The beginning of intracellular recording in spinal neurons: Facts, reflections, and speculations^{☆, ☆☆}

Douglas G. Stuart^{a,*} and Robert M. Brownstone^b

^aDepartment of Physiology, University of Arizona, Tucson, AZ 85721-0093, USA

^bDepartment of Surgery (Neurosurgery) and Anatomy & Neurobiology, Dalhousie University, Halifax, NS, Canada B3H 1X5

Abstract

Intracellular (IC) recording of action potentials in neurons of the vertebrate central nervous system (CNS) was first reported by John Eccles and two colleagues, Walter Brock and John Coombs, in Dunedin, NZL in 1951/1952 and by Walter Woodbury and Harry Patton in Seattle, WA, USA in 1952. Both groups studied spinal cord neurons of the adult cat. In this review, we discuss the precedents to their notable achievement and reflect and speculate on some of the scientific and personal nuances of their work and its immediate and later impact. We then briefly discuss early achievements in IC recording in the study of CNS neurobiology in other laboratories around the world, and some of the methods that led to enhancement of CNS IC-recording techniques. Our modern understanding of CNS neurophysiology directly emanates from the pioneering endeavors of the five who wrote the seminal 1951/1952 articles.

Keywords

Interneuron; Intracellular recording; Mammalian; Motoneuron; Non-mammalian

1. Introduction

In the first article (Barbara and Clarac, 2011) of this sequence of five historical articles on spinal motoneuron (MN) and motor unit (MU) neurobiology (Stuart et al., 2011) it was emphasized that theories on the human body's control of its musculature date back in antiquity to at least the ideas of Hippocrates [~460–380 BC] and Aristotle [384–322 BC], with substantial further advances awaiting the observations of Galen [129–216 AD] and after another long hiatus, work in the renaissance period of the 14th to the 17th C, including, in particular, that of Leonardo da Vinci [1472–1519], Andreas Vesalius [1514–1564], René Descartes [1596–1650], and Giovanni Borelli [1608–1679]. In the articles that follow there is another long hiatus up to the 19th C, and then a focus on the 20th and early 21st C.

[☆]The research of R.M.B. is supported, in part, by the Canadian Institutes of Health Research.

^{☆☆}Note: Countries are indicated by their 3-letter ISO-3166 abbreviation. See: <http://www.davros.org/misc/iso3166.html>.

*Corresponding author at: Physiol-Univ Arizona, PO Box 210093, Tucson, AZ 85721-0093, USA. Fax: +1 520 621 8170. dgstuart@u.arizona.edu (D.G. Stuart).

By the very early 20th C, it was accepted by most neuroscientists despite the vitriolic objections of Golgi (Barbara, 2010) that animal behavior resulted from brain networks that were comprised of individual neurons, as depicted so beautifully by Ramón y Cajal [1852–1934] using anatomical staining techniques (e.g., (1888a,b)). It became clear to many neuroscientists that new methods were necessary to study the activity of single neurons. Although it had been known for over two centuries that electricity was involved (Galvani, 1791; Volta, 1800) methods to study the activity of individual nerve cells were lacking at that time. Furthermore, Charles Sherrington [1856–1953] had pointed out that muscle activation was mediated in its entirety by a “final common path” from MNs to the striated peripheral musculature (Sherrington, 1904). Hence, it became clear that a good starting point in the development of methods to study neural circuits underlying behavior would be through the study of single MNs.

Clarac and Barbara (2011) document in the second article of our sequence clinical findings that set the stage for advances in the understanding of MNs that occurred in the early 20th C. Duchateau and Enoka (2011) summarize in the third article the pioneering of extracellular (EC) recording of the firing patterns of single motor units (MUs) as a means to infer the behavior of MNs in the central nervous system (CNS). We address in this fourth article the beginning of intracellular (IC) recording in vertebrate spinal MNs, which was achieved in the middle of 20th C. It was clear by that time that four essential components were needed: (1) sharp microelectrodes that could penetrate CNS tissue in vivo and then a single cell membrane with minimal damage; (2) high impedance input stages for drift-free DC amplifiers, in order to record rapidly changing bioelectrical potentials; (3) controlled current delivery systems for delivering current through microelectrodes; and (4) high speed display systems to view and record these potentials. In this article, we discuss the precedents for and backgrounds and work of the five key players, and how their work affected later developments that rapidly advanced the understanding of MN behavior. Finally, Brownstone and Stuart (2011) address recent advances in neuroscience and their relevance to the future study of motoneurons, stressing the importance of such studies in understanding human behavior in health and disease.

IC recording from vertebrate neurons in the CNS was first achieved by John Eccles [1903–1997] and two younger colleagues (Lawrence Brock [1923–1996]; John Coombs [1917–1993] in Dunedin, NZL (Brock et al., 1951, 1952a,b) and by J. Walter Woodbury [1923–] and Harry Patton [1918–2002] in Seattle, WA, USA (Woodbury and Patton, 1952a,b). Considering that communication in 1950–1952 was not as it is today, and that the world was therefore a much larger place, it is remarkable that this advance occurred at two such disparate locations at more-or-less the same time. The portraits of these 5 “giants” are shown in Fig. 1, with some of their key findings in Figs. 2 and 3. The various lineages for their pioneering efforts are summarized briefly in Fig. 4.

Both groups began their experiments within a few weeks of each other in May–June 1951 and it has become conventional to consider them the co-pioneers of IC-recording in the CNS. This custom probably began after the June 1952 Cold Spring Harbor (NY, USA) Symposium “The Neuron”, where there were presentations from both groups. Woodbury

presented the Woodbury and Patton (1952b) results, which included IC recording from spinal myelinated nerve axons,¹ interneurons (INs) and MNs.

Woodbury's talk was preceded by that of Eccles (1952), who presented an IC recording of a MN action potential (AP), and a model of the MN's resting potential (RP), excitatory postsynaptic potential (EPSP), and inhibitory postsynaptic potential (IPSP), as based on the results of Brock et al. (1952a,b). This talk and later Eccles' articles exploited the classic results of Alan Hodgkin [1914–1998] and Andrew Huxley [1917–] on the sodium and potassium currents mediating the RP and AP of the giant axons of the squid *Loligo* (Hodgkin and Huxley, 1952; Hodgkin et al. 1952).

At first glance it is puzzling why at this symposium Eccles did not focus on the Brock et al. (1952b,c) work. However, prior to this meeting Eccles and Hodgkin and Huxley had presented their respective IC-recording work at a February 21 Royal Society (London, GBR) meeting on "Excitation and Inhibition." At that meeting, Eccles' presentation had gone into much more detail concerning his team's 1952 findings.

The 1952 Cold Spring Harbor Symposium was a most propitious meeting for Eccles and Woodbury to present their new findings (Brownstone, 2006) because many of the participating scientists were in the process of forming the basic foundation of modern cellular neuroscience. 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).

We begin this tribute to the Dunedin and Seattle groups' pioneering IC results with consideration of their work's precedents, then reflect and speculate on some of the scientific and personal nuances of their work, which was undertaken on spinal neurons of the adult cat, and conclude with their work's immediate and long-sustained impact.

2. Precedents to the pioneering 1951/1952 work of the Eccles' group and that of Woodbury and Patton in 1952

Much of what follows on precedents has been stimulated by the brief but valuable 1983 letters of Graham Hoyle [1923–1985], Charles Edwards [1925–], and Allan Bretag [1943–], a 2003 short review by the latter, and his current preparation of a full-length review on the history of microelectrode construction and usage (Hoyle, 1983; Edwards, 1983; Bretag, 1983, 2003). Prior to these accounts it was conventional for neurophysiology trainees to

¹In 1952, Ichiji Tasaki [1910–2009], a renowned Japanese-born electro physiologist (see Hikosaka, 2009) reported on IC-recordings made within myelinated axons of the dorsal funiculus of the frog SC. This work (Tasaki, 1952), undertaken at the Central Institute for the Deaf, St. Louis, MO, USA, is not generally considered as a component of the pioneering of IC recording in the CNS because the focus was not on recordings from a neuron's soma or proximal dendrites. It would seem that Tasaki agreed because his citations made no reference to the 1951/1952 reports of Brock et al. and Woodbury and Patton even though Tasaki participated in the June 1952 Cold Spring Harbor meeting before submitting his article in September 1952. Rather, the key precedents he cited were Nastuk and Hodgkin (1950) and Woodbury (1952), whose reports on peripheral nerve fibers are discussed below. Like Lorente de N6, Tasaki received much later criticism for his inability to accept the seminal findings of Hodgkin and Huxley. For example, he gave their extraordinarily impactful contribution virtually no credence in a chapter in a particularly widely read handbook (Tasaki, 1960). Fortunately, this wrong was corrected in Woodbury's two chapters in a similarly widely read textbook (Woodbury, 1960a,b) and a later volume of the same handbook series (Woodbury, 1962).

learn that the spinal neuron IC-recording studies in question were preceded in the late 1940s by IC-recording in mammalian muscle cells, as achieved by the Ralph Gerard [1900–1974] group (in particular, Ling and Gerard, 1949). This work may have been inspired by Gerard's 1937 observation of the IC-recording technique being used in plant cells by Karl Umrath [1899–1985] (e.g., Umrath, 1932) at the University of Graz, AUT (Florey, 1966).² The precedents were far more substantial, however!

It is also important for the modern reader to remember that pre-WWII “... the kind of equipment needed for electrophysiological research was not, as it is today, commercially available and was, indeed, rarely found even in major laboratories. Amplifiers, oscilloscopes, stimulators and other electronic gear had to be constructed” (p. 199 in Patton, 1994). In reality, this situation extended into the 1950s and early 1960s, particularly for the repair of electronic equipment. In fact, although commercial amplifiers were in common use by the early 1960s, it was not unusual for many investigators to construct specialized electronic equipment throughout the remainder of the 20th C and in some laboratories this practice continues even to this day. In the 1950s and 1960s, the services of a gifted electronic engineer and/or an electronically proficient neuroscientist gave a substantial advantage to a laboratory, just as computer and modeling/simulation experts are invaluable in present-day laboratories.

2.1. 1946–1951 precedents cited in the Eccles' group 1951/1952 reports

In the short Brock et al. (1951) report, the precedents cited are three highly relevant articles on IC-recording in frog muscle fibers: two of full length (Ling and Gerard, 1949; Nastuk and Hodgkin, 1950) and one an abstract (Fatt and Katz, 1950). The Ling and Gerard paper was limited to RPs but it included details on construction of 0.5–1.0 μm tip microelectrodes. The Hodgkin and Nastuk article included both RPs and APs as recorded with “Ling” electrodes (Hodgkin and Nastuk, 1949; Huxley, 2000). The Fatt and Katz (1950) abstract was also particularly important to Eccles: it focused on the presynaptic AP and its associated postsynaptic end-plate potential at the neuromuscular junction. This invited the possibility that analogous measurements could be made in spinal MNs such that he could address the issue of chemical vs. electrical synaptic transmission in the mammalian CNS.

In the NZL group's full-length 1952b article there is a fuller list of precedents. In addition to the above citations on frog muscle fibers, the RP work of Graham and Gerard (1946) (for their earlier 5- μm tip microelectrode technology) and the AP work of Nastuk (1950) on the frog neuromuscular junction (cf. Fatt and Katz, 1950) were emphasized as were RP and AP

²An interaction between Gerard and Umrath was emphasized by Florey (1966; pp. 385–386) but it seems unlikely to have influenced Gerard's microelectrode achievements. In a detailed biography about Gerard it was emphasized that his interest in the feasibility of making microelectrodes had begun while undertaking his first research project as an undergraduate student at the University of Chicago (p. 191 in Kety, 1982). Furthermore, no mention of German plant physiology microelectrodes was acknowledged by the Gerard group in any of their IC-recording articles, including the PhD dissertations of Graham (1946) and Ling (1948), the group's preceding abstracts, or in Gerard's 1975/1992 autobiographical article, which included mention of his trip to Europe in the mid-thirties and a long report he submitted to the Rockefeller Foundation about European neuroscience and neuroscientists. More revealing was Gerard's statement in his 1975/1992 article that “... I personally have been more excited about some discoveries and interpretations than about methodological considerations” (p. 469). Similarly, Kety (1982) emphasized in his biography about Gerard that while his subject had become interested in developing a microelectrode as an undergraduate he “... indicated more than once that he did not consider the development of the microelectrode to be his most important contribution. This may have been because of its technical rather than its conceptual nature” (p. 193).

work on several excised tissues, including the giant axons of *Sepia* (Weidmann, 1951), frog heart muscle (Woodbury and Woodbury, 1950), mammalian heart muscle (Draper and Weidmann, 1951), frog and mammalian nerve fibers (Woodbury & Woodbury, 1950), and frog dorsal root ganglion cells (pg. 23 in Svaetichin, 1951). Clearly, the Eccles' NZL group was well aware of the rapid post WWII developments in the IC-recording of both RPs and APs across animal species and their excitable tissues.³

2.2. 1949–1951 precedents cited by Woodbury and Patton in their 1952 reports

In the Woodbury and Patton (1952a) abstract that preceded their 1952 article, the only precedent cited was “Eccles.” This was presumably for the Brock et al., 1951 work showing that the MN spike was “... preceded by low amplitude positive potential” (p. 175). In their 1952 4-page article, Woodbury and Patton (1952) cited Brock et al. (1951) and Ling and Gerard (1949), the latter presumably for its technical (microelectrode) precedence. This seems scanty recognition of earlier work (explained below) but Woodbury was already an established IC-recording expert by 1952 (see below) and particularly well versed in the relevant 1939–onwards IC-recording literature.

2.3. The earlier precedents: 1904–1939

As documented above, full-length reports began to appear in 1949–1951 on IC-recorded APs in vertebrate heart and limb muscle fibers, neurons, and nerve axons smaller than the above-mentioned 1939 giant squid axon work, using sharp microelectrodes and an amplifier with an appropriate input stage. It seems that no single laboratory can be considered the sole pioneer of IC recording in the peripheral nervous system, albeit Woodbury's 1950 PhD dissertation and the full-length report of Nastuk and Hodgkin (1950) are on the forefront (for preceding abstracts, see Hodgkin and Nastuk, 1949 and Nastuk and Hodgkin, 1949). IC-recording from animal and plant cells has a far longer history, however.

2.3.1. Precedents up to WWII—The early history of IC-recording using microelectrodes is summarized briefly in the three letters mentioned above, Brownstone (2006; see his pgs. 159–160), much more expansively in Bretag (2003), and in depth in the latter's forthcoming, full-length, invited review (in preparation).

For the present purposes it is sufficient to point out that by reference to the above articles and their respective citations one can appreciate that (1) microelectrodes rather similar to present day ones were introduced in the very early 1900s by Marshall Barber [1868–1953] for studies in bacteriology, (2) IC-recording of RPs was probably first recorded reliably in unicellular *Amoeba* by Tibor Péterfi [1883–1953] in possibly the early 1920s using a self-designed, sophisticated micromanipulator and a then-conventional amplifier, (3) similar IC-recorded RPs were reported for multicellular invertebrates and large plant cells in the late 1920s and early 1930s. Note also that (4) relatively drift-free DC amplifiers could be constructed by the late 1930s and (5) high-impedance input stage circuits could be added to

³This awareness was not, however, without much difficulty and frustration. Eccles emphasized to D.G.S. in 1966 that a major problem his group experienced in NZL and even up to the then-present in Canberra, AUS, was the slowness with which recent volumes of scientific journals would become available in the Antipodes. His sense of scientific isolation, particularly in NZL, was indeed profound (see also Eccles, 1977).

such amplifiers post WWII thereby enabling the 1949/50 IC-recording of both the RPs and APs of muscle and nerve cells in the frog, and other vertebrates by 1951. Furthermore (6), the technology for display systems was based on the cathode ray oscillograph, which was invented by the German, Karl Ferdinand Braun [1850–1918], who shared the 1909 Nobel Prize in Physics with Guglielmo Marconi [1874–1937] for their development of wireless telegraphy.

Interestingly, Braun did not patent the cathode ray oscillograph, but rather published enough detail so that any scientist could build the device. Modifications to this technology were necessary to display the tiny voltages involved in biophysical experiments. The Americans, Joseph Erlanger [1874–1965] and Herbert Gasser [1888–1963], accomplished this advance. They shared the Nobel Prize in Physiology and Medicine in 1944. These developments were all necessary for the future success of IC recording, and they are, in one form or another, present in the modern day IC-recording laboratory. Computers now replace much of the electronic equipment, of course. This change would undoubtedly astonish mid-20th C neurophysiologists should they visit a laboratory today!

2.3.2. Initial focus on the spinal cord (SC)—It is certainly true that by the mid-20th C studies on many areas of the CNS would have benefited from IC recording, but in no such cases could cells be identified as unequivocally as were MNs. By 1950 MNs had been identified using EC recording of their activation by antidromic stimulation. This approach was pioneered by Rafael Lorente de Nó [1902–1990] and Birdsey Renshaw [1911–1948] for oculomotor MNs and Renshaw for spinal MNs (Lorente de Nó and Renshaw, 1939; Renshaw, 1941). Furthermore, over the preceding 50 years, SC physiology had been intensely studied by Sherrington and his trainees.⁴ Their classic 1932 monograph (Creed et al., 1932) was read widely and used in classroom teaching well into even the early 1960s. Through his meticulous experimental approach, Sherrington ushered in modern day CNS neuroscience. In fact, most current motor system scientists of British ancestry and many other neuroscientists trace their scientific lineage to Sherrington; and much has been written about his contributions these past near-60 years (e.g., Liddell, 1952; Shepherd, 2010).

By the advent of WWII, detailed SC studies were being undertaken not only in GBR, but also in the USA, in particular at the Rockefeller Institute with the work of David Lloyd [1911–1985] on the forefront (Patton, 1994). We have not reviewed these studies here. Rather, for our present purposes it is sufficient to emphasize that through solid scientific enquiry, there was more knowledge by 1950 of the physiology of the SC than of any other component of the vertebrate CNS.

3. The Woodbury–Patton collaboration

The research collaboration of Woodbury and Patton was limited largely to 1951–1952, albeit their close academic collaboration in teaching and all-round university affairs extended for another two decades at the University of Washington.

⁴To our knowledge, Sherrington, who shared a Nobel Prize in 1932 with Edgar Adrian [1889–1977], is the only such Laureate who had two of his trainees also win a Nobel Prize, Eccles in 1963 and Ragnar Granit [1900–1991] in 1967. Both wrote touching accounts of their time with Sherrington (Eccles and Gibson, 1979; Granit, 1966).

3.1. The collaborators' initial training and academic career

Both Woodbury and Patton had optimal training for their stellar academic careers in the fields of biophysics, neuroscience and physiology, with each following a different long-range career path.

3.1.1. Woodbury—Even by today's standards, Woodbury's family background and tertiary training were remarkable for his academic career. There are now five generations of the Woodbury family who contributed and continue to contribute to overall academe, with research in biology, biophysics, botanical genetics, neuroscience, and several aspects of physical science!⁵

Woodbury completed a BS in physics in August 1943 at the University of Utah and immediately joined the Radiation Laboratory, MIT, Boston, MA in 1943 where he participated in military-oriented radar research, development, and testing until the end of WWII. He next completed his MS (1947) and PhD (1950) degrees in physiology at the University of Utah. This training was followed by 22+years in the Department of Physiology & Biophysics Department at the University of Washington, Seattle, WA (instructor to professor, 1950–1962), a sabbatical year (1972–1973) with the renowned University of Utah physical chemist, Henry Eyring [1901–1981], and a return to his original physiology department at the University of Utah (1973-present; emeritus since 1993). At both institutions his overall academic career in teaching, research, and service has been outstanding and respected highly (see Bien, 2005). His refereed research publications, which span a 44-year period (1947–1991; see below for other publications) demonstrate biophysical aspects of IC-recording data obtained to study ion flux through membrane channels of muscle and other membranes of excitable CNS and peripheral cells, as well as the regulation of acid-base balance and the control of epileptic seizures. Along the way he mentored 15 predoctoral and 16 postdoctoral trainees. These included several of particular note, including: predoctoral—Allan J. Brady [1927–], Wayne E. Crill [1935–], Michael M. Mackey [1942–], David W. Maughan, [1941–] Stephen H. White [1930–], and John A. Williams [1941–]; postdoctoral—David D. Busath [1952–], Dexter M. Easton [1921–], Albert M. Gordon [1934–], Masayosi Goto [1921–], Kenneth Izutsu [1942–], Theodore H. Kehl [1954–], Philip R. Miles [1942–], and James B. Ranck, Jr [1930–]. These trainees had successful careers in diverse life and physical science areas. For the purpose of this review, however, it is interesting to note that one of his trainees, Crill, became a pioneer in studies on spinal MN biophysics (see, e.g., Crill, 1999). Woodbury also mentored numberless undergraduate student researchers throughout most of his career.

⁵Woodbury is a grandson of a lifelong educator, John T. Woodbury [1863–1936] who in pioneer times secured a certificate in 1882 from the University of Deseret, UT to administrate and teach at the K-12 school level, with most of his career spent in St. George, UT. One of his sons, Angus M. Woodbury [1886–1964] became a particularly well-known biology/ecology professor at the University of Utah. Angus had four sons all of whom completed PhDs, as did his two son-in-laws (Bien, 2005). Walter Woodbury's distinguished siblings and their research specialties include Lowell A. Woodbury [1910–1987] (fish pathology), Max A. Woodbury [1917–2010] (mathematical statistics), and Dixon M. Woodbury [1921–1971] (neuropharmacology). His equally renowned brothers-in-law were A. Herbert Gold [1911–1984] (plant pathology) and Robert C. Pendleton [1918–1982] (biology and radiological health). One of Walter Woodbury's sons, Dixon J. [1956–], a biophysicist, is currently a professor of physiology at Brigham Young University, Provo, UT. Karen W. Hughes [1940–] (Lowell's daughter and Walter's niece), secured her PhD in genetics in 1972, and Nathan Lovell [1976–] (Walter's grandson), a fourth generation Woodbury scientist, has just completed a PhD at MIT in materials science. Further details will be provided in the autobiography of Walter Woodbury, which is in preparation.

