Edgar Adrian and Patrick Merton: Names Blurred with the Passage of Time

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Abstract

Edgar Douglas Adrian and Patrick Anthony Merton are two supreme neurophysiologists from England in the last century whose names are almost forgotten these days. Adrian’s work on all-or-none phenomenon in nerve and muscle excitability ushered in a new era and Merton’s servo theory of muscular movement and muscle fatigue added a new dimension to the understanding of stretch reflex and deep tendon reflexes. Both of them trained and worked at Trinity College, Cambridge and both were elected as Fellow of the Royal Society and Adrian in addition, was awarded the Nobel Prize in 1932 along with Charles Scott Sherrington.

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In the course of human history, certain names and ideas often tend to get smudged with time. Edgar Adrian and Patrick Anthony Merton are two such glaring examples in the field of human neurophysiology.

EDGAR DOUGLAS ADRIAN (1889–1977) [FIGURE 1]

The study of modern neurophysiology began at the time of the early part of the last century with Sir Charles Sherrington, spearheading the proceedings, and if any other neurophysiologist carried out fundamental research to understand the mysteries of the functioning of the human brain at that time, it was Edgar Douglas Adrian, whose stupendous work certainly paved the way for the understanding of neurophysiology as we understand the subject today.

Adrian was born in Hampstead, London, and attended the Westminster School in London. He moved to Trinity College, Cambridge in 1908, where he won a scholarship in science and studied physiology and natural sciences Tripos. In 1911, he took his BA degree, earning First Class in five separate subjects. Two years later, he was elected to a fellowship there for his investigations on the “all or none principle” in the nervous system, where he found men such as JN Langley, Michael Foster, WH Gaskell, Joseph Barcroft, Keith Lucas, and others, as his teachers. Thereafter, he worked in St. Bartholomew’s Hospital, London, for his clinical duties and got his medical degree in 1915. He returned to Cambridge in 1919 and lectured on the principles of the nervous system. In 1925, he started working on the sense organs applying the electrical method which eventually led to his emergence as a supreme neurophysiologist in the future, and during this period, he had been living in the rooms of Sir Isaac Newton, where the great scientist spent his days, about 400 years ago. Four years later, he was elected as the Foulerton Professor of the Royal Society, and in 1937, he succeeded Sir Joseph Bancroft, his one-time teacher, as the Professor of physiology at the University of Cambridge, a post which he held till 1951.[1,2]

Adrian undertook his first research activity with Keith Lucas of Cambridge who had been working on the impulses transmitted by the motor nerves. He showed that a muscle fiber after contraction lost its excitability to some extent. In 1919, he took over from Lucas, who was no more by that time, and this particular exercise made him immortal in the field of neurosciences. To obtain a more sensitive and precise detection of nerve impulses, Adrian used the cathode ray tube, the capillary electrometer, and amplification of the electrical impulses by means of thermionic.
valves and was thus able to amplify them 5000 times. He set up a preparation consisting of a single end organ in a muscle fiber of the frog together with the single nerve fiber related to it and he observed that when the end organ was stimulated, the nerve fiber showed regular impulses with a variable frequency. An accidental discovery 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.”[1,3-5]

By 1928, Adrian concluded that a stimulus of constant intensity applied to the skin immediately excited the end organ but that this excitation progressively decreases for as long as the stimulation continues. At the same time, sensory impulses of constant intensity pass along the nerve from the end organ. These sensory impulses are at first very frequent, but their frequency gradually decreases. AV Hill, the physiologist and the Nobel Laureate of 1922, said that Adrian, by showing the afferent effect in a given neuron had provided a new quantitative basis of nervous behaviour and this experiment finally validated Lucas’ conception of the “all-or-none” character of the propagated nervous impulse. In his Nobel Lecture, he said,

“The sense organs respond to certain changes in their environment by sending messages or signals to the central nervous system. The signals travel rapidly over the long threads of protoplasm which form the sensory nerve fibres, and fresh signals are sent out by the motor fibres to arouse contraction in the appropriate muscles... The signals which they transmit can only be detected as changes of electrical potential, and these changes are very small and of very brief duration...

