The emergence of the “motoneuron concept”: From the early 19th C to the beginning of the 20th C

François Clarac, Jean-Gaël Barbara

To cite this version:

François Clarac, Jean-Gaël Barbara. The emergence of the “motoneuron concept”: From the early 19th C to the beginning of the 20th C. Brain Research, Elsevier, 2011, 1409, pp.23 - 41. 10.1016/j.brainres.2011.06.010 . halshs-03090669

HAL Id: halshs-03090669
https://halshs.archives-ouvertes.fr/halshs-03090669

Submitted on 11 Jan 2021

The emergence the "motoneuron concept:" from the early 19th C to the beginning of the 20th C

version auteur de F. Clarac, J.G. Barbara, 2011, « The emergence of the "motoneuron concept": from the early 19th C to the beginning of the 20th C », Brain Research, 1409, 23-41 (ISSN 0006-8993).

François Clarac,[a,]* Jean-Gaël Barbara[b]

[a]*P3M, CNRS, Université de la Méditerranée, 31 chemin Joseph Aiguier, 13402 Marseille, France*

[b]*Université Pierre et Marie Curie, Centre National de la Recherche Scientifique, UMR7102, Case 14, 7 quai Saint Bernard, 75005, Paris and Université Denis Diderot, CNRS UMR 7218, Paris, France.*

*Corresponding author: P3M, CNRS, Université de la Méditerranée, 31 chemin Joseph Aiguier, 13402 Marseille, France. Tel.: +33 491164139
Fax: +33491775084
E-mail: clarac@dpm.cnrs-mrs.fr (F. Clarac)

The research of F.C. is supported, in part, by CNRS funds and that of J.-G. B. in part by the CNRS.

Key words: motoneuron, motoneuron concept, motor pathologies, neuron theory, pioneering histology, reflexes.

Abstract

This article addresses the emergence of the "motoneuron concept," i.e., the idea that this cell had properties of particular advantage for its control of muscle activation. The motor function of the ventral roots was established early in the 19th C and the term "motor cell," (or "motor nerve cell") was introduced shortly thereafter by Albrecht von Köelliker and some other histologists. They knew that motor cells were among the neurons with the largest soma in vertebrates and for this reason they were, and remained for many decades, the best and most studied neuronal model. The work of clinicians like Guillaume Duchenne de Boulogne and Jean-Martin Charcot on motor degenerative syndromes began before a clear description of motor cells was available, because it was initially more difficult to establish whether the deficits of paralysis and muscle weakness were due to neuronal or muscular lesions**.** Next, the pioneering physiologist, Charles Sherrington, who was influenced greatly by the anatomical contributions and speculations of Santiago Ramón y Cajal, used the term, "motor neuron," rather than motor cell for the neuron that he considered was functionally "the final common path" for providing command signals to the musculature. In the early 20th C he proposed that activation of a motor neuron resulted from the sum of its various excitatory and inhibitory CNS inputs. The contraction of motor neuron to "motoneuron(e)" was put into common usage by John Fulton (among possibly others) in 1926. The motoneuron concept is still evolving with new discoveries on the horizon.

Abbreviations

ALS	amyotrophic lateral sclerosis	MN	motoneuron
SC	spinal cord	CNS	central nervous system

Note: For most of the articles of French neurologists cited in this article see:
http://www.bium.univ-paris5.fr/

Contents

1. Introduction

We began our review of some paths of discovery in motoneuron neurobiology (Stuart et al., 2011) with a prologue on the history of how nerve cells became related to the musculature (Barbara et al., 2011). There was a long history of over 1800 years during which “animal spirits” were thought to make this connection (Barbara et al., 2011). To follow our prologue we now focus on the emergence of the "motoneuron concept," which can be defined as the still-evolving idea that the motoneuron has properties that optimize its ability to send commands to the musculature it innervates[1]

With the advent of new neuroscientific methods of the 19th C in anatomy, histology, physiology, and neurology, the nervous system became the object of intense and detailed description of its "centers" and nerve tracts within the central nervous system (CNS), and the nerve cells (later termed "neurons" by Waldeyer (1890)) that connected the CNS with the musculature and glands. The first electrophysiological experiments, which began in the 1780s, focused on nerve conduction and muscular contraction (see Brazier, 1988). Degenerating nerves and nerve cells permitted the clinical characterization of nervous diseases and the creation and improvement of nosologies. Among the various nerve cells studied in the late 19th C, the motor neuron had a particularly prominent position. This cell type differs from all other nerve cells in the CNS of vertebrates by the location of its soma and dendrites being in neuronal centers of the brainstem and spinal cord (SC) whereas Its axon usually projects for a long distance external to the CNS, terminating at a complex structure, the end-plate of the neuromuscular junction, where a neural signal commands muscle activation.

We first describe the development of the motor cell concept by histologists. This concept actually preceded neuron theory, which proposed that a nerve cell was composed of a cell body (like other bodily cells) together with some extruding processes that made contact with other nerve cells (Barbara, 2006a). These contacts, later named "synapses," were in contiguity rather than continuity with other nerve cells. The initial emphasis was on the “motor cell” or "motor nerve cell," which was described in the context of German cell theory (i.e., all living tissues consisting only of cells) by the presence of rounded unitary elements (cells as found in other tissues) among a diffuse network of nerve fibers.

Before neuron theory developed, Jan Purkinje (1787-1869) and Gabriel Valentin (1810-1883) identified nerve cell bodies but considered that they and nerve fibers were two separate neuronal entities. Robert Remak (1915-1865) was the first to advance the idea that the fibers and cells were in fact connected and constituted a single neural entity. Not all histologists agreed with Remak, however (for citations on this issue see Ochs, 2004). For example, some even considered nerve cells and nerve fibers to be quite different types of histological material (e.g., the viewpoint of Charles Robin (1821-1885)).

A highlight of research on the motor nerve cell occurred when Camillo Golgi (1843-1926) and Santiago Ramón y Cajal (1852-1934; hereafter shortened to Cajal) presented their opposing views on the nature of this cell. Golgi argued that motor nerve cells were characterized by their cell body, but not by their endings. For Cajal, however, neurons were comprised of a cell body and all of its extrusions. He considered neurons to be independent anatomical and functional units, and he defined motor cells as those neurons extending their axon to the muscles.

Next we illustrate the work of clinicians on motor degenerative syndromes and their descriptions of clinical examinations that permitted precise diagnoses. This began before a clear histological description was available for motor cells. As a result, it was then often difficult to establish whether the deficits of paralysis and muscle weakness were caused by a neuronal lesion in the CNS or peripheral nervous system or by a muscular lesion. In France, Guillaume Duchenne de Boulogne (1806-1875) introduced this field of enquiry, which was later expanded upon by Jean-Martin Charcot (1825-1893) and his school at the Salpêtrière Hospital in Paris, FRA (Clarac et al., 2009). Their contributions, and particularly those of Charcot, emphasized a refinement of the anatomo-clinical approach in the study of lesions of the motor centers in the CNS.

Finally, we discuss the pioneering work of Charles Sherrington (1857-1952), who introduced the concept of the "common final path", wherein the "motor neuron" was proposed to integrate various CNS commands for posture and movement into a single command to the musculature. Cajal and Jules Dejerine (1849-1917) occasionally used the term, motor neuron, when referring to neurons involved in the motor command to the musculature. When its use finally became widespread, the contraction to "motoneuron" was used by John Fulton (1899-1960) among possibly others in the USA (Fulton, 1926), while "motoneurone" (spelling of French origin), became popular in GBR (e.g., Creed et al. (1935); Hoff (1962)). Both terms have stood the test of time.

2. "Motor nerve cell" focus before ideas on "neuron theory"

The term, motor cell, was already being applied in the 1850s to cells of the anterior (ventral) horns (columns) of the SC. The best known usage of this term at that time was in reports on cell theory and the 1810s'-1820s' findings of Charles Bell (1774-1842) and François Magendie (1783-1855) on the motor function of the ventral roots of the SC (see Olmsted, 1944). Their studies gave rise to a famous priority quarrel. Magendie summarized succinctly the issue when he responded at the Séance of the French Science Academy (March 1, 1847) to Marie-Jean-Pierre Flourens (1794-1867), who championed the findings of Bell: "In sum, Charles Bell had, before me, but unknown to me, the idea of separately cutting the spinal roots; he likewise discovered that the anterior influences contractility more than does the posterior. This is a question of priority in which I have, from the beginning, honored him. Now, as for having established that these roots have distinct properties, distinct functions, that the anterior ones control movement, and the posterior ones sensation, this discovery belongs to m*e*" (Magendie, 1847, p.320).[2] Magendie collected data using his now infamous vivisection experiments on dogs, with similar data collected shortly thereafter by Johannes Müller (1801-1858) on frogs. They both demonstrated clearly that the ventral roots had a specific motor function. Interestingly, Magendie did not use the term, motor cell. Rather, he described the function of the nerve roots of the SC as "la fonction des racines des nerfs rachidiens" ["the function of the roots of the spinal nerves"]. This function of the ventral roots can be considered as an extension of the "motor principle" of Aristotle (384-322 BC) and Hippocrates (460-327 BC): i.e., the importance of movement for living beings (see Sachs, 2005), the "impetum faciens" [principle of life]" of Hermann Boerhaave (1668-1738), the "archea" [soul] of Jean-Baptist van Helmont (1577-1644), and the "soul" of Georg Ernest Stahl (1660-734). According to Magendie (1817), and to previous authors such as Emanuel Swedenborg (1688-1772), a second motor control center resided in the brain, because specific compressions of the hemispheres prevented the ability to contract muscles. Another concept of a motor center was that of the French philosopher, François-Pierre Maine de Biran (1766-1824) (1805). He proposed (in modern parlance) that a forebrain premotor center was the source of centrally generated signals for the perception of the sense of effort involved in voluntary muscle contractions. This fundamental component of self-experience can now be defined physiologically in accords with modern experimental data (Finger, 1994, Clarac et al 2009).

In summary, by the mid 1850s numerous treatises were discussing the “motor roots” of the SC, i.e., a functional concept had replaced the anatomical term, “anterior roots."

2.1. Von Köelliker's concept of the motor cell

The term, motor cell ("motorischen Zellen”), was first used by histologists, such as the German histologist, Albrecht von Köelliker (1817-1905). This was at a time when the concept of the nerve cell (i.e., a cell that connected fibers together) was already well known (von Köelliker, 1854). The term, motor cell, attributed motor function to the soma of individual cells at a time when many physiologists denied such a function. Rather, most physiologists then claimed that nerve fibers played the major role in neuronal conduction to the musculature, with the cell body having but the trophic function of maintaining the viability of its nerve fiber. (Note that the term "trophic" was introduced by Augustus Waller (1816-1870)). The ideas of von Köelliker were, however, in keeping with those of Otto Deiters (1834-1863) on the continuity of motor cells and their processes, the latter including the fibers ("axis cylinders") of the ventral horn cells exiting from the SC. Deiters also distinguished between cells with a motor and a sensory function.

Von Köelliker (1854) studied motor cells in great detail: “These cells [in the anterior horn of the SC], very remarkable in their size, are considered today generally as motor cells, although this idea is insufficiently proven, being 67 to 135 micrometers in diameter, a nucleus of 11 to 18 micrometers; they are fusiform or polyhedral, often filled with a brown pigment; 2 to 9 large processes, sometimes more, of 9 to 11 micrometers at their origin, depart from their end; these processes can be followed up to 220 to 540 micrometers, and they terminate by extremely slender filaments hardly 0.9 micrometers in the grey substance.” (p. 341).

Von Köelliker (1854) ascribed a motor property to not only the ventral half of the SC and the motor cells of the ventral horn, but also to the ventral roots, muscle nerves, and their end-plates. It certainly seems that he was convinced that there was a functional relation between the fibers of the ventral roots and their cells of origin in the SC. He recognized the great step made by Deiters, to whom he attributed the “ … laws governing the relations between cells and fibers in central organs” (p. 362). Clearly, von Köelliker was in total agreement with Deiters and also with Max Schültze (1825-1874). (For other aspects of von Köelliker's impact, see Lazar, 2010).

2.2. Origin of German cell theory

The above ideas were actually within the rubric of the more general German cell theory, which prevailed at that time. As mentioned above, this theory claimed that all living tissues was composed only of cells. The idea was developed by such luminaries as Matthias Schleiden (1804-1881) and Theodor Schwann (1810-1882). The latter declared that “All living things are composed of cells and cell products” (in Schwann, 1839). Rudolf Virchow (1821-1902) soon extended this theory into the field of pathology. His Pathology Institute at the University of Berlin, which was initiated in 1856, became a world-renowned research center for microscopic studies. By the 1860s cell theory adherents were found in most countries, and the convention was for them to make reference to the findings of the German school. Such promulgation was prominent in France and included the work of well-known clinicians like Charcot, Louis Ranvier

(1835-1922), and Victor Cornil (1837-1908).

