THE BRAIN ON ITSELF: NOBEL LAUREATES AND THE HISTORY OF FUNDAMENTAL NERVOUS SYSTEM FUNCTION

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THE NOBEL PRIZE in Physiology or Medicine has been given in recognition of work in the neurosciences a number of times. Laureates have been awarded for work on both fundamental and more complex nervous system functions. This review is restricted to contributions by 20th century laureates to the understanding of fundamental nervous system function on the cellular level.

In 1906, Camillo Golgi and Ramón y Cajal were awarded for their work on the microscopic structure of the nervous system. Their achievement and those of others within this field, coupled with technological progress, gradually allowed more complex physiological studies. In 1932, the prize was awarded to Charles Sherrington and Edgar Adrian for their discoveries of how neurons function. They were followed in 1944 by Herbert Gasser and Joseph Erlanger who uncovered the highly differentiated functions of single nerve fibers. Alan Hodgkin and Andrew Huxley were awarded for the detection of the ionic mechanism of the action potential and its mathematical explanation in 1963. In 1991, Erwin Neher and Bernd Sakmann were awarded for their work on single ion channels.

Although the scientists who proved the hypothesis (Fridjof Nansen, Wilhelm His, and August Forel) were never awarded by the Nobel Committee, their studies gave rise to one of the most fundamental questions in 20th century neuroscience: How is information carried from one neuron to another or to an effector cell? This was first solved in the vegetative nervous system, and, in 1936, Henry Dale and Otto Loewi received the prize for their discoveries relating to chemical transmission of nerve impulses. In 1963, John Eccles was awarded the prize for his work on the physiology of synapses. In 1970, Bernhard Katz received the Nobel Prize for the discovery of quantal release. Katz shared the prize with Julius Axelrod and Ulf von Euler, who were central in finding that transmitters are stored in presynaptic vesicles and that the effect in many synapses is terminated by reuptake.

This review does not include 21st century laureates, although the prize has already been given to neuroscientists twice this century; Arvid Carlsson, Paul Greengard, and Eric Kandel received the award in 2000 for their discoveries related to signal transduction, and Richard Axel and Linda Buck received the award in 2004 for their work in the field of odorant receptors and the organization of the olfactory system.

KEY WORDS: Action potential, Brain, Nervous system, Neuroscience, Nobel Prize, Synaptic transmission

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When Alfred Nobel passed away in his home in San Remo, Italy on December 10, 1896, his last will, signed in the Swedish-Norwegian Club in Paris a year before, caused significant controversy within his family and in his native Sweden. Although relatives and those close to him benefited, Nobel wanted a considerable portion of his fortune to "…constitute a fund, the interest on which shall be annually distributed in the form of prizes to those who, during the preceding year, shall have conferred the greatest benefit to mankind" (52, p 98). Some of his family members contested the will and many of his compatriots, who wanted to restrict award eligibility to Swedish scientists only, disapproved of the genuinely international spirit of the prizes. Therefore, a number of matters had to be sorted out before the first Nobel prizes were awarded in 1901 (52, 86, 87).

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Nobel further declared that said interest should be divided into five equal parts. The prizes in literature, chemistry, and physics were to be awarded by Swedish academies, the prize for the best work on fraternity among nations and reduction of standing armies by the Norwegian Parliament, and the prize for the most important discovery within the domain of physiology or medicine by the Karolinska Institute (98).

During the 20th century the Nobel Committee in Physiology or Medicine awarded a broad spectrum of achievements from the most fundamental of all biological discoveries (the double helix, Crick and Watson in 1962), to one of the most controversial treatments used in medicine (the leucotomy, Egas Moniz in 1949). On the whole, the Nobel Committee and Nobel Assembly have shown great competence and, using a sound selection routine, they have seldom erred but have rather shown a unique capability of selecting recipients who have made lasting impact in the field of neuroscience. This, together with the amount of awarded money, has given the prize more prestige than even Alfred Nobel possibly envisaged and has made it unique among all international honors.

Alfred Nobel was an inventor and industrialist in a world in which the impact of new discoveries was often great and swift. His will, stating that the prize should be awarded "to those who, during the preceding year, shall have conferred the greatest benefit on mankind…[by] the most important discovery within the domain of physiology or medicine" (98) has wisely been interpreted somewhat liberally and in accordance with contemporary science. First, it would have been difficult for Nobel to appreciate the amount of time required for a breakthrough in present day science. Second, it would hardly have been possible for him to predict the role radical reductionistic strategies would now have. How could he have envisioned that work on the roundworm (*Caenorhabditis elegans*; Brenner, Horwitz, and Sulston in 2002) would lay a foundation for breakthroughs in medicine or that studies on the marine snail *Aplysia* (Eric Kandel in 2000) would have such a significant impact on our understanding of the brain's information processing?

The Brain on Itself

The understanding of the human brain represents a scientific conundrum and ultimately, the human brain in its studies of itself may be incapable of solving many of its mysteries. Many scientists have tried to approach this field in its most complex and interesting form and have often seen less than successful results of their efforts. Others have approached the problem with reductionistic strategies, some of which have produced far-reaching scientific results. More than a century after Fridjof Nansen first described the cell as the basic and individual element of the nervous system, central nervous system (CNS) functioning is fairly well understood at the elemental level but not at the more complex networking levels underlying the human mind.

Some of the central discoveries in fundamental nervous system function have been awarded the Nobel Prize in Physiology or Medicine. This article will briefly review some of these discoveries.

Golgi and Cajal: "In Recognition of their Work on the Structure of the Nervous System," 1906

Microscopic histology developed as a scientific discipline in the 19th century and produced some very significant advances in the field of neurosciences, including the hypothesis that a tissue consists of individual cells (Matthias Jacob Schleiden and Theodor Schwann) and that each cell arises from another cell through cell division (Rudolf Virchow: *Omnis cellula e cellula*). However, this was not accepted as true for the CNS, in which the procedures of the day proved inadequate for studying the detailed microscopic structure of this organ. In particular, it was not possible to visualize neurons in their entirety. The complexity of interlacing fibers, therefore, led Gerlach (1820–1896) to postulate the Reticular Theory, in which the nervous system was considered a net-like structure, i.e., a continuous syncytial reticulum in which fusion of protoplasmic processes allowed the flow of information from one cell to the next in a direct manner (57). The nerve cells were considered as the nodes of the reticulum and the profusely branching fibers were thought to anastomize in the meshwork.

Camillo Golgi and the Reazione Nera

Camillo Golgi is credited with providing the dawning field of neuroscience with a technique that allowed the first discoveries of its intrinsic structure. Golgi, the son of a local medical officer, was born in Corteno near Brescia in northern Italy in 1843. Having graduated from the University of Pavia, he attended the Institute of Psychiatry and began his scientific career by publishing a paper claiming that psychiatric disorders were caused by organic lesions. However, he also found that the understanding of the brain's fine structure was modest at best and, therefore, decided to leave psychiatry to focus on the microanatomy of the nervous system. Golgi found that financing his studies proved difficult and accepted the post of Chief Medical Officer at the Pio Luogo degli Incurabili in Abbiategrasso, not far from Milan and the university, 3 years later (1872). Rather than renouncing his scientific ambitions, he converted a former kitchen into a laboratory where he searched for a suitable staining technique that would allow studying his specimens. The following year he published a short note, "On the structure of the gray matter," in the *Gazzetta Medica Italiana*. In this paper, he described the reazione nera (black reaction), which was nervous tissue hardening in potassium bichromate followed by silver nitrate impregnation (48, 60).

The technique turned out to be of pivotal importance and was used in a number of studies of nervous system structure by Golgi and Ramón y Cajal (*Figs. 1* and *2*) and others. The success of the method, which is still in use today, was to a large extent due to the fact that only a limited and random number of neurons were stained. Thus, it became possible to visualize individual neurons and, often, the nerve cell body, dendrites, and axon could be seen in their entirety.

Gerlach's Reticular Theory was independently challenged by the Norwegian neuroscientist, explorer, and humanist

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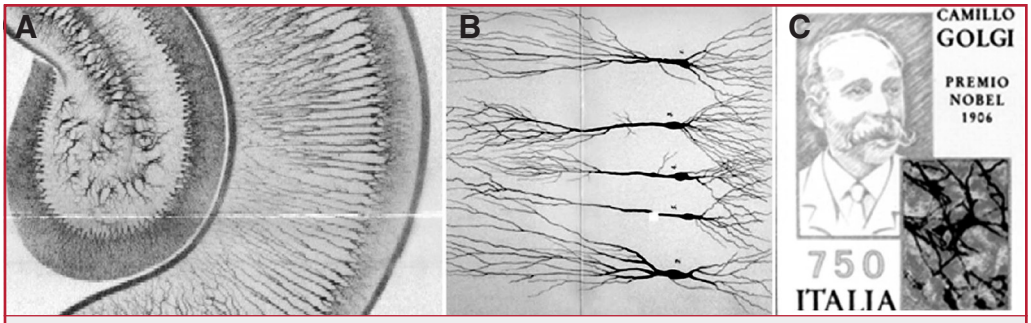

FIGURE 1. *Illustrations showing Golgi's hippocampus. The Golgi technique, or reazione nera, was superior to all earlier histological methods for studying the CNS. It stained only a few neurons, but those that were stained were often visualized in their entirety. These two examples from the hippocampus, prepared and redrawn by Camillo Golgi, show the unique power of his technique at the regional (**A**) and cellular (**B**) level. The European Community commemorated Camillo Golgi with a stamp in 1994 (**C**).* Modified from, *Golgi C, Bentivoglio M, Swanson L: On the fine structure of the pes Hippocampi major (with plates XIII–XXIII). 1886.* ***Brain Res Bull*** *54:461–483, 2001 (61) and Mazzarello P: Camillo Golgi (1843–1926).* ***J Neurol Neurosurg Psychiatry*** *64:212, 1998 (92).*

Fridtjof Nansen, the Swiss embryologist Wilhelm His, and the Swiss psychiatrist August Forel during the 1880s. Nansen was very enthusiastic about the reazione nera and, in April 1886, visited Golgi to learn the new technique. The importance of Golgi's discovery and the quality of his histological sections were clearly illustrated by Nansen's recollection: "Never in my life had I imagined it was possible to prepare such elegant to distinct nerve sections" (78). After a few days, he went on to the *Stazione Zoologica* in Naples, where he used the Golgi method in his own studies and was able to pick out neurons selectively and completely (78). Already in September of that same year an English translation of the results Nansen previously published in Norwegian appeared (93). In that publication, Nansen stressed that he had been unable to demonstrate the anastomoses, the union between nerve cells, that Gerlach had predicted. Moreover, the reazione nera enabled him to disprove the notion of anastomoses altogether, while proving that all nerve units have membranes (41, 49, 78). At the same time, His observed a gap between neurons while studying the development of human embryos (68) and Forel, in his studies of degenerative diseases, discovered that the degeneration in the brain was bounded by the limits of the cell (50). These results were reported only 1 and 4 months, respectively, after Nansen's (English) paper, implying the independence of the work of Nansen, His, and Forel, the three scientists who laid the framework for what Waldeyer in 1891 coined the Neuron Doctrine (122), the view that the nervous system consists of individual elements called neurons.

Despite these findings, Golgi continued to support the reticular theory (81) and even made a point of this during his Nobel Lecture (62). Even so, it was his unique technique that laid the foundation for studies of the overall organization of the CNS, and the development of the reazione nera is still considered one of the greatest leaps in the history of neuroscience. Golgi also made a number of other important contributions, including descriptions of the two fundamental neuronal types (Golgi Type I, the projection neurons; Golgi Type II, the local circuit neurons/interneurons), the morphological traits of glial cells, the relationship between these cells and the blood vessels, and the Golgi tendon organ.

In April 1898, after further studies using the reazione nera, Golgi reported an internal reticular apparatus he had found in neurons. Although it was promptly named the Golgi apparatus, it was considered by many to be an artifact; its existence was disputed until it was finally confirmed by electron microscopy in the mid-1950s (13, 32). This organelle system, which plays a key role in the intracellular sorting, trafficking, and targeting of proteins, makes Golgi a frequently cited scientist in not only neuroscientific works but also in the fields of molecular and cell biology (44).

Santiago Felipe Ramón y Cajal: The Microscopic Structure of the Nervous System

Interestingly, whereas Golgi attacked the Neuron Doctrine as late as during his Nobel lecture in 1906, Ramón y Cajal became a disciple much earlier. Ramón y Cajal was introduced to the Golgi technique 1 year after Nansen and was apparently equally impressed (5, 30). Using the new technique, he published a study in which he expressed the independence of a cellular unit in the CNS 2 years after this was first reported (41).

