Short Historical Survey Professor I.M.L. Donaldson

This is a very brief review, largely in the form of notes, of the history of Neuroscience. Much, though not all, of it is also the history of the study of the control of movement. The works recommended for reading, which take a rather different approach, should complement the material summarized here.

Overall theme - the history of the discovery of localization of function within the central nervous system and how this has been related to the methods available to study the nervous system at various times during the last 4000 years or so.

The functions which we associate with activity within the head have not always been believed to rely on the cranial contents.

" Oh tell me where is fancy bred,
or in the heart or in the head .. " *Merchant of Venice*

was a real question for a very long time.

Sources of relevant information for the ancient world include

ca. 2500 BC	Egyptian Old Kingdom papyri, particularly Ebers and Edwin Smith (written ca. 1650 BC but a copy of an older text)
before 700 BC	Homeric poems, Iliad and Odyssey written down about 700 BC but referring to a much earlier age.
ca. 530 BC	Pre-Socratic fragments, especially Alcmaeon of Croton
ca. 400 BC	Plato, Dialogues (the Timaeus)
ca. 400 BC	Hippocratic School
ca. 360 BC	Aristotle, numerous works, as transmitted, often very indirectly
150 AD	Galen several works

There are formidable problems of interpretation including difficulties of decipherment of hieroglyphics and argument over exact meanings of Greek words.

Summary of Conclusions about ancient opinion about brain function **These were derived principally from philosophical speculation with some empirical observations.**

There was *some* knowledge of the association between some head injuries and neurological deficits such as paralysis and loss of sensation from the earliest times of which we know.

Alcmaeon of Croton is credited with being the first to claim (ca. 531 BC) that the brain was the seat of thought and feeling. Plato and the Hipprocratic School preserved this view. But a more ancient opinion (from Homeric times or earlier) held that the heart - or perhaps the lungs - certainly somewhere within the chest and not the head - was the seat of thought and emotion. This was Aristotle's opinion which (broadly speaking) persisted until the Renaissance. This did not prevent Galen from making some shrewd observations, that were also enormously influential, on the relation of nerve and muscle and of the spinal cord to movement. Since, say, about 1540 the head has taken over again but often with some 'psychological' functions still assigned to the heart; illustrated from remarks of William Harvey in first quarter of the 17th century. But the localization was, principally, of mental attributes; see illustration on page 9 and note, including Matthew Paris' poem of 1715. The cerebral ventricles were often thought to be the anatomical site of these localized functions.

Methods of studying the actions of the nervous system in the ancient world

- Philosophical argument divorced from experiment but often including introspection and combined with interpretation of natural observations, usually within the frame of a rather general cosmology.
- Interpretation of the effects of injury and disease ('natural experiments'). Usually interpreted within a cosmological system rather than used as evidence to test the validity of the system.
- Seeking relationships between structure and function; this process is not simply unidirectional. Function or presumed function may inform the search for structure.
- Intentional manipulation of the animal or human body - alive or dead. The line between systematic observation and planned experiment is often a fine one.
- The making of models, conceptual or physical. It is not always clear to what extent this was intended as a means of explanation of the actions of the real nervous system.

some of these approaches have proved to be of continuing value and interest.

What EVIDENCE was available? What METHODS were used, at various times and with what results? These questions occupy the rest of the historical lectures.

The development of an accurate knowledge of human anatomy

It is hardly possible to overestimate the importance of anatomy especially in ages when there was little other empirical method available to try to explore the mysteries of the functioning of the body, including its brain. For one Pre-renaissance view of the brain see the booklet cover; this was produced a mere 23 years before the publication of what is undoubtedly one of the great landmarks of science, the *Fabrica* of Vesalius, in Basel in 1543.

The difficulties of the early anatomists. The Schools of Bologna, and, particularly, Padua. The importance of a secular state in permitting dissection of the human cadaver. The *Fabrica* of Vesalius. Contrast between inaccuracy of Vesalius on the brain and eye and the precision of his osteology and myology. Some reasons for this. Real structure and fanciful function and vice-versa (see also below, Descartes). William Harvey, student at Padua, discoverer of the circulation of the blood and first modern experimental scientist; some of his views as illustration of opinions about brain etc. of one of the greatest men of the early 17th century. Significantly, he described himself as 'Anatomist'.

