Andreas Vesalius and the brain: limitations of *De humani corporis fabrica libri septem* and some comments on the matter

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REVIEW

Introduction. Andreas Vesalius (1514-1564) was the great innovator in Renaissance anatomy, after centuries of medieval obscurantism. In his magnum opus, *De humani corporis fabrica*, the part dedicated to the brain (*liber septimus*) has been criticised as the most deficient and as a possible source of errors.

Material and methods. I consulted the 1997 Spanish translation of the 1555 edition of *De fabrica*, based on a copy held at the National Library of Spain; this was the first Spanish translation of the work.

Results. Unlike Galen of Pergamon in the second century CE, whose anatomical studies were based on animals, Vesalius defended human dissection, conducting these studies himself without the help of assistants. To study the brain, he left the organ inside the cranial cavity and performed a series of transverse cuts beginning at the top of the brain. While the first sheets in *liber septimus* present the perfection that characterises his work, the rough sketches of the lower slices barely define the anatomical structures.

Discussion. The illustrations of the brain in *De fabrica liber septimus* do not present errors, but rather are conditioned by insurmountable limitations related to decomposition. Noting the need for fresh material, Vesalius convinced judges and influential figures to schedule hangings at the times most convenient to him; this constitutes an example of corruption for scientific purposes.

KEYWORDS

Vesalius, *De humani corporis fabrica libri septem*, neuroanatomy, brain

Introduction

The recovery of Greco-Roman culture during the Renaissance in 16th- and 17th-century Europe, with the rediscovery of Hippocratic and Galenic texts, was based on experimentation and objective observation of the natural world. It had an impact on ideas and the sciences, such as anatomy, which had been prohibited for theological reasons in the Middle Ages.[1-3] The six thick volumes of *De usu partium* ("On the usefulness of the parts of the body"),[2] written in Greek by Claudius Galen in the second century CE, are based on the observation of animals, mainly macaque monkeys, as the laws of the Roman Empire prohibited human dissection (*lex de sepulcris*). The discovery in the 16th century of anatomy works by classical authors, particularly Galen,[4] sparked interest in anatomy, with the availability of accessible and valuable materials enabling the recovery of classical texts; Vesalius was no exception to this trend.[5-9]

Andreas Vesalius (Flanders, Belgium, 1514-Zakynthos, Greece, 1564), was born in Brussels on 31 December 1514 into an influential family of physicians and pharmacists. His father, Andreas van Wesele (1479-1544) was an apothecary and *valet de chambre* in the court of Charles V, Holy Roman Emperor (Charles I of Spain). He studied anatomy in Paris, and trained for a further three years (1530-1533) in Leuven, where he

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graduated, and finally earned a doctorate in medicine at the University of Padua, a liberal and tolerant institution under the Most Serene Republic of Venice, where anatomy and surgery flourished.[10] Vesalius was awarded his doctorate on Wednesday, 5 December 1537, with the highest degree (*nemine penitus dissentiente*, "no internal opposition"). The following day, at the age of 23 years, he began lecturing in surgery and anatomy in Padua.[11-14] Padua enjoyed a long tradition of dissection, which enabled him to acquire key anatomical knowledge for the publication of *De humani corporis fabrica*, as well as *Tabulae anatomicae sex*, and the six sheets of *Epitome*, a summary of *De fabrica* intended for use by students.[15] Vesalius was not the first European anatomist: he was preceded by the Italians Mondino de Luzzi (c. 1270-1326), Jacobo Berengario da Carpi (1460-1530), and Niccolò Massa (1485-1569). The Spanish anatomists Luis Collado (1520-1589) and Pedro Jimeno (1515-1551), who studied under Vesalius in Padua, introduced anatomy in Spain as chairs at the University of Valencia, founded in 1501.[16] Of all these scholars, Vesalius was the most artistic, creating splendid, innovative drawings in *De fabrica*.[17,18] According to the historian Laín Entralgo, an emeritus professor specialising in this period: "he demonstrated that he knew more anatomy than his predecessors and knew it better than them; he also made it clear that he understood it in a different way."[14] After five years of intense work, he completed *De fabrica*, the work that has brought him worldwide fame, in June of 1543.[19] *De humani corporis fabrica* ("On the fabric of the human body") was rapidly disseminated across Europe, largely facilitated by the development of the printing press, invented nearly a century before.

De fabrica is organised into seven "books" or chapters, addressing different parts of the body (skeleton, muscular system, abdomen, etc). The last book, *Liber septimus*, is dedicated to "the harmony of the brain and the organs of sense."[20,21] Besides Vesalius' alleged errors,[22] the section on the brain has been considered "the most deficient of the work."[23,24] The objective of this article is to analyse the possible errors and shortcomings in the seventh book of *De fabrica*. It also addresses limitations facing this immortal Belgian anatomist that may explain the possible deficiencies in his work.