Santiago Felipe Ramón y Cajal (5, 30, 48) was born in the small village of Petilla de Aragón in 1852. He is described as a mischievous youngster with artistic talents who was finally convinced to study medicine by his father, a physician. After an interlude as a medical doctor during the separatist war in Cuba, where he contracted malaria and dysentery, he returned to his alma mater in Zaragoza as an assistant in anatomy. In the late 1870s, he set up a microscope in the attic of his house. This laboratory became the cradle for a scientific enterprise where Ramón y Cajal, through sustained efforts of elegant microscopy, described the structural organization of the nervous system at the cellular level (104).

Ramón y Cajal was first introduced to the Golgi method in 1887 during a visit to Luis Simarro Lacabra in Madrid (5). Yet, it was the introduction to Golgi's text *Sulla fina anatomia degli organi centrali del sistema nervoso* later that same year, after he became professor of pathology at the University of Barcelona, that initiated his use of the technique in a very productive period of his career. The result was his monumental narrative of the microanatomy of the nervous system, which is still in use today. Furthermore, he discovered the dendritic spine, which he first thought of as an artifact, and, through studies of neuronal degeneration and regeneration, he made contributions

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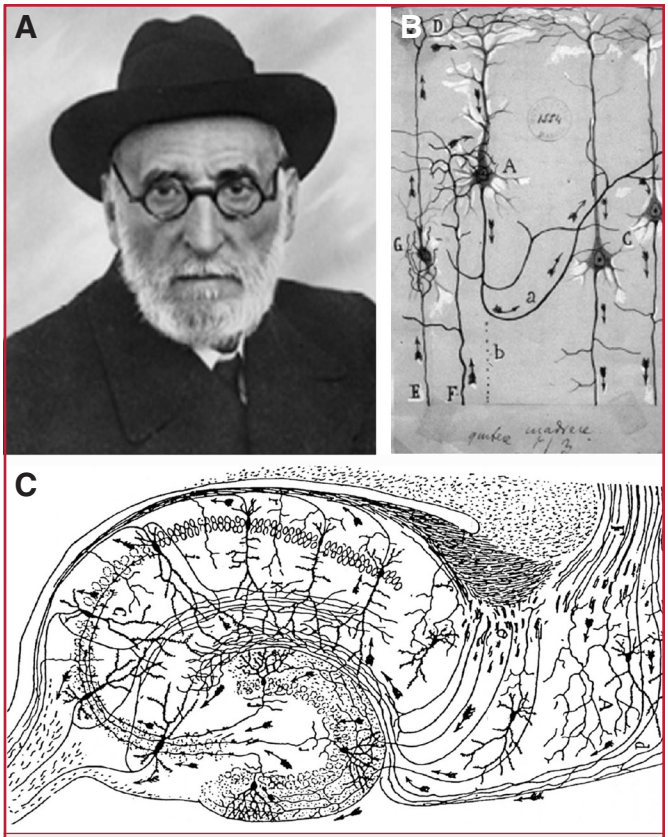

FIGURE 2. *Cajal and the microscopic structure of the CNS. Although Cajal (***A***) is best known for his meticulous description of the fine structure of the CNS, he was also fascinated by other topics such as brain injury and signal transmission.* **B**, *regeneration after brain injury. Note that the outgrowing axon seems to synapse on a neighboring pyramidal cell, a regeneration pattern after injury that possibly may play a role in epileptogenesis.* **C**, *drawing of the hippocampus. Suggested direction of signal transmission indicated by* arrows. From, *Ramón y Cajal S: Histology of the Nervous System of Man and Vertebrates (English translation of the 1909 Histologie du système nerveux de l'homme et des vertébrés). New York, Oxford University Press, 1995 (104).*

to the understanding of neuronal plasticity. Through his embryological work, he became the first to take note of the axonal growth cone. He made early anatomic sketches of reflex pathways and stated that "normally, the dendrites and cell body show axipetal conduction, that is, electrical activity is conducted toward the axon. Conversely, the axon shows somatofugal and dendrifugal conduction, that is, it transmits activity arriving from the parent cell body or dendrites, and does so from its origin to its terminals."

Although Ramón y Cajal was neither the father of the neuron doctrine nor the first scientist to prove it, his work was ultimately important for popularizing it and proving its almost universal validity within the mammalian CNS, and his detailed microscopic studies became a foundation for the developments within the neurosciences in the 20th century.

FIGURE 3. *Sherrington and Cushing. Many of Sherrington's discoveries had profound clinical implications and several of the most excellent clinicians kept contact with him. In this photograph, he appears together with Harvey Cushing at the Royal College of Surgeons on July 12, 1938.* From, *Fulton J: Harvey Cushing. A Biography. Springfield, Charles C. Thomas, 1946 (54).*

Sherrington and Adrian: "For their Discoveries Regarding the Functions of Neurons," 1932

Charles Scott Sherrington: The Reflexes and the Synapse

In a short review, such as this, in which it is impossible to describe Sherrington's monumental work in detail, we chose to concentrate on his study of reflexes, which was a central theme in his research and the primary motivation for awarding him the Nobel Prize. The term "reflex" was first used by Thomas Willis to imply how "spirits" in the peripheral nerves could be reflected back at muscles (48). By the time Sherrington began his investigations, a number of examples of how a specific stimulus could provoke a defined response without the interplay of consciousness had been described, from the simple knee jerk in humans to the more complicated reflex action involved when decapitated birds take to the wings.

Sherrington (*Fig. 3*) was born in London in 1857, but was raised in Ipswich after his father's premature death. Early in his career, he became interested in the cerebral cortex; yet for several years, he was involved in bacteriology, immunology, and pathology. He studied under the tutorage of the day's most notable scholars, both in England and on the continent. Eventually, when he allowed himself time to study the nervous system again, he was advised to investigate it "from the bottom up." Sherrington saw the benefits of such an approach and conceded that the spinal cord and peripheral nerves might prove a simpler system to continue his studies in than the cerebral cortex. Thus, Sherrington became one of the pioneer scientists to select a reductionistic strategy for analyzing nervous system functioning.

He concentrated predominantly on spinal reflexes as he thought these represented a simple type of CNS functioning but exhibited all its basic mechanisms of action (18). He considered the spinal cord in decerebrate animals as a model system for investigations that would also provide an understanding of cellular mechanisms at higher levels of the CNS. Late in his life

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(he died at the age of 95), he told Lord Russel Brain: "The reflex was a very useful idea, but it has served its purpose. What the reflex does is so banal. You don't think that what we are doing now is reflex, do you?" (17).

He started with the knee jerk of Erb and Westphal (43, 123), which was considered one of the simplest of reflexes, and performed a series of systematic experiments on animals. He showed that the knee jerk is based on a reflex arch consisting of a sensory and a motor nerve (88, 110). He dissected the nerves and found that the sensory nerve originated in the muscle. This discovery led him to the idea that muscles had dedicated sensory elements, and by degeneration studies, he learned that many of the nerves connected to muscles actually carried sensory information. In the work on what he termed proprioception and kinesthesia, he suggested that muscle spindles worked as length recorders and the Golgi tendon organs as tension sensors.

Many scientists were still skeptical of the Neuron Doctrine and several even opposed it. Sherrington, however, was quick to adopt the view of neurons as independent elements. This view was substantiated by the delay he observed in propagation from a sensory nerve via the spinal cord to a motor nerve. When Michael Foster of Cambridge asked him to revise a section of his *Textbook of Physiology*, Sherrington seized the opportunity to present his thoughts about the synapse. He explained how the tip of the twig of an axonal arborescence was not in continuity, but only in contact, with the dendrite or cell body and went on to suggest that such a special connection of one nerve cell with another might be called a synapse (111). Johns Fulton, in preparing his well-known textbook, *The Physiology of the Nervous System,* asked Sherrington how he came up with the term synapse. In a letter, Sherrington replied that he originally thought of using "syndesm," but that his Trinity friend, the Euripidean scholar Verall, suggested "synapse" because it yielded a better adjectival form (53).

Sherrington undertook detailed examinations of the spinal nerves and dermatomes and used decerebrated animals to study more complex reflexes. The animals developed decerebrate rigidity (109, 112), a postural pattern dependent on reflexes. Sherrington illustrated this dependency by cutting and stimulating sensory nerves. When a foreleg was stimulated, it would move forward and the hindlimb backwards, whereas the contralateral limbs underwent opposing movements. These and other studies laid the ground work for the discovery of reciprocal innervation in which Sherrington pointed out that activity in one muscle influences activity in others. Movement becomes functional through an orchestrated concerto of excitation and inhibition, leading to coordinated muscle contractions and relaxations.

Two of his students, J.C. Eccles and W.C. Gibson, gave an interesting insight into Sherrington's innovative mind in their biography (36). One of the episodes they recall from their time with him was a morning when Sir Charles Sherrington arrived with an inspired look on his face and [vividly] recounted how he had seen a cat walking solemnly on a stone wall that was interrupted by an open gate. The cat paused, inspected the gap, then leaped exactly the right distance, landed with ease, and resumed its solemn progression. To most, such an incident would represent a trivial happening, but in Sherrington it sparkled scientific questions and prospective experiments.

In 1904, he was invited to give the Silliman Lectures at Yale. These lectures appeared in his famous book, *The Integrative Action of the Nervous System* (113), in which he described the function and evolutionary advances of the reflexes, pointing to the knee jerk as the lowest level of integration and how simple reflexes are combined in more complex actions. When Penfield visited the then 90-plus-year-old Sherrington and told him about cortical mapping in awake patients undergoing epilepsy surgery (15), Sherrington commented with a twinkle in his eyes that it must have been great fun to put a question to the "preparation" and have it answer.

Edgar Douglas Adrian: The All-or-none Principle and Coding of Information

Edgar Douglas Adrian was born to a well-to-do London family in 1889. His primary interest was in the classics rather than the life sciences. Nevertheless, he decided to study physiology and he did his first research work at Cambridge with the famous physiologist Keith Lucas, who was working on the impulses transmitted by motor nerves. Already in 1912, Adrian provided indirect evidence for the action potential being an all-or-none phenomenon. His research was, however, interrupted by World War I. After he obtained his medical degree in 1915, he did clinical work at St Bartholomew's Hospital in London, working with military patients experiencing nerve injuries or nervous disorders. Lucas, who developed new instruments for the Royal Air Force, perished in a midair collision in 1916. After the war, Adrian took over his mentor's lab at Cambridge. Early on, he realized the importance of improved neurophysiological recording techniques and paid much time to technological developments in his lab, "which contained the most glorious clutter ever seen" (103). With input from Alexander Forbes and others (*vide infra*), he established a neurophysiological laboratory with unique qualities (1, 2, 16, 48, 70).

One day Adrian was recording from a suspended frog leg. The recording was quite irregular, leading him to believe that his circuit was oscillating. His first reflection was that he would have to spend months rebuilding the equipment; however, by placing the leg on a glass plate, the oscillations were stopped, only to recur when the leg was re-suspended. It suddenly dawned on him that a stretched muscle sent sensory information up through the nerve and that he had confirmed Sherrington's theory about proprioceptive feedback from muscles (2).

A particularly important experiment took place in 1925 when, after meticulous dissection of a nerve-muscle preparation, he was able to record from a single axon. The action potentials were all of the same amplitude and propagated with the same speed, thus confirming the all-or-none principle. In addition, he realized that the sensory axon from the muscle discharged action potentials at higher frequency when the load on the muscle was increased. When a 0.25 g weight pulled the muscle, the

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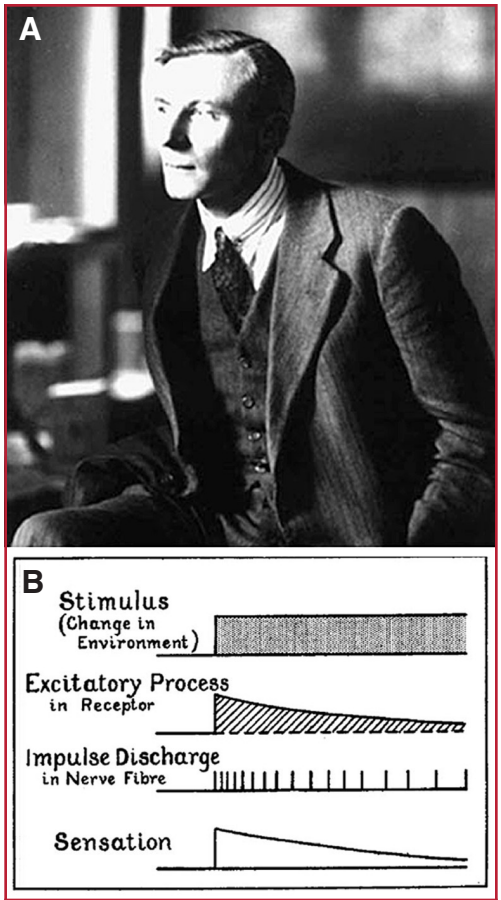

FIGURE 4. *Edgar Douglas Adrian (**A**) discovered how neurons code information (**B**). He later recollected about one of his important experiments: "I had arranged electrodes on the optic nerve of a toad in connection with some experiments on the retina. The room was nearly dark and I was puzzled to hear repeated noises in the loudspeaker attached to the amplifier, noises indicating that a great deal of impulse activity was going on. It was not until I compared the noises with my own movements around the room that I realized I was in the field of vision of the toad's eye and that it was signaling what I was doing…" His conclusion that the intensity of sensation is proportional to the frequency of sensory nerve impulses remains one of the most universal principles in neuroscience (91).*

firing frequency was 21 Hz; with 1.0 g, it increased to 33 Hz. Adrian concluded that the nerves coded information in discharge frequency. He also observed that the firing frequency after a new stimulus peaked in the beginning and then slowed down to a steady state level. Thus, the sensory system could respond both to change and steady-state conditions (*Fig. 4*).

