From Physiology to Neurology: Journeys through the Cambridge Physiological Laboratory

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Every doctor should study the history of medicine. It teaches us how to become better historians (for that is what we become every time we talk to a patient) and, if we are lucky and well taught, we may learn perspective and a degree of humility. History can provide a salutary corrective to the *faux* certainties of the preclinical sciences. It reminds how complex life is at the boundaries of science and society, exactly where we ply our daily trade as doctors.

To my mind one of the most interesting and important topics in the history of medicine is its relationship with experimental science. Ever since the creation of the hugely successful business of modern science at the turn of the nineteenth century, medicine has been irrevocably altered by its complex and multifaceted interactions with the newcomer. These interactions are often portrayed (particularly by those protagonists for science who hope to enrol medicine to its cause) as a simple matter of knowledge being created by scientists and used by doctors. This is a gross simplification, not to say a distortion of the truth. In this paper I have tried to shed some light on the complex relationships of science and medicine on a journey from physiology – more specifically nineteenth century experimental physiology – to neurology – that is, twentieth century neurology as exemplified by advances in that portion of neurological practice which has become known as clinical neurophysiology.

In doing so I shall pose several questions, and try to provide answers, hoping to illustrate some of the complexities to which I have alluded above. Why choose experimental physiology as our starting point? What was different about that enterprise from those which had gone before? What were the aspects of this enterprise that were translated into the clinical arena? And what, if anything, was the influence of these on clinical practice?

Structure and function

The importance of anatomy for medicine has been a constant theme in medical literature from ancient times. The voluminous and garrulous works of Galen (129-c.210) contain numerous exhortations to the reader to learn anatomy well. Galen himself was a brilliant exponent of dissection – in his case of animals – and used his knowledge to excellent effect in his rapid climb up the precipitous greasy pole of medical practice in imperial Rome. Galen's works were the standard medical texts for over 1500 years, and his belief in the importance of anatomical knowledge was reinforced and magnified by the great anatomists of the Renaissance, foremost amongst who was Andreas Vesalius (1514-1564), author of *De Fabrica Corpora Humanis*. Vesalius' illustrations are in the striking humanist tradition which reached its apotheosis in the art of Michaelangelo, Bellini and Titian.

Function remained more elusive. In some areas – most spectacularly William Harvey's discovery of the circulation of the blood – inductions and deductions made from comparative anatomy

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provided a way forward. But while the appearances of the superficial musculature were well known to anatomists and artists, the structure and course of the nerves was more complex, and was not fully elucidated until well into the 18th century. Their function remained obscure, but the discovery of electricity – under the eponymous title of galvanism after its discoverer – in the late 18th century provided an impetus for researches along these lines. Galvanic experiments were performed on animals (here the long-suffering and ubiquitous frog enters our story) and, to a lesser extent, on humans. Those executed for their crimes in the early nineteenth century could expect to be subjected to galvanic experiments, the potential social consequences of which were the subject of Mary Wollstonecraft Shelley's masterly tale of Frankenstein's monster.

These early experiments gradually became codified and structured as part of a new scientific enterprise dubbed experimental physiology. This was an investigation of the function of animate objects under controlled circumstances, which originated in post-Revolutionary France and the new universities of the German republics (particularly, but not exclusively, the University of Berlin in Prussia).

This new way of working was slow to cross the English Channel. The British (which at that time generally meant Scottish) tradition remained anatomical. The differences between the two approaches (and their potential to arrive at the same conclusions independently when meticulously applied) was best demonstrated by the work of the Edinburgh surgeon Charles Bell (1774-1842) and the Parisian physiologist Francois Magendie (1783-1855), who in 1822 both showed – by completely different means – that the motor and sensory nerve roots in the spinal cord are structurally and functionally discrete. This can be regarded as the year in which the ascending curve of physiology crossed the declining curve of anatomy; for much of the next century the *frisson* of discovery would be most keenly and frequently felt in metropolitan laboratories of continental Europe.

