Historical Note

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Abstract

Edgar Douglas Adrian was an outstandingly brilliant, Nobel prize-winning neurophysiologist. He is remembered for developing the all-or-none principle of muscle contraction, and for explaining the minutiae of motor and sensory nerve transmission. He showed that the afferent effect in a neuron depends on the pattern in time of the impulses travelling in it, thereby providing a quantitative basis of nervous behaviour. With Sir Charles Sherrington, he was awarded the Nobel Prize in 1932 for discoveries on the functions of the neurons.

We sometimes forget or take for granted the great neuroscientists who initiated the most fundamental concepts that underlie our daily practices. Mid-nineteenth century physiology in Britain was far behind France and Germany who could boast the names of Magendie, Claude Bernard, Johannes Müller, Helmholtz, or Ludwig, to mention but a few. The first British Chair in physiology was at University College, London in 1836. Until that date, anatomists taught physiology and the students' course was called "general anatomy and physiology [1]." William Sharpey (1802–1880), the first occupant was a histologist from Edinburgh, who gradually acquired knowledge of "practical physiology" and trained the distinguished Sir Michael Foster (1836–1907) and Sir Edward Sharpey-Schafer (1850–1935). Not until 1876 was The Physiological Society founded in reaction to the Cruelty to Animals Act [2].

Lord Adrian (Fig. 1.) was one of several outstanding successors. He should be remembered for developing Keith Lucas's (1879–1916) all-or-none principle of muscle contraction, for explaining the minutiae of motor and sensory nerve transmission, and for introducing the thermionic, triode valve amplifier that advanced experimental electrophysiology. With Sir Charles Sherrington, he was awarded the Nobel Prize in 1932 for discoveries on the functions of the neurons.

Edgar Douglas Adrian (1889–1977) was born in London and lived at 40 Elsworthy Road NW3, opposite the entrance to Primrose Hill. He was the youngest son of Alfred Douglas Adrian, C.B., K.C., legal adviser to the British Local Government Board. At Westminster School, John Sergeaunt, a classicist inspired him. But his major scholarship to Trinity College, Cambridge, was for the Natural Sciences Tripos. In 1911, he took his B.A. degree with first class honours [3]. Sir Alan Lloyd Hodgkin

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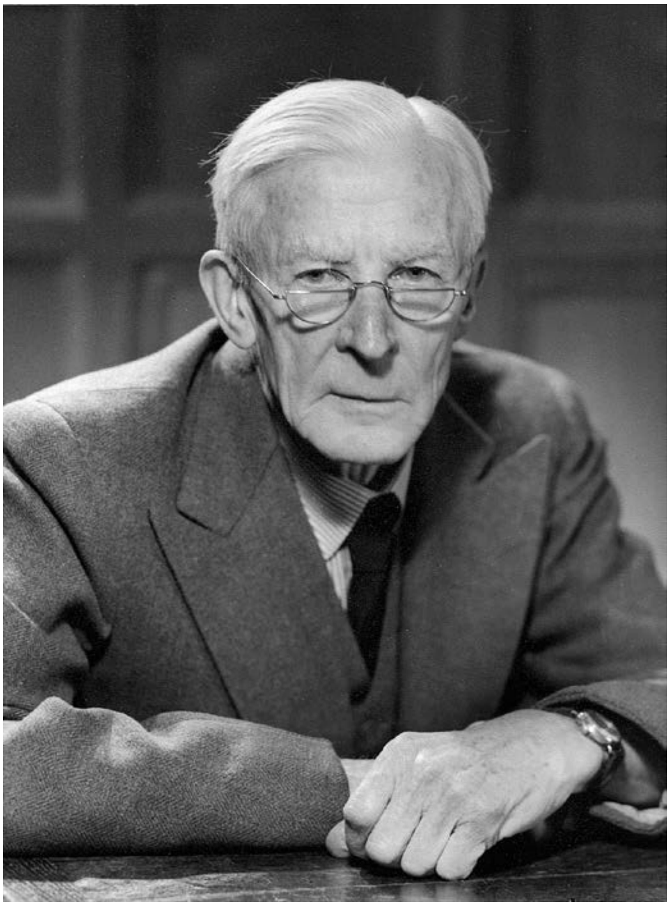

Fig. 1. Lord Adrian. Master and Fellows of Trinity College Cambridge, with permission.

(1914–1998) related how Adrian's tutor, WM Fletcher reported his "exceptional brilliance to his old headmaster [4]." Hodgkin's biography provides a wonderfully written detailed account of Adrian and his many works.

From 1911, his work blossomed under the directorship of Lucas, who in 1905 had shown that skeletal muscle single fibers obeyed the all-or-none law, which also applied to nerve fibers [5, 6]. At the early age of 24, Adrian was elected to a Fellowship of Trinity College for his investigation of the all-or-none principle in nerves.

