ONE

THE VENTRICLES

Apoplexy in the Sixteenth Century

SUMMARY

Hippocratic and Galenic texts, fully rediscovered in the first half of the sixteenth century, defined apoplexy as a sudden collapse, with loss of movement and sensation, except for preserved heart action and respiration. Though this definition leaves room for divergent interpretations, early physicians who made the diagnosis rarely specified the symptoms.

Galen explained apoplexy as blockage of the cerebral ventricles by abnormal fluids, most often phlegm; animated spirits, an extremely subtle vapour, could then no longer reach the nerves. Post-mortem examination of human bodies was rare; the first inspections of the brain after apoplexy mentioned extravasated blood at its base or within the ventricles (Fernel, Duret). Varolio developed a method to remove the brain from the body and suggested that it was the substance of the brain, not its ventricles, that transported animated spirits. Two instances of hydrocephalic infants who had nevertheless shown signs of mental activity (Vesalius, Fabricius Hildanus) contributed to establishing the role of brain tissue. Physicians gradually came to use personal observation as a supplement to, or even a replacement of, written sources of knowledge.

The terms 'apoplexy' and 'stroke' have much in common, since both suggest a sudden collapse from a catastrophic illness. Yet there is a large difference. 'Apoplexy' refers to observable phenomena in patients – the manifestations of a brain disease, according to criteria developed in antiquity. By contrast, today the word 'stroke' evokes, as dictionaries testify, an anatomically defined cause: a disorder of the brain's blood vessels. This transition, from a set of clinical features

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to a morphological notion, is a metamorphosis many other diseases have gone through in the course of history. The difference between the two points of view, that is, what the doctor observes in the patient versus what the pathologist sees in the brain after death, explains not only why terms have changed, but also what is meant by them. As a consequence, some examples of 'apoplexy' would not be called 'stroke' today, and vice versa.

This chapter describes the earliest phase in these early developments, in the second half of the sixteenth century. During this period, the heritage of ancient Greek medicine was fully rediscovered, cleansed of Arab interpretations, and disseminated by the growing book culture.[1] Two themes dominate the chapter. The first is the definition of apoplexy as a clinical syndrome or as a set of coherent clinical features. The second theme is the theory of normal brain function and its disturbance in apoplexy. It will be necessary to switch from manifestations to explanations, and back, a few times.

APOPLEXY: AN AFFLICTION DEFINED BY ITS MANIFESTATIONS

Phenomena are recorded through observation – often, if not always, conditioned by interpretation. Readers, please discard all ideas you may have in relation to what is now called 'stroke', and open your mind to the observations and interpretations of physicians in a distant past who tried to make sense of an acute disease.

Ancient Descriptions

The cardinal feature of apoplexy, as the original term in ancient Greek implies, is that it strikes suddenly and renders the patient senseless and motionless. It is as if the victim is struck by lightning, hence the Latin synonym *morbus attonitus*, or 'stunned disease'. The disease is briefly mentioned in Babylonian texts,[2] and subsequently in Hippocratic writings. Yet the most influential author in antiquity on medical subjects was Galen (129–*c*.216) (Box 1.1). He was a prolific writer with an adventurous life.[3] Galen did not systematically deal with each disease in turn; therefore, the reader has to try and reconstruct Galenic notions from different, and sometimes contradictory, passages. Key features of the disease are found in different sentences, for example:

> When all nerves have simultaneously lost sensation and motion, the affection is called apoplexy. But when this happens on one side, the right

[1] Siraisi (1985), The Canon of Avicenna, 39–41; French (1985), Berengario, 66–71; Maclean (2002), *Medicine in the Renaissance*, 19–20; Wear (1995), Early modern Europe, 251–5.
[2] Reynolds and Kinnier Wilson (2004), Stroke in Babylonia.
[3] Mattern (2013), *The Prince of Medicine*; Nutton (2020), *Galen*.

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Box 1.1 Claudius Galenus (129–c.216).

Galen was the son of an architect and local magistrate in the Greek community of Pergamum (now Bergama, Western coast of Turkey). He studied medicine from the age of 16, first in his home town, then in Smyrna (present-day Izmir) and Alexandria. In 157, he was back in Pergamum, as a physician for the gladiatorial school.

In 162, Galen set out to establish himself in Rome. The professional climate in the capital was highly competitive – apart from educated Greek physicians, also lay citizens or slaves offered their services to the sick. A physician's reputation depended heavily on their ability to predict the outcome of disease and also on anatomical demonstrations in live animals. Galen used pigs, goats, cattle, monkeys, cats, dogs, mice, snakes, fish, and birds. Among the spectators at such sessions was the ex-consul Flavius Boethus; he invoked Galen's help when his wife was ill and became Galen's patron when she recovered. In 166, Galen rather unexpectedly left Rome. Speculations about his motives include an epidemic of infectious disease, rivalry among colleagues, and fear of being conscripted.

He returned two years later to join the medical staff of the joint emperors Marcus Aurelius and Lucius Verus; the latter died soon afterwards. Under subsequent emperors, Galen kept this position, but he did not live in the imperial palace or join military expeditions. This arrangement allowed him to spend much of his time performing private consultations for the Roman elite – and also writing an amazing series of treatises on the structure and function of the body, illustrated with pertinent case histories. Even though, in 192, a fire destroyed his writings on pharmacology, Galen's extant collected works still take up 22 volumes in the nineteenth-century edition by Kühn.

> or the left, it is called paralysis, of the part in which the disorder exists – sometimes the right, sometimes the left.[4]

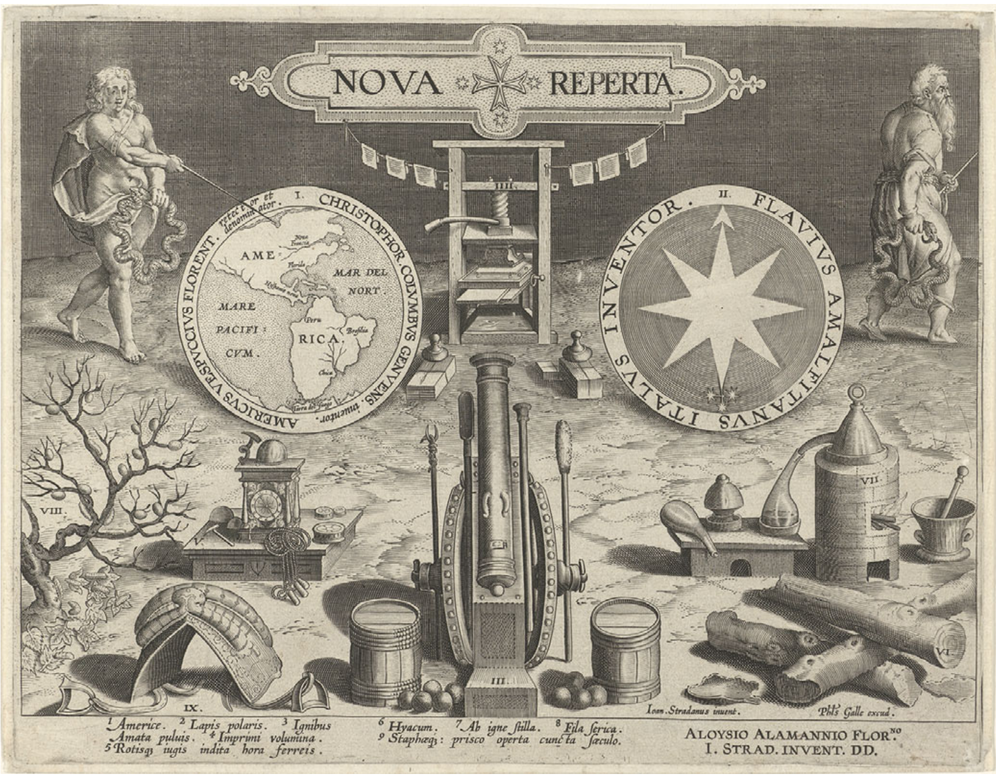
Galen noted elsewhere that respiration was preserved in these patients, though it was laboured. He also found that the pulse of the arteries in the wrist and elsewhere continued to beat in patients with apoplexy:

> But when the respiration is affected to such an extent that [the patient] breathes as in deep sleep, then we speak of apoplexy.[5] [*And also*:] As long as the disease has not gained the upper hand, you will find [in the pulse] no change at all with regard to magnitude, force, speed, frequency and hardness.[6]

[4] Galenus (1625b [*c.*180]), *De Locis affectis* (C4) III, 20H; Kühn, ed. (1821–33), *Galeni Opera,* vol. VIII, 208.

[5] Galenus (1625b [*c.*180]), *De Locis affectis* (C4) IV, 22H; Kühn, ed. (1821–33), *Galeni Opera*, vol. VIII, 231.

[6] Galenus (1625a [*c.*180]), *De Causis Pulsuum* (C4) IV, 102G; Kühn, ed. (1821–33), *Galeni Opera*, vol. IX, 193.



1.1 New discoveries (*Nova reperta*). A printing press is shown directly under the cartouche. On the left, a young woman with the mythical snake Ouroboros (biting its own tail) indicates the Americas. On the right side is a compass rose, with the name of its supposed inventor; an older man, again with Ouroboros, leaves the scene. In the foreground are inventions symbolizing the sixteenth century: the silkworm, a saddle and spurs, a mechanical clock, a cannon and gunpowder, medicinal bark, and an apparatus for distillation. Engraving attributed to Jan Collaert, after drawing by Jan van der Straet, c.1590. *Source:* Courtesy of Rijksmuseum, Amsterdam.

It is justified to say that, at least with regard to the definition of apoplexy, physicians in the middle of the sixteenth century started where Galen had left off more than 13 centuries ago. The term 'Renaissance' may have been coined rather recently, by nineteenth-century historians,[7] but literary humanists in the fourteenth century, such as Petrarch, already saw themselves as harbingers of a new era, after the 'dark ages'.[8] Two hundred years later, many still felt they were living in an age of discoveries (Figure 1.1). In the 'medical Renaissance' of the sixteenth century,[9] recovered and reconstituted Galenic texts came to replace medieval Latino-Arab glossaries on medicine, at a time when prices of

[7] Burckhardt (1860), *Die Kultur der Renaissance in Italien*.
[8] Mommsen (1942), Petrarch's conception of the Dark Ages.
[9] Wear, *et al.*, eds. (1985), *The Medical Renaissance of the Sixteenth Century*.

printed books allowed doctors to build their own library.[10] The young Jean Fernel (1497–1558), about to become an important physician, used similar terms when young: 'These disciplines and arts have clearly come to life again, after having been buried, or rather extinct and lifeless, for almost twelve hundred years.'[11] It is no surprise, therefore, to find an almost Galenic description of apoplexy in the first known treatise on diseases of the nervous system,[12] published in 1549 by Jason Pratensis (*c.*1486–1558; Latinized name for 'van der Velde'); he practised in Zierikzee, in the Southwest of the Low Countries:

> Apoplexy is a disease in which an affected person is deprived of motion and sensation; only breathing remains, though not intact, but abnormal in a variety of ways. Most often this illness arrives without fever, and the person suddenly tumbles down on the floor with a great fall. The collapsed person cannot be woken up by any speech, or by any shouting or poking. The numbness keeping the stricken patient down is so severe that no stimulus can overcome it. [. . .] And in the same way, the arteries originating from the heart are less impeded in this disorder, because they retain their pulsations, though these are much more subtle [. . .][13]

Thus, the standard definition of apoplexy, often repeated and essentially unchanged in the sixteenth and seventeenth centuries, and even later, consists of three main characteristics: (1) a sudden fall; (2) loss of movement and sensation; and (3) preservation of respiration and pulses, at least by and large. Still, there are some loopholes in this definition. A case report can help to clarify this – it is unique for several reasons: it dates from the middle of the sixteenth century and the patient is also the author.