Physiology in Cambridge

In Cambridge, neuroanatomical studies were performed by William Webster Fisher (1797-1874), physician to Addenbrooke's Hospital in the 1830s. Fisher had studied medicine in Montpelier where he had met and befriended Auguste Comte (1798-1857). Achieving the MD at Montpelier in 1825, he had returned to Cambridge where he had become a fellow at the relatively new Downing College. Around this time he became interested in the development of the nervous system and its derangement in conditions such as spina bifida. His interest in ganglionic development theoretically placed him in the vanguard of a vibrant movement in British neuroscience, which was challenging the long-held view that nerves simply existed to carry impulses to the brain, and that the brain was the only organ capable of assimilating sensory information and initiating action. Sadly, however, Fisher gave up his researches to concentrate on college politics and private practice, and it was not until 1883 that a university post in Physiology was created as part of more general reform in medical and scientific education.

The neurological researches of that early generation of British physiologists faltered in the face of public dislike of vivisection and private promotion of more traditional approaches to scientific problems. The doyens of early nineteenth century British science remained cabinet collectors and comparative anatomists. In the 1850s and 1860s, however, a reform movement centred on University College London and the Royal School of Mines started to put experimental physiology back on the agenda of British science. For these reformers (who included Thomas Huxley and George Eliot, amongst others), Cambridge was the prime target.

Their exertions resulted in the election of Huxley's protégé Michael Foster (1836-1907) to a fellowship at Trinity College in 1870. Over the course of the following three decades Foster built up a research school, a laboratory, and ultimately an overwhelming political presence on the committees and boards which ran the medical and biological sciences at Cambridge. From Foster's laboratory ran rich seams of scientific work which formed the basis for much of the best of what early twentieth century Britain had to offer in biochemistry, experimental psychology, endocrinology, pharmacology and, most pertinently for this paper, neurology. It was perhaps no coincidence that other alumni and close friends of the Laboratory presided over the disbursement of foods and the direction of policy during the early decades of the Medical Research Council.

As Gerald Geison has shown in his seminal work on Foster and the Cambridge Phsyiological Laboratory, their central research interest in the 1870s was the origin of the heartbeat.[1] The fundamental question was whether this was neurogenic or myogenic. Foster worked on this problem himself in collaboration with Alfred Dew-Smith, adventurer and friend of Robert Louis Stevenson, before handing on the problem to some of his brightest pupils, including Walter Gaskell and John Langley. The problem was solved by Walter Gaskell (1837-1914) who showed that denervated heart would beat independently if atria were sufficiently filled. He demonstrated that the origin of the heartbeat was myogenic, but as it turned out this did not mean that nerves did not have an influence.

Gaskell delved more deeply into questions of nervous control of the viscera and, with John Langley (1852-1925), developed the concept of the autonomic nervous system. Langley discovered that nicotine selectively interrupted impulses at sympathetic ganglia, providing a stimulus for the new sub-speciality of chemical physiology. Foster had himself suggested that the vagus nerve exerts an inhibitory effect on the heart indirectly through a chemical mediator; Thomas Elliott suggested in 1904, whilst working in the Cambridge Physiological Laboratory, that sympathetic nerves might release adrenalin. Ten years later Henry Dale (1875-1968), who had studied with Langley between 1898 and 1900, demonstrated that parasympathetic activity could be mimicked by acetylcholine. Dale shared the 1936 Nobel Prize for Physiology or Medicine for the discovery of this 'Vagusstoff' with Otto Loewi of Marburg, who had also journeyed through the Cambridge laboratory in the early 1900s.

Dale and his group at the National Institute for Medical Research subsequently showed that acetylcholine is released by motor nerves. Loewi discovered an enzyme anticholinesterase, physostigmine, which his group used in the laboratory to make detection of acetylcholine easier. It was left to Mary Walker (1888-1974), an Assistant Medical Officer at St Alfrege's Hospital, Greenwich, to be the first to use physostigmine to treat myaesthenia gravis in 1934. Walker also pioneered the use of the oral preparation, neostigmine, publishing her results in *The Lancet*.[2] These were perhaps the first specific treatments developed for a neurological condition, stemming from the basic scientific work done in laboratories in Britain and abroad.