3.1.2. Patton—It is unfortunate that a full biographical memoir has not been written on the academic career of Harry Patton. All that are currently available about him are some brief obituaries and a Seattle newspaper article that attest to his scholarly and gentlemanly approach in academe.⁶

Patton was widely known in the USA as a highly respected physiologist. He is best remembered for his contribution to the development of the Department of Physiology & Biophysics at the University of Washington School of Medicine and for his editing and chapter contributions to the many editions of a widely used physiology textbook—"A Textbook of Physiology for Medical Students and Physicians." The first edition was in 1905, and the last ("Physiology and Biophysics") was the 21st edition in 1989. The editors included William H. Howell [1860–1945], John F. Fulton [1899–1960], Theodore C. Ruch [1906–1983], and Patton. The latter was the primary editor of the 1989 edition, which was nearly completely rewritten. Atypically, Patton contributed but one chapter (on the autonomic nervous system). His former IC-recording collaborator, Woodbury, continued to update his chapter on the regulation of body acid-base. (In the far earlier 1965 edition, Woodbury's chapter helped simplify greatly the diagnosis of acid-base disorders in the human.)

Patton completed a BA in zoology in 1939 at the University of Arkansas, and both a PhD in physiology in 1943 and an MD in 1946 at Yale University. He received an honorary L.L.D. degree from the University of Arkansas in 1984. His PhD dissertation on the neurophysiology of taste and smell was mentored by Ruch, with whom he worked as a research assistant at Yale in 1943–1946. He then became an instructor in psychobiology at Johns Hopkins University in 1946–1947 after which he joined Ruch, who had become in 1946 the first chair of in the Department of Physiology & Biophysics at the newly formed University of Washington School of Medicine (Giddens, 1981).

Patton spent the remainder of his academic career in this renowned department (assistant professor to professor, 1947–1964; acting chair, 1964–1966; chair, 1966–1983; emeritus, 1983–2002). His book chapters, edited textbooks of physiology, and refereed publications, which focused on supraspinal interactions with a wide variety of peripheral somatic and autonomic structures, span a 50-year period (1944–94). In all, he mentored a very limited but talented number of trainees who all made valuable contributions to neuroscience. These include Marjorie Anderson [1941–] and Hardress Waller [1928–], who were predoctoral trainees, and Joseph Hwang [1935–], and Thelma Kennedy [1925–2009] at the postdoctoral level.

3.2. Background and training for intracellular (IC) work in the cat SC

Woodbury arrived in Seattle in mid-September 1950 and Patton and he quickly decided that they should undertake IC-recording in the cat SC. This had to await Woodbury's setting up his laboratory and an immediate very heavy teaching load in the university's winter quarter (January to mid-March, 1951). They began their experiments in the early summer (May–

⁶More information on Patton is now available in a departmental history, which was prepared by Majorie Anderson : see <http://depts.washington.edu/pbiopage/pbiohistory.html>.

June) of 1951, spurred on (according to a 2010 personal communication from Woodbury to us) by a letter to Patton from Easton that Eccles had started such experiments in NZL.

3.2.1. Woodbury—In his PhD dissertation, which was undertaken between 1947 and 1950, Woodbury (1950) wrote “During the autumn of 1948, he (*Woodbury*) spent some time with Dester Gilbert Ling at the University of Chicago and learned how to make microelectrodes” (p. 3). He also expressed “... gratitude to Doctors Ralph W. Gerard and Gilbert Ling ... for teaching (*him*) the micro-electrode technique” (p. 85).

Woodbury’s dissertation involved the measurement of both RPs and APs in single myelinated fibers of the frog sciatic nerve. For this, he first needed appropriate microelectrodes. For the pioneering AP studies on nerve axons, Woodbury cited first the independent IC-recording work of Cole and Curtis (1939) and Hodgkin and Huxley (1939) on the squid giant axon using relatively large intra-axonally inserted pipettes (width 140 μm in the former study; 100 μm in the latter) and several articles between 1937 and 1948 on EC-recordings using sharp-tipped metal, metal/glass, and glass microelectrodes. However, Woodbury’s focus was on glass “ultra-microelectrodes.” He cited Graham and Gerard (1946) and Ling and Gerard (1949) for the technical precedent of microelectrode construction (see also Ling and Woodbury, 1949). These electrodes were hand-pulled, which resulted in a smaller tip diameter and a smoothly tapering tip. Woodbury felt that this feature was critical for their success in impaling tiny spinal INs.⁷

Next, Woodbury emphasized the significance of the Nastuk and Hodgkin (1950) report on the IC-recording of APs in mammalian muscle fibers. This work required use of a special amplifier input stage, which had been built in Hodgkin’s laboratory following the design of Martin Ryle (1918–1984), a radio astrophysicist who had worked on the development of radar in WWII and later shared the 1974 Nobel Prize in Physics. (A similar input stage was borrowed from Hodgkin and first used by Huxley and Stämpfli, 1949.) Woodbury’s input stage was his own design, however, which he used in 1948–1950. Indeed, he did not know about the Hodgkin and Nastuk (1950) article until his PhD research was almost completed. The value of Hodgkin’s input stage was nonetheless emphasized in the refereed publication of Woodbury’s dissertation (1952b), where he stated (p. 323) that Nastuk and Hodgkin (1950) “... improved the frequency response of the recording apparatus sufficiently to permit the accurate recording of muscle action potentials.” Interestingly, and in sharp contrast to most present day PhD dissertation defenses, none of his committee, distinguished

⁷Woodbury wrote to us in 2010 that: “Gilbert Ling instructed me in how to pull capillary micro-electrodes (ME) by putting a 3 inch long section of 2 mm diameter capillary tubing into the fringe of a Bunsen burner flame! I was surprised that it worked. After much practice I learned how to make them. I thought it would be a lot easier if you used a small gas flame and it is. You can tell an electrode is no good if (1) you felt it break and (2) there is no detectable resistance when the two ends separate. It is likely to be good if you can feel a slight resistance when separation occurs. Feeling it break means the tip is too large; no resistance means the tip sealed. When I got back to Salt Lake, I perfected my technique by pulling MEs and then looking at them through a compound microscope to see the shape of the tip. Tip diameter <0.5 micrometers are in the visible light range, so diffraction lines obscure the tip. Despite this limitation, I discovered that a good electrode, one having a resistance ≥ 50 megaohms, tapers steadily into the diffraction lines. This is not the case for machine pulled MEs ... After a few years, a few companies brought out automatic pullers and I made the mistake of buying one. My experience with automatic pullers is uniformly negative; they are poor substitutes for hand drawn and I used hand drawn MEs all my career, also pulling them for my students... Every machine pulled electrode that I have looked at through a microscope has the very rapid taper at the tip ... the hand pulled ME slips relatively easily through tissue ... the breaking off of a small part of the tip may not render the electrode useless. A machine pulled electrode gets too fat too fast, resists passage and is useless if the fast tapering tip gets broken off... if you want to go deep into brain or SC, use handmade MEs. In the extremely improbable event that someone would like to try it, I would be glad to teach him/her how to draw them!”

in their own fields as they were, had the background to follow the electronics, mathematics, and interpretation of Woodbury's data. For this he got some input from his brother, Lowell, who was not on his PhD committee.

While working on his PhD research Woodbury also collaborated in 1949 with Lowell and Hans H. Hecht [1913–1971]. They pioneered the IC-recording of RPs and APs from Purkinje fibers of the dog heart (L.A. Woodbury et al., 1950). Later, Woodbury found in 1952 that he could stimulate nerve axons through an intra-axonal IC-inserted microelectrode and in 1955 he developed a floating microelectrode (see Fig. 5 legend). In 1964 he adapted the IC-recording micropipette electrode to measure pressures in capillaries.

In retrospect, Woodbury was a highly original PhD student with gifted technical and theoretical talents and one who extracted great pleasure from his scientific pursuits (Fig. 5), which continue to this day. Clearly, he was thoroughly prepared for his initial foray into IC recording in the CNS!

3.2.2. Patton—In sharp contrast to Woodbury, Patton had no background in IC-recording when they began their collaboration in 1950. Patton was an “all-round” cellular/systems neurophysiologist whose PhD mentor, Ruch, had undertaken spinal reflex research in 1928–1931 in Sherrington's renowned SC laboratory at the University of Oxford, GBR. While Patton was a research assistant at Yale he also had substantial contact in 1943–1945 with Lloyd, a gifted SC neurophysiologist (Patton, 1994), whose PhD mentor had been Eccles at Oxford in the mid-1930s (Stuart and Pierce, 2006). It seems likely that these experiences included much discussion of SC neurobiology and were certainly put to good use when Woodbury and Patton began inserting microelectrodes into the cat SC. For example, in a 2010 personal communication to us Woodbury wrote that: “Pat and I quickly became friends and enjoyed each other's company ... I majored in physics and the only experience I had in animal experimentation was how to pith a frog and dissect out its sciatic nerves. Pat was a meticulous, well-trained animal surgeon. The only way I could possibly have considered recording from cat SC was to team up with somebody with his qualifications. We really enjoyed working together doing those experiments.”

3.3. Significance of the 1952 Woodbury and Patton contribution

In evaluating the Woodbury and Patton 1952b article it is clear that it was particularly unfortunate that the invitation to participate in the June 1952 symposium did not come until the late spring. This was in the form of an invitation to Patton to discuss Eccles' presentation by the organizers of the symposium (Lloyd and Alfred Mersky [1900–1974] of the Rockefeller Institute; and Stephen Kuffler [1913–1980] and Martin Larrabee [1910–2003] of Johns Hopkins University). Patton insisted that Woodbury rather than he both attend and present their own work at the symposium as was then agreed upon by the organizers. Puzzlingly and in retrospect shamefully, their decision that the Woodbury and Patton (1952b) work be included in the symposium publication was not made until immediately after the symposium's conclusion. Woodbury and Patton were therefore given but ten days to submit their article! If given the much longer time made available to the other presenters,

Woodbury and Patton could have written a much fuller account of their results and their interpretation.

Despite the above mishap their article was seminal. Perhaps its main long-range significance was the information they provided on their type 2 units, which they logically presumed were spinal INs. They demonstrated that such cells could have substantial RPs (up to -80 mV), could not be activated by antidromic stimulation of ventral roots (they did not record from Renshaw cells), and had firing patterns that were consistent and observable for up to 20 min of stable IC recording. These units fired transiently at rates up to 1200 Hz in response to peripheral afferent stimulation. Given today's focus on the properties of vertebrate spinal INs it is thus unfortunate that Woodbury and Patton (1952b) lacked the time to provide but one figure about the properties of such cells. This figure, part of which is shown above in Fig. 3E, was indeed a tour-de-force in that it showed repetitive high frequency discharge, which is still difficult to record intracellularly in spinal INs of in vivo spinal mammalian preparations (for review, see McDonagh et al., 1999 and Stauffer et al., 2007).

The Woodbury and Patton 1952b article also provided the first-ever examples of IC recording from axons within the CNS (their type 1 units). This is certainly of historic importance, albeit the information so gained has proven to be not so much greater than that obtained with EC recording of CNS axons.

Their article focused largely on presumed MNs (termed type 3 units), with findings that were largely in concurrence with those of Brock et al. (1952a,b). Interestingly, Woodbury and Patton stated that "... the greatest caution must be exercised in using the (*MN*) findings to support any particular hypothesis as to the nature of synaptic transmission." This was in sharp contrast to the conclusions reached by Brock et al. (1952b,c)! Woodbury and Patton's analysis clearly led to much reflection on the various possibilities that could explain the origin of prepotentials in both MNs and INs because this issue could not be resolved at that time. Interestingly, one explanation in the Woodbury and Patton 1952b article was that "... the size, duration, and form of the recorded prepotential (i.e., *what* Brock et al., 1951 *had referred to as the MN's 'synaptic potential'*) may be influenced by (*the*) position of the electrode in the impaled cell." This noteworthy comment, which was also made about their INs' prepotentials, predated the use of cable theory that was so ably and fully advanced by Rall for over four decades beginning in 1957 (see Rall, 1957, 1992; Segev, 2006). The 1952b Woodbury and Patton article closed with the prescient statement for the much later recording of the MN's dendritic postsynaptic potentials (PSPs) and APs (see below) that "Efforts to mark the position of the intracellular electrode are in progress" (p. 188 for the 3 quotes in this paragraph).

Finally, it is a great shame that Woodbury and Patton did not submit for publication a much longer and fuller account of their seminal work. If they had, the field as a whole would have profited in particular from (1) their IN experience and findings, and (2) their efforts to show that AP features depended on the specific site of neuronal impalement. It is ironic that if they had been working with Eccles, such a manuscript would certainly have been written!

3.4. Later scholarly contributions of Woodbury and Patton

Woodbury and Patton did not extend on their 1951–1952 cat SC work, except for a talk presented at another international meeting the next year (Woodbury and Patton, 1953) and a largely technical note that, in retrospect, was of particular value to those wishing to record from nerve cells in the CNS (Woodbury, 1953).⁸ Rather, Woodbury focused on biophysical issues in a wide variety of excitable and other cells and tissues. In a personal 2010 communication to us he reflected that their initial IC results may have continued if they had been more successful in recording the orthodromic monosynaptic activation of MNs.⁹ Patton came to understand how to solve their problem several years later, but by then they were well entrenched in other areas. In a 1980 discussion with D.G.S., Patton reflected that in the early 1950s he, himself, did not want “to compete with Eccles” in further IC work in the cat SC. An evaluation of this statement would be overly conjectural, albeit many felt Eccles had treated Lloyd harshly in their arguments about the direct inhibition issue.¹⁰ Lloyd had been Eccles’ PhD trainee in GBR and he was a close friend and advisor of Patton.

3.4.1. Woodbury—Between 1952 and 1991 Woodbury published 25 refereed research articles and he currently has two further ones in preparation! Also between 1956 and 1982 he contributed 5 reviews and 14 book chapters and books, and in 2011 is currently writing an autobiography and another book (on how the brain generates normal human behavior). Most of his refereed articles are quite seminal in that they exploited his IC-recording technical and theoretical prowess in studies on many peripheral excitable tissues and one CNS target in a wide variety of animal species, including the human. The tissues included the carotid body and nerve, embryonic and mature cardiac cells (including seminal work on gap junctions), liver cells, muscle cells of the pregnant uterus, myelinated nerve afferents, S1 cells in the somatosensory cortex, striated muscle fibers (including much work on their anionic permeability), and the thyroid gland. The latter was undertaken with his brother, Dixon, with whom he also wrote two articles on the effects of vagal nerve stimulation on experimentally induced seizures in rats. This work set the stage for vagus nerve stimulating patterns which are used today in humans with epilepsy. Tens of thousands of vagal nerve stimulators have been implanted world-wide in patients with epilepsy (Guberman, 2004). In addition, his microelectrode technique for studying pressures in capillary beds is used in both fundamental research and the clinic. Another seminal contribution of Woodbury was his use of Eyring’s rate theory to account for the puzzling shapes of current-voltage relationships in ion channels and to show how the same principles could be applied to the gating process in ion channels. In recognition of this sterling record, Woodbury became a

⁸Woodbury was probably the first biophysicist to introduce negative capacity amplifiers to the field of neuroscience, the concept having been used routinely in radar receivers during WWII. Such amplifiers resolve “... the problem of band width restriction imposed by the high resistance of micropipette electrodes” (personal 2010 communication from Woodbury to us).

⁹Woodbury reflected to us in 2010 that “... we would undoubtedly have continued our studies for quite a while if we had been able to get monosynaptic reflexes routinely. We thought that the absence of monos was due to defective preparation. We got more and more careful about the cat’s environment and got fewer and fewer successful preparations. We had essentially given up before the Cold Spring Harbor Symposium in 1952. It was a few years later that Pat found out that we had been too careful. We were ignorant of one simple fact that was part of the culture of those studying spinal reflexes: in order to get large, reproducible monosynaptic reflexes in anesthetized cats it is necessary to lower core temperature a degree or two. We carefully monitored rectal temperature and kept it at 37 °C. We were really sad but by this time I was heavily engaged in cardiac electrophysiology and Pat had gone his way.”

¹⁰Patton did not attend the Cold Spring Harbor Symposium but he had many friends there, including his collaborator, Woodbury. In a 2010 communication to us, Woodbury reflected that at that meeting the exchanges between Eccles and Lloyd were particularly sharp and harsh, with Lloyd having difficulty countering Eccles aggressive attacks (see also p. 152 in Stuart and Pierce, 2006).

fellow of the American Association for the Advancement of Science in 1960 and received the Biophysical Society Fellow Award at its 2006 meeting.¹¹

3.4.2. Patton—Patton's post 1952 refereed publications on original research were quite sparse, including but ~10 articles on the topics mentioned above. On the other hand, his textbook chapters and other reviews were major contributions not only for graduate and postgraduate trainees but also for mature, seasoned experimentalists.

3.5. Summary reflections on the Woodbury–Patton collaboration

Woodbury and Patton are certainly deserving of recognition for being the co-pioneers of IC recording in the CNS. The 1951/1952 reports of the Eccles' group focused on the MN and the 1952b report of Woodbury and Patton supported the NZL MN findings and added original observations on IC recording from axons and INs in the CNS. In retrospect, the significance of the Woodbury and Patton contribution would have been even greater if (1) they had been given more time to prepare a fuller account of their seminal work for the symposium publication, (2) they had immediately written such a fuller account after the symposium, and sent it to a top-tier refereed journal, (3) more IC-recording teams had immediately grasped the significance of their virtuosic work on spinal INs, and (4) they had solved their problem of orthodromic input to MNs and pursued these studies further.

4. Eccles' 1944–1951 laboratory in Dunedin, NZL

Much has 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; Ito, 2000; Strata, 2000). We, ourselves, have contributed to this overall effort (Brownstone, 2006, Stuart and Pierce, 2006, Stuart and Zigmond, 2006) and Eccles, himself, provided three autobiographical accounts that bear on the present article (Eccles, 1975/1992/1976/1977). Eccles was a man of extraordinary drive and vitality, with “strongly held opinions, which were ... upsetting to some, inspiring to many, and thought provoking to all” (p. 137 in Stuart and Pierce, 2006; see also pp. 116–119 in Shepherd, 2010). In all, he had 568 publications (abstracts, refereed articles, book chapters, reviews, and books) in a 70-year period between 1928 and 1998, with 2 appearing after his death. Many of these publications involved co-authorship with over 180 trainees and collaborators from 21 countries, most of whom have contributed substantially to neuroscience; from the cellular/molecular to the behavioral and philosophical level of enquiry. Eccles had a life-long interest

¹¹In retrospect, Woodbury believes that “... my most important professional contribution were the chapters on nerve impulse conduction I wrote in 1960 for the highly successful textbook “Medical Physiology and Biophysics” (*edited by* Ruch and Fulton, 1960) These chapters were the first readily available, simplified (but not simple) exposition of the mechanisms of the generation and propagation of the nerve impulse based on the Nobel Prize winning research of A. L. Hodgkin and A. F. Huxley published in 1952. Several generations of neuroscientists learned about nerve physiology from these chapters. The integration of these concepts into main stream neurophysiology helped to launch modern neuroscience” (comments expressed in a brief autobiography written when Woodbury retired in 1993 and available upon request to Woodbury or to us). He emphasizes today that his major research project for many years on ion efflux from striated muscle, requiring tracer washout studies, was far from successful. Conversely, his research on epilepsy with his brother, Dixon, was of great value as was his launching of two key areas: in the 1960s he “... developed the concepts and techniques for studying electrical connections between cells” and in the early 1970s he showed “... how to use Eyring reaction rate theory to explain the movements of ions through ion channels in cell membranes and also to explain ion channel gating mechanisms.”

in the so-called mind-brain problem and 18% of the above oeuvre addressed this issue, which is beyond the scope of our article (see pp. 450–452 in Curtis and Andersen, 2001a; also Libet, 2006 and Wiesendanger, 2006).

4.1. Eccles' initial training and academic career up to and including his sojourn in NZL

Eccles, who was gifted in mathematics, completed a post-high-school, 5-year undergraduate medical (MBBS) degree at the University of Melbourne, AUS in 1925 and late that year he arrived at the University of Oxford, GBR as a Rhodes Scholar. There, he completed an advanced undergraduate degree in 1927 in physiology and biochemistry and a PhD in physiology in 1929 under Sherrington's mentorship. He remained at Oxford until mid-1937 with various academic appointments, the last of which was more-or-less equivalent to a N. American assistant professorship. The Oxford phase of his life is summarized nostalgically in Eccles and Gibson (1979).

In August 1937 Eccles became the Director of the Kanematsu Memorial Institute of Pathology at Sydney Hospital, AUS where he undertook research on the CNS and peripheral nervous system.

In January 1944 Eccles began work as the Professor of Physiology and Head of Biochemistry at The University of Otago, Dunedin, NZL, a post in physiology that he held until late 1950 when he accepted the professorship and headship of the Department of Physiology, John Curtin School of Medical Research, Australian National University (ANU), Canberra, AUS. He was given permission to continue working in his Dunedin facilities throughout most of 1951, however, before spending several months in GBR and the USA, returning in late June, 1952 to NZL, and then taking up residence in Canberra, AUS in September, 1952. In all, his NZL sojourn lasted almost 8 years.

Two points stand out when reflecting on Eccles post GBR 14-year sojourn in the Antipodes from mid-1937 until late 1951.