Material and methods

I consulted the Spanish translation of the 1555 Latin edition of *De fabrica*, printed by Johannes Oporinus of Basel. Published in 1997, the translation features a prologue by Pedro Laín Entralgo, chair of history of medicine at the medical school of the Complutense University of Madrid. According to the bibliographic information service of the National Library of Spain, this was the first Spanish translation of the text.[25] *Epitome* was translated in 1985, with an introduction by the same author.[21]

An English translation was published in 1967, and may be consulted online at the Complutense University of Madrid's Marqués de Valdecilla Historical Library. It should be noted that the 1555 edition of *De fabrica* is considered to be superior to the first edition, published in 1543,[26] due to the better quality of the anatomical sheets and the correction of several textual errors present in the first edition.[20] Most of the documentation consulted is available from the National Library of Spain, with the exception of monographs and discontinued books acquired from specialist sellers. For general information, the Spanish translation of the work by Huard and Imbault-Huart[7] and the book in English by Catani and Sandrone are recommended.[27]

Results

Andreas Vesalius' physiognomy

The German-born painter Jan van Calcar (c. 1499-1546) created the only known portrait of Andreas Vesalius (Figure 1), a xylograph on pear wood, before the anatomist turned 28 years old. Van Calcar was 15 years older than Vesalius, and was beginning to stand out as a faithful copyist in Titian's workshop in Venice. Other artists probably also contributed, although their identities have not been confirmed. The work of van Calcar seems to have been confirmed at least in the anatomical sheets from *Tabulae anatomicae sex*,[15] created in 1538 in Venice; these were merely a study for *De fabrica*.

Noteworthy features in the portrait of the anatomist are the large head and the short right arm, perhaps explained by the artist's lack of expertise. In his right hand, Vesalius holds, in a slightly flexed position, the ring finger of a hand that he is in the process of dissecting. The protagonist's commanding gaze is also striking. If he could speak, he may be telling us that this is the only path of an innovative anatomist like himself: dissection, by his own hand, of a human body, and detailed and direct personal observation. Vesalius did without the public dissections

Figure 1. Left: the only known portrait of the author of *De fabrica*, a drawing attributed to van Calcar. Right: a modern artist's impression, displayed at the Vesalius Continuum international conference (Brussels, 4-8 September 2014) held to commemorate the 500th anniversary of his birth.

in crowded, opulent anatomical theatres, as Mondini de Luzzi had used in his *Anathomia* (1513): a "lector" seated on a high platform would read in a monotonous voice from some well-used text of Galen's, a "sector" (autopsy assistant or "assistant autopsy technician" in today's language) would unceremoniously cut up the cadaver, and an "ostensor" would signal approximately what the lector was describing (Figure 2).[25-28] Vesalius was a "one-man show": he would performed dissections himself, and, as he did so, explain his findings. At the bottom of the portrait (Figure 1, left) appear the words *Ocypus, jucunde et tuto*, referring to the duties of surgeons: "safe, quick, and agreeable." The phrase appears to be from Celsus, who in turn took it from Asclepiades of Bithynia (129-19 BCE).

Objectives of *De fabrica*

Starting with Vesalius, dissection was based on information obtained through personal observation of the human body. Furthermore, Vesalius had a global vision; for him, the human body was, perhaps, the edifice upon which the parts were built, pieces whose parts fit perfectly into the whole.[29] It is unsurprising that, with the exception of a small venous foramen on the greater wing of the sphenoid bone, it is futile to search for his eponym in the endless number of details that make human anatomy such a complex subject. He corrected some errors of Galen's, but continued to be a fervent follower of the Greek physician.[23] Jacobus Sylvius (1478-1555; also known as Jacques Dubois), Vesalius' master in Paris, abhorred his former disciple, outraged by his criticism

of Galen and for, in his opinion, desecrating the study of anatomy with his highly unorthodox illustrations.[30]

Publication and difficulties

For the complex publication of such a unique book as *De fabrica*, nearly 700 pages long and featuring more than 200 illustrations, Vesalius did enjoy certain advantages over previous authors of anatomy books: the availability of skilled artisans in the art of printing and artists who were able to engrave wood blocks. From 1545, these were replaced with 42 copper plates thanks to Thomas Lambrit (1510-1562; also known as Thomas Geminus), a Flemish engraver who had settled in England.[31] It is surprising that he chose not to publish the work in Venice, the home of the artists who had contributed so much with their drawings, instead opting for the tolerant city of Basel, which was free of conflict between Catholics and Protestants, where the art of printing had reached the pinnacle of perfection. The highly learned editor Johannes Oporinus (1507-1568) corrected Vesalius' original Latin manuscript,[32] adding clarifications in the margins in Greek.

