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Neuroscience, Early History of Charles G. Gross

Modern neuroscience has roots deep in the history of Western biology, medicine, and philosophy. This article outlines some of the major developments in our understanding of nerve and brain function before the middle of the 19th century.

Ancient Egypt

The first written description of the cerebral cortex and the first indications that the site of brain injury can determine the nature of neurological symptoms are found in the Edwin Smith Surgical Papyrus. Written in about 1700 b.c., it is a copy and gloss of a much older treatise dating back to about 3000 b.c. Legend ascribes the original treatise to Imhotep, grand vizier of the 3rd dynasty pharaoh, Zoser, and later deified as an Egyptian god of medicine.

In describing a case of skull fracture, the author noted the pulsations of the exposed brain and compared the surface of the brain to the rippling surface of copper slag (which indeed has a gyral-sulcal pattern). The laterality of injury was related to the laterality of symptom, and both aphasia ("he speaks not to thee") and seizures ("he shudders exceedingly") after head injury were described.

Overall, the treatise is a coolly empirical and practical handbook, perhaps for a battlefield surgeon. It contrasts with most subsequent ancient Egyptian medical writings, which are amalgams of mysticism, superstition, and elaborate speculation. In them, the heart, not the brain, is the most important organ, the seat of the mind and the center of intellectual activity. This hegemony of heart over brain was the prevailing view in the Ancient Near and Far East, and advocates of this opinion can be found in Europe into the 17th century.

Classical Greece and Rome

The Pre-Socratics (6th-5th Century b.c.). Formal, self-conscious science began in the 6th century b.c. with the naturalistic Ionian philosophers (such as Thales and Anaximenes) and the more mystical Pythagoreans. The Ionians, particularly, were responsible for the idea that the universe could be understood by reason: that it consisted of a set of mechanisms that worked in a consistent fashion according to fixed rules.

Several of these Pre-Socratic philosophers, such as Empedocles and Democritus, were particularly interested in the sense organs and perception. However, the Pre-Socratic most important for the history of neuroscience was Alcmaeon of Croton. He was the first writer to champion the brain as the seat of the senses and the central organ of intellect. According to ancient authorities, he believed,

the seat of sensations is in the brain. This contains the governing faculty. All the senses are connected in some way with the brain; consequently they are incapable of action if the brain is disturbed . . . the power of the brain to synthesize sensations makes it also the seat of thought: the storing up of perceptions gives memory and belief and when these are stabilized you get knowledge.

Alcmaeon dissected the eye, described the optic nerves and Eustachian tubes, and recognized arteries and veins as blood vessels. More generally, he stressed that health was the state of harmony and disease that of discord of the elements composing the body.

Hippocrates (460-375 b.c.). Perhaps the most famous treatise of the Hippocratic corpus and certainly the most relevant one for neuroscience is, "On the Sacred Disease." The so-called sacred disease is epilepsy, but the author is clear about its natural origins:

I do not believe that the sacred disease is any more divine or sacred than any other disease, but, on the contrary, has specific characteristics and a definite course . . . It is my opinion that those who first called it sacred were the sort of people we call witch-doctors, faith-healers, quacks and charlatans . . . By invoking a divine element they . . . conceal their ignorance of its nature.

The author is equally clear about the importance of the brain:

It ought to be generally known that the source of our pleasure, merriment, laughter, and amusement, as of our grief, pain, anxiety, and tears, is none other than the brain. It is specially the organ which enables us to think, see, and hear, and to distinguish the ugly and the beautiful, the bad and

the good, pleasant and unpleasant . . . It is the brain too which is the seat of madness and delirium, of the fears and frights which assail us . . . it is there where lies the cause of insomnia and sleep-walking, of thoughts that will not come, forgotten duties, and eccentricities.

The Hippocratic doctors did not practice dissection, and their knowledge of anatomy was slight. Although they made many perceptive observations and even devised some reasonable treatments, their conception of mechanisms was largely a mixture of false analogy and speculation. Epilepsy, for example, was believed to be caused by phlegm (one of the four humors) descending from the brain and preventing pneuma (roughly, "vital air") from entering the blood vessels.

Plato (428–347 B.C.) and Aristotle (384–322 B.C.). The influence of both Plato and Aristotle on the development of neuroscience was essentially negative, but in different ways.

