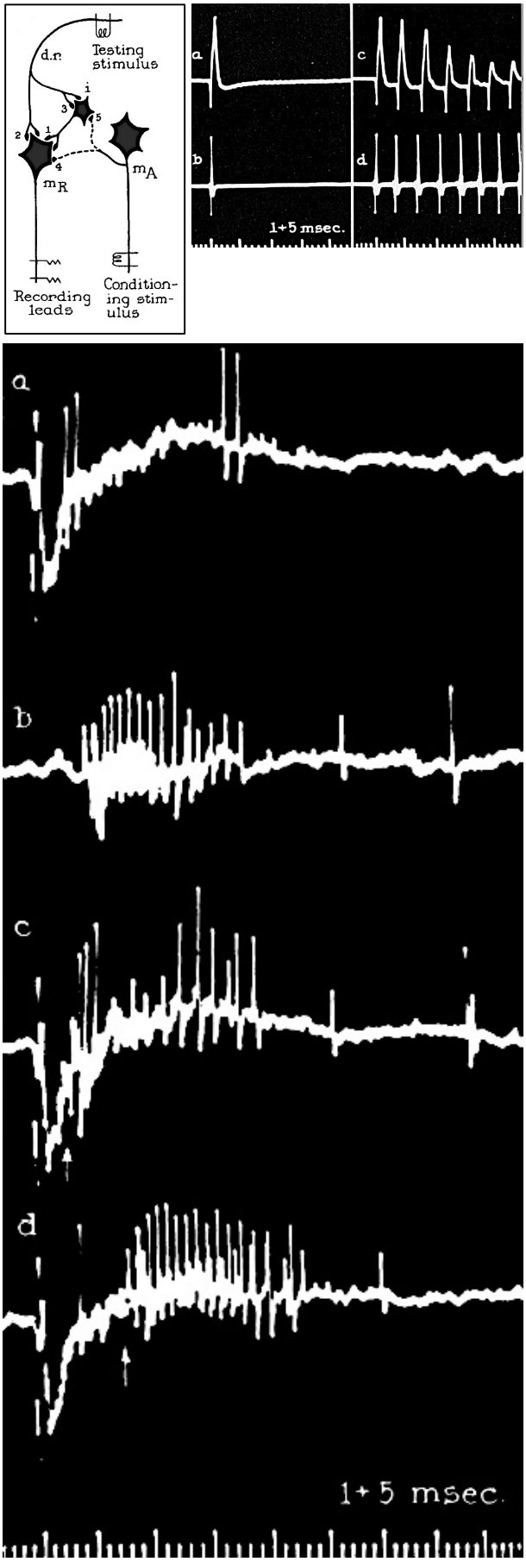

d.r
Testing stimulus
i
3
5
2
1
4
m_R
m_A
Recording leads
Conditioning stimulus
a
b
c
d
1+5 msec.
a
b
c
d
1+5 msec.

