HISTORY OF MEDICINE

The nervous system in antiquity

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This overview of the nervous system in antiquity shows that whereas neuro-anatomy had its heyday in the 4th and 3rd centuries BC (the Alexandrian School) and was later consolidated by Galen in the 2nd century AD, neurophysiology remained largely mired in erroneous concepts. While the descriptions of neurological disease often produced quite apt clinical pictures, poor understanding of pathophysiology resulted in ineffectual therapy. The embryonic origins of modern neurology lie in the gradual evolution of neuro-anatomy and neurophysiology in antiquity. Closely allied to the early understanding of the nervous system was the contested issue of where the control centre of the body *(hegemonikon)* was located. These are the issues that we review.

The body's control centre

The need to place all actions of the body under the control of a single centre or principle (*hegemonikon* – a term coined by the Stoics) was pervasive in Western antiquity.[1] Although the head (brain) was favoured by many, entities such as the chest, heart, liver, blood and the *pneuma* ('vital spirit') also had their supporters. Hippocrates stated that the diaphragm, which was favoured by some, could not be seriously considered because it did not contain a cavity[2] (presumably to house the soul or 'vital spirit').

In Ancient Egypt, the heart was considered to be the chief organ of the body. The brain was viewed as being of little importance – at best, the producer of mucus during illness, subsequently discharged through the nose.[3,4] In Mesopotamia, the liver was thought to be the seat of the soul.[5] In Greece, the so-called Presocratic philosopher-physicians (6th and 5th centuries BC) laid the foundation of empirical science that led to the Hippocratic era. Alcmaeon of Croton, a contemporary of Pythagoras, favoured the head (and brain), as did Diogenes and Democritus.[6] Parmenides[6] and the influential Sicilian, Empedocles,[1] however, thought that the soul was seated in the thorax or the blood surrounding the heart.

The Hippocratic Corpus (mainly 5th and 4th centuries BC) presented divergent views. In *The Sacred Disease* (chapter 19), the brain is called the centre of bodily functions but, in a later text (*The Heart*, chapter 7), the left ventricle of the heart is the seat of the soul. In *Diseases Book II*, higher bodily functions are ascribed to both the heart and the brain.

While Plato favoured the head, Aristotle placed the *hegemonikon* in the heart, stating that a bloodless brain could not house the soul. During the 4th century BC, the Stoics, Epicurians, Praxagoras and Diocles all nominated the heart, while Strato placed the seat of the soul between the eyebrows. At the onset of the Hellenistic era (late 4th century BC), the cardiocentric consensus (heart as control centre) gradually receded, as influential Alexandrians such as Herophilus and Erasistratus brought evidence of an encephalocentric *hegemonikon*.[1] Erasistratus thought it might be located in the meninges rather than the brain.[1] Chrysippus (3rd century BC), however, still favoured the heart,[7] while Asclepiades (1st century BC) taught that there was no *hegemonikon*, since the senses controlled all bodily activities.[1]

In the Roman era, influential figures such as Galen[1] and Rufus (2nd century AD)[7] strongly defended the encephalocentric approach, but Lucretius (1st century BC) and Alexander of Aphrodisias (2nd century AD)[1] were cardiocentrists, defending a point of view that persisted through medieval times and was still reflected by Shakespeare in his play *The Merchant of Venice* (III.ii.63): 'Tell me where is fancy bred, or in the heart, or in the head'?[8]

Phrases such as 'heart and soul', 'with all my heart' and 'heartfelt grief' have their origin in the cardiocentric view of the past.

Neuro-anatomy

In Ancient Egypt, the brain was considered unimportant and there was no real knowledge of the nervous system. During the mummification process, the brain was destroyed and removed via the nose and through the cribriform plate.[3] But in the Edmund Smith Papyrus, the brain is identified as an organ,[4] and limited neuro-anatomical features such as the meninges, cerebrospinal fluid, surface blood vessels and convolutions, which were observed through open skull wounds, are

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mentioned.[3] Similarly, Mesopotamian writings reveal no significant neurological knowledge.[7]

Greece (Classical era)

In pre-Hippocratic times, the philosopher-physician Alcmaeon of Croton (6th century BC) probably took the first tentative steps towards exploring the brain and nervous system. He possibly dissected animals, and was said to have examined an excised human eye. He linked the senses functionally to the brain and postulated passages connecting the eyes, ears, nose and tongue (taste) with the brain. He might have described the optic nerve.[1]