Descartes (mid 17th century), philosopher, mathematician.

Cartesian Dualism.

His best known work, the *Discours de la Méthode,* contains the remark 'je pense, donc je suis' more familiar in Latin as 'cogito ergo sum' an affirmation of his conviction that his knowledge of his own existence derived from his ability to contemplate it. Less well known is his insistence on a search for some criterion which would render an opinion reliable beyond question 'quelquechose en ma créance qui fust entièrement indubitable'. How far he sought such an assurance by real experiment is rather doubtful though there is reason to believe that he did carry out some system-

Descartes did not publish his principal physiological work, *Traité de l'Homme* (though its contents were circulated among his friends), because he considered it unsafe since he was a Copernican and Galileo had recently been condemned by the Inquisition for supporting the Copernican heresy of a heliocentric universe. The book was finally published posthumously in 1664.

His 'physiology' of sensation and motor control. Real anatomy → fanciful physiology → fanciful structure. Influence of hydraulic engineering - the very latest technology! Exposition of several enduringly important principles (e.g. reciprocal innervation) though with no experimental evidence and false mechanisms. Descartes as an experimentalist? - the observations on the ox eye. Cartesian puppets; analogy or mechanistic explanation of cerebral physiology? Compare with modern models of brain action.

The development of the experimental approach.

Francis Bacon (*The Advancement of Learning, 1605*) - beloved of the philosophers but not himself an experimenter. For a penetrating discussion of Bacon's works see Macaulay's long essay *Lord Bacon* (published July 1837 and included in standard editions of Lord Macaulay's Essays). Macaulay analyses Bacon's contributions to philosophy, which he finds to be monumental and his actions as Lord Chancellor of England which he finds generally deplorable.

William Harvey and 'ocular demonstration'; - the dawn of true experimental biology

> I have made known to you many times before, most worthy Doctors, my new opinion concerning the motion and use of the heart and the circulation of the blood in my anatomical lectures, but having now for nine years and more confirmed it by ocular demonstration in your sight....
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> *Exercitatio anatomica de motu cordis et sanguinis in animalibus,* Frankfurt, 1628. Epistle dedicatory to Dr Argent; Translated by G. Whitteridge, 1976.

Harvey's *De Motu Cordis* marks the achievement of much more than just the proof of the circulation of the blood. It is a very early - and still one of the greatest - accounts of a series of experiments designed to test a specific hypothesis which has, itself, arisen from precise observation. The escape from authority; cf. Galileo for the physical sciences. Sme years laterHarvey expressed the new experimental philosophy precisely:

> For although it be a new and difficult way to find out the nature of things by the things themselves rather than by the reading of books to take our knowledge from the opinions of Philosophers, yet must it needs be confessed that the former is a much more open way to the hidden secrets of natural philosophy and one which leads less into error.
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> *De generatione animalium.* 1651. Preface. Translated by G. Whitteridge, 1981

Before the end of the century Swammerdam (before 1680) and Goddard (1669) showed that the volume of muscles did not increase during contraction and so the explanation of muscle action by inflation of the muscle with 'spirits' carried to it by the motor nerves, as Descartes and others had supposed, could not be true. But pitifully few relevant experiments were yet possible on brain function.

Developments in the 17th and 18th century, technological as well as philosophical, were critical for further advance.

The following, from Mary Brazier's account of neurophysiology in the 17th and 18th centuries is a good summary:

The 17th century ended with a glorious record of all that contributes to man's progress, not only in the growth of understanding of the nervous system (which is the core of this study) but also in the activities occurring simultaneously in all fields. In architecture, Wren transformed London with the domineering dome of St. Paul's and his eloquent, spired churches (55 in all, 21 of which were destroyed in the bombings). Mansart, in France, architect to the King, was responsible for the famous Gallerie des Glaces at Versailles (centuries later the site of a momentous treaty) and the solidity of the Hôtel des Invalides, built not as a tomb but as a hospital; and Bernini in Rome had his great colonnade. In drama, the first half of the century witnessed the eruption of the Shakespeare plays; in the second half the theaters of Paris saw for the first time Racine's *Phèdre* and *Le Cid.* Molière, no longer a medical student of Gassendi's, intrigued Paris with his series of plays, giving *La Malade Imaginaire* just before he died. In music, this was the great century of the baroque in which London saw the birth of Purcell, Leipzig the birth of Bach, Venice the birth of Vivaldi, and Darmstadt that of Telemann, a promise of delight for the next century and for all time.