A Self-Reported Case History

Conrad Wolffhart (1518–1561) (Figure 1.2) included an account of his own apoplexy – and his recovery – in a collection he edited of prodigious events spanning from pre-biblical times to the middle of the sixteenth century; his humanist name was Lycosthenes. Born in Rouffach (Alsace), Wolffhart studied philosophy in Heidelberg. In 1542, he moved to Basle where he became Deacon of the Church of St Leonard.[14] This is how he looked back on his disease episode:

> On 21 December of the year 1554, on leaving the building where I was already preparing the edition of my collection of 'Aphorisms' for the press, a horrible incapacity overwhelmed me. I suddenly collapsed on the floor and in a single moment I lost not only my voice, but also all sensation and movement on the right side, from head to heel (except sight and hearing).

10 Jones (1995), Reading medicine, 155–6; Nutton (2005), Printing and medicine, 421–2.
11 Fernelius (1548), *De abditis Rerum Causis*, 2.
12 Pestronk (1988), The first neurology book.
13 Pratensis (1549), *De Cerebri Morbis*, 121.
14 Beyer (2012), Lycosthenes.

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1.2 Conrad Lycosthenes (1518–1561). Etching by Simon Frisius, *c.*1610, 150 × 115 millimetres. *Source:* Courtesy of Rijksmuseum, Amsterdam.

> I could not utter a single word, until 12 days later; I could not stand on my feet or move a finger for three entire months, during which period I was bed-bound. My [right] limbs seemed to be converted not into wood but into the hardest stone; the blood of the affected parts was so much frozen and hardened by the coldness of the humours and the obstruction of my nerves, that rubbing, compresses or any other measures entirely failed to warm them. At that time, owing to the humours that were disappearing from the head and the brain (it is astonishing to say), I lost all memories, to such an extent that the words of my Sunday sermon and all my knowledge of literature had vanished completely. [...]
>
> My excellent friends were witnesses of my disaster. They could not understand me because I could only communicate by nodding, though I was sound of mind and reason. They held up a slate on which the letters were chalked in alphabetical order, so that I could point out the letters in their proper order with the index finger of my left hand; in this way the letters formed syllables and the syllables sounds, which they, after some mulling on my part, made me utter. But my affliction seemed to be a chronic and irreparable disease. As a result, not only I myself, but all who watched this cruel disease despaired about my life. But God in his mercy, on whose power all infirmity depends, overhearing my persistent prayers and those of his church on my behalf, restored me for the greater part, through the effort of Dr Guglielmo Gratarolo from Bergamo. Therefore, if you have possibly thought that in the part of life left to me some products of my pen have some merit for muses and profession, I would like to thank God Almighty in the first place, and thereafter Dr Gratorolo [...][15]

Ambiguity in the Interpretation of Clinical Symptoms

This unique case history also serves to show that the criteria for the diagnosis of apoplexy are somewhat imprecise, that is, open to different interpretations.

Consciousness. Medical treatises of the sixteenth century often distinguish between external senses (sight, hearing, touch, smell, and taste) and internal senses, viz. intellectual activities such as reasoning, imagination, and memory. So 'loss of one's senses' is practically synonymous with the modern term

[15] Lycosthenes (1557), *Prodigiorum ac Ostentorum Chronicon*, 640–1.

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Box 1.2 Pieter van Foreest (1521–1597).

van Foreest was the third child of a wealthy couple in Alkmaar, a city north of Amsterdam. After secondary school, he studied liberal arts and medicine in Louvain (1536–1539), then made a tour of medical faculties in northern Italy. Having graduated in Bologna (1543), he also spent time in Venice, Ferrara, and Padua, made an eventful foot journey to Rome in the company of botanists (1545), and visited Paris and Orléans.

The next year, van Foreest settled in Alkmaar where he married Eva van Teylingen and established a solid reputation. Twelve years later, he accepted the post of city physician in Delft where the plague was raging. He remained in Delft for the next 37 years, a period of political turmoil, religious strife, and revolt of the United Provinces against Spanish rule. In 1574, during the siege of Leiden, he became the personal physician of William the Silent, prince of Orange and leader of the revolt.

In 1595, his wife Eva died, predeceased by their four children; van Foreest, now aged 74, decided to return to Alkmaar as a city physician. Meanwhile he had started to publish a series of books with case histories, followed by comments (*scholia*). These volumes continued to appear after his death, the last with medical subjects (no. 17) in 1606, followed by two more volumes with surgical cases. Reprints of his collected works continued to appear up to 1661.

Source: Portrait courtesy of Rijksmuseum, Amsterdam.

'unconsciousness'. But either term is based on the absence of reactions from the patient, such as speaking and moving the limbs or eyes. Since Lycosthenes, once recovered, could write about his fall and its circumstances, he must, at the time of the event, have been able to think and remember – or others must have recounted later what had happened. At any rate, the reason why a later medical compiler classified the disease as a case of apoplexy[16] must have been that the patient was unable to speak and could not signify he was sentient. Bystanders – and physicians – depend on verbal communication to find out whether someone can think and feel; at any rate, when a patient had collapsed and was speechless, with their eyes closed, it was assumed that all mental activity had been lost.

Language. If, however, a patient was mute but showed signs of awareness by other means, sixteenth-century physicians tended to diagnose 'paralysis of the tongue'. An example is found in the *Observationes et Curationes Medicinales* of Pieter van Foreest or Forestus (1521–97) (Box 1.2). This extensive work, often reprinted,[17] contains the following story in the section on apoplexy:

[16] Schenck von Grafenberg (1609), *Paratereseon*, 91.
[17] Breugelmans and Gnirrep (1997), Bibliografie.

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> A high-born and noble young man, Mr van Cruningen, about 29 years old, was melancholical, more than fitting for his age and nature; this melancholy had increased when, long before, he had been kept in custody in Hoorn, together with Mr de Bossu. Early on the night of March 8, 1581, he suddenly sustained a fairly strong apoplexy, which quickly evolved into a paralysis of the entire right side, arm as well as leg, with impairment of the tongue, so that he could hardly speak; also, he could not properly understand.[18]

Although the report mentioned difficulty in understanding spoken language, the medical community apparently saw language as a purely motor phenomenon.

Paralysis. Van Foreest's report also shows that he designated right-sided hemiplegia after the patient had come round as 'paralysis', in keeping with the rule that apoplexy was diagnosed only if *all* movement was abolished. Yet it is difficult to be sure that a collapsed patient can move anything at all. Lycosthenes was unable to say this; had he been able to speak, his disease might have been classified as 'paralysis'. Perhaps he made no spontaneous movements with the left limbs because he was lying on this 'good' side, or because he was too frightened to stir at all. Of course, someone might have prodded or pinched him, in order to evoke some sort of response. But if this test was done on the affected side and gave no result, there was no good reason in those times to try the other side. Moreover, if a patient happened to be in deep coma, it would have made no difference. Another source of uncertainty is how violent the stimulus should be. Pratensis recommended the application of white-hot iron,[19] but probably he mentioned it only for the sake of didactic drama and never tried it himself.

Respiration. That breathing was preserved, though with some difficulty, while other movements were suspended, continued to puzzle physicians; a common explanation was that it represented 'a movement of nature, not of the will'. Van Foreest followed Galen in distinguishing four types of respiration in apoplectic patients, with different chances of survival.[20] Many authors mentioned frothy sputum around a patient's mouth as an ominous indication of outcome, a sign that goes back to the aphorisms of Hippocrates, though in the context of judicial hanging.[21] Hercules Saxonia (1551–607), appointed Professor of Practical Medicine in Padua in 1575, thought he could distinguish two kinds of sputum on the lips – if frothy and thick, with bubbles from exhalation, patients might recover; but no hope was left, he wrote, if it consisted of lung tissue liquefied by heat, with bubbles from enclosed spirit.[22]

[18] Forestus (1653 [1590]), *Observationes et Curationes*, vol. x, 526.
[19] Pratensis (1549), *De Cerebri Morbis*, 422.
[20] Forestus (1653 [1590]), *Observationes et Curationes*, vol. x, 510.
[21] Hippocrates (1959b [*c.*400 BCE]), Aphorisms, 119 (aphorism 43).
[22] Saxonia (1639), *Opera practica*, 39.

Differential Diagnosis. Physicians had to distinguish apoplexy from other conditions with sudden onset in which the senses were affected, for example epilepsy, paralysis, syncope, and 'suffocation by the uterus', a kind of swooning attributed to vapours rising up from the womb. Van Foreest stipulated that the distinction was difficult if the patient had already died by the time the doctor arrived. His example was the sudden death of a certain Hugo Grotius (not the famous lawyer of the same name); van Foreest ascertained that eyewitnesses had not observed any signs of breathing or of fluid emerging from the patient's mouth, so he concluded that the cause of death was not apoplexy, but syncope, a sudden cessation of heart action through loss of 'innate heat'.[23]

Apoplectic or Dead? A related problem was the distinction between severe apoplexy and death. For the detection of barely perceptible respiration, many authors described tests such as applying a piece of cotton wool or a mirror to the mouth and nose, or putting a mug full of water on the patient's chest.[24] Similarly, van Foreest warned that feeling the pulse could be misleading and even treacherous, as illustrated by horror stories of patients deemed dead and about to be buried until their miraculous recovery – hence the statutory delay of three days between apparent death by apoplexy and the burial.[25] This precautionary interval is a recurring theme in almost every text on the subject from widely different parts of Europe.

In conclusion, it was up to the physician which observations or tests were necessary in deciding whether the criteria for a diagnosis of apoplexy were met. Such details were almost never recorded, at least not until the middle of the seventeenth century – and even then, by only a minority of physicians. As a rule, the reader was supposed to accept the diagnosis on trust.

BRAIN FUNCTION: SPIRITS PERFECTED IN THE VENTRICLES

Despite the possible differences of interpretation, the written criteria for the diagnosis of apoplexy remained largely unchanged until at least the beginning of the nineteenth century. By contrast, ideas about the location of brain function began to shift at an earlier stage. The most influential ancient medical authority in the sixteenth century was Galen; he is our starting point. However, Galen's views on brain function are scattered across different texts.[26] To obtain a coherent account of how he was understood in the sixteenth century, it is best to consult a distinguished interpreter of that era.