...It was made clear that the wave of activity is invariably accompanied by a change of potential, that the activity at any point lasts only for a few thousandths of a second, and that it is followed by a refractory state which must pass away before another wave of activity can occur... The potential wave in a nerve had an equal duration whether it was set up by a strong or a weak stimulus. As it seemed unlikely that a feeble and an intense disturbance would last for the same time... suggested that in each nerve fibre the disturbance was always of the same intensity, and that a strong stimulus set up a larger potential wave merely because it brought more fibres into activity. This agreed with the fact that the rate of conduction and the length of the refractory period were also uninfluenced by the strength of the stimulus. It seemed, therefore, that each pulse of activity in a nerve fibre must be of constant intensity... recorded the contraction of a band of muscle. and it was clear, then, that skeletal muscle fibres followed the all-or-nothing rule.”[6]

Later, Adrian extended his investigations to the study of nociceptive sensations and concluded, the way Sir Henry Head had postulated as a result of his clinical studies, that the nerve fibers subserving pain sensation probably did not pass further into the brain beyond the optic thalamus, while all other sensory impulses terminated in the sensory cortex and he further showed that the part of the cerebral cortex devoted to any particular kind of end organ was related to the special needs of the animal concerned. Thus, in man and the monkey, the sensory area of the cerebral cortex serving the face and hand is relatively large, whereas in the pony, the area devoted to the nostrils is as large as that devoted to the rest of the body. In the pig, almost the whole of the sensory cortex is devoted to the snout which the pig uses to explore its environment, whereas in the cat, it is the forelimbs that are maximally represented there.[6] Later, Adrian used the electroencephalogram to study the electrical activity of the brain in humans. His works on the abnormalities of the alpha rhythm paved the way for subsequent developments in the field of epilepsy and related problems. His final works were concerned about the olfactory nerves. He recorded the electrical...
activities in the olfactory bulbs in cat and showed that at least three different odors could be identified by the cat namely, ethereal, fishy, and oily. He also gathered important evidence on the process of adaptation in the olfactory nerves.[7]

Adrian received numerous distinctions and honors for his extraordinary research works. The volume “Nobel Lectures, Physiology or Medicine, 1922–1941” mentions that he was the President of the British Association for the Advancement of Science in 1954.[6] He received the Royal Medal in 1934 and the Copley Medal, the highest award that can be conferred by the Royal Society, in 1946 and served as its President from 1950 to 1955. He was appointed as Master of Trinity College, Cambridge in 1951, an office which he held until 1965. He was the Vice-Chancellor of the University of Cambridge from 1957 to 1959 and Chancellor from 1968. In 1942, he was awarded the Order of Merit, and in 1955, he was created 1st Baron Adrian of Cambridge. He received honorary degrees from 33 universities around the world and was awarded the Nobel Prize for his fundamental works on the physiology of the nervous system in 1932, which he shared with Sir Charles Sherrington.[1,2] His son, Richard Hume Adrian, too, was an internationally famous neuropathologist who was elected as Fellow of the Royal Society and was the Master of Pembroke College, Cambridge and the Vice-Chancellor of the University of Cambridge. Although he retired from Cambridge in 1965, he continued to live at the college almost until his death in 1977. Y Zotterman and OL Zangwill wrote that, at his funeral Professor Owen Chadwick, the then Master of Selwyn College, said: “I am not sure what wisdom is, but whatever it is, Adrian had it.”[1,2]

PATRICK ANTHONY MERTON (1920–2000) [FIGURE 2]

Merton was one of the most influential neurophysiologists from England in the latter half of the 20th century. Over a period of 35 years, he carried out a series of elegant experiments which elucidated the nervous mechanisms responsible for the control of movement and the nature of muscle fatigue. His works on muscle contraction and movement are fundamental and remarkable and they changed many of the prevailing concepts pertaining to muscle physiology.

He was admitted to Trinity College, Cambridge, and studied Natural Science Tripos and specialized in physiology. His interest in neurophysiology was kindled by the series of lectures delivered by ED Adrian, the co-sharer of the 1932 Nobel Prize with Charles Sherrington, and he used to tell his students that he preserved and consulted Adrian’s notes even 40 years later. However, it is less clear what led him to work on the control of movement, but shortly after arriving in Cambridge, he started working on two fields where he continued to contribute throughout his career. These were the role of muscle spindles in movement and the etiopathogenesis of muscle fatigue, both of which were published as short letters in Nature in 1950. He graduated in 1942 and thereafter joined St. Thomas’ Hospital, London, qualifying for M.B., B.Chir in 1946. He was deeply influenced by his teacher, William Rushton, and was thus driven to research work and instead of applying for the job of a House Physician, he joined Professor EA Carmichael’s Medical Research Council Neurological Research Unit in the National Hospital, Queen Square, London.[1,4]