1. Eccles did not let his profound sense of scientific isolation prevent him from accomplishing first-class research in Sydney, particularly in 1937–1941. Despite the initial lack of any appropriate research equipment (“not even a screwdriver,” as emphasized in a 1966 discussion with D.G.S.), he had the good fortune to work with two neuroscience “giants” at early stages in their careers: Kuffler, a refugee pathologist from Nazi-dominated AUT, whom Eccles met in Sydney purely by chance, and the later 1970 Nobel Laureate, Katz. Together this talented trio advanced understanding of neuromuscular transmission shortly after Eccles and his Australian postdoctoral trainee, Walter O'Connor [1911–1994] had pioneered the electrical recording of end-plate potentials from the surface of strips of striated muscle fibers (p. 442 in Curtis and Andersen, 2001a). Interestingly, despite not being given a courtesy appointment by the University of Sydney, he continued to impart didactic knowledge to its third-year medical students, which must have facilitated his return to academic life in NZL.
2. Eccles accomplished far more for all-round academe at the University of Otago in 1944–1951 than is generally appreciated (see pp. 139–142 in Stuart and

Pierce, 2006). This fact is expressed movingly in Fillenz (2000) and the many personal communications received by D.G.S. in the late 1990s and early 2000s from Eccles' former NZL students, trainees and associates many of whom advanced the overall tertiary academic enterprise throughout NZL and particularly at the Universities of Otago and Auckland and the Portobello Marine Biological Station.

4.2. Eccles' background for IC work in the cat SC

When Eccles began IC-recording (presumably in late May or early June, 1951) in the cat SC, he was already quite experienced in the EC measurement of intraspinal MN focal potential responses to ortho- and antidromic stimulation of dorsal and ventral root axons, respectively. This experience is summarized succinctly and conveniently in Eccles (1950). This most relevant IC-precedent research, all undertaken in his Dunedin laboratory, was described in Brooks and Eccles (1947, 1948), Barakan et al. (1949), and Brooks et al. (1950a,b). The recordings were made with needle electrodes of ~50 μ m diameter insulated except for their tips. Even before Romanes' (1951) maps of the lumbar enlargement of the cat SC became available, Barakan et al. (1949) were able to insert these electrodes into predetermined MN nuclei supplying muscles like the quadriceps, gastrocnemius, and biceps-semitendinosus, by reference to the far earlier work of Marinesco (1904). The technical aspects following conversion to glass microelectrodes, which were used to impale MNs, were thus quite straightforward for Eccles and quickly successful. The IC-recording equipment was another matter, however, as reflected and speculated upon below.

4.3. How IC-recording began in Eccles' Dunedin department

Eccles' IC-recording experiments were preceded in his department in 1950-early 1951 by the preliminary efforts of an outstanding Australian neuroscientist, Archibald "Archie" McIntyre [1913–2002]; see Proske, 2003).¹²

4.3.1. The initial aborted efforts of McIntyre—McIntyre completed an undergraduate medical degree at the University of Sydney, AUS in 1936, where he had clinical and research experiences (1937–1941) before joining the Australian Air Force as an officer in WWII (1941–1946). There, his experience investigating the vestibular system led him into a variety of aviation research investigations that led to, for example, the development of G-suits and ejection seats (he participated as a test subject in both; Porter et al., 2004). This was followed by highly productive research at the Rockefeller Institute in New York City, USA (1946–1948) where he published 7 articles with Lloyd on cat SC neurophysiology. He then had a year with Bryan Matthews [1906–1986] at the University of Cambridge, GBR which included frequent visits to the London laboratory of his very close friend, Katz, who was undertaking IC-recording in frog muscle fibers at that time (see above).

McIntyre joined Eccles' department as a senior lecturer (N. American equivalent, associate professor or professor) in 1950. He became the department's acting head in 1951 and then

¹²This article includes information available in a taped 1994 interview of McIntyre undertaken by Proske. The transcript of this tape is available from the Australian Academy of Science.

its head and professor of physiology for the period 1952–1961. In 1962, he became the first professor and head of physiology at the newly created Monash University in Melbourne, AUS. He held this position until 1974, 4 years before his retirement in 1978 after which he moved to Launceston, Tasmania, AUS. He continued projects at Monash from time to time until the early 1990s, with “... some of them involving through-the-night recordings, exploring the electric sense organs of the platypus” (p. 89 in Porter et al., 2004). In all, McIntyre published 117 abstracts, refereed articles, book chapters, and books over a 55-year span (1938–1993) during which time he mentored, among others, many well-known fundamental neuroscientists and physiologists including, in their alphabetical order: NZL—Ainslee Iggo [1924–], Julian J. Jack [1936–], Richard F. Mark [1934–2003], Wilfred Rall [1922–], and Colwyn Trevarthen [1931–]; AUS—Masao Aoki [1940–], Uwe Proske [1939–], and David J. Tracey [1947–].

What follows on McIntyre’s IC-recording attempts after his 1950 arrival in Dunedin is based on incomplete factual information. He had no prior “hands on” experience with IC recording, albeit presumably much discussion with Katz about its nuances for recording the RPs and APs of frog muscle fibers and certainly extensive experience with Lloyd on cat SC neurophysiology. The latter probably did not include, however, neuroanatomical aspects of locating spinal MN nuclei.

McIntyre brought to Dunedin an unknown amount and type of IC-recording equipment that had been given to him by Katz (Proske, 2003). Most importantly, he had an amplifier constructed by a local electronics engineer, using a circuit diagram given to McIntyre by Lloyd and based on a circuit designed by the gifted German engineer, Jan Tönnies [1902–1970] (personal communication in 2005–2006 from Rall to R.M.B.). Tönnies may have been the first to build a differential amplifier in 1934 and while at the Rockefeller Institute, the first cathode follower for Hodgkin in 1938 (see p. 91, albeit not clear on this point, in Hodgkin, 1938 but more definitely but perhaps inaccurately on pp. 493–495 in Jung, 1975/1992). This suggests that despite the fact that no previous studies at the Rockefeller Institute had involved IC recording with sharp glass microelectrodes, McIntyre’s IC-recording amplifier in Dunedin may well have included a cathode follower for high input impedance recording. Much later, McIntyre imparted to Proske (2003) and other close colleagues (including Carlton “Cuy” Hunt [1918–2008], who communicated this to D.G.S. in a 2007 letter) that he was making headway with IC-recording in the cat SC when Eccles took over his project in probably early 1951. By then Eccles was actually a “visiting” professor in his former Otago department whereas McIntyre was the department’s acting head!

Just how far McIntyre advanced in 1950–1951 with IC recording remains a mystery. While we doubt that it was very far McIntyre seems to have retained powerful memories of the aborted experience throughout much of his lifetime, even though he had a very privileged possibility to be a leader in this area from 1952 onwards (see below).

4.3.2. Eccles’ NZL IC-recording collaborators, Brock and Coombs—In either late 1950, or more likely early 1951, Easton informed Eccles that Woodbury and Patton had begun, or were about to begin, IC-recording in the cat SC in Seattle (personal

communications in 2005–2006 from Easton to R.M.B.; the Woodbury–Patton work actually began in late May or early June, 1951).

Eccles recruited two young colleagues to collaborate with him on IC recording; Brock and Coombs (Fig. 6). They got off to a particularly fast start in either late May or early June. Their 1951 article was read by title at the July 21 meeting of the local society of the medical school and published on July 31. (Much to his chagrin, it was not Eccles' turn to present at the July 21 meeting; p. 164 in Eccles, 1975/1992). By August of that year electrical synaptic transmission had been disproved not as is often supposed by the more accurate measurement of synaptic delay but by the lack of an initial depolarization at the onset of a disynaptic IPSP (see Fig. 3C-2) and, for both monosynaptic EPSPs and disynaptic IPSPs, the wide disparity between the small amplitude and short duration of the presynaptic spike and the large and much longer post-synaptic response. The August 1951 results thereby strongly favored chemical transmission for IPSPs and probably also for monosynaptic EPSPs (see p. 455 in Brock et al., 1952b and pp. 225 in the colorful Eccles, 1976 reminiscence). The work also demolished convincingly the occurrence of direct inhibition in the reciprocal inhibitory pathway of the cat SC, as championed so affirmatively by Lloyd.

Brock, a man of many skills and interests, was already a licensed clinician,¹³ as well as a licensed pilot of small planes and gliders, when he began making microelectrodes in Eccles' laboratory. Previously, he had completed a BS in mathematics, chemistry and physics (1944) at the Auckland University College (then a constituent College of the University of New Zealand) and an undergraduate degree (MBChB) in medicine and surgery (1949) at the University of Otago. He was appointed as an Assistant Lecturer (1950–1952) by Eccles to the Otago Department of Physiology. In 1953–1954, he was awarded a Nuffield Commonwealth Travelling Fellowship to undertake further neuroscience training in GBR at the University of Cambridge (see, e.g., the later published Brock and R. Eccles, 1958 article). Brock then returned to Dunedin, where he was appointed by McIntyre to a Senior Lectureship in the Department of Physiology (1955–57). In 1958, while still in Dunedin, he switched to surgery, then in 1959 traveled to England for further surgical experience and in 1961 he became a Fellow of the Royal College of Surgeons. After a brief period as a temporary lecturer in surgery at the University of Durham, he became a lecturer in the Nuffield Department of Surgery, University of Oxford (1962–68). Because of an intractable prolapsed vertebral disk (he had two laminectomies for this problem), he switched to diagnostic radiology at Oxford (1967–72). He became a well-known, innovative and computer-oriented consulting neuroradiologist at Walton Hospital, Liverpool, GBR (1972–1989). Before his 1989 retirement he started a BA in mathematics at the Open University, which he completed in 1991. In late 1992 he began an MS in the history of science, technology and medicine at the University of Liverpool. This was completed in 1996. Brock's topic was the work of a local 19th C Liverpool jeweler and acclaimed amateur astronomer, George Higgs, who contributed articles to the Royal Astronomical Society. At

¹³Brock demonstrated his clinical competency to his two colleagues on the night they first recorded MN IPSPs. That night Eccles wrote that: "... The wife of one of my two associates (Jack Coombs) was delivered of a baby girl by the other (Dr. Lawrence Brock), I meanwhile tending the cat! It was by then in the early hours of the morning." (p. 225 in Eccles, 1976). Both Brock and Coombs later rejoined Eccles to continue their seminal experiment!

the time of Brock's demise he was planning to embark on a PhD on another historical scientific topic at the age of 73 years (Wright, 1997)!

In summary, Brock appears to us to have been a resourceful and innovative collaborator for Eccles to an extent that far exceeded his well known contribution of microelectrode construction. A detailed biographical memoir on his many capabilities and interests would be a valuable addition to the neuroscience literature. Fortunately, a private family memoir has been written. It includes valuable biographical and autobiographical material about Brock (J. Brock, 2010).

The other initial collaborator in IC-recording, Coombs, was a "shy genius" according to Eccles. Coombs' technical contribution to Eccles' 1951–1966 IC-recording work was absolutely essential according to several accounts by Eccles and others (see, e.g., Eccles, 1975, 1976, 1977; p. 444 in Curtis and Andersen, 2001a; pp. 409, 412, 413 in Fenner and Curtis, 2001). Like Brock, his contributions are clearly deserving of an in-depth biographical memoir.¹⁴

Coombs completed BS (1938) and MS (1940) degrees in physics at the University of Otago where he then held faculty appointments in the department in which he had trained as an Assistant Lecturer (1940–1946), Lecturer (1947–1950), and part-time lecturer (1951) in Physics. "... His involvement in neurophysiological research began in 1950 when asked by J.C. Eccles ... to design and supervise the construction of electronic stimulating and recording equipment having features that were then not provided by commercially available equipment. The highly successful production of the 'ESRU' (*Electronic Stimulating and Recording Unit*), and his close and continuing participation in pioneering intracellular recording from spinal neurons, led to his appointment as a Fellow in the JCSMR (*John Curtin School of Medical Research*) in September 1952 (Electronics Engineer, 1961). In Canberra, from 1952 until his retirement in 1977, he continued to design and make innovative electronic equipment which provided special features of inestimable value to investigators in the Departments of Physiology and Pharmacology" (p. 413 in Fenner and Curtis, 2001). It is also widely known that Coombs was an effective and popular instrumentation mentor of Eccles' many trainees in both Dunedin and Canberra.¹⁵ Given Coombs' expertise in physics, it seems likely that he contributed substantially to both his collaborative research¹⁶ and his instrumentation mentoring.

¹⁴Further 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).

¹⁵Concerning his 1960–1962 experience in Canberra, William D. Willis [1934–] reflected in 2010 to us: "... When I first arrived in Canberra, I had had very little experience with microelectrode recordings. Eccles recognized this quickly and had me have serious interactions with Jack Coombs for his guidance in remedying my disability. Jack Coombs was very helpful, and I am very grateful for this, since I was immediately involved in experiments with Eccles and Franco Magni. The experiments required intercellular recordings, not only from motor neurons but also from primary afferent axons as they entered the SC. Jack Coombs was a very modest individual, but he was a major factor in the technical success of the lab."

¹⁶We have not been able to obtain a copy of Coomb's curriculum vitae so the full extent of his research mentoring remains unknown to us. His refereed publications in neuroscience involved at least 19 articles published between 1951 and 1973. These include 13 written about SC neurobiology (1951–1959) with either Eccles and/or Eccles' close colleagues (e.g., Curtis, Paul Fatt [1924–]) and, after a 10-year hiatus, 6 articles about visual neurobiology (1969–1973; largely on the striate cortex) written with Peter Bishop [1917–] and/or his colleagues.

Coombs received advice from both Eccles and McIntyre when he began to design his ESRU in 1950 (p. 409 in Fenner and Curtis, 2001). Next, for Eccles' entry into IC-recording, he designed and built the input stage and amplifier needed for high input impedance recording (see Fig. 2 in Brock et al., 1952b). There appears to be no clear-cut documentation on whether this essential effort involved modifying McIntyre's recording equipment, which may have been based on Tönnies' above-mentioned circuit diagrams, or whether Coombs took an alternative approach. Similarly, it remains unknown if he discussed with McIntyre his request from Eccles to build him an amplifier with an appropriate input stage to undertake IC recording in the CNS.

In summary on Brock and Coombs, it seems clear that Eccles picked particularly well, in that both collaborators brought substantial experimental gifts to the enterprise.

4.3.3. Reflections and speculations on the absence from the recording team of other capable parties; McIntyre, Rall, and Easton—It is intriguing that other highly capable collaborators were potentially available to Eccles when he began IC recording in 1951. That he limited the recording team to three is not surprising. For his preceding abstracts and full-length articles published between 1928 and 1950 only 11/95 had even this many co-authors! Other capable people were nonetheless available to him and deserving of comment.

Why Eccles chose not to collaborate with McIntyre on IC recording remains a mystery. They did indeed collaborate effectively in 1950 and 1951 on adaptive spinal mechanisms; with 4 refereed articles that were judged much later to be seminal (Wolpaw and Carp, 2006). Admittedly, their personalities and style in science were very different, as emphasized by Proske (2003), and this alone may well have been the reason that Eccles preferred not to have McIntyre as an IC-recording collaborator. It is important to recognize, however, that their individual styles were considered of value by a very talented PhD trainee, Wilfred Rall (1922-), who worked with both of them in Dunedin (see p. 218 in Rall, 1992), and by many others in the Otago department who have communicated with us. Another possibility, which D.G.S. and the late Anders Lundberg (1920–2009) prefer (based on their 2006 discussion), is that McIntyre's close association with Lloyd was of concern to Eccles¹⁷ who, after all, was trying to blaze a new trail in the history of electrophysiological recording at a university that at the time was quite remote from leading world centers of research in general, and neuroscience in particular.

¹⁷This viewpoint is based largely on a 2009 personal communication to D.G.S. from Jay Goldberg [1935–]: “Yes, I did have a conversation with Eccles at a lunch in our Faculty Club (*University of Chicago*) when he was at the ill-fated AMA Institute (*i.e., in 1966–1968*). As I recall, he reminisced about his pioneering work on intracellular recordings. He stated that he was worried that, when he gave preliminary reports on his attempts to record intracellularly from spinal motoneurons (*i.e., presumably in late 1951 possibly at the Rockefeller Institute or in mid-1952 at the Cold Spring Harbor Symposium*), David Lloyd would realize the promise of the approach and beat Eccles to the punch. Eccles was particularly concerned because Lloyd understood the reflex organization of the SC much better than Eccles did ... Eccles told me that when he presented the results ... Lloyd attacked the approach as faulty since intracellular recordings were fraught with artifacts. Eccles went on to state that he could not have been more pleased as it meant that Lloyd would not be competitive.” This communication can also be inferred to some extent on p. 8 in Eccles (1977). Finally, it is well known that McIntyre was very loyal to and a close personal friend of Lloyd (p. 82 in Porter et al., 2004). He was nonetheless continually frustrated and even exasperated by Lloyd's excessive sensitivity to editorial criticisms of their manuscripts, even when the reviewers were quite supportive of the work! (From McIntyre's discussion with D.G.S. during their first meeting in 1974.)

Rall, an American who later advanced considerably our understanding of neuronal integration through the quantitative analysis of mammalian MNs (see Burke, 2006), was invited to join the Eccles' team. He opted, however, to remain with McIntyre as his PhD mentor. "I declined the opportunity because it had become very important to me to pursue independent research (for my PhD.) It was also important to me that my research include both experiments and mathematical modeling" (p. 218 in Rall, 1992).

Another talented American visiting Eccles at that time was Easton, who had come from the Department of Zoology at the University of Washington where he had known Patton but not Woodbury. While with Eccles (1950–1951), Easton was a visiting faculty member on a Fullbright Research Fellowship. His NZL research focused on (1) the analysis of Lloyd's so-called "direct (primary) inhibition," using the EC ventral root recording of monosynaptic MN responses to spindle Ia sensory input in the cat, and (2) the neuromuscular system of the spiny lobster, *Jasus lalandii*. For the latter, Eccles arranged for Easton to work at the Portobello Marine Field Station, where he made mechanical and EC recordings in limb muscles. After returning to the USA, Easton undertook IC-recording on frog muscle fibers in Woodbury's Seattle laboratory in 1952–55 (e.g., Easton, 1955). Interestingly, Easton is still publishing original research of relevance to IC-recorded phenomena at the age of 90 years!¹⁸

It is interesting to speculate on what may have transpired if Eccles, Woodbury and Patton had had the opportunity to meet prior to the 1952 Cold Spring Harbor Symposium. In our opinion such a discussion would have been mutually rewarding: Woodbury and Patton learning about the nuances locating motoneurons rapidly and efficiently and monosynaptic reflex testing in the cat SC, and Eccles learning how to construct and use Woodbury's gently tapered and fine-tipped microelectrodes. Interestingly, Eccles and Woodbury did not have a meaningful discussion about their IC recording experiences at the 1952 meeting (which was not attended by Patton), nor did they ever do so, albeit they had three subsequent meetings with conversations that according to Woodbury (in a 2010 communication to us) were both wide-ranging and collegial (Fig. 7).

4.3.4. IC-recording in Dunedin after Eccles' departure—McIntyre undertook IC-recording experiments in presumably 1952 or 1953 and for several more years, albeit intermittently. This effort, using the same recording equipment used by Brock et al. (1951, 1952b), or its identical facsimile, first mistakenly inferred that Lloyd's concept of direct (reciprocal monosynaptic) inhibition was correct. The findings and the inference, either a mistaken albeit fully scientific interpretation, or one colored by McIntyre's loyalty to Lloyd's arguments, were reported in an abstract (Brock and McIntyre, 1953), which is nonetheless of historic importance. It provided the first description of the use of a double-barreled microelectrode (see below). Their arguments against the Brock et al. (1952b) position on direct inhibition were expanded upon in a brief commentary (McIntyre, 1954).¹⁹ These two abstracts must have later caused McIntyre considerable angst! He was on far

¹⁸Easton has recently written an interesting and valuable autobiography, which is available from him upon request (easton@bio.fsu.edu).

¹⁹McIntyre asserted on pp. 103–104 of his 1954 commentary that "A critical evaluation of the very interesting experiments of Brock, Coombs and Eccles (1952a) with intracellular recordings from motoneurons reveals that rather sweeping conclusions have been drawn

surer ground, however, in his later IC-recording work (e.g., Jack et al., 1959; McIntyre et al., 1956, 1959; McIntyre and Mark, 1960). It bears emphasis that McIntyre participated fully in at least his later IC-recording studies while in Dunedin (personal 2010 communication to D.G.S. from George Somjen (1929–); see Jack et al., 1959).

Others in McIntyre's Dunedin department also published IC-recording articles using the same original Coombs-built equipment that gradually became modified over the years (e.g., Bradley and Somjen, 1961). The overall IC-recording effort in Eccles' and McIntyre's former Dunedin department was somewhat sporadic, however, until John Hubbard [1930–1995], a distinguished Eccles-trained scientist and collaborator (see Anonymous, 1995), became the department's professor of neurophysiology (1972–1995). McIntyre, himself, undertook no further IC-recording during his productive headship at Monash University (1962–1974). Interestingly, he co-edited and contributed a chapter in the Curtis and McIntyre (1965) book that celebrated Eccles 1963 Nobel Prize award (see below). According to a 2003 personal communication from David Curtis [1927–] to D.G.S., McIntyre put much effort and enthusiasm into this book, which must have been much appreciated by Eccles.