Plato argued against every kind of science, preferring pure reason over observation and experimentation, seeking divine principle rather than natural law, and advocating the study of ideas or ideal forms rather than actual objects. His cosmological schema of the universe and the body, particularly as set forth in the *Timaeus*, had a particularly strong and nefarious influence. In it the soul is divided into three parts. The immortal soul, responsible for reason, resides in the head. The superior part of the mortal soul is in the heart, which receives input from sense organs and is the executor of reason. The inferior part, controlling animal desires and emotions, is placed in the liver. This concept of localization of mental functions continued to reverberate for about 2000 years.

Aristotle was the greatest biologist of antiquity, the founder of comparative anatomy, the first embryologist, the first evolutionist, and the first systematic student of animal behavior. Yet he dismissed the brain as wet and cold and devoid of sensation. Rather, the heart was the center of sensation, intellect, and movement. Why did Aristotle reject the views on the hegemony of the brain held by his predecessors such as Alcmaeon, his contemporaries such as Hippocrates, and even his collaborator and successor as head of the Lyceum, Theophrastus? Aristotle produced physiological, comparative, embryological, and introspective arguments for his view of brain function. But the crucial approach in his time was the study of brain-injured humans. Both Alcmaeon and the Hippocratic writers were practicing physicians and their evidence on brain function was strictly clinical. Perhaps because Aristotle's father was a physician and he had been slated to become one himself, medicine was one of the few intellectual endeavors in which Aristotle never showed any interest, and clinical medicine was the key to brain function in 4th century Greece.

Alexandrian neuroscience (3rd Century B.C.). The great Museum at Alexandria has been compared to the National Institutes of Health. The Museum was a vast state-supported institute for research including an astronomical observatory, a zoo, botanical gardens, dissecting and operating rooms, more than one hundred professors and that wonder of the ancient world, the Library. In two ways it was a continuation and expansion of Aristotle's Lyceum. First, the founder and chief patron of the Museum was the first Ptolemy, who had been, together with his boyhood friend Alexander, a young pupil of Aristotle. Second, its main scientific founders were Demetrios and Strato, who had been students of Theophrastus at the Lyceum. Strato himself was interested in the brain and taught that it and not the sense organs (let alone the heart) was the seat of sensation.

The Greek reverence for the body had made human dissection impossible, or at least illegal, in Athens, but in Alexandria,

where dissection of the dead for embalming had been practiced for centuries, this restriction was absent and the systematic study of the human body flourished.

The two great neuroanatomists at the Museum were Herophilos and Erasistratos. Herophilos distinguished the cerebrum and the cerebellum, described the meninges and sinuses, and provided the first clear description of the ventricles. He believed all nerves originated in the brain and traced their courses to sense organs and muscles. Herophilos distinguished sensory and motor nerves by noting that damage to the former produced loss of sensation and damage to the latter loss of movement.

Erasistratos continued Herophilos's anatomical work and was particularly interested in the application of contemporary physical ideas to the study of neural function. He attributed human superior intelligence to the greater number of convolutions in brain and seems to have carried out experiments on the living brain, perhaps including the human brain. He believed the psychic pneuma entered the brain through hollow sensory nerves providing sensation and that movement was caused by the expansion of muscles due to pneuma carried to them from the brain through the motor nerves. Both views were dominant well into the 18th century.

Galen (129–199)

Galen was the most important figure in Classical medical science. He represents its culmination, and his views on the body and brain dominated Western thought for more than 1,500 years. Galen's work on the nervous system included detailed dissections of the brains of a variety of animals, extensive clinical investigations, and a series of systematic studies of the effects of experimental lesions of various parts of the nervous system.

Galen regarded the brain as the site of sensation and thought and the controller of movement. The sensory nerves were "soft" and came from the anterior portions of the brain, whereas the motor nerves were "hard" and came from the posterior portions, particularly the cerebellum. Thus, sensation was a "central process," and the characteristics of nerves derived from their central connections.

Galen's studies of the cranial nerves and spinal cord were outstanding. He described seven of the cranial nerves and experimentally determined the functions of several of them. He studied the effects of transections of the spinal cord at various levels and concluded that the spinal cord was an extension of the brain and the conduit of sensory signals from and motor commands to the body below the head. He noted that specific spinal nerves controlled specific muscles, and had the idea of the reciprocal action of muscles. For the next advance in understanding spinal function we must await Bell and Magendie in the 19th century.