From then on, a dominant theme of the German school was that the motor endplate was the neuronal organ of transmission of the motor command to muscle from a motor cell located in the ventral horn of the SC. This new description of the involvement of nerve cells in movement was made possible in experimental models like the frog, when using a needle to penetrate its SC and induce movements (Hall, 1833). Jules Luys (1828-1897; the discoverer of the subthalamic nucleus) wrote that " … the motor cells of the spinal cord cannot show spontaneous activity … they need to be excited in order to reveal their rhythmic properties" (in Luys, 1865). He also extended the concept of the motor cell to other central nervous structures: " … the cells of the corpus striatum react in turn, and from their secondary reaction arises a descending motor impulse of a different nature, which immediately orders the activity of several vertically arranged groups of motor cells of the spinal cord by way of anterior spinal fibers".

The concept of the motor cell became widespread in the successive works of anatomists and physiologists, notably in France by Ranvier, Achille Longet (1811-1871), Claude Bernard (1813-1878), and Paul Broca (1824-1880). Ranvier also used the motor cell concept in zoology, e.g., for the motor nucleus of the electric organ of *Torpedo* (p. 1098 in Ranvier, 1875). He reasoned that the fact that stimulation of this animal's motor cells triggered an electric discharge was the best argument in favor of (1) a functional relation between cells in the CNS and their fibers in the periphery and (2) a physiological role for the motor cell (see Barbara, 2006b).

2.3. The transition from motor cell to "motor neuron"

The transition from the motor cell concept to that of the motor neuron was made in parallel with development of the neuron concept, after the pioneering studies of Cajal, Wilhelm His (1831-1904), and Auguste Forel (1848-1931). The German, Heinrich Wilhelm Waldeyer (1836-1921), coined the term "neuron", which he introduced in a series of famous articles (Waldeyer, 1890). Neuron theory stipulated that the nerve cell, including its dendrites and axon, was a fundamental and autonomous unit in development and function. Because motor cells were then known to be among the neurons with the largest soma in vertebrates, and because they could be more easily extracted from the SC than other CNS tissue, they were, and remained for many decades, the best cell model of the neuron. This was evident in the original work of Deiters and Cajal in the late 19th and early 20th C, and then that of many others in the later 20th C.

Interestingly, the concept of the motor cell was originally presented entirely independent of ideas on the motor neuron. Motor cells were described originally in an essentially functional fashion: e.g., as one of the structures in the continuous network between sensory and motor fibers of the SC (e.g., see p. 367 in von Köelliker, 1854). Cajal rejected this concept just as he did the similar ideas of Deiters, Golgi, Jacob Clarke (1817-1880), and Joseph von Gerlach (1820-1896). He emphasized numerous errors by these and other workers in the interpretation of certain structures, including the "axo-protoplasmic network" of Gerlach, and the "reticulum axile" of Golgi (see p. 351 in Ramón y Cajal, 1911). Arthur Van Gehuchten (1861-1914) made the same criticism in his first study using the Golgi technique[3] (van Gehuchten, 1891). He emphasized that many cells in the CNS possessed both long and short axons, and many had both centrifugal and centripetal axons. Clearly, functional criteria alone were not enough. Anatomical criteria had also to be taken into account (e.g., localization of cells, cytological properties of the cytoplasm, cell morphology, territory of the axon).

Cajal advocated the necessity of studying the fine structure of the SC according to his “principle of connections”, i.e., using morphology to distinguish between neurons. In this fashion he defined what a motor neuron actually was. He used the term, motor neuron, in the summary of his chapter devoted to this cell type (Ramón y Cajal, 1911). Later, however, he preferred the term motor cell, and no difference can be found in his writings between the meanings of these two terms. He stated that the motor neuron was defined both morphologically and functionally (Fig. 1). To him, its physiology was based on it being located in the ventral horn of the SC, with an axon that exited the SC through the ventral horn (albeit with some processes that entered the posterior horn). Morphologically, he emphasized that the motor neuron possessed a “ … powerful axon-cylinder leaving the cord and forming with companion fibers the anterior or motor roots” (p. 361 in Ramón y Cajal, 1911) Cajal insisted on these fundamental two characterizations, and he reported on additional ones, as well.[4]

Cajal provided a description of the soma of the motor neuron in the general part of this book that dealt with the structure of the neuron (pp. 152 and 163 in Ramón y Cajal, 1911). Dendrites and the axon were also described in great detail, as based on the use of his own Golgi technique on embryonic tissues, which he considered the best possible for such studies (p. 355). The motor neuron was described as a cell “of considerable size,” whose soma was “ … elongated in a transversal direction or antero-posterior, depending on the location of the neuron, with numerous dendritic processes, thick and very long” (pp. 355-356). Cajal used the term motor neuron when focusing on anatomo-physiological aspects of its properties.[5] He also constructed a novel "histophysiology" of the motor neuron. This later became the structural basis of functional reflex studies of the SC conducted in the 1920s-1940s by influential neurophysiologists, including Sherrington, Alexander Forbes (1882-1965), Herbert Gasser (1888-1963) John Eccles (1903-1997), Birdsey Renshaw (1911-1948), and David Lloyd (1911-1985).

For the peripheral components of the motor neuron, the centrifugal structures, Cajal summarized all the then-available anatomical knowledge about its axon, axon collaterals, and the motor end-plate, the latter being well known by then as the organ of transmission between nerves and muscles. The data of past histologists was mentioned with appropriate historical recognition. He acknowledged quite freely and openly that numerous previous workers had studied the end-plate in isolation (Fig.2). Some such authors were Ranvier, Louis Doyère (1811-1863) (see Doyère, 1840), Charles Rouget (1824-1904; see Rouget, 1862), Wilhelm Krause (1833-1909), and Friedrich Kühne (1837-1900). Cajal's descriptions of motor endplates (“motorische Endplatte” in German and “buissons terminaux” in French) were in accords with neuron theory, since his best observations showed free nerve endings on the surface of muscles.[6]

2.4. The motor end plate

During the 1930s, W. Feldberg (1900-1993) demonstrated the presence of cholinergic neurons in different regions of the nervous system and not only in visceral systems. D. Nachmanson (1899-1983) a biochemist has found that a very efficient enzyme, the acetylcholine esterase was able to transform the Ach in choline and in acetate. A. Fessard (1900-1982) a french neurophysiologist invited both at the marine station of Arcachon in 1939 where it was easy to collect a particular fish, *Torpedo marmorata* that possesses an electric organ that corresponded to a giant neuromuscular junction. Nachmanson found in this specimen that Ach enzyme was at a very high concentration (Nachmanson, et al. 1941). Eserin that inhibits the action of the enzyme will rapidly induce a fatigue and the electric organ will not respond at the end. Feldberg and Fessard (1942) have made a detailed study of the electric organ demonstrating that there was 40-100 µgrs of ACh/gr. of fresh tissue. A stimulation of the nerves of the organ, produced Ach. but it was

immediately destroyed by the enzyme. To found Ach, it was necessary to add some eserin.
In the mid 20th C, the French anatomist, René Couteaux (1907–1999), made further descriptions of the elements of the motor end-plate using the supravital dye, Janus green B, a molecule with a methylated quaternary nitrogen group (Lu and Litcham, 2007), which was similar to that in methylene blue, a dye that was used first by the German immunologist, Paul Erlich (1854-1915). Couteaux (1944) discovered the "synaptic gutters" of the sarcolemma beneath the nerve terminal and the lamellar "subneural apparatus" ["appareil sous-neural"]. These structures were to be later investigated with electon microscopy, cryofracture, and histochemistry. in order to quantify the densities of vesicles and that of calcium channels, as well as the localization of acetylcholine and acetylcholinesterase.

In all, the above story shows how the motor neuron concept was progressively refined with the Golgi method, methylene blue, other stains such as Janus green B, and new microscopic techniques. The concept laid the groundwork for issues that would later be considered under the rubric of the term, motoneuron(e). The motor neuron concept also contributed substantially to the strengthening of nosologies on nervous diseases, emphasizing both an anatomical perspective (pp. 178 and 545 in Van Gehuchten, 1894) and an anatomo-pathological perspective (Dejerine and Dejerine-Klumke, 1914). The motor neuron of the 20th C became the rubric for an array of well-defined concepts using anatomical, physiological, and anatomo-pathological data. A synthesis of these three approaches was lacking, however, until the later work of Charles Sherrington and the Oxford School of Physiology (see below).

3. Motor diseases and motor neurons

Anatomical knowledge about the nervous system had changed radically by the beginning of the 19th C.[6] Fifty years later the emphasis was on correlating clinical observations with the anatomo-pathological method of Morgagni-Bichat-Charcot (see below). For example, several types of neuromuscular lesions were depicted by this method in the Paris School of Medicine (Clarac and Boler. 2009). (see Lazar (2010) for contributions by American neurologists in the late 19th C).

3.1. Duchenne de Boulogne and the motor pathologies

Our clinical story begins with Guillaume Duchenne (1806-1872), who was born in Boulogne-sur-Mer, FRA and subsequently became widely known as "Duchenne de Boulogne" (Fig.3B) or often just "Duchenne." He specialized in the use of "electropuncture" to excite particular regions of the body. This technique had been used previously by Magendie and Jean-Baptiste Sarlandière (1787-1838). Duchenne's primary initial aim, like that of other clinicians at that time, was to relieve the pains of patients. He found, in addition, that his method could differentiate between the most refined contractions of muscles, thereby allowing him to quantify various movements. He visited Parisian hospitals, often without appropriate letters of recommendation, in order to use his electrical armamentarium.[7] He achieved near-instant respect and recognition for this work, however, by an elite group of Parisian clinicians, who were to become close colleagues and friends. These included Armand Trousseau (1801-1867) at Hôtel-Dieu Hospital, Pierre-François Rayer (1793-1879) at La Charité Hospital, and most of all Charcot, who welcomed him at La Salpêtrière Hospital in 1862. Duchenne's initial results led him to abandon the idea of Galen of Pergamum (129-216 AD) that movements could feature the isolated contraction of a single muscle Rather, he embraced the approach of Jacques Winslow (1669-1760) on the functional classification of muscles. For example, Duchenne (1867) wrote that " … All these movements of the limbs and trunk [including the thorax and the abdomen] follow a double nervous excitation, by virtue of which two classes of muscles, by their association, possess contrary actions … and simultaneously contract, the former to produce movements, the latter to regulate them" (Duchenne 1867, p. 766). This distinction was later of great importance to Sherrington in his explanation of the coordination of reflexes (see below).

Duchenne's procedures for faradization of neuronal and muscle tissue by progressive continuous electric current were similar to those of Remak.[7] Duchenne's techniques enabled him to report descriptions of numerous neuromuscular pathologies (reviewed in Guilly, 1977). For example, he commented in 1861 on the condition of a young boy with congenital hypertrophic paraplegia.[7] In 1868, Duchenne made a more detailed observation of this disease, which he named "hypertropic muscular dystrophy" and emphasized its potential hereditary origin. It is now known as “Duchenne’s muscular dystrophy.”

What could explain the above and allied pathologies and what could be their origin? Were they due to muscular or neurological diseases? Earlier (in 1850), in parallel with the work of François-Amilcar Aran (1817-1861), Duchenne had distinguished progressive muscular atrophy from other paralyses and he also distinguished its different stages. Electrical stimulation enabled him to excite intact muscles and healthy fibers in pathological muscles, while noting that degenerated muscles and their fibers remained unexcitable. He first thought that muscular dystrophy had a muscular origin. However, the first autopsy by Jean Cruveilhier (1791-1874), first chair of pathological anatomy at the University of Paris, did not reveal primary muscle deficits (Fig.3C). When a new case was autopsied, that of the French street acrobat, Prosper Lecomte (1818-1853), a large atrophy of the ventral horns of spinal nerves was observed. Cruveilhier (1856) wrote about Lecomte that “ … the third observation … demonstrates in the most scientific manner the atrophy of the anterior roots of the spinal nerves, which I could follow up at various degrees from the simple decrease in volume of these roots without any noticeable alteration of their tissue, to their shrinkage to neurilema, the last degree of nervous atrophy” (p. 134). Duchenne doubted this association between degenerated ventral roots and hypertrophic muscular dystrophy. Auguste Axenfeld (1825-1876), a pupil of Gabriel Andral (1797-1876), and German physicians such as Nicolas Friedreich, (1825-1882) also believed that this dystrophy involved deficits that were purely muscular in origin. In 1860, however, the renowned histopathologist, Luys, confirmed that muscle atrophy was attributable to degenerated ventral roots in patients similar to those studied by Duchenne (Fig.3D).