23 Forestus (1653 [1590]), *Observationes et Curationes*, vol. x, 513–14.
24 Forestus (1653 [1590]), *Observationes et Curationes*, vol. x, 513.
25 Forestus (1653 [1590]), *Observationes et Curationes*, vol. x, 529.
26 Rocca (2003), *Galen on the Brain*.

Box 1.3 Jean Fernel (1497–1558).

Fernel's father was a furrier and innkeeper in Montdidier (Somme); the family moved to Clermont (near Paris) when he was 12 years old. Jean's ambition to continue his education at the university was new in his family, but he got his way and became a Master of Arts at *Collège Ste Barbe* in 1519. At around that time, Fernel discovered that the spirit of the 'new times' had not yet reached the University of Paris and that his teachers had provided only medieval glossaries containing Latino-Arabic interpretations of the ancients. Besides, his Latin was 'barbaric'.

In the next five years, Fernel studied on his own – apart from Plato, Aristotle, and Cicero, he developed a keen interest in mathematics and astronomy. Having finally chosen medicine as his profession, Jean provided for his own upkeep by teaching, since his father had to support the younger children. In 1530, he graduated and obtained a licence to practise; in the meantime, he had published three folio volumes on mathematical and astronomical subjects.

After his marriage to Madeleine Tornebüe in 1531, Fernel had to give precedence to his tasks as a physician, but he continued teaching until 1550 when his medical practice had become too large. His medical lectures were probably private, because he was never officially appointed to the university, while the relations with his colleagues at the medical faculty were strained. In 1542, he was appointed physician to the Dauphin; when the latter became King Henri II in 1547, Fernel excused himself from the function of royal physician but accepted it 10 years later.

Source: Portrait courtesy of Wellcome Foundation.

Spirits and the Brain: Jean Fernel's Interpretation of Galen's Model

A didactic synthesis of Galen's ideas about brain function appeared in 1554, in a seminal book called *Medicina* by Jean Fernel (1497–1558) (Box 1.3). His erudition is the more remarkable since he was largely self-taught after his graduation in Paris;[27] unlike young physicians from well-to-do families, he could not finish his education with a tour of foreign universities.[28] The first part of Fernel's book is entitled *Physiologia*. This newly coined term means 'Laws of Nature'; the neologism caught on and eventually withstood the test of time, though its meaning evolved. Fernel's book was the first treatise of its kind after Galen's *On the Function of Body Parts* (*De Usu Partium*).

Fernel systematically represented the Galenic model of the different spirits, with minor adaptations;[29] it is schematically represented in Figure 1.3. The

[27] Sherrington (1946), *The Endeavour of Jean Fernel*, 1–17.

[28] Frank-van Westrienen (1983), *De groote Tour*; Cunningham (2009), *Peregrinatio medica*; de Ridder-Symoens (2009), The mobility of medical students.

[29] Fernelius (1554), *Medicina (Physiologia)*, 120–1.

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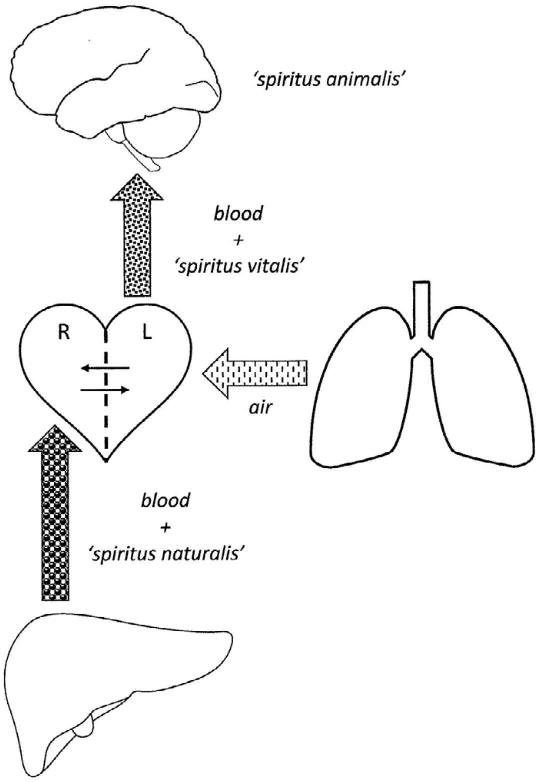

1.3 The synthesis of spirits, in three different phases. Schematic illustration of the Galenic model, according to Jean Fernel. The liver converts nutritional substances into blood and also produces a primitive form of spirit (*spiritus naturalis*). In the heart, a mixture with air and innate heat converts the spirits to a higher form (*spiritus vitalis*); the wall between the right and left ventricle is supposed to have tiny openings, not visible to the human eye. Finally, the brain produces the subtlest form of spirits (*spiritus animales*), which flow into the nerves and carry information about sensation and movement.

liver was thought to synthesize blood from digested food and also to add a vapour-like component, which Fernel and others preferred to call 'natural spirit', though Galen himself had been equivocal about its nomenclature.[30]

The second stage takes place in the heart. There, blood is thought to flow from the right to the left ventricle through small, invisible pores in the septum separating them. Famously, Andreas Vesalius (1514–1564) (Box 1.4), Professor of Anatomy and Surgery in Padua between 1537 and 1542,[31] had wondered about these invisible pores in the first edition of his seminal *Fabrica*;[32] in the second edition, 12 years later, he denied their existence.[33] At any rate, the 'invisible

[30] Rocca (2003), *Galen on the Brain*, 65–6.
[31] O'Malley (1965), *Andreas Vesalius of Brussels 1514–1564*.
[32] Vesalius (1543), *De humani Corporis Fabrica Libri septem*, 589.
[33] Vesalius (1555), *De humani Corporis Fabrica Libri septem*, 734, 746.

Box 1.4 Andreas Vesalius (1514–1564).

Vesalius, a teacher of surgery and anatomy in Padua between 1537 and 1542 and author of the epochal work *De Humani Corporis Fabrica* (1543), has become canonized to such an extent that it is difficult to imagine him as he was seen by his contemporaries.

His surname van Wesele was derived from the town of Wesel in the region of Cleve in Rheinland-Westfalen, at the confluence of the rivers Rhine and Lippe. Andreas' father Andries had distinguished ancestors but was an illegitimate child; he lived with his family in a somewhat inhospitable region of Brussels and was eventually employed as a pharmacist at the court of Emperor Charles V. Andreas went to a Latin school in Brussels, then took elementary university courses at Louvain; he went on to study medicine, mainly in Paris (1533–1536). After a final year in Louvain, he came to Padua, initially as a graduate student; after brilliant examinations, he was soon appointed Professor of Anatomy and Surgery.

Having completed the *Fabrica*, Vesalius became the personal physician to Emperor Charles V. In 1544, he married Anne van Hamme; they had a daughter with the same name. When Charles V abdicated in 1556, Andreas established a private practice and tried to respond to the careful and restrained comments on his anatomical work written by Gabriele Falloppio (*c.*1523–1562), one of his successors. In 1564, Vesalius made a pilgrimage to Jerusalem; on the return journey, he became ill on board and died on the island of Zakynthos, off the Western coast of Greece.

Source: Portrait courtesy of Wellcome Foundation.

pores' in the interventricular septum were an important element of the Galenic model. The mixture of blood and air, as well as the 'innate heat' of the heart, were supposed to transform the primitive spirits into 'vital spirit' – a subtler, energy-carrying principle that sustained all elementary functions of the body.

In the third and final stage, as the theory goes, the vital spirit is transported to the ventricles of the brain, via the choroid plexus. During this passage, it is transformed into the subtlest form of spirit, thanks to the intrinsic properties of the brain, with some contribution from air inhaled through the nose. Galen designated it as πνευμα ψυχικον, 'psychic spirit'. The Latin translation is *spiritus animalis*; the adjectival noun does not refer to beasts (*animalia*), but to *anima* or 'soul', the intrinsic principle of all living creatures, to be distinguished from 'animus', the rational faculty of mankind. The English translation 'animal spirits' is infelicitous, since it plainly refers to animals. The alternative term 'mental' excludes interaction with muscles; 'nervous' comes close, but in the sixteenth century, that designation had not yet included the brain. The best choice seems 'animated spirits'.[34] These spirits, Galen and Fernel thought,

[34] A suggestion of Dr Dirk van Miert.

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perform all the functions of the brain, internal (reasoning, imagination, and memory) as well as external, by flowing either from the cavities of the brain into its nerves and giving rise to movement or, conversely, by mediating sensory impressions.

Since Galen had performed many dissections and experiments on animals,[35] he cleverly introduced empirical details in his writings. Yet a substantial part of his theories remained speculative and heavily influenced by Aristotelian teleology, in that Galen often explained physiological actions by their utility. The notion that the contents of the cerebral ventricles were more important than the surrounding brain tissue was not surprising, given that 'fluidism' was an important principle in ancient medicine. And, practically speaking, the main point of pouring or drinking is the fluid, whereas the can or the cup is a mere utensil. Even at the end of the eighteenth century, at least one serious anatomist still proposed the ventricles as the true 'organ of the soul'.[36]

The Rete Mirabile

An anatomical issue related to the production of animated spirits, controversial for several centuries, was Galen's description of the 'wonderful network' (*rete mirabile*) of vessels at the base of the brain. This structure is present in many kinds of sheep, oxen, and other ungulate animals, mostly outside the *dura mater* or enveloped by a duplicature of this membrane.[37] Galen assumed a similar structure in humans. In most interpretations of Galenic texts, it was this basal network of vessels that was assumed to convert vital spirits into animated spirits; in Fernel's view, we saw, most refinement of the spirits took place in the ventricles, with only a minor role for the network.[38]

An early anatomist, Berengario da Carpi (*c.*1460 to *c.*1530), from Bologna, had expressed doubts about the existence of such a vascular web at the base of the brain.[39] Vesalius initially accepted the existence of the network and even included it in a drawing,[40] but in his later *Fabrica* he made it abundantly clear that such a structure did certainly not exist in man (Figure 1.4).[41] Perhaps Fernel, a 'physiologist' rather than an anatomist, had not yet noticed Vesalius' criticism, or he had decided not to change his views.

35 Mattern (2013), *The Prince of Medicine*, 145–55; Nutton (2020), *Galen*, 62–4.
36 Sömmerring (1796), *Das Organ der Seele*.
37 Gillan (1974), Blood supply to brains of ungulates with and without a rete mirabile caroticum; Rocca (2003), *Galen on the Brain*, 205–10.
38 Fernelius (1554), *Medicina (Physiologia)*, 121.
39 da Carpi (1530), *Isagogae breves et exactissimae in Anatomiam humani Corporis*, O5r–6r.
40 Vesalius (1538), *Tabulae anatomicae sex*, tabula III.
41 Vesalius (1543), *De humani Corporis Fabrica Libri septem*, 310.