It should be stressed that nothing stopped McIntyre becoming an early leader in the use of IC-recording in the mammalian SC. He had (1) the necessary equipment and his department's headship as early as 1952, (2) his own IC-recording expertise that we presume grew progressively throughout the 1950s, (3) Brock's valuable collaboration in 1952 and 1955–1957, (4) other IC-recording-capable faculty for collaboration (including Kenneth Bradley (1925–1986) and Somjen), and (5) as talented a group of students and trainees (including Jack and Mark) as had been available to Eccles in 1944–1951! The fact that he chose not to exploit these advantages therefore seems to have been his choice alone. His career from 1952 onwards was nonetheless stellar and he remains a highly respected figure in the field of neuroscience.

4.3.5. Significance of the Brock, Coombs, and Eccles 1951/52 contributions—

Prior to his IC work, Eccles expertise in mathematics found its major expression in his stout defense of electrical synaptic transmission in the CNS. After his abrupt rejection of this hypothesis in Brock et al. (1952b), his mathematical expertise was immediately put to good use in relating the classical reports of Hodgkin and Huxley to his initial IC-recordings of MN discharge, which began with Eccles (1952). Rall communicated to R.M.B. in 2005–2006 that “I remember his excited reporting to us when he returned to Dunedin after this meeting (*i.e.*, *the Cold Spring Harbor Symposium*). He was so impressed that he included much of H & H in the lectures he presented (and published) in Oxford, only a year later; he

from somewhat slender evidence, as far as transmission mechanisms in monosynaptic pathways are concerned ... an attempt to examine directly this aspect of soma membrane behavior was made last year by Dr. Brock and myself, using double internal micropipettes, stimulating across the membrane with one and recording by way of the other channel (Brock and McIntyre, 1953). Active responses to rectangular depolarizing current pulses were always seen, but none to hyperpolarizing pulses, even though the latter “inhibited” reflex discharge and antidromic invasion. In the light of these observations it therefore seems valid to say that hyperpolarization associated with monosynaptic central inhibition is not likely to be a post-synaptic response.” In a later review of masterly proportions McIntyre (1974) did indeed provide the evidence in support of the original interpretation of Brock et al. (1952a,b,c) but with no further reference to his mistaken 1953 and 1954 statements!

made use of prepublication access to the classical (*J. Physiol. (Lond.)*) H & H papers. It is clear that he actively associated himself with H & H” (p. 159 in Brownstone, 2006).

It seems likely that the Brock et al. (1951) abstract did not attract immediately much attention outside NZL, albeit it quickly became known to Woodbury and Patton in Seattle! By late 1952, however, it became of world-wide renown, particularly for its figure, which showed for the first time IC-recorded APs in the CNS. In contrast, the Brock et al. (1952b,c) articles were of immediate international impact. The 1952b article (submitted in late 1951) is now remembered best for it being the article in which Eccles rejected his electrical transmission hypothesis but it also was and remains an essential all-round article for any investigator, trainee or more advanced, who wishes to begin impaling MNs and measuring their PSPs, APs, and AHPs. Similarly, the 1952c article (submitted in presumably late April, 1952) provides a “PSP student” with the then impeccable thinking about EPSPs and IPSPs. This was the forerunner to the remarkable advances made in laboratories of Eccles and his international peers, who quickly adopted and then progressively improved upon his original IC-recording technique, as did he and his Canberra group.

4.3.6. Eccles’ “golden” 1952–1966 IC-recording period in Canberra, AUS—

Eccles’ “golden” 1952–1966 epoch at the ANU was highlighted by his award of a 1963 Nobel Prize shared with Hodgkin and Huxley. “During this time, 74 investigators from 20 different countries worked in the Department (Physiology, JCSMR) ... Of these 41 from 14 countries collaborated and published with Eccles. He later wrote about this period: ‘... Without doubt it was the high point of my research career scientifically speaking ...’” (p. 445 in Curtis and Andersen, 2001; see also p. 8 in Eccles, 1977). It remains remarkable how many of the Canberra visitors and local trainees and collaborators went on to make major contributions to the field of neuroscience (see Tables 4 and 8 in Stuart and Pierce, 2006). Eccles’ IC-recording contributions with his talented collaborators throughout this remarkable epoch have been summarized succinctly and effectively by Curtis and Andersen (2001a; their pp. 445–449). For the present purposes it is sufficient to point out that Eccles fully exploited the techniques he had acquired in NZL and extended upon them with the essential help of Coombs and his other talented collaborators. The IC work began in the SC²⁰ and then extended to the hippocampus (begun in about 1961) and cerebellum (begun in 1963). In all, Eccles published over 200 abstracts, refereed articles, book chapters, and books throughout his golden Canberra period. His research topics there included in their approximate chronological order (1) MN membrane biophysics of EPSPs and IPSPs using single and double barrel microelectrodes, (2) antidromic, orthodromic, and directly activated (by current injection) MN APs as related to their morphology, (3) synaptology and connectivity of the recurrent Renshaw cell circuit, (4) more accurate measurements of disynaptic MN IPSP pathways, including the location of the critical inhibitory INs (the

²⁰In 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, 1977). This statement, which is considered naïve by current SC neurobiologists, 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 SC 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).

precursor to later studies of other inhibitory INs of the SC, dorsal column nuclei, thalamus, hippocampus and cerebellum), (5) spinal synaptic connections of several types of muscle afferents, (6) extension of his NZL studies on chromatolysed MNs, (7) cells of origin of the ventral and dorsal spinocerebellar tracts (the precursor to later studies on the cerebellar cortex) (8) the relation between MN AHP duration and the activation time of its MU, (9) effects of nerve-cross union on muscle activation properties, (10) mechanisms and organization of presynaptic inhibition, and (11) the supraspinal studies mentioned above. In our opinion, it took a scientist of remarkable discipline and drive to stay “on target,” and contribute so many seminal findings in this 14-year epoch, during which Eccles also made substantial service contributions to Australian neuroscience and the well-being of his newly formed university.²¹

4.3.7. Eccles IC-recording work in Chicago, IL, USA (1966–68) and Buffalo, NY, USA (1968–75)—While Eccles was quite vocal about his unpleasant 2-year experience at the Institution of Biomedical Research of the American Medical Association in Chicago (see p. 15 in Eccles, 1977), Stuart and Pierce (2006) have nonetheless pointed out several of its successes. Eccles continued to advance the IC-recording based circuitry of the cerebellum, co-wrote books on this and other topics, and interacted with the 19 scientists from 6 countries who were attracted to his unit. He also contributed to the re-establishment of Chicago as a neuroscience research center, particularly by his interactions with colleagues at Loyola University and the Universities of Chicago and Illinois-Chicago Circle.

In sharp contrast to Chicago, Eccles’ final phase as an experimental scientist was much happier and more prolonged in the Department of Physiology, State University of New York, Buffalo up to the age of his compulsory retirement at 72 years. His laboratory group, including himself, involved 30 scientists from 11 counties (see Table 6 in Stuart and Pierce, 2006). Between 1969 and 1976 the group published 51 articles in refereed journals, 45 invited book chapters and reviews, a symposium volume and a book. Eccles IC-recording contributions in this epoch focused largely on the cerebellum, but concluded in his last three articles with a revisit to the hippocampus. His other articles addressed philosophical aspects of brain function.

4.3.8. Eccles’ final efforts and interactions in Contra, CHE (1976–1997)—Eccles continued to work in retirement in Contra, CHE up to the age of 91 years when ill-health overtook him. His output continued to be prolific: “... approximately 30 articles in refereed journals, 90 invited articles, book chapters, and reviews, 3 (co-edited) symposium volumes, and 5 books (3 with coauthors)” (p. 148 in Stuart and Pierce, 2006). Few of the refereed articles addressed IC-recording so we conclude this section by emphasizing that Eccles

²¹Eccles was fully aware of the advantages that accrued to his Canberra achievements by the largesse of the Australian federal government. He reflected that “... A remarkable feature of the Australian National University was its international orientation. No preference was given to Australians, and there were unrivaled facilities for overseas scholars. For example, if appointed to a research fellowship, the travel to Australia of the scholar plus wife and children was fully paid and his emoluments dated from the time of departure. The emolument and the scholarship was about twice that for basic living and housing costs in Canberra, and furnished houses were provided for scholars with children. Married and single scholars lived in University House. There were no university or degree fees (*i.e., if pursuing a PhD*), and the return journey was also fully paid. The more senior staff had fellowships at appropriate levels, again with all travel costs paid and housing provided. These generous arrangements explain why there was such an international complex in this remote Australian university” (p. 9 in Eccles, 1977).

remained an interactive internationalist until the end. For this final epoch, he had 17 collaborators from 7 countries (see Table 7 in Stuart and Pierce, 2006)!

4.4. Summary reflections on the Brock, Coombs, and Eccles collaboration

It is still considered remarkable by many in N. America and Europe that as influential and initially difficult a technique as IC-recording in the CNS was co-pioneered in the Antipodes and at an institution which at the time was so far from the world's leading research centers, and not considered at that time a center for research, in general, let alone neuroscience research, in particular. Two points should counter this impression. First, since the mid-to-late 19th C British "colonies" such as AUS, NZL, ZAF, and to a lesser extent CAN, had long supplied GBR with very talented post baccalaureate students who, after advanced training in the "motherland," developed into internationally recognized scientists and academic clinicians who remained largely in GBR to advance that country's scientific armamentarium. There simply were no positions for them in their respective native lands. Sherrington, for example, profited greatly from this influx. The practice began to abate after WWII but it was still evident in AUS and NZL up to the early 1960s. Second, Eccles, himself optimally trained and primed for later IC-recording success at Oxford, was a master spotter of research talent throughout his career as an experimental scientist and research mentor. In NZL he had excellent trainees and collaborators throughout his 8-year tenure.

The situation in NZL is very different today. For example, the University of Otago, which had begun in 1869, is now a full-fledged research university and certainly on par with those in N. America and Europe. Many of our NZL colleagues have emphasized to us that the pioneering Brock et al. (1951, 1952b,c) articles and Eccles' 1963 Nobel Prize helped substantially in this development.

5. MN and IN IC-recording achievements in selected countries after 1951/1952

After 1952, many laboratories began to report their own progress with IC-recording in the CNS and up to at least 1970 they cited at least one of the 1951/1952 reports of our protagonists. Several such groups were already expert in IC-recording from other structures and tissues, like peripheral axons and striated muscle. To emphasize the international nature of this effort Table 1 shows the first such report on vertebrate neurons from several countries. A review of IC-recording work in invertebrates, which also began in the early 1950s, is considered beyond the scope of this article.²²

²²The pioneers of full-length reports on IC recording in invertebrate MNs were Hagiwara and Watanabe (1956) for cells controlling the production of sound in *Cicada*. Work on invertebrate MNs supplying larger movement-producing stomach striated muscles was reported several years later by Takeda and Kennedy (1964) for the crayfish, *Procambarus clarkii* Girard. Studies on invertebrate INs with short latency connections to MNs supplying striated musculature of the stomach was reported near simultaneously for the abdominal ganglion by Tauc (1955a) using *Aplysia depilans* and Arvanitaki et al. (1956) using *Aplysia faciata*. At that time, Tauc also reported dual IC microelectrode recording in the pedio-visceral ganglion of the snail, *Helix pomatia* (Tauc, 1955b). Tauc's first abstract on IC-recording was for the RP of a vertebrate, the electroplaques of the ray fish, *Torpedo marmorata* (Fessard and Tauc, 1951; see also Albe-Fessard and Buser, 1952). Tauc (1952) then had an abstract on the RP and AP of crayfish abdominal neurons, which were probably but not proven to be MNs. In most of the above reports, there was reference to at least one of the Brock et al. 1951, 1952a,b,c or a later IC-recording report from the Eccles' group. For other early IC-recording work on invertebrate neurons, see Hagiwara and Bullock (1957).

Table 1A shows the first IC-recording report in 5 countries, be it an abstract or a short or full-length article, and irrespective of cell type. The first such effort, which was actually in 1952, was an abstract from a very prominent Cambridge, GBR group (Alanis and Matthews, 1952). It described IC recording in frog spinal INs of responses to muscle stretch. Puzzlingly, this report did not include a figure and it was not followed by a full length article so its short and long-range impact was presumably nearly insignificant.

As could be expected, Eccles' laboratory was immediately on the forefront and his first Canberra report described in a short article the use of double-barreled microelectrodes to test for the mechanism underlying MN IPSPs (Coombs et al., 1953). A complete rig for IC recording remained in Eccles' former NZL department when he left NZL and took up residence in Canberra, AUS. As explained above, Brock and McIntyre (1953) used this equipment in an IC study that also tested for this IPSP mechanism. Their abstract was the first to claim success in using double-barreled microelectrodes but they provided no figure and no following full-length report, such that this work has rarely been cited.²³

Another early aborted study was that of Pierre Buser [1921–] and Denise Albe Fessard [1916–2003] (1953; see also Albe-Fessard and Buser, 1953). After a promising beginning with IC recording from neurons in *Torpedo marmorata* (Albe-Fessard and Buser, 1952), these investigators were the first to record from cortical cells in a mammalian species. They were not satisfied with the quality of their initial IC recordings so they aborted their collaborative IC work on the cat cerebral cortex following Albe-Fessard and Buser (1955) (personal communication from Buser to François Clarac in 2010). In retrospect this was a great pity, albeit high-quality IC recording from other cortical cells appeared shortly afterwards (Phillips, 1955; Tasaki et al., 1954).

On the other hand, the 1953 report of Tatsunosuke Araki [1926–2001] and Takuzo Otani [1905–1962] and a colleague on IC-recording from spinal MNs and INs in the toad had significant short and long range impact (see below). Their work spawned a long sequence of high quality Japanese studies of CNS neurons in first non-mammalian vertebrates and then mammalian and invertebrate neurons, as well. Araki, who worked with Eccles in Canberra in 1959–1960 (see Stuart and Pierce, 2006) had much to do with the quality of Japanese cellular neuroscience in the post WWII era.

5.1. Mammalian spinal neurons

5.1.1. Mammalian MNs: 1953–1967—Table 1B shows the predominance of Eccles' Canberra group, beginning with Coombs et al. (1953), in the study of mammalian spinal MNs (see above and also Eccles et al., 1953). By 1955 the NIH (Bethesda, MA, USA)

²³Julian Jack informed us in 2010 that the double-barreled microelectrode was McIntyre's idea, and he prevailed on Brock to make them. Their abstract appeared in May, 1953. Shortly thereafter (August) the short Coombs et al. (1953) study was published. It included work undertaken with double-barreled microelectrodes, which were made in Eccles' new Canberra unit by the British biophysicist, Fatt (personal communication in 2006 from David Curtis to R.M.B.). Fatt was a visiting faculty member and a former student of Katz, with whom he wrote 12 articles between 1950 and 1953. The Coombs et al. (1953) article did not cite the preceding abstract of Brock and McIntyre. When the full length account of the former work appeared (Coombs et al., 1955), a figure of the double-barreled microelectrode was included along with the intimation that the authors had “devised” their construction, themselves. This article did cite Brock and McIntyre (1953), however, but only for two of their results and not for their being the first to use double-barreled microelectrodes.

laboratory of Karl Frank [1916–1993] began to also emerge as a center for IC recording in the mammalian CNS.²⁴ Frank learned to make microelectrodes from Ling (Brownstone, 2006) and his first cathode follower was built as described by Woodbury (1953). His first IC-recording report in 1955 with Michelangelo Fuortes [1917–77] addressed the nuances of recording from spinal MNs and INs in the cat. This was followed by a series of high quality refereed articles including seminal work on presynaptic inhibition, beginning with Frank and Fuortes (1957) and then Frank (1959). He also wrote several reviews of help to those embarking on IC recording in the CNS (e.g., Frank, 1960; Frank and Fuortes, 1961). Frank's IC-recording achievements culminated in a remarkable sequence of five consecutive 1967 articles in the *Journal of Neurophysiology* (see in their chronological sequence Smith et al., 1967; Nelson and Frank, 1967; Burke, 1967; Rall, 1967; Rall et al., 1967). This sequence, which included major collaborative and independent contributions from Rall, Robert Burke [1934–] and Phillip Nelson [1931–], contributed to and summarized virtually all that was known about the cellular properties of mammalian MNs to that point. Importantly, it also brought Rall's cable theory to the forefront of motoneuron neurobiology. By 1967, many other groups were also advancing rapidly the understanding of MN neurobiology (for review of such work and that advancing into the 1970s, see Burke and Rudomin, 1977 and Burke, 1981).

In addition to the above developments, it is important to emphasize work on the repetitive firing properties of MNs. This focus was pioneered by Kolmodin and Skoglund (1958). They studied repetitive AP discharge in cat spinal MNs (and INs, albeit to lesser extent) in response to muscle stretch brought on by various limb movements. This work led to intense investigation by Ragnar Granit [1900–1991], Daniel Kernell [1935–] and colleagues into the repetitive firing properties of motoneurons, studied largely through intracellular current injection and defining the stimulus current–spike frequency (I–f) relation (Granit et al., 1963; Kernell, 1965b). The I–f relation is used today throughout the nervous system to describe the input–output “gain” of neurons (e.g., motoneurons (Lee et al., 2003) and pre-frontal pyramidal neurons (Thurley et al., 2008)). Kernell and colleagues also studied how this current interacted with synaptic current provided by either afferent or descending pathway stimulation (Granit et al., 1966a,b; Kernell, 1965a). At about the same time, Alexander Shapovalov [1932–1983] in Leningrad, SUN was doing remarkable work

²⁴The following biosketch was kindly provided to us by Robert Burke (*see the text*): “Karl Frank was a world-renowned neurophysiologist and biophysicist who spent most of his scientific career at the National Institute of Neurological Disorders and Stroke (NINDS). “Kay”, as he was universally known, joined what was then called the National Institute of Neurological Diseases and Blindness (NINDB) in 1951 to become Chief of the Spinal Cord Section. Here he set up the first laboratory in the United States to do intracellular recording in the SC; the only other one in the world was John Eccles' lab in Canberra, Australia. After a decade of pioneering work on the biophysics of spinal motoneurons with his great friend M. G. F (Mike) Fuortes (*see the text*), and developing methods for intracellular recording that became standard around the world, Kay was persuaded to become the acting Associate Director for intramural research of the NINDS. He acted in this capacity until 1967, when he stepped down to become the first Chief of the new Laboratory of Neural Control (LNLC). Kay viewed LNLC as a center for pursuing his long-time dream of using basic knowledge of the central nervous system to develop applied approaches to improve the quality of life for neurologically handicapped people. Under his leadership, LNLC became a major world center for research on bioengineering and neuroprostheses. Kay left the NINDS Intramural Research Program in 1975 to become the first Director of the Fundamental Neurosciences Program in the NINDS (“S” for “Stroke”) Extramural Program. He retired from the NIH in 1978 and died in 1993 at the age of 76. During his 27 years at the NIH, Kay trained a long string of postdoctoral fellows and was a major force for improving graduate education in neurophysiology and biophysics. He was a founding editor of the journal “Experimental Neurology,” which he envisioned as a forum for papers on the interface between basic science and clinical application. He was also instrumental in the formation of the Society for Neuroscience, which grew in part out of Kay's informal “Neurophysiology Club” which held its meeting at the annual FASEB meeting in Atlantic City in the 1950s and 1960s. Today, Kay is known as much for his efforts to foster the development of what has become known as “neuroscience” and “neuroprosthetics,” as for his pioneering basic research.”

outlining the mechanisms of activating repetitive firing in motoneurons via synaptic current (Shapovalov, 1972; Shapovalov et al., 1966), as were Peter Schwindt [1940–] and William Calvin [1939–] in the USA (Schwindt and Calvin, 1973). This work was a key precedent to work that began to appear in the 1970s on MN discharge during fictive locomotion in the cat (see, e.g., the reviews of Grillner, 1975, Orlovsky and Shik, 1976; Shik and Orlovsky, 1976; Wetzel and Stuart, 1976). This led to the finding that the I–f relations of MNs change during locomotion as a result of AHP modulation (Brownstone et al., 1992; Miles et al., 2005), resulting in a task-dependent change in MN gain (Zagoraïou et al., 2009).

5.1.2. Mammalian INs: 1954–1963—Table 1C begins with the Eccles et al. (1954) article on Renshaw cell discharge and circuitry. This article is quoted widely for well deserved reasons but the quality of the recordings was far from optimal. Indeed it was not until Eccles et al. (1960) that his Canberra group presented spinal IN IC recordings of as high quality as those reported originally by Woodbury and Patton (1952b), Frank and Fuortes (1955), and Kolmodin (1957). The latter had an earlier very brief report (Kolmodin and Skoglund, 1954) with a substantial number of INs (~200) but included no figure. In Kolmodin's PhD thesis, however, high quality recordings were presented including repetitive discharge in response to limb movements (Kolmodin, 1957).

Another set of studies, together with several reviews, featuring high quality IC IN recordings came from the Kiev laboratory of Platon Kostyuk [1924–]. One review followed a presentation D.G.S. was privileged to hear in Villahermosa, MEX over 48 years ago (Kostyuk and Timchenko, 1963). Building on Kostyuk's substantial work, there has been steady and substantial progress on the IC-recorded synaptic responses of mammalian spinal INs in in vivo preparations to input from a wide variety of sensory, propriospinal, and descending sources, with Elzbieta Jankowska [1930–] on the forefront of this research (e.g., Jankowska, 2008). In sharp contrast, there is still very little information in such preparations on the repetitive discharge of spinal INs for reasons that were discussed above (recall also Footnote 6).

5.2. Non-mammalian spinal neurons

In retrospect, and in sharp contrast to invertebrate developments (recall Footnote 23) there was slow progress in the 1950s and 1960s in IC-recording from spinal MNs and INs in non-mammalian vertebrates. At that time there was a flood of highly competent Japanese neuroscientists working in Europe and particularly in N. America such that the Japanese Journal of Physiology was read widely and with great interest (Kato, 1964). For this reason it puzzles us that the Araki et al. (1953) article in this journal did not lead to more work on toad spinal neurons in other countries.