Although Adrian was known by his contemporaries as an exceptionally bright and hardworking person, he later noted that this particular day did not involve any particular hard work, or any particular intelligence on his part. It was one of those things that sometimes just happens in a laboratory if you stick apparatus together and observe the results. To this, Hodgkin, who received a Nobel Prize for his work on the ionic basis of the action potential many years later remarked, "The comment that one wants to make about the last sentence is that when most people stick apparatus together they do not make discoveries of the same importance as those of Adrian" (*Fig. 4*) (70).

FIGURE 5. *Henry Dale (left) and Otto Loewi (right) shared the 1936 Nobel Prize in Physiology or Medicine for discoveries relating to chemical neurotransmission.* From, *Nicholls JG, Martin AR, Wallace BG:* From *Neuron to Brain. Sunderland, Sinauer Associates, 1992 (97).*

Dale and Loewi: "For their Discoveries Relating to Chemical Transmission of Nerve Impulses," 1936

After the Neuron Doctrine was well established, much attention was paid to the mechanism by which a signal is transferred from one neuron to the next or from a neuron to an effector cell. The 1936 prize was awarded to two scientists who had contributed to the understanding of how this occurs in the vegetative nervous system.

Henry Dale, Adrenaline, and Acetylcholine

Henry Dale (*Fig. 5*) was born in London in 1875 and came to Cambridge University in 1894. Like Sherrington, he studied with some of the most influential scientists in the field, Gaskell and Langley, and thus, set out on his studies of the autonomic nervous system under extraordinarily blessed circumstances. Ten years later, after Dale had turned down the notion of a

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medical career due to the authoritarian-style lectures and demeanor of the senior physicians (116), Henry Wellcome offered him a position as a research director at the Wellcome Physiological Research Laboratories outside London. There he was encouraged to study ergot (*Claviceps purpurea*), a fungus that grows on rye, and had been used as a labor-inducing drug for hundreds of years (48, 116). The fungus turned out to contain both histamine, an amine that interacted with vegetative nervous system functions, and acetylcholine, the latter due to contamination with *bacillus acetylcholine,* which ferments sauerkraut. In the following years, Dale and his colleagues described the pharmacological effect and chemical structure of a number of agents that mimic sympathetic and parasympathetic nerve stimulation.

Dale observed that, more than any other drug, acetylcholine duplicated the effects of parasympathetic nerve stimulation (24, 25). He found its action immediate and intense and even suggested that its short-lasting effect might be due to the fact that it was broken down by an esterase. He found that muscarine simulated acetylcholine at certain sites and nicotine at others, and that atropine blocked the effect at muscarinic but not nicotinic sites, thus making early observations in keeping with the later concept of receptor subtypes. In a finding significant for the development of the theory of chemical transmission, he showed that stimulation of nerves may release acetylcholine (26, 27).

One of Dale's collaborators, George Barger, synthesized a number of sympathomimetic compounds (11). Several of these compounds were more effective than adrenaline. This included noradrenaline (norepinephrine), which they mainly thought of as an interesting chemical substance because it was not identified in the body. In the end, Dale introduced the basic distinction between cholinergic nerves releasing acetylcholine and adrenergic nerves releasing an adrenaline-like compound (108).

In the beginning, Dale's research was focused on the pharmacological action of drugs, not synaptic transmission. When he later turned his interests towards the mechanism of synaptic transmission, he became one of the prime defenders of the chemical hypothesis. The time was not ripe for a general acceptance of this point of view, however, and neurophysiologists especially continued to argue that transmission was electric. Dale later recollected that "Transmission by chemical mediators was like a lady with whom the neurophysiologist was willing to live and consort in private, but with whom he was reluctant to be seen in public" (28).

Otto Loewi and Chemical Transmission

The person to design and perform the critical experiment that demonstrated the first example of chemical transmission was Otto Loewi (1873–1961) (*Fig. 5*). The son of a wealthy wine merchant, his intellectual aspirations flowed more in the direction of the fine arts. He was finally convinced to attend medical school, but his interest in arts never abated and he often skipped classes to such an extent that he barely passed the examination at the end of his third year. Later, he left medicine due to the lack of efficient treatment and accepted a research position in Marburg (51, 82, 90, 116).

In 1902, he visited London where he became acquainted with Dale as well as Thomas Renton Elliot, who suggested in 1904 that sympathetic nerves release adrenaline (42). It was later speculated that the idea of chemical transmission came up in conversations between Elliot and Loewi. The following year, Loewi is said to have made a casual remark about how the vagus nerve might inhibit heart rate by secreting something like muscarine (116). In 1908, Loewi became a professor in Graz, Austria. He later reminisced that even if he occasionally thought of synaptic transmission, he did not come up with a method to investigate it until the night before Easter Sunday, 1920. During that night, he had a dream explaining how he could put the hypothesis of chemical transmission to a direct test. Waking briefly, he jotted down a few notes before he fell asleep again but could not decipher his scrawl the next morning. Fortunately, the dream returned and Loewi recounts that "I got up immediately, went to the laboratory, and performed a simple experiment on a frog heart according to the nocturnal design." In this classical experiment (82, 89), he used two frog hearts, which continue to beat spontaneously after isolation. One of the hearts had intact innervation, and the other was denervated. He perfused the first heart while activating the vagus nerve, thereby slowing the heart rate. He then applied the perfusate to the second heart whereupon this also slowed down, "…just as if its vagus had been stimulated." Similarly, he found that Ringer's solution from a heart in which the accelerator nerve was stimulated would increase the heart rate in a second heart (90).

Loewi later reflected that "On mature consideration, in the cold light of the morning, I would not have done it. After all it was an unlikely enough assumption that the vagus should secrete an inhibitory substance" (97). Interestingly, the experiment was carried out at the perfect time in the frog's diurnal cycle. Loewi might not have made his discovery if he had done it during regular working hours (51, 116). Later, Loewi repeated the experiment on a paralyzed heart to exclude the possibility that the humoral effect was produced by the heart itself.

Gasser and Erlanger: "For their Discoveries Relating to the Highly Differentiated Functions of Single Nerve Fibers," 1944

The capillary electrometer used from the late 1800s was based on the observation that a drop of mercury placed on acid changes its shape when small currents pass through it. Neurophysiologists filled capillaries with mercury and acid and then recorded electrical events in nerves by shining bright light through the tube onto a film. The recording instruments used at the turn of the century were far from sensitive enough to record from single neurons or to analyze the shape of the compound action potential in a peripheral nerve.

When Adrian delivered his Nobel address in 1932, he began by giving credit to the scientists who had developed the triode valve amplifier in his book published the same year, he also commented that "the history of electrophysiology has been decided by the history of electrical recording instruments" (1).

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This reference pointed not least to the St. Louis group headed by Herbert Gasser and Joseph Erlanger, as their technical developments had been important for Adrian's work (16).

Joseph Erlanger was born in San Francisco in 1874. After completing his medical training at Johns Hopkins University Medical School in 1900, he became an assistant in the Department of Physiology. In 1910, he was appointed Professor of Physiology at Washington University Medical School. Herbert Spencer Gasser, born 1888 in Platteville, WI, studied physiology under Erlanger. A year after graduating from Johns Hopkins Medical School, he joined up with his former teacher in St. Louis where they began their work on the nervous system. Until that time, Erlanger's primary interest had been the circulatory system (20, 29, 99).

Gasser realized it would be critical to find a better way to amplify currents generated by nerves and turned to H.S. Newcomer and the Western Electrical Company for help. This resulted in a construction that consisted of three vacuum tube amplifiers, in which the output from one vacuum tube was fed into the next (55), amplifying the signal to an order of 560. Some years earlier, German physicist Karl Braun had developed an instrument in which he sent an electronic beam through a vacuum to a fluorescent screen. Inside the vacuum tube, the beam could be deflected by an electric field. In order to display the output from the last amplifier, Gasser and Erlanger ended up using the cathode ray tube. Ultimately, they were not only able to amplify the signal 7000 times but also to display the rapid deflections perfectly.

Recording from peripheral nerves in different animals, they discovered that the configuration of the action potential was complex (56), and that the shape of the potential changed when they moved the recording electrode further away from the stimulation electrode. Knowing that the nerve contained axons with different diameters, they made an analogy to the electric conductivity of wire cables, in which resistance decreases with increasing diameter, and concluded that the different phases of the compound action potential reflected signals propagating at different speeds through different groups of axons. This was followed by experiments in which they identified different types of axons and demonstrated that different axons carry different types of sensory information such as sharp pain, dull pain, touch, and temperature. Thus, the quality of a sensation experienced by the brain is dependent on the particular axons carrying the information from the periphery, and the type of information carried by a particular axon depends on the specificity of the detection mechanism it is activated by in the periphery.

Eccles, Hodgkin and Huxley: "For their Discoveries Concerning the Ionic Mechanisms Involved in Excitation and Inhibition in the Peripheral and Central Portions of the Nerve Cell Membrane," 1963

Hodgkin and Huxley and the Action Potential

With two historians in the immediate family, Alan Lloyd Hodgkin, born in Banbury, Oxfordshire in 1914, found it hard to choose between history and the natural sciences. In the end, he selected the latter and studied at Trinity College, Cambridge from 1932 to 1936. At Trinity, he was also advised to study mathematics and physics, disciplines that were of paramount importance in his later research work. In the late 1930s, he spent a period with K.S. Cole at Woods Hole, where he learned to dissect the giant axon of the squid. During the summer of 1939, he went to the Marine Biological Association in Plymouth to conduct experiments on the squid axon. He invited A.F. Huxley to join him in this endeavor (69, 71, 79, 80, 100).

Andrew Fielding Huxley was born in London in 1917. As a grandson of T.H. Huxley, "Darwin's Bulldog," and son of a classics master, he turned from classics to science in 1932 and came to Trinity College, Cambridge in 1935 to study physics and mathematics. He also studied physiology, as he was required to select an additional subject from another scientific branch, and later added anatomy in order to qualify for medical studies (79, 100).

In a series of papers published in the *Journal of Physiology* in 1952, Hodgkin and Huxley reported their investigations on the action potential in the giant axon of the squid (72–76). This investigation was so elegant, so exceptional in its quantitative nature and so complete that it has remained a scaffold for studies on excitability and other modeling work ever since.

Let us consider the foundation on which they were basing their work. First, the resting potential was thought to be due to a selective permeability of potassium ions (K^+) (14). Second, the action potential was considered as an all-or-none phenomenon (*vide supra*). Third, it was known that the action potential was associated with an increase in the permeability of the neuronal/axonal membrane (21) and it was held that this was nonspecific (i.e., all types of ions would pass).

Huxley later recalled that Hodgkin had a feeling that the action potential might be higher than the resting potential when they joined at the Marine Biological Laboratory in 1939 and that "[at] Plymouth, we pushed an electrode down inside squid fibers and found that this was true: at rest the interior was −45 mV but at the peak of the action potential it was +45 mV" (79). These results were of central importance (21). Had the action potential been due to a nonspecific increase in membrane permeability (i.e., short-circuiting of the membrane), the action potential would have peaked at 0 mV. Huxley later commented that they published the observation with "no discussion or explanation. In a full paper (1945), we gave four possible explanations, all wrong" (80). When asked to review their great scientific achievement on its 50th anniversary in 2002, he showed the ultimate level of modesty by writing a report about all the mistakes they made during the first years, concluding that they "felt stupid not to have considered that ions might pass through channels that are opened and closed by membrane-potential changes, just as we did for failing to think of the Na^+ theory until six years after finding the overshoot" (79).

At that time, they were unaware that Overton (101) had already shown in 1902 that sodium ions (Na^+) were necessary for the action potential, "[otherwise] I am sure we would have reached that conclusion immediately" (80). Regardless, soon afterwards, Hodgkin and Katz (77) found that the action poten-

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tial was affected by changes in extracellular Na^+-concentration (*Fig. 6A*).