The Hippocratic Corpus (the foundation document of empirical medicine) contains little on neuro-anatomy, knowledge of which was gained from general observation and limited animal (but no human) dissection.[1] Two membranes covering the brain (the dura and pia mater, but not the arachnoid) were described; these membranes partially divide the brain down the middle into the right and left hemispheres. Apparently based on dissection of the goat, the brain was said to be oedematous and foul-smelling.[1,2] The spinal cord was described as attached to the brain and of the same consistency, differing from that of bone marrow. The fluid under the brain membranes (meninges) was found to be confluent with that covering the spinal cord.[9] Passages through the skull and meninges linking the eyes and ears to the brain were noted, but no such passage to the nose. Blood vessels, ducts and nerves were confused – *phlebes* were described as hollow tubes carrying various fluids, and *neura* were solid structures (including nerves, tendons and ligaments). Semen was believed to originate in the head and to be conveyed in *neura*. The eye was thought to consist of three tunics (sclera, choroid and retina) and to be nourished by the brain through the hollow optic nerve.[9]

Although not medically trained, Aristotle (4th century BC) performed extensive animal dissections and confirmed that the main brain consisted of two hemispheres. He described a lesser brain (*parenkephalon* (cerebellum)) behind the main brain (*encephalon* (cerebrum)). The brain was thought to be covered by two meninges and to contain few blood vessels. He also found that some animals had small cavities (ventricles) in the cerebrum, and mentioned the presence of a few nerves originating in the brain (cranial nerves).[1] The concept of the *neuron* still included tendons and ligaments besides nerves. He reported that men had larger brains than women and that, relative to body size, man had the largest brain of all creatures.[7] Praxagoras (4th century BC) claimed that blood vessels terminated as nerves, so supporting the argument that the heart was the central controlling organ.[7] He and Philotimus believed that the brain was merely an outgrowth of the spinal cord.[1] Vindicianus later wrote that Diocles (4th century BC, sometimes called the second Hippocrates) had said that the right half of the brain controlled sensation and the left side, intelligence.[10]

Alexandria (Hellenistic era)

Up to the Hellenistic era, all knowledge of neuro-anatomy had been based purely on animal dissections. The heyday of neuro-anatomy dawned when Herophilus and Erasistratus commenced human dissection (probably even vivisection) of condemned criminals, under patronage of the Ptolemaic pharaohs in the newly established city of Alexandria (332 BC). However, with the probable exception of Eudemus (3rd century BC), Numisianus and Marinus (2nd century BC), subsequent Alexandrian physicians did not continue systematic human dissection.[1] Virtually all the extensive original writings of Herophilus and Erasistratus were destroyed, and our knowledge of their contributions is based on comments by later authors such as Theophilus, Oribasius, Rufus, Vindicianus and – in particular – Galen.[6] Herophilus and Erasistratus probably dissected as many, or more, animals than humans, which is indicated by occasional errors in their reported findings, e.g. the description of the presence of a *rete mirabilis* anastomosis at the base of the human brain – a structure found in angulated animals but not in humans. But it can be stated confidently that the basis of human neuro-anatomy was laid by the two Alexandrians.[1] Illustrations were used for the first time in history to clarify descriptions, a technique later disapproved of by Galen.[8] Both performed vivisection on animals (and possibly humans) to verify the function of parts of the brain and nerves. Herophilus' impressive findings included the following:[6,10]

1. A description of skull sutures.
2. Two layers of meninges (the dura mater and pia mater) covering the brain, the outer one involved in the formation of the *tentorium cerebelli*, and lining the intracranial venous sinuses. This included the prominent junction of sinuses named the *lênos* (wine vat) (Galen renamed it the *torcular Herophili*; however, this structure is rarely prominent in man, and the term could represent another example of animal anatomy corrupting knowledge of human anatomy).
3. Differentiation between the cerebrum and cerebellum. Herophilus considered the latter to be responsible for motor activity and equilibrium.
4. The 2 lateral brain ventricles, their openings into the 3rd ventricle, aqueduct of the midbrain and the 4th ventricle, and the choroid plexus (resembling the fetal choroid membrane) lining these spaces.
5. The 4th ventricle was considered to be the seat of the soul, and details such as a pen-like cavity in its floor (*calamus scriptorius* – probably the aperture into the spinal column) were described.
6. The origin of the spinal column from the brain, the pineal body (resembling a pine cone), the structure of the eye and at least some of the cranial nerves (optic with optic chiasma, oculomotor, trigeminal, facial, auditory and hypoglossal nerves) were identified.