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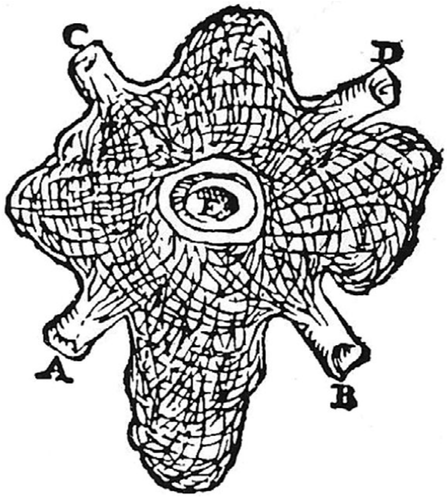

1.4 The 'miraculous network', drawn by Vesalius, though he no longer believed in its existence. His own legend reads: 'In this figure I made up the network as it must be in order to agree with the descriptions of Galen in his book *On the usefulness of the Parts*. A and B might indicate the arteries entering the skull, soon to disperse in that miraculous tangle; as C and D [I drew] the branches in which the elements of this network are assembled; they precisely correspond in size to the arteries I indicated by A and B. E represents the gland receiving the phlegm from the brain.' (Vesalius, 1543, p. 621).

The Exit for Fluid from the Ventricles

The excrements of the brain, Fernel wrote, again following Galen,[42] are a watery substance left over after the brain tissue has been nourished by blood. It is collected in the ventricles of the brain, from which it 'retains a certain cold and humid constitution' before being excreted via the base of the brain to the palate and the nose, from which it is removed by blowing one's nose or by spitting.[43]

Vesalius elaborated on this idea by regarding the most caudal extension of the third ventricle as the passage through which the waste products passed out of the skull. He therefore called this part the *infundibulum*,[44] Latin for 'funnel', 'basin', or 'cup'. He included a small drawing (Figure 1.5) to illustrate how the fluid from the ventricles might pass down to the gland below; he called it the *glandula pituitaria*, or viscous gland. Today it is known as the pituitary gland, or hypophysis, buried in the skull base and separated from extracranial structures by a thin layer of bone. Though Vesalius castigated Galen for his belief that viscous fluid from the brain could pass through the skull base more anteriorly,[45] he did

[42] Galenus (1625c [*c.*180]), *De Usu Partium* (C1) VIII, 168 B-C; Kühn, ed. (1821–33), *Claudii Galeni Opera omnia*, vol. III, *De Usu Partium*, 649–50; Rocca (2003), *Galen on the Brain*, 124–5.
[43] Fernelius (1554), *Medicina (Physiologia)*, 183, 192.
[44] Vesalius (1543), *De humani Corporis Fabrica Libri septem*, 640.
[45] Vesalius (1543), *De humani Corporis Fabrica Libri septem*, 32 and 641.

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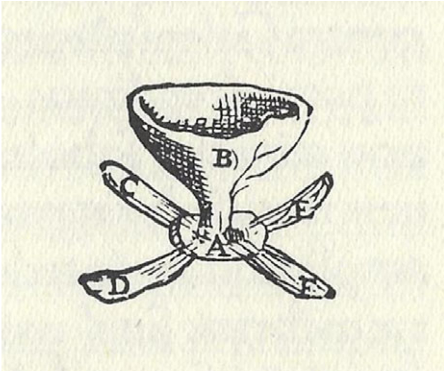

1.5 Vesalius' drawing of the exit for fluid from the ventricular system. His legend reads as follows: 'With this figure I drew the basin ('pelvis') or cup, through which the phlegm (*pituita*) of the brain drips into the gland below it. I also drew four small channels carrying phlegm through openings close to the gland. Thus, A is the gland to which the phlegm trickles down, B the basin through which it is led there; C, D, E and F are the channels fashioned to allow an easier exit for the phlegm that comes down.' (Vesalius, 1543, p. 621)

not shy away from a similar speculation himself; he even adorned his drawing with a number of channels leading away from the pituitary gland.[46]

THE PRESUMED CAUSE OF APOPLEXY: BLOCKED VENTRICLES

The clinical features of apoplexy, with the sudden cessation of all brain functions while breathing and arterial pulsation are preserved, suggested to sixteenth-century physicians a sudden disruption in the traffic of spirits between their storage sites in the brain and their flow into the nerves. They followed Galen's explanation of apoplexy as obstruction within the ventricular system. In the didactic style of Jean Fernel:

> The cause [of apoplexy] resides in the brain, the common origin of all movement and sensation. Actually, it is phlegm, too thick and too cold; for it is improbable that it can occur as a result of blood or black bile, even if these abound in the entire body. And this cold phlegm, despite forming the brain's own excrement, brings about apoplexy when it abundantly fills all its ventricles [...][47]

Different Humours Incriminated as Potential Causes of Obstruction

Despite general agreement on obstruction of the ventricles as the key event in apoplexy, opinions differed on the question of which fluid most often caused such impediment.

[46] Vesalius (1543), *De humani Corporis Fabrica Libri septem*, 641.
[47] Fernelius (1554), *Medicina (Pathologia)*, 133.

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Phlegm. Fernel was rather emphatic in his opinion that phlegm was the exclusive culprit. Many others disagreed. An example is Pieter van Foreest, who determined the nature of the fluid from circumstantial evidence: phlegm if it occurred in someone with a pale complexion and a weak pulse or during cold weather, excess of blood in a plethoric person, or black bile in an individual with a melancholic disposition.[48] Other sixteenth-century physicians favoured blood or black bile as the main causative agent.

Blood. Petrus Salius Diversus (*fl.* second half of the sixteenth century), practising in Faenza, emphasized the importance of identifying blood as the cause of apoplexy. He warned that warming the head, a common treatment for apoplexy if it was attributed to an excess of cold fluids, could be disastrous in sanguineous apoplexy.[49] Felix Platter (1536–1614), Professor of Medicine in Basle, implicated blood more often than phlegm as the cause of apoplexy. He regarded haemorrhage through the nose or mouth as a sign that blood had invaded the brain,[50] a comment suggesting that such 'apoplectic states' actually resulted from trauma, not from spontaneous disease.

An excess of blood could be assumed as the cause of apoplexy not only in a person with a reddish, 'plethoric' face, but also after cessation of customary blood loss, for example menopause. It was in this manner that the German surgeon Wilhelm Fabry (1560–1634) explained apoplexy in a goldsmith from Lausanne who had suppressed his recurrent heavy nosebleeds by wearing an amulet.[51]

Black Bile. It was received knowledge that under some circumstances, accumulation of black bile or melancholy also could give rise to apoplexy. Only Fernel was a conspicuous dissenter. A completely opposite stance was that of Girolamo Cardano (Hieronymus Cardanus; 1501–1596), a philosopher, physician, astronomer, and mathematician, at one time a teacher in Padua, but often moving around because of his great talent for making enemies;[52] he postulated that practically *all* cases of apoplexy are caused by black bile.[53]

The only way to try and end the debates was by having a look.

OPENING THE SKULL

Infringing on the human body after death has always been met with apprehension and taboo. In the eyes of the public, there was – and sometimes is – no great distinction between, on the one hand, necropsy by physicians

[48] Forestus (1653 [1590]), *Observationes et Curationes*, vol. X, 514–15.
[49] Diversus (1584), *Curationes quorundam particularium Morborum*, 231.
[50] Platerus (1602), *De Functionum Laesionibus*, 27.
[51] Fabricius (1614), *Centuria tertia*, 57–8.
[52] Siraisi (1997), *Girolamo Cardano*.
[53] Cardanus (1564), *Aphorismorum Hippocratis Particulas Commentaria*, 727.

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investigating the causes of disease in patients they had been trying to save, and, on the other, dissection as a method to instruct medical students in the details of anatomy.

Dissection and Disgrace

Being 'anatomized' could be the fate of criminals undergoing capital punishment, a disgrace compounded by the perceived ignominy of being denied a proper burial. Such views have largely persisted through time. A somewhat anachronistic, but irresistible, example one finds in the following passage from a well-known nineteenth-century British novel:

> Mrs Dollop became more and more convinced by her own asseveration, that Dr Lydgate meant to let the people die in the Hospital, if not to poison them, for the sake of cutting them up without saying by your leave or with your leave; for it was a known 'fac' that he had wanted to cut up Mrs Goby, as respectable a woman as any in Parley Street, who had money in trust before her marriage — a poor tale for a doctor, who if he was good for anything should know what was the matter with you before you died, and not want to pry into your inside after you were gone.[54]

The Anatomy of Disease

In fact, there are vast differences between the two procedures. Apart from the minds and aims of doctors, the locations where the dissections take place differ – anatomical theatre versus mortuary, improvised or not – and so does the very method of the procedures. It is therefore surprising that some historians make little or no distinction between these two kinds of dissection.[55] As an investigative tool for understanding disease, it is commonly called autopsy, thus with a more restricted meaning than its literal translation from Greek ('to see for oneself').

In the distant past, medical dissection of the human body after death took place only in Alexandria, and presumably only in the third century BCE.[56] The Alexandrian physician Erasistratus (*c.*310–250 BCE) was exceptional in that he investigated solid organs.[57] Autopsy was forbidden in all other periods of antiquity, including Galen's time. An exception is in the preparation for embalming, which was almost always carried out by servants.

[54] Eliot (2011 [1872]), *Middlemarch*, 442–3.
[55] Sawday (1995), *The Body Emblazoned*.
[56] von Staden (1992), Human dissection in ancient Greece.
[57] King and Meehan (1973), A history of the autopsy.

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In the thirteenth and fourteenth centuries, dissection of cadavers occurred in northern Italy on rare occasions, mostly for legal reasons. The attitude of the Catholic Church has often been represented as antagonistic, but there are valid arguments for believing that clerical authorities have favoured, rather than opposed, post-mortem investigations in humans.[58] Autopsy even played a role in the canonisation of saints.[59] If clerical opposition did occur, it tended to be less if the purpose of dissection was scientific, and not didactic.[60] In general, resistance mainly sprang from humanitarian and aesthetic concerns. In the course of the fourteenth century, dissections were gradually introduced in medical schools, as evidenced in the earliest anatomical treatise by Mondino dei Liuzzi.[61]

As long as Galenic texts dominated medical knowledge, there was little aspiration to expand the use of dissection, as it had little relevance to medical practice; exceptions in the late fifteenth and early sixteenth century were Benedetti, Benivieni, and Massa.[62] But in the second half of the sixteenth century, physicians became more inquisitive and increasingly performed post-mortem dissections, either with permission or furtively. Felix Platter (1536–1614), Professor of Medicine in Basle, confessed to once having visited a cemetery in the dead of night and secretly dissected the body of a phthisic boy with a perforated stomach.[63]

First Glances at the Brain after Apoplexy

Thus, to open the skull of a person who had died after apoplexy was a momentous decision, given the resistance of relatives and friends. Even from a purely practical point of view, the procedure is far from easy, since it requires effort, expertise, and equipment. Physicians might have had little, if any, first-hand experience and had to rely on recollections of anatomical demonstrations from their student days; a colleague or surgeon might have assisted. Finally, physicians needed good reasons for doubting the accepted Galenic doctrine that in apoplexy, the cavities of the brain were stuffed, probably with phlegm. Most medical practitioners in the second half of the sixteenth century felt satisfied with that assumption and did not feel the need to verify the dogma and take the trouble to obtain permission and seek assistance.