The original 1543 manuscript was lost until 1930, when it was discovered in storage at the University of Munich.[23] It had survived a long journey in 1542: from Venice to Milan by boat, and then overland to Basel. Most of the 200 original woodcuts were destroyed during the Second World War; now, only 25 blocks are preserved, with images of the brain, blood vessels, excised dura mater, and skull: from the disasters of war to man's carelessness with history.

Text and illustrations

The 1555 edition of *De fabrica liber septimus* is dedicated to the brain and organs of sense (the latter are not addressed in this study). The peripheral nervous system is described in the *liber quartus*, which spans 69 pages and 19 chapters. The cranium, in turn, is studied in the fifth chapter of *liber primus*. Inevitably, reading *De fabrica* today is somewhat disappointing, despite its historical interest. Not only because the nomenclature used is outdated (for example, he refers to the carotid arteries as the "sleep arteries" and to the brainstem as the "dorsal cord"),[23] but also because the text on the brain, which includes explanations of 19 anatomical sheets, attempts to base its functional explanation of the anatomical structures on the imaginative explanations of Galen. Written in medieval Latin, his declamatory style and excessive rhetoric made translation of the work highly challenging.[7]

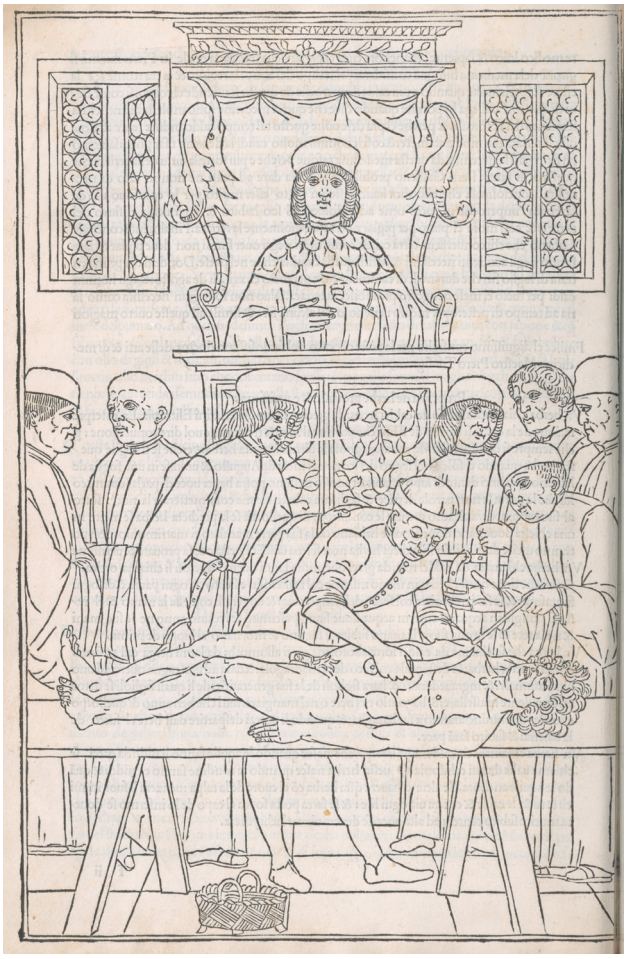


Figure 2. Woodcut from the six-volume medieval treatise *Fasciculus medicinae* by Mondino de Luzzi, published in 1493. The image shows an anatomical theatre of the day, with a "lector" perorating from some text of Galen's, a "sector" armed with an imposing knife, and an "ostensor" indicating the body parts being discussed.[22]

Discussion

Vesalius' unusual means of accessing the brain

Only 2 of the 19 sheets dedicated to the brain show the organ in its entirety, that is, after extraction from the skull. In the majority of his dissections, he performed the whole procedure with the brain remaining inside