In parallel with his work on hypertrophic muscular dystrophy, Duchenne described progressive locomotor ataxia as a major impairment in movement coordination during walking. Others, in important neurological centers throughout Europe, also described this disease. The German neurologist, Moritz Romberg (1795-1873), called it "tabes dorsalis" (Romberg, 1846), with an emphasis on the disease producing tremors of the limbs and of the body, which were exaggerated during darkness. He also described a decrease in muscular sense in these patients and he used his own name to describe its full array of sensorimotor symptoms ("Romberg's sign;" see Pearce, 2005). These deficits were soon correlated with lesions of the dorsal columns of the SC by the British neurologist, Robert Todd (1809–1860) (1847). Another British neurologist, Augustus Clarke (1817-1880) reported other cases of tabes dorsalis, which he discussed with Duchenne, when the latter worked briefly in Clarke's London laboratory in 1869 (Guilly, 1977).

3.2. Charcot's description of amyotrophic lateral sclerosis (ALS)

The work of Charcot on dystrophies was like that of Duchenne. Between 1862 and 1874, Charcot studied pathologies of the SC, including progressive muscular paralyses (see Goetz et al., 1995). With one of his pupils, Alex Joffroy (1844-1908), he described a condition that he named “amyotrophic lateral sclerosis [ALS]” (see Fig. 3). The subjects in their main study (Charcot and Joffroy, 1869) were Catherine Aubel and Adèle C. Aubel's deterioration was described chronologically with a detailed analysis of the progression of her motor paralysis. When she was first studied in Charcot's clinic in 1865, she already displayed all the signs of a muscular atrophy that had started nine months earlier. She was able to shut her mouth, but she was unable to blow or whistle. Although her intelligence was not altered, saliva flowed from her mouth. Her limbs were all affected, especially her arms. She had great difficulty in lifting her hands 10 cm. above her knees. Rather, they remained largely passive below her knees most of the time. Fibrillary contractions occurred in her hands from time to time. She was unable to write with her right hand. Between 1865 and 1869, the progression of her motor paralysis was slow, but in February 1869 her condition abruptly worsened. On February 5, Aubel started to suffocate and she died on February 11.

The second part of Charcots' and Joffroy's report on Aubel concerned a complete analysis after her postmortem examination. It illustrated the value of the improved anatomo-clinical method of Charcot. The case report included every analysis made during the autopsy, which was undertaken on February 15, 1869. The corpse was depicted and measured in great detail, including both external and internal aspects of the muscles, nerves and neuronal centers. Concerning the SC, Charcot and Joffroy (1869) wrote that “It is striking to notice with the naked eye the considerable change in the volume and color of the anterior roots” (p 361).

The last part of their report was a microscopic examination of the muscles: “ … the striation is totally absent in a number of muscle fibers which appear as cylinders filled with a transparent substance with … granulations” (p. 362).

Three new observations were made in the Charcot-Joffroy report on the basis of their inspection of transversal thin sections of the neuronal centers. At the level of the antero-lateral columns of the SC they observed that " … the connective tissue became of a considerable size; they are much thickened and they seem to have increased in number” (p. 365). The posterior columns of the SC were found to be intact. Concerning the grey matter of the SC they wrote that “ … the great state of atrophy … of most of the nerve cells is at first very striking. These cells are mostly those of the internal group or the anterior group which are profoundly altered …” (p. 365). These SC cell groups were compared with those in healthy subjects: “We made comparison with very nice specimens of healthy spinal cords which we owe to the goodness of M. Lockhart-Clarke.” In the brainstem they noted that " … most of the cells of origin of the hypoglossal are profoundly altered, in a state of atrophy or fully destroyed” (p. 365).

Their second ALS patient, Adèle C., exhibited similar symptoms, but with an additional problem in sensation. A.C. sometimes suffered great pain. “These pains are often sharp and always apyretic, displaying a double character; they are located in the continuity of limbs, along the nervous paths, and in the joints…but also in the muscle… (p. 637). The autopsy revealed similar lesions to those seen in Catherine Aubel, most of them in the white lateral columns (see also Fig.4C).

The last part of the Charcot and Joffroy (1969) report was a synthesis of their two case studies, thereby providing the first anatomo-clinical description of ALS pathology; i.e., progressive muscular atrophy associated with lesions of the white columns of the SC and cellular lesions in its grey matter. Moreover, they mentioned similar cases described by other clinicians that reinforced their own conclusions. In particular, they mentioned several cases described by Clarke (described in Turner et al., 2010). The cause of cell loss in the ventral horns was discussed by Charcot and Joffroy but the origin was not found: " … It seems to be … an irritation process with a slow disruption of the cells leading to full atrophy" (p. 753). The relation between neuronal and muscular lesions was also discussed: "There is a close relation between the trophic lesions of the muscles and those of the nervous fibers; in relation with the origin and the distribution of the motor nerves, we were careful to report, in several occasions, a strict agreement between the position of the altered cells in the cord and the particular location of the atrophy of the muscles in the various parts of the body" (p. 754). Although it remained uncertain to the authors whether cells of the SC innervated muscles directly, they came close to advocating this idea: "Today, pathological anatomy seems to point out that the alterations of the cord take place in the grey matter of the anterior horns, and that their nerve cells are precisely the entities whose lesions lead to that of the muscle fibers" (p. 755).

3.3. Further early information on ALS

In one of Charcot's famous "lessons" (for background, see Charcot 1872-1873/1877), which he wrote in 1874, he proposed that spinal amyotrophies should be divided into two groups: "protopathic" amyotrophy, which involved lesions in only the ventral horns (Aran-Duchenne's amyotrophy), and "deuteropathic" amyotrophy (ALS), wherein the lesions of the ventral horn were secondary to lesions in the white substance of the SC.

In 1860 Duchenne reported about lesions in the brain stem and the medulla oblongata. His article began with the statement that "From 1852 onwards, I collected 13 cases with a paralytic disease of unknown origin spreading successively to the muscle of the tongue, the soft palate and the oral orbicular muscle, with subsequent progressive deficits in the articulation of words, deglutition … and complications with frequent suffocating" (p. 283). The German poet, Henri Heine (1797-1856) was affected by this ghastly disease. The French histologist, Albert Gombault (1844-1904), who was a student of Charcot, described lesions of the patient, Elisabeth P., who suffered from a labio-glosso-laryngeal paralysis, and died by suffocation (see Fig. 3F). Severe lesions of the pyramidal tracts at the bulbar level were reported, as well as the loss of cells of the hypoglossal nucleus (Gombault, 1871). Subsequently, Gombault presented his dissertation on ALS in August 1877, with two professors Charcot and Adolphe Gubler (1821–1879) and two qualified teachers ("agrégés") Jean-Baptiste Duguet (1837-1914) and Charles Alexis Fernet (1838-1919) as jury members (Gombault, 1877). Case studies on nine patients were discussed, with three from Charcot, two of his own, two from Stanislas Dumesnil (1823-1890) in Rouen, one from Eugène Woillez (1811-1882) in La Charité Hospital in Paris, and one from Clarke in London.[10]

Duchenne continued to acknowledge the distinction between ALS and progressive muscular atrophy. The German pathologist, Ernst Viktor von Leyden (1832–1910), a specialist in neurological pathologies, opposed this viewpoint, albeit he refused to subsume all lesions of the motor system into a single nosology. Accordingly, he considered bulbar lesions apart, and coined the pathology as "the bulbar paralysis of Leyden" (Leyden, 1878).

Gombault challenged the reasoning of Leyden on the basis of a new case (X, 35 years of age) and the observations of the Czech neurologist, Otto Kalher (1849-1893), and the German neurologist/psychiatrist, Arnold Pick (1851-1924). Debove and Gombault (1879) wrote that "Mr. Leyden thought he could deny the autonomy of the disease we described; he said he considered the symmetrical sclerosis of the lateral columns and the progressive muscular atrophy (Duchenne-Aran type) should not be separated. We should recall, without mention of secondary arguments, that a difference is found with a rigidity of the limbs and contractures in the first disease, whereas none are found in the second" (p. 759). This paper brought out clearer features of these two pathologies, with an emphasis on the progression of these diseases involving progressive lesions of the pyramidal tract. They wrote further that "The lesions of the white matter of the spinal cord are limited to the pyramidal tracts. Recent research by Fleschsig, by which we know the trajectory of these tracks so well, showed us they were lesioned, and moreover, along their full extension" (p.762). Debove and Gombault (1879) also insisted on the altered cranial motor nuclei, but nothing was said on the relation between the pyramidal tract and the lesioned bulbar and spinal motor nuclei. The relation was apparently self-obvious to them.

3.4. Reactions of neurologists to neuron theory

All the above clinical studies were made more-or-less simultaneously, and at the time that Golgi discovered the "*reazone nera*". His polemic with "neuronists" arose because Golgi held to the reticular theory of Joseph von Gerlach (1820-1896), who used a stain with carminate and gold chloride, which was specific to neuronal tissues. His results led to his theory of a syncytial arrangement of nerve cells combined in complex networks (von Gerlach, 1872).

Subsequently, Gombault and Philippe (1902) made the interesting comment that "The great Italian scholar [Golgi] thinks he can see real anastomoses in the grey matter, formed by fibrils of similar nature to that of axon-cylinders; in a study published in 1891, Golgi claimed the existence of an authentic diffuse network "… (p. 702). Gombault and Phillipe (1902) further mentioned Golgi's claim "All nerve cells with a long axon-cylinder are motor; all those with a short axon-cylinder are sensory" (p.701). Cajal could never accept such a simple characterization!

Gombault and Phillipe (1902) also commented that " … Indisputably, this new conception, which follows the old theory of the network of Gerlach, makes easier the interpretation and the synthesis of a great many anatomical, physiological and pathological facts. According to some authors, it should even establish the unique basis to any histological study … However, we feel it cannot be in practice; besides, many facts of human pathology would not fit its framework" (p. 695). They thought it impossible to track the long axons of neurons in their entirety, such as those of motor neurons. However, they recognized a key contribution of Cajal: "We ought to give credit to the Spanish scholar for his demonstration of axon-cylinder processes always ending freely, with no anastomoses, everywhere at the periphery as in the grey matter, as opposed to the doctrine of Golgi" (p. 703).

It is interesting that Gombault and Phillipe (1902) used the terms "motor cells of the spinal cord," or "radicular cells of the anterior horn of the human spinal cord" (see Fig. 4 A,B). Only rarely did they use the term, motor neuron, and never motoneurone.

We conclude that lesions of motor cells were well characterized far before the motor neuron concept appeared. Such pathological and neurological descriptions certainly implied the existence of motor cells, but the conceptualization was incomplete, and the motoneuron concept was absent (Haymaker and Schiller 1970).

4. Sherrington, reflexes, and the term "motoneuron(e)"

In the early 20th C, Sherrington analyzed what he called the “elementary spinal reflex” in the cat. While he was not sure this entity was real or heuristic, he challenged previous studies on spinal reflexes by integrating histological knowledge of the SC into the framework of neuron theory. His rigorous analyses, systematic approaches, and widespread influence all contributed to making his studies widely known and accepted as an all encompassing analysis of the SC, which he considered to be the most accessible nerve center in the CNS that could be studied with the then-available tools. His depictions of the trajectory of nerve fibers involved reflexes, in particular. His work on the functional effects of reflexes provided a new framework for his emerging hypothesis of a single output neuron to the musculature, the effector organ, the motor neuron. “The conception of a reflex therefore embraces that of at least three separable structures-an *effector* organ, e.g., gland cells or muscle cells; a conducting nervous path or *conductor* leading to that organ; and an initiating organ or *receptor* whence the reaction starts” (p.7 Sherrington 1906a).

