The earliest descriptions of the anatomy of the skull base date to the ancient Egyptians and Greeks. It has been claimed that anatomy was born in ancient Egypt or at least was practiced there somewhat systematically, perhaps because of religious rituals involving preparation of the body and its organs for the next realm of life after death. Focusing on the earliest descriptions to the establishment of basic cranial, including the skull base, anatomy in ancient Egypt, this historical review tracks the very beginning of the anatomical journey that eventually formed the knowledge base underlying the success of the neurosurgical specialty of skull base surgery.

**Ancient Egyptian Medicine**

Among the most ancient civilizations, the Egyptians became renowned for the practice of medicine combined with what seems to be a lively inquiry into what might be considered the science or philosophy of the day. The caliber of Egyptian medicine is broadly recognized in numerous references in both modern and ancient literature. In The Odyssey Homer wrote that “for there [in Egypt] the earth, the giver of grain, bears the greatest source of drugs, many that are healing when mixed, and many are baneful, there every man is a physician wise above human kind.” Many kings of other surrounding ancient cultures sought medical advice from Egyptian physicians, often traveling far distances for personal attention. For example, Niqmaddu II, the king of Ugarit, asked the Pharaoh Akhenaten (1375–1334 BC) for an Egyptian physician. King Hattusili III of the Hittites asked Ramses II to provide him a physician to cure his sister, and even Cyrus the Great, the ruler who united the Medes and the Persians, requested an Egyptian ophthalmologist to treat an eye injury. It appears that even though there might have been ongoing international or cultural conflicts, such requests for services from an Egyptian physician were usually met with neutrality or immunity, even when a ruler would travel to Egypt or an Egyptian physician would travel to another country.

According to Breasted, the ancient Egyptians established categories for their physicians. Some of these ranks are recorded in the Edwin Smith Papyrus. The swnw were the “doctors of the people,” while the wabw were “cer-
The saw were guardians who obtained their education and training in the temple palace schools, some of whom reached the position that has been translated as “great palace doctors.” A junior doctor was considered a swnw. A senior doctor was called imy-r-swnw. The registrar was referred to as smsw-swnw. Consultants were called shd-swnw. Furthermore, each specialist had his own title. Importantly, a physician might reach a high rank or be highly regarded, but he was still expected to be available to the common people. The chief physician of the pharaoh was expected, more or less, to set the medical policy for the country.

**Head Anatomy in Ancient Egypt**

Preserved papyri include information that provides glimpses into Egyptian medicine. Egyptian physicians, at least those in roles of royal or ritual responsibility, seem to have been careful to record information on the diagnosis and treatment of various conditions, including head injuries. Other information (for example, methods of extracting the brain through the nose or mouth) appears to relate to the rituals of embalming, supporting a key part of the Egyptian view of the afterlife. Of the known papyri, about 30 relate to medical and magical health. Other sources about such Egyptian information include ostraca, shards or tablets with inscriptions, writings on the walls of tombs (Fig. 1), analysis of mummies, and writings from the Greek, Roman, and Arab civilizations. Among the earliest Egyptian records are those from early 3100 bc, when Manetho, an ancient Egyptian historian is said to have written, “Athothis [or Djer], his [that is, Menes’] son, for fifty-seven years built a palace at Memphis and his anatomical works are extant, for he was a physician.” According to Manetho, between 3100 and 2890 bc, Djer (or Athothis) wrote some of the earliest records on medicine, for example, two works called Practical Medicine and Anatomical Book, which may be the first practical and systematic studies of human anatomy. Although Manetho is consistently cited and what he recorded is reputable, none of his works, like Djer’s, has survived. Consequently, our knowledge of what the Egyptians understood about anatomy is mostly drawn from surviving papyri and ostraca. For example, the Ebers papyrus, which includes paragraphs on anatomical structures referred to as metu (plural of met, which has no equivalent in English but can mean arteries, veins, ducts, tendons, or even nerves), states that there are metu to the back of the head, to the forehead, to the neck, to the eyes, to the eyebrow, to the nose, to the temples, and to the head. Altogether, about 52 metu are described in this papyrus.

The Ebers papyrus also describes human anatomy with more emphasis on the head (paragraph 854g). In this section, 2 metu that supply the nostrils and 4 metu from the temples that supply the eye are well described. Another paragraph (856g) from the same papyrus mentions that 2 additional metu independently supply the eyes, 1 met for each eye. This statement could refer to the optic nerves because the small ocular vessels could easily have escaped notice. According to Egyptian beliefs, there was a met to the right ear, where the breath of life entered the body, and a met to the left ear, where it was believed the breath of death entered the body.