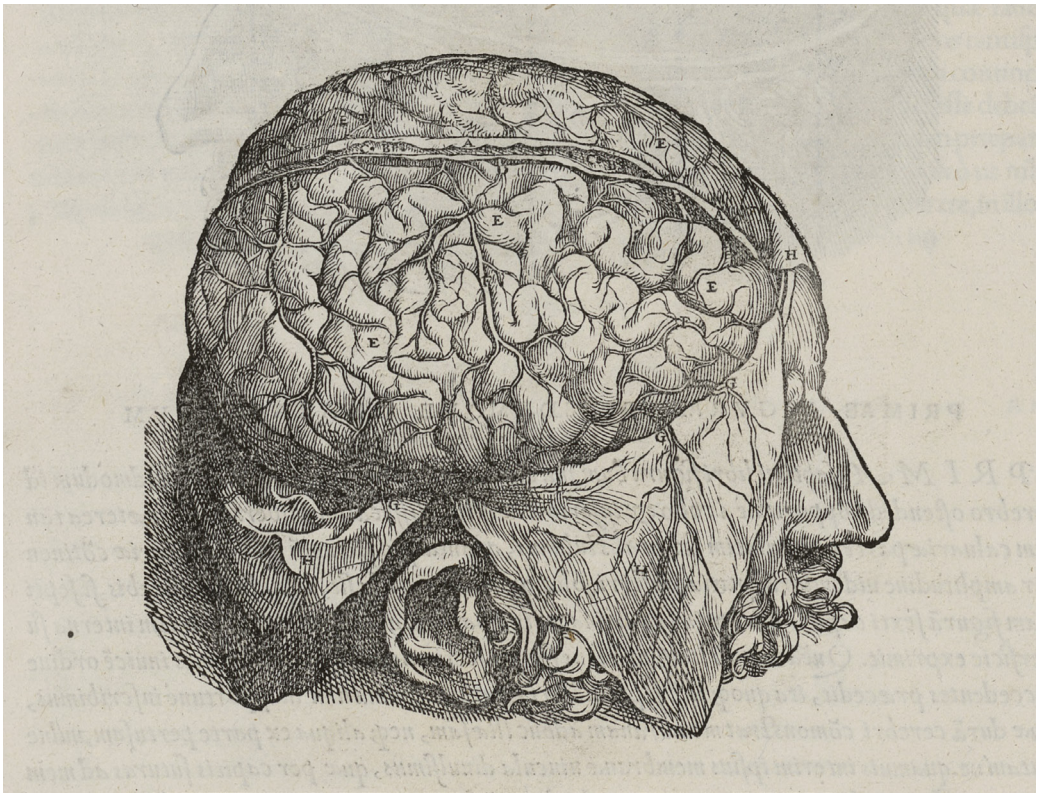


Figure 3. Having removed the skull cap by sawing a transverse cut and excising the dura mater in four flaps, the gyri of the cerebral cortex, wrapped in pia mater, are exposed. The dura mater channel containing the superior longitudinal sinus remains open (*De fabrica liber septimus*).

the cranial cavity. He needed six cadavers to illustrate the *liber septimus*; all were men and the illustrations do not omit their exuberant moustaches, highlighting the realism of the drawings.[23]

The anatomist included numerous details in his description of the procedure. After decapitating the cadaver, he removed the jaw in order to keep the head in position, with the aid of stones or blocks of wood placed on either side of it. He used a cord soaked in ink to mark the circular incision on the skin, "one finger's breadth above the eyebrows to the external occipital protuberance." He removed the skin and epicranial aponeurosis, then sawed the diploë horizontally, subsequently lifting the skull cap to expose the dura mater and its vessels. He made a cruciform incision in the dura mater then folded back the respective quadrants, revealing the cortical gyri, covered by the pia mater (Figure 3). He then used his fingers to separate the two hemispheres, having removed the falx cerebri, and was able to discern the medial part of the corpus callosum (Figure 4A). A second transverse cut revealed the ventricular cavities and the greyish colour of the brain's surface, compared to the white of the deeper areas (Figure 4B).

This technique, with transverse sections of the head performed with the brain in situ, had been described in Mondino de Luizzi's *Anathomia* in two women[33]; however, it was Jacobus Sylvius who taught Vesalius the approach to the brain shown in *De fabrica*.[34] In *The anatomy lesson of Dr Deijman*, the famous 1656 painting by Rembrandt, the brain is also shown in situ, with large flaps of meninges shown to either side. This procedure continued to be used well into the 18th century. Figure 5 shows a wax reproduction, possibly made by the sculptors Juan Cháez and Luigi Franceschi, currently displayed at the Javier Puerta anatomical museum of the Complutense University of Madrid medical school.

Anatomists' zeal for the cerebral cavities is explained by the Galenic dogma of ventricular theory. According to Galen, inhaled air penetrated the cranium through small openings and was transformed in the ventricles into vital spirit, which was eventually transformed into animal spirit in the heart. Renaissance anatomists searched for the *senso comune*, the possible seat of the soul as the source of intelligent life, in the empty cavities of the brain's ventricles.[35]