And what had the students of nervous activity achieved as a heritage for the next generation? They had begun to unseat Aristotle and Galen as explainers of the nervous system; they had begun the microscopic examination of its parts; they had undermined the age-old view of the nerve impulse as the passage of animal spirits; they had recognized (but not assigned to nerve) electricity, the invisible power that the next generation would begin to elucidate; they had drawn to the the great mathematicians and philosophers of the age; they had introduced mensuration into experiment and seen the precursors of the computer. Their comrade in another field had proven that blood moves, not as an ebb and flow, but as a circulation through our bodies. But unlike him, those concerned with the nervous system had moved away from vitalism and, by introducing experiment to test their concepts, had launched the mechanistic explanation that receives recognition today. Essentially the 17th is the century of attack on tradition and the expansion of intellectual freedom.

The 18th century had inherited from the 17th the urge to replace conjecture by demonstration and proof. This goal was sought for the nervous system by groups of workers in the older centers of learning in the Italies, the Netherlands, England, and France with the encouragement of the kings and princes of the great empires and of the duchies and principalities of what would two centuries later become Germany. Influential in this drive to replace unsupported concept by demonstrated fact was the most famous and controversial philosopher of that period: Descartes. Though not himself an experimenter, his statement expressed their goal, namely, that he must have no doubts before he can believe. Progress was remarkable for an age when mighty forces were ranged against any departure from the 1500-year-old Galenic views of nervous action, when the teaching of Aristoteleanism was still mandatory at the ancient universities of Oxford and the Sorbonne, and when acceptance of the heliocentric universe still invoked papal displeasure.

The end of the 17th century had seen a breakaway from some of these earlier restraints for in its closing years two great scientists, Newton and Leibniz, rose into prominence, to be followed by the widely read promoter, Voltaire. But for the nervous system the part having the greatest difficulty for release from vitalism was the brain, so inevitably identified with the soul. And still persisting throughout the 18th century was the concept that some form of animal spirits was responsible for nervous transmission, although in its last decade the crucial experiments on animal electricity were to shake the world. A role for electricity, tentatively suggested in the past by Boyle, and queried by Newton, became in the 1800s the power that was to replace animal spirits. The century closed nine years after the seminal disclosure of Galvani's *Commentary,* but it would be the following one that would offer proof.

Two of the technological advances of these centuries will be pursued here:

Microscopes and 'electricity'

The compound microscope - almost useless except for very low magnifications until 19th century; reasons why. The simple microscope of Leeuvenhoek and some of what it revealed. The *Micrographia* of Robert Hooke.

The experiments of Galvani and his successors; animal electricity.

Cytoarchitectonics

1900 onwards, cyto- and myeloarchitectonics; minute structure of (human) cerebral cortex; parcellation. Brodmann's areas. Changing opinions about their existence and functional significance.

Recording of electrical activity of neural elements (see table on page 8)

Early work. The ECG.. Limitations of equipment. Requirements for great sensitivity combined with very rapid response. The string galvanometer. Keith Lucas' pioneering work around 1911. Need for new technology. The vacuum tube (valve); triode valve amplifiers solved (in principle) the problem of sensitivity. The Matthews oscillograph; overtaken by cathode ray tubes. Adrian and Matthews. The Berger rhythm (later called electroencephalogram, EEG) - a thrilling development which was ultimately very disappointing.

Developments in technique in the 19th century (see table on page 7)

Structure:

Fixatives and stains; coal tar dyes and early photographic chemistry. Nissl stains. Metal-based stains. The description of the minute structure of the nervous system. The rival theories of Cajal (neurone) and Golgi (syncytium). Provisional victory of Cajal's neurone theory; why it took so long to be finally confirmed in the 20th century.