Compared with many cultures, ancient Egyptians placed a high value on preserving the condition of the human body after death because they believed that the same body would accompany them in the afterlife. However, this belief created a barrier when it came to dissecting human bodies for study. Although their mission was purely ritual, embalmers, apart from physicians, possessed knowledge of human anatomy so they could remove the internal organs of the dead and preserve them for further use in the afterlife. Embalmers were trained to approach the human organs with procedures that avoided disfigurement. In fact, Egyptian embalmers were the first individuals in history to purposefully encounter and evaluate the brain through the nasal cavity without having to break through the hard bone of the skull and disfigure it (Fig. 2). This procedure should not be interpreted as transphenoidal surgery. Rather, it was simply a transnasal or transbasal extraction of brain tissue. While some extractions of brain tissue appear to have been accomplished through relatively small and refined approaches, such as through one nasal cavity, or off to the side of the maxillary region, others produced large, more destructive holes at the skull base.
Extraction of the brain was a method practiced not by physicians but by embalmers for a practical means of removing the brain. In addition, in some crania it can be observed that there was preservation of the falx or tentorium, while in others these structures were completely destroyed. In some cases, radiographic scans of cranial vaults appear to show dependent material. It is unknown whether this material is incompletely extracted brain tissue or perhaps other liquid material such as that used for embalming. The brain extraction procedure had no therapeutic implications in life, and there was no aim to preserve brain tissue after death. However, it seems that fine-tuning the approach to remove the brain had exquisite utilitarian purposes in the afterlife, that is, the preservation of skull and facial features to make it easy for the soul of the deceased person to recognize its body by being able to view its face in the afterlife.

Postmortem procedures to extract the brain via a transnasal route date to the Old Kingdom (2686–2181 BC). The practice became more popular during the Middle Kingdom (2080–1773 BC) and the New Kingdom (1550–1070 BC). Unfortunately, the primary written accounts of this practice did not survive. These procedures would not have been performed by physicians but by embalmers or participants in ritual preparation of the dead body. Thus, although the papyri describe ailments and diagnoses for physicians, these sources would not have included this procedural information for ancient Egyptian physicians because it was not part of their practice needs. The oldest available document describing the procedure belongs to Herodotus. He reported that the brain was removed via an approach similar to the transnasal approach, leaving the falx cerebrum and tentorium in place. Apparently, the bone at the superior aspect of the nose was perforated, and a curved hook (Fig. 3) was inserted into the nasal cavity to create a defect about 2 cm in diameter. This technique easily allowed extraction of the contents of the anterior and middle cranial fossae. The contents of the posterior cranial fossa were extracted by enlarging the foramen magnum.

The ancient Egyptians also practiced variations in their technique of brain extraction. After a few days of death, the brain would likely have begun to deteriorate and liquefy, unlike other solid organs that were extracted, preserved, and placed in containers. Perhaps the brain was the first organ to be removed. Some mummies that have been analyzed using modern imaging techniques show evidence that the brain was sometimes removed from the left side of the face and sometimes from the right, sometimes via a transnasal approach, and sometimes via a more transethmoidal approach. The mummy of Djehutynakht represents an example of the latter approach. This mummy shows evidence that the ethmoid air cells were completely destroyed. Several other mummies show similar variations with defects in the ethmoidal sinus while the sphenoid sinus remains intact.

These extractions should not be assumed to be surgical, precisely targeted to preserve the sinuses, or resembling modern minimally invasive approaches; they were utilitarian anatomical procedures. It is generally believed that hook-like instruments were used to pierce bone and pull out brain tissue, dura mater, and other tissues. Scoop instruments were probably also used to extract the brain. There are those who believe that stirring the brain with...
a hook would allow the brain tissue to run out, but those familiar with anatomical preservation methods know that brain tissue rarely runs out and certainly does not do so through relatively small or restricted approaches. More likely it was scooped or even washed out with the aid of special caustic or dissolving fluids through catheters or even specula.

New radiological studies of mummies have improved our understanding of this procedure (Fig. 4). For example, the mummy Djedmaatesankh had the brain removed transnasally from the right side through a defect in the anterior right ethmoid air cell, while the nasal septum, conchae, and left and posterior right ethmoidal air cell walls were left intact. The Lady Hudson mummy had the brain removed through defects in the left ethmoid sinus and the paries medialis orbitae. Damage to the sphenoid sinus wall is also visible. The Pa-Ib mummy had defects in the right ethmoid sinus, the paries medialis orbitae, and the upper part of the sphenoid. These defects were believed to be the approach used to remove the brain. Interestingly, the mummy Hatep-Bastet had intact sphenoid and ethmoid sinuses, conchae, and nasal septum, although the brain appears to have been removed. In this case, it is thought that a transforaminal approach through the foramen magnum was used.

These variations are evidence that Egyptian embalmers had reasonable knowledge of skull base anatomy so that they could use different approaches for extracting the brain. It appears that the approach depended on the preference of the embalmer, who would have gained much working familiarity with such anatomical regions, just as the embalmer knew about the removal of other solid organs. How the embalmers conceptualized the skull base anatomy is unknown, but they must have had terminology for the structures relevant to the procedures so that they could teach the procedures to new or apprentice embalmers. The approach and its extent may also have depended on the social, ceremonial, or religious status of the deceased. Using lateral ethmoidal approaches, approaching through the foramen magnum, or performing a unilateral nasal-sphenoid approach appears to have been known to preserve the face and structure of the nose and thus probably had aesthetic implications for the deceased, both in this world and in the next.

It is thought that the ancient Egyptians believed that the heart, rather than the brain, was the organ responsible for emotions and intelligence. The brain was not regarded as the seat of the soul. Rarely was the brain even observed except in cases of severe open head injury. Even then it would not have been seen in its more normal solid state; rather, it would have been in a state similar to the unformed semisolid piecemeal contents extracted through the nose. Furthermore, *The Papyrus of Ani (The Book of the Dead)*, an ancient name for a funeral text, recounts that the dead pharaoh will be assisted by Osiris (the god of resurrection) to replace his head with the...
Skull base anatomy in ancient Egypt

head of Tem (a god that symbolizes completion). By the end of the journey, the head is to be filled with the brain (white crown). Therefore, the embalmers did not attempt to preserve the brain because they believed it would be replaced with a new one: "Menu is Horis, the Advocate of his father [Osiris], and his coming forth means his birth. The two plumes on his head are Isis and Nephthys, when these goddesses go forth and set themselves thereon, and when they act as his protectors, and when they provide that which his head lacketh." Another passage states, "I have come into thee, to the house wherein food is brought unto me. O Smam, I have come into thee. My heart watch-eth, my head is equipped with the White Crown. I act as the guide of the celestial beings." 