Figure 24

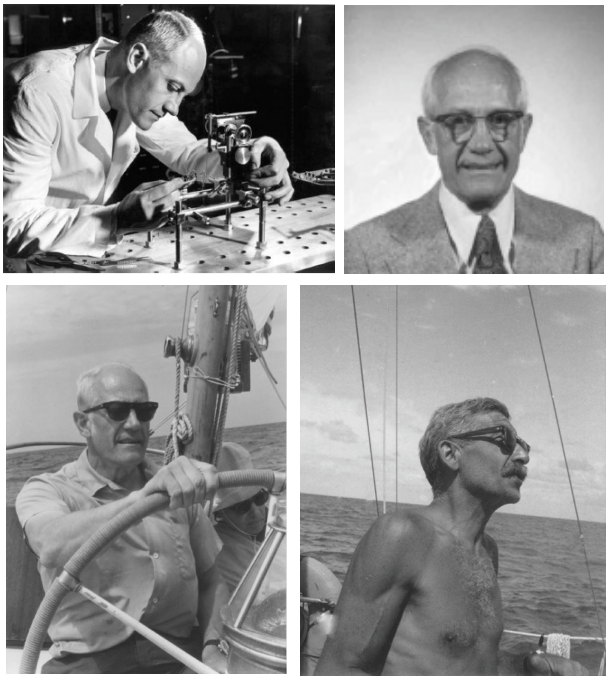


Figure 25

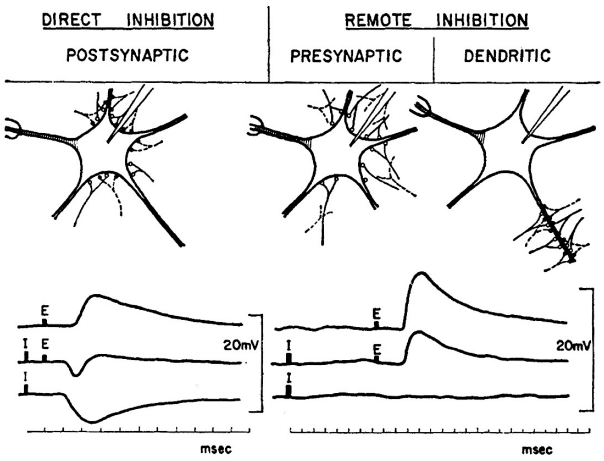

DIRECT INHIBITION
POSTSYNAPTIC
REMOTE INHIBITION
PRESYNAPTIC
DENDRITIC
E
I E
I
20mV
msec
E
I E
I
20mV
msec

Figure 26

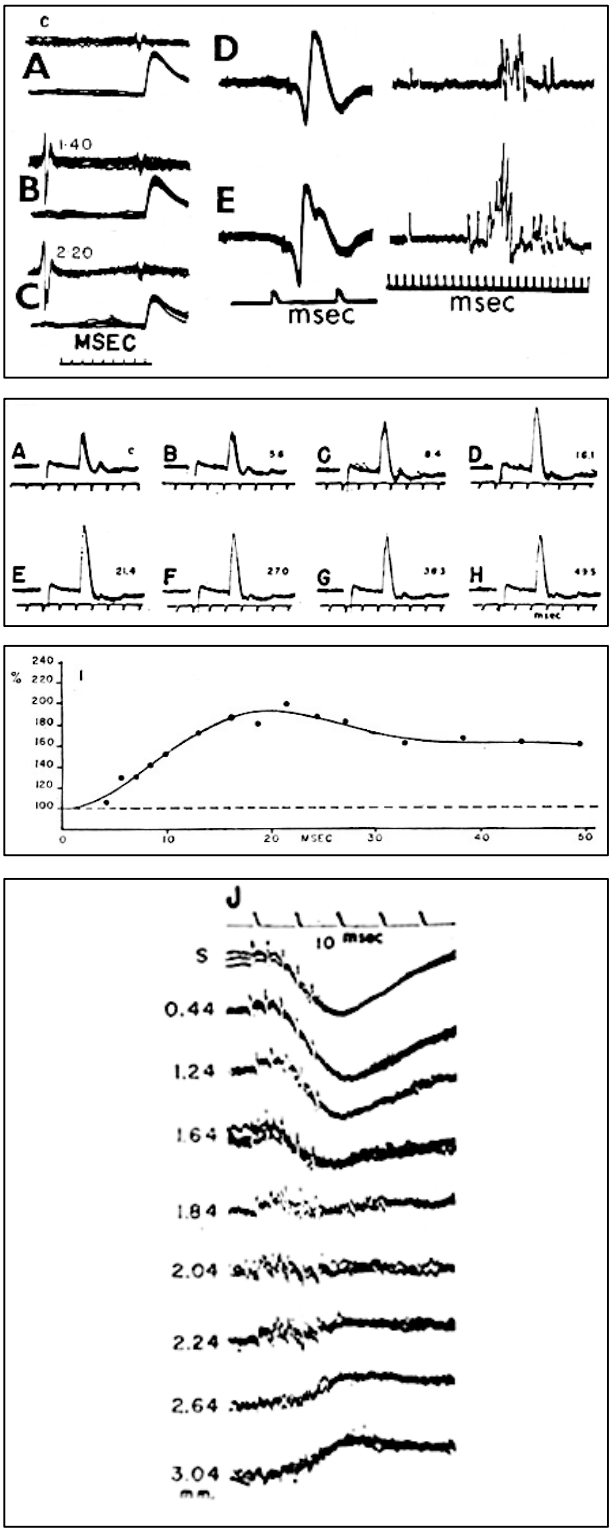

A
B
C
D
E
1:40
2:20
MSEC
msec
msec
A
B
C
D
E
F
G
H
msec
%
I
240
220
200
180
160
140
120
100
0
10
20
MSEC
30
40
50
J
10 msec
S
0.44
1.24
1.64
1.84
2.04
2.24
2.64
3.04
mm