Jean Fernel published in 1548, six years before his seminal *Medicina*, an example of what was probably the first autopsy report of apoplexy, in a book with the

[58] Cunningham (2010), *The Anatomist Anatomis'd*, 12–15.
[59] Bouley (2017), *Pious Postmortems*. [60] Carlino (1994), *Books of the Body*, 182–6.
[61] Dei Liuzzi (1988 [1316]), *Anothomia*. [62] Carlino (1994), *Books of the Body*, 191–3.
[63] Platerus (1614), *Observationum, Libri tres*, 407.

intriguing title *De abditis Rerum Causis*, or *About hidden Causes of Things*. Surprisingly enough, Fernel found the lesion not in the brain, but under it:

> Once I saw that a man, [previously] in perfect health, had suddenly collapsed after a rather strong punch on the left eye, in a stunned state, soon deprived of sensation and motion, with difficult breathing and snoring as well as other signs of a severe apoplexy. He could not be saved by venesection or in another manner and died after twelve hours. I thought therefore that the cause of death was worth investigating. When the head had been dissected and opened, the bone, the membranes and the substance of the brain showed nothing that was broken or bruised; yet I detected that the mere force of the blow had ruptured the internal veins of the eye. From these a volume of two spoonfuls of blood had extended to the base of the brain; having clotted, this narrowed the arteries that form the net-like structure.[64]

The sentence 'I thought therefore that the cause of death was worth investigating' sounds mundane but is, in fact, revolutionary. Fernel must have had qualms about the usual explanation that phlegm had suddenly filled the cavities of the brain, given the preceding blow. Fernel's case, though perhaps attributable to trauma, is important because later generations of physicians often cited it; also, several questions remain open, which exemplifies how difficult it was at the time to investigate the brain without knowing what to look for.

One initial problem is that the blood vessels in the eyes are enclosed in the orbits; it is not impossible to open them, but they are certainly not immediately spotted after the top of the skull has been taken off, which is the usual procedure. More important is the possible contradiction between the finding that the membranes of the brain were intact and that, on the other hand, there were about two spoonfuls of blood at the base of the brain. Was the blood found inside or outside the hard membrane (*dura mater*) surrounding the brain?

Fernel's conclusion that the pool of blood must have compressed the net-like arteries is remarkable, given that he could not have seen such a network – he just assumed it was there. On the same page, Fernel briefly mentioned that he had dissected another patient after 'apoplexy', without details; he found that a thick, viscous fluid compressed this same arterial web he deemed present at the base of the brain, but that he could not truly have seen.

Other observations of brain dissection in the sixteenth century are extremely sparse, at least in reports of individual patients; general comments such as 'After death by apoplexy one often sees . . .' probably reflect opinion rather than perception. There are two more instances from the sixteenth century; in both cases, the reader has to take the diagnosis of apoplexy for granted, because no clinical information is given. One of these cases is by Louis Duret (1527–1585),

64 Fernelius (1548), *De abditis Rerum Causis*, 218.

nominated Professor of Medicine in 1568 at the *Collège de France* in Paris.[65] In his commentaries on Hippocrates' *Coan Ideas*, which appeared posthumously, he briefly alluded to dissections he performed on two dignitaries who had died after apoplexy:

> The exit of animated spirit is blocked because the cavities of the brain are filled by an excessive amount of phlegm, black bile or blood. And when they are being filled, not when they are full, the symptom is that of an epileptic convulsion, which is ended by an apoplectic paralysis. I have seen this in the Bishop of Nevers and in the Tax Collector of Ballon; when they had relinquished their life, it was found that the cavities were filled with blood that had burst into them.[66]

In both patients, the site of obstruction was the ventricular system of the brain, perfectly in line with the Galenic doctrine. However, the observations were cursory, almost timid: the brain must have been cut open to arrive at the ventricles, but there is no information about a possible source of the haemorrhage elsewhere. Moreover, a single, brief sentence summarizes the findings in two different patients.

Details are also sparse in a second report by Duret's contemporary Marcellus Donatus (1538–1602), the personal physician of the Duke of Mantua;[67] he examined the body of a court dignitary:

> I was charged with dissecting the administrator of her Highness Maria Justiniana de Arrivabene [in Mantua], who had died of a severe Apoplexy. I brought with me as witnesses the gentlemen Hippolitus Genifortus from Mantua and Ludovicus Cangerla from Vicenza, both practising surgeons in our town; they were present at the dissection. We found that the entire substance of the brain was drenched and filled with an aqueous fluid, which had also flowed into the ventricles of the brain. And, which was truly remarkable, when the temporal arteries[68] had been opened, thick and black blood flowed out in such great profusion that I could hardly believe that so much could be found in the entire body.[69]

A circumstantial, but noteworthy, detail is the presence of colleagues as witnesses. Still, it seems that, in fact, the three physicians did not find very much. Fluid in the cavities of the brain, as well as in the space between the brain and its membranes, was a normal feature of anatomy, well known at the

65 Hirsch (1884–8), *Biographisches Lexikon*, vol. II, 244.
66 Duretus (1588), *Hippocratis Magni Coacae Praenotiones*, 366.
67 Hirsch (1884–8), *Biographisches Lexikon*, vol. II, 202.
68 It is uncertain whether 'temporal' refers to an extracranial or an intracranial artery.
69 Donatus (1586), *De medica Historia mirabili Libri sex*, 59v.

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time. Apparently, the amount of fluid seemed excessive, as was the volume of blood. A quantitative judgement of this kind presupposes extensive practice in dissecting brains, a level of experience that seems quite unlikely for that period.

THE ROLE OF THE VENTRICLES CHALLENGED

It was a common, and almost sacrosanct, belief that the ventricles of the brain were the production site, or at least the repository, of animated spirits and that these cavities also formed the passage through which all signals of sensation and movement flowed from or into nerves. This idea was finally challenged in the second half of the sixteenth century, on the basis of two different objections. One was based on the structure of the brain; the other was represented by two almost identical reports of infantile hydrocephalus.

A New Dissection Technique: Removing the Brain from the Body

The person who publicly questioned the role of the cerebral ventricles as the passage, if not the smithy, for animated spirits was an ambitious young anatomist from Bologna – Costanzo Varolio (1543–1575) (Box 1.5). Information about his life is regrettably scarce.[70]

Importantly, Varolio introduced a new method of dissecting the brain after the top of the skull had been removed. By carefully tilting the brain and cutting its nerves and blood vessels as they came into view near the skull base, he managed to free the organ from its attachments and remove it entirely from the skull and the rest of the body. Turning the brain upside down and removing the dura mater provided a full view of the basal structures.[71] The woodcut, based on Varolio's own drawing (Figure 1.6A), is less artistic than the corresponding illustration in Vesalius' *Fabrica* of 30 years before (Figure 1.6B), but has more accuracy of detail. Probably Vesalius' version was made at a later stage in the dissection, after most upper parts of the brain had been cut away in the usual fashion, from top to bottom. The longer the time interval between death and dissection, the softer the brain tissue became.

Removal of the brain from a cadaver had far greater implications than the mere practicality of allowing to invert the brain and study its contours in more detail. The new procedure revealed the brain as an isolated object, disengaged from the body and its identity – now a 'thing', inviting close scrutiny.

[70] Tubbs, *et al.* (2008), Costanzo Varolio; Zago and Meraviglia (2009), Costanzo Varolio.
[71] Varolio (1573), *De Nervis opticis*, 11r–12r.

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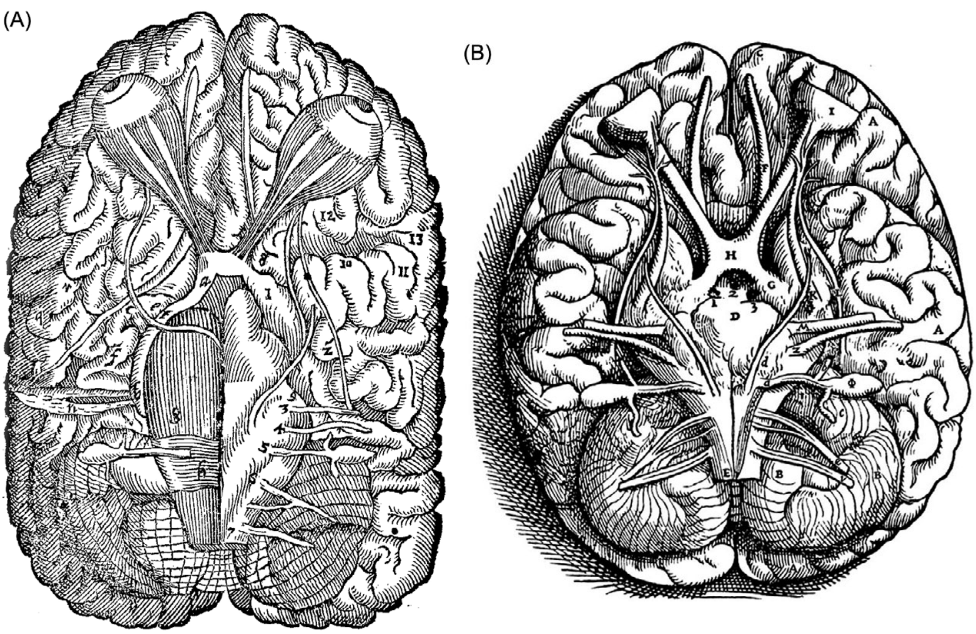
Box 1.5 Costanzo Varolio (1543–1575).

Little is known about Varolio's youth, except that he was born in Bologna, in the year that also saw the first edition of Vesalius' *Fabrica.* Coincidence or not, Varolio always admired Vesalius' work and strived to follow his example. Probably they never met. The profession of Varolio's father is unknown. Costanzo studied medicine at the University of Bologna and graduated in 1566. Anatomy was taught at the time by Julio Caesar Aranzio (1530–1589). In 1569, the senate of Bologna appointed Varolio to an extraordinary professorship of anatomy and surgery; he focused his own investigations on the structure of the brain.

Two years later, Varolio moved to Rome, probably because of the controversies his findings had stirred up in Bologna. He earned a solid reputation as a medical practitioner, especially for removal of stones from the bladder. Rumour has it that he was close to Pope Gregory XIII, but it is uncertain whether he acted as his personal physician. He died from an unknown ailment in 1575, aged 32 years.

Source: © Biblioteca Comunale di Bologna.