The well-known Edwin Smith Papyrus is considered the oldest surgical text. It describes 48 surgical cases, 27 of which are related to head injuries. It is believed that this papyrus was found in the tomb of a physician and that it was written by Imhotep (2655–2600 BC), who served under the King Djoser. Imhotep was an architect, king’s advisor, and one of the earliest recorded physicians (Fig. 5). He founded a medical school in Memphis, where he treated patients. The papyrus includes considerable anatomical knowledge and nomenclature, importantly including descriptions of hard cranial anatomical contents and bone structures, such as a name for the occiput (ha). Another region called the gema is mentioned in Case 18 of the papyrus: “His gema’ (temple): the region thereof between the corner of his eye and the orifice of his ear, at the end of his eye and the orifice of his ear, at the end of his mandible,” appears to describe the zygomatic bone. Another interesting structure was described in Case 7: “As for perforating the tepau [of his skull], it is what is in between shell and shell (papyt) of his skull. The tepau are of leather (or hide).” Tepau could have several interpretations. In 1992 Westendorf suggested that it referred to the falx cerebri. In 1930, however, the American Egyptologist James H. Breasted favored the cranial sutures as the proper interpretation. In Case 6 of the papyrus the dura mater was described as the membrane enclosing the head, and the cerebrospinal fluid was named as “the fluid of the interior of the head.” The papyrus also named the nasal cavity (shetyt) and described it as the chamber of the nose.

Rise of the Greek Empire in Ancient Egypt

Egyptian civilization began to weaken by the end of the 26th dynasty (685–525 BC) as the Egyptians struggled with the Persians. Finally, in 332 BC Alexander the Great conquered Egypt as part of his conquest of the Persian Empire. During this period, the father of medicine, Hippocrates (460–370 BC), accumulated considerable anatomical knowledge of the brain as mentioned in his collections Corpus Hippocraticum, which includes about 70 medical works. For example, one description of the brain from the corpus is as follows: “The brain of man, as in all other animals, is double, and a thin membrane divides it through the middle.” Another example states that “the same thing applies to the membrane which surrounds the brain: for when, by sawing the bone, and removing it from the meninx, you lay the latter bare, you must make it clean and dry as quickly as possible, lest being in a moist state for a considerable time, it become soaked therewith and swelled; for when these things occur, there is danger of its mortifying.” Whether Hippocrates himself wrote the corpus remains a mystery. The volumes may have been produced by his students and followers who practiced medicine and dissections in Egypt.
Compared with the earlier papyri, the Hippocratic writings exhibit an improved understanding of brain function and anatomy.\textsuperscript{30,34} The corpus attributed primary control of the body’s function to the brain, which was likely based on direct observations of injuries or maladies affecting the head: “For this reason I consider the brain to be the most powerful organ of the man’s body for when it is healthy it is our interpreter of the impressions produced by the air; now, the air gives intelligence. The eyes, the ears, the tongue, the hand the feet, act according to the brain’s understanding; in fact, the whole body participates in the intelligence in proportion to its participation in the air; now, the brain is the messenger for the intelligence.”\textsuperscript{23} The Hippocratic writings also tracked the arterial supply of the brain to the carotid arteries: “The remaining part of it rises upward across the clavicle to the right side of the neck, and is superficial so as to be seen; near the ear it is concealed, and there it divides its thickest, largest, and most hollow part ends in the brain.”\textsuperscript{23}

In 332 BC, Alexander the Great conquered Egypt as part of his conquest of the Persian Empire. Including the entire Persian Empire, Alexander’s dominion was composed of Anatolia, Syria, Phoenicia, Judea, Gaza, Egypt, Bactria, and Mesopotamia and extended as far as Punjab and India. His conquests opened communication and the exchange of culture and knowledge over a vast region previously composed of largely hostile neighbors. The Egyptians welcomed Alexander as a man who would free them from Persian rule. Once he entered the capital Memphis, he declared himself as the legitimate successor of the pharaohs. Nonetheless, he seemed to have allowed the resident cultures to flourish.\textsuperscript{13}

Alexander stayed in Egypt for about a year and founded the city that bears his name, Alexandria. For a time, because of its library and museum, this city harbored the greatest concentration of the world’s recorded knowledge, not only in holdings of writings, but also in attracting philosophers, teachers, and those who can be called early scientists. Alexander founded this city on a site that was well known to the Greeks, as described by Homer in \textit{The Odyssey}: “There is an island called Pharos in the rolling seas off the mouth of the Nile, a day’s sail out for a well-found vessel with a roaring wind astern. In this island is a sheltered cove where sailors come to draw their water from a well and can launch their boats on an even keel into the deep sea.”\textsuperscript{25}