4.1. Sherrington's initial research

The scientific life of Sherrington started in 1881, after the 7th International Congress of Medicine in London, when the British neurologist, David Ferrier (1843-1928), argued with the German physiologist, Friedrich Goltz (1834-1902). Ferrier presented findings on a hemiplegic monkey, which lacked the cortical motor region. He argued that the monkey's motor deficits supported the concept of a localization of brain functions. In contrast, Goltz presented a dog with several brain lesions but no apparent deficits, thereby supporting the unitary theory of Flourens.[11] The argument was so fierce that the organizing committee of the congress, which included two of Sherrington's mentors, the British physiologists Walter Gaskell (1847-1914) and John Langley (1852-1925), decided to make an autopsy of the two animals in order to make a judgment. Langley and Sherrington were asked to undertake a histological investigation of the right side of the medulla and the SC of Goltz’s dog. Sherrington's later training emphasized this association between histology and physiology. In 1884-1885, he spent almost nine months in the Strasbourg laboratory of Goltz. In 1886 he had two months in Virchow's Berlin Institute of Pathology followed by a year (1986-1987) in Berlin with the bacteriologist, Robert Koch (1843-1910).

4.2. Sherrington on cell and neuron concepts

Sherrington delivered the first set of Silliman Memorial Lectures at Yale University, USA in 1904. They were published in his renowned book on the integrative actions of the nervous system (Sherrington, 1906a). The first chapter was devoted to new knowledge about the nerve cell and neuron theory, which he considered as important as the theory of evolution. This idea was well accepted by Sherrington's peers because British scientists at that time had emphasized cell theory in all fields of biology, including endocrinology and biochemistry. In contrast, many contemporary physiologists in other countries, including many in France, still considered nerve fibers as the fundamental structural elements of most interest for study of the nervous system. Sherrington considered that nerve cells did indeed have several fundamental properties that were similar to those of other animal cells. For example, in Sherrington (1906a) he stated in the first sentence of the first lecture (chapter 1) that “Nowhere in physiology does the cell-theory reveal its presence more frequently in the very framework of the argument than at present time in the study of nervous reaction. (p. 1) and that " … nerve-cells, like other cells, lead individual lives – they breathe, they assimilate, they dispense their own stores of energy, they repair their own substantial waste” (p. 2). However, Sherrington also emphasized that nerve cells had their own special properties, because they conducted the nerve impulse and displayed integrative properties. He advocated that nerve cells should be studied as a biological unit with integrative properties, and an essential element for conduction of the nerve impulse. He defended neuron theory as a simple generalization of cell theory, which he argued were introduced in GBR by researchers influenced by the German School.

Sherrington defined the connections between neurons with the gusto of a card-carrying cell biologist. For example, Sherrington contributed a chapter on the CNS to the 7th edition of the well-known physiology textbook of Michael Foster (1836-1907). Sherrington and Foster coined the term "synapse" in this chapter: “So far as our present knowledge goes we are led to think that the tip of a twig of the [axon’s] arborescence is not continuous with, but merely in contact with, the substance of dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called a synapsis” (p. 929 in Sherrington and Foster, 1897). Sherrington recalled this episode in a letter dated December 25th 1937 to Fulton: “M. Foster had asked me to get on with the nervous system part … I wrote him of my difficulty, and my wish to introduce a specific name. I suggested using syndesm. He consulted his Trinity friend Verrall, the Euripidean scholar, about it and Verrall suggested “synapse” and as this yields a better adjectival form, it was adopted for the book.”

Sherrington's above-mentioned comment on evolution was made because he promulgated that reflex mechanisms were adaptive processes of living beings as they accommodated to changes in their environment. Hence, reflexes were necessary for evolution. One reason that Sherrington could not agree with the reticular theory of von Gerlach and Golgi was that he believed that nerve impulses entering the SC were unlikely to circulate freely in a diffuse network in order to reach by unknown means a specific motor output. Rather, he supported the idea of contiguity among neurons at synapses and he found several examples in the field of physiology. One was that antidromic nerve conduction was the opposite of the irreversibility of conduction in SC centers, i.e., always proceeding from sensory to motor elements. Sherrington argued that if conduction was not opposed in the nerve, then it must occur at synapses in the SC.

Furthermore, Sherrington measured the delays in conduction of the nerve impulse in SC centers, as opposed to conduction in peripheral nerve trunks. This delay increased as the impulse reached one or more synapses along its path. The synapse concept was also used to explain why activities did not terminate immediately when the stimulus terminated.

In all of his studies Sherrington analyzed physiological phenomena from a cell biologist’s perspective, using the biological knowledge that was available at that time. Although he lacked the later-developed techniques that permitted the study of spinal reflexes at the neuronal level, he elaborated models wherein interactions between nerves and between nerves and the CNS were explained by the integrative properties of neurons. His "final common path" concept was defined as a pool of motor neurons that integrated their descending and sensory input into impulses along their axons, which exited the ventral horn to activate the musculature. Therefore, the motor reflex output was via motor neurons, with no distinction made at that time between alpha and gamma neurons.[12]

4.4. Motor and sensory pathways in a reflex

Sherrington's most significant experimental work was undertaken between 1891 and 1932 (see Burke, 2007). During his first decade of work, he focused near-exclusively on anatomical studies. As a complete physiologist, he was fully aware of the need to have a detailed knowledge of the structures under physiological investigation.

Bell's ideas were important to Sherrington, especially his hypothesis of the "nervous circle," which conceptualized the CNS as a closed system of muscular commands and sensory motor responses, which was influenced by environmental factors, and regulated movement. Bell (1836) wrote that "Between the brain and the muscles there is a circle of nerves; one nerve conveys the influence from the brain to the muscle, another gives the sense of the condition of the muscles to the brain. If the circle be broken by the division of the motor nerve, motion ceases; if it be broken by the division of the other nerve, there is no longer a sense of the condition of the muscle, and therefore no regulation of its activity" (cited on p. 37 in Swazey, 1969).

Examples of Sherrington's anatomical work include a monograph in which he delineated the peripheral distribution of the fibers of the dorsal roots and the afferent nerves (Sherrington, 1892; see also pp. 327-328 in Stuart et al., 2001). Another example was his demonstration of the presence of sensory fibers within the musculature (Sherrington, 1892).

After some work on the delineation of the cerebral motor region in the monkey, Sherrington focused on the study of reflexes in the dog but soon he focused on the cat. The first he investigated was the knee-jerk reflex (tendon reflex, patellar reflex). It involves the patellar tendon of the knee, which when stretched also stretches the quadriceps and causes this muscle group to contract. This reflex was first described clinically, in 1875 by both the German neurologist, Whilhelm Henrich Erb (1840-1921), who using a "reflex hammer" to activate the reflex, and the German psychiatrist, Carl Friedrich Otto Westphal (1833-1890). Westphal should get no credit because he thought the muscular response was direct. Erb correctly described it, however, as a reflex, which he tested in clinical examinations. Erb coined the term "patellar Schenenreflex", which was renamed in 1880 as the "myotatic reflex" by the British neurologist, William Gowers (1845-1915).

Sherrington studied the neuronal pathways of the above reflex in great detail. He described the different motor and sensory nerves involved by sectioning various nerve branches and spinal roots while testing for the viability of the reflex (Sherrington, 1892). This approach revealed that its reflex arc involved a quite limited region of the SC and few dorsal and ventral roots. The necessary (test) spinal roots were then ligated (thereby preventing peripheral impulses reaching the SC) and studied anatomically by using Wallerian degeneration of three roots above and three roots below the test ones (Sherrington 1894). Twenty-eight days after the sections, the isolated test roots were activated by electrical stimulation, in order to show their function in the reflex and to establish the cutaneous fields of the sensory fibers for each dorsal root. (discussed in Swazey, 1969). Sherrington demonstrated that adjacent sensory roots innervated, in part, each body area. He also showed that the motor fibers innervating agonist muscles could come from the same ventral root, even though their central projections were to different motor nuclei in the ventral horn of the SC.

While performing such studies, Sherrington made a fundamental finding: a third to one half of the myelinated fibers of motor nerves[13] did not degenerate after section of their motor roots.

Thus, they were sensory fibers innervating muscles. It was later demonstrated that they came largely from muscle spindles and Golgi tendon organs (for the history of this development, see Matthews, 1972). Spindles had first been observed by the German evolutionary biologist, August Weismann (1834-1914) in 1861, then the German physiologist, Willy Kühne (1837-1900), in 1863, and later by the Italian anatomist, Angelo Ruffini (1864-1929), who wrote several articles about them (e.g., Ruffini, 1897, Ruffini 1898-9). Sherrington defined "proprioception" (the muscular sense) as opposed to exteroception and interoception in an article published in honor of the British neurologist, J. Hughlings Jackson (1835-1911) (Sherrington, 1906b). (For the full subsequent impact of this article, see Evarts, 1981).

4.4. Simple spinal reflexes

Sherrington's initial studies on simple spinal reflexes led him quickly to the concept of inhibition as an active rather than passive process. He was struck, so it was said, by the explanation of the French mathematician and philosopher, René Descartes (1596-1650), on how animal spirits kept antagonist muscles at rest (Descartes, 1662). Sherrington was indeed intrigued by this antagonism of muscles with opposite functions. He suggested there might be some mechanism by which a contracting muscle inhibits a antagonist muscle. This was exactly what Bell (1823) had written about: “The nerves have been considered so generally as instruments for stimulating the muscles, without thought of their acting in the opposite capacity, that some additional illustration may be necessary here. Through the nerves is established the connection by which muscles combine to one effort, but also that relation between the classes of muscles by which the one relaxes and the other contracts” (cited on p. 69 in Swazey, 1969). Several authors in the 19th C emphasized the presence of inhibition during reflex activities. In 1845, the German Weber brothers (Ernst (1795-1878) and Eduard (1806-1871) showed that vagal nerve stimulation had an inhibitory effect on cardiac activity (see Hoff, 1940). The Russian neurophysiologist, Ivan Sechenov (1829-1905), found a lessening of reflex activity during stimulation of the brainstem of the frog (see pp. 358-359 in Stuart et al., 2001). The German physiologist, Ewald Hering (1834-1918), and the Austrian physician, Josef Breuer (1842-1925), showed that sustained lung inflation could cause a transient apnea (see Breuer, 1970). These are but a few such examples.

While Sherrington (1913) was again considering reciprocal inhibition, he stated that “In the simple correlation uniting antagonistic muscle pairs, inhibition of antagonist accompanies excitation of protagonist ... In all cases inhibition is an integral element in the consolidation of the animal mechanism to a unity. It and excitation together compose a chord in the harmony of the healthy working organism" (cited on p. 84 in Swazey, 1969). This mechanism is fundamental to virtually all movement in vertebrates.

In the mid-1920s, Eric Liddell (1895-1981) and Sherrington analyzed myotatic reflexes of the decerebrate cat (Liddell and Sherrington, 1924, 1925). The quadriceps, an extensor group of muscles, was subjected for a few seconds to a sustained stretch of a few millimeters. The immediate reaction was an increase in tension reaching a maximal value, before slowly returning to a lower value, which was maintained as long as the stretch continued. The latency of the initial response was very brief. If the nerve to the muscle was cut, the same stretching induced but a residual tension due to the elastic distortion of the muscle. The reflex response was the difference between the latter tension and that when the nerve was intact. The reflex involved two myotatic components, a fast and intense one produced by the initial component of the stretch, and a tonic one due to the sustained stretch. If an antagonist (flexor) muscle was stretched simultaneously, the quadriceps reflex was inhibited completely.

Much later, Lloyd (1943) measured precisely the delay in the initial phase of the above reflex. He showed that it was monosynaptic and due to sensory input from the large group I fibers.

One of the great strategies of Sherrington was his use of decerebrate animals (largely cats) in most of his reflex experiments. He usually made the brainstem decerebration in the cat under ether anesthesia and from between the brainstem's anterior and posterior colliculi dorsally to the posterior margin of the mammillary bodies ventrally. When the ether was withdrawn, the unanesthetized, pain-free preparation exhibited hyperactive extensor activity, which was particularly suitable for the study of inhibition as well as excitation. Sherrington coined the term “decerebrate rigidity” in 1897 to describe this preparation's control state. Decerebrate preparations of several vertebrate species were well known at that time, however. For example, they had been used previously by Magendie, François Longet (1811-1874), Claude Bernard (1813-1878), and Flourens, among many others.

Sherrington was well aware of the limitations of his work on reflexes. For example he wrote early on that “… a simple reflex is probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts, and it is a system certainly never absolutely at rest. But the simple reflex is a convenient if not probable, fiction" (p. 8 in Sherrington, 1906).