Merton is best remembered for advancing the “servo theory” of muscle contraction.[1,8-11] This concept evolved from the observation that small sense organs in the muscles, the muscle spindles, not only send information from the muscles to the central nervous system but also receive instructions reciprocally, which can adjust their own sensitivity. At the start of the 1950s, little was known about the role of the muscle spindles apart from the fact that they participated in the stretch reflex, of which the most familiar example, though not true in the strictest sense, was the evident tendon jerk. In plain and simple terms, when a tendon is tapped with a hammer, it stretches the muscle briefly, causing an increase in the discharge of the spindles in the muscle. This input to the spinal cord causes a sudden brief contraction of the stretched muscle which results in the characteristic jerk. However, the role of the controlling signal from the central nervous system was not clear. Merton proposed that the whole system worked like the servo system on a car steering. If the brain wished to contract a muscle to a certain length, it commanded the small sense organs to react as if they had been already stretched to the intended position. The result would be reflex contraction of the muscle in question only to the desired extent and this meant that the nervous system only needed to specify the end position of the intended movement and the command to make the muscles contract to that position occurred secondarily, as a result of the reflex. This was the first attempt to explain how the nervous system might achieve accurate control of movements. It turned out that the nervous system always maintains some direct control over the muscle and that the servo system assists, rather than leads to the contraction. Merton’s initial experiments were designed to investigate how the sensory information from muscle spindles was used in normal voluntary movement, like the passive stretch reflex, as opposed to the rather unnatural example of the tendon jerk. [8] At that time, it was well known that if a muscle contracts voluntarily, an electrical stimulus applied to the concerned nerve produces a synchronized electrical potential, the M wave, which is followed by a period of silence persisting for about 100 msec before resumption of the volitional activity. Merton, following on the previous works by Mathews, examined the silent period of the human adductor pollicis produced during voluntary contraction following an electrical stimulus to the ulnar nerve at the wrist and showed that the duration of the silent period correlated strongly with the duration of the induced mechanical twitch which he varied by changing the size of the stimulus and the force of the voluntary contraction. The conclusion was that changes in afferent inflow from the muscle were essential to the silent period.[8,10]

There were two features in Merton’s experiments which almost inevitably led to his significant series of his papers in collaboration with David Marsden, a brilliant young neurologist
and Bert Morton, a former radar engineer and a technical wizard. They showed that the latency of the reflex, evoked on stretching a muscle passively, was about twice as long as that of the corresponding tendon reflex and that the reflex magnitude was controllable by the intent of the subject, being larger if the subject was instructed to contract on perceiving the perturbation and smaller if instructed to allow it to occur. This finding was of stupendous import and it led Marsden et al. to suggest that there might be a stretch reflex pathway through the brain, separate from that subserving the tendon reflex, in addition to the well-known monosynaptic spinal reflex arc, and thus it was a significant addition to the classical Sherringtonian concept which assumes only spinal segmental passage for the genesis of the deep tendon reflex.\[11-14\] Although the precise pathway responsible for the long latency of the stretch response in contracting muscle was first suggested by CG Philips in 1968 and who also coined the term “transcortical stretch reflex,”\[14,15\] the idea was brilliantly exploited by Merton in collaboration with Marsden and Morton from the late 1960s to the mid-1980s and the three of them started a famous collaboration in the Institute of Neurology, Queen Square which formed the famous “3M” team of the 1970s. During this period, he was a frequent overnight user of the computer at the National Physical Laboratory since it was the only machine powerful enough at the time to produce accurate frequency analysis of tremor records. The team showed that the latency of the stretch reflex was compatible with a pathway through the motor cortex and that it was absent in subjects who had lesions within the pathway.\[14,16,17\] The dissociation between the stretch reflex and the tendon reflex led them to argue about the possible existence of two different pathways for the mediation of these two reflexes. They proposed that the stretch reflex has a cortical component where on passively stretching a muscle, the afferent impulse travels up the spinal cord to the sensory cortex and returns to the spinal efferent neurons from the motor cortex to result in a separate reflex of long latency.\[18,19\] PBC Mathews, a consummate neurophysiologist, wrote cogently in this regard, “The essential thing to be kept in mind in thinking about the tonic component of the stretch reflex is that it represents a steady motor output in response to a steady barrage of afferent input. This allows for neural integrative mechanisms of a far higher order of complexity than one can hope to find displayed in the tendon jerk resulting from a single synchronous volley,” and Ragnar Granit, the Nobel Laureate in 1967, fervently held the identical view.\[20,21\]

It appeals to reason that the disparity between the stretch reflex and the tendon reflex would be more pronounced for muscles whose motor neurons are far away from motor cortex in the brain, and in their subsequent experiments, Marsden lent his long flexor of the great toe and the masseter muscle for studies which was supervised by Merton and executed by Morton. The latency for the great toe turned out to be 75 ms and that for the masseter, 13 ms. However, the latency of the ankle tendon jerk was about 37 ms and that of the jaw jerk was 8 ms only.\[13,14\] This study almost incontrovertibly suggested that two different pathways existed for the stretch reflex and the tendon reflex, and that in the former, almost certainly a transcortical contribution operates in its genesis. In recognition of the works of the 3Ms, this pathway has been named M1, M2, and M3 long latency loop by Tatton and Lee in their subsequent works. M1 represents the brief spinal reflex arc, and M2 and M3 are the long ones with a transcortical component, M3 being mediated by the cerebellum.\[22,23\] Further works on this subject have added valuable inputs on the existence of the transcortical loop.\[24-26\]