Early on, both they and Cole realized that a detailed investigation of an explosive phenomenon like the action potential would be difficult with traditional recordings. This led to the development by both groups of the so-called voltage-clamp technique, in which the membrane potential can almost instantly be set to a certain level at the same time the flow of current across the membrane is recorded.

Using current-clamp (i.e., observing voltage changes under constant current), Hodgkin and Huxley could record action potentials (*Fig. 6A*). Then, switching to voltage-clamp (i.e., recording the current while the membrane was held at a given potential), they could record the current across the cell membrane. *Figure 6B* illustrates an experiment in which the membrane potential was first held ("clamped") at −65 mV and then instantly switched to and held at −26 mV. This resulted in an early negative (i.e., inward) current, followed by a later positive (i.e., outward) current. By playing with the membrane potential, they found that the early inward current reversed (*Fig. 6C*) at the Na^+ reversal potential, which can be predicted by the Nernst equation. By manipulating ionic gradients across the axolemma, they showed that the early current was due to an inward flow of Na^+ and that the late current represented outward flow of K^+. Plots of the two currents against the membrane potential (*Fig. 6D*) showed that the slope relation for the sodium Na^+ was negative between −50 and +10 mV, i.e., the conductance increased with depolarization. After a detailed mathematical analysis, they came up with a complete set of differential equations that almost perfectly described the experimental findings, including the shape, threshold, and refractory period of the action potential, as well as propagation along the axon and subthreshold oscillations.

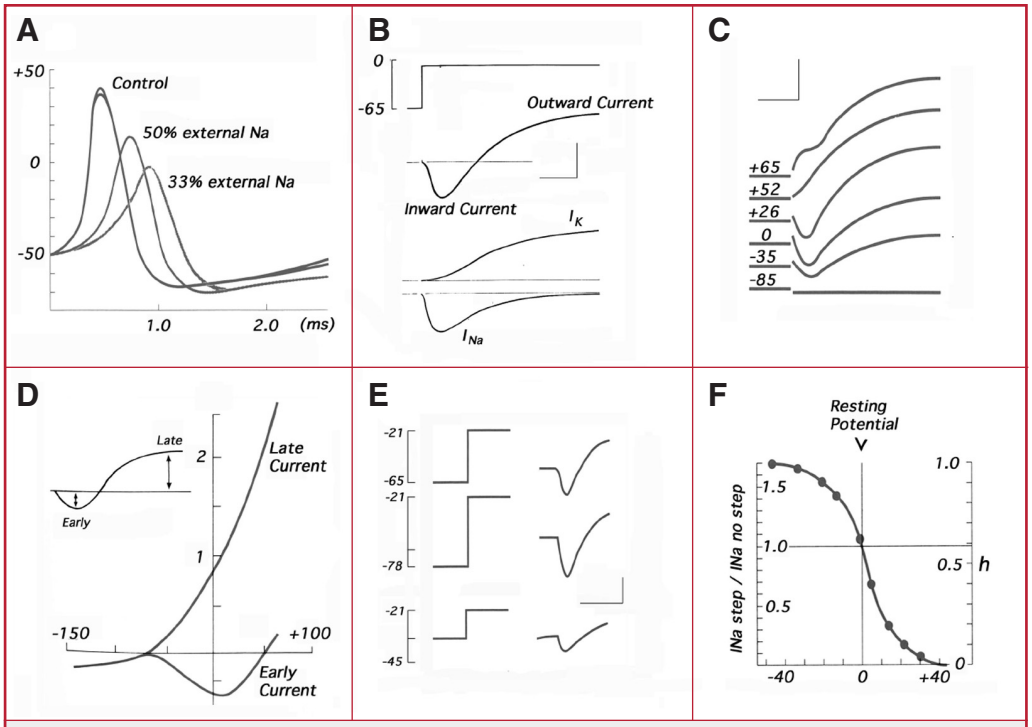

FIGURE 6. *The Hodgkin Huxley Model.* **A**, *in a current clamp, recording the current is kept constant while the voltage changes across the membrane is recorded. The figure shows the change in membrane potential during an action potential in the squid giant axon. The size of the action potential decreased when the external sodium concentration was reduced.* **B**, *voltage clamp recording (the voltage across the membrane is kept constant while the current is recorded). A depolarizing voltage step of 56 mV* (upper trace) *caused a transient inward current followed by a delayed outward current* (middle trace). *Hodgkin and Huxley could show that this current had two separate elements* (lower traces); *an inward sodium current* (I_{Na}) *and an outward potassium current* (I_K). **C**, *current resulting from stepping the membrane potential from −65 mV to a range of potential from −85 to +65 mV. Note that the early transient inward current decreased with depolarization, and was reversed at +65 mV, and that the late current increased with depolarization.* **D**, *amplitude of early and late current* (inset) *plotted versus the potential the membrane was stepped to (x-axis). Note the negative slope of the early current between −50 and +10 mV. This shows that the current is increasing despite the fact that the driving potential (the difference between membrane potential and sodium equilibrium potential) is decreasing. It occurs due to sodium conductance increasing with depolarization.* **E**, *voltage steps* (left) *and resulting transient inward current* (right). *In the control experiment (upper part), the membrane potential was stepped from −65 to −21 mV. One would expect that the current at −21 mV would be the same irrespective of the potential from which the membrane was stepped. A voltage step from a more hyperpolarized level (−78 mV; middle trace) did, however, cause a larger inward current, and a step from a more depolarized level (−45 mV, lower part) a smaller current.* **F**, *the inactivation parameter h. Relative sodium current plotted against the potential the membrane is stepped from (relative to rest-"0" represents the resting potential). "No step" represents the control recording. Calibration B: 1 mA/cm², 1 millisecond; C: 1 mA/cm², 3 milliseconds.* Modified from, *Hodgkin AL, Huxley AF: The components of membrane conductance in the giant axon of Loligo.* ***J Physiol*** *116:473–496, 1952 (72); Hodgkin AL, Huxley AF: Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo.* ***J Physiol*** *116:449–472, 1952 (73); Hodgkin AL, Huxley AF: The dual effect of membrane potential on sodium conductance in the giant axon of Loligo.* ***J Physiol*** *116:497–506, 1952 (74); Hodgkin AL, Huxley AF: A quantitative description of membrane current and its application to conduction and excitation in nerve.* ***J Physiol*** *117:500–544, 1952 (75); Hodgkin AL, Huxley AF, Katz B: Measurement of current-voltage relations in the membrane of the giant axon of Loligo.* ***J Physiol*** *116:424–448, 1952 (76); and Hodgkin AL, Katz B: The effect of sodium ions on the electrical activity of the giant axon of the squid.* ***J Physiol*** *108:37–77, 1949 (77).*

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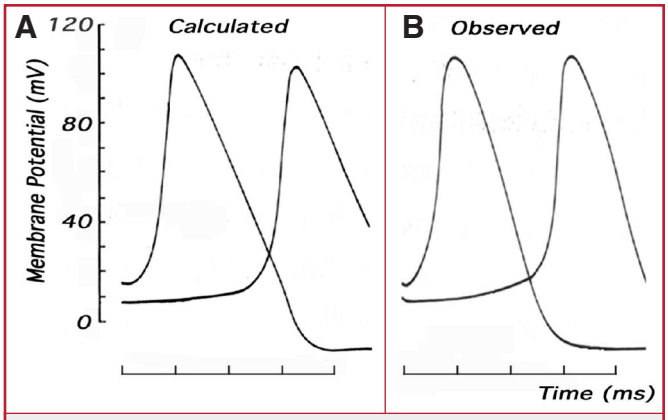

FIGURE 7. *Mathematical simulation of the action potential. Hodgkin and Huxley confirmed the reliability of their biophysical model by comparing calculated action potentials (**A**) to action potentials observed during experiments (**B**).* Modified from, *Hodgkin AL, Huxley AF: A quantitative description of membrane current and its application to conduction and excitation in nerve.* ***J Physiol*** *117:500–544, 1952 (75).*

They found that the Na^+ conductance could be described by:

$$g_{Na} = \tilde{g}_{Na} m^3 h,$$

where $\tilde{g}_{Na}$ represents a maximum current, *m* represents an activation parameter, and *h* represents an inactivation parameter. These activation and inactivation parameters are governed by separate sets of equations. The total current across the membrane as a function of voltage and time was described by:

$$I = \tilde{g}_{Na} m^3 h(V\text{-}E_{Na}) + \tilde{g}_K n^4(V\text{-}E_K) + \tilde{g}_{leak}(V\text{-}E_{leak}).$$

Using the full set of equations, they found a remarkable similarity between calculated and observed action potentials (*Fig. 7*).

Eccles and the Mechanism of Synaptic Transmission

During the 1930s, it became more or less universally accepted that transmission in the peripheral synapses of the autonomic nervous system was chemical. In the brain, and even at the neuromuscular junction, however, the situation was quite different; electrical transmission was favored by many scientists. Among the main opponents of the hypothesis of chemical transmission were two of Sherrington's best known pupils: Jon Eccles and John Fulton.

John Carew Eccles, born in Melbourne, Australia in 1903, owed much of his early training to his father, who was a teacher. He graduated with a bachelor's degree in science and medicine from Melbourne University in 1925, and went to Oxford on a Victorian Rhodes Scholarship. At Oxford, he was a student of Sherrington and worked as his last collaborator until he returned to Australia in 1937. Their studies included work on the "central excitatory and inhibitory states," the last experiments in which Sherrington participated (4, 23, 83).

The controversy between scientists supporting the chemical theory of synaptic transmission and those favoring the electrical hypothesis went on for a number of years, and the discussion between the two camps, which was in itself an attraction at scientific meetings, became known as the "soups versus sparks debate" (108). The physiologists were headed by Eccles, who introduced the concept of a rapid detonator response, where action currents in the presynaptic terminal directly excited the postsynaptic cell (33, 34); and the side supporting chemical transmission was headed by Dale. When finishing a vigorous tennis game at an Oxford seminar, Dale and a colleague opined that the sweat response is generated by acetylcholine. Eccles suggested that they should bioassay their tennis socks; apparently, they did so with a positive result. The chemical side did not lack captiousness, however, as illustrated by Dale's remark that "it was unreasonable to suppose that nature would provide for the liberation in the ganglion of acetylcholine…for the sole purpose of fooling physiologists" (10, 83, 108).

Eccles's work on the electrical theory, however, did have an aspect that is often neglected. While living in New Zealand, he became a life-long friend of Karl Popper (23). At this time, Popper, who was born in Vienna in 1902 and eventually became one of the most influential philosophers of the 20th century, was teaching at the University of Canterbury in New Zealand. Popper's thesis was that scientific hypotheses should be clearly formulated and testable by experiment and that a hypothesis was difficult to prove and, therefore, could be verified mainly through a failure to falsify it. Inspired by the conversations with Popper, Eccles reformulated his theory of electric transmission. As appreciated in the Nobel biography: "this controversy had the effect of defining problems and stimulating much good experimental work, but the decisive victory of the chemical theory had to await the intracellular recording…" (100).

Around 1950, several groups started to use intracellular microelectrodes to record from neurons. In Eccles's lab in Dunedin, New Zealand, L. Brock worked on methods for developing glass microelectrodes and filling them with electrolytes, and the physicist J.S. Coombs worked on the development of amplifiers that could be used with high-resistance electrodes. The critical experiments that clarified the mechanism underlying synaptic transmission in the spinal cord were conducted during the summer of 1951 on a day when Coombs and his wife were delivered a baby by Brock. Meanwhile, Eccles attended an experiment on a cat and observed that direct inhibition was associated with hyperpolarization of the postsynaptic membrane (23, 35, 116). Eccles immediately considered his hypothesis falsified and, at the end of a long day, it was concluded that the inhibitory response not could be transmitted electrically. He described this realization in a letter to his longstanding friend Dale, who replied that his "…newfound enthusiasm [for chemical transmission] is certainly not going to cause any of us embarrassment" (35). Later, Dale observed: "A remarkable conversion indeed. One is reminded almost inevitably of Saul on his way to Damascus when sudden light shone and the scales fell from his eyes" (28).