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[1] G Geison, *Michael Foster and the Cambridge School of Physiology: the Scientific Enterprise in Late Victorian Society* (Princeton, NJ, Princeton University Press, 1978).

[2] M. B. Walker, Treatment of myasthenia gra- vis with physostigmine. *Lancet* (1934);i: 1200-1201.

Representations of reality

The physiological approach implied the primacy of function over structure. But therein lay a problem. Anatomy (i.e. structure) can be seen with the naked eye or through an instrument such as a microscope. Pictures, engravings, models or photographs can be made and disseminated. Physiology (i.e. function) is neither permanent nor stable, however. Some way had to be found to represent reality in a way that was reproducible and could be standardised.

Nineteenth century physiologists were therefore often physicists and instrument builders. The key component to virtually all physiological instruments of this period was the kymograph, an instrument which allowed continuous recording of physiological phenomena. The components of this were straightforward: a power source which drove a rotating electric motor; one or more smooth drums to which recording paper (usually smoke-blackened) could be attached; a series of cogwheels designed to transform the intermittent motion of the motor into a smooth impulse causing the drums to rotate at a known rate; and a recording arm triggered in some way by the physiological changes in the organ being studied. Subtle refinements of the apparatus allowed continuous recording and continuous stimulation.

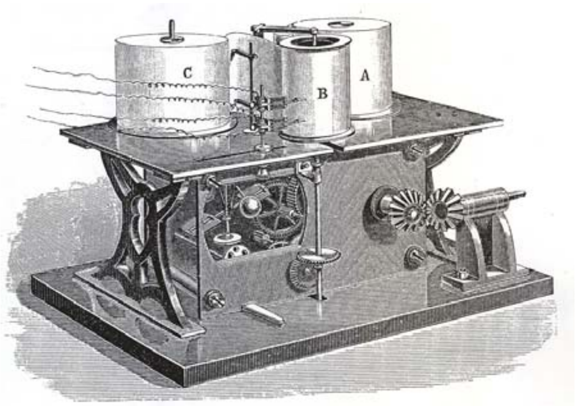

Figure 1: Kymograph from M. Foster, *Textbook of Physiology*
(London, Macmillan, 1879).

The archetypal physiological instrument was the nerve-muscle preparation, familiar to generations of medical students (up to and including the present day), first developed in the laboratory of Hermann von Helmholtz in Heidelberg in the 1850s. The extraordinary thing about this apparatus is just how large and complex it was, dwarfing the actual nerve-muscle preparation (plundered from the long-suffering physiological frog) by many orders of magnitude.

The nerve-muscle apparatus was the mainstay of many of the experiments done in Foster's laboratory in the 1870s and 1880s. It is easy to assume that it soon passed from being a research tool to being a didactic instrument in the undergraduate classrooms, but in fact Edgar Adrian (1889-1977) was still using the apparatus in the 1920s, developing methods of amplifying electrical currents in nerves, with a valve amplifier**.** Adrian's room was specially shielded from vibrations that might disturb the string galvanometers and capillary electrometers. One day a tiresomely oscillating electrical artefact turned out to be interesting:

> 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]

Further experiments followed, which showed that although a constant stimulus could excite an end organ, this excitation progressively decreased as the stimulation continued; Adrian showed that sensory impulses of constant intensity were passing along the nerve from the end organ, at first very frequently, but that their frequency gradually decreased, and as they decreased the sensation in the brain progressively diminished. For this work he shared the 1932 Nobel Prize for Physiology or Medicine with Charles Sherrington (1857-1952).