7. His detailed study of nerves (distinguishing between motor and sensory nerves) was a fundamental contribution. However, he still considered the optic nerve to be hollow, and included tendons and ligaments as terminal extensions of nerves in muscles (this part of the complex mechanism then supposedly enabling voluntary motor activity).

We know more about Erasistratus' neurological concepts as he was quoted more extensively by Galen (often critically) because he dared to differ from Hippocrates.[7] Largely agreeing with Herophilus' neuro-anatomy, he taught that the brain's convolutions related to mental ability (therefore more convolutions in man than in animals, and in the cerebellum rather than the cerebrum). He claimed that not only the optic nerve but all sensory nerves were hollow to enable the flow of 'psychic *pneuma*' (see below); sensory nerves originated in the meninges and motor nerves in the brain.[1,6]

Marinus (2nd century BC) made a detailed study of the cranial nerves, describing the olfactory nerve structure, and a large nerve descending from the lower brain into the thorax (either the vagus or recurrent laryngeal nerve).[6]

Roman era

With human dissection virtually discontinued in Hellenistic times, the subsequent Roman era brought little enhancement of human neuro-anatomical knowledge. At the turn of the 1st century AD, Rufus of Ephesus reviewed known medical information and, although misconception regarding the *neuron* persisted, he elegantly described the brain, spinal cord and nerves as an interconnected nervous system.[7]

Galen (2nd century AD), the most prominent physician of Roman times, whose views became dogma in the medieval era, wrote extensively on medical matters, including the nervous system. His views on neuro-anatomy were based on existing knowledge (mainly the Alexandrian findings) as well as extensive personal dissection of animals (oxen and apes in particular) but not humans. He largely confirmed the work of Herophilus and most of that of Erasistratus. Until then, the ventricles had been much studied, the brain substance being seen as little more than supporting tissue. Galen now described the corpus callosum, thalamus, septum lucidum (separating the lateral ventricles), and the fornix in the roof of the 4th ventricle – the latter he accepted as the centre of the *hegemonikon*. The pituitary gland and its stalk attached to the 3rd ventricle floor were described; like Herophilus, he wrongly placed a retiform plexus at the base of the human brain.[1]

Galen gave a good description of the blood vessels of the brain. The optic nerve and most (but not all) other nerves were believed to be hollow. The spinal cord was said to be a bundle of nerves running together from the brain down the vertebral column to the rest of the body and emerging from its bony cage through intervertebral foramina. He still considered ligaments and tendons as equivalents of nerves, and stated that while sensory nerves were soft and arose from the cerebrum, motor nerves arose from the spinal cord and were hard; nerves arising from the junctional area could be either soft or hard. He was adamant that brain convolutions had no qualitative relationship to brain function.[7,11]

Post-Galenic writers of antiquity (e.g. Oribasius) quoted their predecessors without adding significant new knowledge.[5]

Neurophysiology

Pneuma

Neurophysiological hypotheses largely revolved around concepts regarding the nature and function of *pneuma* (air) as 'vital spirit' essential for life, which entered the body mainly during breathing but also through pores in the skin. Originally postulated by Anaximenes (6th century BC),[1] the concept was supported by Democritus who taught that *pneuma* was transmitted by semen.[12] Diogenes' view (that *pneuma* was breathed in with air and transmitted through the body in blood vessels as well as other ill-defined passages, enabling cognition and intelligence) became widely accepted.[1] The Hippocratic Corpus described *pneuma* as a major enabling factor in brain function, entering the brain through blood vessels, but also directly via pneumatic channels from the mouth and nose.[2] Aristotle stated that, as the central controlling organ of the body, the heart (through 'innate heat') converted *pneuma* (in blood) to 'connate *pneuma*', which was the 'generative heat' in semen, but also enabled organs to experience sensation. In view of its considered bloodlessness, the brain was therefore unimportant in this process. Its main role was seen as thermoregulatory – keeping the body cool. Although Praxagoras referred to 'psychic *pneuma*', this important concept was first formulated by Diogenes (4th century BC) who, as promoter of the heart as seat of the *hegemonikon*, claimed that 'psychic *pneuma*', formed in the heart, spread through the body's vessels to effect voluntary motion. Interruption of this flow resulted in disease. The Stoics made a major contribution to the *pneuma* theory by stating that it was a multifaceted changeable force, capable of *inter alia* becoming 'vital *pneuma*' (the soul itself) or 'psychic *pneuma*' (responsible for consciousness and intelligence). The brain played no direct role in all this.[1]