In the following years, Eccles and his collaborators continued describing the two different mechanisms of synaptic transmission in the spinal cord, one hyperpolarizing (inhibitory postsy-

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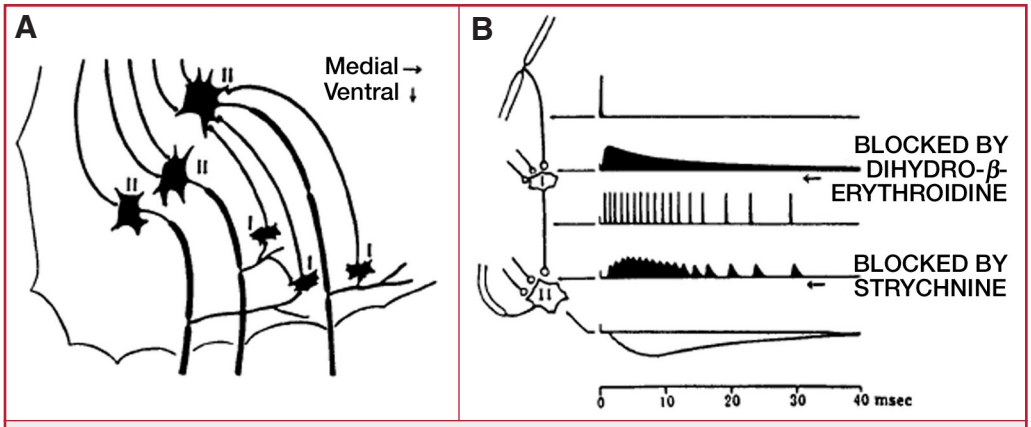

FIGURE 8. *Eccles's Renshaw Experiment.* **A**, *sketch of neurons in ventral horn of the spinal cord. Collaterals given off by motor axons make synaptic contact with Renshaw interneurons* (I). *The axons of these interneurons make contact with motoneurons* (II), *which, by this system, are inhibited. Reflexly active afferents descend onto the motoneurons from the dorsal direction.* **B**, *diagram summarizing the postulated chain of events from the antidromic impulse in motor axons to inhibition of motoneurons. The corresponding histological structures are shown to the left. The five events are from above downwards: 1) impulse in axon collateral; 2) time course of acetylcholine liberated at axon collateral; 3) repetitive discharge in interneuron; 4) time course of inhibitory transmitter substance liberated at interneuronal terminal; and 5) hyperpolarization set up in motoneuron by inhibitory synaptic action. The summation of the synaptic action of several converging interneurons onto a motoneuron is responsible for smoothing the latter part of the motoneuron hyperpolarization.* From, *Eccles JC, Fatt P, Koketsu K: Cholinergic and inhibitory synapses in the central nervous pathway.* ***Austr J Sci*** *16:50–54, 1953 (40) and Karczmar AG: Sir John Eccles, 1903–1997. Part 1. Onto the demonstration of the chemical nature of transmission in the CNS.* ***Perspect Biol Med*** *44:76–86, 2001 (83).*

naptic potential), one depolarizing (excitatory postsynaptic potential [EPSP]), and both chemically mediated. Furthermore, they found that the inhibitory postsynaptic potentials were generated by ions with an equilibrium potential negative to the resting membrane potential (i.e., K^+ and Cl^-), and that the EPSP was produced by a virtual short-circuiting of the postsynaptic membrane (*Figs. 8* and *9*). Together with Per Andersen, Eccles later uncovered synaptic transmission in and between various parts of the brain. Their studies included the discovery of presynaptic inhibition, recurrent inhibition and description of the ionic mechanism of synaptic inhibiton in different brain areas. The experiments indicating the ionic mechanisms of the EPSP were based on only a few cells and were more difficult to reproduce. Thirty years later, however, it was found that the EPSP and the glutamate-evoked potential in hippocampal pyramidal cells were produced by an increased conductance to Na^+/K^+ with a reversal potential similar to that observed by Eccles and collaborators in the spinal cord (64, 85).

Axelrod, Katz, and von Euler: "For their Discoveries Concerning the Humoral Transmittors in the Nerve Terminals and the Mechanism for their Storage, Release and Inactivation," 1970

Katz and Vesicular Transmitter Release

Bernhard Katz was born to stateless Jewish parents in Leipzig in 1911. After an early orientation towards philology and philosophy, he decided to go to medical school. There he was fascinated by the possibility of recording electrical currents from the nervous system, and, after following his preclinical examinations, he began doing research work and found that stretching a muscle led to a change in its electrical impedance. In the 1930s, it became clear to him that the increasing Nazi influence would make life challenging. Therefore, he contacted A.V. Hill at University College in London and was accepted in his laboratory as "an experiment" (12).

In the late 1930s, it was discovered that a strong depolarization of the local muscle membrane took place between the action potential of the nerve and the action potential of the muscle membrane (39, 63). This potential, the endplate potential (epp), became the focus in 1939 when Katz went to Sydney, Australia where he joined John Eccles and Stephen Kuffler. Using extracellular recording electrodes, they found that the delay from the arrival of the action potential to the start of the epp was as short as 0.5 milliseconds (37, 38) and that the declining phase of the epp was a passive decay of the membrane potential taking place after the depolarizing agent had ceased to act.

During World War II, Katz worked as a radar officer in the Royal Australian Air Force and, at the age of 30, became a citizen of Australia. After the war, he returned to England where he participated in the experiments showing that the overshoot of the action potential is due to sodium influx (77).

He then returned to the endplate again with intracellular microelectrodes. Together with Paul Fatt, he confirmed that the epp alone initiated the muscle action potential and that the epp was generated by acetylcholine opening ionic channels in the membrane. Microelectrodes were also found to be useful for topical application of bioactive substances. Using this method, del Castillo and Katz found that acetylcholine depolarized the muscle, but only in the endplate region and only when applied to the exterior of the muscle cell; injection into the cytoplasm had no effect (31, 46, 47).

Using intracellular electrodes, Katz observed a particular form of biological noise in the postsynaptic membrane potential; it was mainly his studies of this phenomenon that earned him the Nobel Prize. The noise that appeared in his recordings is illustrated in *Figure 10A*. Many of us might have failed to see the significance of such an observation or blamed it on the equipment, but Katz and his colleagues did not stop there. First, they found that although these fluctuations had a

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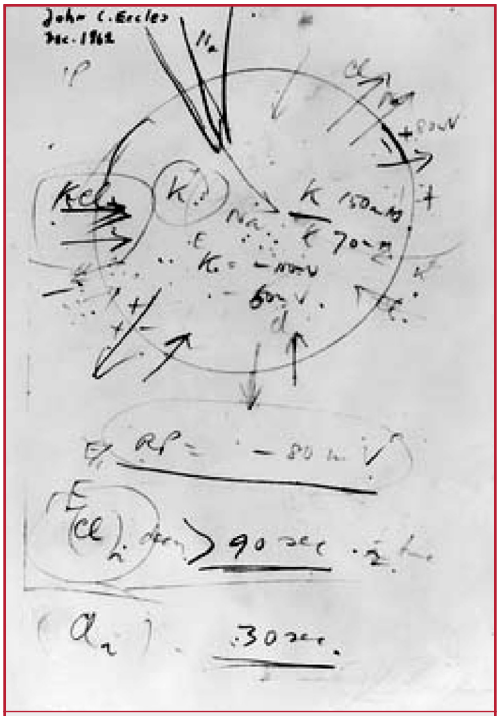

FIGURE 9. *Diagram drawn by John Eccles in 1962 to illustrate ionic gradients across the cell membrane and ionic fluxes underlying changes in the membrane potential.* From, *Karczmar AG: Sir John Eccles, 1903–1997. Part 1. Onto the demonstration of the chemical nature of transmission in the CNS.* ***Perspect Biol Med*** *44:76–86, 2001 (83).*

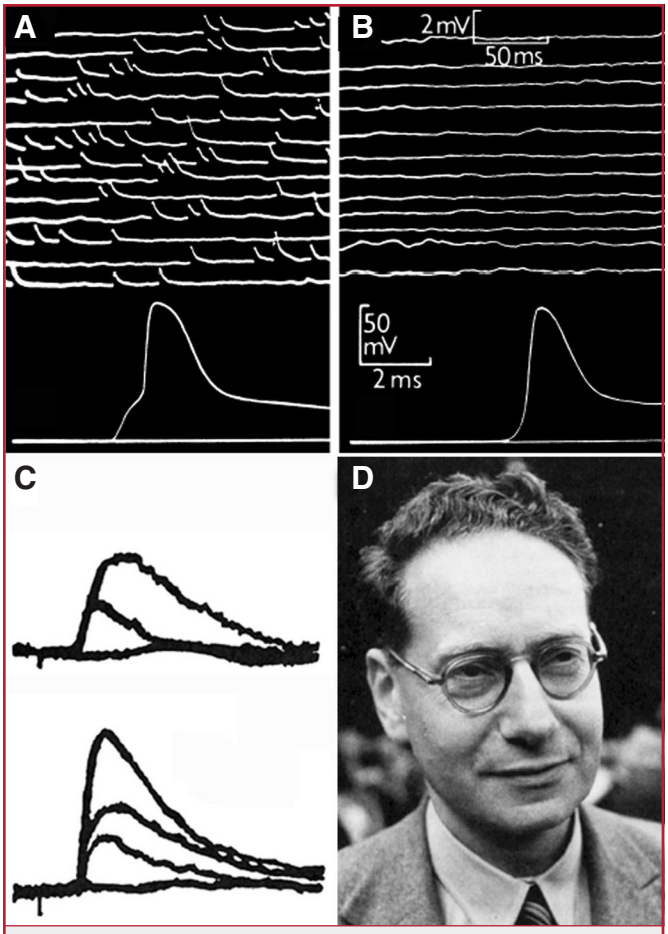

FIGURE 10. *Katz and quantal release of transmitter. Intracellular recordings from single muscle fibers of a frog.* **A**, *recording at the motor end-plate revealed spontaneous miniature epps arising from the sudden discharge of packets of acetylcholine, each containing thousands of molecules.* Bottom, *nerve impulse started by electric shock causes a large epp due to the synchronous release of many packets of acetylcholine, leading to a full size action potential.* **B**, *traces recorded in the same muscle fiber, 2 mm away from end-plate.* Top, *the much attenuated and barely recognizable residues of miniature epps;* bottom, *propagated action potential, delayed by conduction over 2 mm distance and not preceded by end-plate step.* **C**, *superimposed recordings during lowered extracellular calcium pointed towards release of acetylcholine in quanta.* **D**, *Sir Bernard Katz.* Modified from, *Bennett MR: Obituary: Sir Bernard Katz (1911–2003).* ***J Neurocytol*** *32:431–436, 2003 (12); Fatt P, Katz B: Some observations on biological noise.* ***Nature*** *166:597–598, 1950 (45); and Fatt P, Katz B: Spontaneous subthreshold activity at motor nerve endings.* ***J Physiol*** *117:109–128, 1952 (47).*

Gaussian distribution, there were discharges with an amplitude approximately two to four times as high as the amplitude of the mean discharge. This indicated that the events, denoted miniature epps, could represent a type of all-or-none or quantal phenomenon. They correctly related the quanta to the vesicles discovered in presynaptic terminals by electron microscopy. Considering the possibility that he had made an observation that might lead to further understanding of synaptic transmission, Katz continued to study these events. Hence, in the following years, he showed that whereas the size of the miniature epp was influenced by drugs affecting the postsynaptic membrane, the frequency was changed by factors affecting the presynaptic axon. He further established the relation between presynaptic depolarization and transmitter release, namely that synaptic delay was due to the transmitter release mechanism and the role of calcium influx in the presynaptic terminal.

von Euler and Noradrenaline (Norepinephrine)

Ulf S. von Euler was born in Stockholm in 1905 as the second son of Hans von Euler-Chelpin, the 1929 Nobel Laureate in Chemistry, and professor Astrid Cleve. He attended medical school at Karolinska Institute. Having published his first scientific paper at the age of 17 together with his father, he defended his Ph.D. thesis at the age of 25, under the supervision of the pharmacologist G. Liljestrand (100, 115).

A Rockefeller Fellowship for studies abroad (1930–1931) allowed him to study with Henry Dale in London, as well as with other European scientists. Working together with J.H. Gaddum in Dale's laboratory, von Euler discovered that extracts from the brain and intestine caused contractions in the

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rabbit jejunum (120). In their laboratory protocol, they used the term "preparation P." In a later report, Gaddum used the term "Substance P," and the first peptide neurotransmitter to be discovered has been known under this name since then, despite the fact that Gaddum later found it impossible to justify the use of this term.

A few years later, von Euler and Goldblatt independently discovered a bioactive substance in seminal fluid (59, 117). The term "prostaglandin" was coined by von Euler in 1935. He followed up with a series of studies where he defined it as an unsaturated, lipid-soluble organic acid and described methods for its purification and extraction. The work was later continued by Bergström and Samuelsson at Karolinska Institute, and John Vane in London, all of whom shared the Nobel Prize for this work in 1982.

Ulf von Euler, on the other hand, earned his Nobel Prize for his work on noradrenaline (norepinephrine). After Loewi's landmark experiment, it was thought that adrenaline was also the sympathetic transmitter in higher animals. Walter Cannon at Harvard, however, had shown that activation of sympathetic nerves caused actions that did not conform entirely to those of adrenaline. von Euler found that a number of organs contained a blood pressure raising substance that, although having several effects in common with adrenaline, differed both with regard to some physiological effects and chemical properties. In a series of systematic experiments, he showed that even if extracts from a frog's heart contained a substance with the properties of adrenaline, sympathetic nerve endings from higher animals contained a substance with effects and chemical properties identical to that of noradrenaline (norepinephrine), the nonmethylated homologue of adrenaline synthesized by Stolz in 1904 (118).