5.2.1. Non-mammalian MNs: 1953–1973—While more original work on toad MNs emanated from Japan after 1953 (e.g., Araki and Otani, 1955; Kuno, 1957), Table 1D shows that the only truly other innovative non-mammalian work to emerge from other countries between 1953 and the late 1960s was in GBR, beginning with the Katz and Miledi (1963) report on miniature EPSPs. The situation changed rapidly in the 1970s, however (see below).

5.2.2. Non-mammalian INs: 1953–1985—Progress on non-mammalian vertebrate spinal preparations was even slower for INs than MNs except for the above-emphasized Japanese work. In our opinion, the two outstanding developments in Table 1E after Araki et al. (1953) were the reports of Rovainen (1967) on lamprey INs and Soffe et al. (1984) on spinal INs of the frog embryo. Mention should also be made of the 1973–85 publications of Shapovalov, who provided high quality recordings (often combined with cell morphology) and reasoning about lamprey, goldfish, and frog MNs and INs. These developments were associated with a flood of valuable work from the early 1970s onwards, as investigators recognized the value of lamprey, turtle and frog embryo preparations for the study of central pattern generation in the vertebrate SC. This emphasis is on the role of spinal INs in generating rhythmic MN discharge during aquatic, aerial, and terrestrial locomotion (for review, see Delcomyn, 1980; Orlovsky et al., 1999, Stuart, 2007, Grillner and Jessell, 2009).

One interesting article was that of Saadé et al. (1972). Antidromic stimulation of a ventral root in the frog was claimed to activate unidentified spinal INs, albeit at very high stimulus strengths (see, in particular, their Fig. 5). Given the shapes of the action potentials illustrated, it is not clear whether the authors appreciated when their recordings were intracellular. No mention was made of Renshaw cells or Renshaw-like INs, which were certainly known at that time (see above) and are now known to exist in other species such as the chick (Wenner and O'Donovan, 1999). It is also known now that motor axon collaterals exist in the frog (Chmykhova et al., 2005; Chmykhova and Babalian, 1993). Perhaps the IN results of Saadé et al. (1972), which were described vaguely to say the least, should not be taken on their face value but their work is nonetheless of historic interest.

5.3. Summary

When reflecting on Table 1, we find it remarkable that all of the reports written between 1952 and 1970 cited at least one of the 1951/1952 reports of Brock et al. or another article from Eccles' Canberra group. By 1970 they had written far more articles, of course, but the field as a whole seems to have continued to recognize the significance of the initial NZL IC recording work in the mammalian CNS. Among mammalian workers, this was also the case for the 1952/1953 Woodbury and Patton abstracts and article, but to far less extent in the non-mammalian literature. The initial invertebrate developments in the 1950s and 1960s, which are not covered here, also paid substantial homage to the 1951/1952 NZL work.

6. Further developments in the use of IC-recording techniques

In this final section we reflect quite idiosyncratically on highly selected IC-recording advances, focusing largely on their introduction. The focus is on MNs and INs of the mammalian lumbosacral SC, with advances limited to those that can be considered as having more-or-less direct precedents in 1951/1952 reports of the Eccles' team in NZL and the 1952/1953 reports of Woodbury and Patton in the USA.

We do not present advances in electronic and computer technology for data collection and analysis, which are considered beyond the scope of this article. Similarly, the application of molecular genetics to spinal MN and IN neurobiology is addressed in the following article (Brownstone and Stuart, 2011).

6.1. Stimulation and recording with sharp microelectrodes

6.1.1. Double-barrel microelectrodes—As mentioned above the first such report was that of Brock and McIntyre (1953), which lacked a figure and a follow-up full length report. For this reason it is not surprising that credit for originality has near universally been attributed to Coombs et al. (1955). An historical account of the application of this technique to study the inhibitory glycine receptor is provided in Callister and Graham (2010).

6.1.2. Single microelectrode for stimulation and recording—It was clear to Eccles' and others' groups that based on the work of Hodgkin and Huxley, the ability to deliver current through the recording microelectrode in the CNS would provide significant advantages. In 1955 Araki and Otani developed a Wheatstone bridge circuit with which they could pass current through the recording microelectrode (Araki and Otani, 1955). Independently, in Eccles' group, Curtis and Coombs developed a similar circuit (Coombs et al., 1959; see also Brownstone, 2006).

6.1.3. Microelectrophoresis—This technique involves the recording of neuronal activity during and after application of drugs directly into their immediate extracellular environment (for review see Curtis, 1964; Phillis, 1970). Microelectrophoresis continues to play a critical role in determining the transmitters and their antagonists in synaptic transmission at sites on spinal MNs and INs. Its lineage involves (1) 2 microelectrodes (1 EC, 1 IC) for single frog muscle fibers (Nastuk, 1951), (2) a double-barrel micro-electrode (1 EC or IC, the other IC) for the frog neuromuscular junction (del Castillo and Katz, 1957), (3) multibarrel micro-electrodes (all EC) for Renshaw cells in the cat SC (Curtis and R.M. Eccles, 1958), and (4), double-barrel microelectrodes (1 EC, 1 IC) for MNs in the same preparation (Curtis et al., 1959).

6.1.4. Spike-triggered averaging—In order to determine whether a particular recorded afferent fiber formed a functional synapse on the recorded MN, Henneman and Mendell (1968) introduced a form of cross-correlation later termed “spike-triggered averaging” (STA, a term coined by Watt et al., 1976). This involved averaging many sweeps of the intracellular recording triggered from the spike of the afferent fiber. From this average, a PSP waveform emerges which is attributable to the “in-continuity” afferent fiber. This method was soon used widely in the CNS and peripheral neuromuscular system of animals and humans (Fetz et al., 1979; Stein and Yang, 1990). For example, STA, together with various variations of the technique (e.g., Lüscher et al., 1980) led to substantial advances in the understanding of the location, density, and distribution of the terminals of single spindle Ia afferents on MNs (Henneman and Mendell, 1981), the spinal connections of other afferent types (e.g., Kirkwood and Sears (1974)), and the connections of INs with MNs (Butt and Kiehn, 2003; Jankowska, 2008). There are still many open issues concerning the spinal connections of muscle and other sensory afferents, an area in which seminal research was undertaken in Eccles' Canberra laboratory (see above) and Lundberg's Göteborg, SWE group (see Baldissera et al., 1981). It is likely that the STA technique will continue to contribute to our understanding of these and other connections.

6.1.5. Single electrode voltage clamp and discontinuous current clamp—

Following the advent of the voltage clamp technique as applied to the giant squid axon (Cole, 1949; Hodgkin et al., 1952; Marmont, 1949) there was considerable interest in whether a voltage clamp could be used in the CNS. This was probably first achieved in *Aplysia* neurons by Fessard and Tauc (1956) using two IC microelectrodes, one of which clamped the cell soma. The same technique was first applied to cat SC MNs by Frank et al. (1959) and used thereafter by several investigators. The single electrode voltage clamp was later described (Merickel, 1980) and used initially in invertebrates (Merickel and Gray, 1980). The laboratory of Stephen Redman [1938–] refined the electrodes (Finkel and Redman, 1983; Redman, 1976) and then the amplifier (Finkel and Redman, 1984), demonstrating its use in spinal MNs. This led to the “discontinuous current clamp,” a technique proved very useful in further study of spinal MNs (Brownstone et al., 1994). In addition, a functional voltage clamp of cat SC MNs was reported by Heckman and Binder (1988), which provided the means to “... measure the total amount of current from a synaptic input system that reaches the soma of a MN under steady state conditions ...” (p. 1946). The authors termed this the “effective” synaptic current because “... only that fraction of the current that actually reaches the soma and initial segment of the cell affects its recruitment threshold and firing frequency” (p. 1946; see also Binder et al., 1996 and Powers and Binder, 2001). Today, voltage clamp techniques are used much more frequently in vitro than in vivo SC preparations (see below).

6.2. Patch clamp recording

Erwin Neher [1944–] and Bert Sakmann [1942–] developed the patch clamp technique to first study ion channel currents at the neuromuscular junction (Neher and Sakmann, 1976). They received a 1991 Nobel Prize for this achievement and its further development (Hamill et al., 1981) to study single ion channel properties in neuronal and muscle membranes. The technique was soon applied to in vitro slices of various CNS regions including the SC (Sakmann et al., 1983; see also Edwards et al., 1989, and 6.4 below). It was also used in vivo to measure small fluctuations in membrane potential in the visual cortex of the cat (Jagadeesh et al., 1993). A technical account of the application of patch clamp recording in in vivo preparations was provided in Margrie et al. (2002). Sharp vs. patch electrode recordings were compared head-to-head in the *Xenopus* SC by Li et al. (2004), who demonstrated similarity in neuronal properties despite a significant leak current introduced by sharp electrodes. Today, patch clamp techniques in the SC are used primarily in vitro (see below), although recent work has demonstrated its utility in the in vivo study of dorsal interneurons involved in pain processing (Graham et al., 2004, 2007c).

6.3. IC-recording in unanaesthetized animal preparations –fictive locomotion

The seminal 1951–1953 IC-recording work of the Eccles’ team and Woodbury and Patton was undertaken on deeply anesthetized, surgically reduced cat preparations whose spinal MNs and INs behaved essentially passively. There have been innumerable further developments, a key goal being to record from MNs and INs when they are active for the elaboration of a particular movement. Some such preparations are described below.

To ensure stable recording conditions, IC-recording from active MNs and INs requires that the movements produced be fictive: i.e., abolished by a paralyzing agent. Mammalian preparations were first on the forefront, with a focus on fictive locomotion, including spinal preparations that were chemo-activated, and decerebrate preparations in which the fictive movement was elicited by brainstem stimulation (see Jordan et al. (1979) and Jordan (1983) for the initial post-1960 history of such work).

Three notable principles resulted from these IC-recording experiments, with the laboratory of Hans Hultborn [1943–] playing a critical role. The first was that MN dendrites do not behave passively, and thus contribute to plateau potentials, input amplification, and thus neuronal integration (Bui et al., 2008; Heckman et al., 2005; Hultborn et al., 2003). The second principle was the concept that spinal reflexes are modulatable, with a given sensory input having “... either an excitatory or inhibitory effect on a given MN as dependent on a CNS selection process related to the phase and intent of the movement” (p. 250 in Stuart 2002; see also Hultborn, 2001 and McCrea, 2001). The third advance was that significant knowledge about the principles of organization of spinal networks effecting rhythmic motor activity were gleaned through IC-recording of spinal neuron activity in fictive locomotion preparations (e.g., Edgerton et al., 1976; Grillner, 1981; Orlovsky et al., 1999; Rossignol, 1996; Shefchyk and Jordan, 1985). It seems likely that such latter work will continue to advance understanding of spinal pattern generators for the foreseeable future (e.g., Frigon and Gossard, 2010).

6.4. IC-recording in in vitro SC preparations

Otsuka and Konishi (1974) were the first to develop a viable, isolated, in vitro neonatal rat SC preparation for a more precise control of the concentrations of ions and drugs than could be achieved in in vivo preparations. Their preparation permitted, however, only extracellular ventral root recording of mono-synaptic and polysynaptic reflexes. Bagust and Kerkut (1979) and Hernandez et al. (1991) used the isolated mouse and hamster SC to study motor activity, although these preparations were not used to study IC activity (Bagust et al., 1982). Arasaki et al. (1984) studied MNs using IC recording techniques in the isolated immature rat SC, and Smith et al. (1988) studied phrenic MN activity in the isolated rat cord. McDonagh et al. (1999) reviewed the development of such in vitro SC mammalian preparations up to 1999. By then, such recordings and preparations were contributing important information on both MN and IN activity during spinal pattern generation in non-mammalian isolated SC preparations, particularly those for the lamprey, frog, toad, and turtle (Grillner et al., 2008; Orlovsky et al., 1999). One such non-mammalian model, yet to be fully exploited, is an isolated cervical segment of the mudpuppy's SC with an attached forelimb. This preparation, with 5 cervical segments, was used to note the IC-recorded responses of both MNs and INs during chemo-activated forelimb locomotion (Wheatley and Stein, 1992). In a 2-cervical-segment model, 4 classes of IN were identified (Wheatley et al., 1994). Intriguingly, a similar neonatal rat model has recently been developed consisting of the isolated lumbosacral cord and both hindlimbs (Hayes et al., 2009).

Following the advent of IC-recording with sharp micro-electrodes in slices of mammalian guinea-pig hippocampus (Yamamoto, 1972), there was a flurry of effort to make such

recordings in slices of SC. The history of IC-recording in slices of mammalian SC has been reviewed by McDonagh et al. (1999). The first such recordings were made in non-mammalian SC slices of the adult frog (Barrett and Barrett, 1976). Jorn Hounsgaard [1948-] chose to work on turtle slices because this animal's low metabolic rate and resistance to anoxia "... allow viable cross-sections of the spinal cord to be thick enough to include motoneurons with undamaged dendritic trees" (Hounsgaard et al., 1988). In a sequence of articles exploiting IC recording from MNs in turtle SC slices and other in vitro turtle SC models, Hounsgaard and his colleagues continue to contribute to the current understanding of not only the ion channels contributing to MN behavior under passive and active conditions, but also the contributions of such cellular properties to the elaboration of movement by vertebrates (see, e.g., Berg and Hounsgaard, 2009)).

An important advance in the study of spinal neurons using patch clamp recording in vitro was that of infra-red differential interference contrast video microscopy (Dodt and Zieglgänsberger, 1990) and other contrast techniques, which have enabled the visualization of the neurons to be patched. In the SC, an early success was that of Takahashi and Momiyama (1991), who used slices from neonatal rats in which they undertook patch clamp recording in dorsal horn neurons. Next, Takahashi (1992) applied this technique to MNs in thin, 120 μm -thick slices from neonatal (P3-5) rats. Such techniques have now been used, for example, to advance the study of lumbosacral dorsal horn INs implicated in pain perception (e.g., Graham et al., 2007a,b), and MNs involved in the control of breathing and other respiratory-related movements (e.g., Garcia-Campany et al., 2010; Reklings et al., 1996). In addition, these techniques have been used to study MN physiology (e.g., Miles et al., 2005), INs involved in rhythmic activity (e.g., Butt and Kiehn, 2003; Dai and Jordan, 2010; Wilson et al., 2005; Zagoraiou et al., 2009; Zhang et al. 2008), and sympathetic preganglionic neurons (Zimmerman and Hochman, 2010). The use of voltage clamp recordings in these preparations has led to increased understanding of the complexity of MN dendrites in neuronal integration (Carlin et al., 2000, 2009).

One major limitation in the investigation of spinal MN properties is the difficulty in recording from these cells in slices from animals much older than P15 (Thurbon et al., 1998). This likely results from the vulnerability of MNs to hypoxic/ischemic conditions during slice preparation (MNs are large and metabolically very active). To date, it has been possible to record from adult brainstem MNs, such as those in the hypoglossal nucleus (Haddad et al., 1990). Accordingly, these cells have become a prototypical adult MN for studying the in vitro properties of MNs (see, e.g., Graham et al., 2006). Recent progress has also been made in recording from adult mouse spinal MNs in slice preparations (Mitra and Brownstone, unpublished).

6.5. Cell staining and histological reconstruction

Since the onset of IC recording in cat lumbosacral SC MNs and the early theoretical work of Rall (1955) it was obvious that much was to be gained by combining such recording with staining the test cell and reconstructing the morphology of its soma and dendritic arborization. Stretton and Kravitz (1968) reviewed the initial developments (1967–1968) for invertebrate neurons. For vertebrate neurons, the initial focus was on cat lumbosacral MNs

and INs. The initial reports, in their chronological order, were by Globus et al. (1968), using tritiated glycine staining of MNs, and two studies using Procion dyes to stain MNs (Barrett and Graubard, 1970) and ventral spinocerebellar tract INs (Jankowska and Lindström, 1970). Subsequent studies involved the use of staining agents that enabled a fuller resolution of the dendritic tree: first, horse-radish peroxidase (introduced by Kristensson and Olsson, 1971); then biocytin (Horikawa and Armstrong, 1988); and finally, fluorescent proteins with the advent of molecular genetics (see Brownstone and Stuart, 2011).

6.6. A summary reflection on the above advances

It is well known to many of his former collaborators and trainees that Eccles kept up with advances in the field of motoneuron neurobiology throughout his lifetime, as well as many other developments in neuroscientific enquiry. For example, at the age of 87 years he reviewed with much insight and detailed knowledge the field of synaptic transmission (Eccles, 1990). One year earlier, he waxed enthusiastically and at length to D.G.S. on the then-current state of the play in MN neurobiology. Similarly in his emails to us and extensive discussions with D.G.S., Woodbury has revealed his enduring interest and deep knowledge about the physiology and biophysics of MNs and other excitable cells. The abilities that these pioneering “giants” displayed in their initial IC-recording work endured in their later endeavors and insights and are an inspiration to all who have stood on their shoulders!²⁵

7. Concluding thoughts

There are very few modern-day laboratories in which MN and IN neurobiology experiments using electrophysiology involve the all-night sessions on surgically-reduced whole animal (largely cat) preparations that were required in the pioneering IC-recording work of Eccles’ team and Woodbury and Patton, and which persisted in many laboratories throughout at least the next four decades. In current work on MNs and INs, however, the relevant literature is much more extensive and demanding, particularly with its emphasis on molecular genetics. As a result, to be successful present-day workers must have a level of motivation and experimental talent as high as that of the five subjects of this review. Their innovative findings and adventuresome, even fun-loving, approach to experimental research should continue to inspire those who are attracted to this field.

Acknowledgments

Some of the above was presented by D.G.S. in collaboration with R.M.B. in an historical session at a meeting of the International Motoneuron Society, “Towards translational research in motoneurons,” Paris, FRA, July 91–3, 2010 (Organizers: CJ Heckman, Didier Orsal, Jean-François Perrier, Daniel Zytnicki). For the preparation of our article we thank: Marjorie Anderson and Marc Binder (and their helpful staff at the University of Washington), Robert Burke, Patricia Cragg (and her similarly capable and cooperative University of Otago staff), David Curtis, the late John Eccles, Dexter Easton, Eric Frank, Jay Goldberg, Julian Jack, the late Anders Lundberg, Wilfrid Rall, George Somjen, and Walter Woodbury, in particular, for providing some historical details; Nga Nguyen (Arizona Health Sciences Library, University of Arizona) for her library research; and Wulfila Groneneberg for helping D.G.S. with

²⁵Recognition in various fields that its participants “stand on the shoulders of giants” is often attributed to a 1676 communication between Isaac Newton and his physics rival, Robert Hooke. John of Salisbury expressed this laudation much earlier, however, in “Metalogicon” (1159; in Latin). We would argue that given the nature of the human experience, the expression probably appeared in antiquity, and it certainly is appropriate for the five scientists focused upon in this article.

several translations from German into English. We also thank Jean-Gaël Barbara, Robert Callister, Tuan Bui, and Walter Woodbury for their helpful comments on various drafts of our article.