4.5. The complex scratch reflex

Sherrington not only analyzed short-latency reflexes, but also longer duration, more complex ones. He focused on the scratch reflex of the spinal cat and dog, which he found to be quite pronounced. With Ernest Laslett (1875-1958) he showed that scratching the skin of the back or neck in these two preparations induced a forward ipsilateral flexion of the hind limb that featured a series of flexion-extension movements of the hip, knee, and ankle (Sherrington and Laslett, 1903; see Fig. 5). When the foot scratched the neck and the flank, the reflex began with plantar flexion. Using various stimuli of various sites, it was shown in another study that movements were directed toward the point of scratching (Fig. 5B; Sherrington 1906c). The relation between the ventral stimulation and the lumbar motor response was always ipsilateral. Sherrington and Laslett (1903) reevaluated the famous and widely accepted reflex "laws" of the German physiologist, Eduard Pflüger (1829-1900) (1853). Sherrington did not accept Pflüger's fourth law about nervous conduction and the concept of a preferred direction of irradiation. With Laslett, Sherrington confirmed the distinction between short-latency spinal reflexes (the response limited to the region stimulated) and a "long" spinal reflex (the response extending to other body regions). They argued that the scratch reflex belonged to the second group because it engaged conduction in the long ipsilateral tracts of the SC's white matter. There was no preferential irradiation towards the medulla oblongata, as Pflüger had thought. Rather, Sherrington and Laslett (1903) showed that connections were made by descending and ascending tracts in every direction throughout the segmental levels of the SC.

The scratch reflex was of great importance to Sherrington (Sherrington 1906c). In his 1906 book, he twice provided his famous sketch of it, which is still reproduced in physiology textbooks. The first time it was introduced in Sherrington (1906) the purpose was to explain the concept of the refractory period. He described how electrical stimulation at 4 Hz could produce the scratch reflex whereas it was not evoked at 40 Hz. The sketch showed a parasagittal view of a dog and the limited region whose stimulation induced the reflex. Below, the sketch showed three regions of the SC. In the first two, the afferent field of the reflex was shown together with a generalized afferent neuron reaching the SC. A synapse was drawn between this neuron and a descending propriospinal neuron. The third region showed a generalized motoneuron innervating muscles of the hind limb. It was then demonstrated that " … the seat of the refractory phase seems therefore to lie somewhere central to the receptive neurones in the afferent arc" (p. 60 in Sherrington, 1906a). The second presentation of the figure was to show how sensory stimulation for this reflex could be far away from the motor output. It is also explained how various types of stimulation could induce different forms of the reflex.

Sherrington used the scratch reflex to demonstrate that during reflexes, the motor neurons of the SC received different signals, excitatory and inhibitory, irrespective of whether their input was via short or long axons. The sum of all the input actions was integrated by motoneurons to produce a single "final common path" to the musculature (1904) (Fig.6A). He emphasized the diversity of actions originating at both supraspinal and segmental SC levels, and their convergence onto a single motor neuron: " … at the termination of every reflex-arc we find a final neurone, the ultimate conductive link to an effector organ, (muscle or gland). This last link in the chain, e.g. the motor neurone, differs obviously in one important respect from the first link of the chain. It does not subserve exclusively impulses generated at one single receptive source, but receives impulses from many receptive sources situated in many and various regions of the body. It is the sole path which all impulses, no matter whence they come, must travel if they are to act on the muscle fibres to which it leads" (p.115 in Sherrington, 1906a). The second scratch reflex sketch in Sherrington (1906a) appeared after the above quotation and it showed the final common path. Sherrington explained that different pools of motor neurons were activated in the scratch according to the set of stimulated afferent fibers, while the amplitude of the movement increased to reach the site of stimulation.**[14]**

In his Ferrier lecture, Sherrington (1929) emphasized the crucial role of the motoneuron as the key element of a motor unit (Fig. 6B). He maintained that this neuron was a "convergence-point," wherein its activity was mainly dependent on the sum of excitatory and inhibitory inputs that were converging onto it. He considered the possibility of "occlusion" when two similar stimuli acted on the same motor nucleus (i.e., an ensemble of motoneurons innervating the same muscle). He concluded that "The motoneurone lies at a focus of interplay of these reactions [excitatory, inhibitory] and its motor unit gives their net upshot, always expressed, in terms of motor impulses and contraction." (p. 361).

In the 20th C, the motoneuron became a major focus of research that was and still is of critical importance in the field of movement neuroscience. It was first presented under the rubric of integrative and functional physiology, far from present-day reductionist studies of the molecular genetics of individual neurons!

4.6.5. Summary thoughts about Sherrington

Sherrington was able as a physiologist to characterize several functional properties of the particular nervous cell that joined the CNS to the musclature. In contrast, his contemporary anatomists were only able to define a particular spinal nervous cell "of considerable" size. Similarly, while his clinical contemporaries used their observations of progressive lesions to advance understanding of the connection between the CNS and the musculature, Sherrington was able to show that motoneuronal function was indeed the crucial CNS output for motor function.

In his investigation of reflex action and its diversity, from the relative simple knee jerk to the more complex pattern of scratching, Sherrington considered the motoneuron as the final common path. With a vision of the CNS like a telephone exchange, he suggested that the final common path was the result of a combination of spatial and temporal data contained in sensory input and descending commands to the SC.

It was only after the much later advent of intracellular recording from spinal motoneurons and interneurons (see Stuart and Brownstone (2011) in this volume) that it became necessary to revise Sherrington's concept of the final common path. It is now known that spinal interneurons that connect with motoneurons via one or two synapses are the major sites of the convergence of sensory input and descending command signals rather than the motoneurons, themselves. As well stated by Burke (1985) " The current picture of the vertebrate spinal cord emerging from current research is that the modulation and control takes place largely in segmental INs [interneurons] that integrate precisely defined patterns of afferent and descending signals. The MNs [motoneurons] remain the final common path but the computational load is taken by the INs " (p. 60; see Fig. 7)

Given the experimental tools that were available to him, we must pay homage to Sherrington's major contributions to the motoneuron concept and to neuroscience, in general. Such homage was provided by Swazey (1969) in her statement that "Out of the mountains of data collected in the course of these researches, Sherrington developed a number of basic functional principles: reciprocal innervation, interaction between higher and lower centers of motor control, and the muscular sense, inhibition, and facilitation as three key mechanisms of muscle management at the spinal level. And, recognizing the import of the neurone theory for his work, he had perceived that many of the characteristic properties of reflex pathways might, at root, be explicable by the events at the synapse" (p. 103).

5. Electrophysiological recording of MN activity

The first recordings of single motor neuron activity were made by Sherrington's co-Nobel Laureate (1932), Edgar Adrian (1889-1977) in collaboration with the American, Detlev Bronk (1897-1975). They dissociated mechanically phrenic nerves into a few single or a small group of fibers in anesthetized rabbits. Extra-axonal action potentials of these fibers were then recorded during breathing (Adrian and Bronk, 1928), using electrophysiological apparatus that had recently become available. Action potential discharge was at a relatively low frequency (20-30 Hz) during resting breathing. If the inspiration was augmented experimentally, discharge frequency increased to 50-80 Hz. The contraction of the diaphragm was clearly regulated by the frequency of the motor impulses.

Their second study (Adrian and Bronk, 1929) first involved fibers of nerves to flexor and extensor muscles of the cat hindlimb in decerebrate cats, some of which were also spinalized. The nerve fibers were dissociated and recorded from as above. In addition, an audiophone (highly praised by Adrian) translated electrical activities into sound at an intensity proportional to the frequency of the impulses. The discharge of sensory and motor fibers could be distinguished by ear with ease: sensory action potentials elicited a sharp sound, whereas those of motor fibers were of lower tone. These discharges were recorded during the flexor reflex in spinal decerebrate cats and the crossed extension reflex in decerebrate cats. Rate and recruitment coding of both sensory and motor fiber discharge were evident for both reflexes.

Adrian and Bronk (1929) also used a concentric needle electrode to record the compound action potential of muscle fibers innervated by a single motoneuron (i.e., a single motor unit recording). During voluntary contractions in human subjects, motor unit discharge in their triceps muscle was of similar frequency to that in the quadriceps muscle of the cat. This pioneering work on motor unit recording also showed that " … the force exerted by a muscle during a voluntary contraction was the result of the concurrent recruitment of motor units and modulation of the rate at which they discharged action potentials" (from the abstract of the following article by Duchateau and Enoka (2011)). Clearly, the two seminal Adrian and Bronk papers were a major step forward in motoneuron theory in that they suggested that a bridge might be built between what could be studied about motoneuron behavior during the voluntary contractions of human subjects and the mechanisms of motoneuron and reflex function that could be studied in reduced animal preparations.

The motor neuron concept became more complex when Renshaw demonstrated definitively that a set of ventral horn SC interneurons (subsequently termed "Renshaw cells") contributed to the control of motoneuron discharge via a recurrent inhibitory feedback loop from a motoneuron back onto a set of renshaw cells that projected to the same motoneuron and some of its neighbours (Renshaw, 1946).

Since Renshaw's seminal (indeed remarkable) electrophysiological research, the Renshaw cell and its spinal interconnections have been studied and conjectured upon in great detail by a host of truly gifted fundamental neurobiologists and clinical neuroscientists (e.g., see Alvarez and Ffyffe (2007); Windhorst, 2007; Pierrot-Deseilligny and Burke, 2005; Mazzocchio and Rossi, 2010). A major challenge, however, is that the true function of these cells and their recurrent inhibitory effects are still a matter of conjecture. The motoneuron concept will certainly not be complete until this issue is resolved!

6. Concluding thoughts

Motoneurons provide the motor command linkage between the CNS and the musculature. This role was hypothesized well before the neuron's complete histological description became available. Clinical research in the 19th C contributed importantly to the development of ideas about this neuron. It remained, however, for physiologists with a functionalist perspective to play the major role in the evolution of this neuron's current name and study of its actions in the control of posture and movement. The motoneuron's biochemical-biophysical-physiological properties, trophic interactions with the muscle it innervates, and pathophysiological propensities are all of major continuing interest such that the motoneuron concept is still evolving and remaining ripe for new discoveries. Due to its size and often its very long axon, the spinal motoneuron has been often presented as the ideal model for the study of neurons. It was indeed the first neuron to be studied in great detail. All students have learned the stellate shape of its cellular body, and they can all conceptualize its axon that can be well over 1 meter in length. This "popularity" has often retarded general understanding of the wide variety of neuronal shapes and the diversity of their organization across vertebrates. At the same time, few neuroscientists would dispute the fact that study of the motoneuron continues to blaze the trail in the ever-advancing understanding of neuronal structure and function.

Footnotes

[1] The motoneuron concept emerged iteratively from a preceding set of concepts including: "cell theory," the concept that all living material is composed solely of cells; "neuron theory," which emphasized that each neuron in the CNS had an axon and other extrusions (later known to be dendrites) that made synaptic contact with other neurons and their extrusions; and "motor cell concept," the idea that a particular cell was implicated in the control of movement. A similar evolution of terms was also evident, their chronological order being "nerve cell," "motor cell/motor nerve cell," "neuron," "motor neuron," and currently, "motoneuron (e)." It is true that due to its experimentally favorable position in the CNS, it was studied far before other neurons in CNS nerworks. Even today it remains on the forefront of neuronal research because of its direct association with muscle fibers.

[2] Originally in French. Note that all translations from French and German… into English were made by the authors.

[3] The Golgi technique involved originally about a 2-d fixation of the test block of nervous tissue with formol and a 2% aqueous solution of postassium dichromate. The block was then immersed for another 2 d in a 2% solution of silver nitrate. Next, the block was cut into serial sections with a thickness of 100-300µ. The particular value of this method was (ironically) its selectivity. The black staining operated only on some neurons in a given section. For such stained cells, the reaction was evident in not only the soma but also all the extrusions down to even the very fine endings (see Fig. 4B).

[4] Cajal showed that motor neurons were surrounded by other “funicular” and “commissural” neurons. They were described as being vertically arranged and superimposed metamerically, i.e., exactly as were the motor centers of the nerves emanating from the medulla oblongata and the Varol bridge (see p. 354 in Ramón y Cajal, 1911).

[5] Cajal posed the question “What is the physiological meaning of the great diversity of protoplasmic processes of the motor neurons?” His answer was that “We cannot escape from thinking that the topographic diversity of their numerous dendrites aims at making contacts between the different parts of the protoplasm or receptor of the cell and every type of collaterals spreading in the anterior horn” (p. 359 in Ramón y Cajal, 1911). To extend on this idea he provided a typology of the neuronal impingements onto motor cells, including “the voluntary or cerebral excitation,” “the sensory direct or homolateral excitation,” “the sensitive indirect excitation,” and “the sensory crossed direct and indirect excitations” (p. 360).