1.6 (A) View of the base of the brain after the entire brain has been detached from the skull and turned upside down (Varolio, 1573). The cranial nerves are numbered from 1 (optic nerve) to 7. A main issue on which Varolio wanted to insist was that the optic nerve continued much further backwards (to the bottom of the drawing) than had been assumed previously. Incidentally, Varolio also identified the 'bridge' (*pons*), the transversely striped structure marked 'h'. (B) The base of the brain, in Vesalius' *Fabrica.* The optic nerves, having crossed, seem to end in the medial part of the temporal lobes. The structure of the brainstem, especially the outline of the pons, is less accurately represented than in Varolio's illustration (A). Both illustrations leave out blood vessels. The pit between 'H' and 'D' indicates where the funnel-like structure drawn in Figure 1.5 is thought to excrete superfluous fluid from the brain into the pituitary gland. (Vesalius, 1543, p. 315).

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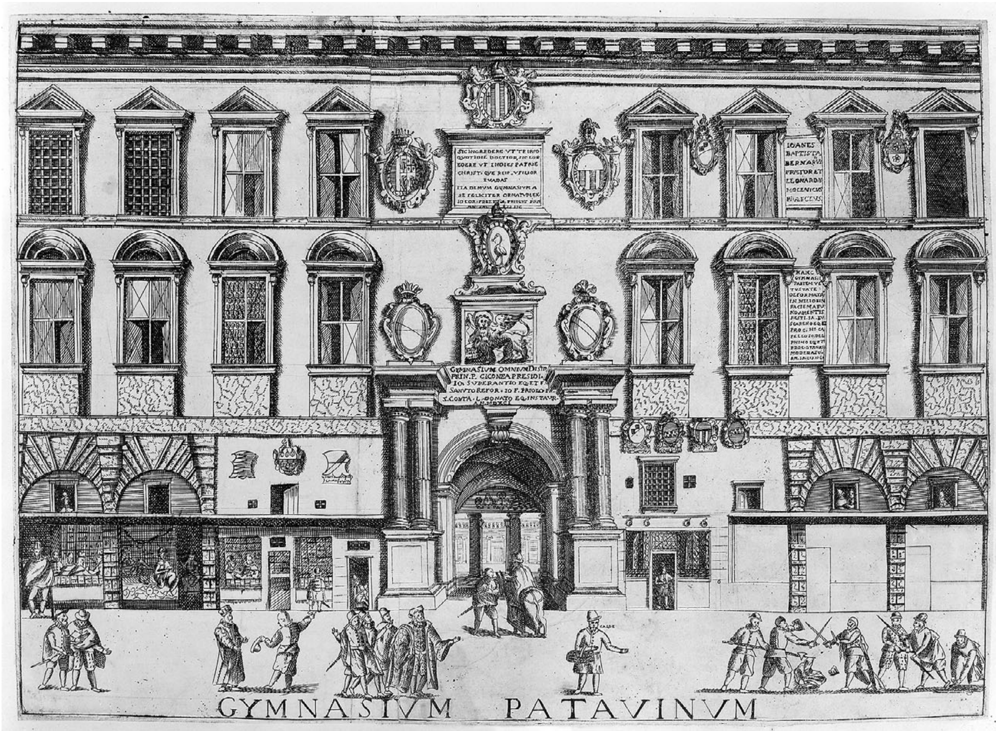

1.7 The university building (*archiginnasio*) of Padua. Engraving by Giacomo Filippo Tomaselli, 1654. *Source:* Courtesy of the Wellcome collection.

A Revolutionary Idea: Ventricles Mainly Serving as the Sewer of the Brain?

In 1572, shortly before Varolio's departure from Bologna to Rome, where he was to die three years later, he wrote a letter to Hieronimus Mercurialis (Girolamo Mercuriale; 1530–1606), who had been appointed in 1569 as Professor of Theoretical Medicine in Padua. Padua was another centre of medical learning (Figure 1.7),[72] governed by the powerful city state of Venice, and therefore less subject to ecclesiastical rule than Bologna. The Paduan university attracted the best professors from abroad, for example Vesalius for anatomy and surgery, at least between 1537 and 1542. Also, the senate of Venice allowed admission of students from all regions of Europe, including Protestants and Jews.[73]

Mercurialis enjoyed a great reputation by virtue of his expertise in ancient Greek medical texts.[74] It is clear from the tone of Varolio's letter that he regarded Mercurialis, his senior by 13 years, as a higher authority; he appealed to him as an impartial judge to whom he submitted his new findings on the

[72] Gallo (2001), *L'Età Medioevale*. [73] Bylebyl (1979), The School of Padua.
[74] Hirsch (1884–8), *Biographisches Lexikon*, vol. IV, 209–10; Ongaro (2007a), Girolamo Mercuriale.

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anatomy of the brain.[75] Some controversy had arisen between Varolio and his colleagues in Bologna about the structures at the base of the brain, especially the course of the optic nerves and the structure of the brainstem – findings that were in conflict with received opinion;[76] apparently, the young anatomist sought support from Mercurialis. But in the course of his argumentation, Varolio came up with a revolutionary proposition on another subject, that of the cerebral ventricles. To soften the blow, he introduced it with a polite and tentative phrase:

> Highly esteemed Mercurialis, the principal target I aim for in this work must be to be engaged with an account of [the structure of] the head, disregarding all speculations. Yet I shall not be silent on what I feel about the function of the ventricles of the brain. As you know, the common and most widespread opinion is that the ventricles of the brain are the home of the animated spirits, in the same way as the left ventricle of the heart is the home of the vital spirits. Surely, I would not dare to attack this opinion, since nobody could ever undertake this without the stigma of defiance. Yet I will propose for your consideration a single function as the main one. I should like you to think that I submit it in a doubtful manner rather than as a certainty. [. . .]
>
> Presently it is known to all that phlegm drips from the brain to the palate via the infundibulum; if one considers the arrangement of the body parts through which the phlegm passes, it will be easily understood that it is first collected in the ventricles. [. . .] Therefore, I conclude that the primary function of the ventricles of the brain is to serve as receptacles for viscous fluid that is generated in the brain and excreted via the palate. And this is not incompatible with the very common convictions of those who think they are the home of animated spirits, since (as has been said before) more functions can be assigned to a single part [of the body].[77]

Animated Spirits Conveyed by the Substance of the Brain?

Mercurialis flatly disagreed. After many compliments about Varolio's new anatomical findings, he adduced many citations from Hippocrates, Plato, and Galen, before opposing the idea of an excretory function of the ventricles in his own words:

[75] Varolio's letter was printed in 1573 in Padua, together with Mercurialis' response and Varolio's rejoinder; in 1591, a reprint appeared in Frankfurt.

[76] The most important novelty in Varolio's findings was that the optic 'nerves' continued much further backwards than traditionally assumed; the conventional opinion was that they ended in the thalamus – hence its full name 'thalamus opticus'.

[77] Varolio (1573), *De Nervis opticis*, 7v–9v.

> By the manner in which you have used that peculiarly sharp mind of yours to explain the function of the ventricles of the brain, you have at the same time (please allow me to say this) got yourself entangled in inextricable difficulties. For how can it happen that at the same site where the most pure and subtle bodies, the spirits, are concocted and perfected, in a stove as it were – that in that same place a thick, cold, dark fluid is collected, [a fluid that is], let me say it with a single word, highly toxic for the spirits themselves? What is more, when apoplexy occurs, completed or in progress, or epilepsy, or a nightmare, all writers of medicine implicate the following as causes, that phlegm, black bile or too thick winds are retained in the ventricles. These [fluids], filling them entirely or for the largest part, strangle the spirits, as it were.[78]

Varolio reciprocated, after profuse expressions of gratitude towards Mercurialis, that he persisted in his opinion about the excretory function of the ventricles. He went as far as proposing a different medium for the transport of spirits: the tissue of the brain! He introduced a new argument, on top of his earlier proposal that excretion of waste products might be the main function of the ventricles. This was the fact, supported by Galen, that most nerves in the skull originate from the brainstem. Large-scale transport of spirits by the brainstem would be at odds with the absence of a corresponding central cavity, if ventricles indeed acted as a store room for spirits; conversely, very few nerves take their origin from the brain area with large ventricles.

> Galen says in *De usu partium* (Book 8, Chapter 13) that animated spirit is contained in large amounts in the entire mass of the brain, and similarly in that of the cerebellum, which he regards as the beginning of the nerves of the entire body; he even infers from this that [the cerebellum] must necessarily be crammed with spirits. If therefore the cerebellum, though lacking any cavity, contains such an excess of spirits in its substance that these [spirits] can flow from there to all parts of the body; for what reason, I beseech you, have such large cavities been created for the sake of animated spirits for the brain, which conveys only nerves and spirits to the parts in and around the head, according to Galen? If spirit flows from the cerebellum to so many nerves, over such great distance, why does it not rather flow in the same way, without cavities and channels, from the brain to fewer and much closer parts?[79]

Normal Ventricles in Victims of Apoplexy?

One of Mercurialis' objections was that assigning the transport of animated spirits to the brain tissue itself undermined the time-honoured belief that

[78] Mercurialis (1573), Responsio, 23r–v. [79] Varolio (1573), *De Nervis opticis*, 26r–v.

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blocked ventricles were the cause of apoplexy and other acute brain disorders. But Varolio, recalling from Galen that apoplexy could also occur with lesions of 'the beginning of the spinal medulla' (currently called *medulla oblongata*), now came up with an astonishing fact:

> You will perhaps admit, to paraphrase Galen (*De locis affectis*, Book 3, Chapter 7) at least in part, that epilepsy and other, similar affections arise because obstruction of spirits has occurred by humours abnormally irrigating the beginning of the spinal medulla. This point of view is supported by dissections of patients who have died of Apoplexy in whom (please believe me) no greater quantity of excrements is found than one usually finds in all others.[80]

Varolio's surprising argument that post-mortem studies of patients who had died of apoplexy had shown the same quantity of fluid in the ventricles as in persons without brain disease seems important in the light of later developments. Yet it was a casual, almost offhand remark, not substantiated with details about person, time, or place, let alone supported by witnesses. By contrast, Varolio's exclamation 'please believe me' rings with such conviction that the observation was perhaps his own, not just hearsay.

Why did the striking finding that patients with fatal apoplexy had normal ventricles fail to be publicized? Presumably because the finding conflicted with received opinion – such facts were inconvenient, unwelcome, and unheard of, things one might gossip about but not openly discuss. The same cognitive distortion that caused Fernel to see a non-existent structure because he supposed it was there could have led others to deny, or at least suppress, observations that went against the grain of common tradition.

Infantile Hydrocephalus: Occluded Ventricles, Yet Sensation and Motion

Two almost identical observations cast even more doubt on the notion that brain function depended on its cavities. Both concerned a young child with progressive and ultimately fatal enlargement of the lateral ventricles; the salient point with regard to brain function was that the children had for a long time been able to move and interact.

The first report appeared in print in the middle of the sixteenth century; it did not attract immediate attention but was increasingly cited as time went on. Its author was none other than Andreas Vesalius, in the second edition of his *Fabrica*:

> In Augsburg I saw a girl of two years whose head had enlarged in about seven months to such an extent that no head of any man I have ever seen

[80] Varolio (1573), *De Nervis opticis*, 28r–v.