Alexandria is where the systematic study of anatomy appears to have begun, and in those efforts we find evidence of investigation of the cranium. The Musaeum, or Mouseion at Alexandria, which included the Royal Library of Alexandria, was founded by Ptolemy I Soter (323–283 BC) or by Ptolemy II Philadelphus (283–246 BC)\textsuperscript{26} and was continuously supported by the Ptolemaic royal family (Ptolemy III is credited with founding a smaller library nearby).\textsuperscript{1} The Library, at one time holding perhaps as many as 700,000 texts, was a part of the Mouseion. Rather than being simply a museum, it was an institution for the best scholars of the Hellenistic world. Archimedes, Aristarchus of Samos, Callimachus, Euclid, Herophilus, Erasistratus, Pappus, Hero, and others performed what appear to be well-organized scientific investigations and active education. They were supported with meals, rooms, and servants, and the facility was overseen by an administrative priest of the pharaoh.\textsuperscript{9}

Mouseion facilities were located in several parts of Alexandria, including theaters, lecture halls, gardens, roofed walkways, residential quarters, a communal dining room, and several private study rooms where scholars shared ideas, studied, conducted research, and were supported by servants, staff, and scholars (perhaps as many as 1000 lived in the campus-like facility), as noted by Bagnall (Fig. 6).\textsuperscript{3,6} We can infer that there was at least some space specifically devoted to the study of anatomy, where the first documented and detailed human and animal dissections, including those of the brain and skull base, were performed.\textsuperscript{22} "Doubtless the Egyptian of the period considered the work of the Ptolemaic anatomists an unspeakable profanation, and, indeed, it was nothing less than revolutionary—so revolutionary that it could not be sustained in subsequent generations. . . . [T]he great Galen, at Rome, five centuries after the time of Herophilus, was prohibited from dissecting the human subject."\textsuperscript{22}

The Mouseion and Library flourished until about the time of the Roman conquest of Egypt in 30 BC or perhaps later in AD 272, when, under the orders of Aurelian, a section of Alexandria (the Bruchion, or palace quarter, along the beautiful coastline) was burned.\textsuperscript{18} Destruction of the Mouseion and library appears to have occurred over centuries and at the impetus of various people or groups.\textsuperscript{18} As with most ancient locations in cities, stones and blocks of the destroyed Mouseion and library were used to construct other buildings that now reside over the ancient structures. Today, it is difficult if not impossible to exactly locate the original structures. Visiting the beautiful coastline of Alexandria today, one can only imagine the grandeur and revolutionary exploratory spirit that must have pervaded the area.

Of significant impetus to the study of anatomy was the establishment of a medical school in Alexandria around the end of the 3rd century BC.\textsuperscript{37} The medical school was probably integrated into studies at the Mouseion and may have even been part of it. It is in Alexandria that Aristotle’s notions on biology were first challenged. We can trace systematic anatomical studies of the cranium, even of the skull base, and the beginnings of definitions of the origins of cerebral arteries and nerves to several key figures who performed their work in Alexandria at the medical school and the Mouseion.

The next sections of this article review the work of Herophilus, Erasistratus, Rufus, and Galen with regard to cranial anatomy and their significant tenures in Alexandria. No other ancient center had as much influence on the knowledge of medicine and anatomy as Alexandria.

\textbf{Herophilus of Chalcedon: 335–280 BC}

Herophilus was born in Chalcedon, a settlement on the Bosporus, directly across from ancient Byzantium. As a teenager, he moved to Cos where the medical faculty formed by Hippocrates was located. At this time, Hippocrates had been dead for more than 60 years. Nonetheless, he greatly influenced Herophilus’ work.\textsuperscript{1}
After completing his medical education, Herophilus traveled to Alexandria in 300 bc at about the same time that the city had become fully equipped to support medical education. It was there that Herophilus, along with his contemporary Erasistratus, was able to perform systemic dissections and vivisections on humans and animals, because Ptolemy I and Ptolemy II had authorized vivisections of criminals sentenced to death. In fact, Herophilus often performed such vivisections publicly so that he could better demonstrate the effects of his methods. This practice on live humans was occasionally opposed by religious and moral beliefs. Cornelius Celsus wrote as follows:

Moreover, since both pains and various types of diseases arise in the internal parts, they [scil. the "Rationalists"] think that no one who is ignorant of these parts can apply remedies to them. It therefore is necessary to dissect the bodies of the dead and to examine their viscera and intestines. Herophilus and Erasistratus, they say, did this in the best way by far when they cut open people who were alive, criminals out of prison, received from kings. And while breath still remained in these criminals, they inspected those parts which nature previously had concealed, also their position, color, shape, size, arrangement, hardness, softness, smoothness, connection, and the projections and depressions of each, and whether anything is inserted into another thing or receives a part of another into itself. For, they say, when pain occurs internally, it is impossible for one who has not learned in which part each internal organ or intestine lies, to know what hurts the patient. Nor can that part which is ill be treated by one who does not know what it is. And when a person’s viscera are exposed by a wound, one who does not know the color of an [internal] part in its healthy state, cannot recognize which part is intact and which damaged; thus he cannot even come to the aid of the damaged parts. External remedies also can be applied more suitably by people acquainted with the positions, shapes, and size of the internal parts. . . . Nor is it cruel, as most people maintain, that remedies for innocent people of all times should be sought in the sacrifice of people guilty of crimes, and of only a few such people at that.

Celsus and later Tertullian remarked that Herophilus vivisected at least 600 live prisoners.