[6] Re the motor end-plate, Cajal concluded that “Studies by Cajal, Arnstein, Dogiel, Van Gehuchten, and Retzius are recent and done with up-to-date histological techniques; they entirely confirmed the discoveries made by previous anatomists and they added very few novel findings” (p. 372 in Ramón y Cajal, 1911). He also provided the general description that “Each of the fibrils born from the breaking up of a motor axon approaches the muscle bundle by various paths. Then, the fibril first loses its sheath of Henle, which spreads in the sarcolemma; the sheath of Schwann and the sheath of myelin are also soon interrupted; the nude fibril is no more than an axon-cylinder alone which divides in various minute pale branches, plunged in the end-

plate. The motor end-plate is a granular discoid mass, more or less rounded, slightly elevated upon the surface of the muscular fiber. It is made of four elements: a granular substance, the arborization of the axon-cylinder, neurofibrills, and the nucleus." (p. 373) (see also Fig. 2).

7The Italian, Luigi Rolando (1773-1831), studied brain gyri, including the one bearing his name, and cerebral localizations. He pointed out the complexity of the grey substance and described the "gelatinous substance". Rolando inferred that the CNS was comprised of networks traversed by electric impulses. The Italian surgeon, Vincenzo Malacarne (1744-1816), who was inspired by the electricity experiments of Luigi Galvani (1737-1798) and Alessandro Volta, (1745-1827), studied parts of the cerebellum. He suggested that this structure's lamella alternate layers would form a disc-like battery and produce electricity (Cherici, 2006). Rolando (1809) and Flourens (1822) used ablation studies in birds to advance understanding of the role of the cerebellum in the control of movement. Karl Burdach (1776-1847) described the lenticular nucleus, pulvinar, claustrum, external and intern capsules, amygdala, and red nucleus. In France, François Leuret (1797-1851) and Pierre Gratiolet (1815-1865) localized a variety of brain regions (Leuret and Gratiolet, 1839/1857). At that time brain lobes and gyri were the basic reference points of the brain. As early as 1840, the French psychiatrist, Jules Baillarger (1809-1890), used the microscope to depict six layers in thin sections of the cerebral cortex, these being alternatively transparent and opaque. This stratification was studied further by Remak in 1841 and von Kölliker in 1850. Ollivier d'Angers (1796–1845) studied detailed aspects of the human SC in 1823 (see Grossmann et al., 2006). He focused on anatomy, function and various pathologies (including syringomyélie with an abnormal channel or duct (syrinx)). Posterior ascending columns of the SC were described by Clarke in GBR.

8Duchenne was also a keen photographer although his cameras were not as advanced as were then available. Nonetheless, he made beautiful photographs using wet collodion negatives and positive albumen prints (Parent, 2005). He first made photographs of all the effects of faradization on the facial musculature, as well as some pathological reactions of these muscles. He put these photos in an album that he published in 1862. Later, he made micrographs using a camera attached to a microscope and composed a detailed atlas of the human brainstem, which he presented at the Académie des Sciences in 1869 but did not publish.

9Duchenne devised a "histological punch" in order to study the muscular lesions of this disease. "Today, we can cut small pieces of a living muscle with a armless instrument, my histological punch, and bring light into the diagnosis of muscular diseases with the anatomical examination of paralyzed muscles. This new diagnostic tool, with such a living anatomopathology, was already very useful to me" (in Parent, 2005)

10In his 1877 doctorate, Gombault made a summarized description of ALS: " … [a] chronic disease with progressive course; in the spinal cord, it is characterized anatomically by the cellular atrophy of the anterior horns, associated with the symetrical sclerosis of the lateral columns of the white matter. Of these two lesions, the first is associated with the progressive atrophy of the skeletal muscle, the second is associated with a paralyses with contractures quite rapidly extending to the four limbs, and in some cases to the muscle of the trunk ; in the absence of any morbid phenomena in the bladder or rectum. In order to make a complete list, I must add that the symptoms of the labio-glosso-laryngal paralysis always appear at some stage (p. 3) (see

Fig. 4C).

[11] There was much debate toward the end of the 19th C about the functional organization of the brain. Some argued in the holistic tradition that the brain was a homogeneous organ with no specific subparts. This group included Goltz, the Professor of Physiology at the new university of Strasburg (the city was at that time in Germany). This viewpoint was countered by "the localizationists" like Ferrier, who argued that the brain was organized in functionally distinct cortical areas. Paul Broca (1824-1880) may have been one of the first to demonstrate localization. In a 1961 report, he attributed aphasia to damage of the frontal cortex in M. Lebrogne. The controversy was particularly obvious at the Medical Congress of 1881 in London. Goltz presented a live dog that had undergone five operations with ablation on the parietal and occipital lobes. He showed that the animal was not paralyzed but that it has limited psychical reactions. Ferrier presented a monkey where the somatosensory and motor areas on one side has been removed. He was hemiplegic. When Charcot saw it he claimed “It is a patient!”

[12] Sherrington did not discover gamma motor axons, albeit he well could have done so if he and Eccles had interpreted correctly the data in one of their seminal articles (Eccles and Sherrington, 1930). The history of the delineation of gamma motor axons and their motoneurons is covered fully in Matthews (1972). Lars Leksell (1907-1986) was the first to describe gamma motor fibers (diameter, 4-10 µm) while working under the mentorship of Granit. He demonstrated their inability to bring about muscle contraction, but rather, their selective action on the sensory fusorial afferent fibers (Leksell, 1945). The motoneurons of these fibers were identified by their physiological properties as being either dynamic or static gamma motoneurons. Moreover, Paul Bessou (1926-2008) et al. (1963) demonstrated that slow alpha fibers of the deep lumbrical muscle in the cat stimulated intrafusal as well as skeleto-motor muscle fibers. Such axons were called beta motoneurons.

[13] The scratch reflex is far more complex than was imagined by Sherrington (Fig. 5). Deliagina et al. (1975) showed in the decerebrate cat that if the hindlimbs were de-afferented, rhythmic movements persisted, albeit with less smoothness. In paralyzed animals, stimulation of the C1-C2 SC segments induced rhythmic fictive scratch movements of the hindlimb. These authors later showed that this activity resembled locomotor activity in several but not all respects: “The pattern of fictive scratching differs from the pattern of fictive stepping in that the scratch cycle is much shorter, and the extensor burst contitutes a smaller portion of the cycle than the flexor burst… However, a motor pattern with a spontaneous gradual transition from the cycle characteristic for stepping to the cycle characteristics for scratching was observed…This observation strongly suggests that the same neuronal network, with one changeable parameter, is responsible for the generation of both motor patterns” (p.177 in Orlovsky et al., 1999). The scratch reaction is in fact far more complex. It must be dissociated: an initial input induced by a peripheral stimulation, a protraction stage and a rhythmic spinal rhythm. Sherrington shied away from research that showed that the SC possessed intrinsic networks that could elicit the protraction and the rhythmic motor activity, even though Graham Brown had demonstrated this property quite clearly in Sherrington's Liverpool laboratory in 1911 (for this history see Stuart and Hultborn, 2008).

14The concept of the common final path can be applied to all vertebrates, but not to invertebrates, whose inhibitory motoneurons diminish muscle force produced by excitatory motoneurons (Clarac and Perlstein, 2007). The muscle fibers of invertebrates are innervated usually by both excitatory and inhibitory motoneurons. Charles Richet, (1850-1935), Wilhelm Biederman (1852-1929), and C.A.G. Wiersma (1905-1979) were on the forefront in the demonstration of this dual excitatory and inhibitory CNS command to the musculature in invertebrates.

Acknowledgements

F.C. presented some of the above in an historical session chaired by J.-G.B. at a meeting of the International Motoneuron Society, "Towards translational research in motoneurons," Paris, FRA, July 91-3, 2009 (Organizers: CJ Heckman, Didier Orsal, Jean-François Perrier**,** Daniel Zytnicki). We thank Robert Brownstone, Jacques Duchateau, Roger Enoka, and Douglas Stuart for their helpful comments on various drafts of our article.

References

Adrian, E.D, Bronk, DW,, 1928. The discharge of impulses in motor nerve fibres. Part 1. J. Physiol. (Lond.), 66, 81-101.

Adrian, E.D., Bronk, DW,, 1929. The discharge of impulses in motor nerve fibres. Part 2. The frequency of discharge in reflex and voluntary contractions. J. Physiol. (Lond.), 67, 119-151.

Alvarez, F.J., Fyffe, R.E.W., 2007. The continuing case for the Renshaw cell. J. Physiol. (Lond.) 584 (Pt. 1), 31-45.

Barbara. J.-G., 2006a. The physiological construction of the neurone concept (1891-1952), C. R. Biol. 329, 437-449.

Barbara. J-G., 2006b. Louis Ranvier (1835-1922): the contribution of microscopy to physiology, and the renewal of French general anatomy, J. Hist. Neurosci., 16, 413-431.

Barbara et al. 2011 prologue

Bell, C., 1823. Second part of the paper on the nerves of the orbit. Philos. Trans.113, 289-307.

Bell, C.,1836. The Nervous System of the Human Body as Explained In a Series of Papers Read Before the Royal Society of London. Black, Edinburgh.

Bessou, P., Emonet-Denand, F., Laporte, Y., 1965. Motor fibers innervating extrafusal and intrafusal muscle fibers in the cat. J. Physiol. (Lond.) 180, 649-672.

Brazier, M. A. B. (1988). A History of Neurophysiology in the 19th Century. New York: Raven Press.

Breuer, J. (1970). The self-steering of respiration through the nervous vagus. Translated by E. Ullmann. In R. Poter (Ed.), Breathing: Hering-Breuer Centenary Symposium.

Burke, R.E., 1985. Integration of sensory information and motor commands in the spinal cord. In: Stein, P.S.G. (Ed.), Short Course Syllabus – Motor control: From Movement Trajectories to Neural Mechanisms. Society for Neuroscience, Bethesda, MD, pp. 44-66.

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

Charcot, J.M., 1872-1873/1877. Oeuvres Complètes, Vol. 1 [Complete works, Vol. 1]. Bureaux du Progrès Médical, Paris 1872-1873. (Also available In English as translated by G. Sigerson. Charcot, J. M. 1877. Lectures on the Diseases of the Nervous System, New

Sydenham Society, London).

Charcot, J.M., Joffroy A.,1869. Deux cas d’atrophie musculaire progressive avec lésions de la substance grise et des faisceaux antéro-latéraux de la moelle épinière [two cases of progressive muscular atrophy with lesions of the grey mater and of the antero-lateral white matter fascicules of the spinal cord] Archiv. Physiol. Neurol. Path. 2, 354-367, 629-649, 744-760.

Cherici, C., 2006. " Vincenzo Malacarne (1744-1816): a researcher in neurophysiology between anatomophysiology and electrical physiology of the human brain**."**. C.R. Biol. 329 (5-6), 319-329.

Clarac, F., Perlstein, E., 2007. Invertebrate preparations and their contribution to neurobiology in the second half of the 20th century. Brain Res. Rev. 2007, 54 (1):113-161.

Clarac F., Boller F. 2009. The history of neurology in France**.** In: Finger, S., Boller, F., Tyler, K. (Eds.), Handbook of Clinical Neurology 95, 629-656.

Clarac, F., Massion, J., Smith, A. 2009. Duchenne, Charcot and Babinski, three neurologists of La Salpetrière Hospital and their contribution to concepts of the central organization of motor synergy; J. Physiol. (Paris).

Couteaux, R., 1944. Nouvelles observations sur la structure de la plaque motrice et interprétation des rapports myo-neuraux [New observations of the structure the neuromuscular junction and interpretation of nervous -motor connections] , C. R. Soc. Biol. 138, 976-978

Creed, R.S., Denny-Brown, D., Eccles, J.C., Liddell, E.G.T., Sherrington, C.S., 1932. Reflex Activity of the Spinal Cord. Clarendon Press, Oxford.

Cruveillhier, J. (1856) Traité d’anatomie pathologique générale. [Textbook of general pathological anatomy] Baillière, J.B. Librairie de l’Académie impériale de médecine. Paris, Londres.

Debove, G.M., Gombault, A. 1879. Contribution a` l’étude de la sclérose latérale amyotrophique [contribution.to the study of amyotrophic lateral sclerosis] Archiv. Physiol. 2eme serie VI, 751–771.

Dejerine, J., Dejerine-Klumke, A.M., 1914. Sémiologie des Affections du Système Nerveux [Semiology of nervous system pathlogies]. Masson, Paris.

Deliagina, T.G., Feldman, G., Gelfand, I.M., Orlovsky, G.N. 1975. On the role of central program and afferent inflow in the control of scratching movements in the cat. Br; Res. 100, 297-313.