Perhaps the final vindication of the transcortical loop came from the observations on stimulus sensitive myoclonus or cortical loop reflex myoclonus in the 1970s. Shibasaki and Kuroiwa observed a cortical component in spontaneous myoclonus, whereas Sutton and Mayer and Rosen et al. studied focal stimulus sensitive myoclonus.\[27-29\] At around the same time, Marsden et al. investigated one subject by extending the flexed thumb and observed myoclonic jerk involving the upper extremity and the shoulder, and the latency was in the range of 50 ms which was equal to the normal stretch reflex for the said muscle. It was felt that the cerebral cortex was involved in its genesis since the latency of the jerk was the same as that of the normal stretch reflex.\[10,14\] In a seminal paper in 1979, Hallett et al. classified cortical reflex myoclonus into cortical reflex loop myoclonus and reticular reflex myoclonus. In the former, the electroencephalogram correlates are time locked to the electromyographic bursts, while it is not so in the latter.\[30,32\] That the myoclonic jerks are of cortical origin is also evident from the work of Kugelberg and Widen, on a patient who presented with myoclonus in the lower limb. During operation, abnormal spikes were recorded from the contralateral cortical leg area, and focal cortical excision led the amelioration of the symptom.\[32\]

These works led Merton to coin terms such as, the “alpha neuron route” and the “gamma neuron route.” Thirty-three much earlier in 1952, Merton went to the laboratory of Granit in Stockholm, where he performed his experiments on decerebrate cats and this was the only series of experiments he conducted on animals in his life. In Cambridge, he inspired his students to take up research on human beings for what he called “neurophysiology on man.”\[1-10\]

Apart from these series of brilliant works, for which Merton is recognized universally, his works on muscle fatigue and whether the loss of strength that occurs during voluntary contraction is of central or peripheral origin are of great importance in the field of neurophysiology. He developed the twitch interpolation test that quantifies the degree to which human subjects can recruit the maximum power available in their muscles when they make a voluntary contraction. His works showed that at least in the adductor pollicis muscle, fatigue during maximum sustained contraction was of peripheral origin.\[8\] He further showed that if an electrical stimulus was applied to a motor nerve during maximum contraction, the extra discharge of motor units failed to generate any additional force. However,
if the contraction was less than maximum, the stimulus generated a superimposed muscle twitch whose amplitude was approximately proportional to the contraction.[9] This work showed that if a muscle was fatigued to the extent that it was no longer able to exert any further force, electrical stimulation of the motor nerve could still evoke an action potential in the muscle that was only marginally smaller than normal. He also proved through a series of elegant experiments on the eye that stimulation of muscle spindles do not reach consciousness level.[9]

In 1979, Merton was elected Fellow of the Royal Society and was appointed as Honorary Consultant in Clinical Neurophysiology in Queen Square. He received his MD degree in 1982 and FRCP in 1991. In Cambridge, he made a Reader in 1977 and Professor of Human Physiology in 1984. He was a Fellow of Trinity College from 1962 until his death.[1,8]

Merton was an inspiring teacher and he was much loved by his colleagues and pupils. Andrew Lees of the Institute of Neurology wrote that even a neuroscientist of the stature of David Marsden possibly looked up to him as his only mentor.[24] He was ever ready to render his help and service to his fellow men. He was a great propagandist of the advantages of performing experiments on human subjects and made remarkable insights into the control of movement from relatively simple observations made on himself and others. John Rothwell of the Institute or Neurology, Queen Square who trained with him wrote, “The staircase to his flat in Mecklenburgh Square, London, was littered with bowls of paraffin and parts from his Bullnose Morris and 1930s Hotchkiss, just as much as his laboratory was filled with ideas about how the brain might control the way we move”. With time, his health deteriorated and he became almost a recluse in his later life. As he started losing his friends with whom he liked to communicate, he committed suicide at the age of seventy nine.[1,8]

One photograph shows Pat Merton seated in a chair and Richard Adrian, son of the Nobel Laureate, Edgar Adrian, standing behind him, testing the effects of magnetic stimulation of the brain on him before a bunch of students in Cambridge (Courtesy: Professor John Rothwell, Institute of Neurology, Queen Square, London).

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