Herophilus contributed to the knowledge of brain anatomy as he dissected the ventricles, choroid plexus, venous sinuses, arachnoid, cranial nerves and their foramina, and many other neuroanatomical structures. He named certain structures of the brain based on their shape, for example, the cerebrum (encephalon), cerebellum (parencephalon), torcular herophili, calamus scriptorum, and choroid plexus. He described the bones forming the skull, the intervening sutures, and the membranous coverings of the brain. He described the lower brainstem and spinal cord as one structure he referred to as "spinal marrow." Herophilus and Erasistratus established the importance of the brain and the sensory and motor functions of the nerves.

According to Galen, Herophilus was the first to describe the connection between the cerebrum and cerebellum through the ventricular system and the structural distinction between the cerebrum and cerebellum. Herophilus extensively studied the lateral, third, and fourth ventricles because he thought they were part of the seat of the soul. He also described the inner lining of the ventricles as "choroid meninx or choroid twisted clusters." Galen writes about Herophilus’ description of the venous sinuses: "At the crown of the head the folds of the membrane [sinus transversus] that conduct the blood come together into a common space like a cistern, and for this very reason it was Herophilus’ custom to call it "wine vat" [torcular herophili]. From this point, as from some acropolis, they [sinuses] send forth canals to all the parts lying below them. Herophilus not only named the confluence of sinuses (torcular herophili), but he also compared it to the confluence in the ox, noting that it divides evenly in the ox but unevenly in humans.

When describing the human cranial nerves, Herophilus and Marinus (a contemporary who lived ad 70–130) debated the number of cranial nerves, especially the low-
Erasistratus contributed to physiology and functional research. He described the cavity in the floor of the fourth ventricle as the calamus scriptorius (calamus means “reed pen”) because this cavity resembled the groove of a writing pen. A consequence of sinuses in the skull was originally named torcular herophili after him.

Erasistratus differentiated between nerves and blood vessels and discovered the differences between motor and sensory nerves. He believed that the sensory and motor nerves exited the brain and that neural transmission occurred by means of the pneuma, which was thought to be a substance that flowed through the arteries along with the blood. Although Herophilus stated that diseases occurred when an excess of one of the four humors impeded the pneuma from reaching the brain, it is clear that he studied the base of the brain and the cranium in detailed fashion to make such observations.

Erasistratus pioneered the physiology of nerves, considering them responsible for voluntary movement. He possessed a considerable amount of knowledge on at least seven cranial nerves: the optic, oculomotor, trigeminal, motor root of the trigeminal, facial, auditory, and hypoglossal nerves. According to Galen, Herophilus called the optic nerve “conduits” because it displays visible channels for the passage of animal spirits. Herophilus also mentioned a single nerve that has three roots coming from the brain. This nerve was further explained by Galen as the glosopharyngeal, accessory, and vagus nerves “wrapped” together in one sheath. Herophilus described the structures entering the eye as two large nerves (V1 and optic) and a smaller one (oculomotor). He also first described the styloid process, naming it after stylois, a pen used in Alexandria to write on wax paper. He also compared it to the famous lighthouse on the Island of Pharos (Fig. 7). Herophilus also studied the blood vessels at the base of the brain, which were named rete mirabile. Unfortunately, none of the detailed writings of Herophilus survive, although many of his contributions were mentioned and confirmed by later historians or physicians.

Erasistratus also introduced many of the scientific terms used to this day to describe anatomical phenomena. He was among the first to introduce the notion of conventional terminology, as opposed to the use of “natural names.” He created terms to systematically describe the objects of study, named them for the first time, and established nomenclature so that there was some uniformity for study and description.

**Erasistratus of Chios: 304–250 BC**

Erasistratus was a well-known physician born on the island of Chios. He worked with Herophilus, and some believe that he continued Herophilus’ work after his death. Together, they contributed considerably to medical investigations and teaching in Alexandria. While Herophilus was very talented in describing human anatomy, Erasistratus contributed to physiology and functional anatomy. Erasistratus received his medical education in Athens. It is believed that he came from a family of doctors, although Pliny records that he was a grandson of Aristotle through his daughter Pythias.

Erasistratus became famous when he cured the disease of Antiochus, the son of King Seleucus, Nicator I of Syria, to whom he had served as a courtier. Erasistratus is famed for his interaction with the aged King Seleucus, who married a young woman (Stratonice). She was so beautiful that Antiochus fell ardently in love with her. Because Stratonice was his mother-in-law, however, Antiochus hid his passion and pined away in silence. Physicians were unable to determine the cause of Antiochus’ disease. Even Erasistratus himself found nothing wrong with Antiochus’ body until he noticed that whenever Stratonice entered the room, Antiochus’ skin would become hotter, his color would heighten, and his pulse would increase (Fig. 8).

Erasistratus began to think that Antiochus’ disease was in his mind and suspected that he might be in love. Erasistratus told the king that his son’s malady was incurable because he was in love and that it was impossible for his passion to be gratified. The king asked Erasistratus with whom his son was in love, to which Erasistratus (untruthfully) replied, “My wife.” Erasistratus then inquired whether the king would be willing to give up his own wife if the object of his son’s affection was Stratonice. The king was willing to do so to cure his son. Erasistratus then told the king that his son was indeed in love with Stratonice. The king not only gave up Stratonice, but he gave his son several provinces of his empire to rule. Erasistratus received 100 talents for restoring the prince’s health, which could be a record for the largest sum ever received for a medical fee.