Figure 27

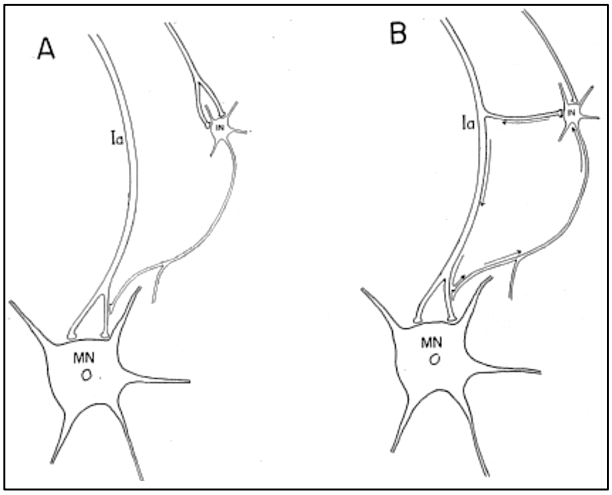


Figure 28

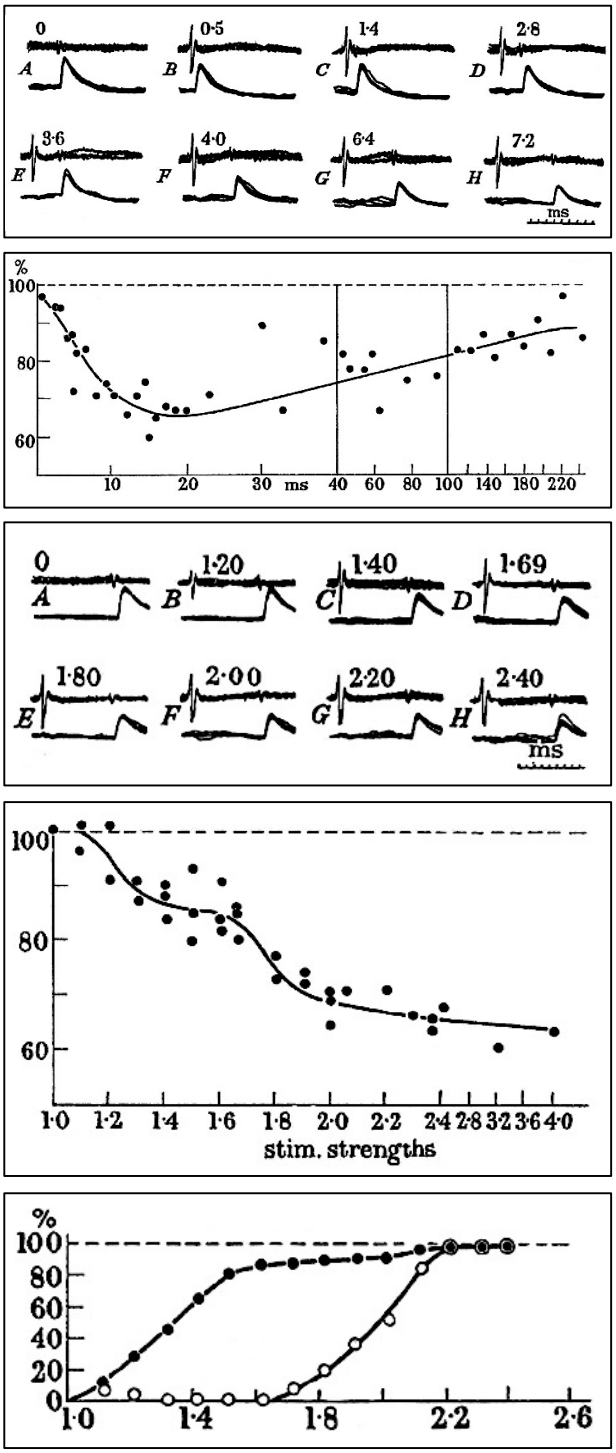

0
A
0·5
B
1·4
C
2·8
D
3·6
E
4·0
F
6·4
G
7·2
H
ms
%
100
80
60
10
20
30 ms
40
60
80
100
140
180
220
0
A
1·20
B
1·40
C
1·69
D
1·80
E
2·00
F
2·20
G
2·40
H
ms
100
80
60
1·0
1·2
1·4
1·6
1·8
2·0
2·2
2·4
2·8
3·2
3·6
4·0
stim. strengths
%
100
80
60
40
20
0
1·0
1·4
1·8
2·2
2·6