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> could compare with that mass. This was the affection the ancients called hydrocephalus, from water retained and gradually collected in the head. [. . .] Here it was in the cavity of the brain itself, in fact in the right and left ventricle; their volume and width had enlarged to such an extent, and the brain itself was so much stretched that they contained – so help me God – almost nine pounds of water, or three Augsburg measures of wine. As a result, the brain at the top of the head was thin like a sheet and somehow continuous with its tender membrane. The skull also was quite soft; only the lower part was bony, corresponding to the width of the girl's skull before her head had expanded abnormally. [. . .] In conclusion, I was exceptionally astonished – with the Physicians who were present – that such a mass of water had for such a long time been collected in the ventricles of the brain without major symptoms. [. . .] Until her death the girl has been in complete command of her senses.[81]

The second record is in the writings of the surgeon Wilhelm Fabry or Guilhelmus Fabricius (1560–1634) (Box 1.6);[82] he had also contributed the case of the goldsmith and his suppressed nosebleeds. The sad story of the young child had occurred in 1594:

> In a neighbourhood of Cologne called *Ehrestrasse* I saw several times a boy, son of parents in robust health. [. . .] His head started to grow enormously when he had barely reached the age of seven months. No disease had preceded this; yet the rest of the body was poorly developed. Within 30 months the head increased to the size I indicated. In the end he lapsed into a lethargic sopor and died not much later, on February 19, 1594. When the head was dissected, in the presence of the very learned physicians *Joannes Slotanus* and *Henricus Pallantius*, we found water in the two anterior ventricles, clearer than crystal, with a volume of 18 Cologne pounds. This [fluid] stretched not only the ventricles, but also the substance of the brain, to such an extent that the entire brain (with the exception of the cerebellum) was as thin as the cloth of a bag. [. . .]
>
> Indeed, he had eaten, drunk, excreted and slept like a normal [child]; only proper growth had been lacking, for his entire body (with the exception of the head) remained quite small and diminutive, as appears from the picture drawn true to life that I have at home.[83]

Several aspects of these case histories are noteworthy. To begin with, it is a vital piece of information that both infants had moved and interacted with their parents long after enlargement of the ventricles had started to occur. A second peculiarity is the very fact of the autopsies, for which the children's parents must have given their permission. As intimated above, it was an uncommon

81 Vesalius (1555), *De humani Corporis Fabrica Libri septem*, 24.
82 Jones (1960), Fabricius Hildanus. The addition 'Hildanus' refers to Fabry's birthplace Hilden.
83 Fabricius (1606), *Observationum & Curationum chirurgicarum Centuriae*, 60–1.

Box 1.6 Guilhelmus Fabricius (1560–1634).

Wilhelm Fabry, the 'father of German surgery', was born in Hilden, Nordrhein-Westphalia, where now a bust of him overlooks a central square. His father, a court clerk, died when Wilhelm was still young; his mother remarried but was soon widowed again. At school, Wilhelm showed great talents; he might have gone to university, had not the Thirty Years War caused a complete upheaval of normal life. Eventually Fabry had to give up his ambition of being a doctor. Instead, he became an apprentice to several surgeons; one of them was Cosmas Slotanus, a surgeon at the ducal court in Düsseldorf and a pupil of Vesalius. Wilhelm not only was introduced to modern anatomy, but also learnt much from the physicians at the palace.

When Slotanus died in 1585, Fabry began a wandering existence. At first, he practised in Metz and Geneva, where he married Marie Colinet, herself a surgeon and an obstetrician. Further peregrinations included Cologne and Lausanne. As his fame increased, he travelled far and wide to wherever patients lived. From 1598 onwards, he published his case histories, one hundred at a time (*centuriae*). Several editions followed, in Latin and in vernacular language. In 1615, Fabry finally settled in Berne, as a surgeon to the town and canton. His later years were troubled by gout. On his death in 1634, Fabry left a wife and a son Johann, also a surgeon; seven other children did not survive him.

Source: Portrait courtesy of Wellcome Foundation.

event for physicians to dissect a cadaver. Fabry was an exception; he provided more examples of autopsy in his reports.[84]

Finally, both physicians enhanced the trustworthiness of their observations by inviting other physicians to attend and perhaps to participate; Vesalius only hints at the presence of colleagues, whereas Fabry even recorded their names. This is an early example of establishing 'matters of fact' by engaging witnesses of appropriate social stature to confirm new observations. This practice in medicine predates similar approaches to the advancement of knowledge by the experimentalists of the Royal Society a century later.[85] What is more, Fabry preserved some of the evidence by keeping the bony part of the skull and a drawing of the patient's body as exhibits in the 'Museum' at his home.

THE BRAIN SUBSTANCE VINDICATED AS THE SITE OF APOPLEXY

A few years after the Varolio–Mercurialis correspondence, the French-Swiss medical student Gaspard Bauhin, or Caspar Bauhinus, (1560–1634) (Box 1.7)

[84] Fabricius (1606), *Observationum & Curationum chirurgicarum Centuriae*, 132, 139–40, 197–9.
[85] Shapin (1994), *The Social History of Truth*, 212–32.

Box 1.7 Gaspard Bauhin (1560–1632).

Gaspard Bauhin was born in Basle as the second son of the physician Jean Bauhin. The father had studied in Paris under Sylvius (Jacques Dubois) and became a successful practitioner in the French capital, until 1532 when persecution of Protestant citizens forced the elder Bauhin to seek refuge in England. On his return, three years later, he narrowly escaped death on the pyre, thanks to the intervention of the princesses he had previously treated. Eventually father Jean settled in Basle.

Gaspard also studied medicine, first in Basle, then in Padua (1577–1579), and two more years in Montpellier; he settled in his home town in 1581. In addition to his medical practice, he taught anatomy and botany. In 1582, Bauhin also became Professor of Greek at the University of Basle. Seven years later, the same university appointed him Professor of Anatomy and Botany and, finally, in 1614, chair of Practical Medicine as the successor to Felix Platter. In 1623, Bauhin published *Pinax Theatri Botanici*, in which he described thousands of plants, with a simplified nomenclature predating the binomial system of Linnaeus. His elder brother Jean was also a botanist.

Source: Portrait courtesy of *Bibliothèque interuniversitaire de Santé*, Paris.

visited the universities of Northern Italy. Among the many books Bauhin published later in his career, the best known is his textbook of anatomy *Theatrum Anatomicum*, first published in 1605.[86]

The contents of the *Theatrum* make it abundantly clear that a printed version of the correspondence between Varolio and Mercurialis must have come to Bauhin's attention. He copied large portions of text, including Mercurialis' objections and also Varolio's woodcuts.[87] Nowadays it seems strange that Bauhin failed to cite Varolio, apart from casual acknowledgements elsewhere in the text, but laws or conventions for authorship and copyright were non-existent. Bauhin included parts of Varolio's argumentation not yet cited above; an example is Varolio's appeal to common sense in favour of his proposal that the fluid in the ventricles represents waste products from the brain:

> Indeed, we see before our eyes that if someone is voluntarily spitting, he first grates and grunts, as it were [to clear] the upper parts of the palate, [then] collects the portion of excrement in the cavity of his mouth and finally discharges it. If he immediately wants to spit again, he produces a smaller portion of sputum, and if he tries this once more without delay, he produces even less, so that soon a stage is reached where he comes up with nothing to spit out, although he forcibly clears his palate. But after

[86] Hirsch (1884–8), *Biographisches Lexikon*, vol. VI, 460–1.
[87] Bauhinus (1605), *Theatrum anatomicum*, 687.

> some time has elapsed, the excrement again easily descends into the oral cavity. This is a most obvious sign that the material is collected in some quantity before it is expelled, as we see with urine and faeces.[88]

At the end of the paragraph on the cerebral ventricles, Bauhin addressed the main issue: the location of animated spirits within the brain tissue. There he reproduced another argument of Varolio. Spirits do not take up space, Varolio reasoned; not even the cerebellum, which Galen supposed to be crammed with spirits, has discernible channels. Therefore, spirits do not require visible space either:

> Since Galen showed that animated spirit can flow and reflow without any discernible channel, [. . .] why can't we therefore assign it to the substance of the brain, [only] because some people assign it to the ventricles, which they have not properly studied?[89]

Later authors mostly cited Bauhin on this issue, instead of Varolio, who had first proposed it. Probably the original text had a modest circulation, in contrast to Bauhin's anatomy book, which became popular and was reprinted in 1621.[90]

The Seat of Apoplexy: Ideas Change Slowly

Bauhin, once back in Basle, must have disseminated the Varolian idea that animated spirits travelled via the tissue of the brain. Such relocation of the seat of movement and sensation to the substance of the brain did not fail to change ideas about the location of brain lesions causing apoplexy. At any rate, one finds this new opinion in the textbook written by Bauhin's older colleague and Professor of Medicine in Basle Felix Platter, or Platerus (1534–1614) (Box 1.8), whom Bauhin later succeeded. In Platter's explanation of apoplexy, he categorically and boldly located animated spirits in brain tissue, though partly retaining the traditional theory by his suggestion that abnormal fluids could affect brain tissue also indirectly, by inundation of its surface or by overfilling of the ventricles.

> If [phlegm] persistently inundates the brain substance to such an extent that the great mass of the brain is made too soft and too slack, it suddenly dissolves and collapses. [Then] it presses on the beginning of the nerves at the base of the skull, blocks the transit of the animated spirit, and gives

[88] Bauhinus (1605), *Theatrum anatomicum*, 696 (corresponding to Varolio (1573), *De Nervis opticis*, 31r–v).
[89] Bauhinus (1605), *Theatrum anatomicum*, 698 (corresponding to Varolio (1573), *De Nervis opticis*, 26v–27r).
[90] Bauhinus (1621), *Theatrum anatomicum*.

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Box 1.8 Felix Platter (1536–1614).

Felix Platter was born in Basle. His father Thomas, a humanist and self-educated teacher of Latin, Greek, and Hebrew, was headmaster of the local gymnasium and also functioned as printer and publisher. In 1552, Felix departed on horseback to study medicine in Montpellier, in the company of a friend. On his return, five years later, he extensively travelled in France before graduating in Basle and marrying Madlen Jekermann, the daughter of a local surgeon.

In 1562, Platter became Professor of Anatomy at the University of Basle, and in 1571 a city physician and Professor of Practical Medicine. Among the conditions he described were two affections now called 'meningioma' and 'Dupuytren's disease'. Felix Platter kept an accurate diary of his life as a student, which has been preserved.

Source: Portrait courtesy of Wellcome Foundation.