Abbreviations

AP	action potential
AHP	afterhyperpolarization
CNS	central nervous system
CPG	central pattern generator
EPSP	excitatory PSP
EC	extracellular
Ext	extensor
Fl	flexor
IN	interneuron
IC	intracellular
IPSP	inhibitory PSP
MN	motoneuron
PSP	postsynaptic potential
SC	spinal cord

References

- Alanis J, Matthews BHC. The mechano-receptor properties of central neurons. *J Physiol (Lond)*. 1952; 117:59P–60P.
- Albe-Fessard D, Buser P. Réception intracellulaire de l'activité d'un neurone des lobes électriques de *Torpedo marmorata* (Intracellular recording of the activity of a neuron in the electric lobes of *Torpedo marmorata*). *CR Acad Sci Paris*. 1952; 235:1688–1690. [PubMed: 13033294]
- Albe-Fessard D, Buser P. L'exploration de certaines activités du cortex moteur du Chat par microélectrodes; dérivations endosomatiques (Study with microelectrodes of selected activities of the cat motor cortex; endosomatic recordings). *J Physiol (Paris)*. 1953; 45:14–16. [PubMed: 13062117]
- Albe-Fessard D, Buser P. Intracellular activities collected in the sigmoid cortex of the cat; participation of the pyramidal neurons in the somesthetic evoked potential. *J Physiol (Paris)*. 1955; 47:67–69. [PubMed: 13243256]
- Alstermark B, Hultborn H, Jankowska E, Pettersson LG. Anders Lundberg (1920–2009). *Exp Brain Res*. 2010; 20:209–214.
- Andersen P, Lundberg A, John C. Eccles (1903–1997). *Trends Neurosci*. 1997; 20:324–325. [PubMed: 9289898]
- John Ingram Hubbard. Otago Med Sch Alumnus Assoc Newsl. 1995; 20:15.
- Araki T, Otani T. Response of single motoneurons to direct stimulation in toad's spinal cord. *J Neurophysiol*. 1955; 18:472–485. [PubMed: 13252436]

- Araki T, Otani T, Furukawa T. The electrical activities of single motoneurons in toad's spinal cord, recorded with intracellular electrodes. *Jpn J Physiol.* 1953; 3:254–267. [PubMed: 13232850]
- Arasaki K, Kudo N, Nakanishi T. Firing of spinal motoneurons due to electrical interaction in the rat: an in vitro study. *Exp Brain Res.* 1984; 54:437–445. [PubMed: 6723863]
- Arvanitaki A, Chalazonitis N, Otsuka M. Activité paroxystique du soma neuronique d'Aplysia sous l'effet de lastrychnine. (Dérivation endosomique des potentiels) (Paroxysmal activity of the neuronal soma in Aplysia under the effect of strychnine (endosomatic origin of potentials)). *C R Acad Sci.* 1956; 243:307–309. [PubMed: 13343612]
- Bagust J, Kerkut GA. Some effects of magnesium ions upon conduction and synaptic activity in the isolated spinal cord of the mouse. *Brain Res.* 1979; 177:410–413. [PubMed: 227539]
- Bagust J, Forsythe ID, Kerkut GA, Loots JM. Synaptic and non-synaptic components of the dorsal horn potential in isolated hamster spinal cord. *Brain Res.* 1982; 233:186–194. [PubMed: 7059800]
- Baldissera, F., Hultborn, H., Illert, M. Integration in spinal neuronal systems. In: Brookhart, JM., Mountcastle, VB., editors. *Handbook of Physiology*, sec. 1, vol. II, pt. 1. : The Nervous System: Motor Control. Am. Physiol. Soc; Bethesda, MD: 1981. p. 509-595.
- Barakan TH, Downman CBB, Eccles JC. Electrical potentials generated by antidromic volleys in quadriceps and hamstring motoneurons. *J Neurophysiol.* 1949; 12:393–424. [PubMed: 15397161]
- Barbara JG. La contraversion Cajal-Golgi: Stockholm. 1906 (The controversy Cajal-Golgi: Stockholm 1906). *Morphologie.* 2010; 94:4–7. [PubMed: 19850504]
- Barbara JG, Clarac F. Historical concepts on the relations between nerves and muscles. *Brain Res Rev.* 2011; 1409:3–22. (this issue).
- Barrett EF, Barrett JN. Separation of two voltage-sensitive potassium currents, and demonstration of a tetrodotoxin-resistant calcium current in frog motoneurons. *J Physiol (Lond).* 1976; 255:737–774. [PubMed: 1083431]
- Barrett JN, Graubard K. Fluorescent staining of cat motoneurons *in vivo* with beveled microelectrodes. *Brain Res.* 1970; 18:565–568. [PubMed: 4101877]
- Berg RW, Hounsgaard J. Signaling in large-scale neural networks. *Cogn Process.* 2009; 10(Suppl 1):S9–S15. [PubMed: 19009313]
- Bien L. Biophysics in profile — J. Walter Woodbury. *Biophysical Society Nov/Dec Newsletter.* 2005:11–12.
- Binder, MD., Heckman, CJ., Powers, RK. The physiological control of motoneuron activity. In: Rowell, LB. Shepherd, JT., Smith, JL., editors. *Handbook of Physiology*, sec. 12, Exercise: Regulation and Integration of Multiple Systems. Oxford University Press; New York: 1996. p. 3-53.
- Bradley K, Somjen GG. Accommodation in motoneurons of the rat and the cat. *J Physiol (Lond).* 1961; 156:75–92. [PubMed: 16992074]
- Bretag A. Who did invent the intracellular microelectrode? *Trends Neurosci.* 1983; 6:365.
- Bretag AH. A history of the glass micropipette electrode. *AxoBits-Axon Instrum.* 2003; 39(11–12):13–14.
- Brock, J. Lawrence Gordon Brock 1923–1996. In: Brock, J., editor. *The Gordon Brocks.* 2010. p. 16-21.(37–40. Privately prepared family memoir available upon request from J. Brock or the present authors)
- Brock LG, Eccles RM. The membrane potentials during rest and activity of the ray electroplate. *J Physiol (Lond).* 1958; 142:251–274. [PubMed: 13564434]
- Brock LG, McIntyre AK. Responses of motor neurons to stimulation by internal microelectrodes. *Proc Univ Otago Med Sch.* 1953; 31:19–20.
- Brock LG, Coombs JS, Eccles JC. Action potentials of motoneurons with intracellular electrode. *Proc Univ Otago Med Sch.* 1951; 29:14–15.
- Brock LG, Coombs JS, Eccles JC. Synaptic excitation and inhibition. *J Physiol (Lond).* 1952a; 117:8.
- Brock LG, Coombs JS, Eccles JC. The recording of potentials from motoneurons with an intracellular electrode. *J Physiol (Lond).* 1952b; 117:431–460. [PubMed: 12991232]
- Brock LG, Coombs JS, Eccles JC. The nature of the monosynaptic excitatory and inhibitory processes in the spinal cord. *Proc R Soc Lond B.* 1952c; 140:169–176. [PubMed: 13003920]

- Brooks, CMcC, Eccles, JC. Electrical investigation of the monosynaptic pathway through the spinal cord. *J Neurophysiol.* 1947; 10:251–274. [PubMed: 20252622]
- Brooks, CMc, Eccles, JC. An analysis of synaptic excitatory action. *J Neurophysiol.* 1948; 11:365–376. [PubMed: 18872404]
- Brooks, CMc, Downman, CBB., Eccles, JC. After-potentials and excitability of spinal motoneurons following antidromic activation. *J Neurophysiol.* 1950a; 13:9–38. [PubMed: 15402624]
- Brooks, CMc, Downman, CBB., Eccles, JC. After-potentials and excitability of spinal motoneurons following orthodromic activation. *J Neurophysiol.* 1950b; 13:157–176.
- Brownstone RM. Beginning at the end: repetitive firing properties in the final common pathway. *Prog Neurobiol.* 2006; 78:156–172. [PubMed: 16725251]
- Brownstone RM, Stuart DG. Whither motoneurons? *Brain Res Rev.* 2011; 1409:93–103. (this issue).
- Brownstone RM, Gossard JP, Hultborn H. Voltage-dependent excitation of motoneurons from spinal locomotor centres in the cat. *Exp Brain Res.* 1994; 102:34–44. [PubMed: 7895797]
- Brownstone RM, Jordan LM, Kriellaars DJ, Noga B, Shefchyk SJ. On the regulation of repetitive firing in lumbar motoneurons during fictive locomotion in the cat. *Exp Brain Res.* 1992; 90:441–455. [PubMed: 1426105]
- Bui TV, Grande G, Rose PK. Multiple modes of amplification of synaptic inhibition to motoneurons by persistent inward currents. *J Neurophysiol.* 2008; 99:571–582. [PubMed: 18046007]
- Burke RE. The composite nature of the monosynaptic excitatory postsynaptic potential. *J Neurophysiol.* 1967; 30:1114–1137. [PubMed: 6055350]
- Burke, RE. Motor units: Anatomy, physiology and functional organization. In: Brookhart, JM., Mountcastle, VB., editors. *Handbook of Physiology*, sec. 1, vol. II, pt 1., *The Nervous System: Motor Control*. Bethesda (MD): American Physiological Society; 1981. p. 345–422.
- Burke RE. John Eccles' pioneering role in understanding central synaptic transmission. *Prog Neurobiol.* 2006; 78:173–188. [PubMed: 16647800]
- Burke, RE., Rudomin, P. Spinal neurons and synapses. In: Brookhart, JM., Mountcastle, VB., Kandel, E., editors. *Handbook of Physiology*, Sect. 1: Vol. 1, Pt. 2. : *The Nervous System: Cellular Biology of Neurons*. Am. Physiol. Soc; Bethesda, MD: 1977. p. 877–944.
- Buser P, Albe-Fessard D. Premiers résultats d'une analyse de l'activité électrique du cortex cérébral du chat par microélectrodes intracellulaires [First results of an analysis of the electrical activity of the cerebral cortex of the cat using intracellular microelectrodes]. *C R Acad Sci Paris.* 1953; 236:1197–1199. [PubMed: 13059962]
- Butt SJ, Kiehn O. Functional identification of interneurons responsible for left–right coordination of hindlimbs in mammals. *Neuron.* 2003; 38:953–963. [PubMed: 12818180]
- Callister RJ, Graham BA. Early history of glycine receptor biology in mammalian spinal cord circuits. *Front Mol Neurosci.* 2010; 3:1–13. [PubMed: 20162032]
- Carlin KP, Bui TV, Dai Y, Brownstone RM. Staircase currents in motoneurons: insight into the spatial arrangement of calcium channels in the dendritic tree. *J Neurosci.* 2009; 29:5343–5353. [PubMed: 19386931]
- Carlin KP, Jones KE, Jiang Z, Jordan LM, Brownstone RM. Dendritic L-type calcium currents in mouse spinal motoneurons: implications for bistability. *Eur J Neurosci.* 2000; 12:1635–1646. [PubMed: 10792441]
- Chmykhova NM, Babalian AL. Structure of recurrent axon collaterals of frog lumbar motoneurons as revealed by intracellular HRP labeling. *Brain Res.* 1993; 603:289–295. [PubMed: 7681718]
- Chmykhova NM, Adanina VO, Karamian OA, Kozhanov VM, Vesselkin NP, Clamann HP. Comparative study of spinal motoneuron axon collaterals. *Brain Res Bull.* 2005; 66:381–386. [PubMed: 16144619]
- Clarac F, Barbara J-G. The emergence of the “motoneuron concept”: From the early 19th C to the beginning of the 20th C. *Brain Res.* 2011; 1409:23–41. (this issue). [PubMed: 21723536]
- Cole KS. Dynamic electrical characteristics of the squid giant axon membrane. *Arch Sci Physiol.* 1949; 3:253–258.
- Cole KS, Curtis HJ. Electric impedance of the squid giant axon during activity. *J Gen Physiol.* 1939; 22:649–670. [PubMed: 19873125]

- Coombs JS, Eccles JC, Fatt P. The action of the inhibitory transmitter. *Aust J Sci.* 1953; 16:1–5.
- Coombs JS, Eccles JC, Fatt P. The electrical properties of the motoneurone membrane. *J Physiol (Lond).* 1955; 130:291–325. [PubMed: 13278904]
- Coombs JS, Curtis DR, Eccles JC. The electrical constants of the motoneurone membrane. *J Physiol (Lond).* 1959; 145:505–528. [PubMed: 13642317]
- Creed, RS., Denny-Brown, D., Eccles, JC., Liddell, EGT., Sherrington, CS. *Reflex Activity of the Spinal Cord.* Clarendon Press; Oxford: 1932.
- Crill WE. Functional implications of dendritic voltage-dependent conductances. *J Physiol (Paris).* 1999; 93:17–21. [PubMed: 10084705]
- Curtis, DR. Microelectrophoresis. In: Nastuk, WL., editor. *Physical Techniques in Biological Research.* Vol. 5. Academic Press; New York: 1964. p. 144–190.
- Curtis DR, Andersen P. John Carew Eccles 1903–1997. *Hist Rec Aust Sci.* 2001a; 13:439–473. (~12,000 words with JCE's full bibliography of 568 publications). [PubMed: 17929397]
- Curtis DR, Andersen P. Sir John Eccles, A.C. 27 January 1903 – 2 May 1997. *Biogr Mem Fellows R Soc.* 2001b; 47:159–187. (~7,000 words with a selected bibliography of 96 publications). [PubMed: 15124645]
- Curtis DR, Eccles RM. The excitation of Renshaw cells by pharmacological agents applied electrophoretically. *J Physiol (Lond).* 1958; 141:435–445. [PubMed: 13550252]
- Curtis, DR., McIntyre, AK. *Studies in Physiology — Presented to John C. Eccles.* Springer-Verlag; New York: 1965.
- Curtis DR, Phillis JW, Watkins JC. The depression of spinal neurons by γ -amino-*n*-butyric acid and β -alanine. *J Physiol (Lond).* 1959; 146:185–203. [PubMed: 13655226]
- Czéh G, Székely G. Monosynaptic spike discharge initiated by dorsal root activation of spinal motoneurons in the frog. *Acta Physiol Acad Sci Hung.* 1971; 39:401–406. [PubMed: 5119195]
- Dai Y, Jordan LM. Multiple effects of serotonin and acetylcholine on hyperpolarization-activated inward current in locomotor activity-related neurons in *Clos-EGFP* mice. *J Neurophysiol.* 2010; 103:1712–1727. [PubMed: 20164390]
- del Castillo J, Katz B. I. Curare action studied by an electrical micro-method. *Proc R Soc B.* 1957; 146:339–356. [PubMed: 13431859]
- Delcomyn F. Neural basis of rhythmic behavior in animals. *Science.* 1980; 210:492–498. [PubMed: 7423199]
- Dotl HU, Zieglgänsberger W. Visualizing unstained neurones in living brain slices by infrared DIC-videomicroscopy. *Brain Res.* 1990; 537:333–336. [PubMed: 2085783]
- Draper MH, Weidmann S. Cardiac resting and action potentials recorded with an intracellular electrode. *J Physiol (Lond).* 1951; 115:74–94.
- Duchateau J, Enoka RM. Human motor unit recordings: Origins and insight about the integrated motor system. *Brain Res.* 2011; 1409:42–61. (this issue). [PubMed: 21762884]
- Easton DM. Intracellular action potentials modified at muscle end-plate by adjacent fiber activity. *J Neurophysiol.* 1955; 18:375–387. [PubMed: 13243144]
- Eccles JC. The responses of motoneurons. *Br Med Bull.* 1950; 6:304–311. [PubMed: 15420394]
- Eccles JC. The electrophysiological properties of the motoneurone. *Cold Spring Harb Symp Quant Biol.* 1952; 17:175–183. [PubMed: 13049164]
- Eccles, JC. Under the spell of the synapse. In: Worden, FG, Swazey, JP., Adelman, G., editors. *The Neurosciences: Paths of Discovery.* MIT Press; Cambridge (USA): 1975/1992. p. 158–179. (and Birkhäuser, Boston, 1992 (Vol I), pp. 159–179)
- Eccles JC. From electrical to chemical transmission in the central nervous system. *Notes Rec R Soc Lond.* 1976; 30:219–230. [PubMed: 12152632]
- Eccles JC. My scientific odyssey. *Annu Rev Physiol.* 1977; 39:1–18. [PubMed: 322594]
- Eccles JC. Developing concepts of the synapses. *J Neurosci.* 1990; 10:3769–3781. [PubMed: 1980129]
- Eccles, JC., Gibson, WC. *Sherrington — His Life and Thought.* Springer-Verlag; Berlin: 1979.
- Eccles JC, Fatt P, Koketsu K. Cholinergic and inhibitory synapses in a central nervous pathway. *Aust J Sci.* 1953; 16:50–54.

- Eccles JC, Fatt P, Koketsu K. Cholinergic and inhibitory synapses in a pathway from motor-axon collaterals to motoneurons. *J Physiol (Lond)*. 1954; 126:524–562. [PubMed: 13222354]
- Eccles JC, Eccles RM, Lundberg A. Types of neurone in and around the intermediate nucleus of the lumbosacral cord. *J Physiol (Lond)*. 1960; 154:89–114. [PubMed: 13725575]
- Edgerton, VR., Grillner, S., Sjöström, A., Zangger, P. Central generation of locomotion in vertebrates. In: Herman, RM, Grillner, S, Stein, PSG., Stuart, DG., editors. *Neural Control of Locomotion*. Plenum Press; New York: 1976. p. 439–464.
- Edwards C. Who invented the intracellular microelectrode? *Trends Neurosci*. 1983; 6:44.
- Edwards F, Konnerth A, Sakmann B, Takahashi T. A thin slice preparation for patch clamp recordings from neurons of the mammalian central nervous system. *Pflugers Arch*. 1989; 414:600–612. [PubMed: 2780225]
- Fatt P, Katz B. Membrane potentials at the motor end-plate. *J Physiol (Lond)*. 1950; 111:46–47.
- Fenner, F., Curtis, DR. *The John Curtin School of Medical Research — The First Fifty Years*. 1948–1998. Brolga Press; Gundaroo, NSW, AUS: 2001.
- Fessard A, Tauc L. Détermination microélectrométrique du potentiel de repos de l'élément électrogène chez *Torpedo marmorata* [Micro-electrical determination of the resting potential of the electroplaque in *Torpedo marmorata*]. *C R Acad Sci*. 1951; 232:1228–1230.
- Fessard A, Tauc L. Capacité, résistance et variations actives d'impédance d'un soma neuronique (Capacity, resistance and active variations of impedance in a neuronal soma). *J Physiol Paris*. 1956; 48:541–544. [PubMed: 13346553]
- Fetz, EE., Henneman, E., Mendell, LM., Stein, RB., Stuart, DG. Properties of single cells in vertebrate motor systems revealed by spike-triggered averaging. Society for Neuroscience, 8th Annual Meeting. Summaries of Symposia. (BIS Conference Report #49); Los Angeles: UCLA, Brain Information Service/BR1 Publications Office; 1979. p. 11–32.
- Fillenz, M. Memories of Sir John Eccles in New Zealand. In: Eccles, H., Biersack, HJ., editors. *Sir John Eccles in Memoriam — A Tireless Warrior for Dualism*. Ecomed; Landsberg, GER: 2000. p. 11–28.
- Finkel AS, Redman SJ. The synaptic current evoked in cat spinal motoneurone by impulses in single group Ia axons. *J Physiol (Lond)*. 1983; 342:615–632. [PubMed: 6313911]
- Finkel AS, Redman SJ. Theory and operation of a single microelectrode voltage clamp. *J Neurosci Methods*. 1984; 11:101–127. [PubMed: 6482502]
- Florey, E. *An Introduction to General and Comparative Animal Physiology*. Saunders; Philadelphia: 1966.
- Frank K. Basic mechanisms of synaptic transmission in the central nervous system. *Radiol Eng Trans Med Electron*. 1959; ME-6:85–88.
- Frank, K. Identification and analysis of single unit activity in the central nervous system. In: Field, J, Magoun, HW., Hall, VE., editors. *Handbook of Physiology, Sect. 1: Neurophysiology*. Vol. 1. Am. Physiol. Soc; Bethesda, MD: 1960. p. 261–277.
- Frank K, Fuortes MGF. Potentials recorded from the spinal cord with microelectrodes. *J Physiol (Lond)*. 1955; 130:625–654. [PubMed: 13278925]
- Frank K, Fuortes MGF. Presynaptic and postsynaptic inhibition of monosynaptic reflexes. *Fed Proc*. 1957; 16:39–40.
- Frank K, Fuortes MGF. Excitation and conduction. *Annu Rev Physiol*. 1961; 23:257–386.
- Frank K, Fuortes MGF, Nelson PG. Voltage clamp of motoneuron soma. *Science*. 1959; 130:38–39. [PubMed: 13668533]
- Frigon A, Gossard JP. Evidence for specialized rhythm-generating mechanisms in the adult mammalian spinal cord. *J Neurosci*. 2010; 30:7061–7071. [PubMed: 20484648]
- Galvani, A. De Viribus Electricitatis in Motu Musculari Commentarius (Note on the effect of electricity on muscular motion). *Typographia Instituti Scientiarum*; Bologna: 1791.
- García-Campmany L, Stam FJ, Goulding M. From circuits to behavior: motor networks in vertebrates. *Curr Opin Neurobiol*. 2010; 20:116–125. [PubMed: 20138753]

- Gerard, RW. The minute experiment and the large picture. In: Worden, FG, Swazey, JP., Adelman, G., editors. *The Neurosciences: Paths of Discovery*. MIT Press; Cambridge (USA): 1975/1992. p. 457-474. (and Birkhäuser, Boston, 1992 (Vol I), pp. 457-474)
- Giddens WE Jr. Professor Theodore C. Ruch Vet Pathol. 1981; 18(Suppl 6):iii-iv. [PubMed: 7046200]
- Globus A, Lux HD, Schubert P. Somadendritic spread of intracellularly injected tritiated glycine in cat spinal motoneurons. *Brain Res*. 1968; 11:440-445. [PubMed: 5701206]
- Graham BA, Brichta AM, Callister RJ. An in vivo mouse spinal cord preparation for patch-clamp analysis of nociceptive processing. *J Neurosci Methods*. 2004; 136:221-228. [PubMed: 15183274]
- Graham BA, Schofield PR, Sah P, Margrie TW, Callister RJ. Distinct physiological mechanisms underlie altered glycinergic synaptic transmission in the murine mutants spastic, spasmodic, and oscillator. *J Neurosci*. 2006; 26:4880-4890. [PubMed: 16672662]
- Graham BA, Brichta AM, Callister RJ. Pinch-current injection defines two discharge profiles in mouse superficial dorsal horn neurons, in vitro. *J Physiol (Lond)*. 2007a; 578(3):787-798. [PubMed: 17124264]
- Graham BA, Brichta AM, Callister RJ. Moving from an averaged to a specific view of spinal cord pain processing circuits. *J Neurophysiol*. 2007b; 98:1057-1063. [PubMed: 17567772]
- Graham BA, Brichta AM, Schofield PR, Callister RJ. Altered potassium channel function in the superficial dorsal horn of the spastic mouse. *J Physiol (Lond)*. 2007c; 584:121-136. [PubMed: 17690143]
- Graham, JE. PhD Dissertation. University of Chicago; Chicago: 1946. Membrane Potentials and Excitation of Impaled Single Muscle Fibers; p. 21
- Graham JE, Gerard RW. Membrane potentials and excitation of impaled single muscle fibers. *J Cell Comp Physiol*. 1946; 28:99-117. [PubMed: 21002959]
- Granit, R. Charles Scott Sherrington — An Appraisal. Nelson; London: 1966.
- Granit R, Kernell D, Shortess GK. Quantitative aspects of repetitive firing of mammalian motoneurons, caused by injected currents. *J Physiol*. 1963; 168:911-931. [PubMed: 14072865]
- Granit R, Kernell D, Lamarre Y. Algebraical summation in synaptic activation of motoneurons firing within the 'primary range' to injected currents. *J Physiol*. 1966a; 187:379-399. [PubMed: 5972179]
- Granit R, Kernell D, Lamarre Y. Synaptic stimulation superimposed on motoneurons firing in the 'secondary range' to injected current. *J Physiol*. 1966b; 187:401-415. [PubMed: 5972180]
- Grillner S. Locomotion in vertebrates: central mechanisms and reflex interaction. *Physiol Rev*. 1975; 55:247-304. [PubMed: 1144530]
- Grillner, S. Control of locomotion in bipeds, tetrapods and fish. In: Brookhart, JM., Mountcastle, VB., editors. *Handbook of Physiology*, sec. 1, vol. II, pt. 2. : *The Nervous System: Motor Control*. Am. Physiol. Soc; Bethesda (MD): 1981. p. 1179-1236.
- Grillner S, Jessell TM. Measuring motion: searching for simplicity in spinal locomotor networks. *Curr Opin Neurobiol*. 2009; 19:572-586. [PubMed: 19896834]
- Grillner S, El Manira A, Kiehn O, Rossignol S, Stein PSG. Networks in motion. *Brain Res, Rev*. 2008; 57:1-269.
- Guberman A. Vagus nerve stimulation in the treatment of epilepsy. *CMAJ*. 2004; 171:1165-1166. [PubMed: 15534307]
- Haddad GG, Donnelly DF, Getting PA. Biophysical properties of hypoglossal neurons in vitro: intracellular studies in adult and neonatal rats. *J Appl Physiol*. 1990; 69:1509-1517. [PubMed: 2262474]
- Hagiwara S, Bullock TH. Intracellular potentials in pacemaker and integrative neurons of the lobster cardiac ganglion. *J Cell Comp Physiol*. 1957; 59:25-47.
- Hagiwara S, Watanabe A. Discharges in motoneurons of Cicada. *J Cell Comp Physiol*. 1956; 47:415-428. [PubMed: 13367104]
- Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ. Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflügers Arch*. 1981; 391:85-100. [PubMed: 6270629]