> The nerve impulse was a brief wave of activity depending in no way on the intensity of the stimulus which set it up [3].

By now a respected physiologist, he read Medicine at St. Bartholomew's Hospital, London, obtaining his degree in 1915 during the First World War. In spite of efforts to get to France, he was placed at the Military Hospital at Aldershot, where he fell under the spell of Adolphe Abrahams, founder of British sports science, and Francis Walshe, the eminent Neurologist. He worked principally on nerve injuries, and "shell shock," which prompted ideas relating the physiological and psychological bases of neuroses, a theme to which he later returned. With Yealland from 1915, he investigated the controversial electroconvulsive therapy on shell-shocked soldiers suffering from "hysteria" returned from the war [7].

He returned to Cambridge in 1919 to take over the laboratory of Keith Lucas, who was tragically killed in 1916 when his aircraft collided in mid-air over Salisbury Plain. Adrian later recounted how Lucas, Gowland Hopkins, A.V. Hill, Joseph Barcroft, W.M. Fletcher, W.B. Hardy, G.R. Mines, and others worked, crowded together in cellars, which flooded so easily that they had to walk on duckboards. He published physiology researches of such caliber that he was made a Fellow of the Royal Society on May 3, 1923.

Two years later, by using the capillary electrometer, he investigated sensory function in the frog's sciatic nerve. He demonstrated the refractory period and the nature of the nerve action potential. He was rewarded in 1929 with the Foulerton Professorship of the Royal Society. In 1937, he was elected Professor of Physiology at Cambridge. This department was home to many notable physiologists, including six Nobel Laureates (Adrian, Edwards, Hill, Hodgkin, Huxley, Tsien). Adrian succeeded Sir Joseph Barcroft, continuing until 1951, when he became Master of Trinity.

Adrian's first research was done with Keith Lucas, FRS. They showed that, when a muscle fibre contracts, the passage of the nerve impulse that causes the contractions leaves the motor nerve in a state of diminished excitability, that is, the refractory period. One day Adrian suddenly realised while recording using his new amplifier from a frog nerve-muscle preparation that what seemed to be a tiresomely oscillating electrical artefact only occurred when the muscle was hanging unsupported:

> The explanation suddenly dawned on me... a muscle hanging under its own weight ought, if you come to think of it, to be sending sensory impulses up the nerves coming from the muscle spindles... That particular day's work, I think, had all the elements that one could wish for. The new apparatus seemed to be misbehaving very badly indeed, and I suddenly found it was behaving so well that it was opening up an entire new range of data... it didn't involve any particular hard work, or any particular intelligence on my part. It was just one of those things which sometimes happens in a laboratory if you stick apparatus together and see what results you get [3, 10].

In 1925, he started to use a triode valve amplifier employed by Erlanger (1874–1965) and Gasser (1888–1963), physiologists at Washington University in St. Louis, who were the first to record nerve impulses with a cathode ray oscilloscope and valve amplifier. To get a more sensitive detection and higher amplification of nerve impulses, Adrian used thermionic valves. By these means, he showed that when an end organ was stimulated, the nerve fiber showed regular impulses with a variable frequency. Assisted by Sybil Cooper and Yngve Zotterman, he recorded the electrical discharges in single nerve fibers [5].

He showed that the nerve fiber is:

> A signaling mechanism that can only transmit a succession of brief explosive waves, and the message can only be varied by changes in the frequency and in the total number of these waves. Moreover, the frequency depends on the rate of development of the stimulus, as well as on its intensity; … in the body the nervous units do not act in isolation as they do in our experiments. A sensory stimulus will usually affect a number of receptor organs, and its result will depend on the composite message in many nerve fibers [3].

Thus, the frequency code of sensation was an essential characteristic of nerve action. With DW Bronk, in 1928, he showed similar features in motor nerve action: only one kind of nerve impulse is present, and the force of contraction, like sensation, varies by the frequency of the nerve impulses and the number of fibers.

He used a capillary electrometer and cathode ray tube to amplify the signals produced and was able to record the electrical discharge of single nerve fibers under physical stimuli. Another accidental discovery by Adrian in 1928 proved the presence of electricity within nerve cells. Adrian said,

> 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 [10, 11].

A key result published in 1928, stated that the excitation of the skin under constant stimulus is initially strong but gradually decreases over time, whereas the sensory impulses passing along the nerves from the point of contact are constant in strength, yet are reduced in frequency over time, and the sensation in the brain diminishes as a result. In his Nobel lecture he deduced:

> Sense organs and nerve cells send out impulses because some part of their surface has become depolarised, a breakdown which is repaired as soon as the mechanical stress (stretch or touch) is removed.