Methods and stains for tracing neural pathways. Importance to neurophysiology. Marchi. Bielschowsky's stain and its children, Glees, Nauta, Fink-Heimer. Experimental lesions and intracerebral tracing of pathways.

Function:

Vitalism. Influence of Magendie's insistence on experimentation and exclusion of hypotheses; Claude Bernard's approval of a symbiosis of experiment and theory. The controversy about the use of living animals for physiological experiments. The situation, but not necessarily the critics' view of it, radically changed after the discovery of anaesthetics.

The deduction of function from the effects of lesions:

Attempts to deduce function from the effects of pathological lesions of the nervous system; 'natural experiments'. The observation of the effects of lesions was not new - indeed it is as old as Man's interest in his own behaviour. In the 19th century, however, the French and English schools of experimental physiology, in particular, began to explore cerebral function by making experimental lesions in the nervous system of animals and observing the results. But the attempt to deduce function from the observation of lesions was desultory, and interpretation was hardly possible, until the concepts of localisation of function in separate regions of the nervous system became established. The limitations of deducing function from the disturbances that follow even very localised brain lesions require serious consideration. In spite of the limitations the method continues in use today - experiments on 'blindsight' following visual cortical destruction in monkeys and the comparison with 'blindsight' in Man are a good example of the continuing use of lesions to explore cerebral function.

Return to late 18th and early 19th century to pursue ideas of cerebral localization.

Phrenology

Gall (Vienna 1800 on) and Spurzheim (about 1825). Localization of 'faculties'; skull shape as model of brain shape; a system of social engineering? No verifiable basis; dismissed by savants as quackery (though very popular among others) and thoroughly disreputable. Important effect in prejudicing scientific opinion against the idea of *any kind* of cerebral localization of function.

Electrical stimulation etc and motor cortical areas.

BUT there were a few experimentalists (Fritz & Hitzig; Ferrier 1872 on) and a clinical neurologist (Hughlings Jackson around 1873) who were to change all that. Use of electrical stimulation of cortex to map 'motor' areas. Correlation of neuropathology and motor disorder (especially focal, Jacksonian, epilepsy). Sherrington, Woolsey, motor maps. Penfield, motor mapping in man (late 1930s). Limitations of technique of electrical stimulation.

Single-unit recording; ED (the first Lord) Adrian and his pupils from mid 1920s

Discovery of the frequency code in periphery; indications of sensory receptor specificity. Mapping of receptive ('sensory') cortices by multi-unit recordings. Cortical magnifications. Vindication of reality of functional implications of Brodmann's areas. Many technical problems wereovercome to allow *single unit* recording to be used in central nervous system as well as peripheral nervous system from 1950s. Enormous volume of information including proliferation of sensory maps brings us to modern neuroscience. Too soon to evaluate these methods finally though a great deal could be said; they certainly have confirmed ideas of localization of functions within the brain.

New methods of examining structure and connections

Since 1970s, replacement of silver degeneration methods by techniques which use neural transport of proteins (such as horse radish peroxidase (HRP), cholera toxin) and radiolabelled amino-acids to trace pathways. Combined light and electron microscopy. Microanatomical studies of individual neurones whose function has been previously examined by electrical recording.

New functional neuroanatomy

In last decade, modern imaging methods allow new approaches to localization of complex functions in human cerebral cortex; see particularly work of Zeki.

Suggested reading

Bear, M.F., Conners, B.W. & Paradiso, M.A. *Neuroscience: exploring the brain* (Williams & Wilkins, 1996) Chapter 1 and Chapter 2 section 1, contain a brief historical survey

Blakemore, C. *Mechanics of the mind* (Cambridge University Press, 1977)

Finger, S. *Origins of neuroscience* (Oxford University Press, 1994) has short articles on many topics which are interesting though not particularly scholarly.

Zeki, S. *A vision of the brain* (Blackwell, 1993)

A brief survey of histological methods used to examine nervous tissue up to the early 20th century

17 century - recorded use of ‘spirits of wine’ to preserve tissue e.g. Coxe, 1665 demonstrated human foetuses in alcohol to Royal Society.

1623 - Power seems to have sectioned frozen material - but this is an isolated instance.