Erasistratus moved to Alexandria and worked with his contemporary Herophilus in medical teaching and anatomy. Erasistratus wrote extensively on anatomy, practical medicine, and pharmacy, although we know only the titles of his works. Galen, Caelius Aurelianus, and others record many of the shorter fragments of Erasistratus’ writings. In fact, Erasistratus may be called the father of ancient anatomy because of the celebrated systematic observations that he recorded. For example, he appears to have been very close to discovering the circulation of the blood: “The vein arises from the part where the arteries, that are distributed to the whole body, have their origin, and penetrates to the sanguineous [or right] ventricle of the heart; and the artery [or pulmonary vein] arises from the part where the veins have their origin, and penetrates to the pneumatic [or left] ventricle of the heart.”

Erasistratus’ observations were only surpassed much later in the 17th century by William Harvey. Erasistratus was a talented observer. He noticed that all veins and arteries arise from the heart but believed that they carried air. He described the ventricular system of the brain much as it is known today: “I investigated the nature of the brain. . . . And it had a ventricle placed longitudinally on each side, and these were pierced through into another one at the junction of the two parts. This one extended to the so-called cerebellum, where there was another, smaller ventricle, each side walled off by membranes; for the cerebellum was set off by itself.”
Erasistratus differentiated between motor and sensory nerves, although he thought that they were hollow and carried a kind of animal spirit. When carried to the muscle (through motor nerves), this animal spirit caused the muscle to balloon and shorten. So Erasistratus explained muscle contraction. He thought that the sensory nerves arose from the membranes covering the brain and that the motor nerves arose from the brain matter itself. Rufus of Ephesus wrote, “According to Erasistratus there are two kinds of nerves, sensory and motor nerves; the beginning of the sensory nerves which are hollow, you could find in the meninges of the brain, and those of the motor nerves in the cerebrum [enkephalos] and in the cerebellum [prenkephalos]. According to Herophilus on the other hand, the neura that make voluntary motion possible have their origin in the cerebrum [enkephalos] and spinal marrow, and some grow from bone to bone, others from muscle to muscle, and some also bind joints together.”

Erasistratus followed certain nerves from their origin to their target organs: “All the processes of the nerves were from the cerebrum; and, in brief, the brain appeared to be the origin of the nerves of the body; for the sensation which comes from the nostrils reaches this opening [olfactory plate?], likewise coming from the ears. Processes were also carried from the brain to the tongue and eyes.” With these words, Erasistratus corrects his previous thoughts about the sensory nerves originating from the meninges. Rather, he states that all nerves originate from the brain matter.

From his studies we can be certain that Erasistratus was a careful observer and dissector of the skull base and base of the brain. At the time, this was a remarkable accomplishment given that the brain tissue or crania were probably not preserved in any manner. These investigations must have resulted from vivisections or dissections performed soon after the death of his subjects. One can only imagine the team of Herophilus and Erasistratus in what must have been a filthy, bloody, fly-ridden scene probably performing demonstrations in an outdoor portico or courtyard for light. We would regard such demonstrations as nothing short of horrid. However, for the ancient Alexandrians, death, perhaps even gruesome death, was a familiar part of everyday life. Such events would have been regarded as the most progressive education of the period to which students flocked from all over the Mediterranean world.

Erasistratus provided a clear distinction between the cerebrum and cerebellum and viewed the brain as the source of intelligence. He compared the human brain with the brains of other animals and concluded that the
greater the number of convolutions, the greater the intelligence: “the Cerebrum was constructed from even more and differing foldings. From this the observer may learn that as in those animals that surpass the others in speed of running such as the stag and hare, well constructed with muscles and nerves also for this, so also, since the man greatly surpasses other beings in intelligence, his brain was greatly convoluted.”14 Interestingly, Erasistratus was interested in knowing the blood supply of the nerves, introducing the idea that the nerves had small veins that supplied them with nourishment and that these veins varied according to the size and territory of the nerve. If a nerve had a rich supply around it, it did not need an independent supply.

Together, Herophilus of Chalcedon and Erasistratus of Chios defined considerable skull base anatomy, which opened the door to future discoveries. Because they were contemporaries, one cannot be mentioned without the other. Despite the reputation and outstanding medical education offered by the medical school in Alexandria, most of their work and that of the ancient Egyptians were stored in the Royal Library of Alexandria. In 48 BC, however, Julius Caesar burned this library,15 perhaps accidentally, during his war on Alexandria. The fire that Caesar had set to destroy the Egyptian fleet extended from the dockyards to the library, which at that time housed almost 500,000 scientific and historical scrolls among others. This loss may account for the subsequent fragmentation of medical knowledge and explain why most of the information that is now known dates from later historians. After Herophilus and Erasistratus, no one contributed as much to the field of neuroanatomy for nearly 3 centuries until Rufus of Ephesus came to Alexandria.12