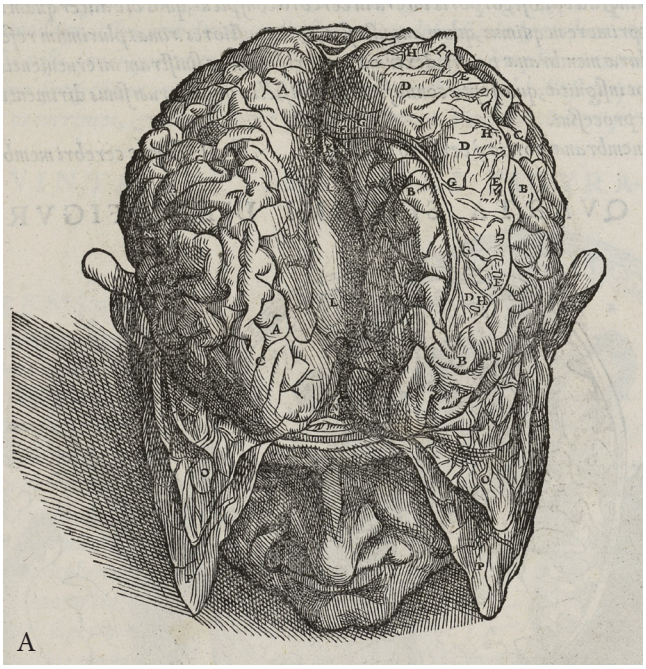
Vesalius' search for fresh brains

Until relatively recently, procuring cadavers for dissection at university medical schools was highly problematic. For instance, under the Crown of Aragon (1340), the Montpellier medical school was permitted to dissect one cadaver every two years; the University of Lleida was allowed to perform an autopsy on an executed criminal every three years.[36(p54)] The anatomist Pedro Ara Sarriá (Zaragoza, 1898-Buenos Aires, 1973), known for embalming Eva Perón and Manuel de Falla, describes the difficulties that Andreas Vesalius faced in performing his studies: "He would keep stolen cadavers in his room for days on end, at a time when the art of preventing putrefaction was not understood."[36] Vesalius' work was thorough and time-consuming. For example, his dissection of an 18-year-old man in Padua is known to have taken several weeks.[36-41]

Fixation of the brain: from Vieussens to formaldehyde

Anatomical knowledge of the brain has always been linked to the fight against natural decomposition, beginning on the third day after death.[42] After boiling specimens in water or oil, Raymond Vieussens (1641-1716) identified bundles of fibres by careful scraping away the parenchyma.[43] In 1664, Marcello Malpighi (1628-1694) used the same method, as well as a rudimentary microscope, to demonstrate that nerve fibres extend from higher levels to the medulla oblongata.[44] During the 18th century, alcohol began to be used as a fixative for brain tissue; it was first used by Félix Vicq d'Azyr (1748-1794). One noteworthy example is that of Admiral Horatio Nelson, who died after being left paraplegic in the Battle of Trafalgar on 21 October 1805: his body was submerged in a cask of brandy to preserve it until the ship landed in Portsmouth for funeral preparations.[45,46]

Students of medicine will have a clear memory of the teary eyes and sensation of asphyxiation caused by formol,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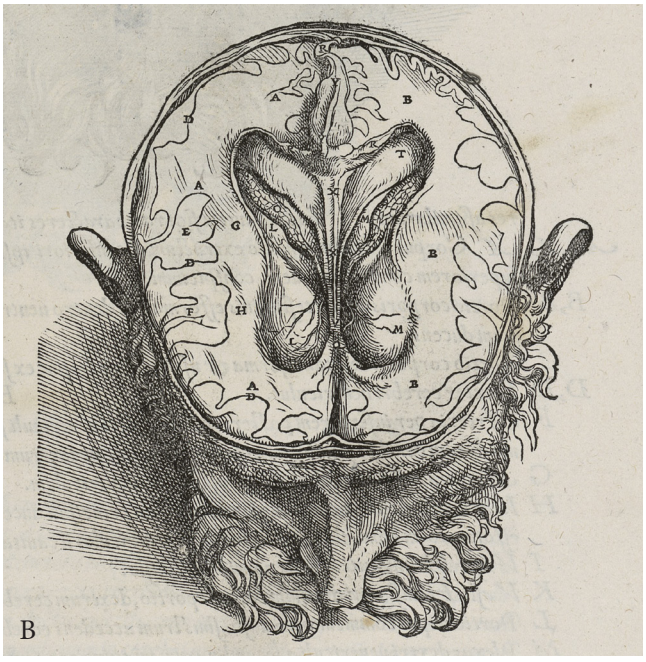
B

Figure 4. A) After removal of the pia mater (except on part of the left hemisphere), the two hemispheres are separated by force to expose the corpus callosum, connecting both. B) A cut at a lower level reveals the lateral ventricles. It also enabled visualisation of the difference in colouration, greyish at the surface and white at deeper levels (*De fabrica liber septimus*).