Galen's writings on mental and nervous diseases, although often bizarre from our point of view, were no less influential. Mental diseases were attributed to the obstruction of the passage of pneuma in the brain by one of the four humors or sometimes to an excess of a particular humor. For example, melancholia was due to an excess of black bile and epilepsy to an excess of phlegm. He attempted to attribute particular nervous diseases to dysfunctions of specific brain regions. Epilepsy was supposed to involve the posterior ventricles and apoplexy the posterior cerebral matter itself. He ridiculed Erasistratus's correlation of intelligence with the cerebral convolutions, and in general, minimized the importance of the cerebral cortex, a view that remained prevalent until Gall. Although Galen believed the ventricles were important for the passage of pneuma, he vigorously denied that the soul was situated

in them, because animals and humans could survive damage to the ventricles.

After his death Galen's ideas became frozen dogma. Rather than extend his discoveries and experimental innovations, his successors in Europe accepted as undisputed and indisputable his views in every branch of medicine.

Medieval Europe

The advances in understanding the brain in medieval Europe are easy to summarize: there were none. The central feature of the medieval view of the brain was the localization of the mental faculties in the ventricles of the brain. The church fathers were very much concerned with the nonmaterial nature of the soul. Thus, rather than localize the soul, they ascribed loci for Aristotle's classifications of its functions, namely, the functions of the mind such as sensation, reasoning, and memory. Furthermore, they felt that brain tissue was too mundane to act as an intermediary between the earthly body and the heavenly soul, so they placed the mental faculties in the empty spaces in the brain—the ventricles. Sensation was assigned to the anterior ventricle because according to Galen, the anterior cerebrum was soft and impressionable. Cognition and reason were in the middle ventricle, an appropriate central place for the "digestion" of the sensations. Memory was in the posterior ventricle, as that region of the brain was hard and thus a good place for storage.

During the European Middle Ages, however, much of Classical medicine was kept alive and further developed in Islamic civilization. Thus, the writings of Hippocrates, Galen, and other Greek medical figures usually came to Europe through Syrian, Persian, Hebrew, or Arabic translations and then into Latin.

Vesalius and the rebirth of neuroscience

The first person to break the stronghold of Galen and rekindle neuroscience was Andreas Vesalius—the founder of modern anatomy and, with Nicholas Copernicus, the initiator of the scientific revolution. By the beginning of the 16th century, the foundations for Vesalius's achievement were well under way. Galen's original works had become available, and the invention of movable type helped disseminate them, as well as more recent anatomical studies. Naturalism in Renaissance art had generated interest in at least superficial human anatomy. Public dissections of the human body in medical schools, originally for forensic purposes, were common and drew large audiences.

Those dissections, however, were largely demonstrations, if not ceremonial celebrations of Galenic anatomy, not investigations of the human body. Indeed, only gradually did even Vesalius realize, and then only partially, that Galen's descriptions tended to be of the brain and body of the ox or barbary ape, rather than of humans. It is only with Vesalius's great work, "On the Fabric of the Human Body," that the structure of the human body began again to be studied systematically and directly.

Vesalius ridiculed the crude medieval drawings of ventricular localization of mental function, saying, "Such are the inventions of those who never look into our Maker's ingenuity in the building of the human body." Although largely accepting Galen's pneumatic physiology, he was modest about the potential of anatomy for understanding brain function: "How the brain performs its functions in imagination, in reasoning, in thinking and in memory . . . I can form no opinion whatso-

ever. Nor do I think that anything more will be found out by anatomy."

The reflex: From Descartes to Marshall Hall

René Descartes (1596–1650) combined Galenic physiology with a conception of the body as a machine to provide the first idea of reflex action. Within a nerve, Descartes thought, there are thin threads attached at one end to the sense organs. External stimuli pull on the threads to open little gates to the ventricles allowing pneuma to flow back out of the ventricles (reflected) through the same hollow nerves, causing movement by inflating the muscles. The flow of the pneuma is directed by the pineal gland, extending from the midline into the ventricles. In animals this is a strictly mechanical process. However, in humans, which unlike animals have a soul, the soul interacts with the body at the pineal gland and thus can influence the flow of pneuma to the muscles.

Thomas Willis (1621–1675), anatomist, physician, and Oxford professor, took this idea further and related it to actual brain structures. His *Cerebri Anatome*, illustrated by Christopher Wren, was the most complete description of the brain to that date. Sense impressions, Willis speculated, were carried by pneuma within the nerves to the *sensus communis* in the corpus striatum and then on to the corpus callosum and the cerebral cortex, where they were perceived and remembered. However, some were "reflected" back to the muscles by way of the cerebellum. Thus, voluntary movement was controlled by the cerebrum and involuntary, or "reflex," movement by the cerebellum.