Rufus of Ephesus: AD 80–150

Rufus of Ephesus, a Greek physician, was thought to have been born in Ephesus, on the west coast of Asia Minor. In his later years he returned to Ephesus, from which he takes his moniker. However, the young Rufus studied and practiced medicine in Alexandria (http://www.faqs.org).10 Unlike his contemporary Soranus or later Galen, Rufus never lived in Rome. Instead, he spent a considerable amount of time in Egypt, where he continuously wrote about life there. He described several of its endemic diseases such as filariasis and other worm infestations and commented on the general state of health of the Alexandrian citizenry. According to historians, Rufus wrote most of his anatomical books while in Egypt, where he received anatomical training. He was convinced that studying anatomy was crucial to understanding diseases. More than 90 medical works are attributed to him. A few of his works were preserved in Latin. However, the legacy of his studies originates from the translation of most of his books into Arabic. The fate of his works and reputation is bound up with that of Galen and Galenism. In typical fashion, although praising him, Galen does not refer to Rufus directly and took direct issue with him only rarely. To gauge the contribution of Rufus, one must access the compilers of later Greek medical encyclopedias, Oribasius, Aetius, and Paul of Aegina, all of whom often cited Rufus at length. For the Byzantines, Rufus was one of the four great names in their medical literature. In medieval literature, Rufus was subsumed under the reputation of Galen, even to the extent that his philosophy, studies, and writings were credited to Galen. Recent interest in the Arabic sources has vindicated and reinvigorated knowledge of his contributions.

Rufus contributed greatly to the anatomical nomenclature, especially in his book On Naming of the Parts of the Body. During his life, unlike those of Herophilus and Erasistratus,33 dissecting the human body was no longer permitted in Alexandria. It is rumored that Rufus was disappointed with the prohibition on dissecting human bodies. He therefore dissected monkeys and pigs instead. Alexandria must still have been a center of medical and anatomical education during his lifetime. He was a contemporary of Statilius Crito, who was chief physician and procurator to the emperor Trajan (AD 98–117). In his prologue to the Canterbury Tales, Geoffrey Chaucer (1342–1400) named Rufus among the great physicians.

Although Rufus explained the brain much like his predecessors Herophilus and Erasistratus, he was the first to introduce the fact that the brain, spinal cord, and nerves are composed of the same substance, while simultaneously distinguishing them as separate anatomical entities. Previously, it was thought that they were connected together:14

The marrow [spinal cord] arises from the brain and escapes through the hole of the cranium at the occiput [foramen magnum] and descends as far as the base of the spine through all vertebrae; it is not a special substance but an extension from the brain; it is called the marrow of the back. Nervous channels [nerves] which are distributed to sense arise and emerge from the brain: for example, to the ear, to the nose, and to other sensory parts. One of these processes comes off in front from the base of the brain, is divided into two branches [optic nerves], and inclines towards each of the eyes in the part called the basin or cavity of vision, in the form of a fossa, and which is found on each side of the nose.

To permit such comparisons, the tissue he studied must have been relatively fresh. Rufus described the optic nerve in more detail than previous anatomists. He was a very well-respected physician and anatomist who named many body parts. In terms of skull base anatomy, he described the color of the brain and mentioned that two layers covered the brain: a freely mobile outer layer and an inner layer fixed to the brain. His writings mention the carotid vessels and explain that the name, carotid, derives from the process which emerges from the mastoid region and orifice under the name karoein: “when it is compressed the individual goes to sleep.”58

Galen of Pergamon: AD 129–199

Galen, a Greek physician, surgeon, and philosopher, has garnered the greatest reputation of all physicians of ancient times. He came from a wealthy family. His father, an architect, died when Galen was 19 years old, leaving his fortune to his young son. Following the Hippocratic teachings, Galen traveled to Smyrna, Corinth, Crete, Cilicia, Cyprus, and finally to the great medical school of Alexandria to learn medicine.4,15,32 He stayed in Alexandria until he was 28 years old.
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He returned to Pergamon as physician to the gladiators of the High Priest of Asia, who was the wealthiest man in Asia at that time. Galen is said to have acquired this position after he eviscerated an ape in front of the priest and challenged other physicians to repair the damage. The physicians refused. Galen performed the surgery by himself and in so doing won the favor of the High Priest of Asia.

Galen learned most of his anatomical knowledge through dissections of apes and pigs because he studied in Alexandria during the period when human dissections were no longer allowed. This is considered to be one of the reasons why distortions of anatomy are apparent in his writings. Based on the content of his writings, however, it is strongly believed that he participated in human dissections while living in Egypt. His knowledge of human anatomy was probably reinforced through trauma cases he attended to as physician to the gladiators. The basis of the anatomical education that he received in Alexandria certainly served him well in subsequent years.

Galen is responsible for some of the most voluminous medical writings of ancient times. In his work, he presented extensive arguments directed against Aristotle, who claimed that the brain came second to the heart. Aristotle thought that the brain's main function was to cool the heart through phlegm produced by the brain. Galen opposed this concept. He clearly explains that the brain is the primary organ in the body that controls all vital activities, and when it is injured or compressed, individuals lose sensation and movements: “If you press so much upon a cerebral ventricle that you wound it, immediately the living being will be without movement and sensation, without spirit and voice.”

Galen’s work showcases the extent of neuroanatomical knowledge at that time. He understood that it is impossible to ignore the function of the brain because it had connections to all parts of the body, especially to the sense organs near the brain. Like his contemporaries, he described the meninges and mentions that the inner membrane enclosed many arteries and veins as it followed the sulci of the brain (arachnoid).