Figure 5. Wax figures at the Javier Puerta anatomical museum of the Complutense University of Madrid medical school, ca. 18th century. Transverse sections were made across the head to expose the ventricular system. This technique is similar to Vesalius', with the exception that the latter made the cut "one finger's breadth above the eyebrows."

the aqueous solution of formaldehyde, in the dissection laboratory. Formaldehyde is a volatile and inflammable liquid, highly soluble in water, that was discovered in 1859 by the Russian Aleksandr Mikhailovich Butlerov (1828-1886).[47] In recent years, its use has been questioned by anatomy department technicians due to its carcinogenic potential.[A]

The anatomical sheets depicting lower levels of the brain in *liber septimus* show a gradual decrease in quality, presumably owing to the advancing deterioration of the material. In the dissection shown in Figure 6A, Vesalius performed a surprising manoeuvre: he placed both hands inside the cranial cavity, lifted out the cerebellum and brainstem, and pulled the whole piece toward the frontal lobe, exposing the fourth ventricle. Imaginatively, he compared the structure to "the pointed part of a scribe's quill," whereas the vermis evoked the image of a worm. Figure 6B appears to show the specimen at an advanced stage of putrefaction, with the brain having become a shapeless mass on the base of the skull. A specimen at the highest level of deterioration is shown in Figure 7A, a rough sketch of the pituitary stalk that suggests the role of the pituitary gland as a reservoir of mucus or phlegm. A similar sketch is shown in Figure 7B, depicting the lower half of the floor of the fourth ventricle, the dissected restiform bodies, and the lower part of the quadrigeminal plate, with its "*eminentia natiformes*" and "*eminentia testiformes*" (buttocks and testicles); these "indecent" terms were used by 16th-century anatomists due to the supposed resemblance to these parts of the body.[39]

To summarise, even in the winter months, Vesalius' work was subject to the inescapable laws of biological matter, at a time when no method existed of protecting organs from rapid putrefaction.[2,24] Fresh brains present rosy colouration and a soft, oily texture: while removing the brain from the cranial cavity and its subsequent slicing was a challenging procedure, the greatest problem in the 16th century was preserving the tissue. Vesalius was aware of the need to work on fresh material, and he was no longer able to make treacherous nocturnal excursions to local cemeteries, as he had in his youth, as an incipient "resurrectionist," a scourge that extended to the early 19th century.[40] Twelve of the 33 bodies dissected by Vesalius for which information is available were hanged criminals (including few women, who were mainly prostitutes, as well as a cleric's lover).

[A]Alsedo Q, Herráez P. La Universidad Complutense de Madrid llegó a prohibir la utilización de cadáveres en las salas de disección. *El Mundo*. 25 May 2014.

The gallows did not guarantee the suitability of the cadavers: Vesalius was able to convince prefects and judges, one of whom has been identified as Marcantonio Contarini, to schedule executions at "convenient" times.[38] We may also recall that Ramón y Cajal needed the cadavers of very recently deceased children, which was prohibited by the civil registration law in force at the time. With the help of influential figures and physicians from the maternity hospital and the foundlings' home in Madrid, he was able to obtain "hundreds of fetuses and children of various ages, some still warm."[41]

Plagiarists or admirers? The case of Juan Valverde de Amusco

Juan Valverde de Amusco (ca. 1525, Amusco, Palencia, Spain-ca. 1588, Rome) learned anatomy in Rome with the anatomist Matteo Realdo Colombo (ca. 1516, Cremona, Italy-1559, Rome), who described the pulmonary circulation and became Vesalius' successor as chair in Padua.[B] Valverde's 1556 work *History of the composition of the human body*,[47] which was republished numerous times, was written in Spanish and translated to Latin, Italian, and Dutch. Several of the illustrations in Valverde's book were inspired by anatomical sheets from *De fabrica*, whereas others, original in this case, are thought to have been engraved with a burin on copper by Nicolas Béatrizet. Accusations of plagiarism[48] have recently been reiterated, with charges of "unauthorised" use of the work for the sake of "shameful profit."[49] The valiant defence of Valverde by Martín-Araguz et al.,[50] written two decades ago, remains valid today: "Those accusing Valverde of plagiarism not only are not familiar with his work; rather, these are the subjective opinions of individuals who appear also to be unfamiliar with Vesalius' work and the historical context in which both authors were writing."

Vesalius in Madrid

Vesalius' career as an anatomist ended in Madrid in 1544, when Charles V requested him as a personal physician. He attended numerous Flemings installed in the Emperor's court and followed him on his continuous travels and military campaigns. In reality, he had never ceased to practice medicine from the time he trained under Giovanni Battista Monte (1498-1551) in Padua.[51]

[B]Montoya L. Mateo Realdo Colombo. *Historia y Biografía*. 20 Aug 2020.