1837 - Purkinje used alcohol hardening

1839 - Hannover used chromic acid as fixative

1840 - ? silver stain by Recklinghausen

1842 - Frozen sections made by accident.

1842 - Helmholtz, MD thesis

1862/3 - First use of analine dye as stain

1864 - or before - Deiters used combination of chromic acid fixation and carmine stain.

1871- Freezing microtome (using ether) invented by Rutherford in Edinburgh.

1871 - Ranvier, silver stain.

1873 - Golgi silver chromate stain; followed later by the stain which bears his name.

1880 - Ehrlich’s methylene blue; also used as intra-vital stain.

1883 - Cajal; various metal stains, gold chloride and

1903 - reduced silver method.

1906 - Both Golgi & Cajal awarded the Nobel Prize - effectively for coming to opposite conclusions.

The relations between nerve cells and between nerve fibres and cells

1665 - Robert Hooke probably saw cells (not nerve cells) under his compound microscope.

ca 1675 - Leeuwenhoek described nerve fibres using his simple microscope.

1837 - First definite view of neural cell bodies by Purkinje in cerebellum.

1842 - Helmholtz (in MD thesis) ‘some nerve fibres may come from nerve cells but others do not and come from “partibus centralibus”’(Liddell, 1960).

1870s - Golgi proposes syncytial theory

1889 - Cajal announces he can find no sign of diffuse network.

1897 - ‘boutons terminaux’ described

1897 - ‘synapse’ first used to describe relations by Sherrington; repeated in 1900.

Electricity and excitation of the nervous system

1678 - Swammerdam, contraction of frog muscle when its nerve contacts dissimilar metals (copper and silver)

1756 - Shock from Leiden jar (invented 1745) - a convenient source of 'electric fluid' - causes muscle to contract

1771 - Galvani - frog muscle contracts on exposure to electrical influence machine, even at a distance

1772 - Electric shocks of Torpedo (electric eel) demonstrated in La Rochelle

1780 - Galvani - contraction of frog muscles induced by 'natural' electricity collected by an aerial during thunder storms

1786 - Contraction of muscle by contact with damp metals (later, 'Voltaic pile')

1821 onwards - Galvanometers invented and steadily improved

1833 - Müller said 'we shall probably never attain the power of measuring the velocity of nervous action' (in fact this power was attained by his pupil 17 years later - see below)

1841- A test neuro-muscular preparation contracts when its nerve contacts contracting muscle the 'Galvanoscopic frog'

1850 (ca) - du Bois-Reymond writes volumes on the 'current of rest' but this proves (1867) to be an artefact of injury

1850 - Helmholtz *measures* conduction velocity of frog nerve finding values of 25-40 m/sec. (previous estimates ranged from 9000 feet/min to 57,600 million feet/min!). Later in Man finds values of 35 m/sec resulting in a long-held but erroneous belief that no human nerves conduct faster than this

1870 - Fritsch & Hitzig demonstrate movements from electrical stimulation of dog anterior cerebral cortex

1871 - Capillary electrometer invented - the first instrument to detect reliably currents arising in activated nerve

1876 - Ferrier makes detailed motor map by stimulating monkey cortex electrically

1901 - String galvanometer allows recording of electrocardiogram

1910 to about 1914 - Keith Lucas studies individual 'action potentials' using capillary electrometer

1910 - Adrian demonstrates 'all or nothing' nature of action potentials

1920 - Forbes & Thatcher first use electronic valve (vacuum tube) amplifier with string galvanometer to record action potentials

1922- Gasser & Erlanger use cathode ray tube (with valve amplifier) to display action potentials but the trace is too faint to see clearly or photograph without superposing many events

1926 - Adrian & Zotterman discover that stimulus intensity is coded by the frequency of firing of 'all or nothing' action potentials

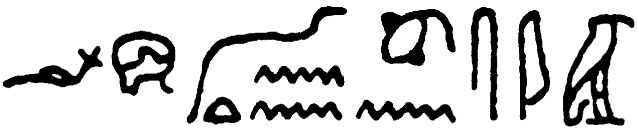
1929 - Berger describes his rhythm - the electroencephalogram (EEG)