Figure 29

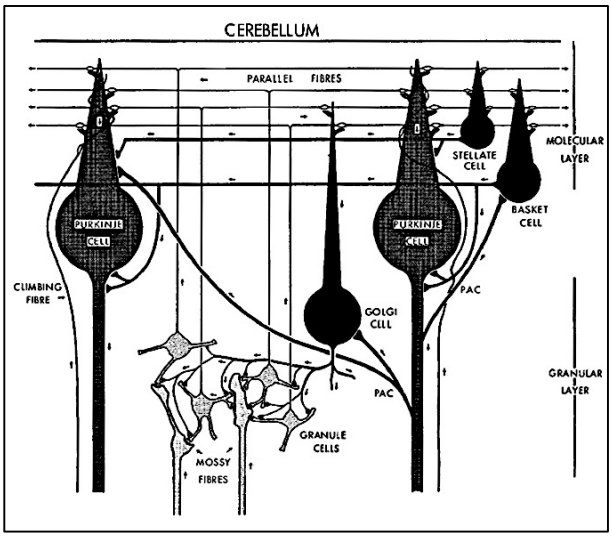

CEREBELLUM
PARALLEL FIBRES
STELLATE CELL
MOLECULAR LAYER
BASKET CELL
PURKINJE CELL
PURKINJE CELL
CLIMBING FIBRE
GOLGI CELL
PAC
PAC
GRANULAR LAYER
GRANULE CELLS
MOSSY FIBRES

Figure 30

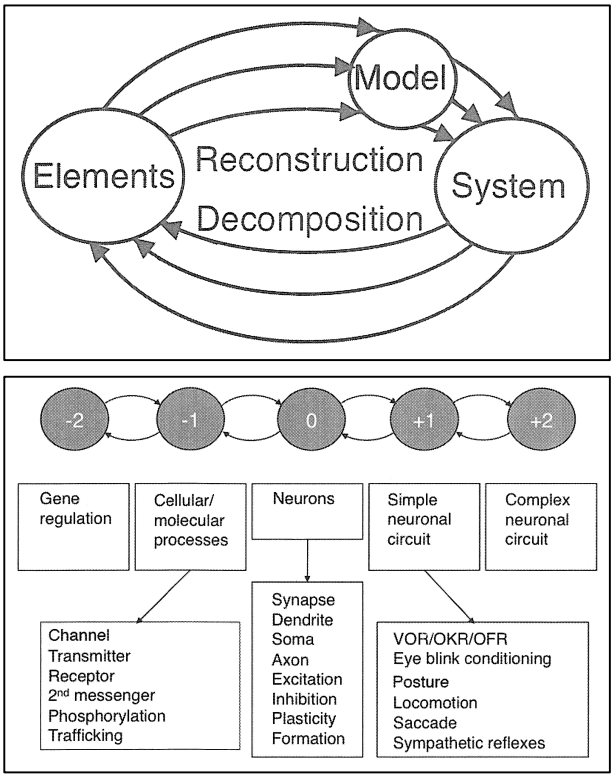
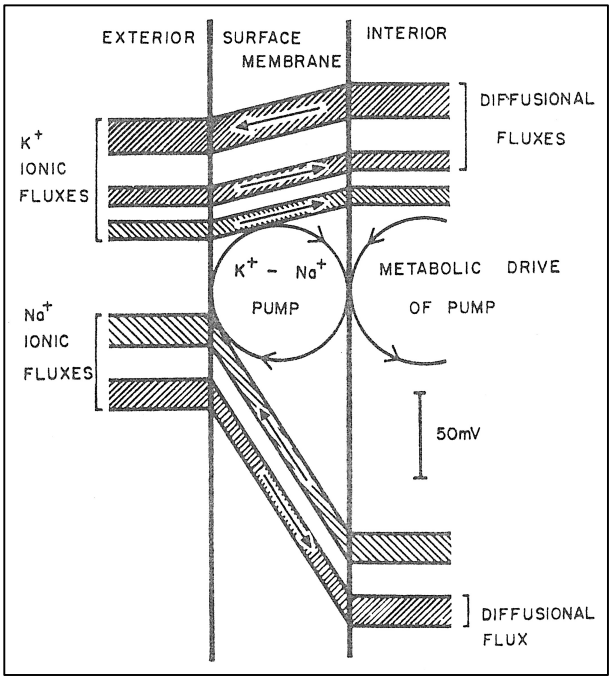

Model
Elements
Reconstruction
Decomposition
System
-2
-1
0
+1
+2
Gene regulation
Cellular/ molecular processes
Neurons
Simple neuronal circuit
Complex neuronal circuit
Channel
Transmitter
Receptor
2nd messenger
Phosphorylation
Trafficking
Synapse
Dendrite
Soma
Axon
Excitation
Inhibition
Plasticity
Formation
VOR/OKR/OFR
Eye blink conditioning
Posture
Locomotion
Saccade
Sympathetic reflexes

Figure 31


EXTERIOR
SURFACE MEMBRANE
INTERIOR
DIFFUSIONAL FLUXES
K+ IONIC FLUXES
K+ - Na+ PUMP
METABOLIC DRIVE OF PUMP
Na+ IONIC FLUXES
50mV
DIFFUSIONAL FLUX