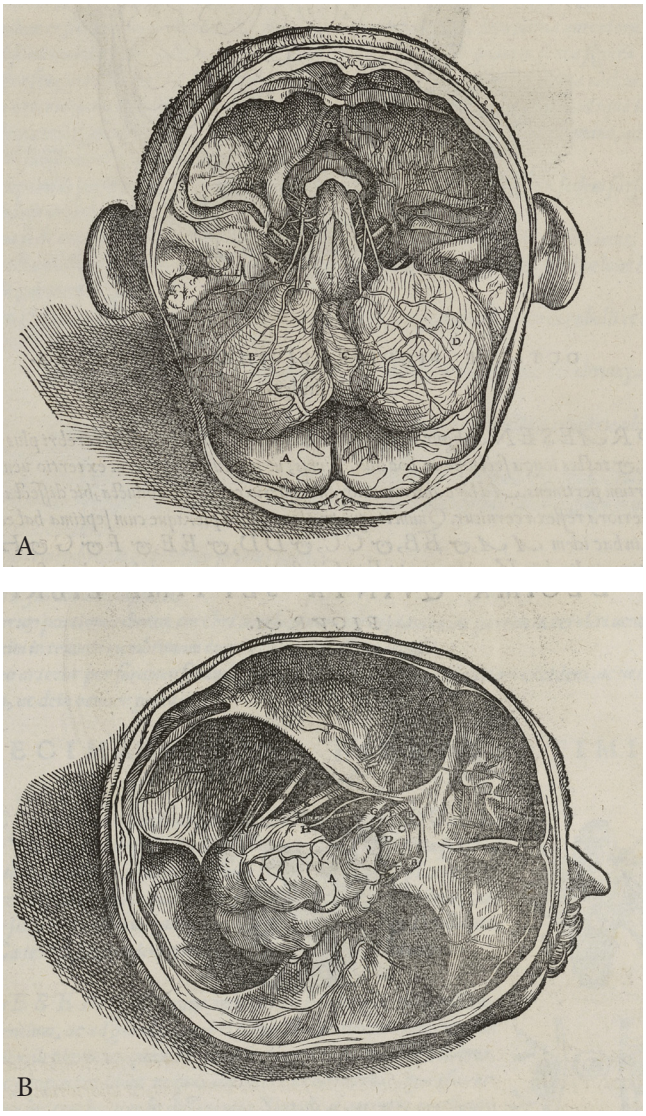

Figure 6. A) An unorthodox technique of exposing the cerebellum, brainstem, and part of the fourth ventricle. The cerebellum and brainstem are lifted from their position in the posterior fossa and clivus and pulled sharply forward to rest on the frontal part of the hemispheres. B) In this preparation, parts of the dura mater remain on the base of the skull. The brain is reduced to a shapeless mass, and the gyri and vessels are difficult to identify (*De fabrica liber septimus*).

However, he was never allowed to have even a skull: the papal bull of Pope Boniface VIII was de facto law, and threatened excommunication of any who dared practice human dissection.[38] After Charles V retired to the Monastery of Yuste, his son Philip II also requested Vesalius' services. He was also occasionally involved in the treatment of highly problematic processes: for