Descartes, R., 1662. *De Homine* [On Man]. in « Œuvres complètes [complete works]» 1937, La Pléiade, Gallimard Paris.

Doyère, L. (1840). Mémoire sur les tardigrades, Annals. Sci. Nat., sér.. 2, 269–361.

Duchateau Enoka 2011

Duchenne (de Boulogne), G.B.A., 1860. Paralysie musculaire de la langue, du voile du palais et des lèvres; affection non encore décrite comme entité morbide distincte. [Muscular paralysis of the tongue, of the velum and of the lips, affection not yet bdescribed as a morbid original entity] Arch Gén Méd 1860; 16: 283-296, 431-445.

Duchenne (de Boulogne), G.B.A. (1867). Physiologie des Mouvements Démontrée a L'Aide de L'Expérimentation Electrique et de L'Observation Clinique, et Applicable a L'Etude des Paralysies et des Déformations [Physiology of Movements, Demonstrated by Means of Electrical Stimulations and Clinical Observations of Paralysis and Limb Deformations]. Baillière et Fils, Paris.

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

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

Flourens, M.-J.-P., 1824. Recherches expérimentales sur les propriétés et les fonctions du système nerveux dons les animaux vertébrés [Experimental Researches on the Properties and the Functions of the Nervous System in Vertebrate Animals]. Crévot, Paris.

Finger, S., 1994. Origins of Neuroscience. Oxford University Press, New York

Fulton, J.F., 1926. Muscular Contraction and the Reflex Control of Movement. Doctorate thesis. Baltimore, Williams & Wilkins.

Gombault, A., 1871. Recueils de faits: sclérose symétrique des cordons latéraux de la moelle et des pyramides antérieures dans le bulbe [Collection of facts : symetrical sclerosis of the lateral columns of the cord and of the anterior pyramids of the bulb]. Arch. Physiol. Norm. Path. 4, 509–518.

Gombault, A., 1877. Etude sur la sclérose latérale amyotrophique [Study on amyotrophic lateral sclerosis] Prog. Méd. 1–86.

Gombault A., Philippe, C.,1902. Histologie pathologique du système nerveux central. In: Cornil, V., Ranvier L.A. (Eds.), Manuel d'Histologie Pathologique.[textbook of pathological histology] Felix Alcan, Paris. pp. 695–856.

Goetz, C.G., Bonduelle, M, Gelfand, T., 1995. Constructing Neurology: Jean-Martin Charcot. Oxford University Press, New York.

Granit, R., 1957. Systems for control of movements. Premier congrès international des Sciences neurologiques. Bruxelles. Acta Med. Belg. 1, 63-99. Getaud, Sneeck-Ducagy Fils.

Grosmann, S., Maeder, IM., Dollfus, P., 2006. Treatise on the spinal marrow and its diseases [anatomy, functions and general consoderation on its diseases] by Ollivier d'Angers CP. (1796-1845). Spinal Cord, 44 (12), 700-707.

Guilly, P., 1977. Duchenne de Boulogne. Laffitte, Marseille.

Hall, M. (1833). On the reflex function of the medulla oblongata and medulla spinalis. Phil. Trans.R. Soc., 123, 635–665.

Held, H., 1897. Beitrage zur Strucktur des nervenzellen und ihren Fortsätze [A contribution to the study of nerve cells and theirs processes]. Archiv. Anat. Physiol. Suppl. 204, 273.

Haymaker, W., Schiller, F., 1970. The Founders of Neurology. 2nd edition. Charles Thomas, Springfield, IL. p. 616.

Hoff, H.E. 1940. The history of vagal inhibition. Bull. Hist. Med. 8, 461-496.

Hoff, H. 1962. John Fulton's contribution to neurophysiology. J. Hist. Neurosci. 17,16-37.

Lazar, J.W., 2010. Acceptance of the neuron theory by clinical neurologists of the late-nineteenth century. J. Hist. Neuro. 19, 349-364.

Leksell, L., 1945. The action potential and excitatory effects oF small ventral root fibres to skeletal muscle. Acta Physiol. Scand**.** 10 (Suppl. 31), 31-81.

Leuret, F., Gratiolet, P., 1839/1857. Anatomie Comparée du Système Nerveux [comparative anatomy of the nervous system]. J.B. Baillière, Paris.

Leyden, E.V., 1878. Ueber progressive amyotrophic Bulbar-paralyse und ihre Beziehungen zur symmetrischen Seittengsklerose. Archiv. f. Psychiat. p.641

Liddell, E.G.T., Sherrington, CS., 1924. Reflexes in response to stretch (myotatic reflexes). Proc. R. Soc. XCV B, 212-242.

Liddell, E.G.T., Sherrington, CS, 1925. Remarks on some aspects of reflex inhibition. Proc. R. Soc. XCVII B, 519-545.

Lloyd, D.P.C., 1943. Conduction and synaptic transmission of reflex response to stretch in spinal cats. J. Neurophysiol. 6, 316-326.

Lu, J., Lichtman, J.W., 2007. Imaging the neuromuscular junction over the past centuries. Acta Physiol. Sinica. 59, 683-693.

Luys, J.B.,1865. Recherches sur le système nerveux cérébro-spinal : sa structure, ses functions, et ses maladies [Researches on the nervous system, Brain and spinal cord: its structure, its functions and its pathologies]. Germer-Baillière, Paris,

MacDougall, W..,1903. The nature of inhibitor processes within the nervous sstem. Brain 26, 153-191.

Magendie, F., 1817. Précis Elémentaire de Physiologie [Textbook of general physiology). Méquignon-Marvis, París.

Magendie, F. 1847. Remarques de M. Magendie à l'occasion de la note de Mr. Flourens [Remarks from M. Magendie in response to the comments from Flourens] C. R. Acad.Sci., 24, 319-320.

Maine de Biran, F.-P., 1805. Mémoire sur la Décomposition de Pensée. Tome III [Report on the decomposition of the mind. Vol. III]. Vrin, Paris.

Matthews, P.B.C., 1972. Mammalian Muscle Receptors and Their Central Actions. London, Arnold, London.

Mazzocchio, R., Rossi, A., 2010. Role of Renshaw cells in amyotrophic lateral sclerosis. Muscle Nerve 41, 441-443.

Ochs, S., 2004. A History of Nerve Functions. Cambridge University Press, Cambridge.

Olmsted, J.M.D., 1944. François Magendie. Pioneer in Experimental Physiology and Scientific MedIcine in XIX century France. Schuman, New York.

Orlovsky, G., Deliagina, T.G., 1999. Neuronal Control Of Locomotion: From Mollusc To Man. Oxford University Press.

Parent A., 2005. Duchenne De Boulogne: A pioneer in neurology and medical photography. Can. J. Neurol. Sci. 35, 369-377.

Pearce, J.M.S., 2005. Romberg and his sign. Eur. Neurol. 53, 210-213.

Pflüger, E.F.W., 1853. Die Sensorischen Functionen des Rückenmarks der Wirbelthiere [The Sensory Functions of the Spinal Cord of Vertebrate Animals]. August Hirschwald Berlin.

Pierrot-Deseilligny, E., Burke, D., 2005. The Circuitry of the Human Spinal Cord. Cambridge University Press, Cambridge.

Ramon y Cajal, S., 1911. Histologie du Système Nerveux de l'Homme et des Vertébrés [Histology of the nervous system of man and vertebrates]. Translation by L. Azoulay in 1909-1911. Paris, éd., Maloine. 2e Edition, Instituto Ramón y Cajal. Raycar, SA, Madrid, 1972.

Ranvier, L.A., 1875. Traité Technique d'Histologie [Technical Textbook of Histology]. Savy, Paris.

Renshaw, B., 1946. Central effects of centripetal impulses in axons of spinal ventral roots. J. Neurophysiol. 9, 191-204.

Rolando, L., 1809. Saggio sopra la vera Struttura del cervello dell'Uomo e degli Animali e sopra le funzioni del sistema Nervoso.[On the true structure of the human and of the animal brain and on the function of the nervous system] Sassari: Stamperia Da S. S .R.M Privilegiata.

Romberg, M.H., 1846. Lehrbuch des Nervenkrankeiten des Menschen. Bd. 1. [A Manual of the Nervous Diseases of Man. Vol. 1]. Duncker, Berlin.

Rouget, C.M.B., 1862. Notes sur la terminaison des nerfs moteurs dans les muscles chez les reptiles, les oiseaux et les mammifères [Notes of the termination of the motor nerves in muscles of Reptiles, Birds and Mammals]. C. R. A. S. 55, 548-551.

Ruffini, A. (1897) Observations on sensory nerve endings in voluntary muscles Brain, 20, 368-374.

Ruffini, A. (1898-9) On the minute anatomy of the neuromucular spindles of the cat, and on their physiological significance. J. of Physiol. (LOND.), 23, 190-208.

Sachs, J., 2005. Aristotle: motion and its place in nature. Internet Encycl. Philos. http://www.iep.utm.edu/aris-mot/

Schwann, T., (1839/1847). Mikroscopische Untersuchungen über die Übereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen [Microscopical Researches into the Accordance in the Structure and Growth of Plants and Animals]. Berlin :G.E.Reimer. (English translation in 1847 by H. Smith, London, Sydenham Society).

Sherrington, C.S. 1892. Notes on the arrangement of some motor fibres in the lumbosacral plexus. J. Physiol. (LOND.), 13, 621-772.

Sherrington, C. S. 1894. On the anatomical constitution of the nerves of skeletal muscles; with remarks on recurrent fibres in the ventral spinal nerve-root. . J. Physiol. (Lond.) 17, 211-258.

Sherrington, C.S., 1904. Correlation of reflexes and the principle of the common path. Brit. Assoc. Rep. 74, 728-741.

Sherrington, C.S., 1906a. The Integrative Action of the Nervous System. Cambridge University Press, Cambridge (5th edition, 1947).

Sherrington, C.S., 1906b. On the proprio-ceptive system, especially in its reflex aspect. Brain 29, 467-482.

Sherrington, C.S., 1906c. Observations on the scratch-reflex in the spinal dog. J. Physiol. (Lond.) 34, 1-50.

Sherrington, C.S., 1913. Reflex inhibition as a factor in the co-ordination of movements and postures. Quart. J. Exptl. Physiol. 6, 307-308.

Sherrington, C.S., 1929. Some functional problems attaching to convergence. Ferrier lecture. Proc. R. Soc. B 105, 332-362.

Sherrington, C.S., Foster, M., 1897. The central nervous system. In: Foster, M. (Ed.), A Textbook of Physiology, 7th ed., Pt. III. Macmillan, London, pp. 915-1252.

Sherrington, C.S., Laslett, E.E., 1903. Observations on some spinal reflexes and the interconnection of spinal segments. J. Physiol. (Lond.) 29. 58-96.

Stuart, D.G., 2002. Reflections on spinal reflexes. Adv. Exp. Biol. Med. 508, 249–257.

Stuart D.G., Hultborn H. 2008. Thomas Graham Brown (1882-1965), Anders Lundberg (1920-), and the neural control of stepping. Brain Res Rev. 59, 74-95.

Stuart, D.G., Pierce, P. A., Callister, R. J., Brichta, A., McDonagh, J.C., 2001. Sir Charles Sherrington: humanist, mentor, and movement neuroscientist. In: Latash, M.L., Zatsiorsky, V. (Eds.), Classical Papers in Movement Science. Human Kinetics, Champaign, IL, pp. 317-374.

Swazey, J.P. 1969. Reflexes and Motor Integration: Sherrington's Concept of Integrative Action. Harvard University Press. Cambridge, MA.

Todd, R.B., 1847. Encyclopaedia of Anatomy and Physiology. Longman & Roberts, London.

Turner, M.R., Swash, M., Ebers, G.C. 2010. Lockhart Clarke's contribution to the description of amyotrophic lateral sclerosis. Brain in press.

van Gehuchten, A., (1891). La structure des centres nerveux : La moelle épinière et le cervelet. [Structure of the nervous centers : The spinal cord and the cerebellum]. La Cellule, 7, 1-44.

van Gehuchten, A., 1894. Le Système Nerveux de L'Homme: Leçons Professées à l'Université de Louvain [The Human nervous system: lessons from the University of Louvain]. Uystpruyst-Dieudonné, Louvain.

von Gerlach, J., 1872. Über die struktur der grauen Substanz des menschlichen Grosshirns [About the structure of the grey substance of the human cerebrum]. Z. Med. Wiss. 10, 273-275.

von Köelliker, A., 1854. Mikroskopische Anatomie oder Gewebelehre des Menschen [Human microscopic anatomy and histology]. Verlag von Wilhelm Engelman, Leipzig.