Galen also tracked most of the cranial nerves. But, said Aristotle, all the organs of the senses do not abut on the brain. What is this language? I blush even today to cite this statement. Does not a considerable nerve enter into one and the other ear with the membranes? Does not a part of the brain descend to each side of the nose [olfactory nerves], even more important than that which goes to the ears? Does not each of the eyes receive a soft [sensory] and a hard [motor] nerves, the one inserting at its root, the other on the moving muscles? Do not four of them go to the tongue, two soft ones penetrating by the palate [hypoglossal?], two hard ones descending through the ear [chorda tympani]? Thus, if one must put faith in one’s eyes and touch, all the senses are in relationship with the brain. Shall I announce the other parts that enter into the structure of the brain? Shall I say what use is provided by the meninges, the reticular plexus [rete mirabile], the pineal gland, the pituitary body, the infundibulum, the lyre [fornix], the vermiform eminence [vermis], the multiplicity of the ventricles, the openings by which they communicate with one another and the variety of configurations, the two meninges, the processes that go to the spinal marrow, the roots of the nerves that abut not only on the organs of the senses but also on the pharynx, on the larynx, the oesophagus, the stomach, and all the viscera and all the intestines, and go to all the parts of the face? Aristotle did not attempt to explain the use of any of these parts… but the brain is the source of all the nerves.

Since the Alexandrian anatomists had first mentioned the name rete mirabile (attributed to Herophilus), no description of the blood vessels of the brain was known until the time of Galen. He described the blood supply of the brain as follows:

That plexus called reticular by anatomists, the plexus that embraces the [pituitary] gland itself and extends for a great distance posteriorly, is the most remarkable of the bodies found in this region. Indeed, it extends over almost the whole base of the brain. This network is not simple; one might say [it is] like the many threads of fishermen’s nets placed one upon the other. But this naturally occurring net has the special quality that the meshes are so attached to one another that one would find it impossible to remove one of the threads without the other. If one of them is lifted up they are all lifted at the same time because they are all held together and attached to each other. No threads produced by the hand of man can compare with them in delicacy of composition or density of network. Moreover, its formation is no ordinary matter; the largest part of the arteries ascending from the heart to the head [carotid] has been employed by nature for this admirable network. Little branches are given off from these [carotid] arteries to the neck, face, and external parts of the head; all the rest, ascending in a straight line from their source, and mounting towards the head though the thorax and neck, are favorably gathered in that part of the cranium which, pierced with holes [carotid canal], allows them to pass without danger into the interior of the head.

It is impossible for Galen to have described the rete mirabile in such detail without his having repeatedly dissected the base of the brain and floor of the cranium to become intimately familiar with this cranial anatomy.

Galen detailed the course of the carotid artery as it is pierced and divided by the dura mater. He never provided names for these branches but stated the following:

They are first divided into a great number of very small branches in the region between the skull and dura mater then traveling, some to the anterior part of the head, some to the posterior, some to the left side, some to the right, and interweaving, they give the impression that they have forgotten their route in the brain. But that is not all the case. In fact, all these numerous arteries come together again and unite like the roots of a trunk and form another pair of arteries like those that have already given birth to the network these latter arteries then penetrate into the brain by holes in the dura mater.

Galen also explained the venous system in great detail. He mentioned the different sinuses and their anatomical distributions; the great cerebral vein; and the dural folds, including the falk cerebrum, falk cerebellum, and tentorium. That he used fresh brains or even vivisected brains is obvious given that he also described how to dissect the human brain.

It is then desirable to dissect the brain itself, beginning with the membranes dividing the anterior part [falk cerebrum]. When you have dissected or torn away from this the origins of the veins that extend laterally, beginning with the forward termination, raise it up with your fingers until you reach that large vein [great cerebral?] which extends from it and which we have said is carried deep downwards. Again raising this upwards, give it to someone to hold, and then you yourself loosen it along its length and gently separate it with your fingers.

Galen extensively described the relationships among
the brain, spinal cord, and cranial nerves. He believed that there were three kinds of nerves: sensory, motor, and hard nerves (tendons), which travel from bone to bone. He also described the spinal cord and numerous different levels of spinal cord injuries: “After the incision, in all the nerves which lie below the place where transaction has been made, both the two potentialities are lost, I mean the capacity of sensation and the capacity of movements. . . . Hence from the anatomy of nerves, you can easily infer the derangement.”14 The Alexandrian anatomists regarded the human cerebellum and the fourth ventricle as very important structures, and Galen agreed. He even considered the cerebellum as the source of motor function in association with the spinal cord. He claimed that the vermis acts as a valve to regulate the flow of the animal spirit through the ventricular system. Galen’s extensive contributions provide a solid basis for understanding the extent to which skull base anatomy had been investigated in Egypt by the beginning of the 3rd century AD.

Conclusions

Knowledge about the anatomy of the human cranium and brain began in Egypt 5 millennia ago. The process began with the ancient Egyptians, whose embalmers, either accidentally or because of their profession, acquired anatomical knowledge to perform mumification rituals. By the time of Galen, anatomical knowledge had advanced considerably through human dissection and often by vivisection. By the end of the 4th century BC, the great city of Alexandria was founded. The establishment of the medical school and the library in Alexandria, coupled with the feasibility of human and animal dissection at the Mouseion, created an incredible atmosphere for developing knowledge about one of the most concealed anatomical structures of the human body: the skull base. This understanding influenced Arabic anatomists (for example, Rhaza and Ibn Sina) and numerous contemporary Western anatomists, including Vesalius, Piccolomini, Willis, Tiedemann, Owen, Leuret, and others who continued their work based on the foundation provided by those who came to Alexandria.

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References

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