Two years later, he published further evidence that the sympathomimetic agent in extracts of the splenic nerves from cattle is noradrenaline and also indicated that the active principle occurred in its levoform (L-noradrenaline) (119). He observed that nerve section and subsequent degeneration caused noradrenaline levels to fall to very low levels. He noted that noradrenaline was low in patients with postural hypotension and increased in control persons when shifting from the horizontal to the vertical position. Another important discovery was that noradrenaline was stored in subcellular particles which had a diameter of 300 to 1500 Å and were surrounded by a 70 Å thick membrane (121).

Ulf von Euler is described as an aristocrat and cosmopolitan, carrying on with the dignity and style of the intellectual and cultural tradition that he had inherited. On the other hand, he had an open mind and was never one to flatly reject even more extreme theses proposed by younger colleagues. As he once stated, "We must always guard the liberties of mind and remember that some degree of heresy is often a sign of health in spiritual life."

Axelrod and Presynaptic Reuptake of Neurotransmitters

It was established early on that the action of the neurotransmitter acetylcholine was rapidly terminated by acetylcholinesterase. A similar effect of monoamine oxidase with respect to norepinephrine had, however, been ruled out. It was Julius Axelrod who finally elucidated the mechanism by which the action of most neurotransmitters is terminated.

Axelrod, the son of a poor basketmaker, was born in New York in 1912. In 1933, he graduated from tuition-free City College of New York with a bachelor's degree in biology. He applied to a number of medical schools, but was not accepted by any of them. This was during the depths of the Great Depression and it was difficult to get a job, but he was hired as a technician at the Harriman Research Laboratories for $25.00 a month (6, 114); he remained in this position for many years.

Although he published independent papers, it was difficult for him to achieve a promotion because he lacked an academic degree. Therefore, he decided to earn a doctoral degree and, at the age of 42, received a Ph.D. from George Washington University in 1955 (6). Under the influence of Seymore Kety, he then changed the direction of his research to the biochemistry of the nervous system. He observed that little was known about the metabolism of epinephrine and began investigations that ultimately led to the identification of the enzyme *catechol-O-methyltransferase* (COMT) (7, 8) that methylates norepinephrine, dopamine, and L-dopa. He found that the enzyme was widely distributed in the tissues including the brain and that it was inhibited by pyrogallol. Inhibition of this enzyme was later to be used in the clinical treatment of Parkinson's disease.

In an attempt to investigate a possible role of COMT in terminating the synaptic action of norepinephrine, Axelrod studied the blood pressure-elevating effect of norepinephrine with and without COMT-inhibition by pyrogallol. Even when COMT was inhibited with pyrogallol, however, the effect of norepinephrine on blood pressure rapidly ended. This suggested that there was another mechanism for the inactivation of norepinephrine (6).

Through Kety, he had an opportunity to work with [^{3}H]-norepinephrine (NE) and found that it accumulated in sites rich in sympathetic nerves and that its concentration remained unchanged long after the physiological effect concluded. This gave him the idea the NE may be sequestrated in sympathetic nerves. According to Axelrod (6), the crucial experiment was suggested by the visiting scientist Georg Hertting. The sympathetic nerves to the eye and salivary glands were degenerated by removing the superior cervical ganglia of cats. After [^{3}H]-NE administration, radioactivity was almost only seen on the contralateral side. This was followed by investigations showing that [^{3}H]-NE taken up in nerve terminals was released when the nerves were activated (66, 67). Hence, they suggested that NE was inactivated by reuptake into the nerve terminals. Soon thereafter, it was shown that the effect of a number of neurotransmitters was terminated by reuptake in presynaptic nerve terminals.

It was known that cocaine caused supersensitivity to epinephrine. Interested in psychopharmacology he decided to test the effect of psychoactive drugs on NE uptake (9, 124). He found that both cocaine and amphetamine blocked NE. Later,

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working on [^{3}H]-NE uptake in the brain subsequent to intraventricular administration, he found that tricyclic antidepressants discovered in 1957 inhibit uptake (58, 84). Soon thereafter, tests of NE, serotonin, and dopamine uptake into synaptosomes became a method for screening new psychoactive drugs.

Throughout his life as a scientist, Axelrod preferred to work with a small group and kept his desk within the lab so that he could enjoy uninterrupted contact with the people he was working with. According to S.H. Snyder, he had such a gift for experimental design that he could solve three or four important scientific questions with just 25 test tubes (114). He preferred to design experiments that were so conclusive that statistics were not needed to prove his point and when statistical analysis were mentioned he bridled a little and commented: "If you have to do a *t*-test to prove something is different, it probably isn't important" (22).

Neher and Sakmann: "For their Discoveries Concerning the Function of Single Ion Channels in Cells," 1991

Throughout the century, new cell types were studied using the electrophysiological techniques developed by Adrian, Hodgkin, Huxley, Eccles, and others. It was found that all cells have a membrane potential that mainly depend on an inside-out K^+ gradient combined with a selective permeability to K^+ in the resting situation.

Not only was the resting potential found to be critical for maintaining cell metabolism and function, but changes in the potential were found to be of literally vital importance from the beginning of life when the first sperm entering an egg sets off a change in the membrane potential that prohibits other sperm to enter to the anoxic death of a neuron where the membrane undergoes a rapid depolarization. The understanding of the ionic channels of cell membranes was brought to a completely new level by developments made by Erwin Neher and Bert Sakmann, the 1991 Nobel colaureates.

Born in 1944, Erwin Neher grew up in Huchloe, Bavaria. From the age of 10, he was influenced by dedicated teachers at the gymnasium Maristenkolleg in nearby Mindelheim, where mathematics and physics were the subjects he found most interesting. He decided to become a biophysicist by first studying mathematics and then biology. Already in high school, he studied everything in his reach regarding the Hodgkin-Huxley model of nerve excitation. After his graduate studies in Germany and the United States, he entered a Ph.D. project with Hans Dieter Lux at the Max-Planck-Institut für Psychiatrie in Munich (94). Professor Lux, a leading cellular neurophysiologist at that time, suggested using suction pipettes for local measurement of current density.

Bert Sakmann, born in 1942, attended the gymnasium in Stuttgart. He states that his only real interest in school was the physics lessons and that he spent most of his time at home designing and building model motors and remote control airplanes. He would have become an engineer had he not been introduced to cybernetics in his final year in school. This interested him as "it seemed to me that living organisms could be understood in engineering terms" (105). Subsequently, he selected medical school and chose to pursue a Ph.D. in neurophysiology, as this was closest to engineering. After studying with Creutzfeldt and Lux in Munich and with Bernard Katz's group in London, Creutzfeldt offered him independent conditions at the Max-Planck-Institute for Biophysical Chemistry in Göttingen, where he joined forces with Erwin Neher (105).

At the time when Neher and Sakmann started their collaboration in Göttingen (1973), there was no direct evidence for the existence of channels across cell membranes. It was known, however, that artificial membranes, which are efficient electrical insulators, may conduct electricity if doped with certain antibiotics or proteins. Furthermore, trace amounts of dope could induce step-like changes in the current. The main problem with recording from individual ionic channels was that the level of electrical noise was a couple of magnitudes higher than the current thought to be produced by the potential unit of an ionic channel. As already suggested by Hodgkin and Huxley in 1952, an ionic channel may be represented as an ohmic resistor. Thermic noise in such a resistor will be:

$$\sigma = \sqrt{4kT\,\Delta f/R},$$

where k is Boltzmann's constant, T is the temperature in Kelvin, f is the bandwidth, and R is the resistance of the signal source. From this, it was evident that in order to record current in the picoampere region, the internal resistance had to be increased to the gigaohm class (95).

The logical way to do this was to try to isolate a patch of the membrane under the diameter of a small glass pipette used as a recording electrode. It was clear to them, however, that this technique would only work if they could obtain a very good seal between the glass electrode and the cell membrane. The problem with the intracellular microelectrode in use since approximately 1950 was that it had a high internal resistance (often approximately 100 mol/LΩ), and that there was combined with a very considerable leak between the outside of the electrode wall and the cell membrane. In the beginning, Neher and Sakmann also experienced substantial leakage between the patch electrode and the cell membrane. This was a problem as the electrode should only "see" current passing through the cell membrane and not current passing between the electrode tip and the membrane. Although initially, the resistance in the seal between electrode tip and cell membrane failed to rise above 10 to 20 mol/LΩ, two orders of magnitude below the required gigaohm seal, they obtained some recordings interpreted as single-channel currents (96). This suggested that channels open and close stochastically in an all-or-none manner and represented the first instance of real-time observation of conformational changes in biological macromolecules (95).

The background noise was, however, still excessive, concealing smaller changes until they discovered, by chance, that slight suction through the pipette increased the resistance of the seal by two orders of magnitude. The nature of this gigaseal is such that the patch may be removed from the cell and transferred to a bath or ruptured by suction or short

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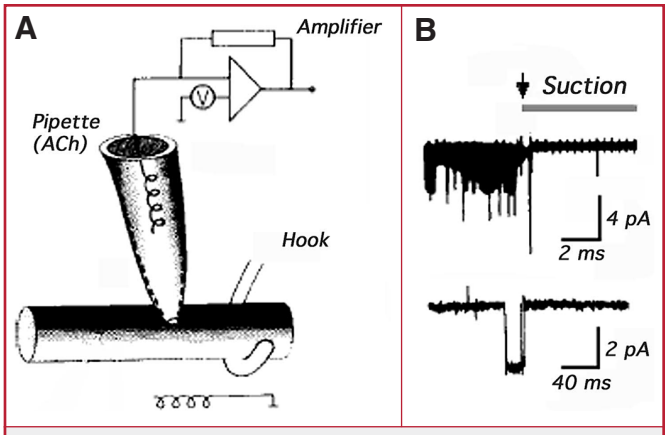

FIGURE 11. *The patch clamp technique. Recording from a patch of the neuromuscular end-plate membrane.* **A**, *schematic diagram of a muscle fiber suspended by a hook. The tip of the patch pipette is sealed against the cleaned surface of the muscle fiber.* **B**, *recording with seal resistances in the MΩ and GΩ range, respectively. Application of negative pressure (suction) to pipette interior causes reduced noise level (compare left and right part of upper trace) and allows monitoring of single channel opening (lower trace).* Modified from, *Hamill OP, Sakmann B: Multiple conductance states of single acetylcholine receptor channels in embryonic muscle cells.* ***Nature*** *294:462–464, 1981 (65) and Sakmann B: Elementary steps in synaptic transmission revealed by currents through single ion channels, in Ringertz N (ed): Nobel Lectures, Physiology or Medicine 1991–1995. Singapore, World Scientific Publishing Co., 1997, pp 31–59 (107).*

pulses in order to obtain a whole cell recording with low access resistance (19, 65, 96, 107).

After having demonstrated the existence of single ionic channels (*Fig. 11*), the patch clamp has been used together with other techniques to study both the detailed mechanism of conduction through individual channels (106, 107) and other important biological phenomena, such as secretion (*Fig. 12*) (3, 102). The technique has brought the understanding of a number of biological processes a quantum leap forward.

The 21st Century

In this review, we have focused on some of the most important discoveries of the 20th century. Since the beginning of the 21st century, the Nobel Prize has already been awarded to neuroscientists on two occassions. Arvid Carlsson, Paul Greengard, and Eric Kandel shared the prize in 2000 for their discoveries concerning signal transduction in the nervous system and, in 2004, Richard Axel and Linda Buck received the prize for their discoveries of odorant receptors and studies on the organization of the olfactory system.

An important success factor in 20th century brain research was the use of reductionist thinking. In keeping with the approach recommended by the French philosopher René Descartes in the 17th century in his *Discours de la Methode*, scientists studied individual elements in order to understand complex processes. In doing this, they built their work on data from colleagues and predecessors both within their own discipline and other areas of science. Interestingly, false interpretation of data was not uncommon. In keeping with the Popper-Eccles philosophy, hypotheses were put forward and rejected. These excellent researchers seem to have pursued the truth relentlessly, meticulously explored different possibilities, and accepted contradictory views when confronted with facts.

The basic concepts regarding the microscopic structure of the nervous system that emerged by the end of the 19th century provided, together with new technical developments, a stepping stone for understanding CNS physiology. One hundred years later, we have detailed knowledge of CNS function at the cellular level and, thus, an excellent point of departure for studying more complex processes and developing new treatments for CNS diseases.