- Hayes HB, Chang YH, Hochman S. An in vitro spinal cord-hindlimb preparation for studying behaviorally relevant rat locomotor function. *J Neurophysiol.* 2009; 101:1114–1122. [PubMed: 19073815]
- Heckman CJ, Binder MD. Analysis of effective synaptic currents generated by homonymous Ia afferent fibers in motoneurons of the cat. *J Neurophysiol.* 1988; 60:1948–1966.
- Heckman CJ, Gorassini MA, Bennett DJ. Persistent inward currents in motoneuron dendrites: implications for motor output. *Muscle Nerve.* 2005; 31:135–156. [PubMed: 15736297]
- Henneman E, Mendell LM. Terminals of single Ia fibers: distribution within a pool of 300 homonymous motor neurons. *Science.* 1968; 160:96–98. [PubMed: 4296007]
- Henneman, E., Mendell, LM. Functional organization of motoneuron pool and its inputs. In: Brookhart, JM., Mountcastle, VB., editors. *Handbook of Physiology*, sec. 1, vol. II, pt 1. The Nervous System. Am. Physiol. Soc; Bethesda (MD): 1981. p. 423-507.
- Hernandez P, Elbert K, Droge MH. Spontaneous and NMDA evoked motor rhythms in the neonatal mouse spinal cord: an in vitro study with comparisons to in situ activity. *Exp Brain Res.* 1991; 85:66–74. [PubMed: 1884765]
- Hikosaka O. Obituary: Dr. Ichiji Tasaki. *Neurosci Res.* 2009; 64:1–2.
- Hodgkin AL. The subthreshold potentials in a crustacean nerve fibre. *Proc R Soc Lond B.* 1938; 126:87–121.
- Hodgkin AL, Huxley AF. Action potentials recorded from inside a nerve fiber. *Nature.* 1939; 144:710–711.
- Hodgkin AL, Huxley AF. Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*. *J Physiol (Lond).* 1952; 116:449–472. [PubMed: 14946713]
- Hodgkin AL, Nastuk WL. Membrane potentials in single fibres of the frog's sartorius muscle. *J Physiol (Lond).* 1949; 108:P42–P43.
- Hodgkin AL, Huxley AF, Katz B. Measurement of the current–voltage relations in the membrane of the giant axon of *Loligo*. *J Physiol (Lond).* 1952; 116:422–448.
- Horikawa K, Armstrong WE. A versatile means of intracellular labeling: injection of biocytin and its detection with avidin conjugates. *J Neurosci Methods.* 1988; 25:1–11. [PubMed: 3146670]
- Hounsgaard J, Kiehn O, Mintz I. Response properties of motoneurons in a slice preparation of the turtle spinal cord. *J Physiol (Lond).* 1988; 398:575–589. [PubMed: 2455803]
- Hoyle G. Origins of intracellular microelectrodes. *Trends Neurosci.* 1983; 6:163.
- Hultborn H. State-dependent modulation of sensory feedback. *J Physiol (Lond).* 2001; 533(1):5–13. [PubMed: 11351007]
- Hultborn H, Denton ME, Wienecke J, Nielsen JB. Variable amplification of synaptic input to cat spinal motoneurons by dendritic persistent inward current. *J Physiol.* 2003; 552:945–952. [PubMed: 14500771]
- Huxley AF. Sir Alan Lloyd Hodgkin, O.M., K.B.E. 5 February 1914 – 20 December 1998. *Biogr Mem Fell R Soc.* 2000; 46:219–241.
- Huxley AF, Stämpfli R. Evidence for saltatory conduction in peripheral myelinated nerve fibres. *J Physiol (Lond).* 1949; 108:315–339.
- Ito, M. My years with Sir John. In: Eccles, H., Biersack, HJ., editors. *Sir John Eccles in Memoriam — A Tireless Warrior for Dualism*. Ecomed; Landsberg, GER: 2000. p. 29-36.
- Jack J, McIntyre AK, Somjen GG. Excitability of motoneurons during reflex facilitation and inhibition. *Proc 21st Int Physiol Congr.* 1959:136.
- Jagadeesh B, Wheat HS, Ferster D. Linearity of summation of synaptic potentials underlying direction selectivity in simple cells of the cat visual cortex. 1993
- Jankowska E. Spinal interneuronal networks in the cat: Elementary components. *Brain Res Rev.* 2008; 57:46–55. [PubMed: 17884173]
- Jankowska E, Lindström S. Morphological identification of physiologically defined neurons in the cat. *Brain Res.* 1970; 20:323–326. [PubMed: 4101883]
- Jordan, LM. Factors determining motoneuron rhythmicity during fictive locomotion. In: Roberts, A., Roberts, BL., editors. *Neurobiology of Vertebrate Locomotion. : Symposia of the Society of Experimental Biology*. Cambridge University Press; London: 1983. p. 423-444.

- Jordan LM, Pratt CA, Menzies JE. Locomotion evoked by brainstem stimulation: Occurrence without phasic segmental afferent input. *Brain Res.* 1979; 177:204–207. [PubMed: 497822]
- Jung, R. Some European neuroscientists : a personal tribute. In: Worden, FG, Swazey, JP., Adelman, G., editors. *The Neurosciences: Paths of Discovery*. MIT Press; Cambridge (USA): 1975/1992. p. 457–474. (and Birkhäuser, Boston, 1992 (Vol. I), pp. 477–511)
- Kato, G. *Japanese Physiology — Past and Present*. Subcommittee of the Organizing Committee, XXIII Int. Congr. Physiol. Sci; Tokyo. 1964. (Ch.)
- Karczmar AG. Sir John Eccles, 1903–1997. Part 1 Onto the demonstration of the chemical nature of transmission in the CNS. *Perspect Biol Med.* 2001a; 44:76–86. [PubMed: 11253306]
- Karczmar AG. Sir John Eccles, 1903–1997. Part 2 The brain as a machine or as a site of free will? *Perspect Biol Med.* 2001b; 44:250–262. [PubMed: 11370159]
- Katz B, Miledi R. A study of miniature potentials in spinal motoneurons. *J Physiol (Lond).* 1963; 168:399–422.
- Kernell D. Synaptic influences on the repetitive activity elicited in cat lumbosacral motoneurons by long-lasting injected currents. *Acta Physiol Scand.* 1965a; 63:409–410. [PubMed: 14324076]
- Kernell D. The adaptation and the relation between discharge frequency and current strength of cat lumbosacral motoneurons stimulated by longlasting injected current. *Acta Physiol Scand.* 1965b; 65:65–73.
- Kety SS. Ralph Waldo Gerard: October 7, 1900–February 17, 1974. *Biogr Mem Natl Acad Sci.* 1982; 53:179–210. [PubMed: 11620792]
- Kirkwood PA, Sears TA. Monosynaptic excitation of motoneurons from secondary endings of muscle spindles. *Nature.* 1974; 252:243–244. [PubMed: 4278994]
- Kolmodin GM. Integrative processes in single spinal interneurons with proprioceptive connections. *Acta Physiol Scand Suppl.* 1957; 40:1–89.
- Kolmodin GM, Skoglund CR. Properties and functional differentiation of interneurons in the ventral horn of the cat's lumbar cord as revealed by intracellular recording. *Experientia.* 1954; 10:505–506. [PubMed: 14353094]
- Kolmodin GM, Skoglund CR. Slow membrane potential changes accompanying excitation and inhibition in spinal moto- and interneurons in the cat during their natural activation. *Acta Physiol Scand.* 1958; 44:11–54. [PubMed: 13605806]
- Kostyuk PG. Electrophysiological characteristics of individual spinal cord neurons. *Sechenov Physiol J USSR.* 1960; 46:10–22.
- Kostyuk PG. The nature of excitation and inhibition in single interneurons of the spinal cord. *Sechenov Physiol J USSR.* 1961; 47(10):18–27.
- Kostyuk PG, Timchenko VB. Feedback control of activity of spinal interneurons. *Bol Inst Estud Med Biol Univ Nac Auton Mex.* 1963; 21:287–302. [PubMed: 14122262]
- Kristensson K, Olsson Y. Retrograde axonal transport of protein. *Brain Res.* 1971; 29:363–365. [PubMed: 4107258]
- Kuno M. Effects of strychnine on the intracellular potentials of spinal motoneurons of the toad. *Jpn J Physiol.* 1957; 15:42–50.
- Lee RH, Kuo JJ, Jiang MC, Heckman CJ. Influence of active dendritic currents on input–output processing in spinal motoneurons in vivo. *J Neurophysiol.* 2003; 89:27–39. [PubMed: 12522157]
- Li WC, Soffe SR, Roberts A. A direct comparison of whole cell patch and sharp electrodes by simultaneous recording from single spinal neurons in frog tadpoles. *J Neurophysiol.* 2004; 92:380–386. [PubMed: 14999043]
- Libet B. Reflections on the interaction of the mind and brain. *Prog Neurobiol.* 2006; 78:322–326. [PubMed: 16675090]
- Liddell EGT. Charles Scott Sherrington: 1857–1952. *Obit Not Fellows R Soc.* 1952; 8:241–270.
- Ling, GN. PhD Dissertation. University of Chicago; Chicago: 1948. *Membrane Potential and Metabolism of Muscle Fibers*; p. 15–16.
- Ling G, Gerard RW. The normal membrane potential of frog sartorius fibers. *J Cell Comp Physiol.* 1949; 34:383–396. [PubMed: 15410483]

- Ling G, Woodbury JW. Effect of temperature on the membrane potential of frog muscle fibers. *J Cell Comp Physiol.* 1949; 34:407–412. [PubMed: 15406360]
- Lorente de Nó R, Renshaw B. Transmission of impulses through cranial motor nuclei. *J Neurophysiol.* 1939; 2:402–464.
- Lüscher HR, Ruenzel P, Henneman E. Topographic distribution of terminals of Ia and group II fibers in SC, as revealed by postsynaptic population potentials. *J Neurophysiol.* 1980; 43:968–985. [PubMed: 6244374]
- Machne X, Fadiga E, Brookhart JM. Antidromic and synaptic activation of frog motoneurons. *J Neurophysiol.* 1959; 22:483–503. [PubMed: 14419426]
- Margrie T, Brecht M, Sakmann B. In vivo, low-resistance, whole-cell recordings from neurons in the anaesthetized and awake mammalian brain. *Pflügers Arch.* 2002; 444:491–498. [PubMed: 12136268]
- Marinesco G. Recherches sur les localisations motrices spinale [Studies on spinal motor locations]. *Sem Méd.* 1904; 24:225–231.
- Marmont G. Studies on the axon membrane. *J Cell Comp Physiol.* 1949; 34:351–382. [PubMed: 15406358]
- McCrea DA. Spinal circuitry of sensorimotor control of locomotion. *J Physiol (Lond).* 2001; 533(1): 41–50. [PubMed: 11351011]
- McDonagh, JC., Callister, RJ., Brichta, AM., Reinking, RM., Stuart, DG. A commentary on the properties of spinal interneurons vs. motoneurons in vertebrates, and their firing-rate behavior during movement. In: Gantchev, G., editor. *Motor Control Today and Tomorrow*. Academic Publishing House “Prof. M. Drinov”; Sofia: 1999. p. 3-29.
- McIntyre AK. Central and sensory transmission. *Pharm Rev.* 1954; 6:103–104. [PubMed: 13155159]
- McIntyre, AK. Central actions of impulses in muscle afferent fibres. In: Hunt, CC., editor. *Muscle Receptors*. Springer-Verlag; Berlin: 1974. p. 235-238.
- McIntyre AK, Mark RF. Synaptic linkage between afferent fibres of the cat's hind limb and ascending fibres in the dorsolateral funiculus. *J Physiol (Lond).* 1960; 153:306–330. [PubMed: 13774010]
- McIntyre AK, Mark RF, Steiner J. Multiple firing at central synapses. *Nature.* 1956; 178:302–304. [PubMed: 13358721]
- McIntyre AK, Bradley K, Brock LG. Responses of motoneurons undergoing chromatolysis. *J Gen Physiol.* 1959:931–938. [PubMed: 13654743]
- Merickel M. Design of a single electrode voltage clamp. *J Neurosci Meth.* 1980; 2:87–96.
- Merickel M, Gray R. Investigation of burst generation by the electrically coupled cyberchron network in the snail *Helisoma* using a single-electrode voltage clamp. *J Neurobiol.* 1980; 11:73–102. [PubMed: 7354323]
- Miles GB, Dai Y, Brownstone RM. Mechanisms underlying the early phase of spike frequency adaptation in mouse spinal motoneurons. *J Physiol (Lond).* 2005; 566:519–532. [PubMed: 15878947]
- Nastuk WL. Electrical activity of single muscle fibers at the neuromuscular junction. *Fed Proc.* 1950; 9:94.
- Nastuk WL. Membrane potential changes at a single end plate produced by acetylcholine. *Fed Proc.* 1951; 10:96.
- Nastuk WL, Hodgkin AL. Action potentials in single muscle fibers. *Fed Proc.* 1949; 8:175.
- Nastuk WL, Hodgkin AL. The electrical activity of single muscle fibers. *J Cell Comp Physiol.* 1950; 35:39–73.
- Neher E, Sakmann B. Single-channel currents recorded from membrane of denervated frog muscle fibers. *Nature.* 1976; 260:799–802. [PubMed: 1083489]
- Nelson PG, Frank K. Anomalous rectification in cat spinal motoneurons and effect of polarizing currents on excitatory postsynaptic potential. *J Neurophysiol.* 1967; 30:1097–1113. [PubMed: 6055349]
- Orlovsky, G., Shik, ML. Control of locomotion: a neurophysiological analysis of the cat locomotor system. In: Porter, R., editor. *Neurophysiology II : International Review of Neurophysiology*. Vol. 10. University Park Press; Baltimore: 1976. p. 291-317.

- Orlovsky, GN., Deliagina, TG., Grillner, S. Neuronal Control of Locomotion — From Mollusc to Man. Oxford University Press; New York: 1999.
- Otsuka M, Konishi S. Electrophysiology of mammalian spinal cord in vitro. *Nature*. 1974; 252:733–734. [PubMed: 4437630]
- Patton HD, David P.C, Lloyd, Biogr Mem Natl Acad Sci. 1994; 65:197–209. [PubMed: 11616338]
- Phillips CG. The dimensions of a cortical motor point. *J Physiol (Lond)*. 1955; 129:20P–21P. [PubMed: 13252609]
- Phillis, JW. The Pharmacology of Synapses. Pergamon; Oxford: 1970.
- Porter R, Proske U, Mark RF. Archibald Keverall McIntyre 1913–2002. *Hist Rec Aust Sci*. 2004; 15:77–94.
- Powers RK, Binder MD. Input–output functions of mammalian motoneurons. *Rev Physiol Biochem Pharmacol*. 2001; 143:137–263. [PubMed: 11428264]
- Proske U. Archie McIntyre (1913–2002). *Clin Exp Pharmacol Physiol*. 2003; 30:303–306.
- Rall W. A statistical theory of monosynaptic input-output relations. *J Cell Physiol*. 1955; 46:373–411.
- Rall W. Membrane time constant of motoneurons. *Science*. 1957; 126:454. [PubMed: 13467230]
- Rall W. Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *J Neurophysiol*. 1967; 30:1138–1168. [PubMed: 6055351]
- Rall, W. Path to biophysical insights about dendrites and synaptic function. In: Samson, F., Adelman, G., editors. *The Neurosciences: Paths of Discovery*, II. Birkhäuser; Boston: 1992. p. 214–238.
- Rall W, Burke RE, Nelson PG, Smith T, Frank K. The dendritic location of synapses and possible mechanisms for the monosynaptic EPSP in motoneurons. *J Neurophysiol*. 1967; 30:1169–1193. [PubMed: 4293410]
- Ramón y Cajal S. Estructura de los centro nerviosos de la aves (Structure of the central nervous system of birds). *Rev Trim Histol Norm Patol*. 1888a; 1:1–10.
- Ramón y Cajal S. Sobre las fibras nerviosas de la capa molecular del cerebello (About the nerve fibres of the molecular layer of the cerebellum). *Rev Trim Histol Norm Patol*. 1888b; 1:33–49.
- Redman, R. A quantitative approach to the integrative function of dendrites. In: Porter, R., editor. *International Review of Physiology: Neuroscience*. Vol. 10. University Park Press; Baltimore: 1976. p. 1–36.
- Rekling JC, Champagnat J, Denavit-Saubié M. Electroresponsive properties and membrane potential trajectories of three types of inspiratory neurons in the newborn mouse brain stem in vitro. *J Neurophysiol*. 1996; 75:795–810. [PubMed: 8714653]
- Renshaw B. Influence of discharge of motoneurons upon excitation of neighbouring motoneurons. *J Neurophysiol*. 1941; 4:167–183.
- Romanes GJ. The motor cell columns of the lumbosacral spinal cord of the cat. *J Comp Neurol*. 1951; 94:313–364. [PubMed: 14832391]
- Rossignol, S. Neural control of stereotypic limb movements. In: Rowell, LB, Shepherd, JT., Smith, JL., editors. *Handbook of Physiology*, sec. 12, Exercise: Regulation and Integration of Multiple Systems. Oxford University Press; New York: 1996. p. 173–216.
- Rovainen CM. Physiological and anatomical studies on large neurons of central nervous system of the sea lamprey (*Petromyzon Marinus*). II Dorsal cells and giant interneurons. *J Neurophysiol*. 1967; 30:1024–1042. [PubMed: 6069725]
- Ruch, TC., Fulton, JF., editors. *Medical Physiology and Biophysics* (18th ed. of Howell's Textbook of Physiology). Saunders; Philadelphia: 1960.
- Saadé NE, Chanelet J, Lonchampt P. Mise en évidence et rôle fonctionnel d'interneurones actives antidromiquement dans la moelle de Grenouille [Demonstration and functional role of antidromically activated interneurons in the frog spinal cord]. *C R Seances Soc Biol Fil*. 1972; 166:1261–1269. [PubMed: 4663941]
- Sakmann B, Hamill OP, Bormann J. Patch-clamp measurements of elementary chloride currents activated by the putative inhibitory transmitter GABA and glycine in mammalian spinal neurons. *J Neural Transm Suppl*. 1983; 18:83–95. [PubMed: 6308154]
- Sasaki K, Namikawa A, Hashiramoto S. The effect of midbrain stimulation on alpha motoneurons in lumbar spinal cord of the cat. *Jpn J Physiol*. 1960; 10:303–316. [PubMed: 14441861]