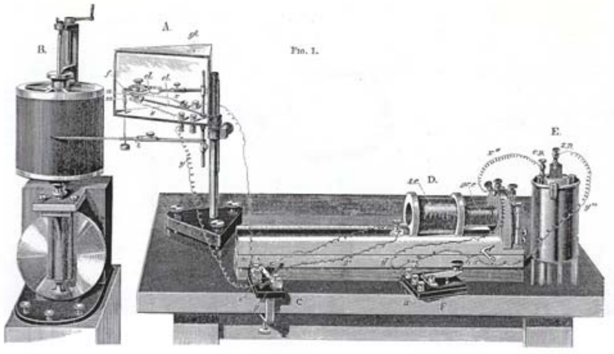

Figure 2: Nerve Muscle machine, from M. Foster, *Textbook of Physiology* (London, Macmillan, 1879).

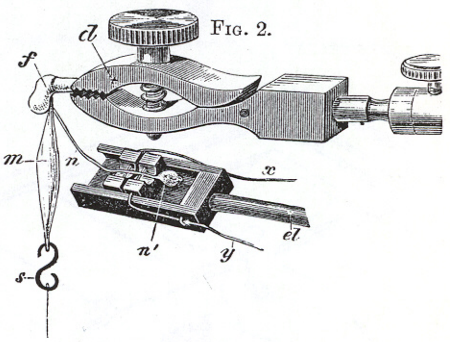

Figure 3: Nerve Muscle Machine from M. Foster, *Textbook of Physiology* (London, Macmillan, 1879).

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[3] E D Adrian, 'Memorable experiences in research', *Diabetes* (1954) 3: 17-18.

Sherrington had also studied physiology with Foster in 1879, before entering Caius College to study medicine in 1880; during his period in the laboratory he had been strongly influenced by Gaskell. In 1885 he visited Spain as part of Commission sent to investigate an outbreak of cholera; there he met Ramon y Cajal (1852-1934, winner of the Nobel Prize for Medicine in 1906), and beginning a lifelong friendship. Sherrington was interested in the spinal reflexes and the efferent nerve supply of muscles; he demonstrated the reflex inhibition of antagonistic muscles, studied the pyramidal tracts, and described the distribution of segmented skin fields; all this work was summarised in his 1906 monograph, *Integrative Action of the Nervous System*.

Sherrington's work on the distribution of areas served by sensory nerves was paralleled by another Cambridge graduate, Henry Head (1861-1940). In three long articles, published in the journal *Brain* in 1893, 1894 and 1896, Head described zones of skin hyperalgesia associated with visceral disease; these zones eventually became labelled eponymously in honour of this work. In pursuit of knowledge, Head even had the superficial branch of his left radial nerve sectioned; following this he stayed with W H Rivers in his rooms at St John's College, so that the latter could map his sensory loss and recovery. Rivers was a pioneer in the branch of physiology then known as psychophysics; this eventually became subsumed within the new discipline of experimental psychology.

Studies of nerve and muscle were the archetype, but other physiological systems such as respiration and the control of the blood pressure were also subject to graphical recording methods. A whole new industry was created, devoted to making scientific instruments. In the vanguard of this new business sector was the Cambridge Scientific Instrument Company, founded by none other than Foster's old collaborator Alfred Dew-Smith.

Towards medicine

The clinical application of graphical methods came first in cardiology when the Dutch physiologist Willem Einthoven (1860-1927) developed a simple string-galvanometer to measure the electrical activity of the heart. The Cambridge Scientific Instrument Company was quick to market a version of Einthoven's string galvanometer, using a picture of Einthoven with its product in its advertisements. As Christopher Lawrence has elegantly demonstrated, the clinical application of electrocardiography took time to be accepted in the cardiological community, but eventually it became the basis of the 'new cardiology' in the 1930s and 1940s.[4]

Can the same story be told for neurology? To a certain extent it can. The galvanometer had been applied to the head as far back as 1874 by the Liverpool surgeon Richard Caton (1842-1926), but the first reproducible scalp recordings of human cerebral electrical potentials was in fact reported in 1929 by Hans Berger (1873-1941). His report, which was the first to describe alpha rhythm, was not widely recognised, mainly because he had published it in some rather obscure (to the British medical and scientific communities, at least) psychiatric journals. It was read, however, by two Cambridge physiologists, Edgar Adrian and Brian Matthews (1906-1986),

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[4] C J Lawrence, 'Moderns and Ancients: the "New Cardiology" in Britain 1880-1930', *Medical History* (1985), supplement 5.

who credited Berger with his discovery before repeated and extending his work, not least by substituting an electron beam and a cathode-ray oscilloscope for the string galvanometer.