Erasistratus taught that 'psychic *pneuma*', converted from ordinary pneuma in the meninges, was the vital force necessary for nervous function.[1] Herophilus apparently believed that 'psychic *pneuma*' was formed in the choroid plexus of the lateral ventricles (out of 'natural *pneuma*') from where it permeated through to the 4th ventricle (command centre) and activated all nerve action (there being a 'sensory *pneuma*' for sensory nerves, and 'motor *pneuma*' for motor nerves). Praxagoras' hypothesis was that voluntary and involuntary movement, spasms, palpitations and tremors were due to arterial (not nervous) activities. Galen's views, which remained in vogue for the next millennium, represented a further evolutionary development,

which stated that a '*pneuma*-like substance' absorbed in the lungs reached the heart where, under influence of 'innate heat', it converted to 'vital *pneuma*', which passed to all organs via the arteries. On reaching the brain, this was converted to 'psychic *pneuma*' in the retiform plexus or choroid plexus in the lateral ventricles. 'Psychic *pneuma*' could also be formed in the brain ventricles from *pneuma* absorbed directly through the nose (and cribriform plates). 'Psychic *pneuma*' then permeated the ventricular system and the cerebellum in particular, activating nerves by flowing through them; it also passed via the optic nerve to the eye. The role of *pneuma* in interaction with the soul or activation of neuro-psychiatric functions was not elaborated on by Galen.[6,8]

Other mechanisms

The popular hypothesis of antiquity (that health was dependent on an equilibrium between body humours and basic elements) also held for neurophysiology. Scarborough[13] suggests that the concept of four humours (blood, phlegm, yellow and black bile) probably originated with Thales (early 6th century BC), while Alcmaeon first stressed the importance of an internal equilibrium of natural phenomena.[10] Empedocles added four basic elements (water, fire, earth and air)[12] and Philistion ascribed four qualities (hot, cold, dry and moist) to these elements.[10] Disease would then result from internal imbalances, which in turn could be caused by external factors (such as excessive variation in temperature or humidity, trauma, incorrect diet or physical activity) or the blockage of passages that conveyed the humours and elements. Hippocrates' consolidation of these theories remained dogma throughout antiquity, although the early Alexandrians disagreed with mainly the humoural theories.[14]

Aristotle believed that the brain's main function was that of cooling the body and the hot heart in particular.[1] Hippocrates stated that the spinal cord was indeed warmer than the brain,[1] and Galen confirmed the brain's supposed cooling function.[7] Plato maintained that the brain was the body's controlling organ, and that the soul consisted of three parts – the main or rational soul was in the brain, but the heart and upper abdomen also housed components.[7]

Neurological illness

Although the symptoms and signs of disease were often quite well described, ignorance about relevant pathophysiology barred the ancients from prescribing effective therapy. Recognisable neurological illnesses included the following:

Papyri from ancient Egypt mention unilateral facial palsy which could be Bell's paralysis, unilateral headache possibly compatible with migraine, and a variety of paralyses caused by cranio-spinal injury.[3] The Hippocratic Corpus devotes a book to epilepsy (*The Sacred Disease*), clearly describing variants of the disease.[2] Erasistratus recognised apoplexy[1] and, 800 years later, Caelius Aurelianus differentiated it from epilepsy, hysterical conditions, 'paralysis' and 'general lethargy'. The latter two conditions clearly represented a hodge-podge of ill-understood neurological problems which, like most illnesses, were blamed on disequilibrium within people or abnormal *pneuma*.[16] Head wounds received prominent attention but there was limited comment on neurological complications, although Hippocrates did describe contralateral convulsions.[17] Headache was recognised as a complex symptom associated with many diseases,[18] and Hippocrates attributed mental disease to derangement of the brain.[2] In the 1st century AD, Celsus[19] recognised four kinds of insanity: melancholia, progressive 'foolishness of the spirit' (possibly dementia), illusions in an otherwise healthy person, and 'phrenitis' (delirium associated with fever). Hydrophobia (rabies), first described in Hellenistic times, was clearly defined by Caelius Aurelianus.[16]

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