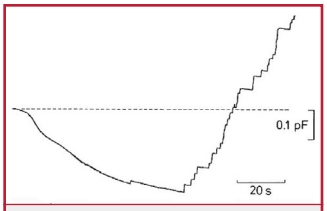

FIGURE 12. *Patch clamp recording of vesicular release. High resolution capacitance recording during the onset of a mast cell degranulation. Whole cell recording where initially the capacitance slowly decreased, probably due to retrieval of very small pinocytotic vesicles. After some delay, degranulation started, leading to a staircase-like increase in capacitance, each step representing fusion of a single granule.* From, *Almers W, Neher E: Gradual and stepwise changes in the membrane capacitance of rat peritoneal mast cells.* ***J Physiol*** *386:205–217, 1987 (3) and Neher E: Ion Channels for Communication Between and Within Cells, in Ringertz N (ed): Nobel Lectures, Physiology or Medicine 1991–1995. Singapore, World Scientific Publishing Co., 1997, pp 10–25 (95).*

REFERENCES

1. Adrian ED: *The Mechanism of Nervous Action. Electrical Studies of the Neurone.* Philadelphia, University of Pennsylvania Press, 1932.
2. Adrian ED: Memorable experiences in research. **Diabetes** 3:17–18, 1954.
3. Almers W, Neher E: Gradual and stepwise changes in the membrane capacitance of rat peritoneal mast cells. **J Physiol** 386:205–217, 1987.
4. Andersen P, Lundberg A: John C. Eccles (1903–1997). **Trends Neurosci** 20:324–325, 1997.
5. Andres-Barquin PJ: Santiago Ramón y Cajal and the Spanish school of neurology. **Lancet Neurol** 1:445–452, 2002.
6. Axelrod J: Journey of a late blooming biochemical neuroscientist. **J Biol Chem** 278:1–13, 2003.
7. Axelrod J, Inscoe JK, Senoh S, Witkop B: O-methylation, the principal pathway for the metabolism of epinephrine and norepinephrine in the rat. **Biochim Biophys Acta** 27:210–211, 1958.
8. Axelrod J, Laroche MJ: Inhibitor of O-methylation of epinephrine and norepinephrine in vitro and in vivo. **Science** 130:800, 1959.
9. Axelrod J, Whitby LG, Hertting G: Effect of psychotropic drugs on the uptake of H3-norepinephrine by tissues. **Science** 133:383–384, 1961.
10. Bacq ZM: *Chemical Transmission of Nerve Impulse: A Historical Sketch.* Oxford, Pergamon, 1975.
11. Barger G, Dale HH: Chemical structure and sympathomimetic action of amines. **J Phyisol** 41:19–59, 1910.
12. Bennett MR: Obituary: Sir Bernard Katz (1911–2003). **J Neurocytol** 32:431–436, 2003.
13. Bentivoglio M: The discovery of the Golgi apparatus. **J Hist Neurosci** 8:202–208, 1999.

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14. Bernstein J: Untersuchungen zur thermodynamik der bioelektrischen Ströme [in German]. **Pflügers Arch** 92:521–562, 1902.
15. Birkenhead LC: *Sherrington: Physiologist, Philosopher and Poet*. Liverpool, Liverpool University Press, 1958.
16. Bradley JK, Tansey EM: The coming of the electronic age to the Cambridge Physiological Laboratory: E.D. Adrian's valve amplifier in 1921. **Notes Rec R Soc Lond** 50:217–228, 1996.
17. Brain R: Discussion of "Early developments of ideas relating the mind to the brain" by H.W. Magoun, in Wolstenholme GEW, O'Connor CM (eds): *Ciba Foundation Symposium on the Neurological Base of Behavior, in Commemoration of Sir Charles Scott Sherrington*. Boston, Little Brown, 1948, p 24.
18. Breathnach CS: Charles Scott Sherrington's Integrative action: A centenary notice. **J R Soc Med** 97:34–36, 2004.
19. Cahalan M, Neher E: Patch clamp techniques: An overview. **Methods Enzymol** 207:3–14, 1992.
20. Chase MW, Hunt CC: Herbert Spencer Gasser—July 5, 1888–May 11, 1963. **Biogr Mem Natl Acad Sci** 67:147–177, 1995.
21. Cole KS, Curtis HJ: Electric impedance of the squid giant axon during activity. **J Gen Physiol** 22:649–670, 1939.
22. Coyle JT: Julius Axelrod (1912–2004). **Mol Psychiatry** 10:225–226, 2005.
23. Curtis DR, Andersen P: Sir John Carew Eccles, A.C. **Biogr Mem Fellows R Soc** 47:159–187, 2001.
24. Dale HH: The action of certain esters and ethers of choline and their relation to muscarine. **J Pharmacol Exp Ther** 6:147–190, 1914.
25. Dale HH: The occurence in ergot and action of acetyl-choline. **J Physiol** 48, 1914.
26. Dale HH: The chemical transmission of secretory impulses to the sweat glands of the cat. **J Physiol** 82:121–128, 1934.
27. Dale HH: Chemical transmission of the effects of nerve impulses. **Br Med J** 1:835–841, 1934.
28. Dale HH: The beginnings and the prospects of neurohumoral transmission. **Pharmacol Rev** 6:7–13, 1954.
29. Davis H: Joseph Erlanger, January 5, 1874–December 5, 1965. **Biogr Mem Natl Acad Sci** 41:111–139, 1970.
30. DeFelipe J: Sesquicentenary of the birthday of Santiago Ramón y Cajal, the father of modern neuroscience. **Trends Neurosci** 25:481–484, 2002.
31. Del Castillo J, Katz B: On the localization of acetylcholine receptors. **J Physiol** 128:157–181, 1955.
32. Dröscher A: From the "apparato reticolare interno" to "the Golgi": 100 years of Golgi apparatus research. **Virchows Arch** 434:103–107, 1999.
33. Eccles J: Synaptic and neuro-muscular transmission. **Ergebn Physiol** 38:339–444, 1936.
34. Eccles J: Synaptic and neuro-muscular transmission. **Physiol Rev** 17:339–344, 1937.
35. Eccles J: From electrical to chemical transmission in the central nervous system. **Notes Rec R Soc Lond** 30:219–230, 1976.
36. Eccles J, Gibson WC: *Sherrington: His Life and Thought*. New York, Springer International, 1979.
37. Eccles J, Katz B, Kuffler SW: Nature of the "endplate potential" in curarized muscle. **J Neurophysiol** 4:362–387, 1941.
38. Eccles J, Katz B, Kuffler SW: Effect of eserine on neuromuscular transmission. **J Neurophysiol** 5:211–230, 1942.
39. Eccles J, O'Connor WJ: Responses which nerve impulses evoke in mammalian striated muscles. **J Physiol** 97:44–102, 1939.
40. Eccles JC, Fatt P, Koketsu K: Cholinergic and inhibitory synapses in the central nervous pathway. **Austr J Sci** 16:50–54, 1953.
41. Edwards JS, Huntford R: Fridtjof Nansen: From the neuron to the North Polar Sea. **Endeavour** 22:76–80, 1998.
42. Elliot TR: On the action of adrenaline. **J Physiol** 31:xx-xxi, 1904.
43. Erb WH: Über sehenreflexe bei Gesunden und Rückenmarkskranken [in German]. **Arch Psychiat Nervenkr** 5:792, 1975.
44. Fabene PF, Bentivoglio M: 1898–1998: Camillo Golgi and "the Golgi": one hundred years of terminological clones. **Brain Res Bull** 47:195–198, 1998.
45. Fatt P, Katz B: Some observations on biological noise. **Nature** 166:597–598, 1950.
46. Fatt P, Katz B: An analysis of the end-plate potential recorded with an intracellular electrode. **J Physiol** 115:320–370, 1951.
47. Fatt P, Katz B: Spontaneous subthreshold activity at motor nerve endings. **J Physiol** 117:109–128, 1952.
48. Finger S: *The Minds Behind the Brain*. Oxford, Oxford University Press, 2000.
49. Fodstad H, Kondziolka D, de Lotbinière A: The neuron doctrine, the mind, and the arctic. **Neurosurgery** 47:1381–1389, 2000.
50. Forel A: Einige Hirnanatomische Betrachtungen und Ergebnisse [in German]. **Arch Psychiat Nervenkr** 18:162–198, 1887.
51. Friedman AH: Circumstances influencing Otto Loewi's discovery of chemical transmission in the nervous system. **Pflugers Arch** 325:85–86, 1971.
52. Frängsmyr T: Life and Philosophy of Alfred Nobel. http://nobelprize.org/alfred_nobel/biographical/articles/frangsmyr/index.html. Accessed January 10, 2007.
53. Fulton J: *Physiology of the Nervous System*. Oxford, Oxford University Press, 1928.
54. Fulton J: *Harvey Cushing. A Biography*. Springfield, Charles C. Thomas, 1946.
55. Gasser HS, Erlanger J: The cathode ray oscilliograph as a means of recording nerve action currents and induction of shocks. **Am J Physiol** 59:473–475, 1921.
56. Gasser HS, Erlanger J: The compound nature of the action current as disclosed by the cathode ray oscilloscope. **Am J Physiol** 70:624–666, 1924.
57. Gerlach J: Von dem Rückenmarke, in Stricker S (ed): *Handbuch der Lehre von den Geweben des Menschen und der Thiere*. Leipzig, W. Engelmann, 1871, pp 866–1248.
58. Glowinski J, Axelrod J: Inhibition of uptake of tritiated-noradrenaline in the intact rat brain by imipramine and structurally related compounds. **Nature** 204:1318–1319, 1964.
59. Goldblatt MW: A depressor substance in seminal fluid. **J Soc Chem Ind** 52:1056, 1933.
60. Golgi C: Sulla struttura della sostanza grigia del cervello (Comunicazione preventiva) [in Italian]. **Gazz Med Ital Lombardia** 33, 1873.
61. Golgi C, Bentivoglio M, Swanson L: On the fine structure of the pes Hippocampi major (with plates XIII–XXIII). 1886. **Brain Res Bull** 54:461–483, 2001.
62. Golgi C: The neuron doctrine-theory and fact. Nobel Lecture December 11, 1906. http://nobelprize.org/medicine/laureates/1906/golgi-lecture.html. Accessed January 10, 2007.
63. Göpfert H, Schaefer H: Über den direkt und indirekt erregten Aktionsström und die Funktion der motorischen Endplatte [in German]. **Pflugers Arch** 239:597–619, 1938.
64. Hablitz JJ, Langmoen IA: Excitation of hippocampal pyramidal cells by glutamate in the guinea-pig and rat. **J Physiol** 325:317–331, 1982.
65. Hamill OP, Sakmann B: Multiple conductance states of single acetylcholine receptor channels in embryonic muscle cells. **Nature** 294:462–464, 1981.
66. Hertting G, Axelrod J: Fate of tritiated noradrenaline at the sympathetic nerve-endings. **Nature** 192:172–173, 1961.
67. Hertting G, Axelrod J, Kopin IJ, Whitby LG: Lack of uptake of catecholamines after chronic denervation of sympathetic nerves. **Nature** 189:66, 1961.
68. His W: *Abhandlung der Matematisch-physischen Classe der Königl. Sächsichen Gesellschaft der Wissenshcaften suchen* [in German]. 1886, vol XIII, pp 479–513.
69. Hodgkin AL: Chance and design in electrophysiology: An informal account of certain experiments on nerve carried out between 1934 and 1952. **J Physiol** 263:1–21, 1976.
70. Hodgkin AL: Obituary: Lord Adrian, 1889–1977. **Nature** 269:543–544, 1977.
71. Hodgkin AL: *Chance & Design: Reminiscences of Science in Peace and War*. Cambridge, Cambridge University Press, 1992.
72. Hodgkin AL, Huxley AF: The components of membrane conductance in the giant axon of Loligo. **J Physiol** 116:473–496, 1952.
73. Hodgkin AL, Huxley AF: Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. **J Physiol** 116:449–472, 1952.
74. Hodgkin AL, Huxley AF: The dual effect of membrane potential on sodium conductance in the giant axon of Loligo. **J Physiol** 116:497–506, 1952.
75. Hodgkin AL, Huxley AF: A quantitative description of membrane current and its application to conduction and excitation in nerve. **J Physiol** 117:500–544, 1952.
76. Hodgkin AL, Huxley AF, Katz B: Measurement of current-voltage relations in the membrane of the giant axon of Loligo. **J Physiol** 116:424–448, 1952.