1930s - Matthews invents his oscillograph and an amplifier to go with it. This becomes the best way of recording action potentials until it is overtaken by advances in cathode ray tubes

1933 - Adrian & Matthews confirm the cerebral origin of the EEG

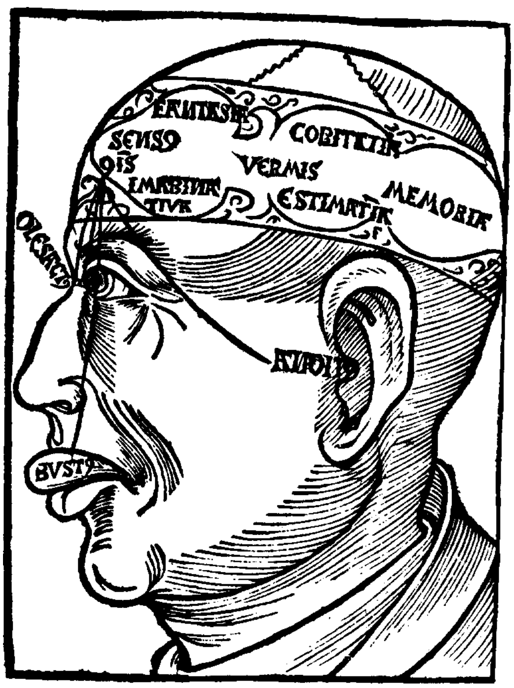
1937 - Penfield & Boldrey demonstrate motor and sensory maps on electrical stimulation of human cortex

1940s - Adrian carries out extensive comparisons of somatosensory maps using electrical recording from the cortex



The hieroglyphics read, from right to left, ‘the brain of his skull’. They are from the Smith Surgical Papyrus written about 4500 years ago in Old Kingdom Egypt and the rightmost four characters form the oldest written word for ‘brain’ which is known. The Smith papyrus seems to be a textbook for surgeons and contains a number of descriptions of the effects of injuries to the head and neck which make it clear that the associations between some head injuries and paralysis and loss of speech were known. The illustration is from a facsimile text of the Smith Papyrus published by J.H. Breasted in 1930.

René Descartes is best known as a philosopher and mathematician; he invented Cartesian geometry. He was a philosopher in the wide sense and wrote on sensation, particularly on vision and touch, as well as on the control of movement. Probably influenced by the contemporary hydraulic engineering which produced the fountains at Versailles, he believed that motor nervous influence was conducted by flow of fluid along the nerves. The picture illustrates the mechanical transmission of information leading to pain from the foot to the brain ventricles. From Descartes *De l’homme,* 1664.



From the earliest times from which we have surviving detailed philosophical texts there was disagreement about where in the body various functions might be located. Though the pre-Socratic and Platonic view seems to have been that ‘feeling’ and ‘thought’ are to be found in - or, at least, associated with - the contents of the skull, the doctrine which was transmitted to Western thought was that of Aristotle which placed the seat of the senses firmly extracranially. The details are complex and confusing but the most popular localization of ‘feeling’ was in the heart. Such expressions as ‘faint-hearted’ and ‘heavy-hearted’ are survivals of this philosophical opinion in common speech. The extracranial localization of sensation, though by then decidedly old-fashioned, persisted certainly as late as the eighteenth century so that Matthew Prior could contrast - with entirely malicious intent one suspects - the old-fashioned Aristotelian opinion which he ascribes to the Oxford men with that of his own enlightened Cambridge wits:

‘Alma in verse, in prose the mind....
....
Alma they strenuously maintain
Sits cock-horse on her throne the brain
And from that seat of thought dispenses
Her sovereign pleasure to the senses.’

In fact there were those throughout the Renaissance who held or revived the ancient cephalocentric view of the senses. This picture is an early illustration of the supposed localization of the ‘faculties of the soul’ by G de Rusconibus, 1520. In the first cerebral ventricle are found fantasy, ‘common sensation’ and imagination. In the second ventricle, separated from the first by the vermis, are thought and judgement and in the third, memory. This type of division of cognitive function foreshadows that of the phrenologists of the eighteenth and nineteenth centuries and is very different from our beliefs about localization of brain functions at the beginnning of third millenium.