The first actual experiments on neural mechanisms of reflexes were carried out by Robert Whytt (1714–1766) of Edinburgh. Using frogs, he showed that the spinal cord, indeed only a segment of the cord, was necessary and sufficient for reflex responses to stimulation of the skin. He also demonstrated that the pupillary reflex was dependent on the midbrain. He stressed, more than Descartes had, the protective function of reflexes. Whereas movement was strictly mechanical for Descartes, Whytt believed it was dependent on "sentient principle," even when involuntary or reflex, an idea that persisted into the 19th century.

The modern concept of a reflex largely began with the English physiologist and physician, Marshall Hall (1790–1857). He used Charles Bell and Francois Magendie's distinction of sensory and motor roots (1811, 1822) to develop the idea of the reflex arc. Reflexes were now, by definition, dependent on the spinal cord, independent of the brain, and strictly unconscious and involuntary. Hall also described the excitation or inhibition of reflex movements by various drugs. Finally, he was the first to use reflexes in medical diagnosis and treatment. The next significant development was C.S. Sherrington's.

Bioelectricity: From frog's legs to action potential

By the middle of the 18th century the stage was set for Galvani and the beginning of electrophysiology. The Leyden jar as a source of electricity and the electroscope to measure electricity had been invented, the electrical nature of lightning was known, and ideas about animal electricity were widespread among the intelligentsia. Using his frog nerve-muscle preparation, Luigi Galvani (1737–1798) produced muscle contraction by stimulation with an electrostatic machine, by atmospheric electricity, by hanging the frog's legs by brass hooks on an iron railing, and by placing the cut end of a nerve on the muscle. He interpreted these observations as reflecting intrinsic animal electricity. Alessandro Volta (1745–1827), on the other

hand, in a long and acrimonious controversy with Galvani, explained these and similar results as due to electricity produced by currents generated by two dissimilar metals and quite independent of any animal electricity.

Frederick von Humboldt (1769–1859) finally sorted out the controversy and demonstrated that Galvani was dealing with two independent phenomena, intrinsic animal electricity and bimetallic electricity. Carlo Matteucci (1811–1868) went a step further to detect current flow in muscle both with an electroscope and another nerve muscle preparation.

Soon after, Emil du Bois-Reymond (1818–1896) differentiated nerve from muscle current. Du Bois-Reymond's theory of electromotive particles lined up along the surface of nerve and muscle was further developed by his student Julius Bernstein (1839–1917) into the beginning of the modern membrane theory of the action potential. Further development awaited J.Z. Young's (1936) discovery of the squid giant axon and A.L. Hodgkin and A.F. Huxley's brilliant use of it to elucidate the biophysical basis of the action potential.

From globules to neurons

Cells were first described (in plants) by Robert Hooke (1635–1703) and in what he called nerve fibers by Anton van Leeuwenhoek (1632–1723), but it was not until the development of achromatic lenses and methods of embedding and staining in the middle of the 19th century that the study of the fine structure of the nervous system could begin. Until then, and even somewhat after, nerves were considered to be hollow as Galen had suggested, gray matter was made up of "globules," and the relationship between the fibers of white matter and globules was unclear.

Although M.J. Schleiden in 1838 pointed out that cells were the basic unit of plant life and T. Schwann in 1839 extended this idea to animals, the nervous system resisted an interpretation in terms of their cell theory for at least another 60 to 70

years. Even after R.A. Von Kolliker (1817–1905) demonstrated that nerve fibers came from nerve cells and O.F.K. Deiters (1834–1863) distinguished axons from dendrites, the nervous system was thought to consist of an interconnected network. Nerve cells were thought to be nodes of this reticular structure and the fibers originating from them to anastomose completely. J. Gerlach (1820–1896) is usually considered the founder of this reticular doctrine, and Camillo Golgi (1844–1926) its most famous advocate. Yet, by using Golgi's silver stain the great Spanish anatomist Salvador Ramón y Cajal (1852–1936) was able to demonstrate that each nerve cell with its dendrites and axon is an independent unit. This extension of cell theory to the nervous system is known as the *neuron doctrine*. Cajal further demonstrated that neurons come in a great variety of specific shapes that are characteristic of their location and often constant from animal to animal and species to species. When they shared the Nobel Prize in 1906, Golgi and Cajal's addresses were violent attacks on one another, and the reticular concept did not entirely disappear for a few more decades. Indeed, the definitive disproof of the reticular doctrine and confirmation of the neuron doctrine had to await the electron microscope.

See also Neuroscience, Biographies of Contributors (Appendix I); Phrenology

Further reading

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