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77. Hodgkin AL, Katz B: The effect of sodium ions on the electrical activity of the giant axon of the squid. **J Physiol** 108:37–77, 1949.
78. Huntford R: *Nansen. The explorer as Hero.* London, Gerald Duckworth & Co, 1997.
79. Huxley A: From overshoot to voltage clamp. **Trends Neurosci** 25:553–558, 2002.
80. Huxley AF: Hodgkin and the action potential 1935–1952. **J Physiol** 538:2, 2002.
81. Jones EG: Colgi, Cajal and the Neuron Doctrine. **J Hist Neurosci** 8:170–178, 1999.
82. Karczmar AG: The Otto Loewi Lecture. Loewi's discovery and the XXI century. **Prog Brain Res** 109:1–27, xvii, 1996.
83. Karczmar AG: Sir John Eccles, 1903–1997. Part 1. Onto the demonstration of the chemical nature of transmission in the CNS. **Perspect Biol Med** 44:76–86, 2001.
84. Kuhn R: Treatment of depressive states with an iminodibenzyl derivative (G 22355) [in German]. **Schweiz Med Wochenschr** 87:1135–1140, 1957.
85. Langmoen IA, Hablitz JJ: Reversal potential for glutamate in hippocampal pyramidal cells. **Neurosci Lett** 23:61–65, 1981.
86. Larsson U: *Cultures of Creativity: The Centennial Exhibition of the Nobel Prize.* Canton, Science History Publications, 2001.
87. Levinovitz AW, Ringertz N: *The Nobel Prize. The First 100 Years.* London, Imperial College Press, 2001.
88. Liddell DP, Sherrington CS: Reflexes in response to strech (myotatic reflexes). **Proc R Soc Lond B Biol Sci** 96:212, 1924.
89. Loewi O: Über humorale Übertragbarkeit der Herznervenwirkung [in German]. **Phlügers Arch** 189:239–242, 1921.
90. Loewi O: An autobiographical sketch. **Perspect Biol Med** 4:3–25, 1960.
91. Martin KA: The Pope and grandmother—A frog's-eye view of theory. **Nat Neurosci** [Suppl 3]:1169, 2000.
92. Mazzarello P: Camillo Golgi (1843–1926). **J Neurol Neurosurg Psychiatry** 64:212, 1998.
93. Nansen F: Preliminary communications on some investigations upon the histological structure of the nervous system in the ascidia and in *Myxine glutinosa*. **Ann Mag Nat Hist** 18:209–226, 1986.
94. Neher E: Nobel Prize Autobiography. http://nobelprize.org/nobel_prizes/medicine/laureates/1991/neher-autobio.html. Accessed January 10, 2007.
95. Neher E: Ion Channels for Communication Between and Within Cells, in Ringertz N (ed): *Nobel Lectures, Physiology or Medicine 1991–1995.* Singapore, World Scientific Publishing Co., 1997, pp 10–25.
96. Neher E, Sakmann B: Single-channel currents recorded from membrane of denervated frog muscle fibres. **Nature** 260:799–802, 1976.
97. Nicholls JG, Martin AR, Wallace BG: *From Neuron to Brain.* Sunderland, Sinauer Associates, 1992.
98. Nobel AB: Alfred Nobel's Will, 1895. http://nobelprize.org/alfred_nobel/will/will-full.html. Accessed January 10, 2007.
99. Nobel Foundation: *Nobel Lectures, Physiology or Medicine 1942–1962.* Amsterdam, Elsevier Publishing Co., 1964.
100. Nobel Foundation: *Nobel Lectures, Physiology or Medicine 1963–1970.* Amsterdam, Elsevier Publishing Co., 1972.
101. Overton E: Beitrage zur allgemeinen Muskel- und Nervenphysiologie. II. Über die Unentbehrlichkeit von Natrium- (oder Lithium-) Ionen für den Kontraktionsakt des Muskels [in German]. **Pflugers Arch** 92:346–386, 1902.
102. Penner R, Neher E: The patch-clamp technique in the study of secretion. **Trends Neurosci** 12:159–163, 1989.
103. Pfaffman C: Taste electrophysiology, sensory coding and behavior, in Dawson JME (ed): *Foundations of Sensory Science.* New York, Springer Verlag, 1984, pp 325–349.
104. Ramón y Cajal S: *Histology of the Nervous System of Man and Vertebrates (English translation of the 1909 Histologie du système nerveux de l'homme et des vertébrés).* New York, Oxford University Press, 1995.
105. Sakmann B: Nobel Prize Autobiography. http://nobelprize.org/nobel_prizes/medicine/laureates/1991/sakmann-autobio.html. Accessed January 10, 2007.
106. Sakmann B: Elementary steps in synaptic transmission revealed by currents trough single ion channels. **Science** 256:503–512, 1992.
107. Sakmann B: Elementary steps in synaptic transmission revealed by currents through single ion channels, in Ringertz N (ed): *Nobel Lectures, Physiology or Medicine 1991–1995.* Singapore, World Scientific Publishing Co., 1997, pp 31–59.
108. Shepherd GM, Erulkar SD: Centenary of the synapse: From Sherrington to the molecular biology of the synapse and beyond. **Trends Neurosci** 20: 385–392, 1997.
109. Sherrington CS: Decerebrate rigidity, and reflex co-ordination of movements. **J Physiol** 12:319–332, 1889.
110. Sherrington CS: Note on the knee-jerk. **St Thomas Hosp Rep** 21:145–147, 1891.
111. Sherrington CS: The central nervous system, in Foster M (ed): *Textbook of Physiology.* London, Macmillian, 1897, p 60.
112. Sherrington CS: Decerebrate rigidity. **J Physiol** 22:319, 1897.
113. Sherrington CS: *The Integrative Action of the Nervous System.* New Haven, Yale University Press, 1906.
114. Snyder SH: Obituary: Julius Axelrod (1912–2004). **Nature** 433:593, 2005.
115. Stjarne L: Ulf von euler. **Physiologist** 26:282–283, 1983.
116. Valenstein ES: The discovery of chemical neurotransmitters. **Brain Cogn** 49:73–95, 2002.
117. von Euler US: Zur Kenntnis der pharmacologischen Wirkungen von Nativsekreten und Extrakten männlicher accessorischer Geslechtdrüsen [in German]. **Arch Exp Path Pharmacol** 175:78, 1934.
118. von Euler US: A specific sympathomimetic ergone in adrenergic nerve fibres (sympathin) and its relations to adreneline and nor-adrenealine. **Acta Physiol Scand** 12:73–97, 1946.
119. von Euler US: Identification of the sympathomimetic ergone in adrenergic nerves of cattle (Sympathin N) with laevo-noradrenaline. **Acta Physiol Scand** 16:63–74, 1948.
120. von Euler US, Gaddum JH: An unidentified depressor substance in certain tissue extracts. **J Physiol (Lond)** 72:74–87, 1931.
121. von Euler US, Hillarp NA: Evidence for the presence of noradrenaline in submicroscopic structures of adrenergic axons. **Nature** 177:44–45, 1956.
122. Waldeyer HW: Über eine neurere Forschung im Gebiete der Anatomie des Zentralnervensystems [in German]. **Deutsche Medisinische Wochenschrift** 17:1213–1218, 1891.
123. Westphal CIO: Über einige Bewegungserscheinungen an gelämten Gleidern [in German]. **Arch Psychiat Nervenkr** 5:803, 1875.
124. Whitby LG, Hertting G, Axelrod J: Effect of cocaine on the disposition of noradrenaline labelled with tritium. **Nature** 187:604–605, 1960.

COMMENTS

This is a charming review of some of the great neuroscience discoveries that form the foundation of how we think about the nervous system. There are so many valuable lessons in this article that it is hard to choose the most important. To me, at least, the singular characteristic of the men who produced this kind of work is the simple clarity of their ideas and their experiments. Those who have not read Hodgkin and Huxley or the papers by Fatt and Katz should do so. They show that a large volume of papers is not needed to make or promote major intellectual contributions. Furthermore, the quality of the work is dictated by the importance and basic simplicity of the questions asked and experiments performed, combined with penetrating insight. There are lessons for all of us in the work of the great scientists discussed here.

Charles J. Hodge, Jr.
Syracuse, New York

This article is an excellent comprehensive review of the neuroscientific achievements of 20th century Nobel Laureates, scientists who made significant contributions to our understanding of fundamental mechanisms at the cellular level. The wisdom of the Nobel Committee in the selection of awardees was acknowledged at the time and has stood up retrospectively. It should be noted, however, that this cannot be said uniformly about the Committee's choice of awardees in clinical fields of physiology or medicine. The authors do not cover this

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subject, but it is an open secret that intense lobbying behind the scenes is sometimes an important determining factor and has led to some dubious awards. A case in point is the 1949 awardee, the Portuguese neurologist Egas Moniz, who was given the Nobel for his pioneering work in popularizing psychosurgery. A member of the political elite, having served as minister of foreign affairs and ambassador to Spain, he energetically promoted his candidacy for the prize that eluded him when he earlier pressed his case based on his 1927 cerebral arteriography experiments (3). Overlooked by the committee in the 1930s, despite several nominations, were both Harvey Cushing (1) and Walter Dandy (2) who, with the benefit of hindsight, seem equally deserving. But, as President John F. Kennedy remarked in a press conference, "Life is unfair."

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1. Bliss M: *Harvey Cushing. A Life in Surgery.* Oxford, Oxford Press, 2005, pp 509.
2. Fox WL: *Dandy of Johns Hopkins.* Baltimore, Williams & Wilkins, 1984, pp 175.
3. Greenblatt SH (ed): *A History of Neurosurgery.* Rolling Meadows, AANS, 1997, pp 504.

In the field of medicine and physiology, the Nobel Prize for research has been the ultimate award since the turn of the last century. Nobel was a rather eccentric figure but, nevertheless, his decision to create this award has led to an interesting selection of talented individuals who have received the prize. Almost without exception, the awardees have been deserving of the prize. In this article, the authors provided some interesting and succinct biographical vignettes on the figures who have been awarded this grand prize. It was a pleasure to read of their contributions and a bit on their backgrounds; each vignette was also nicely illustrated with a pertinent figure or photograph. Each of these contributions was clearly enormous in the field of medicine and physiology, as clearly outlined in this article.

James T. Goodrich
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In this article, the authors provide a fascinating overview of the history of the study of fundamental nervous system function as taken from the perspective of the Nobel Laureates' work of the 20th century. The authors trace the highlights of almost 40 people who have received Nobel Prizes in Physiology or Medicine for their work in the neurosciences. This review begins with the pioneering work of Golgi and Ramón y Cajal and takes the readers through the cellular structure of the nervous system. This leads to a review of the concepts of neuron function, highly differentiated functions of single nerve fibers and ionic mechanisms, as well as mathematical and biochemical explanations of their ability to communicate with each other.

The message from this article is clear: great work is done by the careful synthesis of the contributions of many researchers and that science builds upon those who came before. In addition, the report stresses that our predecessors studied large questions by "reduction" to elemental components of a process. Finally, this article shows how important it is for us, clinically, to understand the cellular and subcellular phenomena which govern the function of the central and peripheral nervous systems. This is illustrated in a beautiful explanation of the work on chemical transmission of nerve impulses and its importance to neuropsychological treatment throughout the 20th century. This illuminating review puts into perspective the primary position of basic scientific inquiry in the understanding of the clinical problems of neurosurgery.

In summary, this article provides several important points regarding the place of neuroscience in research. This includes the idea of reductionist thinking, that is, looking at basic components will help with the understanding of an overall process. Another significant point is the importance of scientific work, which builds upon the work of colleagues and predecessors. Finally, the authors put forth excellent notion that false steps in the interpretation of data are common and are important in understanding and changing one's ideas, just as Golgi had to change his ideas about cellular function. In the end, science and medicine are inexorably linked and their importance to the clinician and practice should never be underestimated as we attempt to improve upon our still rather primitive treatments for a wide variety of neurological disorders.

Robert J. Dempsey
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Langmoen and Apuzzo are to be congratulated for writing a timeless and informative review outlining the historical contributions of several 20th century Nobel Prize winners in cellular neuroscience. Their descriptions of the groundbreaking science accomplished in a mere century begins with Golgi's and Ramón y Cajal's elucidation of the microscopic structure of nervous tissue, and ends with Neher's and Sakmann's work on cell membrane ion channels and their function. The true value of this article, however, lies in the authors' insightful accounts of the personal backgrounds of the Nobel Laureates themselves. The biographical descriptions of the foibles of these pillars of cellular neuroscience are coupled with the historical context within which their discoveries were made. One begins to appreciate the gravity of their discoveries at the time they were produced and to see the evolution of neuroscientific investigations towards the successful reductionist strategy used so commonly today. The reader is left hoping that the authors will consider writing further pieces in this format, perhaps on major contributions made before the Nobel era, such as Luigi Galvani's uncovering of the electric nature of nervous action in 1791 and Wilhelm Ostwald's discovery of the membrane theory of nerve conduction in 1890 (1,2). Undoubtedly, this review will prove invaluable in helping future generations of neurosurgeons and neuroscientists to understand how and by whom the foundation of modern neuroscience was created.

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Toronto, Canada

1. Galvani L: *De viribus electricitatis in motu musculari.* Bologna, Tip. Istituto delle Scienze, 1791.
2. Ostwald W: Elektrische Eigenschaften halbdurchlässiger Scheidewände. **Z Phys Chem** 6:71–82, 1890.

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