Adrian studied EEG responses to stimuli in sleep and wake states, and became the first President of the Electroencephalographic Society, founded in 1943. EEG entered clinical practice around this time, followed in the late 1940s and early 1950s by electromyography. But there were significant differences between the development of cardiology and that of neurology. While cardiology became almost exclusively physiological, clinico-anatomical correlation remained the central clinical approach in neurology. While the functional derangement of the heart quickly became the central question in cardiological practice, the functional derangement of neural processes has, perhaps because of its complexity, remained subordinate to the simpler question of the anatomical localisation of neuropathological processes, a question encapsulated by the neurologist's traditional enquiry: "where is the lesion?"

The drive to correlate clinical signs in life with pathological signs at *post mortem* proved a fertile field for neurologists throughout the period covered in this paper. The contributions of clinicians such as Charcot, Hughlings Jackson, Tourette and Gowers (to name but four of the neurological pantheon) created an ongoing anatomical tradition that provided the clinicians that founded the Association of British Neurologists (not one of whom has been mentioned in this paper so far) with more than enough ancestors to worship. EEG and EMG never achieved the pivotal position in neurology that ECG came to occupy in cardiology, a fact tacitly recognised by the creation of a sub-speciality of clinical neurophysiology. The development of increasingly sophisticated imaging techniques in the late twentieth century (computed tomography, magnetic resonance imaging, and positron emission tomography, for example) served only to reinforce this trend, though perhaps some redress is finally beginning to come with the development of 'functional' refinements of these techniques. As another neurological aphorism puts it, "things only get interesting when the scans are normal".

Concluding reflections

Experimental physiology opened up whole new ways of understanding the nervous system, ultimately leading to new methods of diagnosis and new types of treatment. In addition, experimental physiology set the benchmark for the techniques needed to represent reality in reproducible and standardized ways. But (and perhaps this is where humility enters our story) 80 years elapsed between Helmholtz's first experiments on nerve conduction and Mary Walker's use of physostigmine to treat myasthenia gravis; for all their Nobel Prizes the work of Head, Dale, Sherrington and Adrian did not immediately translate into clinical benefit, nor did they manage to establish the primacy of the physiological approach to neurology over the well-established (and highly successful) clinico-anatomical approach. Only now are the functional aspects of many neurological diseases beginning to be studied with what Sherrington dubbed (exactly a century ago) an 'integrative approach to the nervous system'. The relations of science and medicine were – and remain – complex.

Further reading

W Coleman & F L Holmes (eds), *The Investigative Enterprise: Experimental Physiology in Nineteenth-Century Medicine* (Berkeley: University of California Press, 1988).

S Finger, *Minds Behind the Brain. A History of the Pioneers and their Discoveries* (Oxford: Oxford University Press, 2000).

L S Jacyna, *Nineteenth-Century Origins of Neuroscientific Concepts* (Berkeley: University of California Press, 1987).

E M Tansey, ‘The Physiological Tradition’, in: W F Bynum & R Porter (eds), *Companion Encyclopaedia of the History of Medicine* (London: Routledge, 1993) vol 1, pp. 120-152.

M W Weatherall, *Gentlemen, Scientists and Doctors: Medicine at Cambridge 1800-1940* (Woodbridge: The Boydell Press, 2000).

Sherrington, Adrian and Dale’s Nobel Prize lectures are available online:
http://nobelprize.org/nobel_prizes/medicine/.

Pictures of some of those mentioned in this essay can be found in R H S Carpenter’s historical contribution to the modern department’s website: http://www.pdn.cam.ac.uk/history/phys/.