> rise to severe apoplexy. Of course, when phlegm suddenly fills the ventricles or cavities of the brain it can also cause apoplexy, [but] not through obstruction, since the animated spirit has its seat not in these [ventricles] but everywhere in the substance of the brain and in the nerves, and since [the phlegm] does not pass via the ventricles, but by compressing the base of the brain in the same manner.[91]

On the same page, Platter briefly referred to the autopsy he had witnessed as a student at the University of Montpellier;[92] in the 1550s; he used a few more words to describe the event in a book with medical observations, published later in 1614, the year he died:

> An old woman from Montpellier suddenly died after she had been struck by apoplexy. When I opened her skull in the monastery before she was buried, I found that her brain within the thick membrane fluctuated on both sides. When the hard membrane had been cut and opened, some rather thick and whitish fluid resembling porridge flowed down over her entire face and was scattered over the cloth on both sides.[93]

Platter's report clearly indicates that the abnormality was found in the substance of the brain, but leaves most other questions unanswered. As in earlier examples, the clinical features that led to the diagnosis of apoplexy are unknown. Especially important is the time course of the disease: did the word 'sudden' apply to her death or to the apoplexy? If the brain tissue was actually

91 Platerus (1602), *De Functionum Laesionibus*, 24.
92 Platter chronicled his *grand tour*: Le Roy Ladurie (1995), *Le Mendiant et le Professeur*.
93 Platerus (1614), *Observationum, Libri tres*, 14–15.

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'dissolved', one might think of inflammatory disease, or of decay owing to a delay between death and autopsy. Moreover, the description of the abnormal texture of the brain is global, without distinction between its parts.

Bauhin's anatomical compendium and Platter's textbook on diseases did not influence physicians until the early seventeenth century; even then, it took some 50 more years before the traditional interpretation of Galenic physiology had faded. For example, as late as in 1641, a few years after Bauhin's death, an academic thesis on apoplexy defended in Basle still mentioned the ventricles, as well as the substance of the brain, as the site where the flow of animated spirits could be interrupted.[94] But as the sixteenth century drew to a close, more and more physicians became used to the idea that the science of medicine was incomplete and ancient writings no longer sufficed. Practical physicians like Pieter van Foreest paid much attention to new observations recorded by colleagues, in letters or books; one-third of the hundreds of citations in his text on apoplexy refers to contemporaries. Also, younger physicians were less fettered by tradition, whereas the prestige of university professors still depended on literary expertise. 'Research' as an academic activity was not just non-existent; it was entirely unknown.

All in all, the 'ventricular hypothesis' died a slow death, even in northern Italy. In the account of apoplexy by Alexander Massaria (1510–1598), appointed in 1587 to succeed Mercurialis as Professor of Theoretical Medicine in Padua,[95] he assigned a prominent role not only to the ventricles, but also to the *rete mirabile*:

> [. . .] the heart continuously provides [the brain] with heat and vital spirit, mediated by those vessels forming a considerable network, commonly called the miraculous net, by which the animated spirit, very subtle and easily soluble, can be continuously regenerated and stored. If, therefore, the arteries forming this network happen to be obstructed and impeded, so that less vital spirit can be transported to the ventricles of the brain, then necessarily also the vital spirit will be destroyed and wanting, since it lacks its nourishment. Through this deficiency the actions of the brain necessarily desist, the person is deprived of sensation and motion, and apoplexy occurs.[96]

In contrast, Ercole Sassonia (Hercules Saxonia; 1551–1607), Professor of Practical Medicine in Padua during the 1570s,[97] firmly located apoplexy in the tissue of the brain: 'Its immediate site (no matter what others say), is the substance of the brain.'[98]

[94] Falkhusius (1641), *De Apoplexia Positiones*, thesis VIII.
[95] Hirsch (1884–8), *Biographisches Lexikon*, vol. IV, 161.
[96] Massaria (1601), *Practica medica*, 80. [97] Hirsch (1884–8), *Biographisches Lexikon*, vol. V, 182.
[98] Saxonia (1610), *Prognoseon Practicarum*, 53.

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Still, at the dawn of the seventeenth century, there was no firm evidence that apoplexy could be caused by lesions of brain tissue itself. A few post-mortem dissections had been carried out, but they had been performed, or at least described, in a cursory fashion, while the clinical features that had led to the diagnosis of apoplexy remained unspecified. That theories dominated medical thinking is not very different from today, but a vital difference was the inflexibility of the theory. Eyes had to be taught to see what there actually was, instead of what ought to be seen. This is what caused Varolio to write, when he had been met not only with disbelief, but also with accusations of cheating when he had demonstrated that basal structures of the brain differed from ancient descriptions:[99]

> Indeed, so great is the power of established opinion of men, that many even seemed to be in doubt while they were beholding the very truth with their own eyes.[100]

Observation as a source of knowledge, instead of scriptures, required a routine that had to be learnt.

THE ART OF OBSERVATION

The distinction between observation and interpretation is never sharp, not even today,[101] not even in particle physics where some conclusions are based on the interpretation of photographs of events in bubble chambers.[102] Seeing is always, to some extent, believing; visual impressions are often selective or fraught with meaning. Medicine is no exception; this applies not only to clinical features of illness, such as the interpretation of a reflex,[103] but also to pathological–anatomical observations after death.

It is therefore appropriate to review the advance of medical knowledge in the second half of the sixteenth century from a somewhat broader perspective than that of a particular disease. Several writings, not exclusively in medicine, emanated a presentiment that nature had not yet revealed all her secrets. Accordingly, there was a slow transition from recognition of known patterns to attempts at learning. The process of observation, to see what is in front of one's eyes, to use Varolio's expression, was a key element.

Clinical Observations

In recording clinical phenomena of disease, the word 'observation' did not always have the same connotation. 'To observe' may also imply a form of

99 Varolio (1573), *De Nervis opticis*, 13v. 100 Varolio (1573), *De Nervis opticis*, 11r.
101 Hanson (1958), *Patterns of Discovery*, 4–30.
102 Pickering (1984), Against putting the phenomena first.
103 van Gijn and Bonke (1977), Interpretation of plantar reflexes.

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obeisance, or 'observance', in the sense of acknowledgement, recognition, and confirmation of something already known and perhaps even expected. Gianna Pomata has argued that in the period between 1500 and 1650, 'observation' gradually evolved from a prescriptive to a descriptive meaning and so came to represent a new epistemic genre, of facts on their own – especially in astronomy and medicine.[104] It is in the modern sense of the word that *observationes* became popular in the medical world of the late sixteenth century: case records of patients, with clinical phenomena; the corresponding theories were relegated to a sequel with explanatory notes (*scholia*). This method of presentation, first applied in northern Italy, became the template of published case records. But it was not easy to disengage perceptions from preconceptions; theoretical notions invariably tended to creep in.

Looking inside the Head

The very decision to try and have a look at the brain of a patient who succumbed after apoplexy was a momentous step, given the practical and moral obstacles. Up to the middle of the sixteenth century, doubt about causes of disease was scarce.[105] Physicians were generally satisfied with interpretations of the clinical phenomena of apoplexy in Galenic terms: phlegm overfilling the cerebral cavities. Though early post-mortem investigations were sometimes prompted by judicial arguments, doubt must have been the driving force in at least some of them.

Questioning Galen was indeed a bold step. Around 1550, physicians like Fernel felt they were part of a medical Renaissance: their art had come to life again, thanks to the restoration of ancient Greek wisdom, purged from barbarisms. These ancient medical texts, almost matching the Bible in age and peremptory style, had a status far outstripping the bare fact that they were actually based on observations, and, what is more, observations anybody could repeat and check. Even so, their contents were almost universally regarded as inviolate truths, defying the capacity of the senses, in the same way as in ancient times the rules of mathematics were felt to surpass the physical reality of material objects or of visual representations by means of lines and angles.[106] In addition, the synthesis between Aristotelian natural philosophy and Christian theology, crafted by Thomas of Aquino and other theologians in the thirteenth century, endowed the Greek heritage with an

[104] Pomata (2011), Observation rising.
[105] Gulczynski, *et al.* (2009), Short history of the autopsy.
[106] Dijksterhuis (1961), *The Mechanisation of the World Picture*, 50–3.

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almost religious supremacy.[107] Any censure or objection might be felt to border on heresy.

As we saw, the first reports in which physicians inspected the brain of victims of apoplexy were not very informative. The lack of detail proved the inspection could not have been more than a quick peek: blood or phlegm at the base of the brain, compressing a fictitious network of vessels, or ventricles of the brain filled with blood or aqueous fluid.

Similarly, Varolio's almost casual comment that he had witnessed dissections of patients with apoplexy where the ventricles contained 'no greater quantity of excrements than one usually finds in all others' was not supported by information on identities or on the patients' symptoms before death. This finding, in fact great news in medicine, was apparently muffled because it did not agree with ancient theory.

Handling and Exploring the Brain as an Object

Varolio's name is remembered by medical students solely – if at all, because eponyms are going out of fashion – by his description of a prominent structure at the base of the brain he called 'the bridge' (*pons*; Figure 1.6A). He deserves to be remembered for more. First of these is the technique he developed for removing the brain from the rest of the corpse. Though acknowledged by early historians of medicine,[108] this feat has become obliterated; one finds it only in historical compendia of brain anatomy.[109] The psychological, almost metaphysical consequences of the Varolian technique far outshine the practical advantages. Until then, the brain, considered the seat of reason, but also of morality, had remained part of the corpse as a whole and represented almost the very core of the person. But by entirely removing the brain from the rest of the body, like the heart, the lungs, the spleen, or other organs, Varolio opened the way to the exploration of not only its inner structure, but also its diseases.

Finally, perhaps his most important feat, Varolio proposed that the substance of the brain, not its cavities, was the location of 'animated spirits'. He derived this premise from his observation that most nerves originated near the part of the ventricular system with the smallest cavity. His additional, teleological argument that a storage site was needed for secretions from the nose and throat was eventually to be disproved.

[107] Dijksterhuis (1961), *The Mechanisation of the World Picture* 128–35.
[108] Sprengel (1821–8), *Geschichte der Arzneykunde*, vol. III, 126; Neuburger (1897), *Entwicklung der experimentellen Gehirn-und Rückenmarksphysiologie*, 125.
[109] Clarke and O'Malley (1996), *The Human Brain and Spinal Cord*, 820–3.

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The Combination of Brain Dissection and Clinical Signs and Symptoms

Vesalius and Fabry had each dissected an infant with exceedingly large ventricles. Both children had died at the age of around two and a half years. Sparse, but vital pieces of clinical information attested that each child had made limb movements and had manifested 'sensation' in the sense of interaction with the parents, even at a stage of enormous expansion of the cerebral ventricles. These two case reports were often cited by contemporaries and later generations because they removed the last foothold in the notion that the cerebral ventricles were essential for the production and transport of animated spirits. The resulting conceptual turn, in which the 'signals of thought' were relocated in the substance of the brain instead of in its watery cavities, was an indispensable step in the understanding of apoplexy.

In conclusion, recording clinical facts was an art that had to be developed, not in a single physician's lifetime, but in the course of several generations. The same applied to recording changes in the brain of patients who had died of apoplexy – the anatomy of disease. In the sixteenth century, this started with fragmentary information on manifestations of disease and anatomical changes. Only the combination of clinical and pathological characteristics allowed further understanding of brain disease.