As AV. Hill said,

> Adrian, by thus showing that the afferent effect in a given neuron depends on the pattern in time of the impulses travelling in it, has provided a new quantitative basis of nervous behaviour [8].

He investigated the reception of signals in the brain and their spatial distribution in various areas of the cortex in different animals. This led to the idea of a sensory map, the homunculus, in the somatosensory system. He included electrical responses to pain concluding, like Henry Head, that nerve fibers which conduct pain impulses probably pass to the thalamus, but that all other sensory impulses can be distinguished in the sensory cortex. In man and the monkey, the sensory area of the cortex (homunculus) devoted to the mouth area and hand is relatively large, and relatively little is given to the trunk.

For his work about the functions of neurons Adrian was awarded, jointly with Sir Charles Sherrington, the Nobel Prize. In his Nobel Lecture, December 12, 1932, entitled: *The Activity of the Nerve Fibres,* he stated:

> Here again there is reason to suppose that discharge of impulses is due to a breakdown in the polarized surface, a breakdown which is repaired as soon as the mechanical stress is removed. Analogies of this kind suggest that sense organs and nerve cells send out impulses because some part of their surface has become depolarized. There are certain difficulties to be faced before this can be treated as more than a crude working hypothesis, but it is one which has important consequences. If the regions from which the discharge originates remain partly or wholly depolarized as long as they are excited, it should be possible to detect potential changes of relatively long duration in sense organs and in the motor nerve centers. Such changes are well known to occur in the eye, and they have been found in the vertebrate brain stem and in the nerve ganglia of insects. Unfortunately, the structures in which they occur are so complex that it is difficult to be sure of their interpretation, but at least they suggest the possibility of obtaining direct records of the activities of the grey matter [3].

In turn, Sherrington in his speech at the Nobel Banquet of the same date endearingly remarked:

> … It is delightful to be associated in this visit with my friend, Professor Adrian, who treats the nerves as a sort of electric power house, and makes even their minutest leakages audible to us. With him we can, so to say, hear the gold fish 'thinking,' a new fairy-tale for Christmas Eve, now nearly here.

The equally brilliant Sherrington, whom Adrian revered, had shown that most reflexes are coordinated; that the nervous system functions … to integrate the organism, making it an individual whole, not just a collection of cells and organs [9]. This explained aspects of how nerve cells affected behaviour.

Adrian then became interested in the synchronization of neuronal discharge, and with BHC Matthews and later with Yamagiwa analyzed the Berger rhythm and began the search for its neuronal basis. This led to clinical electroencephalography. The results were published in numerous scientific papers and in his books: *The Basis of Sensation* (1927) [10], *The Mechanism of Nervous Action* (1932) [11] and *The Physical background of Perception* (1946) [12].

His early interests in psychoanalysis, hypnosis, and brain-mind disorders, prompted by his experience of victims of the Great War [7], became of increasing importance to him in later life. Adrian enjoyed numerous honours. He was a Nobel Laureate, President of the Royal Society, and Master of Trinity College. He was a member of some 48 learned societies and was given 29 honorary degrees. In 1954, he was President of the British Association for the Advancement of Science. He became Chevalier of the French Legion of Honour, and was made 1st Baron Adrian of Cambridge in 1955.

A man of tireless energy and industry, it is hard to do justice to his immense influence on the development of neurophysiological research [3]. He was described as a lean, small figure, dominated by the forward thrust of the nose and chin and the set expression of purpose, as he threaded his way at high speed on a bicycle through the crowded streets of the city. An expert fencer, enthusiastic mountaineer, he also enjoyed sailing, and appreciated the arts. A superb after-dinner speaker, like Churchill, all his lectures and speeches were the result of repeated, meticulous preparation.

In 1923, Adrian married Hester Agnes Pinsent, DBE, daughter of Hume Pinsent of Birmingham, and a descendant of the philosopher David Hume. They had two daughters, and their son Richard, Richard Hume Adrian, 2nd Baron Adrian (FRS 1977), Professor of Cell Physiology at Cambridge and Fellow of Corpus Christi, Churchill College, then Vice-Chancellor of Cambridge University.

After his wife's death, he spent his last years in rooms in Nevile's Court, Cambridge. By 1975, his health began to deteriorate. He died on August 4, 1977, at Evelyn Nursing Home in Cambridge. His memorial inscription in Trinity College Chapel, translated from the Latin reads:

> Edgar Douglas, Lord Adrian of Cambridge, O.M., was Scholar, Fellow, and Master of the College, Professor of Physiology, and later Chancellor of the University. It was he who first heard the signals that in sensation and movement pass to and from the brain, and he caught whispers of its innermost workings. A man as modest as he was illustrious, and a witty and charming speaker, he won the affection of the whole Fellowship. He died in 1977 at the age of 87.

Disclosure Statement

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