- Schwindt PC, Calvin WH. Equivalence of synaptic and injected current in determining the membrane potential trajectory during motoneuron rhythmic firing. *Brain Res.* 1973; 59:389–394. [PubMed: 4355888]
- Segev I. What do dendrites and their synapses tell the neuron? *J Neurophysiol.* 2006; 95:1205–1207.
- Shapovalov AI. Extrapyramidal monosynaptic and disynaptic control of mammalian alpha-motoneurons. *Brain Res.* 1972; 40:105–115. [PubMed: 4624482]
- Shapovalov AI. Interneuronal synapses with electrical and chemical mechanisms of transmission and the evolution of the nervous system. *Zh Evol Biokhim Fiziol.* 1977; 13:621–632. (In Russian). [PubMed: 21498]
- Shapovalov AI, Shiryaev BI. Reticulospinal and propriospinal monosynaptic influences on frog motoneurons. *Neurophysiol USSR.* 1973; 5:126–133.
- Shapovalov AI, Kurchavyi GG, Smrtonova MP. Synaptic mechanisms of vestibulo-spinal influences on alpha-motoneurons. *Fiziol Zh SSSR Im I M Sechenova.* 1966; 52:1401–1409. [PubMed: 4303630]
- Shefchyk SJ, Jordan LM. Excitatory and inhibitory postsynaptic potentials in alpha-motoneurons produced during fictive locomotion by stimulation of the mesencephalic locomotor region. *J Neurophysiol.* 1985; 53:1345–1355. [PubMed: 4009222]
- Shepherd, GM. *Creating Modern Neuroscience — The Revolutionary 1950s.* Oxford University Press; Oxford: 2010.
- Sherrington CS. The correlation of reflexes and the principle of the common path. Report of the British Association for the Advancement of Science. 1904; 74:1–14.
- Shik ML, Orlovsky GN. Neurophysiology of locomotor automatism. *Physiol Rev.* 1976; 56:465–501. [PubMed: 778867]
- Smith T, Wuerker R, Frank K. Membrane impedance changes during synaptic transmission in cat spinal motoneurons. *J Neurophysiol.* 1967; 30:1072–1096. [PubMed: 4293409]
- Smith JC, Liu G, Feldman JL. Intracellular recording from phrenic motoneurons receiving respiratory drive in vitro. *Neurosci Lett.* 1988; 88:27–32. [PubMed: 3399129]
- Soffe SR, Clarje JDW, Roberts A. Activity of commissural interneurons in spinal cord of *Xenopus* embryos. *J Neurophysiol.* 1984; 51:1257–1267. [PubMed: 6737030]
- Stauffer EK, McDonagh JC, Hornby TG, Reinking RM, Stuart DG. Historical reflections on the afterhyperpolarization–firing rate relation of vertebrate spinal neurons. *J Comp Physiol A.* 2007; 193:145–158.
- Stein RB, Yang JF. Methods for estimating the number of motor units in human muscles. *Ann Neurol.* 1990; 28:487–495. [PubMed: 2252361]
- Strata, P. Recollections of my life with Sir John Eccles. In: Eccles, H., Biersack, HJ., editors. *Sir John Eccles in Memoriam — A Tireless Warrior for Dualism.* Ecomed; GER: 2000. p. 13–47.
- Stretton AOW, Kravitz EA. Neuronal geometry: determination with a technique of intracellular dye injection. *Science.* 1968; 162:132–134. [PubMed: 4175300]
- Stuart DG. Reflections on integrative and comparative movement neuroscience. *Integr Comp Biol.* 2007; 47:482–504. [PubMed: 21672857]
- Stuart DG, Pierce PA. The academic lineage of Sir John Carew Eccles (1903–1997). *Prog Neurobiol.* 2006; 78:136–155. [PubMed: 16632168]
- Stuart DG, Zigmund MJ. The Contributions of John Carew Eccles to Contemporary Neuroscience. *Prog Neurobiol.* 2006; 78:135–326.
- Stuart DG, Clarac F, Barbara JG, Brownstone RM, Duchateau J, Enoka RM. Paths of Discovery in Motoneuron Neurobiology. *Brain Res.* 2011; 1409:1–2. (this issue). [PubMed: 21864736]
- Svaetichin G. Electrophysiological investigations of single ganglion cells. *Acta Physiol Scand.* 1951; 24(Suppl 86):1–57. [PubMed: 14877579]
- Takahashi T. The minimal inhibitory synaptic currents evoked in neonatal rat motoneurons. *J Physiol (Lond).* 1992; 450:593–611. [PubMed: 1432720]
- Takahashi T, Momiyama A. Single-channel currents underlying glycinergic inhibitory postsynaptic responses in spinal neurons. *Neuron.* 1991; 7:965–969. [PubMed: 1722412]

- Takeda K, Kennedy D. Soma potentials and modes of activation of crayfish motoneurons. *J Cell Comp Physiol.* 1964; 64:165–181. [PubMed: 14219651]
- Tasaki I. Properties of myelinated fibers in frog sciatic nerve and inspinal cord as examined with micro-electrodes. *Jpn J Physiol.* 1952; 3:73–94. [PubMed: 13034379]
- Tasaki, I. Conduction of the nerve impulse. In: Field, J. Magoun, HW., Hall, VE., editors. *Handbook of Physiology, Sect. 1. Neurophysiology. Vol. 1.* Am. Physiol. Soc; Bethesda, MD: 1960. p. 75-121.
- Tasaki I, Polley EH, Orrego F. Action potentials from individual elements in cat geniculate and striate cortex. *J Neurophysiol.* 1954; 17:454–474. [PubMed: 13201978]
- Tauc L. Potentiels de repos et d'action des cellules ganglionnaires de l'écrevisse étudiés à l'aide de microélectrodes capillaires (Resting and action potentials of ganglion cells of the crayfish studied with the aid of microelectrodes). *C R Soc Biol Paris.* 1952; 146:1688–1690.
- Tauc L. Étude de l'activité élémentaire des cellules du ganglion abdominal de l'Aplysie (Studies on fundamental activity of cells of the abdominal ganglion of Aplysia). *J Physiol Paris.* 1955a; 47(4):769–792. [PubMed: 13307464]
- Tauc L. Activités électrique fractionnées observées dans des cellules ganglionnaires de l'Escargot (*Helix pomatia*) (Fractionated electrical activity observed in ganglion cells of the snail (*Helix pomatia*)). *C R Acad Sci.* 1955b; 241:1070–1073. [PubMed: 13277199]
- Thurbon D, Luscher HR, Hofstetter T, Redman SJ. Passive electrical properties of ventral horn neurones in rat spinal cord slices. *J Neurophysiol.* 1998; 80:2485–2502. [PubMed: 9722433]
- Thurley K, Senn W, Lüscher HR. Dopamine increases the gain of the input–output response of rat prefrontal pyramidal neurons. *J Neurophysiol.* 2008; 99:2985–2997. [PubMed: 18400958]
- Umrath K. Der Erregungsvorgang Bei *Nitella mucronata* (The excitation process in Nitella Mucronata). *Protoplasma.* 1932; 17:258–300.
- Volta A. On the electricity excited by the mere contact of conductors of different kinds. *Philos Trans R Soc Lond.* 1800; 90:403–431.
- Watt DGD, Stauffer EK, Taylor A, Reinking RM, Stuart DG. Analysis of muscle receptor connections by spike-triggered averaging: 1. Spindle primary and tendon organ afferents. *J Neurophysiol.* 1976; 39:1375–1392. [PubMed: 136500]
- Weidmann S. Electrical characteristics of *Sepia* axons. *J Physiol (Lond).* 1951; 114:372–381. [PubMed: 14861821]
- Wenner P, O'Donovan MJ. Identification of an interneuronal population that mediates recurrent inhibition of motoneurons in the developing chick spinal cord. *J Neurosci.* 1999; 19:7557–7567. [PubMed: 10460262]
- Wetzel MC, Stuart DG. Ensemble characteristics of cat locomotion and its neural control. *Prog Neurobiol.* 1976; 7:1–98. [PubMed: 785547]
- Wheatley M, Stein RB. An in vitro preparation of the mudpuppy for simultaneous intracellular and electromyographic recording during locomotion. *J Neurosci Methods.* 1992; 42:129–137. [PubMed: 1405730]
- Wheatley M, Jovanovic K, Stein RB, Lawson V. The activity of interneurons during locomotion in the in vitro necturus spinal cord. *J Neurophysiol.* 1994; 71:2025–2032. [PubMed: 7931500]
- Wiesendanger M. Eccles' perspective of the forebrain, its role in skilled movement, and the mind-brain problem. *Prog Neurobiol.* 2006; 78:304–321. [PubMed: 16647799]
- Wilson JM, Hartley R, Maxwell DJ, et al. Conditional rhythmicity of ventral spinal interneurons defined by expression of the Hb9 homeodomain protein. *J Neurosci.* 2005; 25:5710–5719. [PubMed: 15958737]
- Wolpaw JR, Carp JS. Plasticity from muscle to brain. *Prog Neurobiol.* 2006; 76:233–264.
- Woodbury, JW. PhD Dissertation. University of Utah; Salt Lake City: 1950. Membrane Resting and Action Potentials From Single Myelinated Nerve Fibers. (publication no. AAT0181623)
- Woodbury JW. Direct membrane resting and action potentials from single myelinated nerve fibers. *J Cell Comp Physiol.* 1952; 39:323–340. [PubMed: 14946242]
- Woodbury JW. Recording central nervous activity with intracellular ultramicroelectrodes: use of a negative-capacity amplifier to improve transient response. *Fed Proc.* 1953; 12:159.

- Woodbury, JW. The cell membrane; ionic and potential gradients and active transport. In: Ruch, TC., Fulton, JF., editors. *Medical Physiology and Biophysics*. 18. Saunders; Philadelphia: 1960a. p. 1-25.
- Woodbury, JW. Action potential; properties of excitable membranes. In: Ruch, TC., Fulton, JF., editors. *Medical Physiology and Biophysics*. 18. Saunders; Philadelphia: 1960b. p. 26-72.
- Woodbury, JW. Cellular electrophysiology of the heart. In: Page, H.Fozzard, HA., Solaro, RJ., editors. *Handbook of Physiology. Section 2: Circulation. : The heart*. Vol. 1. Am. Physiol. Soc; Bethesda, MD: 1962. p. 237-286.
- Woodbury JW, Brady AJ. Intracellular recording from moving tissues with a flexibly mounted ultra-microelectrode. *Science*. 1956; 123:100–101.
- Woodbury JW, Patton HD. Properties of spinal cord elements studied with intracellular ultramicroelectrodes. *Fed Proc*. 1952a; 11:175.
- Woodbury JW, Patton HD. Electrical activity of single spinal cord elements. *Cold Spring Harb Symp Quant Biol*. 1952b; 17:185–188. [PubMed: 13049165]
- Woodbury JW, Patton HD. Intracellular ultramicroelectrode recording from single spinal elements. *Proc XIX Int Congr Physiol Sci, Montreal, CAN*. 1953; 19:327.
- Woodbury JW, Woodbury LA. Membrane resting and action potentials of excitable tissues. *Fed Proc*. 1950; 9:139–140.
- Woodbury LA, Woodbury JW, Hecht HH. Membrane resting potential and action potentials of single cardiac muscle fibers. *Circulation*. 1950; 1:264–266. [PubMed: 15403030]
- Woodbury JW, Lee J, Brady AJ, Merendino KA. Trans-membranal potentials from the human heart. *Circ Res*. 1957; 5:179. [PubMed: 13414092]
- Wright FW. Lawrence (“Laurie”) Gordon Brock. *Br Med J*. 1997; 314:150.
- Yamamoto C. Activation of hippocampal neurons by mossy fiber stimulation in thin brain sections in Vitro. *Exp Brain Res*. 1972; 14:423–435. [PubMed: 4340851]
- Zagoraoui L, Akay T, Martin JF, Brownstone RM, Jessell TM, Miles GB. A cluster of cholinergic premotor interneurons modulates mouse locomotor activity. *Neuron*. 2009; 64:645–662. [PubMed: 20005822]
- Zhang Y, Narayan S, Geiman E, et al. V3 spinal neurons establish a robust and balanced locomotor rhythm during walking. *Neuron*. 2008; 60:84–96. [PubMed: 18940590]
- Zimmerman A, Hochman S. Heterogeneity of membrane properties in sympathetic preganglionic neurons of neonatal mice: evidence of four subpopulations in the intermediolateral nucleus. *J Neurophysiol*. 2010; 103:490–498. [PubMed: 19923248]

Fig. 1.

The five key subjects of this article. (Top left) Lawrence G. Brock [1923–1996] at the age of about 68 years, (Presented with permission of the Brock family). (Top middle) John S. Coombs [1917–1993] when about 45 years of age. (Top right) John C. Eccles [1903–1997] when about 60 years of age. Presumably the latter two photos were the personal property of Coombs and Eccles, respectively. (Bottom left) J. Walter Woodbury [1923–] when about 72 years of age. (Presented with permission of J. W. Woodbury). (Bottom right) Harry D. Patton [1918–2002] at 65 years of age (Presented with permission of J. W. Woodbury who took this photo of Patton's retirement portrait, which is located in the Department of Physiology and Biophysics, University of Washington School of Medicine).

Fig. 2.

A seminal figure in neuroscience. It shows a “... photomicrograph of a cat spinal motoneurone and axon (pyridine silver stain) with superimposed tracing of a microelectrode tip at the same magnification to indicate small proportion of total cell surface which will be damaged by direct cell puncture” (Fig. 1A legend in Brock et al. (1952b)). (Panel presented with permission of the publisher).

Fig. 3.

Examples of key findings in the 1951/1952 work of the Eccles' group (A–C) and Woodbury and Patton (D–F). (A) AP recordings showing response to orthodromic sensory stimulation (1; EPSP shown in lower trace) and antidromic activation of the cell's motor axon (2; dotted line shows superimposed orthodromic spike). The authors commented that "... With motoneurons in good condition ... the negative after-potential reverses at about 4 ms to a positive after-potential (*recognized later as a misnomer and the term changed to AHP*) that reaches 3–4 mV at 20 ms, the total duration being about 120 ms" (p. 15 in Brock et al., 1951; modified version of their Fig. 1 presented with permission of the publisher.). (B) Recordings of clear cut AHPs in MNs supplying a hamstring (1) and a calf (2) muscle (excerpted and modified from Fig. 5 in Brock et al., 1952b). (C) Recordings that resulted in Eccles' instant rejection of his electrical transmission hypothesis for cat MNs. Note the respective sizes of the biceps semitendinosus (BSt) monosynaptic EPSP set up by a small afferent volley in the BSt nerve (C1) as compared to a disynaptic IPSP in the same MN (C2) 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). The B–C panels are presented with permission of the publisher. (D) RP and AP of two dorsal column axons, with the AP of one exceeding (1) and the other (2) less than the RP. E3 shows the spontaneous 29 spike/s repetitive IC-recorded discharge of another dorsal column axon that could be increased to 35 spike/s by

ventriflextion of the ankle (E4) and decreased to 23 spikes/s by dorsiflexion E5). The authors stated that “Since the discharge rate can be modified as much as 25% by tension changes in the appropriate leg muscles, we believe such units are intramedullary extensions of primary afferent fibers supplying stretch receptors” (p. 185 in Woodbury and Patton, 1952b; panel is an excerpted and modified version of their Fig. 1). (E) High frequency discharge (e.g., 1200 spikes/s) of a presumed spinal IN in response to single maximal shocks of the L6 (E1) and L7 (E2) dorsal roots. Note the large and prolonged lower-trace cord dorsum potentials. A mV calibration was not provided but the authors stated that “... Resting potentials up to 80 mV have been recorded; action potentials are usually smaller” (modified version of Fig. 2A–B in Woodbury and Patton, 1952b). (F) Superimposed AP profiles of a presumed MN’s response to a dorsal root (DR) and a ventral root (VR) volley. Note the similarity of these responses to those shown in the A2 panel. Also shown is part of the non-spiking response (dotted line) to another dorsal root volley (DRS) delivered when the MN was spike-silenced by a preceding ventral root volley (excerpted and modified substantially from Fig. 3 in Woodbury and Patton, 1952b). The E–F panels are presented with permission of the publisher.

Fig. 4.

Brief lineage interactions for the 5 key players in this article: Brock, Coombs, and Eccles in NZL, and Woodbury, and Patton in the USA. We have added McIntyre, Rall, and Easton in view of events described in the text about certain key interactions that occurred in 1951–1952 in the Department of Physiology, University of Otago. The one-sided arrows (blue) represent mentor–trainee relationships, whereas the two-sided arrows (red) represent collaborative relationships. Not shown is a two-sided arrow between Brock and Coombs. Interestingly, Huxley did not undertake a PhD degree and he had no primary mentor for his illustrious career. He had substantial early interactions, however, with several outstanding scientists at the University of Cambridge (for details, see http://nobelprize.org/nobel_prizes/medicine/laureates/1963/huxley-bio.html).

Fig. 5.

Woodbury at work. (Left side) Photo taken in 1950 while he was writing up his PhD dissertation at the University of Utah. (Right side) A still photo taken during a Seattle TV station's 1-min interview in which Woodbury explained his and his colleagues' first-ever recording IC-potentials in a human heart muscle. The recording was obtained using a floating microelectrode designed by Woodbury and Brady (1956) and used but once during open heart surgery, with the surgeon allowing but a few tens of seconds for the measurement to be made (Woodbury et al., 1957). In the photo, Woodbury's right hand is holding the electronic probe to which the microelectrode was attached (but not shown in this photo). (Both photos presented with the permission by J. W. Woodbury).

Fig. 6.

Photo of Coombs, Rall, Eccles and Brock taken in late 1951. This panel is excerpted from an 18-person photo of Eccles and most of his trainees, which was taken prior to Eccles' extended late 1951–mid 1952 trip to GBR and the USA. (Presented with permission of the Department of Physiology, University of Otago).

Fig. 7.

Photo of Eccles and Woodbury taken by Dixon Woodbury in 1960 on the patio of the Friday Harbor Marine Station, San Juan Island, WA, USA. Eccles is not really scowling! He had turned his head abruptly for the photo shot. According to Woodbury, the conversation that day was particularly pleasant. (Presented with permission of J. W. Woodbury).

Table 1

CNS IC-recording studies on both RPs and APs undertaken in different nations after the pioneering 1951–1952 reports.

Model ^a	Nat. ^b	Citation ^c	Main finding(s) relevant to present article
(A) First cell type studied ^{d,e}			
Frog ventral horn INs ^f	GBR	Alanis/Matthews '52	Recorded 60 mV AP spikes, which responded rhythmically to various limb movements
Cat lumbosacral MNs	AUS	Coombs et al. '53 ^g	See below
Cat cerebral cortex cells	FRA	Buser/Albe Fessard '53	Recorded >40 mV, 1.5 ms AP spikes w/40–80 ms AHPs
Toad spinal cord MNs and INs ^h	JPN	Araki et al. '53	See below
Cat lumbosacral MNs	NZL	Brock/McIntyre '53 ⁱ	See below
(B) Mammalian spinal MNs ^j			
Cat lumbosacral spinal cord	AUS	Coombs et al. '53 ^{e,g}	Used double-barreled microelectrodes to advance understanding of IPSP mechanism
	NZL	Brock/McIntyre '53 ^{e,g,i}	First use of double-barreled microelectrodes to test (albeit incorrectly) for the IPSP mechanism
	USA	Frank/Fuortes '55 ^{e,g,i}	Provided detailed, valuable technical results and information on MN/IN IC-recording nuances
	SWE	Kolmodin/Skoglund '58 ^{e,i,m}	First study on evolution of RP/AP during natural activation w/ focus on AHP changes
	JPN	Sasaki et al. '60 ^g	Recorded “conventional” FI/Ext MN RPs/APs except for some w/spontaneous discharge
(C) Mammalian spinal INs ^{j,k}			
Cat lumbosacral spinal cord	AUS	Eccles et al. '54 ^{e,g,l}	First report showing cholinergic excitation of repetitive Renshaw cell discharge
	SWE	Kolmodin/Skoglund '54 ^{e,i,m}	In ~200 cells RPs were 80 mV and APs 88 mV; most cells responded to multimodal input
	USA	Frank/Fuortes '55 ^{e,g,i}	Emphasized criteria for distinguishing IN cell body discharge from IN axonal and MN discharge
	NZL	McIntyre et al. '56 ^g	Excellent records of repetitive discharge of 2 spinal INs; one a Renshaw cell
	SUN	Kostyuk '60 ^{e,g,i,n}	Recorded properties like many mentioned above; also reported continuous IN discharge
(D) Nonmammalian spinal MNs ^{g,j}			
Toad spinal cord ^h	JPN	Araki et al. '53 ^e	Smaller RPs and AP spikes than in cat, perhaps due to use of excised “anemic” spinal cords
Frog spinal cord	USA	Machne et al. '59 ^{e,g}	Broad features of APs like those of cat and toad
	GBR	Katz/Miledi '63 ^{e,g}	Described post-synaptic subthreshold membrane potentials like miniature end-plate potentials
	HUN	Czéh/Szekely '71 ^o	Emphasized ease of monosynaptic orthodromic activation of MNs via their dendrites
Frog medulla/spinal cord ^h	SUN	Shapovalov/Shiryaev '73 ^o	Delineated relationship between reticulospinal and propriospinal monosynaptic pathways to MNs
(E) Nonmammalian spinal INs ^{g,j,k}			
Toad spinal cord ^h	JPN	Araki et al. '53 ^e	RPs & AP spikes <20 mV; emphasized cell damage
Lamprey spinal cord ^{h,n}	USA	Rouvainen '67 ^g	RPs 70–80 mV & AP spikes >100 mV in giant cells; smaller values for dorsal cells

Model ^a	Nat. ^b	Citation ^c	Main finding(s) relevant to present article
Frog spinal cord	FRA	Saadé et al. '72 ^o	Uncertainly explained IN AP responses to antidromic stimulation of ventral roots
Frog/lamprey spinal cord ^{h,p}	SUN	Shapovalov '77 ^{e,g,p}	IN PSP responses to reticulospinal, local INs, and sensory feedback input
Frog embryo spinal cord	GBR	Soffe et al., '84 ^o	Commissural IN discharge during fictive swimming w/ anatomical follow-up in HRP-filled cells

^aExcept for the footnote h studies, the animal models were surgically reduced in vivo preparations.

^bLimited to 5 nations for each cell type, with the nations indicated by their three-letter ISO-3166 abbreviation. Note that SUN is for the former USSR.

^cPresented in their chronological order and, if necessary, the alphabetical order of the nation in which the work was done.

^dIncludes abstracts of first IC-recording studies on any cell type in CNS of any vertebrate species.

^eCited one or more of the Brock et al., 1951/1952a,b,c abstracts and/or articles.

^fFrog species not provided.

^gCited one or more Eccles' articles or books that appeared subsequent to 1951/1952.

^hIn vitro preparation of spinal cord.

ⁱAlso cited a Woodbury and Patton 1952 abstract and/or article.

^jMN and IN studies limited to full-length (including short) published reports.

^kLimited largely to INs with short (same segment) projections to MNs.

^lThis group's later article (Eccles et al., 1960), with improved and more detailed examples of IN IC-recordings, is discussed in the text.

^mA more extensive report by Kolmodin (1957) is mentioned in the text.

ⁿPreliminary IN findings were reported in 1958 and a more extensive report on INs appeared in Kostyuk (1961).

^oCited neither an Eccles' nor a Woodbury and Patton publication.

^pSome of the experiments were on lower brainstem-spinal cord preparations.