Waldeyer, H.W.,1891. Ueber einige neuere Forschungen im Gebiete der Anatomie des Centralnervensystems [Some new findings on the anatomy of the central nervous system]. Deutsche Med. Woch. 17, 1213-1218, 1244-1246, 1287-1289, 1331-1332, 1350-1356.

Windhorst, U., 2007. Muscle proprioceptive feedback and spinal networks. Brain Res. Bull. 73, 561-575.

Figure legends

Fig. 1 – 1913 drawing of a “Celula nerviosa motora” ["motor nervous cell”] by Cajal in“Ciença y arte Ramon y Cajal (2003)” (A) dendrites. (B) axon. (C) terminal endings.

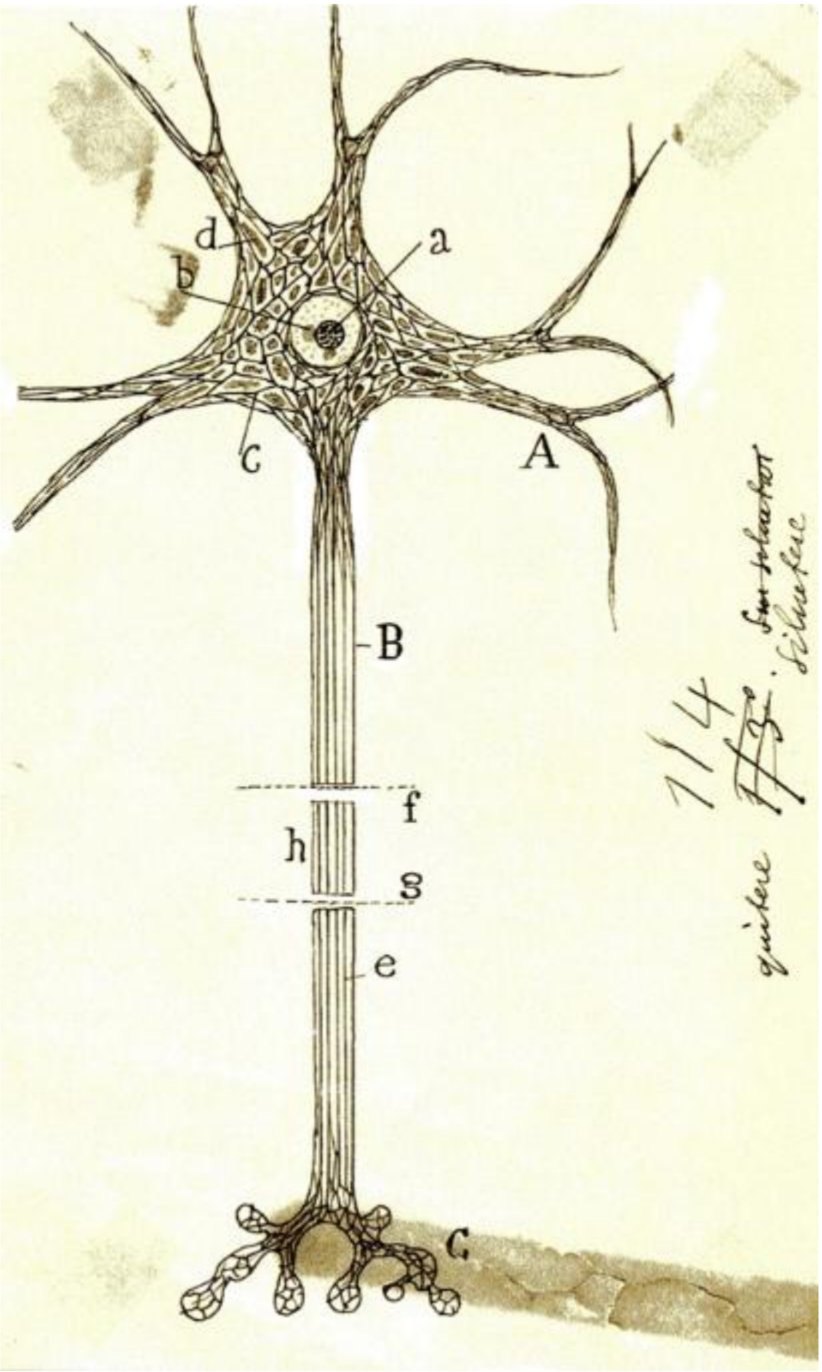

Fig. 2 – Motor plaque of a portion of the intercostal muscle of a rabbit. Method: gold chloride stain of Löwit. (Cajal Histologie du système nerveux. Tome I. 1972. p.372. fig. 135). (**a)** Terminal arborisation of the axon. (**b)** Nuclei and granular substance. (**d**) End of the myelin sheath. (**n)** Thin nervous endings.

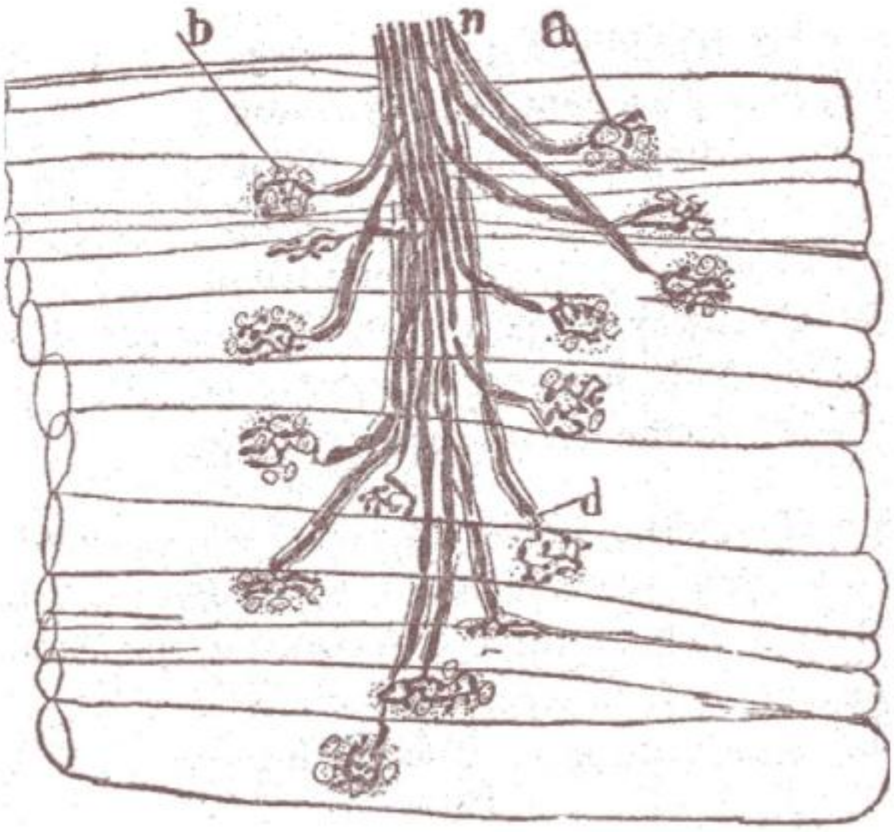

Fig. 3 – French neurologists who studied motor pathologies: There were all located in Paris and worked mainly at the La Salpetrière Hospital. (A) Jean-Martin Charcot in his official dress. (B) Duchenne de Boulogne. (C) Jean Cruveilhier. (D) Jules Luys. (E)
Alex Joffroy. (F) Albert Gombault. See the text for their various contributions.

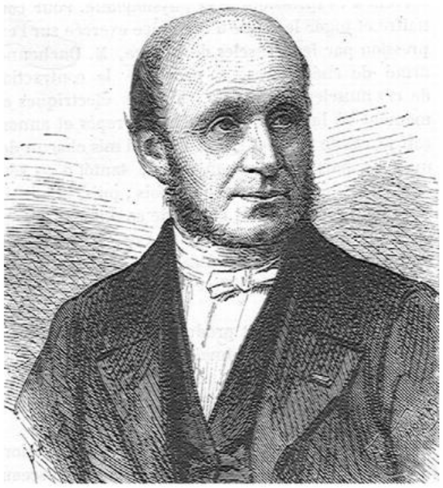

Fig. 4 – Motor cells in the human. (A) grandes cellules radiculaires [large radicular cells] stained with the Nissl method (from Gombault). (B) Multipolar cell of spinal cord of WHAT (from Van Gehuchten). (C) Spinal cord sections in ALS patients. The lateral spinal column is sclerosed mainly at the upper levels of the SC.

Fig. 5 – The scratch reflex (figure13 from p.46 and fig. 38 p.121 in Sherrington 1906a) and the response with two skin points stimulation.

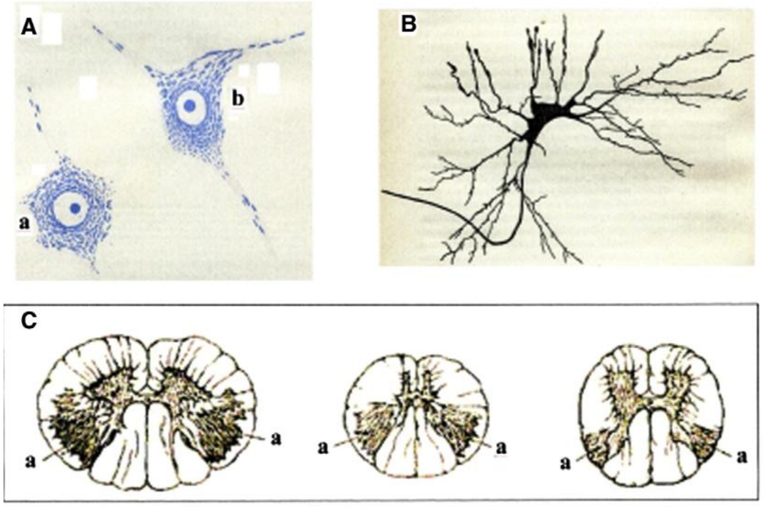

Fig. 6 – Two examples of Sherrington's concepts about motoneurons. (A) His final common path for a motoneuron to the vastus crureus muscle of either a dog or a cat (from Fig. 11 in Swazey (1969). (B) The motoneuron is a “convergence-point:” i.e. (from Fig. 1 in his Ferrier lecture (Sherrington, 1929)

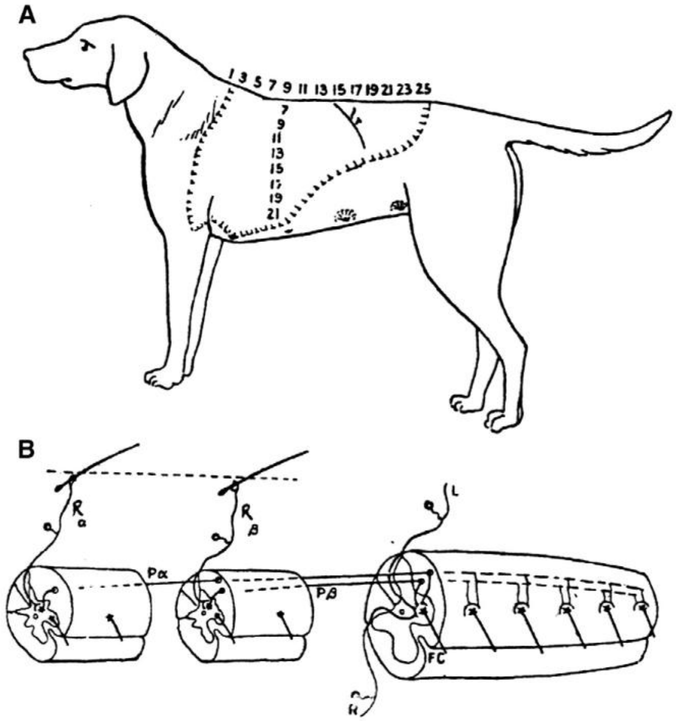

Fig. 7 – The evolving final common path. (A) Burke's (1985) conception of "Sherrington's spinal cord" with the convergence of sensory input from primary (1^{o}) afferents and descending input occurring at the motoneuron level. This model is the basis for Sherrington's concept of the final common path. (B) In contrast, Burke's conception of the "Lundbergian" spinal cord with the same sensory-descending convergence occurring largely at the interneuron level. This concept suggests an evolving final common path as more details become available about spinal interneuronal connectivity. Adapted from Figs. 1 and 4, respectively, in Burke (1985) with permission of the respective publishers.