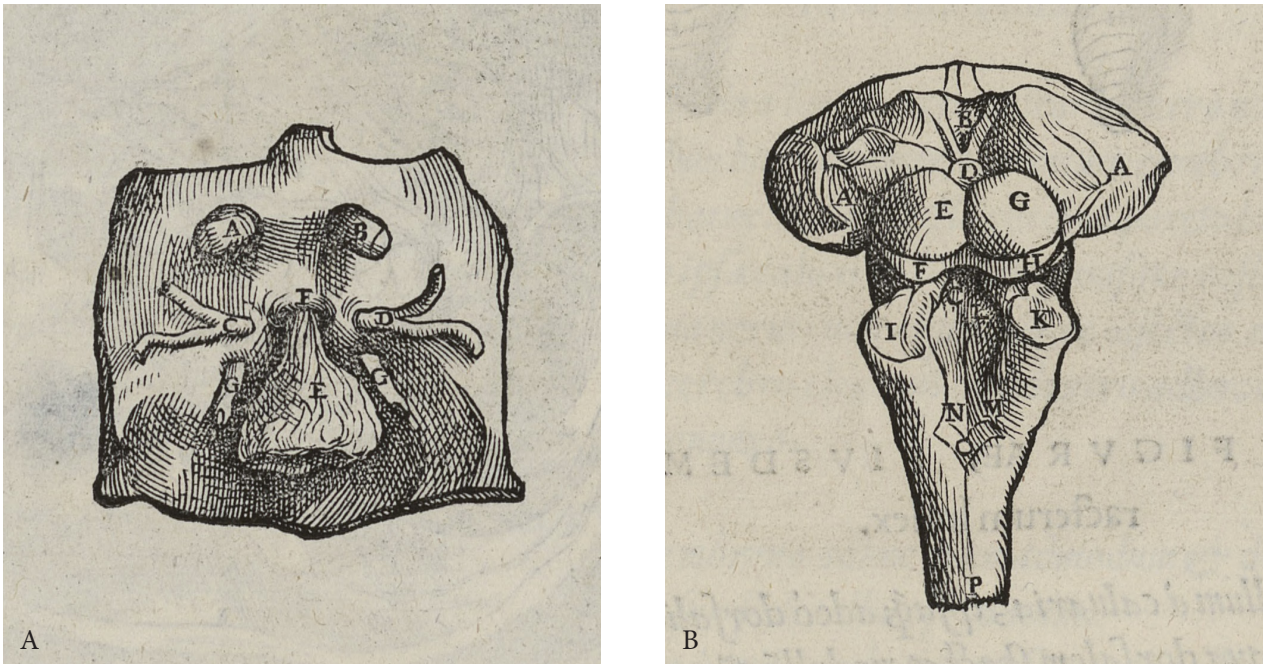

Figure 7. A) A low-quality sketch showing a fragment of the base of the skull; the dura mater is adhered to the surface and the optic nerves (labelled A and B) have been sectioned. The pituitary gland resembles a sac, supposedly full of phlegm. B) Lower part of the brainstem and fourth ventricle after removal of the restiform bodies. The "testicles" and "buttocks" are shown above.

instance, Henry II, King of France, presented an abscess after a lance penetrated his eye during a tournament held for the marriage of his daughter Elisabeth of Valois with the king of Spain[51]; or the severe brain trauma suffered by Don Carlos, Prince of Asturias, after he fell down a staircase.[52]

For this immortal anatomist, his time in Madrid was not a pleasant experience. Professional rivalries, a flagrant scientific regression, and perhaps ill health led him to visit the Holy Sepulchre in Jerusalem. According to letters preserved at the General Archive of Simancas, the king himself facilitated the trip, sending 500 ducats as a donation to the custodians of the holy site.[53] Vesalius departed on the return voyage to Spain on 26 May 1564, but the ship was wrecked on Zakynthos, a small island in the Ionian sea. A humble monument was erected in 1965, commemorating his death with inscriptions in Greek and Latin; more recently, a bronze statue of Vesalius, resembling the "muscle man" from his famous anatomical sheets, was installed during a congress held on the island (Figure 8). Vesalius is thought to have been buried at the small church of Santa Maria delle Grazie, which was erased from the map by an earthquake in 1953. Plans are still underway to locate his tomb.[54,55]

Conclusions

This study analyses the reasons for which some of the anatomical sheets depicting the brain in the seventh book of *De fabrica* are of poorer quality than the rest of the illustrations. It should be noted that Vesalius expressly wished to perform dissections himself, without delegating the task to barber surgeons who were little more than clumsy butchers. Given his revolutionary status in the development of anatomical technique, it is surprising that, like previous anatomists, he opted not to remove the brain from the cranial cavity. This is probably explained by the long time it took to create his detailed, artistic drawings. This would have been an excessive time to maintain this fragile organ without preservation, especially when he needed to reproduce deep cuts, for which reason he would have needed at least six different cadavers. In his article "La otra

cara de Vesalio" ("The other face of Vesalius"), Barcia Goyanes[23] (1901-2003) lists up to seven errors in the general part of *De fabrica*. We found none in the section dedicated to the brain. While the imprecise lines of the drawings of deeper sections of the brain (see Figure 7) may be considered errors, I consider them not to be a mistake on Vesalius' part. Rather, they are explained by the insurmountable difficulty at the time of preserving such a fragile tissue as the brain. Vesalius was aware of the need for "fresh material," which he obtained from executed criminals, who were hanged at a "convenient time" thanks to the immoral complicity of judges and friends in positions of influence. This would be repeated centuries later, during the Nazi regime (1933-1945), when some neuropathologists exploited more than 2000 brains from executed patients with chronic neurological diseases. These researchers justified their actions with the unacceptable argument of "scientific and teaching interest."[56,57]

Acknowledgements

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Conflicts of interest

The author has no conflicts of interest to declare.

Figure 8. A monolith with Greek and Latin inscriptions, erected on the island of Zakynthos in 1965. A full-body bronze statue depicting Vesalius as the "muscle man," studying a human skull held in his right hand. The piece was created by the medical artist Pascale Pollier and the forensic artist Richard Neave, an expert in facial reconstruction.

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